SPECIFIC AIMS

The Fred Hutchinson/University of Washington Cancer Consortium (Consortium) brings together more than 450 members with research interests in basic, clinical and public health sciences related to cancer. The goal of the Consortium is the elimination of cancer through more effective prevention, diagnostics and treatment, deriving from fundamental insights into the biology of the disease. The extensive interdisciplinary collaboration among the partner institutions in the cancer research disciplines of basic, clinical, and public health sciences affords new opportunities to reduce suffering and mortality from cancer.

Over the next grant period, the Consortium will seek to:

1. Continue its leadership in cellular immunotherapy, with the goal of making this therapeutic platform the standard of care for many malignancies;

2. Build on our outstanding strengths in cancer basic biology to increase collaborative translational research, including using genomic and epigenomic technologies to develop effective prognostic tests for solid tumor cancers, applying protein engineering to novel cancer therapeutics, and developing robust mouse models of cancer for rapid screening of drug response prior to therapeutic intervention;

3. Expand our pioneering efforts to reduce the global burden of cancer through translational research on infection-related malignancies, application of global disease surveillance data, and unique international partnerships in Africa (Uganda and South Africa) and more recently China to establish robust platforms to improve our understanding of the spectrum of cancer biology and disease worldwide;

4. Lead research that supports provision of efficient, effective and cost-effective cancer care through research in health economics, cancer outcomes and comparative effectiveness; and

5. Lead population-based research to uncover new insights into the link between obesity and cancer, and to reduce disparities in cancer risk, outcomes and access to care in underserved populations.
OVERALL COMPONENT

PART I: DIRECTORS OVERVIEW

The Fred Hutchinson/University of Washington Cancer Consortium was established in 2002 to build upon the complementary strengths and resources of three partner institutions: the Fred Hutchinson Cancer Research Center, which had been an NCI-designated Comprehensive Cancer Center since 1976, the University of Washington, which had significant strength in cancer care and laboratory sciences, and Seattle Children’s, the region’s major pediatric academic center. In 2008, the Seattle Cancer Care Alliance, the cancer treatment center founded and equally co-owned by the three institutions, was formally added as a fourth partner.

The Consortium’s total funding base (direct dollars) is $389M, of which $87.5M is from the NCI, $98.1M from the other NIH institutes and $17.2M is other peer-reviewed funding. HIV grants and other non-cancer grants have been excluded from the funding base, except for the portion of some grants that is cancer-relevant. During this period, membership has grown by 10% to 464, despite a tightening of membership criteria. In the most recent year, there were 412 therapeutic clinical trials that accrued 958 local subjects. 31% of these trials were investigator initiated and 19% were Phase I. The ratio of accruals to newly registered patients was 23%.

The Consortium serves a catchment area of 13 counties in Western Washington. This equates to the region in which 70 percent of our patients reside. As the only NCI-designated comprehensive cancer center in a five-state region (Washington, Wyoming, Alaska, Montana and Idaho), we not only seek to serve the health needs of the catchment area through research, training and outreach, but also to ensure high impact in the region.

The Consortium continues to build upon historic strength in basic cancer biology, immunotherapy, population based research, health care outcomes and economics and global health. It is well poised to continue its exceptional level of research in these areas. The CCSG continues to have a high impact at our center, fostering new inter-institutional collaborations, strengthening the translational research platform, and intensifying research efforts on problems of the catchment area. Partner institutions committed nearly $580M in institutional support during the project period, including investment in the clinical research infrastructure and solid tumor translational research. The partners were involved in the appointment of Larry Corey, MD, as Consortium Director and as President and Director of FHCRC in 2011. Dr. Corey succeeded Lee Hartwell, PhD, who led the FHCRC and the Consortium for 13 years. Dr. Corey has worked with faculty and the Board of Trustees at FHCRC to conduct a comprehensive review of FHCRC scientific priorities, and, in collaboration with leaders of the partner institutions, the scientific priorities of the Consortium. The alterations and adjustments of many of the programs outlined in this proposal are a direct result of these processes.

As described later, major scientific advances during the project period include:

- Mapping functional elements in the genome that may serve as therapeutic targets for cancer;
- Engineering computationally designed proteins that inhibit tumor proteins;
- Novel tools to analyze the human immune cell genomic repertoire with utility to improve cancer prognostic tests;
- Identification of mechanisms of chemotherapy resistance that may lead to improvements in therapy;
- A gene therapy approach with potential to improve glioblastoma treatment;
- Strategies to improve management of Merkel cell carcinoma;
- Immunotherapies using genetically engineered T cells for hematologic and solid tumor cancers;
- An effective strategy for engraftment using cord blood transplantation;
- Multiple contributions that are reducing mortality from hematopoietic stem cell transplantation;
- Determination of the impact of dietary supplements (vitamin E) on prostate cancer;
- Assessing the economic return of a major national prevention trial;
- The first global study on the levels, trends and impact of cancer in the developed and developing world.
Rationale for Formation of the Consortium

The structure of the Consortium is shown in Figure 1.

For over 40 years, FHCRC and UW School of Medicine (UWSOM) have had a joint clinical research program. One individual serves as both the director of FHCRC’s Clinical Research Division and as head of Medical Oncology at UWSOM. In 2013, Fred Appelbaum stepped down from these roles following his appointment as Deputy Director of FHCRC and the Consortium. A national search jointly conducted by all Consortium partners is underway to identify a single individual to fill these roles as it is apparent that a unified model has served the institutions well. Many faculty hold secondary appointments at one or more of the other partner institutions. 77% of the Consortium faculty based at FHCRC and 26% of UW-based faculty hold secondary appointments at the other institution. All Children’s faculty have appointments in the UW Department of Pediatrics. In 1994, the FHCRC and UW signed a formal agreement to pursue joint cancer research, care and education and in 1998, FHCRC and UW entered into an agreement with Children’s to create and then operate a cancer treatment center. The three institutions are equal partners and co-owners. Known as the Seattle Cancer Care Alliance (SCCA), its goal is to promote, enhance and integrate the cancer research, teaching and clinical programs of the partner institutions. Thus, the partners are united financially and in patient care through the SCCA. The CCSG binds their investigative interests, uniting their oncology research programs. Further cementing this integration, Dr. Appelbaum has been SCCA Executive Director since its founding. The successor to his FHCRC and UW roles will also assume Dr. Appelbaum’s SCCA role when he steps down from that position.

Deep collaborations in graduate education also exist. These include a graduate program that is jointly administered by FHCRC and UW and spans the biological sciences at the two institutions. FHCRC faculty have long participated in UW School of Public Health graduate education as teachers and advisors. They also participate in University training grants in epidemiology, biostatistics and cancer prevention. Several T32s support trainees at both FHCRC and UW, and faculty from both institutions serve as PIs. Since FHCRC’s founding in 1972 there has been joint hematology/oncology fellowship training with UWSOM, and there are also joint fellowship programs in pediatric oncology and other clinical subspecialties.

In 2002, the three institutions signed an MOU to form the Fred Hutchinson/University of Washington Cancer Consortium. The Consortium built upon the FHCRC as an NCI-designated Comprehensive Cancer Center, while adding the vital research and resources of the new partners. In 2008, at the time of the last CCSG renewal, SCCA was formally added to the cancer center designation.
Scientific Contributions of Member Institutions

Fred Hutchinson Cancer Research Center (FHCRC). FHCRC was founded in 1972, received its first CCSG in 1973, and was designated a comprehensive cancer center in 1976. Today, it has more than 200 faculty and an annual research budget (total costs) of $400M. The institution has always emphasized research on the biology, prevention, diagnosis and treatment of cancer and its founding premise has been to eliminate cancer as a cause of human suffering and death. 205 Consortium members have their primary appointment at FHCRC. FHCRC is comprised of five scientific divisions. Basic Sciences Division faculty lead research in cell biology, chromosome biology and metabolism, epigenetics, structural biology and cellular metabolism. Its research into the basic underpinnings of cancer informs research in other scientific divisions. Human Biology Division members apply interdisciplinary research to advance understanding of human biology and the complex problems of neoplasia and other human diseases. Eric Holland, a prominent neurosurgeon and laboratory-based brain tumor research scientist, was recently recruited to head this Division and expand solid tumor translational research. Clinical Research Division faculty include clinical and lab-based members. In addition to its world leadership in the development of bone marrow transplantation, other treatments for hematologic diseases, and cellular and antibody-based immunotherapy, there has been recent expansion of activities in solid tumor pre-clinical and clinical research. Public Health Sciences Division faculty study cancer in the general population, leading research on genetic and environmental cancer risk factors, interventions to prevent or mitigate risk, design and analysis of clinical trials and observational studies, mathematical modeling of disease, cancer epidemiology, computational biology, biostatistical methods and research of racial and ethnic disparities in cancer incidence and treatment. Its scientists coordinate numerous large prevention and epidemiology studies, including the Women’s Health Initiative, among the world’s largest public health studies. The division’s many biostatistical and coordinating centers partner with ~50 NCI Cancer Centers. The Vaccine and Infectious Disease Division was founded in 2010 and houses global oncology research, a direct offshoot of its original work on infection-associated cancers. Collaboration with faculty in other FHCRC divisions and the UW Institute for Health Metrics and Evaluation has led to the establishment of the new Global Oncology program of this proposal. The Division has research initiatives in Uganda, China and South Africa.

University of Washington School of Medicine (UWSOM). The UWSOM was founded in 1946 and has a wide range of oncology programs that support patient care, research and training. It is one of the nation’s top-ranking scientific institutions and a leader in physician education. UWSOM is second among all medical schools in federal research funding. The school has 2,300 faculty members, and more than 4,600 affiliated clinical faculty across the regional WWAMI (Washington, Wyoming, Alaska, Montana, Idaho) program who teach medical students, residents and fellows. UWSOM is a leader in human genome mapping, the genetics of breast cancer risk, and stem cell biology and biodesign. UW was awarded a CTSA grant in 2007 (called the Institute of Translational Health Sciences) under the leadership of Mary (Nora) Disis. The School has an annual research budget of $630M. ~200 Consortium members have their primary appointment in the UWSOM.

Organizationally, UWSOM is part of an umbrella entity called UW Medicine. UW Medicine encompasses owned or operated hospitals (e.g., Harborview Medical Center, Northwest Hospital & Medical Center, Valley Medical Center, University of Washington Medical Center), as well as a physician practice plan (UW Physicians). It also has a network of nine neighborhood clinics that provide primary and secondary care. UW Medicine is the regional referral center for both primary care and highly specialized services. It offers a wide range of oncology patient care services, in addition to conducting significant cancer research and training.

University of Washington School of Public Health. Established in 1970, the UW School of Public Health (UWSPH) has as its mission to promote better health, prevent illness and injury, and more efficient and cost-effective health care services through education, research and service. The departments that emphasize cancer research are Biostatistics, Epidemiology, Environmental Health and Health Services. The school has strong ties with the UW Institute for Health Metrics and Evaluation, which develops innovative measurement systems that facilitate informed decision making in health policy and whose director, Christopher Murray, is co-head of the new Consortium Global Oncology Program. The school has 151 primary faculty, more than 1100 students, and an research operating budget of $233M. 34 UWSPH faculty are Consortium members.

Seattle Children’s Hospital. Seattle Children’s is a private, nonprofit hospital providing tertiary pediatric care to children throughout the Pacific Northwest. It has 250 inpatient beds and 40 outpatient clinics that provide care in over 50 pediatric subspecialties. As the only academic tertiary care pediatric hospital serving Washington, Wyoming, Alaska, Montana and Idaho, Children’s has access to a large, diverse pediatric population. In addition to the main hospital campus in northeast Seattle, Children’s operates Seattle Children’s Research
Institute (SCRI), where the Ben Towne Center for Childhood Cancer Research was established in 2011. SCRI serves as the primary research site for the UW Department of Pediatrics and other pediatric subspecialties; major areas of focus include brain tumor biology, immunotherapy, sarcoma, immunodeficiency disease, hematologic cancers and blood diseases, and cancer survivorship. 14 Consortium faculty are based at SCRI.

Seattle Cancer Care Alliance. The Seattle Cancer Care Alliance (SCCA) was established in 1998 as the clinical care, education and research arm of the Cancer Consortium. The formation of the SCCA derives from the strong research ties of the partners. The SCCA is a 501c3 organization equally co-owned by FHCRC, UWSOM and Children’s, and organizes and integrates cancer clinical services for the partner institutions. The initial clinic building of 150,000 sq feet, located on the Fred Hutch campus, was built in 1998 and expanded by 55,000 sq feet in 2006. Clinical care and research are delivered in a patient-centered environment and multidisciplinary clinics serve as the site for clinical research. All faculty practicing at SCCA have primary appointments at UW or FHCRC; pediatric oncologists have academic appointments in UW Pediatrics.

The outpatient facility houses the FHCRC transplant program as well as multidisciplinary clinical programs in breast, gastrointestinal, gynecologic, lung/head and neck, melanoma, prostate, and sarcoma. It also serves as the primary outpatient site for the UWSOM Divisions of Medical Oncology and Hematology and the Radiology Department’s breast imaging program. To support the Consortium’s focus on prevention and early detection, the SCCA houses a Cancer Prevention Clinic that helps patients reduce their risk of getting cancer. While most adult hematology and oncology outpatient care is provided in the main SCCA facility, there are also clinics at EvergreenHealth and Northwest Hospital. Some surgical and radiation procedures are performed at UWMC, while proton therapy is provided on the Northwest Hospital campus. The SCCA also has a regional network with nine hospitals including sites in rural areas of Washington, Montana and Alaska.

SCCA serves over 6,200 new patients a year and averages about 300 patient visits a day. It is designated as a prospective payment system (PPS)-exempt cancer hospital. There are 80 adult inpatient oncology beds at UW Medical Center, including 40 for transplant, of which 20 are operated by the SCCA. Outpatient pediatric hematopoietic cell transplantation services are provided at the main SCCA facility. Other pediatric care services are delivered on the Children’s Laurelhurst campus.

Collaborative Inter-Institutional Research Builds on Complementary Strengths

The complementary strengths of the partner institutions have resulted in many important inter-institutional, NIH-funded collaborations that span the basic, clinical and population sciences. Some examples include:

<table>
<thead>
<tr>
<th>Research Area</th>
<th>Faculty Leaders/Collaborators (not inclusive)</th>
<th>Project</th>
</tr>
</thead>
</table>
| Basic Sciences     | David Baker (UW)  
  Barry Stoddard, Hans-Peter Kiem (FHCRC)  
  Andrew Scharenberg (Children’s)  
  John Stamatoyannopoulos, Jay Shendure (UW)  
  Mark Groudine, Michael Bender (FHCRC) | Northwest Genome Engineering Consortium.  
(NIH Roadmap for Medical Research) |
|                    |                                                                                                      | Encyclopedia of DNA Elements (NHGRI)                                     |
| Clinical Research  | Peter Nelson, Janet Stanford, Ruth Etzioni (FHCRC)  
  Daniel Lin, Bruce Montgomery, Stephen Plymate, Paul Lange, Robert Vessela, Lawrence True (UW)  
  Nicole Urban, Charles Drescher, Toshi Taniguchi, Martin McIntosh (FHCRC)  
  Elizabeth Swisher, Nora Disis, Lupe Salazar (UW) | Pacific Northwest Prostate Cancer SPORE (NCI)  
Pacific Ovarian Cancer Research Consortium SPORE (NCI, SPORE) |
|                    |                                                                                                      | Seattle Cancer Consortium Breast SPORE (NCI)                            |
|                    |                                                                                                      | Institute of Translational Health Sciences/CTSA (NCATS)                 |
| Population Sciences| Garnet Anderson, Christopher Li (FHCRC)  
  Shirley Beresford, Alex Reiner, Deborah Nickerson (UW)  
  Ulrike Peters (FHCRC)  
  Deborah Nickerson (UW) | Women’s Health Initiative (NHLBI)                                       |
|                    |                                                                                                      | Genetics and Epidemiology of Colorectal Cancer Consortium (NCI)          |
## Selected Major Scientific Discoveries and Impact Made During the Project Period

The following table demonstrates our scientific innovation, breadth and translational impact in basic, clinical, and population sciences. More detailed descriptions and references for these findings follow the table. Many represent team science. CCSG resources and grants supporting this work are noted.

<table>
<thead>
<tr>
<th>Innovation</th>
<th>Impact</th>
<th>Grants</th>
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<tbody>
<tr>
<td>Mapping functional noncoding elements in the genome through the Encyclopedia of DNA Elements (ENCODE) study, including areas in which somatic mutation is suppressed.</td>
<td>Functional elements may have important roles in tumor cells and are possible therapeutic targets.</td>
<td>U54 HG004592, U01 ES01156, P30 DK056465, RC2 HG005654, and R01 HG006768</td>
</tr>
<tr>
<td>Computational design and optimization of an inhibitor of an Epstein-Barr Virus survival protein.</td>
<td>The designed protein has preferential apoptotic activity against an EBV-infected cell line, implicating it in EBV-associated cancers as a potential therapeutic target and the overall strategy as having broad therapeutic potential.</td>
<td>P41 GM103533, R01 GM49857</td>
</tr>
<tr>
<td>Developed multiplex PCR, high-throughput sequencing and algorithms to analyze the human immune cell genomic repertoire.</td>
<td>Application to development of highly sensitive cancer prognostic tests for hematologic and solid tumor cancers, and for identification of immunotherapy targets.</td>
<td>R56 AI081860</td>
</tr>
<tr>
<td>Identified WNT gene expression in the tumor microenvironment as a mechanism of chemotherapy resistance in solid tumors.</td>
<td>Affords strategy to block this treatment response to overcome lethal chemotherapy resistance and improve therapeutic outcomes.</td>
<td>P50 CA83636, R01 CA119125, U54 126540, P50 CA097186</td>
</tr>
<tr>
<td>Developed a gene therapy approach to overcome resistance to alkylation agent chemotherapy for glioblastoma.</td>
<td>Affords a method to select in vivo gene modified stem cells and escalate chemotherapy dosage – improving outcomes for brain cancer patients.</td>
<td>R01 CA114218, R01 AI080326, R01 HL098489, P30 DK056465, K01 DK076973, R01 HL074162</td>
</tr>
<tr>
<td>Discovered antibodies to the Merkel cell polyomavirus oncoprotein; developed an assay for diagnosis and early detection of recurrence of Merkel cell carcinoma.</td>
<td>Potential improved outcomes for Merkel cell carcinoma, a skin cancer whose incidence has quadrupled in 20 years and has 5-year mortality of over 40% (far higher than melanoma).</td>
<td>R01 CA162522, K24 CA139052, R01 CA176841, RC2 CA147820, P01 CA042792, R01 AI 38382</td>
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<tr>
<td>Developed novel immunotherapies using genetically engineered T cells for hematologic and solid tumor cancers.</td>
<td>Identified T-cell subsets that persist long-term after adoptive transfer and that can be engineered for greater tumor specificity. Developed novel selection method to identify and clone naturally occurring high affinity TCRs to tumor markers such as WT-1, cyclin A1 and mesothelin, with clinical trials underway.</td>
<td>R01 CA136551, R01 CA114536, P50 CA138293, P01 CA018029, CA033084, Leukemia and Lymphoma Society LLS-7008-09</td>
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<tr>
<td>A strategy using ex vivo expansion of cord blood stem cells with Notch 1 to accelerate engraftment using cord blood transplantation.</td>
<td>Increases CD-4 T cells by 200-fold with a 2-fold increase in rate of engraftment, thus increasing availability of transplants and reducing its morbidity and mortality for patients with rare HLA types including those of mixed race backgrounds.</td>
<td>R24 HL74445, K23 HL077446, K12 CA076930, R01 HL080245, P30 DK56465</td>
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<tr>
<td>Developed changes in practice for hematologic stem-cell transplantation for blood cancers, such as including individualized busulfan dosing, improvements in GVHD prophylaxis, and use of better anti-microbials and anti-virals to reduce infectious disease complications.</td>
<td>Significant reduction in transplant-related mortality (60%), malignant disease recurrence (21%) and overall mortality (41%) between transplants performed 1993 – 1997 and a decade later.</td>
<td>P01 CA18029, P01 CA78902, P01 HL36444, R01 HL088201, K99 HL088021, K23 HL096831, K23 DK063038</td>
</tr>
<tr>
<td>Assessing the economic value of the Women’s Health Initiative, finding $140 in net economic value for each dollar invested in the trial.</td>
<td>These results can inform consideration of the future role of public funding for large prospective trials with high potential for public health impact.</td>
<td>HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, HHSN271201100004C</td>
</tr>
<tr>
<td>Determination of the impact of dietary supplements (vitamin E) on prostate cancer.</td>
<td>Potential harm of dietary supplements reinforces need for skepticism of benefit of unregulated over-the-counter products in the absence of evidence of benefit demonstrated in clinical trials.</td>
<td>U10 CA37429</td>
</tr>
<tr>
<td>First global study on the levels, trends and impact of cancer in the developed and developing world.</td>
<td>The study sets a benchmark for understanding and informing health policy on the current burden of malignancies in countries around the world.</td>
<td>Bill and Melinda Gates Foundation grants OPP48046, 51229, OPP1070441</td>
</tr>
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</table>
Defining the Function of Non-coding Regions of the Genome (Program in Cancer Basic Biology). The NHGRI-funded Encyclopedia of DNA Elements (ENCODE) project aims to identify all functional elements in the human genome, particularly those outside protein coding regions. ENCODE has emerged as a major advance in the understanding of cancer by linking both somatic mutations and disease-associated single nucleotide polymorphisms to recently identified functional elements of the genome. Systematically mapping regions of transcription, transcription factor association, chromatin structure and histone modification, ENCODE assigned biochemical function to 80% of the genome. John Stamatoyannopoulos (UW) is PI of one of 7 major ENCODE projects cataloging cis-regulatory sites in human and mouse cells, with Mark Groudine (FHCRC) as a collaborator. Jay Shendure (UW) leads one of 11 technology development centers developing methods to multiplex gene reporter assays to functionally characterize human regulatory elements. Dr. Stamatoyannopoulos’s group has shown that somatic mutation is suppressed in regions annotated by ENCODE, suggesting that these functional elements may play key roles in tumor cells and are possible therapeutic targets. Publications include: Maurano et al., Science, 2012; Thurman et al., Nature, 2012; Neph et al., Nature, 2012; Neph et al., Cell, 2012; Smith et al., Nat Genet, 2012). This work has been supported by the CCGS Comparative Medicine Shared Resource.

Computational Design and Optimization of an Inhibitor of an Epstein-Barr Virus Survival Protein (Program in Cancer Basic Biology). To prevent virus spread, infected cells may undergo apoptosis. Some viruses have adapted by co-opting prosurvival genes from the host, including the Epstein-Barr virus (EBV) gene BHRF1, a homologue of human Bcl-2 proteins that block apoptosis. David Baker (UW), collaborating with Barry Stoddard (FHCRC), used computational design and experimental optimization to generate a novel protein called BINDI that binds BHRF1 with picomolar affinity. BINDI recognizes the hydrophobic cleft of BHRF1 in a manner similar to other Bcl-2 protein interactions, but makes many additional contacts over an extensive interface to achieve exceptional affinity and specificity. Alternative interactions with human Bcl-2 proteins are weak; BINDI binds Mcl-1 with 180-fold weaker affinity, and Bcl-B, Bfl-1, Bcl-w, Bcl-XL and Bcl-2 with greater than 4,000-fold weaker affinities. The designed protein has preferential apoptotic activity against an EBV-infected cell line, implicating BHRF1 in EBV-associated cancers as a potential therapeutic target (submitted for publication). Work is underway to apply this method to the design of inhibitors of other cancer cell proteins.

Sequencing the T-cell Repertoire for Applications to Cancer Prognostics (Programs in Biostatistics & Computational Biology and Immunology & Vaccine Development). The human DNA loci that encode the B- and T-cell receptor genes rearrange somatically in adaptive immune cells to produce an enormous variety of receptors for pathogen recognition. Harlan Robins and colleagues at FHCRC and UW developed multiplex PCR technology to quantitatively amplify all possible rearrangements; a procedure for high-throughput sequencing of these molecules; and algorithms for data analysis (Robins HS et al., Sci Transl Med, 2010; Sherwood AM et al., Sci Transl Med, 2011; Robins H, et al., J Immuno Meth, 2012; Larimore K et al., J Immunol, 2012; Emerson R et al., J Immunol Methods, 2013). The technology has been applied to detection of minimal residual disease for hematologic malignancies, demonstrating in acute lymphoblastic leukemia to be far more sensitive and accurate than state of the art flow cytometry (Wu et al., Sci Transl Med, 42012). This technology has been spun off into a company, Adaptive Biotechnologies, and is being used in clinical trials. The investigators are also assessing T cell quantity and clonal expansion in tumor infiltrating lymphocytes (TIL) to define potential immunotherapy targets (Sherwood et al., Cancer Immunol Immunother, 2013). They have completed studies in colorectal cancer, ovarian carcinoma, and melanoma that show that clonal expansion in TIL is an independent and informative prognostic biomarker for disease-free survival (Robins et al., Sci Transl Med, 2013). This work was supported by the CCGS Genomics and Prevention Center Shared Resources.

New Mechanism of Resistance to Solid Tumor Chemotherapy (Program in Prostate Cancer). Developing resistance to chemotherapy is a nearly universal and ultimately lethal consequence for cancer patients with solid tumors that have metastasized. Components of tissue microenvironments are recognized to profoundly influence cellular phenotypes, including susceptibilities to toxic insults. Peter Nelson (FHCRC) and colleagues at FHCRC and UW performed genome-wide analysis of transcriptional responses to genotoxic stress induced by cancer therapy (Sun et al., Nature Medicine, 2012). They found that expression of WNT16B in the prostate tumor microenvironment attenuated the effects of cytotoxic chemotherapy in vivo, promoting tumor cell survival and disease progression. These results delineate a mechanism by which genotoxic therapies given in a cyclical manner can enhance subsequent treatment resistance through effects that are contributed by the tumor microenvironment. The discovery suggests that finding a way to block this treatment response in the
tumor microenvironment may improve the effectiveness of therapy. This work was enabled by the CCSG Comparative Medicine and Northwest BioTrust resources, and Clinical Research Support.

**Application of Gene Therapy and Stem-Cell Transplantation to Glioblastoma Treatment (Program in Hematologic Malignancies).** For many cancers treated with alkylating agent chemotherapy, including glioblastoma, the most common primary brain tumor found in adults, tumor cell expression of the protein methylguanine methyltransferase (MGMT) can cause chemotherapy resistance and decreased treatment efficacy. Chemical inhibition of MGMT, in combination with alkylating agent chemotherapy, causes severe bone marrow toxicity. Hans-Peter Kim and colleagues at FHCRC and UW developed a strategy to genetically modify autologous bone marrow stem cells with a mutant version of the MGMT gene that resists inhibition. A phase I trial in poor-prognosis glioblastoma patients demonstrated that re-infusion of the modified cells into patients resulted in persistence of these cells, allowing administration of additional rounds of chemotherapy with alkylating agents (Adair et al., Sci Transl Med, 2012). To date, we have treated seven patients, six of whom have surpassed the median survival for poor-prognosis glioblastoma. The first patient has survived 4 years since diagnosis with no additional therapy or evidence of disease progression. The investigators are pursuing this strategy in other brain tumors and other cancer populations treated with alkylating agent chemotherapy. This work was supported by the CCSG Therapeutic Manufacturing Shared Resource.

**Improving the Management of Merkel Cell Carcinoma (Programs in Cancer Epidemiology, Prevention & Control, Immunology & Vaccine Development, and Global Oncology).** Merkel cell carcinoma is an aggressive, polyomavirus-associated skin cancer whose incidence has quadrupled in 20 years and has 5-year disease-associated mortality of over 40% (far higher than melanoma). The Merkel cell polyomavirus (MCPyV) is involved in the pathogenesis of over 80% of MCC tumors. Our center has the nation's largest cohort of Merkel's patients, with novel therapeutic trials being developed from Consortium laboratory research. Paul Nghiem (UW), Denise Galloway (FHCRC) and colleagues have discovered that antibodies to the MCPyV oncoprotein can be used to track disease burden in Merkel cell patients (Carter JJ et al., J Natl Can Inst, 2009; Paulson KG et al, Cancer Res, 2010). An antibody assay for sensitive initial diagnosis and early detection of recurrence in previously diagnosed patients has been developed and is in late stage clinical testing. Studies demonstrating an inverse correlation between T cell responses to the large T antigen and outcome (Paulson KG et al., J Clin Onc, 2011; Iyer JG et al., Clin Cancer Res, 2011) have stimulated several immunotherapy studies. These include a Phase I/II adoptive T cell treatment trial for patients with metastatic Merkel cell carcinoma, an anti-PD1 trial, and a trial of intratumoral injection of a TLR 4 agonist. A phase I/II study of antibody-dependent cellular cytotoxicity and a phase I trial of intratumoral injection of a TLR 4 agonist. The latter two are being planned in conjunction with the NCI Cancer Immunotherapy Trials Network, led by Consortium member Martin Cheever. Support was provided by the Research Pathology resource and Clinical Research Support.

**Discovery of T-cell Subsets to Enhance Adoptive T-cell Cancer Immunotherapy (Program in Immunology & Vaccine Development).** A major challenge for adoptive transfer of cancer specific T cells has been identifying T cells that after in vitro expansion can reproducibly persist and proliferate in vivo until tumor cells are eradicated. Stanley Riddell (FHCRC) and Michael Jensen (Children's) have made major inroads into this problem with the demonstration that antigen-specific CD8+ T cells derived from the central memory (TCM), but not the effector memory (TEM) subset, persist long-term after adoptive transfer in vivo in a non-human primate model and proliferate to antigen challenge (Berger et al., JCI, 2008). They demonstrated in murine models that therapeutic efficacy of genetically engineered T cells can be enhanced using cell products consisting of defined compositions of CD8+ TCM and subsets of CD4+ T helper cells (Hudacek et al., Clin Cancer Res, 2013). Synthetic chimeric antigen receptors (CARs) to target specific cancer antigens for hematologic and solid-tumor cancers have been designed and the first trials to test the safety and efficacy of CAR T cells of defined composition have been initiated for hematologic and solid-tumor malignancies. Initial results indicate in vivo proliferation of these T cells even at the lowest doses tested. Seattle-based Juno Therapeutics, Inc. was launched in 2013 from these discoveries. CCSG Developmental Funds supported Dr. Jensen's recruitment, and Therapeutic Manufacturing, Immune Monitoring, and Clinical Research Support resources were used.

**Enhancing Adoptive T-Cell Therapy Using High-Affinity TCRs to Improve Patient Outcomes after Hematopoietic Cell Transplantation (Program in Immunology & Vaccine Development).** Relapse remains a leading cause of death after allogeneic hematopoietic cell transplantation (HCT) for patients with high-risk leukemias. Although clinical benefit can be derived by donor lymphocyte infusions to achieve a T cell-mediated graft-vs-leukemia (GVL) effect, this is often mitigated by toxicity from graft-vs-host disease (GVHD). Phil Greenberg (UW) and FHCRC colleagues have developed a more targeted approach using T cells specific for the Wilms' tumor antigen 1 (WT1) to promote antileukemic activity without inducing GVHD. They led a Phase I trial that administered WT1-specific CD8 cytotoxic T cell (CTL) clones to high-risk leukemia patients (Chapuis...
et al., Sci Transl Med, 2013). Four of the 11 patients in the trial received infusions of T cells targeting WT1 that were generated in the presence of IL-21. All 4 survived relapse-free after treatment for more than 30 months without GVHD and required no additional anti-leukemic treatment. Among seven patients who received infused T cells generated without the presence of IL-21, two showed direct evidence of anti-leukemic activity. Based on a strategy to efficiently introduce T-cell receptors in CD8 T cells (Provasi E, et al., Nature Medicine, 2012), the investigators have now initiated a clinical trial in which donor CD8 T cells are transduced with this TCR and then infused into patients to treat or prevent leukemia relapse after HCT. This work was made possible by the CCGS Therapeutic Manufacturing Shared Resource and Early Phase Clinical Research Support.

Improving Transplant Outcomes for Hematopoietic Cell Cancers through Cord-Blood Transplantation (Program in Hematologic Malignancies). Delayed myeloid engraftment is a major risk factor for cord blood transplant (CBT) recipients and is closely tied to increased transplant-related mortality. Delayed engraftment is associated with the low hematopoietic stem and progenitor cell doses provided in a single or double cord blood (CB) graft. Colleen Delaney (FHCRC) and colleagues developed methods and then demonstrated preliminary clinical results using a novel ex vivo stem and progenitor cell expansion strategy in which the number of marrow repopulating cells can be increased nearly 200-fold by culture with the Notch ligand Delta1 (Delaney et al, Nat Med 16:232-236, 2010). Infusion of the partially HLA-matched expanded CB product along with a second non-manipulated CB graft resulted in a median time to neutrophil recovery of just 12 days, compared to a median time of 25 days in a concurrent cohort of 40 patients undergoing identical treatment but with two non-manipulated CB units. Current work is aimed at developing an economically feasible “off-the-shelf” source of expanded cells capable of providing rapid neutrophil recovery. Clinical trials are underway utilizing this off-the-shelf cell therapy to bridge myeloopoiesis in both the CBT and post-induction chemotherapy setting. CCGS Therapeutic Manufacturing, Immune Monitoring and Clinical Research Support resources were used.

Improved Outcomes in Allogeneic Transplantation (Programs in Hematologic Malignancies and Biostatistics & Computational Biology). Ted Gooley, George MacDonald and FHCRC colleagues conducted an analysis to define whether alterations in clinical practice have improved outcomes for hematopoietic cell transplantation (Gooley, NEJM, 2010). They analyzed mortality, transplant-related mortality, malignant disease recurrence, and the frequency and severity of major complications among 1418 patients transplanted by Consortium members between 2003 and 2007 compared to those a decade earlier (1993 - 1997). Their analysis demonstrated a significant reduction in transplant-related mortality (60%), malignant disease recurrence (21%), overall mortality (41%) and a concomitant decrease in the risk of severe graft-vs-host disease (GVHD) and damage to the liver, kidneys, and lungs. Changes in practice based on prior studies, many conducted by our group, may have contributed to these results, including individualized busulfan dosing, improvements in GVHD prophylaxis, and use of better anti-microbials and anti-virals to reduce infectious disease complications. This work was enabled by CCGS Clinical Research Support and the Biostatistics Shared Resource.

Assessing the economic value of the Women’s Health Initiative (Programs in Cancer Epidemiology, Prevention and Control and Biostatistics and Computational Biology). The findings of the Women’s Health Initiative (WHI) estrogen plus progestin (E+P) clinical trial led to a substantial reduction in combined hormone therapy (cHT) use among postmenopausal women in the U.S. over the past decade. The overall economic impact of this shift has not been previously evaluated relative to the trial’s $260 million cost (2012 USD). Scott Ramsey and WHI colleagues developed an analytic model to simulate health outcomes for a “WHI scenario” with observed cHT use and a “no WHI scenario” with cHT use extrapolated from the pre-trial period to estimate the economic return from the WHI E+P trial through changes in cHT use, morbidity, mortality, and expenditure during a time horizon of 2003 to 2012. They found that the WHI scenario resulted in 4.3 million fewer cHT users, 126,000 fewer breast cancer cases, 76,000 fewer cardiovascular disease cases, 263,000 more fractures, 145,000 more QALYs, and expenditure savings of $35.2 billion. The corresponding net economic return of the trial was $37.1 billion at a societal willingness to pay of $100,000 per QALY, a return of $140 in net economic value for each dollar invested in the trial. They conclude that the WHI E+P clinical trial was a high-value investment of public funds with a substantial return on investment. These results can inform consideration of the future role of public funding for large prospective trials with high potential for public health impact (provisionally accepted at Annals of Internal Medicine).

Impact of Dietary Supplements on Prostate Cancer Prevention (Programs in Biostatistics & Computational Biology and Cancer Epidemiology, Prevention & Control). SELECT is the national randomized, placebo controlled Phase III trial of selenium, vitamin E or both for prostate cancer prevention. The SWOG Statistical Center, housed at FHCRC and Cancer Research and Biostatistics (a Seattle nonprofit founded by a former FHCRC member), served as the data center and contributed to its design, conduct and analysis. The study
demonstrated that neither selenium nor vitamin E reduced the risk of prostate cancer (Lippman et al., JAMA, 2009). SELECT investigators reported a 17% increased risk of prostate cancer in the vitamin E group, a 9% increase in the selenium group and a 5% increase in the selenium plus vitamin E group (Klein et al., JAMA, 2011). The vitamin E finding demonstrates the potential for seemingly innocuous yet biologically active substances such as vitamins to cause harm. The lack of benefit from dietary supplementation and its potential harm underscore the need for consumer skepticism of health claims for unregulated over-the-counter products in the absence of strong evidence of benefit demonstrated in clinical trials.

Measuring the World’s Cancers and their Impact on Human Life and Well-being (Program in Global Oncology). Christopher Murray and colleagues at the UW Institute for Health Metrics and Evaluation (IHME) led the Global Burden of Disease (GBD) Study 2010, funded by the Bill and Melinda Gates Foundation. The study provides unprecedented detail on the status of health, morbidity and mortality among the world’s population, measuring the levels, trends and the impact of 28 different cancers on the years of life lost due to premature death or poor health. Globally, the number of neoplasms among all ages has grown from 5,779,120 deaths in 1990 to 7,977,920 in 2010 – largely the result of a growing burden of cancer in developing countries. In developed countries, cancer deaths have remained relatively steady, while in developing countries, deaths have increased from 3.19 million to 4.90 million with the largest increases seen for lung, colon, breast, ovarian and prostate. The study sets a benchmark for understanding and informing health policy on the current burden of malignancies in countries around the world. Dr. Murray is the CCSG co-Program Leader of the new program in Global Oncology. The GBD data provide an enormous opportunity to evaluate risk factors and co-morbidities associated with cancer in middle ad lower income countries. It also may provide the first detailed look at the spectrum of cancer in HIV-affected regions. (Lozano et al., Lancet, 2012; Murray et al., Lancet, 2012; Salomon et al., Lancet 2012; Wang et al., Lancet, 2012; Vos et al., Lancet, 2012; and Lim et al., Lancet 2012.)

Organizational Accomplishments During the Project Period

While evidence of the Consortium’s success can, in many ways, be measured by its numerous scientific accomplishments, success measures must also include the consistent, demonstrated commitment of the partners to a shared vision, collaborative program development and investment of resources. During the project period, we have used our organizational capabilities and integrated resources to further our translational research potential, improve our clinical research infrastructure, build solid tumor translational research and intensify our focus on research of value to our catchment. Below are some examples of these accomplishments; others are found throughout this application. Despite his relatively short tenure, Dr. Corey’s leadership has been essential to these accomplishments. He has engaged leaders of the partners to accomplish joint recruitments and large scale collaborative initiatives. For example, Eric Holland was recruited to leadership positions at FHCRC and UWSOM, and his recruitment was catalyzed by the Neurosurgery Chief at Children’s. His recruitment includes six additional FHCRC recruits and four UW endowed brain cancer chairs. Collaborative initiatives in global oncology, health economics, biomedical informatics, minority health and precision oncology were also launched in the last three years.

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<th>Area of Focus</th>
<th>Achievement</th>
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<tr>
<td>Strategic Faculty Recruitments</td>
<td>Eric Holland as leader of Solid Tumor Translational Research, with commitment of 10 additional recruitments; Garnet Anderson as Population Sciences leader; Michael Jensen as director of the Ben Towne Center for Pediatric Cancer Research at Children’s; Stephen Schmechel as leader of the biospecimen resource; talented scientists in targeted areas such as cancer disparities research and health economics.</td>
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<td>Biomedical Informatics</td>
<td>Launched new developing Biomedical Informatics core (see Developmental Funds) to integrate Consortium clinical research data through new Hutchinson Integrated Data Repository and Archive (HIDRA) resource; appointed new leader, Paul Fearn.</td>
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<tr>
<td>Research Initiatives</td>
<td>Engagement of UW Institute for Health Metrics and Evaluation with FHCRC Public Health Sciences to strengthen risk factor assessment in cancer and related diseases; FHCRC $8M commitment to a research and training clinic in Kampaala, Uganda and a new $3M cellular immunology laboratory in Capetown, South Africa. Established Hutchinson Institute for Cancer Outcomes Research (HICOR) for health economics/comparative effectiveness research. UWSOM $25M initiative for the Institute for Protein Design led by David Baker, the leading architect of protein design. Projects devoted to synthesizing new agonists/antagonists to extracellular and intracellular cancer targets are underway.</td>
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**Area of Focus** | **Achievement**
---|---
Access to Biospecimens | Developed Northwest BioTrust (biospecimen) resource (see Shared Resources); initiated new process for universal patient consent to participate in research.
Clinical Research Support | New Clinical Research Support Office to consolidate functions; appointed new medical director and senior administrator; expanded breadth and number of oncology trials.
Precision Oncology | Drs. Corey and Ramsey appointed working group for a Precision Oncology initiative to expand efforts to identify new actionable targets for therapy and create a robust pipeline to develop these into CLIA-approved tests; commitment to joint fundraising.
Phase I Clinical Trials | Established a Phase I Clinical Trials initiative, which has nearly tripled phase I enrollments during the project period, and opening of a Phase I unit at SCCA in 2010.
Minority Health/Health Disparities Research | Established a new Consortium Health Disparities Research Center and appointed an Associate Director for Minority Health and Health Disparities, Betty Thompson.

**Research Priorities for the Next Project Period**

Dr. Corey has led a number of strategic partnership meetings with his counterparts at UWSOM and Children's that have leveraged marked expansion in programs and resource commitments. These commitments are linked to the strategic scientific plans that our leadership team has developed for five areas of laboratory, clinical and population-based cancer research in which we feel we can make the most impact in the next grant period and to which we will commit additional institutional and CCSG funds.

**Basic Biology of Cancer.** A foundational goal of the Consortium has been to develop insights into cancer biology and translate these into clinical practice through novel molecular and computational approaches. Under Dr. Corey, we have devoted attention and resources with success. Notable accomplishments include the use of next-generation DNA sequencing to complete the first comprehensive exome sequencing of the genome of advanced lethal prostate cancer, which identified potential key drivers of disease progression. Others include development and application of targeted gene-correction technology as novel therapeutics, application of shRNA technology to identify genes that might be required in human glioblastoma-type tumors, and the application of functional genomics to identify synthetic-lethal interactions with overexpression of c-MYC oncoproteins, previously considered “undruggable” because of their widespread roles in transcription and proliferation. The UW Institute for Protein Design has begun using computational methods to design synthetic agonists and antagonists of novel cancer tissue markers, such as development of a peptide that selectively targets Mcl-1, a survival protein over-expressed in multiple tumor types (myeloma, AML, B cell lymphoma, melanoma, non-small cell lung cancer, glioblastoma, colorectal cancer, prostate cancer, pancreatic cancer).

CCSG Shared Resources such as Computational Biology and Northwest BioTrust (biospecimen resource) have been essential to supporting these research efforts. Two CCSG New Investigator awards have been used to recruit basic scientists and 14 CCSG pilot awards supported cancer basic biology projects. Several have leveraged substantial extramural funding, including a $4M NCI U01 Cancer Target Discovery and Development Award to identify potential therapeutic targets in patient-derived tumor cells.

Areas of emphasis in the next grant period will include genomic and epigenomic technologies to develop effective prognostic tests for solid tumor cancers, applying targeted gene correction and protein engineering to improve cancer therapy, and developing robust mouse models of solid tumors to enable rapid screening of drug response prior to therapeutic intervention. We will use CCSG and institutional funds to expand our biospecimen (Northwest BioTrust) and Patient-Derived Xenograft (PDX) resources, recruit laboratory-based solid tumor translational researchers, and invest in a precision oncology (molecular diagnostics) initiative.

**Cancer Immunotherapy.** The FHCRC’s work on bone-marrow transplantation provided the first example of the human immune system’s ability to cure cancer. Over the subsequent three decades, we have substantially increased our understanding of this effect and developed novel approaches to harness it for the treatment of hematologic cancers and more recently, solid tumors. Consortium members have identified target molecules on cancer cells and T cells that recognize tumors, and developed procedures to expand these cells and re-infuse them into patients such that the cells survive, multiply and migrate to the tumor where they will be functionally active. This basic biology has developed to a point at which we and others have demonstrated that clinical cures can be achieved for several types of cancers — and that therefore, immunotherapy can be applied to establish a broad-based platform for treating a wide variety of human cancers. We believe we are exceptionally well positioned to make this therapeutic platform the standard of care for many malignancies.
We have used our structure and resources to catalyze these achievements and strengthen our potential. We have developed CCSG Resources in Therapeutic Manufacturing, Immune Monitoring and Genomics, which have enabled target discovery and product manufacturing. The CCSG program structure has stimulated inter- and intra-programmatic collaborations, resulting in large grants that would otherwise not be possible (e.g., Stand Up to Cancer Award, NCI U01 Cancer Target and Discovery Award and the NCI Cancer Immunotherapy Trials Network). We have used CCSG and institutional funds to recruit Michael Jensen, a leader in adoptive T-cell therapy, and junior faculty. And, we have garnered more than $20M in philanthropic support during the project period to develop additional shared resources and fund fellowships. In 2013, FHCRC led the development of Seattle-based Juno Therapeutics, Inc., in collaboration with Children's and Memorial Sloan-Kettering Cancer Center. Juno’s Scientific Advisory Board and Board of Directors include FHCRC and MSKCC representatives. The company is devoted to leading clinical development of these first generation genetically engineered T cells. Advanced clinical trials have been designed for CD-19 and ROR-1 CARs and WT-1 high affinity TCRs in hematologic cancers (ALL, AML, NHL) and solid tumors (NSCLC and ovarian cancer).

During the next 5 years, we will focus on developing genetically engineered T cells that may include means to overcome checkpoint inhibition locally as well as mixtures of purified cell populations to improve the efficacy and safety of cellular immunotherapy. We will use CCSG and institutional funds to recruit immunologists and clinical trialists; continue to invest in the above described resources; develop an enhanced program for novel target discovery and seek philanthropic and commercial partners to support these activities.

Global Oncology. Over the past two decades, cancer deaths have remained relatively constant in developed countries, while developing countries have seen a 65% increase. By 2030, it is estimated that there will be greater than 13 million deaths from cancer worldwide, with two-thirds occurring in the developing world. The Consortium has a long history of collaborative research in global oncology, including the NCI-funded Randomized Trial of Breast Self-Examination in Shanghai and U.S. Office of Naval Research-funded studies of radiation exposure and projects on thyroid cancer in Chernobyl. More recently, we established a unique and robust partnership with Uganda Cancer Institute (UCI) to develop a program in infection-related cancers including HIV-related malignancies. In addition to more than $14M in institutional commitment from FHCRC, this effort has been supported by a USAID grant to build a new clinic, training center and research institute in Kampala, and an NCI D43 training grant to provide doctoral-level training and other research training for Ugandan researchers and staff in HIV-related malignancies. A major success of the program has been the development of the human resources to allow effective research collaborations to flourish and to capitalize on the investments in facilities. Since 2004 we have trained over 15 oncologists, as well as nurses, research staff, epidemiologists and pharmacists, who have returned to Uganda. To date, the UCI collaboration has focused on research largely in Kaposi sarcoma, Burkitt lymphoma, anogenital malignancies and novel approaches to population screening for breast cancer. The program is poised for major expansion over the next five years.

Most importantly, the global oncology research portfolio has matured to the point that it merits major programmatic support, and we present this multidisciplinary program for NCI CCSG approval for the first time. The program structure leverages many Consortium strengths and supports inter-institutional, interdisciplinary research that we believe will impact the global burden of cancer and provide novel cancer biology insights into cancers of relevance to the United States, such as NHL, Burkitt lymphoma and triple negative breast cancer. The Program in Global Oncology (PiGO) is designed to be comprehensive, involving collaborations in cancer biology, epidemiology and prevention, vaccines and infectious diseases, tumor-specific research, imaging and health metrics. Leading the program are Corey Casper, an FHCRC member who directs the UCI/FHCRC collaborative program, and Christopher Murray, director of the UW Institute for Health Metrics and Evaluation and leader of the seminal Global Burden of Disease Study (funded by the Gates Foundation). The CCSG has aided PiGO’s development, including two pilot awards. We have also engaged in a collaboration with NCI scientists to define the molecular genetics of NHL, lung cancer and anogenital tumors in both HIV-infected and HIV-negative Ugandans. Program members have received two CCSG supplemental awards in AIDS-Related Malignancies for pilot grants, supporting projects such as Cervical Cancer Screening among HIV-Positive Women Using p16/Ki-67 and Identifying KSHV and KS Antibody Signatures Using Antigen Microarrays.

Dr. Murray and colleagues have engaged Consortium collaborators to develop more accurate metrics of cancer incidence and mortality as well as develop “real time” assessment of the cancer burden in the developing world. These advances will afford insight into the factors that influence the growing burden of cancer worldwide. PiGO will expand its research base by bringing members together through seminars and symposia, recruiting faculty to work in the discipline of cancer-specific health metrics, mentoring young faculty and those who have not conducted global health research, and initiating large collaborative research projects.
where translational and clinical research is informed by data on global surveillance of cancer. The program will facilitate international cancer studies by providing a platform for research through design and conduct of clinical trials at established international sites and by leveraging the center’s large and growing specimen repositories, with collections from three continents. CCSG and institutional funds will be used to recruit a pediatric oncologist in infection-related cancers (currently underway), additional scientists with expertise in biostatistics and genome analysis, provide support for fellows and continue investment in the Kampala site infrastructure. We believe our program is a world leader in this area. Our goal is to demonstrate that world-class cancer research can be successfully conducted in the developing world, and that unique insights can be made effectively and efficiently. Our hope is that other institutions in the U.S. and the developed world will benefit from what we have learned to lead and expand their global health programs into oncology in the future.

Health Care Economics and Outcomes Research. There is a growing awareness of the impact of rising medical costs and their relationship to cancer outcomes in our society. While our center’s mission is to prevent and cure cancers, we also seek to ensure that the therapies we utilize are selected carefully, from both a clinical and economic perspective. Cancer patients and families also confront vast disparities in care. There is a great need to collect, analyze and provide evidence that supports provision of efficient, effective and cost-effective cancer care. For example, a recent economic analysis of the Women’s Health Initiative findings led by Consortium member Scott Ramsey found a $35B savings in expenditures associated with the reduction in breast cancer and cardiovascular events following reduction in combined hormone therapy use among post-menopausal women – a return on investment of $140 for each dollar invested in this one large trial.

The Consortium is home to leaders in cancer outcomes and health economics research. During this grant period we have catalyzed several new programmatic interactions. An NCI Center for Comparative Effectiveness Research in Cancer Genomics was established at FHCRC in collaboration with the Center for Medical Technology Policy in Baltimore, and the UW Pharmaceutical Outcomes Program. This project integrates prospective comparative effectiveness research studies of newly developed genomics and personalized medicine approaches into the SWOG clinical trials network. In 2013, the Hutchinson Institute for Cancer Outcomes Research (HICOR) was founded under Dr. Ramsey’s leadership, with institutional commitment for five faculty recruitments, including Gary Lyman, who was recruited in 2013 from Duke University, where he was Director of the Comparative Effectiveness and Outcomes Research Program.

HICOR is an interdisciplinary institute within FHCRC that is based in the CCSG Cancer Epidemiology, Preventon and Control Program, and includes FHCRC and UW faculty from multiple schools and divisions. It integrates Consortium health economics, outcomes, clinical and public health sciences research, and is planning an applied cancer outcomes research and evaluation program in partnership with regional cancer care delivery systems and payers. This will involve the Seattle Cancer Care Alliance and its affiliated network, Swedish Medical Center, Premera Blue Cross, Region 10 Centers for Medicare and Medicaid, and corporate partners. The goal is to create a “cancer care delivery laboratory” for health economic and outcomes research in the same settings where results will be applied. Other goals are to translate research findings into actionable, system-level interventions and evaluate the impact of practice changes on patients, systems, and the health economy. In the next three years, HICOR will implement two demonstration projects to establish the feasibility and potential impact of a stakeholder-based research network.

During the project period, CCSG Developmental funds aided recruitment of Anirban Basu, a healthcare economist, and Janie Lee, a radiologist who conducts research on the cost-effectiveness of breast imaging technologies for cancer screening. CCSG and institutional funds will also be used to further develop our informatics capabilities, including the HIDRA data warehouse described in Developmental Funds, to expand our capacity to link patient care and outcomes.

Population Based Research. The Consortium is a world leader in population-based research with particular expertise in cancer prevention and epidemiology, biostatistical methods and clinical trial design, and computational biology. Reflecting this, and our commitment to team science, the center serves as the coordinating site for many of the nation’s NIH-funded research networks. These include SWOG, the Early Detection Research Network (EDRN), the Women’s Health Initiative (WHI), the Transdisciplinary Research on Energetics and Cancer Network (TREC), and the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO). Through these networks, our center has established an enormous number of collaborations; members contribute their expertise to nearly 50 NCI Cancer Centers in 28 states. These efforts have led to major discoveries such as the WHI finding that combination hormone replacement therapy increases the risk of heart disease, stroke and breast cancer (Rossouw et al., JAMA, 2002). This prompted changes in hormone
usage and resulted in 15,000-20,000 fewer cases of breast cancer each year in the United States. Other major findings during the project period include: intermittent prostate cancer treatment has quality of life benefits, but continuous therapy improves overall survival (SWOG; Hussain et al., NEJM, 2013); two biomarkers in urine associated with cancers likely to be aggressive among men who take a 'watchful waiting' approach (EDRN; Lin et al., Clin Cancer Res, 2013); genome-wide association analyses to identify new susceptibility loci for colorectal cancer (GECO; Jia et al., Nat Genet, 2013); and associations of insulin resistance and adiponectin with mortality in women with breast cancer (TREC; Duggan et al., J Clin Oncol, 2011).

Eight CCSG pilots have launched population sciences projects, including one led by Jonathan Bricker that leveraged a $3M NCI grant to develop a randomized trial of a Web-based smoking cessation intervention.

During the past two years, we have recruited a new leader for population sciences, Garnet Anderson, and engaged in planning activities to identify areas of focus for the next grant period. The first will be on identifying the mechanistic links between obesity, physical activity and cancer. We have committed funds to recruit faculty with expertise in obesity-related research whose work will complement current Consortium members such as Jay Mendoza, a pediatrician specializing in obesity in the Cancer Epidemiology, Prevention and Control Program. Our second focus will be on developing strategies to reduce racial and ethnic disparities in cancer incidence and outcome. To provide the appropriate leadership and organizational framework we have established a new Consortium Health Disparities Research Center and appointed Beti Thompson as the first Associate Director of Minority Health and Health Disparities. FHCRC, UW and Children’s have recently recruited four new faculty members (Linda Ko, Rachel Ceballos, Jason Mendoza, India Ornelas) with research interests in this area, two with CCSG funds. CCSG and institutional funds will be used for additional recruitment, with one search underway for researcher in the area of population-based interventions to reduce obesity rates and promote energy balance. We will continue to support the Prevention Center shared resource, pilot projects, and Dr. Thompson and two CCSG Special Populations Staff Investigators.

PART II: SIX ESSENTIAL CHARACTERISTICS OF A CANCER CENTER

PHYSICAL SPACE
All Consortium partners contribute substantial space and an exceptional environment for research, training and care. Facilities were rated “Outstanding” at the last CCSG review, and we continue to add to and modernize the facilities that support our programs. FHCRC, UW and Children’s have added substantial space during the project period to accommodate future recruitment and research, including FHCRC’s Eastlake Building; (total ~100K NASF), UW South Lake Union Phase 3 (total ~240K NASF) and Children’s Research Institute (total ~45K NASF).

Per the revised CCSG guidelines, reviewers are directed to the following sections for detailed physical space/facilities information:

- Descriptions of each site’s facilities, map of the partner sites, and tables of institutional space commitments are provided in the Facilities and Other Resources attachment.
- Shared Resources physical space and equipment are described in the Shared Resources sections.

Consortium research is conducted in four nearby locations: 1) FHCRC’s Day Campus in South Lake Union (SLU); 2) UW’s Health Sciences Center Campus; 3) UW’s South Lake Union Campus; and 4) the Seattle Children’s Research Institute Campus (SCRI) in downtown Seattle, adjacent to the SLU district. Clinical research is conducted at Seattle Cancer Care Alliance Clinic (SCCA) on the FHCRC Day Campus; Seattle Children’s Hospital (SCH) in the Laurelhurst neighborhood; and UW Medicine at the UW Health Sciences Center on its main campus in the University District. Collectively, the partner sites provide outstanding facilities for all of the laboratory, clinic and office space needed to conduct all aspects of Consortium basic, clinical and population-based cancer research. The distance from one partner location to the next is small: it is 0.6 mile from FHCRC and the UW-SLU campus and 0.8 miles from FHCRC to SCRI. Both locations are serviced by a city-run streetcar that stops nearly door to door between the institutions as well as a private shuttle service supported by the Consortium. Three miles separate the FHCRC campus and the UW-Health Sciences campus, and it is 6 miles from FHCRC to Children’s Hospital. These are also linked via private shuttle with stops every ~20 minutes. The SCCA clinic building is located on the FHCRC campus. There is also regular city bus service between the UW main campus, FHCRC and downtown. Additionally, the the center offers “Dial-A-Ride,” which is a free van service available to Consortium faculty and staff with limited mobility.
Consortium space devoted to cancer research has increased by ~190,000 NASF since the last renewal. There is sufficient space at FHCRC, UW and Children’s to support the new recruitments outlined in this proposal. In addition, there is a new 25,000 sq. ft. research and training center and clinic in Kampala, Uganda, under construction for our global oncology studies with the Uganda Cancer Institute. In 2013, we opened a 10,000 sq. ft., $4M state-of-the-art cellular immunology facility in Capetown, South Africa, to support FHCRC’s HIV and TB vaccine research programs. Discussions are underway to utilize this lab for studies associated with our Uganda program and other new cancer research programs that are being initiated in South Africa.

The Consortium campus structure poses no barriers to collaborative activities and information exchange; members regularly attend seminars and other events at partner campuses other than their own. In addition to transporting faculty, staff and patients, the shuttles described above deliver urgent commodities – such as specimens and patient records – and abide by the U.S. Department of Transportation’s regulation for transporting hazardous materials. All four campuses are linked by high-speed facilities for voice and data communications. These high-speed facilities also support video conferencing among the partners and SCCA. Approximately 20 video-conferenced seminars, meetings, and lectures are transmitted each week among the participating institutions. The data networks provide very high-speed connectivity (Gb/s) among the participating institutions and the SCCA; this can be used for real-time viewing of diagnostic images, medical records, and other clinical applications. The Consortium Web site provides comprehensive information about funding opportunities, seminars and other events, and all Shared Resource services, including Clinical Research Support, as well as on-line scheduling for Shared Resource usage. For some resources, on-line tutorials are available. There is also a listserv for all members via which timely information is shared.

**ORGANIZATIONAL CAPABILITIES**

The Consortium’s leadership and program structure promotes scientific and organizational interactions and collaborations among its members as well external partners. Senior leadership is cohesive and interactive through formal committees and daily interactions. Deputy Directors and Associate Directors have focused roles that target the priorities of the center. Senior and Program Leaders are prominent scientists who are committed to the center’s mission, facilitate collaborations and translation, reflect the scientific disciplines of the membership, and represent the interests of partners. An organizational chart of the committee and governance structure is shown in Figure 2. Committee rosters and charters will be available at the site visit.

In 2008, Organizational Capabilities was rated Excellent to Outstanding. The major comment was “some concern about overlapping goals among programs and some shared resources.” Dr. Corey and his team evaluated this issue and reviewed their findings and recommendations with the External Advisory Board. We present nine programs and 13 Shared Resources with clearly defined and non-overlapping areas of emphasis.

**Governance.** The Director reports to the Governance Committee, which is composed of the senior officials at partner institutions and relevant entities considered essential to the center’s success: Dean of the UW School of Medicine, Paul Ramsey; Dean of the School of Public Health, Howard Frumkin; CEO of Children’s, Tom Hansen; President and Executive Director of the SCCA, Fred Appelbaum; and Chair of the FHCRC Board of Trustees, Paula Reynolds. The structure assures that the Director has the needed authority, resources and institutional backing to make all organizational, financial, and policy decisions for the center.

At their request, Dr. Corey meets monthly with Governance Committee members to provide briefings and facilitate decision making. Through this, he has markedly strengthened relationships with the leaders at partner institutions and removed barriers inherent in consortia. He has garnered significant institutional support for strategic initiatives and catalyzed new inter-institutional activities to support translational research. The Governance Committee has appointed a working group on collaborative philanthropy.

**Senior Leadership.** Dr. Corey has evaluated the leadership and committee structure and clarified roles and responsibilities. Senior leader roles are described in the Administrative Core. During the project period, leaders and committees have focused on program goals, supporting facilities and resources, and strengthening the clinical trials enterprise, which remains an ongoing priority for the next grant period.
Senior Leadership includes two Deputy Directors and eight Associate Directors (ADs), with all partner institutions represented. As Director, Dr. Corey has ultimate responsibility for the center's strategic development and performance. The Deputy Directors, Fred Appelbaum and Mark Groudine, have complementary expertise and serve as Dr. Corey's key advisors. The ADs report to the Director and oversee areas determined to be of such high priority to the success of the Consortium that they require ongoing leadership expertise, oversight, direction, facilitation and advocacy. Areas include Basic, Solid Tumor Translational Research and Population Sciences Research; Childhood Cancers; Global Oncology; Inter-Institutional Initiatives; Minority Health and Health Disparities; and Administration. Deputy Director Appelbaum oversees Clinical Research. Senior leaders integrate and coordinate the Consortium's scientific agenda through collaboration with Scientific Program leaders; oversee specific aspects of Consortium and CCSG activities, such as member participation in shared resource and program review, allocation of developmental funds and leadership of working groups for new initiatives; and both represent their institutions and make their institution aware of Consortium activities and issues.

**Internal Committee Structure.** Four committees provide forums for communication, information exchange, oversight of key activities, planning and decision-making, and institutional and discipline representation.

Institutional Planning Committee (IPC). The IPC is the executive decision making body of the Consortium and is chaired by Deputy Director Groudine, who sets the agenda and manages meetings with the support of the AD for Administration. The Committee meets quarterly and includes members from all institutions. Members include the Director, Senior Leaders (Deputy Directors and ADs), PI of the local CTSA, and other key institutional or Consortium leaders. Several other individuals are invited to attend IPC meetings due to their roles within the Consortium structure and/or partner institutions, thereby assuring appropriate communication and participation. This leadership forum provides ongoing advice to the Director, conducts planning and evaluation, secures institutional resource commitments, and addresses other matters affecting the Consortium and its abilities to meet or exceed CCSG requirements. It develops strategies that utilize Consortium resources and maximize collaboration in research. During the current grant period, the IPC focused on several priority areas to strengthen clinical translational research. As a result: the Clinical Research Support office was restructured; a Phase I clinical trials initiative was developed; a Shared Resource for centralized biospecimen acquisition (NW BioTrust) was developed; planning for a Precision Oncology initiative commenced; a universal consent process for participation in research was initiated; a Health Disparities Research Center was established; and a Biomedical Informatics Shared Resource was created. These activities are described in more detail in other sections. The IPC was responsible for establishing the strategic scientific priorities presented in the Director's Overview; relevant planning documents will be available at the site visit.

The IPC has facilitated the successful recruitment or appointment and resources needed of key individuals. These include Eric Holland as Solid Tumor Translational Research leader, Garnet Anderson as Population Sciences leader, Michael Jensen as director of the Ben Towne Center for Childhood Cancer Research at Children’s, and Stephen Schmechel as leader of the NW BioTrust shared resource, as well as several talented scientists in priority areas such as cancer disparities research and health economics. Priorities for Developmental Funds are set by the IPC. During the project period, it chose to prioritize innovative pilot projects on cancer prevention, diagnosis or treatment, as well as three areas targeted for development: Global Oncology, collaborative Solid Tumor Translational Research, and Health Disparities Research.
The IPC has supported the development of educational opportunities for health professionals and for scientists from underserved populations. Programs include the U54 Partnership for the Advancement of Research program (Thompson PI), a partnership with New Mexico State University, and the Continuing Umbrella of Research Excellence (CURE) program. The IPC has also been responsible for improving coordination and collaboration with the Institute for Translational Health Sciences (the local CTSA). This has been facilitated by the recent appointment of the CTSA PI, Nora Disis, to the committee during the project period.

A subcommittee of the IPC is responsible for review and approval of Consortium membership. A second subcommittee provides guidance to the Director on faculty recruitment and allocation of CCSG New Investigator funds. Both subcommittees include members from all partner institutions. Examples of ad hoc working groups that report to the IPC have included those focusing on collaborative opportunities between the Consortium and CTSA programs, biomedical informatics planning and solid tumor translational research.

Scientific Steering Committee. The Scientific Steering Committee (SSC) helps the Director and IPC implement the scientific strategies and recommendations defined by the IPC. It also identifies and encourages development of new scientific directions, such as through organization of scientific symposia and by providing input on priorities for Developmental Funds and implementing pilot award competitions. With Dr. Groudine, the SSC is responsible for reviewing Scientific Programs to ensure that they are organized for maximum cancer impact and are meeting objectives. Annually, the Shared Resource Director presents the status of cores and the progress of developing resources to the SSC, which provides feedback and helps chart future core plans in order to address unmet member needs and ensure that services support the changing needs of the members.

Johanna Lampe (co-associate head, Cancer Epidemiology, Prevention and Control Program) and Peter Nelson (co-head, Prostate Cancer Program) chair the SSC, which includes at least one leader from each Research Program, the AD for Administration, the Shared Resource Director, and administrators from FHCRC and UW are also members. Membership is well balanced from an institutional perspective.

The co-chairs set the agenda and manage meetings with the support of the AD for Administration, Marion Dorer. The committee ensures appropriate allocation of pilot funds based on the strategic priorities set by senior leadership, with administrative support from Dr. Dorer. During the grant period, the co-chairs worked with Dr. Groudine to conduct a mid-grant cycle program review, and, with feedback from the External Advisory Board, recommended the revised program and Shared Resource structure presented in this application.

Clinical Oncology Oversight Committee. Reporting to the IPC and the Seattle Cancer Care Alliance’s Board of Directors, the Clinical Oncology Oversight Committee (COOC) oversees clinical research and practice for SCCA and Consortium activities. Dr. Appelbaum, who serves as a Consortium Deputy Director and as Executive Director of the SCCA, chairs the committee. This dual role insures that recommendations are received and implemented at the highest institutional levels. The COOC recommends and oversees implementation of the strategic plan for oncology across the care delivery system; supports clinical faculty recruitment in light of center goals; supports resolution of implementation challenges and resource needs; and charters ad hoc committees to address strategic issues. The IPC and the COOC have yearly joint meetings, which have been highly successful in aligning priorities and standards for oncology care, as evidenced by the continued growth in patient volume, faculty recruitment and strategic growth of SCCA.

To provide greater executive leadership for clinical trials, a Clinical Research Oversight Committee was recently formed to oversee all aspects of clinical research conducted at the Consortium and make final decisions on all issues related to clinical trials. This committee reports to Dr. Corey and also to the COOC, and ensures that all aspects of the clinical research process at the Consortium are conducted according to prescribed standard operating procedures.

Scientific Program Structure. We present nine Scientific Programs in this application. This structure results from substantial strategic planning of Consortium committees and input from our External Advisory Board.

The current program structure reflects the cancer research strengths of the Consortium, its future directions and priorities, and answers concerns expressed at our 2008 review about the overlap in goals between some programs and the cancer focus of the Basic Sciences program. A number of changes have been made to address these issues. Because of the extensive collaboration and synergy of goals in the Clinical Transplantation and Transplantation Biology programs, we have melded them into a new Hematologic Malignancies program. For similar reasons, the programs in Cancer Prevention and Epidemiology programs have been eliminated with the support of the EAB, with cancer-focused members re-aligned in programs where they have
natural affinities. We have added a Global Oncology Program as a new Established Program given the extensive interactions, research and impact in this area. With the input from the EAB and IPC, the Cancer Imaging Program will not be presented as an Established Program; rather, imaging researchers have largely been aligned with other clinical programs that match their research interests. These changes are further described in Planning and Evaluation.

Program Leaders have scientific expertise and national prominence in their field, and complementary leadership skills and focus. All Programs Leaders are selected by the Director with input from the IPC and leaders of the partners. While scientific leadership is the most important criterion for appointment as a Program Leader, care has been taken to provide institutional balance in leadership roles as much as possible. Leaders foster high levels of transdisciplinary research, promote collaborative development of research ideas and grant proposals, encourage translational research, and maintain a strong focus on education. As appropriate, they also seek to address the research issues of high importance to the catchment area.

**Shared Resources.** Each Consortium Shared Resource must be equally accessible to members regardless of their physical location or academic affiliation. Cores that do not meet this expectation, no longer serve the innovative research needs of members, or underperform, may be terminated by the Director with the support of IPC and the EAB. Each Shared Resource has an oversight committee composed of faculty members who are frequent users, experts in the field of focus and provide institutional representation. The Shared Resource Director assures that the committees complete annual reviews, which are then presented to the SSC for input, the results of which are then reported to the IPC.

**Consortium Administration.** The AD for Administration, Marion Dorer, is a full-time employee and oversees all administrative functions related to CCSG programs and financial management. This includes fostering and evaluating member collaboration and interaction, planning and development of strategic initiatives, ensuring availability and easy access to well managed shared resources, activities that foster member engagement, and the management and appropriate use of Consortium funds and resources. Dr. Dorer develops and maintains excellent communication and coordination with the administrators at partner institutions and other relevant entities, and keeps abreast of CCSG and other relevant Comprehensive Cancer Center administrative matters nationally. Her group provides support for budgeting and fund disbursement, implementation of processes and technologies that increase efficiency, ensures clear communication with members, and aids in the collection of data needed for reporting. She serves as project manager for CCSG applications and facilitates communications with NCI Program staff. More detail is provided in the Administrative Core.

Dr. Dorer is a member of the IPC and SSC and works closely with these committee chairs to develop agendas and long range committee plans, coordinate efforts in order to maximize efficiency, prevent overlapping goals, and ensure communication between committees and Senior Leaders. She also serves as the liaison with the local CTSA, known as the Institute for Translational Health Sciences (ITHS). She meets at least monthly with the Deputy Directors and quarterly with Dr. Corey, and weekly with Dr. Corey’s Chief of Staff, Barbara Berg.

**Planning and Evaluation.** Planning and Evaluation is the responsibility of the Institutional Planning Committee, which, as described above, includes Consortium senior leaders and key institutional officials. Senior leaders are responsible for identifying opportunities for growth and development of new investigative areas and resource requirements, as well as for identifying deficiencies that represent barriers to the center’s strategic objectives. Dr. Corey and the senior leadership team rely on counsel from the External Advisory Board (EAB), which is valued for its candid evaluation of the center’s ongoing activities and proposed new initiatives.

Following the 2008 CCSG review, the IPC launched a review of strategic directions and developed an action plan for new initiatives as well as to respond to reviewer comments. Priority areas were identified, feedback was solicited from the EAB, and working groups were appointed to develop and implement plans, which were then monitored by the IPC. The IPC was responsible for establishing the strategic scientific priorities presented in the Director’s Overview; relevant planning documents will be available at the site visit. More detail on process and accomplishments are provided in the Planning and Evaluation section.

**External Advisors.** External Advisory Board (EAB) members have been selected for their deep experience in clinical and translational research, population sciences, health economics, basic sciences, global health and administration. Board composition is reviewed annually by the Director. The EAB meets annually for a full day followed by an informal dinner and provides critical independent review of the Consortium’s scientific progress, clinical trials activities, Research Programs, use of Developmental Funds, and plans for development of Consortium services and other investments. The EAB provides written highly influential recommendations that
are integrated into senior leadership’s strategic planning activities; all of the EAB’s major recommendations during the project period have been addressed. The center also periodically engages external consultants with expertise in areas of development or undergoing rapid change. More detail, including the EAB roster and recommendations, is provided in the Planning and Evaluation section.

**Training and Education.** The Consortium has fostered a robust training and educational environment. Partner institutions award degrees in medicine, nursing, basic sciences, public health, and behavioral sciences, and promote specialized skills needed to practice in cancer-related fields. Graduate students at FHCRC and Children’s are enrolled in various degree programs at UW. The Consortium currently holds 19 NIH T32 and one TL1 grant totaling $7.5M (annual direct costs) including 8 from the NCI. Several interdisciplinary training programs with cancer relevance, including programs through the local CTSA, are described in the Transdisciplinary Collaboration and Coordination section. Among the many degree and fellowship programs are UW School of Medicine programs for MD, MD/PhD, and MD concurrent degree programs for Masters in Health Administration, Masters in Public Health, or Masters in Biomedical and Health Informatics. There are 15 graduate programs with cancer relevance in areas that span the biological and medical sciences (e.g., immunology, genome sciences, biophysics). The UW School of Public Health offers graduate programs in Epidemiology, Biostatistics and a number of other interdisciplinary programs.

Cancer-relevant medical fellowship and residency programs that are jointly offered by Consortium institutions and have members as mentors include: Hematology-Oncology, Pediatric Hematology-Oncology, Pulmonary/Critical Care Medicine, Radiation Oncology, Urology, Gastroenterology, Infectious Diseases, Otolaryngology, Neurology, and Neurological Surgery. Consortium investigators mentor trainees in all of these interdisciplinary training programs.

Consortium partners have programs that support under-represented minority students and post-doctoral researchers. Members actively seek graduate students from under-represented minority populations through multiple initiatives. These include recruitment trips to universities and colleges with high numbers of underrepresented student populations; attendance at college fairs and national conferences; initiation of the Early Identification Program, which works closely with outstanding minority students for three years prior to graduation; and hosting a Graduate and Information Day for current undergraduate students. UW and FHCRC also provide support for underrepresented students through the Post-Baccalaureate Research Education Program (PREP) funded by NIH. This includes opportunities for students to work in research labs under direct mentorship; supplemental training in scientific writing, literature evaluation and interaction with the academic scientific community; graduate school application assistance; and tuition assistance. In 2012, the annual Society for Advancement of Hispanics/Chicanos and Native Americans in Science (SACNAS) Conference was held in Seattle, and the UW and FHCRC each committed $10,000 to support this annual meeting. Consortium partners co-sponsor regional meetings that encourage under-represented minority students to pursue higher education, such as the 2012 Annual Summit for Pacific Islander Resources and Education (ASPIRE).

**Membership Process.** Oncology researchers at the Assistant Professor (called Assistant Member at FHCRC) level or above at partner institutions are eligible for full Consortium membership. Foremost in the selection of members is their cancer focus, alignment with programmatic goals, and evidence of collaboration within the Consortium. Members must be a PI or project leader on a cancer-related research grant or involved in cancer-related clinical or population science protocol development or execution. Long-standing participants on cancer grants or collaborative projects within a program project, including preclinical or clinical trials (therapeutic or non-therapeutic), researchers who bring specialized skills important to program goals, and those with significant involvement in program activities may also be considered for membership.

The Scientific Steering Committee established these criteria with approval from the Institutional Planning Committee and the Director, and reviews the criteria occasionally, responding to changes in the CCSG guidelines or Consortium goals.

Affiliate membership is available for clinical investigators who enroll patients on Consortium-sponsored clinical trials and researchers who use the Consortium IRB but who do not meet the criteria for full membership.

Affiliate membership gives these individuals access to Consortium Clinical Research Support, the ability to participate in center seminars and retreats and to receive center communications.

All individuals who meet the membership criteria must have letters of recommendation from a collaborator in the program and one leader of the program. Membership requires approval of both co-leaders of a program. The Membership Subcommittee of the Institutional Planning Committee reviews applications and recommends approval or rejection of an application, or requests clarification, most often of the cancer focus of a potential member. Dr. Corey has ultimate authority over cancer center membership.
Scientific Programs leaders review their membership annually and may recommend membership termination to the Membership Committee. The program leaders conduct a full membership review mid-cycle and in preparation for the CCSG renewal. Each of the past three years, for example, about 20 members have been removed as a result of retirement or departure, and about 30-40 new members added. In 2013, as part of a full member review and program realignment, 72 members were eliminated for lack of current cancer focus or other changes in their membership qualifications that deemed them ineligible.

Response to the Needs of the Catchment. Our primary catchment area is the 13 counties of western Washington. This is where 70% of our cancer patients reside. UW serves as the medical school for the five-state “WWAMI” region (Washington, Wyoming, Alaska, Montana and Idaho). The Consortium is the only NCI CCC in the five-state area and as such, through our research and other activities we strive to ensure a regional impact as well. This is manifested through the incorporation of collaborating clinical trial sites in selected areas within the SCCA network and the regional focus of a large number of our specialty multidisciplinary clinics. Consortium leadership supports gathering of knowledge on cancer problems within the catchment area. It has hosted the NCI SEER registry for the catchment for over 30 years. Washington State ranks 19th in the country in cancer incidence; the highest incidence in the state is in the catchment area. Cancers with the highest incidence are (in decreasing order) prostate, breast, lung, colorectal and melanoma. With respect to mortality ranking by state, Washington is in the middle; cancers with the highest mortality (in decreasing order) are lung, colorectal, breast, pancreas and prostate. In order to improve access to clinical research, Consortium leaders have worked hard to improve services at the SCCA, creating pathways that ensure each patient is provided with efficient and effective evidence based care. Creation and support of the SCCA Network provides education to community physicians and offers patients direct access to clinical trials at their local hospital.

To reduce the incidence of cancer in the catchment, the center has long fostered cancer prevention research; the first Cancer Prevention Program in the country was established by FHCRC. This program, which is now an inter-institutional Consortium program (Cancer Epidemiology, Prevention and Control), hosts many large studies, including the Women’s Health Initiative, one of the largest prevention trials in the country. It also has supported major studies on smoking cessation. In the current project period, for example, Jonathan Bricker completed an NCI R21 project that offered free quitline service to study participants randomized to a novel cessation intervention at a time when our state’s funding for quitlines was significantly decreased. In addition, a CCSG funded pilot project led by Dr. Bricker leveraged a second large NCI grant to implement this novel behavioral intervention via the Web. Additional information on Consortium leadership’s support of research in the catchment area is described in the Senior Leadership section of the Administrative Core.

Underserved Populations: Our population scientists are working to better identify health disparities in WA state and to create interventions that decrease disparities in cancer treatment and outcome. There are several cancers for which incidence and mortality in the catchment are greater in minorities compared to whites. For example, the incidence and mortality of prostate cancer is greater in black vs. white males. Though the Pacific Northwest does not have a large African American population, we have endeavored to emphasize the recruitment of African Americans into research studies (e.g. the Prostate Cancer Genetic Research Study led by Janet Stanford to identify causal mutations for hereditary prostate cancer) and provide education pertinent to known lifestyle factors that influence prostate cancer development and behavior. Some studies are conducted in the state but beyond the catchment area, where there is sufficient population to conduct research, while yielding findings that are directly relevant to the catchment. For example, Beti Thompson leads NCI studies with Hispanic populations in eastern Washington including Breast Cancer Disparities among Latinas (P50), and Hispanic Health Promotion: Reducing Cancer Disparities (U54), a Community Networks Program targeted to Hispanics and American Indians in Yakima and Franklin Counties. Vicky Taylor leads projects on Cambodian populations in the catchment, including an epidemiological study for HPV vaccination that will provide the background necessary to improve vaccine availability and uptake in this community.

The WWAMI region is home to over 25% of the Native American and Alaska Native population. This group has the poorest five-year survival from all cancers among all U.S. racial/ethnic groups and access to cancer clinical trials is difficult. In collaboration with the Native American and Alaska Native partners, Dedra Buchwald of the Cancer Epidemiology and Prevention Program leads a Center for Native Population Health Disparities, which is focused on improving cancer health outcomes and quality of life for American Indian and Alaska Native populations, and Native People for Cancer Control, a regional Community Networks Program serving Washington and seven states in the region. In addition, Dr. Buchwald serves as Director of the NIA-funded
Native Investigator Development Program, a two-year career training program for American Indian and Alaska Native postdoctoral fellows designed to increase the number of independent Native researchers.

As described in the Clinical Protocol and Data Management Core (Inclusion of Women and Minorities in Research section), we have created a new Health Disparities Research Center whose strategic plan includes several activities to increase minority participation in cancer research and monitor our progress in this area.

**Partnerships.** The Cancer Center recognizes the inherent value in developing partnerships with other entities at the partner institutions (e.g. the CTSA), other Comprehensive Cancer Centers, and external organizations that offer expertise, resources, and capabilities that extend the vision, priorities, capabilities and scientific interests of our center. Selected examples of such partnerships are presented below.

**Clinical and Translational Science Award.** Our CTSA, which is called the Institute for Translational Health Science (ITHS), has the same partner institutions as the Consortium. The Consortium has partnered with the ITHS since its inception in 2005. Nora Disis, the PI, serves on the Consortium Institutional Planning Committee. Recent efforts have focused on increasing links between Consortium and ITHS educational offerings, expanding training for research coordinators to include cancer specific topics, collaborations in medical informatics, and the establishment of inpatient research nursing services for clinical trials.

**Partnerships with other Cancer Centers.** The Consortium is strongly committed to team science and supports many large multi-investigator, multi-center NCI studies. These include three SPORES, Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO), Colon Cancer Family Registry (CCFR), Consortium of Contralateral Breast Cancer (CCBC), Women, Cancer and Radiation Exposure (WECARE), Testicular Cancer Consortium (TECAC), and Genetic Associations and Mechanisms in Oncology Initiative (GAME-ON). The Consortium is home to 10 Coordinating Centers, providing crucial research support at 950-plus trial sites and over 300 studies on every continent except Antarctica. Examples include the Women’s Health Initiative (WHI), Transdisciplinary Research in Energetics and Cancer (TREC), the Cancer Immunotherapy Trials Network (CITN), and the Whole Genome Studies Coordinating Center. Through these coordinating centers, Consortium members provide expertise and research leadership to ~50 NCI Cancer Centers in 28 states.

**International Partnerships.** The FHCRC and the Uganda Cancer Institute (UCI) have developed a robust partnership for research on infection-related cancers, training, and clinical care. The partnership has also focused on improving both human and physical infrastructure in Kampala, Uganda. In 2004, with FHCRC support and subsequent support from the Fogarty International Center, we initiated a training program in which groups of initially two and later five Ugandan physicians came to Seattle for a 13-month intensive didactic and clinical program. Physicians attended clinics at the SCCA, and specialized courses in epidemiology, statistics and clinical trial design. Importantly, mentors and trainees were paired in areas of mutual research. To improve the research infrastructure, Dr. Corey and Corey Casper successfully applied for USAID funding to establish a clinic, research and training center on the UCI campus. Additional FHCRC funds have been provided for the 25,000 sq ft facility now under construction. In 2010, Dr. Casper was awarded an NCI D43 grant to expand training of research leaders, managers and implementers in Uganda (see Global Oncology Program).

Over the past five years, the Consortium has developed a relationship with the China Center for Disease Control. A joint venture is under development to provide a platform for Consortium members to complete research in China, giving them access to both unique populations of cancer patients and funding from the Chinese government. Led by Steven Self, former Program Leader of the Biostatistics Program, initial collaborations were in the area of infectious disease. Since 2011, oncology projects have been established, including those focused on human papilloma virus and cervical cancer and esophageal cancer.

**Other entities.** The recently established Hutchinson Institute for Cancer Outcomes Research (HICOR), based in the Cancer Epidemiology, Prevention and Control Program, integrates health economics and outcomes research, and is building an applied cancer outcomes research and evaluation partnership with regional cancer care delivery systems and payers. Current partners include the Seattle Cancer Care Alliance Network, Swedish Medical Center, Premera Blue Cross, Region 10 Centers for Medicare and Medicaid, and regional corporate partners. HICOR is described in greater detail in the Directors Overview.

**Consortium Agreement.** In 2002, FHCRC, UW, and Children’s signed an agreement to establish the Cancer Consortium, affirming their longstanding affiliation for the purpose of collaboration on cancer research and education. This agreement was a logical extension of the clinical care affiliation established in 1998 to form the Seattle Cancer Care Alliance (SCCA), and further cemented the relationships among the three institutions in research, training and clinical care. In 2008, the SCCA was formally added as the Consortium site of clinical
practice. This agreement will be available at the site visit. Partner institutions are primarily responsible to their governing body, but acknowledge that their mutual interests in cancer research, education, and care can be further advanced by working together to extend knowledge and serve the community. The Consortium respects prior affiliation agreements related to faculty appointments, graduate training, research grants and contracts, recognition and use of names, joint planning, and termination of relationships.

The Consortium agreement establishes that the Director of the Consortium will be the President and Director of the FHCRC, unless that person requests that a different individual serve as Consortium Director or if the President and Director of the FHCRC vacates the position and an interim Director is needed. Faculty recruitment occurs both on the institutional and Consortium level. Targeted recruitment serving high level Consortium goals are identified and supported through the action of the Institutional Planning Committee. The successful joint recruitment of Eric Holland was noted in the Director’s Overview. All partners are involved in the search underway for Dr. Appelbaum’s successor as Director of FHCRC Clinical Research Division, UW Division of Medical Oncology, and Executive Director of the SCCA (when he steps down from the latter role).

**Succession.** Should Dr. Corey be unable to fulfill his role for an extended period due to illness, termination or another reason, a Deputy Director would serve as Interim Director until a new Director is appointed.

**Dispute Resolution.** The role of the Governance Committee is to form and terminate the Consortium, make changes to the Consortium organizational structure, review internal and external evaluations of the Consortium, and address inter-institutional disputes that may arise among the partner institutions in regard to Consortium business. Every effort is made by the Director and senior leaders to resolve matters related to the center. In the instance where there is inter-institutional conflict, the matter will be brought to the Governance Committee, which serves as the final arbiter and all institutions agree to abide by its decision. Fortunately, the dispute resolution process has never been needed, nor is it foreseen for the future.

**TRANSDISCIPLINARY COLLABORATION AND COORDINATION**

Transdisciplinary Collaboration and Coordination was rated Excellent to Outstanding in 2008. Reviewers noted, “Consortium Program Leaders … foster and facilitate inter- and intraprogrammatic collaborations amongst Consortium members. This interaction and collaboration was judged to be variably successful amongst the programs as assessed by joint publications, which ranged from 9-63%. However…Consortium members serve as PI on over 45 multi-investigator, collaborative grants, an outstanding number.”

We have devoted considerable effort during the project period to further strengthen interactions among disciplines. As noted in the 2008 review, the Consortium has a large number of multi-investigator grants. This portfolio has grown, evidence of leadership’s encouragement of team science. Consortium members serve as PI on 70 multi-investigator, collaborative grants (including 3 SPORES, 25 U01s, 9 P01s and others). As described below, several significant multi-investigator grants were newly awarded during the project period, including a breast cancer SPORE. Joint publications among Consortium members are abundant. They average 18%, 19% and 31% for inter-institutional, intra-programmatic, and inter-programmatic publications, with no program below 10% for each of these measures. As illustrated in the scientific accomplishments in the Director’s Overview, our research advances are highly interdisciplinary and collaborative, including not only Consortium members but investigators at other NCI centers and institutions.

**Mechanisms to Promote Transdisciplinary and Translational Research.** As described in the Director’s Overview, the partner institutions have long maintained and promoted integrated cancer research, care and training activities. Beginning with the bone marrow transplantation program, and extending to the population and basic sciences, research has been strongly collaborative. The oncology training programs have always involved FHCRC, UW and Children’s, and all faculty physicians (and many other Consortium faculty) have joint appointments at least two of the partner institutions. Idea exchange and work flow among members and leaders at the partners is a natural “way of life.” All our CCSG programs cross institutional lines, and many of our other major programs are Seattle based or even WWAMI (WA, WY, AK, MT, ID) based, not limited to a single institution. All Consortium senior leaders have joint appointments in at least two institutions. As example, Dr. Corey’s own career has included leadership of research programs at FHCRC, UW and Children’s.

These types of interactions help “cement” the partners, facilitating efficient and effective strategic planning and importantly, the administrative implementation of initiatives across the center. Communication lines are well established as are administrative mechanisms for funds flow and other business.
Committees charged with fostering transdisciplinary research. The Consortium has standing committees (see Organizational Capabilities) that are charged with setting and implementing new initiatives and activities and that include members from multiple disciplines and institutions. The Institutional Planning Committee (IPC) is the forum through which Senior Leaders identify and evaluate opportunities, needs, and gaps. The Scientific Steering Committee (SSC), whose members represent all CCSG research programs, is charged with organizing symposia focusing on transdisciplinary research. It also manages the annual CCSG pilot award competition, which catalyzes new translational research such as through recent pilot award RFAs that required lab-based and clinical co-PIs. This structure has been successful, as illustrated by our significant progress in immunotherapy and biospecimen resource development, as highlighted in other sections. These and other initiatives have been strongly stimulated by input from the SSC, and strong endorsement from the IPC and Governance Committees, leading to appointment of working groups and subsequent commitment of resources.

Research programs that encourage member innovation, interaction and collaboration. Research Programs must have a strong transdisciplinary focus and are led by program heads and associate program heads with complementary expertise that spans multiple scientific disciplines and institutions (see Research Program membership lists). During the project period, senior leadership reviewed all Scientific Programs, including their continued ability to promote leading-edge transdisciplinary and translational science. Using comments from the site visitors and the External Advisory Board, changes were made to assure the future vibrancy and effectiveness of the programmatic structure. These changes are described in Organizational Capabilities.

Seminars, retreats, and events that target innovative scientific areas and cross-fertilize ideas. The cancer center sponsors numerous symposia designed to stimulate transdisciplinary collaboration and new research directions. Consortium events are well attended; a few symposia from the project period are listed below.

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<td>2010</td>
<td>Exploring Opportunities to Extend the Application of Molecular Diagnostics to Cancer Care</td>
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<td>2010</td>
<td>Small Nucleic Acids in Biology and Disease</td>
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<td>2011</td>
<td>Long Term Effects of Cancer Treatment</td>
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<td>2011</td>
<td>Metabolism and Cancer</td>
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<td>2012</td>
<td>Will Genomics Revolutionize Cancer Therapy?</td>
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<td>Advances in Pediatric Hematopoietic Cell Transplantation and Cellular Therapy</td>
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<td>2013</td>
<td>Preventing Cancer in WA State</td>
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<td>2013</td>
<td>Seattle Genetic Instability and Cancer Symposium</td>
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All Scientific Programs also have regular (weekly or monthly) seminar series.

Shared Resources. Shared Resources provide cost-effective access to advanced technologies and expertise necessary for translational, transdisciplinary research. Through training and individualized support, members can incorporate new investigative approaches into their research. Increasingly, Consortium shared resources emphasize computational and biostatistical tools and expertise. For example, the new Computational Biology resource has created standardized tools for commonly used data analyses to make it straightforward for investigators to incorporate large scale genomic and proteomic experiments into their work. Other resources developed during the grant period include Biomedical Informatics (see Developmental Funds); we have recruited an outstanding bioinformatician, Paul Fearn to integrate clinical data systems with genomic databases. He has engaged all partners in strategic plan development for a robust clinical data warehouse (Hutchinson Integrated Data Repository and Archive, or “HIDRA”). We have also developed Northwest BioTrust, launched with Developmental Funds, into an established CCSG resource that unifies existing systems to enable efficient biospecimen retrieval and distribution. Developmental Funds also supported the recruitment of its leader, Steve Schmechel. Members are encouraged to identify new resource needs through surveys and committees, while Senior Leaders are also expected to propose valuable additional services.

Recruitment of faculty with track records in interdisciplinary/translational science. To bolster solid tumor transdisciplinary research, we recruited Eric Holland in 2013 as Associate Director of Solid Tumor Translational
Research. A noted neurosurgeon and lab-based brain tumor researcher from Memorial Sloan- Kettering Cancer Center, Dr. Holland directs solid tumor translational research across the Consortium, and has leadership positions at FHCRC and UW. Among his priorities is to broaden the interdisciplinary membership of the solid tumor research teams to include more basic scientists and clinical investigators from a wide range of subspecialties. Ten new faculty positions have been committed to his program by FHCRC and UWSOM.

CCSG New Investigator Awards and institutional funds have been used to recruit other faculty who stimulate transdisciplinary collaboration. Examples include: Dan Raftery, who is developing metabolomics technologies in the CCSG Proteomics Shared Resource; Janie Lee, a radiologist who conducts cost-effectiveness research on breast imaging technologies; Leslie Kean, a pediatrician who spans basic immunology and hematologic malignancies; and Rachel Ceballos, Jason Mendoza, India Ornelas, and Linda Ko, who lend their expertise in health disparities research to members working on many different cancer research problems.

**Targeted use of pilot project funds to promote transdisciplinary and translational science.** During the project period, the SSC targeted three annual pilot funding award competitions for collaborative clinical translational projects. Among them was a $40,000 award to Patrick Paddison and Jim Olson for “Identification of synergistic combination therapies for glioblastoma.” This pilot stimulated a collaboration that would not otherwise have happened and provided preliminary data leading to three follow-on grants totalling $2.4M, including an NCI Provocative Questions R21 Award. Other pilot awards were targeted toward increasing inclusion of underserved populations in research and global oncology (see Developmental Funds for detailed outcomes).

**Special working groups and initiatives to promote transdisciplinary and translational science.** To catalyze collaborative team research across disciplines and stimulate the application of basic cancer biology discoveries to more clinically focused problems, Dr. Corey conceived and launched a “transformative ideas” initiative. This program solicited proposals for innovative strategies that address important and unsolved problems in cancer. Several have garnered significant NCI funding, including an inter-institutional NCI Provocative Question R01 on pathogen-associated cancers (Denise Galloway and Paul Nghiem) and two inter-programmatic U01s from the NCI Cancer Target Discovery and Development Program (Martin McIntosh and Chris Kemp).

One of Dr. Corey’s priorities is to ensure that the Consortium is poised to capitalize on advances in cancer genome analysis to improve patient outcomes through development and application of accurate diagnostic and prognostic tests. In 2012, he and Paul Ramsey appointed a planning committee for a “Precision Oncology” initiative and have committed to joint fundraising for this area. A goal of this initiative is to integrate multiple molecular diagnostics services as a single entity to improve access, efficiency and effectiveness. This effort builds on accomplishments such as the development by Colin Pritchard (GI Oncology Program) and colleagues of Onco-Plex, a multiplexed gene sequencing panel that detects mutations (single nucleotide variants, small insertions and deletions, gene amplifications, and selected gene-fusions) in tumor tissue in 194 cancer-related genes. This test is available to all newly diagnosed patients with cancer treated at our center.

**A clinical trials platform to support early stage and multimodal research.** To support translational research, we needed to improve our clinical research infrastructure. An experienced clinical trialist, Paul Martin, was appointed Consortium medical director. A number of operating functions were integrated into a Clinical Research Support office headed by a senior administrator. The next major project is the implementation of a clinical trials management system and further review and re-organization of the clinical trials operation. Also, a Phase I clinical trials initiative was launched; Phase I enrollments have tripled during the current project period.

**Interdisciplinary Training.** The scientific problems that members are working on increasingly require interdisciplinarity. Training grants that develop the next generation also foster member interaction and collaboration across disciplines. Examples of NCI training programs that bring member mentors together on transdisciplinary, translational issues include: the T32 Interdisciplinary Training in Cancer Research Training Grant, and the T32 Nanotechnology and Physical Sciences Training Program in Cancer Research, which produces scientists, engineers and medical practitioners who have the knowledge and skills to integrate innovations in nanotechnology and physical sciences to cancer diagnosis and treatment. The center has a total of 19 NIH T-type training grants, including 8 that are NCI funded.

**Metrics of Success.** Evidence of the high impact of our transdisciplinary, inter-institutional interactions is the large number of collaborative grants and publications of our members. They serve as objective indicators that the Consortium has been highly successful in research that cross disciplines and programs to make breakthrough discoveries. Consortium members serve as PI on 70 multi-investigator, collaborative grants (including 3 SPORES, 25 U01s, 9 P01s and others). It is notable that at least half of these grants were new
advances during the current CCSG cycle. The number and percentage of intra- and inter-programmatic joint publications by program are shown in each of the Research Program sections. As noted earlier, joint publications average 18%, 19% and 31% for inter-institutional, intra-programmatic, and inter-programmatic publications, with no program below 10% for any of these measures.

**Advancing Consortium Research Through the Translational Pipeline.** The Consortium provides many avenues for translating discoveries to public benefit. These include collaborative grants that bring together basic and more applied researchers within the center as well as partnerships with other centers, the NCI, industry and other Consortium-sponsored initiatives. The Consortium structure, which brings together members from multiple disciplines in the basic, translational, clinical and population sciences, has been instrumental to our ability to garner large collaborative grants to translate discovery to application.

As noted earlier, the center has three SPOREs in Prostate Cancer, Ovarian Cancer and Breast Cancer. SPOREs include “horizontal collaborations” (groups working together to accomplish research aims on a single level such as in the laboratory, or at the clinical trial stage) and “vertical collaborations” (those intended to move a discovery up the translational pipeline). The SPOREs also support cores, such as biospecimen repositories and biostatistics, which anchor translational projects. All of the SPORES involve collaborations within the Consortium and with other institutions. Two examples (in prostate and ovarian cancer) of the value of our SPORE grants to translational science are described in the table later in this section.

Mac Cheever leads the Central Operations and Statistical Center for the NCI Cancer Immunotherapy Trials Network (CITN). CITN is a multi-institutional consortium for early phase clinical trials of immunotherapeutic agents and modalities to treat cancer patients. It also integrates tumor immunology laboratories across the country to enable the use of specimens obtained from patients on CITN clinical trials for immunomonitoring, biomarker development and credentialing, and facilitating an understanding of the biological mechanisms that underlie the results of the clinical trials. Our center also serves as one of the 27 performance sites. An example of how the CITN is facilitating translation of Consortium science is described in the Merkel cell research accomplishment in the Director's Overview.

The Institute for Translational Health Sciences (ITHS), the local CTSA, is led by Nora Disis. In addition to involving all Consortium partner institutions, the ITHS collaborates with regional institutions, communities, and tribal groups in the WWAMI (Washington, Wyoming, Alaska, Montana and Idaho) region. ITHS provides training opportunities in transdisciplinary and translational research, and makes accessible translational research resources, such as study and data management, laboratory core facilities, and support for community-based research in the catchment area.

We see enormous opportunity in developing mechanisms to translate and disseminate our research to health care delivery settings. In 2012, FHCRC launched the Hutchinson Institute for Cancer Outcomes Research (HICOR), based in the Cancer Epidemiology, Prevention and Control Program. Led by Scott Ramsey, a physician and health economist, HICOR promotes collaboration among health economists, physicians, industry partners and other stakeholders to enable comparative-effectiveness research on cancer therapies, diagnostics and preventive strategies that support provision of efficient, effective and cost-effective care.

Several commercialization opportunities have been pursued for technologies developed. In the prior cycle, Jim Olson (FHCRC pediatric oncologist and lab investigator) and colleagues at UW (bioengineering) and Children's (neurosurgery) developed “tumor paint” to enable surgeons to more accurately distinguish between brain tumor and normal tissue. The approach is based on linking a fluorescent beacon to a peptide derived from scorpion toxin that targets a receptor on cancer cells. A spinoff company, Blaze Biosciences, has been formed to develop and commercialize the technology. In another example, transdisciplinary research has led to the development of genomic technology for analyzing the human T-cell repertoire. This work, led by Harlan Robins (a computational biologist), Chris Carlson (a statistical geneticist), and Edus Warren (lab-based immunologist and physician-scientist), has formed the basis for spinoff, Adaptive Biotechnologies. Among the clinical applications the company is pursuing is the development of an assay to measure minimal residual disease for several blood cancers and a highly sensitive assay to quantify tumor-infiltrating lymphocytes (TILs). In 2013, FHCRC led the development of Seattle-based Juno Therapeutics, Inc., to accelerate clinical application of cellular immunotherapies developed by Consortium members Stan Riddell (FHCRC), Phil Greenberg (UW) and Michael Jensen (Children's). Memorial Sloan Kettering Cancer Center is a partner in this endeavor.

The Consortium is unique in the large number of coordinating centers it manages for multi-investigator, multi-institutional studies. Examples include the NHLBI Women's Health Initiative; NCI Cancer Immunotherapy Trials
Network (described above); the SWOG statistical center; the NCI Early Detection Research Network’s (EDRN) Data Management and Coordinating Center, three EDRN Biomarker Development Laboratories and one EDRN Clinical Validation Center; and the NCI Transdisciplinary Research on Energetics and Cancer Coordinating Center. By their very nature, these activities facilitate collaborative cancer research studies that involve 50 other NCI cancer centers as well as other research institutions throughout the country.

**Participation in NCI Steering Committees and Contributions to Development of NCTN Clinical Trials**

Our members play substantial roles in NCI Scientific Steering Committees, with 23 members on 13 of the 16 committees, including two co-chairs. These committees play a significant role in national clinical trial design and prioritization. Many Consortium members are involved with SWOG, ACRIN and other national groups. Sixteen Consortium members are chairs or co-chairs of cooperative group disease committees; 29 Consortium members serve as PI or Co-PI on group studies. Deputy Director Applebaum was recently awarded a NCI National Clinical Trials Network- Lead Academic Participating Site grant (U10 CA180828).

**Impact: Examples of Successful Translational Accomplishments.**

The strongest evidence of our center’s effectiveness in promoting translational research is in the discoveries that are making an impact in the lives of cancer patients or those at increased risk of cancer. In the Director’s Overview, we list a number of major scientific accomplishments from our Center. Here we list additional examples of Consortium discoveries that have progressed through the translational pipeline, from laboratory observations to phase II or III trials – often utilizing SPORES, national trial groups and industry collaborations – that represent research achievements of our basic, clinical and population sciences programs.

<table>
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<th>Discovery, Lead Investigator(s) and Program</th>
<th>Translation</th>
<th>Relevant grants, publications, clinical trials</th>
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<td>Discovered a mechanism by which retinoids induce apoptosis in medulloblastoma, a fast growing high-grade tumor primarily afflicting children, and development of mouse models of the disease through which the efficacy of retinoids was demonstrated. Jim Olson (Cancer Basic Biology)</td>
<td>Dr. Olson now leads a national Phase III trial of high risk medulloblastoma patients to assess benefit of carboplatin radiosensitization or 13-cis retinoic acid with cisplatin-based chemotherapy.</td>
<td>Spiller et al., J Neuro-Onc, 2008 Children’s Oncology Group ACNS0332</td>
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<td>Development of an anti-CD45, I-131 labeled radioantibody and demonstrating its effective targeting to hematopoietic tissue and ablation of bone marrow in preparation for hematopoietic stem cell transplantation for acute myeloid leukemia (AML). Fred Appelbaum, Ollie Press, John Pagel (Heme Malignancies)</td>
<td>Phase I and II studies in older AML and MDS patients; collaboration with Actinium Pharmaceuticals, Inc., to develop the antibody for all uses. A Phase III randomized multi-center trial of 150 AML patients over age 55 will be initiated with the goal of FDA licensure. This work has the potential to significantly improve care for AML, for which there are no FDA-approved therapies.</td>
<td>Pagel JM et al., Blood, 2009</td>
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<td>Demonstrated that signaling through the insulin like growth factor receptor (IGFR) promotes survival and proliferation of prostate cancer cells, and demonstration that IGFR1 antibodies (IMC-A12, developed by Imclone) substantially suppress the growth of prostate cancer xenografts and augment responses to castration. Stephen Plymate, Bruce Montgomery, Tia Higano, Evan Yu (Prostate Cancer)</td>
<td>Phase I and II studies of IMC-A12 in men with advanced prostate cancer to demonstrate safety and efficacy; Phase II neoadjuvant trial of IMC-A12 with androgen deprivation in men with high-risk localized prostate cancer; a large Phase II randomized clinical trial of IMC-A12 developed through SWOG is in follow up.</td>
<td>P50 CA097186 (SPORE) Dean et al., J Clin Endocrinol Metab, 2013 SWOG 0925</td>
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<td>Development of cancer biomarkers for early detection of ovarian cancer, which is frequently diagnosed at late and incurable stages. Nicole Urban, Christopher Li, Charles Drescher (Women’s Cancer); Martin McIntosh (Biostat &amp; Computational Biology)</td>
<td>Inter-SPORE study with three other cancer centers to identify the best markers to include in an ovarian cancer early detection panel; An NCI EDRN Phase 3 validation study is underway to evaluate three markers (including those developed at our center) in preclinical serial samples from the NCI Prostate, Lung, Colon, and Ovary screening trial, the UK Collaborative Trial of Ovarian Cancer Screening, the Women’s Health Initiative Observational Study and Clinical Trial.</td>
<td>U01 CA152637, P50 CA083636 (SPORE) Drescher et al.; J Clin Oncol, 2013; Cramer et al., Cancer Prev Res, 2011; Zhu et al., Cancer Prev Res, 2011; Hellstrom et al., Cancer Res, 2003; McIntosh et al., Gynecol Oncol, 2004; Palmer, PloS</td>
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<tr>
<td>Discovery, Lead Investigator(s) and Program</td>
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| Defining a potential role for Notch signaling in hematopoiesis.  
*Irwin Bernstein, Colleen Delaney (Heme Malignancies)* | Applied Notch discovery to develop methods for ex vivo expansion of stem and progenitor cells for cord-blood transplantation; conducted phase I and phase II studies in acute myeloid leukemia patients to demonstrate rapid engraftment; now leading randomized Phase II study with five other NCI cancer centers of 160 AML patients receiving a "standard of care" cord blood transplant with or without the universal donor product. | P50 HL110787  
| Application of a novel behavioral intervention (Acceptance and Commitment Therapy, or ACT) to smoking cessation to reduce incidence of lung cancer.  
*Jonathan Bricker (Cancer Epi, Prevention & Control)* | Conducted a CCSG-funded pilot trial to deliver ACT via the Web, finding it more than doubles the quit rate over the NCI's smokefree.gov website; now leading a two-arm randomized controlled trial of 2500 participants comparing the ACT website with Smokefree.gov to demonstrate that ACT has significantly higher smoking cessation rates. | R01 CA166646  
Bricker J et al., Nicotine Tob Res. 2013 |

**CANCER FOCUS**

Our mission is to foster innovative, high impact cancer research through interactions and collaborations of our members. The Consortium was specifically created to provide the needed leadership, organization, resources and infrastructure required to integrate and foster cancer research across disciplines and institutions and focus collective energies in order to impact the cancer issues facing the catchment area and five-state region.

At the time of the last CCSG application, Cancer Focus was given Outstanding merit. Over the project period, we have: 1) increased our standards and internal scrutiny of initial and ongoing membership, thereby ensuring that members are highly engaged in cancer research and in Consortium activities; 2) tightened our definition of cancer-relevant grants; and 3) reviewed and modified our programmatic structure, reorganizing some programs to ensure that they are directly relevant to cancer, non-overlapping, reflect member interests, and foster innovative directions in cancer research; and 4) all partners have made significant institutional investments to further our mission including research space and faculty recruitment. Members have been highly productive during this period, securing major cancer grants and publishing significant findings.

**Membership.** Membership criteria have been more carefully defined to ensure members are active and their work and funding is cancer focused. Members may be eliminated for lack of current cancer focus.

**Grant Funding.** Using more narrowly defined (cancer-focused) criteria in this application, members have a total funding base of $389M (direct costs), of which $87.5 is from the NCI, $98.1M is from other NIH institutes, and $17.2M is from other peer-reviewed funding sources. To be highly conservative, we have eliminated AIDS-related grants except for that portion that is related to cancer (for example AIDS-related malignancies or vaccine development relevant to cancer vaccine development). A portion of total funding was included for particular grants when the PIs affirmed that cancer was a primary aim of the grant.

Members hold many multi-investigator and multi-institutional cancer grants. Examples include: three SPORES grants noted earlier; two U01 Cancer Target Discovery and Development Network grants (Marty McIntosh, Chris Kemp); U01 Cancer Immunotherapy Trials Network Central Operations and Statistical Center (Mac Cheever); P50 Understanding and Preventing Breast Cancer Disparities in Latinas (Beti Thompson); U01 Colorectal Cancer Genome-Wide Association Studies Consortium (PI Ulrike Peters) and U01 Detection of Colorectal Cancer Susceptibility Loci Using Genome-Wide Sequencing (PI Ulrike Peters).

Members have received NCI Provocative Questions grant awards, which focus on creative solutions to difficult-to-solve cancer problems. These include: R01 Novel Pathogen Associated Cancers (Denise Galloway); R01 Aspirin and Inflammation: Mutations, Genes, Pathways and Prevention (Brian Reid); R21 Evolution of Cancer-Specific Molecular Requirements for Glioblastoma Multiforme (Patrick Padison); and R21 Directed Evaluation of Peptide Inhibitors of Myc-Max Dimerization (Bob Eisenman).
Clinical Trials. The Center's cancer clinical trials portfolio includes 607 trials, of which 486 are interventional, 61 are ancillary/corollary, and 60 are observational. Of the interventional trials, 411 are therapeutic. The center has remained active in cooperative groups, particularly SWOG, Children's Oncology Group, Gynecologic Oncology Group and American College of Radiology Imaging Network, and has a newly awarded U10 NCI National Clinical Trials Network - Network Lead Academic Participating Site grant.

Training and Education. There are 8 T awards from the NCI in areas including pediatric oncology, chromosome metabolism and cancer, and cancer epidemiology. Additional training information is provided in Organizational Capabilities.

Strategic Recruitments. We have made many targeted recruitments to build our cancer capabilities. UWSOM Division of Oncology has recruited 15 medical oncologists during the grant period; FHCRC has recruited 6 lab based solid tumor investigators; Seattle Children’s has recruited Michael Jensen, a nationally recognized cancer immunotherapy expert, to direct their Towne Center for Childhood Cancer Research and Leslie Kean to help lead transplantation biology research. Other recruitments are noted in Developmental Funds.

Cancer Scientific Programs. All Programs have been reviewed internally and externally. Scientific aims have been tightened to ensure cancer focus and prevent overlap. Four programs are tumor specific (Heme Malignancies, GI Cancer, Womens' Cancer, Prostate Cancer), while the the Immunology and Vaccine Development Program develops immune-based cancer therapies, improves infection control in immune-compromised cancer patients, and leverages insights from vaccine biology to enhance cancer immunotherapy. The personnel and validated procedures of the GCP T-cell laboratory originally developed for HIV vaccines is now being utilized for immune monitoring for our cancer vaccine and immunotherapy trials.

Complementing these are four discipline-based programs. The Cancer Epidemiology, Prevention and Control Program conducts research on the causes of cancer and its progression, and seeks to improve screening and prevention strategies to reduce cancer morbidity and mortality, with special emphasis on underserved populations. The newest program, Global Oncology, focuses on developing systems for global surveillance of cancer, understanding and eliminating infection-related cancers, and improving cancer treatment and prevention in low- and middle-income countries. The remaining discipline-based programs provide foundational work or tools that are critical to the other programs. The Biostatistics and Computational Biology program develops statistical and mathematical models relevant to predictive and personalized medicine for cancer, models to gain understanding of cancer’s natural history, and computational methods for cancer research. The Cancer Basic Biology Program includes a broad range of laboratory investigators whose work deepens the understanding of the mechanisms that underlie tumorigenesis. We responded to comments from the last CCGS review regarding the cancer focus of the Basic Sciences Program. It has been reorganized, grant and membership criteria have been tightened, and new translational collaborations in cancer have been stimulated.

Scientific Accomplishments. The strongest evidence of cancer focus is the impact of member research on cancer. The Director's overview and all of the Research Program sections describe major advances in laboratory, clinical and population cancer research and publication in prominent peer-reviewed journals.

INSTITUTIONAL COMMITMENT

All partner institutions recognize the Consortium within their organizational structures and demonstrate their commitment through joint planning, joint recruitment, engagement of their faculty, development and housing of Shared Resources and financial investments. Institutional Commitment received was rated Outstanding at the 2008 review with no significant critiques. By all criteria, institutional commitment to oncology has increased since this assessment and is well documented in the attached letters of support from leaders of all partners.

Partner space commitments and a table of partner funding commitments during the project period are provided in the Facilities and Other Resources attachment.

Organizational Status and Institutional Engagement. By agreement, the President and Director of FHCRC is the Consortium Director.

The Consortium “presence” is fully integrated into the FHCRC culture and structure through high faculty engagement, collaborative science, and use of resources. The two FHCRC Deputy Directors are Consortium Deputy Directors, and four of five FHCRC division directors are Consortium Associate Directors. The Chair of the FHCRC Board of Trustees is a member of the Governance Committee.
The UW Vice Dean for Research and Graduate Education, John Slattery, and Chair of the Department of Medicine, William Bremner, are Consortium leaders and liaisons, respectively. They represent the Consortium at School meetings and are in regular contact with the Dean and school administration. Both make Consortium goals a priority and have supported recruitments that benefit the Consortium. Dr. Slattery is responsible for school laboratory research and works with the Center Director and senior leaders when space is needed for recruitment or Shared Resources. He was instrumental in the development of new cores and a strong advocate for a collaborative biomedical informatics initiative between UWSOM and FHCRC.

To coordinate planning for clinical research, leaders from all relevant departments from the three partner institutions participate in the Clinical Oncology Oversight Committee (COOC). All clinical department chairs in the UW School of Medicine are members. Strategic plans for clinical research are vetted through this group, as are decisions about recruitment priorities and institutional commitments for new clinical oncology recruits.

The UW School of Public Health’s (SPH) interests are represented by the Senior Associate Dean, Shirley Beresford, who is also a member of FHCRC. She represents the Consortium at senior leader meetings at the School and has frequent contact with the Dean and with School administration. The majority of SPH faculty who are Consortium members are based at FHCRC, which supports their research. Dr. Beresford ensures that the School and the Consortium are apprised of one another’s activities, strategic plans and scientific directions.

At Children’s, Bruder Stapleton, Chief Academic Officer at Children’s and Chair of Pediatrics at the University, and Jim Hendricks, President of Children’s Research Institute, participate in the IPC. Dr. Stapleton ensures that pediatric oncology planning at Children’s is conducted with the full engagement of Consortium leadership. Dr. Hendricks coordinates translational research between Children’s and the Consortium. As such, he meets regularly with Ulrich Mueller, Director of Consortium Clinical Research Support. Michael Jensen directs Children’s Ben Towne Center for Childhood Cancer Research and is both Consortium AD for Childhood Cancers and an Associate Program Head for Immunology and Vaccine Development.

The SCCA Executive Director and President, Fred Appelbaum, is Deputy Director of the Consortium. The Executive Vice President of the SCCA, Norm Hubbard, serves on the COOC and ensures that SCCA senior management is cognizant of ongoing resource requirements for recruitment and research support. Together, these leaders are responsible to partner institutions for ensuring that Consortium research priorities are met at the SCCA or through patient care partnerships with UWMC and Children’s.

**Formal Agreement.** All Consortium institutions have signed a Memorandum of Understanding (copy will be available at the site visit) committing them to a shared vision, joint planning and institutional support for oncology research. Institutional commitment letters are included in this application. The SCCA bylaws state that the Executive Director and President of the SCCA will simultaneously hold leadership roles at FHCRC and UWSOM, so the relationship between Consortium and SCCA leadership is also codified.

**Financial Commitment.** All Consortium partners have demonstrated their commitment to the Consortium through substantial investments in recruitment and infrastructure. As outlined in the attached institutional letters and the funding commitments stated in Facilities and Other Resources, partners have invested nearly $580M million during the project period to support Consortium faculty and related research, a clear indication of the high priority placed on cancer research among the participant institutions.

**Fund Raising.** The entire FHCRC Development Department is devoted to cancer. FHCRC, UW and Children’s share the salary expense of an SCCA-based development office and each partner’s senior official for fundraising meet regularly to discuss potential cancer-related opportunities. Further commitment was achieved in 2012 when Dr. Corey and Paul Ramsey, MD, Dean of UWSOM, signed a formal agreement for collaborative fundraising for adult oncology research. This has been associated with a marked increase in philanthropic efforts in areas including prostate, brain and pancreatic cancer. Drs. Corey, Ramsey, and Tom Hansen, CEO of Seattle Children’s, jointly plan major philanthropic proposals for collaborative activities.

**Change in Director.** The MOU specifies that the President of FHCRC serves as the Consortium Director. The Governance Committee assures that Consortium’s goals and needs are taken into consideration during the search process. In the event that the Director decides to leave the FHCRC or becomes disabled, a Deputy Director will assume the role until a new Director is selected and hired.

**Space.** Consortium partners have substantial space dedicated to cancer, as detailed in the institutional space commitment table provided in the Facilities and Other Resources section. Combined, the Consortium has ~ 1.3
Dr. Corey works directly with leaders of the partner institutions to ensure that there is ample space for Consortium development. Space has never been a barrier to growth or recruitment.

**Recruitments.** While recruiting is directed by institutions, joint planning for strategic cancer recruitments is routine. For appointments in the UW School of Medicine, the COOC, which includes all School department chairs and the clinical leader from FHCRC, is the forum through which key recruitments are planned. Since Children’s-based members have appointments in the UW Department of Pediatrics, and nearly all UWSPH-based members have appointments at FHCRC, collaborative recruitment is standard practice. For scientific leadership positions at FHCRC and UW, search committees typically include at least one representative from the other institution, and for other recruitments, faculty from another institution frequently participate in the process either through the search committee or meeting with candidates during their interview. More than one institution frequently contributes to a recruitment package. The Recruitment Subcommittee of the IPC, which allocates CCSG New Investigator funds, includes representatives from all Consortium partners.

**Clinical Research.** Members of Consortium partner institutions use a single Protocol Review and Monitoring System and Data and Safety Monitoring Plan for cancer clinical trial protocols.

**Team Science.** Team science is a cornerstone of the Consortium and its partner institutions. The commitment begins at the top with Dr. Corey, whose leadership of the HIV Vaccine Trials Network, one of the largest multi-institutional clinical trial efforts, serves as a prime example. Faculty are now, in part, recruited because of their collaborative track record. While appointment and promotion criteria are the responsibility of institutions, a vast majority of Consortium members reside in departments whose promotion criteria include collaborative contributions, and ensuring this recognition is a goal of the Director and Governance Committee.

**CENTER DIRECTOR**

**Scientific, Administrative and Leadership Qualifications.** Larry Corey was appointed Center Director and President and Director of the FHCRC in 2011 after a national search. He is an internationally renowned expert in virology, immunology and vaccine development and a member of the Institute of Medicine of the National Academy of Sciences (2008) and the American Academy of Arts and Sciences (2012). His research focuses on herpes viruses, HIV and other viral infections, particularly those associated with cancer. A major body of his work has centered on reducing the infectious disease morbidity of cancer patients undergoing chemotherapy and bone marrow transplantation for hematologic cancer.

Dr. Corey is an experienced laboratory scientist who has directed a clinical diagnostic laboratory for much of his career and is also an experienced clinical trialist. He is widely recognized as one of the founders of the field of antiviral chemotherapy with major contribution to development of the initial antivirals in the herpes virus and HIV fields. Under his leadership of the AIDS Clinical Trials Group, antiviral therapy to reduce maternal-to-fetal transmission of HIV and combination antiretrovirals to control HIV replication were implemented. In the last 15 years, his work has centered on T-cell biology of HSV and HIV, and in 1999 he founded the NIAID-supported and FHCRC-based HIV Vaccine Trials Network (HVTN). The HVTN is one of the largest clinical trials groups in the world and has conducted more than 100 phase I/II and 4 phase IIB trials of candidate HIV vaccines. The network includes investigators on four continents and involves 28 cores and at times, an additional 30 active clinical trial sites. Prior to his appointment as Director, to increase FHCRC’s impact in reducing the global burden of disease, Dr. Corey established a new FHCRC scientific division. Known as the Vaccine and Infectious Disease Division (VIDD), it has a large program on infection-related malignancies through which FHCRC has established a robust research collaboration with the Uganda Cancer Institute. These activities laid the foundation for the Consortium’s new Program in Global Oncology. As a leader in global oncology, Dr. Corey has been a consultant for the NCI during its establishment of its Center for Global Health.

**Activities and Authority.** Dr. Corey is responsible for the direction, planning and development of the Consortium. He oversees all operations, including the CCSG, although some day-to-day activities are delegated to Deputy Directors Mark Groudine and Fred Appelbaum, among others. He devotes 50% effort to CCSG activities, and the rest of the time to his role as FHCRC director and PI of the HVTN. He is ultimately responsible for allocation of CCSG funds, and appoints Associate Directors, members of the Institutional Planning Committee and Scientific Steering Committee, and leaders of Consortium programs. He has authority to add, modify, move or disband CCSG-funded Shared Resources. He is ultimately responsible for ensuring the Consortium’s Data Safety and Monitory Plan is executed, and with the Governance Committee, assures that the SCCA furthers the research aims of the center and serves as a primary site for patient-focused research.
Establishing a Vision and Integration across the Consortium. Consortium partners have a long history of scientific interaction that has yielded many advances and peer-reviewed funding. Dr. Corey recognized that fulfilling the true intent and achieving the full potential of a consortium goes beyond scientific collaboration. It requires shared vision, planning and commitment of institutional resources. During his tenure, Dr. Corey has deepened interactions among the institutional leaders and solidified their partnership, garnered significant institutional support for strategic initiatives, and catalyzed a number of new activities. Beyond this, he has specifically strengthened institutional commitment to key objectives initiated prior to his appointment.

With the Governance committee, Dr. Corey oversaw development of the cancer center’s strategic objectives, ensuring that objectives of the institutions are complementary and coalesce into a unified strategic plan for the cancer center. To catalyze team research across disciplines, he launched a “transformative ideas” initiative to solicit proposals from Consortium faculty of innovative strategies that address important and unsolved cancer problems. This initiative was cross-disciplinary and inter-institutional by design, and was conceived to promote aspirational directions for research teams. The process was rigorous and included outside reviewers including former NCI Director Rick Klausner. After review, proposals were developed including strategic plans for grant and/or philanthropic funding. This effort has yielded results. Several have garnered significant NCI funding, and the approach has helped define a strategic plan for solid tumor translational research, which has been beneficial to Dr. Holland. In 2012, Drs. Corey and Ramsey appointed a planning committee for a joint precision oncology initiative to better integrate molecular diagnostic services across the Consortium, expand efforts to identify new actionable targets for therapy and create a robust pipeline to develop these into CLIA-approved tests. Drs. Corey and Ramsey also signed an agreement in 2012 to conduct joint philanthropy for adult solid tumor oncology research. Additional strategic initiatives during the past 18 months include the linkage of the UW-based Institute of Health Metrics with FHCRC’s global oncology program to create a new CCSG program, creation of the Hutchinson Institute for Health Outcomes Research (HICOR) to expand health economics and comparative effectiveness research, and increased focus on bioinformatics and computational biology.

While much has been accomplished in the last three years, several areas require attention during the next grant period. One is to increase research of priority to the catchment area and minority accruals to trials. Dr. Corey has been a leader in including underserved populations in clinical trials and in developing community programs to increase access to optimal care. The Legacy Program he initiated in the HVTN to to increase the participation of people of color in HIV vaccine trials has been incorporated into all of the other NIAID HIV networks. Extending this focus to cancer research is a major objective. He has appointed an Associate Director in Health Disparities; established a Health Disparities Research Center; and dedicated CCSG pilot funds to enhance minority population participation in clinical trials. A second area is to continue to build the clinical research infrastructure. The Clinical Research Support Office was created under Dr. Corey’s tenure. It brings together several previously distinct services. Dr. Corey also appointed a new medical director and senior administrator to oversee the office, and has engaged partner organizations to implement a clinical trials management system. Future plans including expanding clinical research training, enhancing quality oversight and centralized support, and increasing consistency across institutions. Dr. Corey’s expertise in managing clinical trial networks and implementing large, high-risk, multi-institutional clinical trials provides the experience needed to improve these functions during the current grant period.
FACILITIES AND OTHER RESOURCES

Facilities

The Consortium partners (Fred Hutchinson Cancer Research Center, the University of Washington, Seattle Children’s, and The Seattle Cancer Care Alliance) collectively provide outstanding facilities and a scientific environment to support the full spectrum of basic, clinical and population-based cancer research conducted by our members. As there are several components of this application that include information about physical space, we have made every effort not to duplicate information in multiple sections.

Reviewers are directed to the following sections for additional information:

- Laboratory facilities: Detailed information about the physical space and equipment of Shared Resources that support this application is provided in each of the resources in the Shared Resources sections. There are 13 CCSG-funded resources that support basic, clinical and population sciences research: Cellular Imaging, Computational Biology, Experimental Histopathology, Genomics, Proteomics and Metabolomics, Comparative Medicine, Immune Monitoring, Northwest Biotrust (biospecimen resource), Therapeutic Manufacturing, Translational Imaging, Biostatistics, Collaborative Data Services, Prevention Center.

- Information about site linkages that promote effective interaction among the Consortium partner campuses and members is provided in the Overall Core/Six Essential Characteristics/Physical Space section of this application.

Information in this section is organized by institutional site to most effectively summarize the overall characteristics of our center’s facilities, noting unique aspects where applicable. Included in this section are tables that describe the space commitments to the cancer center of each partner institution, followed by a map illustrating all Consortium sites.

FHCRC Campus Facilities

Fred Hutchinson Cancer Research Center

The FHCRC has 12 buildings on the 15-acre Day Campus in Seattle’s SLU neighborhood. FHCRC has five research divisions (Clinical Research, Basic Sciences, Human Biology, Public Health Sciences, and Vaccine and Infectious Disease) and one administrative division, representing a total of 766,000 NASF of research, meeting and office space in these six divisions. The most recent building addition to the campus is the Eastlake Building, opened in 2012 to house the Vaccine and Infectious Diseases Division as well as the SCCA Cellular Lab, Cancer Immunotherapy Trial Network and a data center with significant room for growth. Among the Consortium Shared Resources on the FHCRC campus are laboratory resources such as Genomics and a GMP-grade Therapeutic Manufacturing resource; population resources such as a state-of-the-art Prevention Center with exercise facility, clinic space and research kitchen for dietary studies; and the Clinical Research Support Office. Consortium Administration is housed in 500 square feet at in FHCRC’s administrative (Yale) building.

FHCRC central IT is staffed with 87 FTE and provides support for a complex heterogeneous computing environment. Center IT manages the FHCRC Storage Area Network (SAN) that allows maximum collaboration of Windows, Linux and Macintosh computer users. In order to accommodate the growing demand for computer resources and mitigate the power demands of physical systems, many of the server services are now being provided by virtual systems using the advanced VMWare ESX technology. Center IT also provides support for over 60 applications that are made available to the entire Center including an enterprise level SharePoint Collaboration platform. FHCRC also has a Scientific Computing group that provides high performance computing, general Linux/Unix support, software development support, training, file and data management assistance/data archiving.
<table>
<thead>
<tr>
<th>Type of Space</th>
<th>Net assignable square footage (NASF) FY2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td>130,000</td>
</tr>
<tr>
<td>Clinical Research</td>
<td>113,000</td>
</tr>
<tr>
<td>Basic Sciences &amp; Human Biology Research</td>
<td>128,000</td>
</tr>
<tr>
<td>Public Health Sciences Research</td>
<td>202,000</td>
</tr>
<tr>
<td>Vaccine and Infectious Diseases</td>
<td>98,000</td>
</tr>
<tr>
<td>Shared Resource Space</td>
<td>95,000</td>
</tr>
<tr>
<td>Total</td>
<td>766,000</td>
</tr>
</tbody>
</table>

Seattle Cancer Care Alliance

The SCCA clinic, where most adult hematology and oncology outpatient care is provided, resides in a seven-story, 188,000 NASF facility on the FHCRC campus. It houses outpatient clinics, radiation oncology, diagnostic imaging, clinical laboratory, infusion therapy, apheresis, minor procedures, physical therapy, pharmacy, patient support services, and faculty and administrative offices. In 2010 the SCCA opened the Phase 1 Clinical Trials Unit, which has 1,483 NASF of dedicated space for cancer patients participating in first-phase clinical drug studies. The SCCA Cellular Therapy Laboratory, responsible for all minimally manipulated therapeutic cell processing at the SCCA, has 4,068 NASF in the Eastlake Building (see above). The SCCA has a second Prostate Center (18,380 NASF) at the UW Medical Center Health Sciences Campus on the first floor of the Surgery Pavilion. Additionally, the SCCA inpatient unit at UW Medical Center has 20 beds (9,873 NASF) on the 8th floor inpatient unit.

UW Medicine Northwest Hospital houses two SCCA care facilities. SCCA Radiation Oncology at the hospital (6,687 NASF) serves adults who need therapy for primary cancer. Opened in March 2013, the SCCA Proton Therapy Center is a partnership with ProCure Treatment Center, Inc., and occupies 48,780 NASF at Northwest Hospital (located in North Seattle). It is currently the only proton therapy within 1000 miles of Seattle. Located in Kirkland, Washington (~15 miles northeast of the SCCA outpatient clinic), Evergreen Health Medical Center has 1,080 NASF dedicated space for SCCA patients to receive treatments and participate in the Cancer Center’s clinical studies.

The SCCA Network includes eight community medical facilities throughout Washington and neighboring states. Patients at these facilities can be referred to Consortium physicians and participate in clinical studies.

SCCA IT oversees and manages the provision of the technology infrastructure. The group of 35 staff members supports over 1500 workstations, 500 mobile devices, and 1500 users. Support is provided for desktop and mobile device management, security, server operations, network, data center and co-location management, business and administrative applications including Epic Prelude, Cadence, ADT, HB and SharePoint, essential service applications including RIS/PACS for radiology, Mosaiq for radiation oncology, lab information management systems, and medical equipment IT. A clinical information systems team manages the functionality, use, and development of the Electronic Medical Record. Currently the team is implementing a fully Electronic Medical Record and will be completing a major initiative Computer Provider Order Entry (CPOE) of complex chemotherapy, radiology, and lab electronic orders in 2014.
<table>
<thead>
<tr>
<th>Type of Space</th>
<th>Location</th>
<th>Net Assignable Square Footage (NASF) - FY2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCCA Clinic Total Space</td>
<td>SCCA Clinic</td>
<td>188,000</td>
</tr>
<tr>
<td>SCCA Patient Care and Patient Support Space</td>
<td>SCCA Clinic</td>
<td>78,377</td>
</tr>
<tr>
<td>SCCA Labs and Lab Support</td>
<td>SCCA Clinic</td>
<td>17,737</td>
</tr>
<tr>
<td>SCCA Phase I Clinical Trials Unit</td>
<td>SCCA Clinic</td>
<td>1,485</td>
</tr>
<tr>
<td>SCCA Cellular Therapy Laboratory at Hutchinson Campus</td>
<td>Hutchinson Center Campus – Eastlake Building</td>
<td>4,068</td>
</tr>
<tr>
<td>SCCA Administration and IT</td>
<td>SCCA Clinic, Hutchinson Center Campus Buildings, and leased space off campus</td>
<td>78,807</td>
</tr>
<tr>
<td>SCCA Prostate Cancer Center</td>
<td>UW Medical Center</td>
<td>18,380</td>
</tr>
<tr>
<td>SCCA Inpatient Unit at UWMC</td>
<td>UW Medical Center</td>
<td>9,873</td>
</tr>
<tr>
<td>SCCA Radiation Oncology</td>
<td>UW Medicine Northwest Hospital</td>
<td>6,687</td>
</tr>
<tr>
<td>SCCA Proton Therapy Center</td>
<td>UW Medicine Northwest Hospital</td>
<td>48,780</td>
</tr>
<tr>
<td>SCCA at Evergreen Health</td>
<td>Evergreen Health in Kirkland, Washington</td>
<td>11,080</td>
</tr>
</tbody>
</table>

**University of Washington Health Sciences Campus (UW-HSC)**

**School of Medicine, School of Public Health and Other Cancer-Related Departments**

UW Medicine at UW Medical Center (UWMC) on the main university campus occupies a total of 1,311,255 NASF. UWMC is the primary teaching hospital for the UW School of Medicine (UWSOM), UW School of Public Health (UWSPH) and UW School of Nursing. 40 departments or divisions within the UWSOM have dedicated cancer research programs; within UWSPHCM 4 departments have dedicated cancer research programs. Additionally, there are cancer research programs in the Schools of Nursing, Engineering and Dentistry.

**UW Medicine at University of Washington Medical Center**

54,394 NASF of UW Medicine at UWMC is dedicated to three cancer treatment inpatient units with 96 dedicated oncology beds. The SCCA also has an inpatient unit at UWMC with 20 dedicated oncology beds within 9,873 NASF (also described in the SCCA section above.) The Clinical Research Center, part of the Clinical Translational Science Award-funded Institute of Translational Health Sciences, has 7,081 NASF, and there is an infusion area of 10,811 NASF. 25,865 NASF of space is dedicated to radiation oncology at UWMC. Space dedicated to cancer surgical specialties – including neurological, lung, gastrointestinal, urology, among others – is approximately 19,040 NASF.
Consortium Shared Resources located at UWMC include Translational Imaging, which houses HSB microPET; HSB DISC 3T; SLU 3T; SHB 4.7T; and Primate PET, housed within 3,000 NASF.

UW Medicine at Harborview Medical Center (HMC)

Located in the First Hill Neighborhood in Seattle, HMC provides specialty care in nearly every area of medicine and is the only Level 1 adult and pediatric trauma and burn center serving Washington, Alaska, Montana and Idaho. HMC sees many patients who have financial barriers including gaps in funding for health care. In FY12, 222 of the 346 Gamma Knife procedures at HMC were done on patients having cancer malignancies as principal diagnosis. In FY12, 45 of the 1,541 neurosurgery patients had cancer malignancies. Approximately 500 patients with HIV-related malignancies are seen at Harborview on a yearly basis.

A PET/CT, part of the Translational Imaging Shared Resource, is dedicated to cancer research at HMC within 765 NASF.

UW Medicine South Lake Union (SLU)

Established in 2008 and recently expanded in 2013, UW Medicine SLU campus (242,275 NASF) houses over 600 scientists, biotechnology and medical research labs, and an administrative building with computational lab space. The campus has nine labs, of which two are dedicated to cancer research: Tumor Vaccine Group (2,925 NASF) and Ngheim Lab (975 NASF) that studies Merkel cell carcinoma and the genetic responses to skin cancer. 333 NASF of the Translational Imaging Shared Resources is dedicated to cancer research at SLU.

Of particular relevance to Consortium research, the Department of Genome Sciences provides critical IT services for 27 departmental research labs as well as affiliated organizations including the Northwest Genome Center, the Northwest Institute of Genetic Medicine, the UW Proteomics Resource, the UW Center for Mendelian Genomics and collaborating researchers worldwide. The research computing environment at Genome Sciences currently includes 5000+ CPU cores, 6 Petabytes of network available disk based storage, and $15M in IT equipment purchased over the last 5 years.

The Northwest Genome Center has significant information technology resources. The analysis cluster servers (2,000+ total CPU cores), storage (2.6 Petabytes usable) and backup system (14 drives, 3.2 PB native capacity) are interconnected with high-speed, low-latency 40Gbs Infiniband or 10Gig Ethernet interconnects, allowing data to be quickly moved through the analysis pipeline. In addition, there are two database servers, two Java application servers, five virtualized servers for development, 6 large memory systems with RAM sizes of 384GB to 1TB and an Aspera server for data dissemination to the research community.

<table>
<thead>
<tr>
<th>TABLE III: University of Washington Cancer Research and Treatment Space</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Space / Location</strong></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Treatment Space</strong></td>
</tr>
<tr>
<td>UW Medical Center Total Space</td>
</tr>
<tr>
<td>UW Inpatient Unit at UWMC / 96 beds</td>
</tr>
<tr>
<td>Infusion Unit</td>
</tr>
<tr>
<td>Radiation Oncology at UWMC</td>
</tr>
<tr>
<td>Cancer-Related Surgical Specialties at UWMC</td>
</tr>
<tr>
<td>Harborview Medical Center/ UW Medicine</td>
</tr>
<tr>
<td>Harborview, 9th &amp; Jefferson Building</td>
</tr>
</tbody>
</table>

Data represented above
TABLE III: University of Washington Cancer Research and Treatment Space

<table>
<thead>
<tr>
<th>Shared Resources</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>UW Campus Health Sciences Building</td>
<td>3,000</td>
</tr>
<tr>
<td>Harborview Medical Center Ninth &amp; Jefferson Building</td>
<td>765</td>
</tr>
<tr>
<td>UW South Lake Union Campus</td>
<td>333</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Research Space</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>UWMC South Lake Union Campus Total Space</td>
<td>242,275</td>
</tr>
<tr>
<td>Cancer Research Labs at SLU</td>
<td>3,900</td>
</tr>
<tr>
<td>UW General Clinical Research Center at UWMC</td>
<td>7,081</td>
</tr>
</tbody>
</table>

Seattle Children’s

SCH Laurelhurst Main Campus (Hospital)

Seattle Children’s main campus is approximately 979,882 NASF, of which approximately 47,898 NASF is dedicated to cancer treatment and research. SCH provides inpatient, outpatient, diagnostic, surgical, and rehabilitative services and is a primary teaching, clinical site for the Department of Pediatrics at the University of Washington’s School of Medicine. The Hematology/Oncology Outpatient Unit and Infusion Center occupies approximately 5,691 NASF. SCH has 48 oncology patient beds and approximately 34,146 NASF for its Hematology/Oncology Inpatient and Bone Marrow Transplant Units. Administrative offices dedicated to cancer treatment and research occupies approximately 3,500 NASF.

Seattle Children’s Research Institute (SCRI)

Seattle Children’s Research Institute houses nine interdisciplinary centers across areas central to pediatric health. In 2006, Children’s acquired two adjacent research buildings totally nearly 500,000 NASF of clinical and laboratory space in downtown Seattle. Since then, Children’s Research Institute has expanded into two additional buildings nearby. Within these research buildings, approximately 44,993 NASF is dedicated to cancer research and administrative space. Formed in 2012, the Ben Towne Center for Childhood Cancer Research houses a majority of the cancer research at the downtown institute with 22,628 NASF at the Olive and Stewart Building. Other cancer-dedicated space includes 1,166 NASF, at the Center for Clinical and Translational Research approximately 3,000 NASF at the Center for Immunity and Immunotherapies; and 1,500 NASF at the Center for Integrative Brain Research (formed in 2008). 16,000 NASF is dedicated to cancer research administration at the institute.

Seattle Children’s Information Services (IS) has a staff of approximately 340 FTE who support the overall IT environment of the Hospital and Institute including infrastructure, applications and security. Seattle Children’s network spans 4 main sites and multiple remote locations. There are redundant, high bandwidth circuits connecting SCRI users to central computing services. The Seattle Children’s network is protected by redundant firewalls and intrusion detection systems. The SCH Network & Security teams support research facilities over dedicated fiber. High speed connection to the National LambdaRail (NLR) is available via a 1 to 2.4 GB connection with Pacific Northwest GigaPop Network (PNWGP).

SCRI Currently has an installed base of approximately 200TB of dedicated storage primarily Hitachi HNAS. This data footprint is expected to increase %100+ over the next 12 months. Storage is physically located at the primary SCRI location as well as at Seattle Children’s primary data center which SCRI connects to via redundant, high bandwidth links. IS supports a mixture of Windows and Linux systems both virtual and physical. In addition to a large server footprint, there are ~75 SCRI specific systems consisting of a mixture of physical and virtual (ESX) Windows and Linux hosts that IS maintains. The IS Systems Team supports about thirty server based business/research applications that are specific to SCRI including Geneious and SANTA. IS also provides standard enterprise suites that support SCRI as well as the Hospital, clinics and support teams. These include Microsoft Exchange, SharePoint and others.
TABLE IV: Seattle Children’s Cancer Research and Treatment Space

<table>
<thead>
<tr>
<th>Type of Space</th>
<th>Net Assignable Square Footage (NASF) - FY 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seattle Children’s Campus at Laurelhurst Campus</td>
<td>979,882</td>
</tr>
<tr>
<td>Administration</td>
<td>3,500</td>
</tr>
<tr>
<td>Inpatient Hem/Onc and BMT Unit</td>
<td>34,146</td>
</tr>
<tr>
<td>Hem/Onc Outpatient Clinic and Infusion Center</td>
<td>7,000</td>
</tr>
<tr>
<td>Seattle Children’s Research Institute in Downtown Seattle</td>
<td>~ 500,000</td>
</tr>
<tr>
<td>Center for Clinical and Translational Research</td>
<td>1,166</td>
</tr>
<tr>
<td>Center for Immunology and Immunotherapies</td>
<td>~1,850 – 3,699</td>
</tr>
<tr>
<td>Center for Integrative Brain Research</td>
<td>1,500</td>
</tr>
<tr>
<td>Ben Towne Center for Childhood Cancer Research</td>
<td>22,628</td>
</tr>
<tr>
<td>Research Administration – West 8th Building</td>
<td>16,000</td>
</tr>
</tbody>
</table>
### INSTITUTIONAL COMMITMENT

Total Funding Commitments of the Partners During the Current Project Period
*(Institutional Space Commitment to Consortium Research is Outlined Above in Facilities)*

<table>
<thead>
<tr>
<th>Institution</th>
<th>Resource</th>
<th>Amount Funded (in millions)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>FHCRC</td>
<td>Faculty Recruitment</td>
<td>17.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shared Resources Operating</td>
<td>44.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Scientific Equipment</td>
<td>34.9</td>
<td>Shared Resources and Research Divisions</td>
</tr>
<tr>
<td></td>
<td>Laboratory Alterations</td>
<td>12.9</td>
<td>Shared Resources and Faculty Labs</td>
</tr>
<tr>
<td></td>
<td>Faculty Salary Support</td>
<td>65.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interim Funding</td>
<td>21.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>New Research Initiatives</td>
<td>5.2</td>
<td>Support for specific investigator-driven projects, pilot initiatives</td>
</tr>
<tr>
<td></td>
<td>Administration</td>
<td>63.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other Research Support</td>
<td>20.5</td>
<td>Non-faculty research personnel and expenses</td>
</tr>
<tr>
<td></td>
<td>Fellowship support</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Foregone F&amp;A Recovery</td>
<td>114.6</td>
<td>Support for foundation and other cancer research grants that do not cover full F &amp; A rate</td>
</tr>
<tr>
<td></td>
<td>Clinical Trials Support and IRO</td>
<td>21.1</td>
<td>Clinical Research Support Office and Institutional Review Office</td>
</tr>
<tr>
<td></td>
<td>New Biomedical Informatics Developing Resource</td>
<td>1.5</td>
<td>Total 4M committed to date; 1.5 expended as of submission for Hutchinson Integrated Data Repository and Archive (HIDRA)</td>
</tr>
<tr>
<td></td>
<td>Uganda Cancer Institute Facility</td>
<td>8.0</td>
<td>Capital investment for Kampala facility; part of FHCRC/UCI collaboration for global oncology research</td>
</tr>
<tr>
<td>UW</td>
<td>Faculty Recruitment</td>
<td>9.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Capital for Biomedical Informatics</td>
<td>75.0</td>
<td>Amalga data warehouse, EMR improvements</td>
</tr>
<tr>
<td>Institution</td>
<td>Resource</td>
<td>Amount Funded (in millions)</td>
<td>Notes</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------------------</td>
<td>----------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Fellowship support</td>
<td>8.0</td>
<td>Oncology related training programs in Hematology-Oncology, Endocrinology, Gastroenterology, Hem/Onc, Infectious Diseases, Internal Medicine, Neurosurgery, Otolaryngology, Pathology, Pediatrics and Pulmonary Medicine</td>
</tr>
<tr>
<td>Oncology Administration</td>
<td></td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td>Clinical Trials Support and IRO</td>
<td></td>
<td>0.8</td>
<td>Combined total annual investment in Consortium Clinical Research Support Office and Institutional Review Office</td>
</tr>
<tr>
<td>Global Health Department</td>
<td></td>
<td>5.0</td>
<td>Annual support, includes Institute for Health Metrics and Evaluation (Global Oncology program)</td>
</tr>
<tr>
<td>Children's</td>
<td>Faculty Recruitment</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Capital</td>
<td>4.0</td>
<td>Cancer research labs/facilities</td>
</tr>
<tr>
<td></td>
<td>Fellowship support</td>
<td>1.3</td>
<td>Pediatric Oncology</td>
</tr>
<tr>
<td>SCCA</td>
<td>Clinical Faculty Support</td>
<td>19.3</td>
<td>Medical Oncology faculty</td>
</tr>
<tr>
<td></td>
<td>Clinical Research Support</td>
<td>0.9</td>
<td>Research pharmacy, research implementation, patient consenting for research, research billing</td>
</tr>
<tr>
<td></td>
<td>High-Risk/Prevention Clinics</td>
<td>0.3</td>
<td>Clinics for cancer screening for high-risk individuals, linked to cancer prevention research studies</td>
</tr>
<tr>
<td></td>
<td>Phase I Clinical Trials Initiative</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Support for Immunotherapy Research</td>
<td>0.3</td>
<td>Includes unfunded clinical trial expenses</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td><strong>579.0</strong></td>
<td></td>
</tr>
</tbody>
</table>
**ADMINISTRATIVE CORE**

**Specific Aims**

The Administrative Core includes Consortium Administration and Senior Leadership. The Specific Aims of this core are to provide:

1. Efficient and cost-effective administrative coordination for the cancer center including support for CCSG grant administration, budget management, communication and coordination across the partners, and other administrative functions to support and optimize the Consortium’s research productivity.

2. Efficient oversight and management of CCSG Shared Resources to assure provision of services of the highest quality.

3. Senior leadership for clinical, basic and population-based cancer research; additional areas that are high strategic priorities of the center, including Solid Tumor Translational Research, Global Oncology, Minority Health and Health Disparities, and Inter-Institutional Initiatives; and Administration.

4. Senior leadership for planning and execution of the cancer center vision; fostering interdisciplinary translational and inter-institutional research of the center; fostering team science and career development; and addressing the health needs of the catchment area through research.

**PART I: CANCER CENTER ADMINISTRATION**

The administrative leaders assure that the Consortium partners (Fred Hutchinson Cancer Research Center, University of Washington, Seattle Children's and Seattle Cancer Care Alliance) plan, coordinate and communicate their activities in a manner that supports Consortium goals and strategies. All of the Consortium partners are well established with large grant bases and have their own administrative staff members who conduct their ongoing business functions.

The goal of Consortium Administration is to provide high quality, efficient and effective support to Cancer Center leaders, programs and members. Administration plays a major role in enabling the Consortium’s scientific leaders to define the center’s vision and strategic goals, implement initiatives, monitor progress in achieving objectives and secure needed resources to develop the requisite infrastructure.

Consortium administrative staff have the responsibility to assure that the following joint cancer center activities are managed in a coordinated and collaborative manner: strategic planning and implementation; program development and evaluation; membership recruitment and review; recruitment support; shared resource development and review; shared resource management; space planning; planning and evaluation; pilot funding initiatives; clinical trials reporting; communication of Consortium activities; data collection and reporting as required by the CCSG; cross-institutional funds flow; grant accounting and expenditure monitoring; and Consortium committee support. The impact of Administration and its development of outstanding partner relationships, despite its modest size, is a testament to its effectiveness and efficiency. High-level praise and support from the Center Director, Senior Leaders, members and Shared Resources are indicators of the impact of Administration.

**Response to Comments in the 2008 Review**

Administration was rated Excellent to Outstanding at our 2008 review. With the support of Senior Leaders and EAB, we have addressed all of the comments of the last site visit team. These include: 1) *There were concerns regarding the readiness of Administration to address potential new administrative institutional barriers posed by program changes, faculty recruitment, new physical facilities and changes in regulatory environment.* Dr. Corey has significantly strengthened collaboration and interaction with the Consortium institutional leaders; he meets monthly with members of the Governance Committee to assure coordination of strategic objectives, progress toward Consortium goals and resource allocation. As a result of this greater integration at the most senior level of leadership, Consortium Administration facilitated: the successful review and restructuring of scientific programs presented in this application; collaborative recruitment of many new faculty, including a new Director of Solid Tumor Translational Research; and establishment of a new clinical research oversight committee that ensures that regulatory frameworks are communicated and coordinated across institutions. Administration has also engaged Beverly Ginsburg-Cooper, a highly experienced cancer center administrator, as a consultant to advise on best practices of complex consortium-type centers. There have been no barriers posed by the
development of new physical space; several new facilities that house cancer-related activities have opened during the project period and house laboratories and other facilities that have provided benefit to the center. These include expansion of the UW South Lake Union site, which has increased collaborative opportunities through its proximity to the FHCRC and Children’s research campuses, and the new Ben Towne Center for Childhood Cancers at Children’s downtown campus in close proximity to FHCRC and UW South Lake Union.

2) There were concerns about inadequacies in clinical and management information systems, particularly incompatibilities across institutions, and in Shared Resources management and reporting. Strengthening information systems has been a major focus during the project period. As described in Developmental Funds, the Consortium has established a developing Biomedical Informatics resource to establish an inter-institutional data warehouse for clinical research. The SCCA has begun expansion of its Cerner electronic medical record for clinical and provider documentation and will launch Computerized Physician Order Entry on October 1, 2014, which will facilitate electronic order sets for all clinical trials. Shared Resources has implemented the iLab system to provide greater efficiency in Shared Resource tracking and reporting, and the Consortium partners have committed to the implementation of a clinical trials management system, with work initiated during the current project period. Importantly, IT leaders from the Consortium partners meet regularly to assure that initiatives and goals are aligned.

Services

Key Services. The team of individuals that make up Administration focus on the following areas of direct service and support: 1) Strategic and programmatic planning; 2) Shared resource planning, oversight and quality performance review; 3) CCSG guideline communication and grant application preparation; 4) Cancer Center budgeting, fiscal management, and expenditure monitoring; 5) Administrative coordination, communication, and integration across Consortium institutions; 6) Membership management and tracking; 7) Member communication and feedback and maintenance of the website; 8) Coordination and management of the EAB and other advisory groups; 9) Management of pilot project programs; 10) Metrics and analytics; 11) Planning, coordination and documentation of seminars, retreats and events; 12) Coordination with CTSA and other inter-institutional projects; 13) Interface with NCI and other external organizations; 14) Support of new initiatives, especially those involving inter-institutional Shared Resources; 15) Management of administrative IT systems (e.g. member and developmental fund tracking databases).

Non-Overlap with Partner Institution Administration. Center Administration responsibilities and duties, as highlighted above, are well defined and, by design, are non-overlapping with the management services and support provided to members as faculty affiliated with partner institutions. The services provided directly by partner institutions may include: space management, lab management, information technology support, purchasing, human resources, grants management, faculty and post-doc recruitment, and faculty promotion and tenure. The well-articulated separation of roles and responsibilities between Consortium administration and institutional administration assures that Center Administration focuses its efforts on adding value to members within the context of CCSG principles.

Administration’s Organizational Structure and Chart

Appendix 1 shows the organizational structure and staffing of Administration. The structure is appropriate and directly relevant to the nature of the Consortium and its environment. Staffing levels are continuously monitored by the Director and Associate Director of Administration to assure that this resource is highly responsive and continues to meet the needs of the Consortium.

Qualifications, Roles and Responsibilities

Associate Director for Administration. The prior Administrator who helped to craft and establish the Consortium, Janet Leeds, left in order to take a senior administrative position within the SCCA. The Consortium appointed Barbara Berg, PhD, MBA who had considerable understanding and knowledge of the Consortium, had played a key role in the development of the 2008 competing renewal application, and was well known by Senior Leadership for her administrative and facilitative skills. Given the maturity and stability of the Consortium administrative structure, Dr. Corey promoted Dr. Berg to a newly created Chief of Staff position within the FHCRC. Dr. Berg’s knowledge and commitment to the Consortium enables her to support Dr. Corey’s dual role of both Center Director and President of FHCRC, thereby enabling the integration of vision, decision making, and resource allocation across the Consortium. Dr. Corey with Dr. Berg’s support, in planning for the transition, recruited Marion Dorer in 2011 to the position of Associate Director for Administration, with the full and enthusiastic support of senior leadership and partner institutions.
Central Administration Staffing and Reporting Lines and Location. Consortium Administration comprises three dedicated FTEs. Marion Dorer serves as the full-time Associate Director for Administration, a position she has held since May 2011. Dr. Dorer holds a PhD in Molecular Biology and conducted cancer-related basic research for 11 years after the awarding of her degree. Although Dr. Dorer held no previous administrative positions prior to her appointment as Consortium Administrator, she was well known to Consortium Administration for her strong communication skills and scientific achievement. To build her experience as a research administrator, Dr. Berg has closely mentored Dr. Dorer, meeting with her formally every week and maintaining daily informal communication. Dr. Berg has closely overseen Dr. Dorer’s management of all CCSG functions. To increase her knowledge of grants management, administration, and the CCSG, Dr. Dorer has attended an NIH seminar on funding and grants, a course for laboratory management at Cold Spring Harbor, and two meetings of the Cancer Center Administrators Forum. Her combined administrative and scientific skills have made her an exceptionally effective AD for Administration; her contributions are highly valued by Director Corey and his leadership team.

Reporting directly to Dr. Dorer is a financial and administrative manager, Ms. Jennifer Jacyszyn, and an administrative assistant, Ms. Danielle Parsons. Each of these individuals is well qualified and has clearly defined roles and responsibilities. The Consortium Administrative team meets weekly and Dr. Dorer meets individually with Ms. Jacyszyn and Ms. Parsons weekly. Dr. Berg meets twice a month with the Administrative team, providing her continued oversight of Consortium operations. Administration occupies 500 square feet at FHCRC in the administrative building, providing them close proximity to the Office of Sponsored Research, IT services, Biomedical Informatics, the Shared Resource Director, clinical trials reporting, and clinical research support services. The Director’s office is a short walk across the FHCRC campus.

Dr. Dorer reports directly to the Center Director, Dr. Corey. They meet formally on a monthly basis. To facilitate efficient planning and decision making, Dr. Dorer has a secondary reporting line to Dr. Berg, with whom she also meets on a weekly basis and serves as a mentor. This relationship has been extremely beneficial to the Consortium and has made the change in administrative leadership seamless. Further mentoring and support, particularly in terms of managing complex consortia, has been provided by Beverly Ginsburg-Cooper, who has served as the EAB administrative reviewer and as consultant on consortia development to Dr. Dorer.

Shared Resource Management. Given the nature of a consortium cancer center, all Shared Resources are physically housed within partner institution space. To be most efficient, the day to day management of space and renovations, equipment acquisition, human resources, budgeting and billing, and other traditional research administrative functions are the responsibility of the institution where the resource resides. Nevertheless, the Consortium plays a very significant role in: setting core policies (e.g., access, fee setting); planning, developing, overseeing, evaluating and terminating cores; promotion of core services; and ensuring member access and satisfaction. All partner institutions agree to abide by CCSG/Consortium Shared Resource policies and expectations before CCSG funding is provided for a particular facility.

Regardless of institutional location of the resource, Dr. Paul Woloshin, Consortium Shared Resource Director, oversees all Consortium-approved core facilities. Dr. Woloshin has over 30 years’ experience in finance, budgeting and scientific resource management both in for-profit and non-profit institutions. He reports to Deputy Director Mark Groudine.

As Center Director, Dr. Corey controls all space of CCSG-funded cores, regardless of location; as such, he retains authority to reduce or terminate support of cores that do not achieve Consortium goals or adhere to CCSG guidelines, with the support of Dr. Woloshin and senior leadership. Importantly, Dr. Woloshin is also Vice President of Shared Resources at FHCRC. As such, he is fully responsible for managing, overseeing and addressing the resource needs of all Shared Resources (CCSG and non-CCSG) at FHCRC. There is no equivalent central leadership within the School of Medicine that oversees or manages core facilities. Instead, cores are managed on a daily basis by the department in which the facility is housed. As a result, Dr. Woloshin is responsible to all institutions and the Consortium for ensuring that any Shared Resource is equally accessible to Consortium members.

Consortium Institutional Liaisons. Given the inherent structure of our center, which has three academic institutions (FHCRC, UW, Children’s) and the SCCA, Dr. Dorer has evolved a highly collaborative and successful Consortium administrative structure that engages and integrates senior administrators from each of the partner institutions into the administrative fabric of the Consortium. The result has been a high degree of support, interaction, collaboration and action by the administrators at partner institutions.
Currently, Barbara Berg serves as the lead administrative representative for FHCRC. As noted above, Dr. Berg previously served as Consortium Administrator and now serves at the FHCRC President’s Chief of Staff. As such, Dr. Berg is well positioned to ensure that Consortium interests are well represented in the decision making processes of FHCRC and that the strategic goals and activities of the Consortium and FHCRC are synergistic.

Mr. Marc Provence has served as the UW Consortium Administrator since the time of its formation in 2002. Reporting directly to Dr. John Slattery, the Consortium Associate Director for Inter-Institutional Initiatives and Vice Dean for Research and Graduate Education in the UW School of Medicine, Mr. Provence is well positioned to work with faculty across clinical and basic science departments and between health sciences schools. In this capacity, he represents the interests of UW in administrative matters, promotes Consortium engagement at UW, facilitates communication of center activities and priorities with UW members, manages all sub-award budgets, and enables access to data on UW members. He participates in key meetings of the Consortium, including visits of the External Advisory Board as well as the Scientific Steering and Institutional Planning committees. Drs. Berg and Dorer and Mr. Provence meet bi-weekly to discuss a wide range of Consortium matters.

Ms. Dedra Schendzielos, Director of Business Operations and Finance, Clinical and Translational Research at Seattle Children’s, serves as Consortium liaison for Seattle Children’s. She meets with Mr. Provence and Dr. Dorer as needed and Dr. Dorer and her staff communicate regularly with Ms. Schendzielos to ensure proper financial reporting and connection to Seattle Children’s members.

**Priority Responsibilities of Administration**

Administration is responsible for fulfilling the requirements of an NCI designated Comprehensive Cancer Center, fostering collaborations and interactions, and achieving the vision and plans of the center. Selected highlights of Administration’s instrumental role in the success and advancement of the center include:

**Support of Planning and Evaluation Mechanisms and Processes.** Consortium Administration assists in the planning, preparation, coordination and documentation of internal and external planning and evaluation processes. This includes supporting the activities described in Planning and Evaluation, such as scheduling, organizing, and documenting planning activities of senior leadership, programs, cores, external advisors, and consultants focused on particular issues; regular evaluation of cores and other CSG initiatives; and tracking and monitoring progress towards strategic goals, development of budgets and management of funds that support strategic initiatives. During the project period, Dr. Dorer has developed an easy yet effective strategic planning tracking grid that enables senior leaders and external advisors to monitor progress in achieving center goals and facilitates multi-year budget and resource planning.

**Management of Pilot Project and New Investigator Fund Allocation.** Administration manages the annual competition for CSG pilot grants, which typically generate 60 or more applications and 5-9 awards. Administration is responsible for widely promoting the availability of pilot project programs to all members, receiving applications, ensuring applicant eligibility, reviewing budget requests, scheduling committee meetings, announcing awardees, and managing budget allocations. Dr. Dorer works directly with the committee chair to identify appropriate reviewers for each cycle and then assigns individual grants to appropriate reviewers. Dr. Dorer also works directly with the Recruitment Subcommittee of the IPC to ensure that the priorities for CSG new investigator funds as determined by Senior Leaders are communicated to the committee, promotes the availability of new investigator funds to appropriate stakeholders, and manages the process for award allocation. Administration tracks publications, external grants, and collaborations resulting from developmental funding using a database developed during the current project period.

**Support of Senior Leadership.** Administration facilitates on-boarding of Consortium of senior leaders, including new members of the Institutional Planning Committee, and meets with new program leaders to define their role and help develop new seminar series and symposia.

**Support of Consortium Committee Meetings.** Administration partners with committee chairs of the Scientific Steering Committee (SSC), responsible for identifying new scientific opportunities and program and shared resource review, and the Institutional Planning Committee (IPC), which oversees planning and evaluation, to identify appropriate topics for committee meetings, develop agendas, invite speakers, inform committee members, record meeting minutes, and ensure progress on follow-up items. Dr. Dorer serves on the IPC and SSC, providing key knowledge of CSG finance, developmental funds, and all CSG business operations.
Support of Planning, Business Management and Evaluation of Shared Resources. As described above, Shared Resources are managed in partnership with FHCRC Vice President for Shared Resources for resources based at the FHCRC and the UW Consortium Administrator for resources based at UW. As the Shared Resource Director, Dr. Woloshin is directly responsible to Senior Leadership for planning and evaluation; compliance with CCSG guidelines; policies and procedures; access; fees and chargebacks; user committees and oversight; quality control; and financial management.

Preparation of the CCSG Applications (Continuing and Competing Renewals and Progress Reports). Administration works with the Director, Senior Leaders, Program Leaders, and others to prepare and submit CCSG applications, including providing support for submission of all CCSG supplements. Staff develop a timeline for completion, provide data and guidance on specific sections, provide program specific data and assist in development of narrative sections by Program Leaders, prepare data tables through coordination with staff from partner institutions, and complete all other necessary components.

Space Allocation and Management. The Consortium Director manages all space at FHCRC and Governance committee members control space at their institutions (see above for exception related to CCSG cores). These institutions are accordingly responsible for developing and executing policies on assignment and retention of space based on institutional polices and metrics.

Management of Administrative IT Systems and Facilitation of the Use of Technology. These activities are managed in partnership with FHCRC IT, although Administration provides oversight and project management for certain IT-related projects – for example, database development to track developmental funds outcomes.

Communications and Fundraising. Each institution has communications and fundraising departments. The leaders of these departments have strong working relationships that enable them to successfully coordinate communications and philanthropic activities that cross institutional lines. For example, the partners collaborated on the recent development and launch of a new Solid Tumor Translational Research web site, and Dr. Corey and Paul Ramsey, Dean of UW School of Medicine, signed a collaborative fundraising agreement in 2012. The Consortium website and listserv are managed by Consortium Administration.

Major Accomplishments During the Project Period

During the current grant cycle, Consortium Administration has made significant improvements to business operations, communication with Consortium members, expanding IT systems for CCSG and Shared Resources, and improving integration with the Institute for Translational Health Sciences (ITHS, the local CTSA). Given space limitations, a selected number are listed below.

- Consolidated disparate communications through creation of a unified, Consortium-wide newsletter that updates members on a range of topics relevant to its members such as Consortium policy updates, funding opportunities, and symposia.
- Redesigned the Consortium Website, which includes a new online membership process and expanded content for investigators conducting clinical trials.
- Created an automated system for member publications management, which has significantly improved the accuracy and timeliness of publications data.
- Designed a new member database, which now houses information on member research interests and CTSA membership. As a result, Administration regularly provides this data to both Cancer Center and CTSA leadership, thereby enabling leaders to identify common interests and potential joint efforts.
- Created a unified site (Sharepoint) that allows distribution of member data to Program Leaders, thereby eliminating manual, paper-based processes. As a result, up-to-date member profiles, grants, and publications are available to program leaders through this centralized, online folder, which is regularly and easily updated by Administration.
- Developed an awards database (Sharepoint) of recipients, level of funding, publications and external grants resulting from all developmental awards, including those via SPOREs and supplemental grants. The improved tracking system has enhanced the ability of Administration to provide Senior Leaders with accurate and timely information on the scientific impact and grant return on investment of CCSG developmental funds.
- Spurred the creation of a dedicated information technology (IT) group in Clinical Research Services, which has completed an overall analysis of clinical research IT needs and assessment for purchase of a clinical trials management system.
- Significantly improved communication, coordination and planning between the Consortium and the local CTSA, including appointment of Dr. Dorer to the CTSA leadership team and appointment of the CTSA director to the IPC.

Management of Center Funds

The total CCSG budget for 2013 was $6,454,558 (direct costs). Each spring, prior to developing the CCSG budget for the next fiscal year, Dr. Dorer meets with the Director and Deputy Directors to review the Consortium’s commitments from the previous year to ensure that performance and expenditure goals have been met and to re-verify that the budget reflects the overall goals of the operating strategic plan. The Director makes final budget allocation decisions. Ad hoc budget requests occur throughout the year; the Director makes the decision on these requests based on senior leadership recommendations.

Administration Budget, Funding and CCSG Request

The current CCSG Administration budget totals $375,206. Administration currently makes up 6% of the overall CCSG budget. 15% of the overall administration budget (projected for next project period) is provided from the institutions (see attached table). In this application, the total requested from the CCSG for the Administration is $348K, which represents 5% of the overall CCSG budget.

Future Plans

In the next project period, Administration will A) work with the Director of Clinical Research Support to ensure effective implementation of the clinical trials management system; strengthen the consistency and coordination of policies and procedures across institutions; and enhance the protocol review process; B) further cement interactions with the CTSA, including development of education programs particularly for clinical investigators; C) collaborate with the AD for Minority Health and Health Disparities to develop programs and processes to increase research in the catchment area and inclusion of minorities in Consortium trials; D) provide planning and evaluation support for leaders of new initiatives and programs, including the new program in Global Oncology, the Biomedical Informatics developing resource and the Precision Oncology Initiative.

PART II: SENIOR LEADERSHIP

Overview

Current Structure. In addition to the Center Director, Dr. Corey, senior leadership includes two Deputy Directors, three scientific Associate Directors (Basic, Population Sciences, Childhood Cancers), four ADs for special areas that are high strategic priorities of the center (Solid Tumor Translational Research, Global Oncology, Minority Health and Health Disparities, Inter-Institutional Initiatives), and an AD for Administration. Deputy Director Fred Appelbaum oversees Clinical Research, so there is no AD for this area.

Response to Site Visitor Critique. Senior Leadership was rated Excellent to Outstanding at the 2008 review. Together, and with the support of our other leaders and EAB, we have addressed all of the criticisms of the last site visit team. These include: 1) concerns regarding the cancer focus of some of the research programs, such as Basic Science. This has been addressed through a rigorous review of each program (internal, and external by EAB), modifications to the program structure, tightening of cancer research aims, more narrow definition of cancer focused research grants, and greater scrutiny of membership. 2) Some programs had low levels of intra-programmatic interaction. It was felt that the senior leaders should provide guidance to these programs and encourage them to consider ways to apply their basic research findings to issues pertinent to the oncologic sciences. This has been a priority under new leadership. Senior leaders and program leaders alike focus on building team science, within programs and across. Program leaders use seminars, retreats, pilot funding, and mentoring among other efforts to foster interaction. Program activities are reviewed internally and by the EAB. Intra-programmatic publications now range from 10% to 32%. 3) Reviewers recommended that program directors be encouraged to use Consortium resources as a means of improving the interactions between researchers with different areas of expertise, including clinical research resources. As evidenced by the high usage of core facilities, excellent response to CCSG and other pilot programs, and high attendance at events, this issue has been addressed. All investigators conducting clinical studies utilize the revamped Research Trials Office, now called Clinical Research Support. In addition, Senior Leaders allocated CCSG pilot funds during the project period to support the inclusion of new Shared Resource technologies into their research. 4) An apparent difficulty in capturing data pertaining to race and ethnicity of clinical trials participants was of some concern to the review committee. Historical issues have been addressed under the new Director of Clinical Research Services; supporting data is in the Clinical Protocol and Data Management section. 5) Lastly, it was
felt that several Shared Resources, while largely of excellent caliber, could have benefited from additional oversight from the leadership group and that this would have eliminated some instances of overlap and poor planning. This issue has also been rectified. Deputy Director Groudine leads an annual shared resource planning and evaluation process. Evidence of effective planning is the progress made in the Developing Biomedical Informatics Resource as well as the successful establishment of several Developing resources initiated during the project period that have matured into established resources.

In addition, at the time of our last renewal application, reviewers felt that Senior Leader roles and responsibilities were diffuse and responsibilities were shared by multiple individuals, with less than optimal oversight of programs, shared resources and clinical trials. Upon his appointment as Director in 2011, Dr. Corey recognized these issues and immediately embarked on an evaluation of the senior leadership structure. As a result, the roles of Senior Leaders were clarified, overlap was removed, and job descriptions were revised to clearly define roles, responsibilities and expectations. Titles were changed as appropriate.

**Selection of Senior Leaders**

Each leader who serves under Dr. Corey was initially selected for their recognized expertise in a particular scientific or operational area, as well as their demonstrated ability to build collaborations across disciplines, be strong advocates for their respective area, and work effectively across institutions. Additional factors included a demonstrated commitment to the values of the CCSG and to the cancer center (e.g., team science, transdisciplinary research, fostering collaborative cancer research, effective use of center resources to support new initiatives, training, including young faculty mentorship, and a commitment to serving the catchment’s needs). While these qualities were requirements, the importance of institutional balance was also recognized and care was taken to assure appropriate institutional representation such that all partners are represented in Dr. Corey’s leadership team. Brief descriptions of each Senior Leader follow; additional information about their roles and qualifications is provided in the Budget Justification and attached biosketches.

Larry Corey, MD, the **Consortium Director**, has ultimate responsibility for the strategic development and performance of the center. He sets the overall vision for the Consortium, including scientific direction and programmatic development, recruitment, and Shared Resources with input from the Governance Committee, the External Advisory Board and his leadership team. He is responsible for fund raising and disbursement of Consortium and CCSG funds; appointment of all senior and program leaders in consultation with his leadership team and the Governance Committee; works closely with his senior and program leadership team in executing his responsibilities; and engages the Governance Committee to ensure ongoing institutional support and balance in all key matters.

Mark Groudine, MD, PhD, has and will continue to serve as a **Deputy Director**. The Deputy Director extends the Office of the Director by serving in place of the Director when there are multiple commitments. Dr. Groudine has led implementation of the overall vision during the project period. He chairs the Institutional Planning Committee (IPC) and is responsible for Shared Resources. He provides executive oversight of Consortium operations by leading program and shared resources reviews in collaboration with the Scientific Steering Committee (SSC) that support decision making by the Director, IPC, and Governance Committee.

To further strengthen executive oversight of key functions, Dr. Corey promoted Dr. Fred Appelbaum to a second **Deputy Director** position. Dr. Appelbaum will be responsible for developmental funds, planning and evaluation, and clinical research. Formerly AD for Clinical Research, Dr. Appelbaum provides day-to-day leadership focus to these high priority areas. Dr. Appelbaum is head of the Hematologic Malignancies program and chairs the Clinical Oncology Oversight Committee, responsible for Consortium wide planning of clinical research activities including recruitment, and the new Clinical Research Oversight Committee, which assures that policies and procedures for clinical research activities are coordinated across the Consortium. He is also PI of a T32 NCI Training Grant in Cancer Biology and Transplantation for physician/scientist fellows.

Pursuant to established policy, should the Director be unable to fulfill his role for an extended period due to illness, termination or another such reason, a Deputy Director would serve in an acting capacity until a new Director or interim Director is appointed by the Governance Committee.

Eric Holland, MD, PhD, was jointly recruited by FHCRC and UW in 2013 and is the **AD for Solid Tumor Translational Research**. Dr. Holland replaces Mac Cheever, MD, who stepped away from this role to lead the NCI Cancer Immunotherapy Trials Network. Dr. Holland defines the need for recruitment, Shared Resources, and other resources that promote the translation of research findings to the clinic, catalyze development of investigator-initiated protocols, support the conduct of trials of the NCI and key external groups, and further
inter-programmatic and inter-institutional interactions for solid tumor research. Dr. Holland will broaden the transdisciplinary composition of solid tumor research groups to include more cancer basic biologists and other clinical subspecialties in established Consortium solid tumor programs and in key developmental areas, including brain, lung, and head and neck cancers. He will provide oversight for Early Phase Clinical Research Support.

John Slattery, PhD, **AD for Inter-Institutional Initiatives**, promotes and supports the development of resources and programs that foster successful interdisciplin ary and inter-institutional research. During the project period, Dr. Slattery has provided executive leadership for the development of Northwest Biotrust, the Consortium’s new shared resource for centralized biospecimen acquisition, and led planning for a process for universal patient consent for participation in research. He will continue to implement these and other resources to facilitate inter-institutional research, such as improved systems for research billing. Dr. Slattery also oversees graduate education at the UW School of Medicine in his role as Vice Dean of Research and Graduate Education. The UW School of Medicine Associate Dean for Translational Research and PI of the local CTSA, Dr. Nora Disis, reports to Dr. Slattery, and as such he provides guidance to the Director regarding opportunities for CTSA-Consortium collaboration.

The **AD for Population Sciences**, Garnet Anderson, PhD, promotes collaboration and interdiscipl inary research in population sciences, determines the need for recruitment and resources in this area, identifies strategic partnerships and grant opportunities, and stimulates transdisciplinary coordination between population scientists and clinical researchers as well as basic scientists. This position was held by Ross Prentice, PhD, who retired in 2011 as Director of Public Health Sciences (PHS) at FHCRC. Dr. Anderson was appointed PHS Director following a national search. She will establish strategic research directions in population sciences, with emphasis on obesity, health economics and cancer outcomes research. She is as a member of the Consortium Membership Subcommittee, charged with approving appointment of new members.

The **AD for Basic Sciences** (Jon Cooper, PhD) is responsible for identifying research opportunities and determining recruitments and resource needs for Basic Sciences, and promoting the integration of basic research with transdisciplinary and translational science to enhance cancer focus. Dr. Cooper been instrumental in restructuring the new Cancer Basic Biology Program to have a sharper cancer focused membership and grant base, and has fostered interaction that underpins several new, translational cancer-focused projects, publications and grants. Dr. Cooper is co-head of the Cancer Basic Biology Program, serves on the Consortium Membership Committee, and is PI of the T32 Chromosome Metabolism and Cancer Training Grant. Dr. Cooper was appointed FHCRC Basic Sciences Division Director and AD in 2010, when Jim Roberts, MD, PhD, stepped down from these roles to devote greater time to his scientific activities.

The **AD for Childhood Cancers** is a new position held by Michael Jensen, MD, who provides strategic leadership in pediatric cancer research, assuring that pediatric cancer research activities are integrated across the Consortium, fully represented in senior leadership, and integrated into strategic planning and resource allocation processes. Seattle Children’s recruited Dr. Jensen, a cancer immunotherapy expert and pediatric oncologist, in 2010 to direct the new Ben Towne Center for Childhood Cancer Research. Dr. Jensen is a co-associate head of the Immunology and Vaccine Development Program.

Reflecting the center’s deep commitment to global oncology, Corey Casper, MD, has been appointed to a new **AD for Global Oncology** position. He is a noted authority in infection-related cancers and leads the center’s collaboration with the Uganda Cancer Institute, and is co-head of the Global Oncology Program presented for the first time in this application. He leads the development of new research, education, and clinical care initiatives in Global Oncology, building upon existing activities and expansion through leadership, organization, recruitment, investment of other resources, and new collaborative opportunities with the UW Institute for Health Metrics and Evaluation. Dr. Casper is PI of NCI D43 Training Grant Building Sustainable Translational Research Teams in HIV-Associated Malignancies.

Beti Thompson, PhD, has been appointed to a new position, **AD for Minority Health and Health Disparities**. This reflects senior leadership’s recognition of its responsibility to assure inclusivity of underserved populations in research and to expand research that addresses the cancer needs of the catchment area. Dr. Thompson will expand and unify these activities across the Consortium, and direct a new Consortium Health Disparities Research Center. Dr. Thompson will also oversee a recently implemented annual pilot award competition specifically targeted toward health disparities research; lead activities to increase inclusion of underserved populations in Consortium studies; advocate for recruitment of minority health researchers; and promote collaborations among the Consortium’s health-disparities researchers and other members.
The Consortium Administrator role has been elevated to **AD for Administration**, held by Marion Dorer, PhD, to recognize the critical leadership this position provides and the support it lends to the Director, senior and program leaders, and members. Dr. Dorer was recruited to fill this expanded role when the prior administrator stepped down to become Dr. Corey’s Chief of Staff. Under the direction of the Consortium Director and in partnership with the senior leaders, she oversees all aspects of Consortium administration, including managing the CCSG budget, coordinating non-competing and competing CCSG grant submissions, interfacing with administrative counterparts at partner institutions, and managing CCSG funds allocations. Her role is described in greater detail in the Administration section above.

**Changes in Senior Leadership from the prior grant period.** To reduce overlap of roles, four AD positions that served as institutional liaisons were eliminated as senior leaders. While several of these individuals remain members of the Institutional Planning Committee due to their continued engagement, position at their home institution or their Consortium role, their prior roles have been assigned to other senior leaders who are responsible for the eight well-defined areas described above. In addition, three Deputy Associate Directors (the chairs and the vice chairs of the SSC) were eliminated as senior leaders. The AD for Clinical Research position was eliminated as this role is now held by Deputy Director Appelbaum, and the AD for Interdisciplinary Research was eliminated.

The net result of these changes is that the total number of senior leader positions was reduced by 1/3 to 11. We believe that the new structure and appointees provide leadership for all important areas, and are consistent with the concerns raised at the last competitive review to eliminate overlap and better define areas of responsibility. The team is strong, stable and highly engaged and interactive, and committed to team science involving all disciplines. And, they have the range of expertise, focus, and advocacy needed to achieve the vision of the center for the decade ahead.

**Senior Leader Roles and Responsibilities**

Under Dr. Corey’s leadership, senior leaders have developed a cohesive leadership model. They work together to establish a vision and implement strategies of high importance to the cancer center’s development. As described above, the Director is responsible for setting the vision for the center and working with his senior leadership team to plan and execute that vision. Two Deputy Directors extend the Office of the Director by serving in place of the Director when there are multiple commitments, and by providing senior day-to-day guidance and oversight to critical CCSG functions.

Associate Directors oversee, integrate and coordinate the Consortium’s scientific agenda, paying special attention to inclusion of multiple disciplines. They oversee specific aspects of Consortium and CCSG activities, such as member participation in shared resource and program review, allocation of developmental funds and leadership of special working groups for strategic initiatives. And, they both represent their institutions and make their institution aware of activities and issues of the Consortium. Individually and collectively, they provide advice to the director from their respective scientific perspective, represent and advocate for their discipline on strategic, programmatic and resource matters, and harmonize inter-institutional balance and needs. Together, they focus on building the cancer research base, fostering team science, building successful research programs and core facilities, energize and engage members in center activities, oversee and lead educational and training opportunities in cancer, and ensure the center meets its obligations to the catchment area through service, outreach and research.

**Senior Leader Activities and Impact**

Individually and collectively, the current group of senior leaders has been highly productive. The group is highly interactive; in addition to regular Institutional Planning Committee meetings, many subgroups or individuals meet on a weekly basis or even daily basis. Collectively, the team provides ongoing advice to the Director; conducts strategic planning and evaluation; appoints and participates in *ad hoc* working groups for new initiatives; helps allocate resources; and addresses other key matters affecting the Consortium and its ability to meet or exceed CCSG requirements.

The strategic priorities of the Consortium have been set and plans have been executed. The table below describes targeted areas and achievements during the project period.
<table>
<thead>
<tr>
<th>Strategy/Priority</th>
<th>Accomplishment</th>
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<tbody>
<tr>
<td>Increase and integrate global oncology research</td>
<td>Established Program formed; strong leadership appointed including new AD position for Global Oncology Institutional investment (~$8M) in new cancer facility in Kampala, Uganda</td>
</tr>
<tr>
<td>Increase cancer focus</td>
<td>Reviewed and modified program goals, as needed. Sought collaborative grants from NCI; renewed 2 SPORES and received new SPORE in breast cancer. Reviewed membership. Made changes as appropriate. Redefined acceptable grants and publications.</td>
</tr>
<tr>
<td>Increase oversight of shared resources</td>
<td>Conducted annual shared resource review and evaluation. Reconfigured the Proteomics resource to include Metabolomics, and Comparative Medicine to include a new Patient Derived Xenograft program; launched biospecimen resource (Northwest BioTrust) – all of which integrate components based at FHCRC and UW thus reflecting strong cross-institutional planning. Launched new developing bioinformatics resource.</td>
</tr>
<tr>
<td>Increase Phase I clinical trial activity</td>
<td>Established Phase I initiative and clinic area in the SCCA, resulting in tripling of phase I enrollment during the project period and six-fold increase in the number of investigator-initiated phase I studies.</td>
</tr>
<tr>
<td>Improve clinical research infrastructure</td>
<td>Appointed seasoned medical director and administrator; increased centralized services; cross-Consortium engagement for CTMS implementation, engaged consultant to optimize clinical research platform.</td>
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<tr>
<td>Increase access to biospecimens</td>
<td>Established Shared Resource (Northwest BioTrust) for centralized biospecimen acquisition; universal patient consent documents have been IRB-approved and pilot-tested in a number of clinics.</td>
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<tr>
<td>Enhance molecular diagnostics</td>
<td>Planning of a major Cancer Precision Medicine initiative has been launched and resources committed.</td>
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<tr>
<td>Build capabilities in biomedical informatics</td>
<td>New leader, Paul Fearn, has been appointed, developing shared resource established.</td>
</tr>
<tr>
<td>Recruit faculty in target areas</td>
<td>Dr. Holland as Solid Tumor Translational Research leader. Dr. Anderson as Population Sciences leader. Dr. Jensen as director of the Ben Towne Center for Pediatric Cancer Research at Seattle Children's. Dr. Stephen Schmechel as leader of the biospecimen resource. Talented scientists in key development areas such as cancer disparities research and health economics.</td>
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<tr>
<td>Use Developmental Funds to build research and collaborations in targeted areas</td>
<td>Pilot projects allocated to cancer prevention, diagnosis and treatment, as well as four areas targeted for development: Global Oncology, collaborative Solid Tumor Translational Research, Health Disparities Research, and application of new shared resource technologies.</td>
</tr>
<tr>
<td>Increase focus on research in catchment areas</td>
<td>Appointed new AD for Minority Health and Health Disparities, who has established new Consortium Health Disparities Research Center. Provide demographic information on the catchment area for members on the Consortium web site.</td>
</tr>
<tr>
<td>Increase accrual of minorities</td>
<td>Created new AD for Minority Health and Health Disparities; will lead accrual of minorities committee. Proposed two Special Populations Staff Investigator positions in this</td>
</tr>
<tr>
<td>Strategy/Priority</td>
<td>Accomplishment</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Maintaining critical review and feedback from</td>
<td>Made changes to membership; requested critical assessments from members.</td>
</tr>
<tr>
<td>EAB</td>
<td></td>
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<tr>
<td>Increase program and shared resource</td>
<td>Administration facilitated three year plans.</td>
</tr>
<tr>
<td>planning</td>
<td></td>
</tr>
<tr>
<td>Increase discretionary funds for priority</td>
<td>Agreement to commence joint fund raising.</td>
</tr>
<tr>
<td>areas</td>
<td></td>
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<tr>
<td>Increase collaboration with CTSA</td>
<td>New liaison to CTSA; appointment of CTSA PI to Institutional Planning</td>
</tr>
<tr>
<td></td>
<td>Committee.</td>
</tr>
<tr>
<td></td>
<td>CTSA has contributed IT support to development of Consortium biospecimen</td>
</tr>
<tr>
<td></td>
<td>resource.</td>
</tr>
<tr>
<td>Increase oversight of training and education</td>
<td>Identification of training as senior leadership responsibility; appointment</td>
</tr>
<tr>
<td></td>
<td>of leaders responsible for training at home institution to senior</td>
</tr>
<tr>
<td></td>
<td>leadership.</td>
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</table>

**Enabling Research Related to the Catchment Area and that Benefits Underserved Populations**

Nearly 70 percent of patients treated at the Seattle Cancer Care Alliance are from the catchment area, defined as the 13 contiguous counties that comprise Western Washington. Cancers with the highest incidence are (in decreasing order) prostate, breast, lung, colorectal and melanoma. With respect to mortality ranking by state, Washington is in the middle; cancers with the highest mortality (in decreasing order) are lung, colorectal, breast, pancreas and prostate. Notably, WA has among the highest incidence of leukemia and non-Hodgkin lymphoma in the United States. There are several cancers for which incidence and mortality in the catchment are greater in minorities compared to whites; for example, the incidence and cancer of prostate cancer is greater in black vs. white males.

Senior leaders have strongly facilitated research on cancers with high incidence (or greater than the national average) in the catchment area, through establishing CCSG programs in Women’s Cancer, Prostate Cancer, and GI Cancer and Hematologic Malignancies, as well as in Cancer Epidemiology, Control and Prevention, which includes major projects on breast, prostate and colorectal cancer, and smoking cessation.

As the individuals responsible for oversight and coordination of the Consortium’s scientific disciplines, senior leaders ensure that the leaders of the programs under their direction are knowledgeable about the problems in the catchment area, and focused on conducting research on cancers of priority to the catchment area or with special populations. Some of these studies are carried out in parts of WA state or the Pacific Northwest outside the catchment area, where there is sufficient population to conduct research, yielding findings that can then be applied to the catchment area.

Specific research areas facilitated through recruitment and allocation of CCSG and institutional resources include: genomic studies of prostate cancer risk, including in men of African descent; targeted smoking cessation and lung cancer prevention research using culturally-appropriate interventions among Native Alaskan populations in Eskimo villages in Alaska, and among American Indian youth; development of cord-blood transplantation for hematologic malignancies, making transplantation more feasible for ethnic minorities or those of mixed-race ancestry who lack tissue-matched donors; and novel immunotherapies for non-Hodgkin lymphoma.

While there is no formal CCSG program for lung cancer, a disease with higher incidence in Blacks and Native Americans in WA State, senior leaders have focused on augmenting research in this area. For example, Dr. Holland has identified lung cancer as one of several solid tumor translational research areas to be strengthened during the new project period using CCSG and institutional funds, with the goal of submitting a SPORE application during the project period and potential CCSG program development. In addition, Consortium investigator Jonathan Bricker leads an NCI-funded smoking cessation study that was catalyzed with CCSG developmental funds. Several new Consortium members who work on lung cancer were recruited during the project period, including one with CCSG new investigator funds (Laura Chow, MD.)
Dr. Corey has made the inclusion of underrepresented minorities in the catchment area in Consortium research a strategic priority and has appointed Dr. Thompson to oversee this effort through leadership of a new Consortium Health Disparities Research Center. This center's strategic plan includes a committee to increase minority accrual to clinical trials. In addition, senior leaders have proposed two Staff Investigators for Special Populations (Hannah Linden and Jason Mendoza, from UW and Children's, respectively) to stimulate new research activities in this area across the Consortium, and allocated developmental funds for pilot projects targeted at increasing inclusion of minorities in research. Senior leaders also awarded CCSG new investigator funds to two health disparities investigators, including Dr. Rachel Ceballo, who is conducting an assessment of gaps and successes in the provision of information or services to African-American breast cancer survivors in the Seattle area. Senior leaders also work together to ensure that faculty recruitment committees and trainee programs make efforts to recruit from historically underrepresented racial and ethnic groups.

Senior leaders have assured that inclusivity of minorities has been included as a criterion in review of protocols in the Protocol Review and Monitoring System. In addition, Sea Mar Community Health Centers, Washington's largest community health provider to Latino patients has been made an outreach affiliate of the Seattle Cancer Care Alliance Network during the project period. Language and other cultural barriers have been mitigated with Sea Mar providers as intermediaries.

**Integrating Training, Including Those from Minority and Other Underserved Populations, into Programmatic Research Efforts**

Senior leaders work together to support a strong training and educational environment. Five senior leaders (Appelbaum, Cooper, Casper, Slattery, Thompson) are PIs of NIH-funded training grants and/or have leadership responsibilities for education and training at their home institutions. While institutional departments and divisions have primary responsibility for overseeing development of their faculty, Consortium senior leaders are dedicated to mentorship in cancer research and thus provide opportunities for career development within the center structure. Specific concerns about an individual member’s academic progress are discussed and individualized mentorship efforts are developed. In addition, particularly through Dr. Corey’s and Dr. Anderson’s expertise in leading large-scale multi-institutional trials, senior leaders promote team science in training and seek opportunities for collaborative research. For example, during the project period, they have committed institutional support for training activities associated with SPORE programs and strongly encourage members to apply for large collaborative grants, such as the Genetics and Epidemiology of Colorectal Cancer Consortium (based at FHCRC) and an ENcyclopedia Of DNA Elements (ENCODE) center (based at UW).

As described in the Transdisciplinary Coordination and Organizational Capabilities sections, the Consortium has a large number of programs for training biomedical scientists and health care professionals. As a group, senior leaders have supported the development of the highest quality educational opportunities for health professionals and create opportunities for scientists from underserved populations through such programs as the U54 Partnership for the Advancement of Research program led by Dr. Beti Thompson, which is a partnership with New Mexico State University, and a Contining Umbrella of Research Excellence (CURE) CCSG supplement to support undergraduate internships to enhance diversity in cancer and cancer health disparities research. Senior leaders have committed institutional funds to increase the number of internship slots, and leaders actively encourage Consortium members to participate in the program. Drs. Slattery and Dorer have also been responsible for improving coordination and collaboration with the local CTSA, which supports numerous training and educational activities for translational science; this collaboration has been facilitated by the recent appointment of a Consortium administrator to the ITHS Educational Committee. In response to perceived gaps in training and mentorship, the senior leaders have promoted several new activities during the project period. Recent examples include a new program through which senior faculty provide intensive grant writing mentorship for new and junior faculty; a new educational program in biostatistics for clinical scientists and fellows; and, with the ITHS, a seminar on tools and technologies for biostatistics, bioinformatics, and data visualization. In addition, Research Program leaders are expected to encourage trainees to present in programmatic seminars and in national meetings. Other senior leader activities include the creation of new fellowship programs, such as an Immunotherapy Fellows Program established during the project period with institutional funds.
PLANNING AND EVALUATION

Overview and Specific Aims

Dr. Corey sets the overarching vision for the center. To accomplish this he engages internal and external leaders, committees and individuals to help chart the future directions, plans and strategic investments for the center. Planning is achieved through both formal and informal mechanisms. The same approach is applied to evaluation, so that leadership can assess how effectively it is achieving the center’s goals and determine whether mid-course changes are needed. This planning and evaluation process has led to timely and successful implementation of new strategies and changes in the organization and direction of cancer research conducted at the Consortium.

The Specific Aims of Planning and Evaluation are to:

1. Provide an effective structure that engages all Consortium partners in planning and evaluation activities such that institutional objectives are well aligned with common Consortium cancer research objectives.

2. Support and maximize the value of internal and external Consortium mechanisms (internal committees and external advisors) to identify areas of greatest strategic importance to the Consortium and their associated resource requirements, and dedicate sufficient leadership and institutional and CCSG funds to achieve measurable success.

3. Provide structure for ongoing evaluation of progress toward Consortium objectives. Major areas of emphasis during the new project period are to further develop solid tumor translational research; improve coordination and consistency of clinical trials support across the center; build biomedical informatics capabilities; expand research in the catchment area and with underserved populations; and build research capacity in cancer health economics, global oncology and obesity.

4. Engage Consortium members in identifying new areas of scientific opportunity, through provision of CCSG and other funds to support scientific symposia and workshops on emerging research areas.

As seen below and in other sections, such as Organization Capabilities, internal planning and evaluation involves, but is not limited to: the Director and Governance Committee Members who lead each partner institution; Senior Leaders who represent all scientific and programmatic priorities of the center; Research Program Leaders who reflect both the interests of their members and the future directions in their scientific field; Shared Resource leaders who strive to bring innovations in their field to member researchers; and members from all institutions and disciplines. Other contributors include department chairs, the CTSA director and those with responsibilities that directly affect the center’s mission and the strategic ability to advance cancer research. The center also relies heavily on a highly experienced External Advisory Board and ad hoc advisors. Receiving external guidance and responding to feedback is a major priority.

The Consortium has been successful in leveraging planning and evaluation into progress during the project period. The following are examples of accomplishments resulting from planning in a number of strategic areas, including scientific program development, new Shared Resources and services, and the use of non-CCSG funded resources to foster successful translational research.

- Development and launch of a robust Phase I clinical trials initiative, which has nearly tripled Phase I patient enrollment over the project period;
- Opening of a centralized biospecimen acquisition and distribution resource, Northwest BioTrust, which was planned during the current project period with CCSG Developmental and institutional funds and is now presented in this application as an Established Shared Resource;
- Expansion of the center’s portfolio of global oncology research including a robust partnership with the Uganda Cancer Institute for infection-related cancer research, resulting in the inclusion of a dedicated Program in Global Oncology in this application;
- Expansion of a cellular immunotherapy program, which, in turn, has led to the formation of a new Seattle company to accelerate the translation of Consortium research into clinical application;
- Development of a biomedical informatics plan with implementation underway under a recently recruited bioinformatics director, Paul Fearn, presented as a Developing Shared Resource in this application;
- Development of a new Consortium Health Disparities Research Center, and appointment of a new Associate Director of Minority Health and Health Disparities Research, Beti Thompson, to increase inclusion of minorities in research and research in the catchment area;
• Development and implementation of a plan to enhance clinical research services and support, which has already resulted in the appointment of new leadership and changes in process and resources (see Clinical Protocol and Data Monitoring Section, and below);
• Initiation of a new Precision Medicine (cancer molecular diagnostics) initiative;
• Targeted recruitments, including a new Director of Solid Tumor Translational Research, Eric Holland;
• Restructuring of several Research Programs to maximize cancer focus and translational research opportunities.

Several of these activities are described in more detail below.

Administration has provided support for all of these activities, contributing the essential staff support, organization, and data. As a result, scientific leadership has ably moved strategies forward by successfully implementing initiatives, wisely targeting resources and effort, and regularly monitoring progress over time.

Changes in Planning and Evaluation Mechanisms over the Project Period

Planning and Evaluation was rated Excellent to Outstanding by the 2008 reviewers, with no specific comments for improvement. However, Consortium leaders have devoted attention to achieving a higher level of internal engagement, as well as changes in the composition and impact of the EAB during the current project period. As a result, there has been an increase in the pace of strategic accomplishments since Dr. Corey’s appointment. While there has been considerable success in this regard, we continue to make refinements. Over the past year, for example, we introduced a new three-year planning tool that has been particularly effective for new programs, cores, administration, and other groups. The tool aids such groups in identifying their specific strategies and tactics, enable groups to monitor their progress more effectively over time, and determine resource needs. This tool was particularly effective in planning for the scientific strategic objectives outlined in the Director’s Overview, resulting for example in plans to allocate CCSG funds for targeted pilot projects in health disparities research and targeted Early Phase Clinical Research Support to stimulate further solid tumor translational research. Administration helps support this process. Copies of EAB reports and planning documents will be available at the site visit.

External Planning and Evaluation

The External Advisory Board (EAB) provides external critical advice on future directions and progress. The Consortium’s EAB is comprised of cancer investigators whose expertise spans the basic, translational, population and clinical sciences as well as cancer center administration.

Committee composition. A number of EAB members have had significant tenure on the committee and therefore have valuable insight into the Consortium’s progress over time. Membership is evaluated each year to ensure that there is sufficient expertise in areas of new development as well as a balance between new and long-standing members. Among the current EAB members who have been appointed by Dr. Corey are Drs. Nancy Davidson, Brian Druker and Tom Sellers, who provide valuable perspective as seasoned cancer center directors to a new cancer center director while, at the same time, contributing their scientific expertise in solid tumor cancers, translational research and population research, respectively. Other new members include: Dr. Harold Sox, an expert on health economics and comparative effectiveness, which is one of the Consortium’s scientific objectives for the new project period; and Beverly Ginsburg-Cooper, who brings valuable perspective from her role as a senior administrator for a large and complex consortium-type center. The table below lists current EAB members and their credentials.

<table>
<thead>
<tr>
<th>Consortium External Advisory Board</th>
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<tbody>
<tr>
<td><strong>John Minna, MD (CHAIR)</strong></td>
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<tr>
<td>Director, Hamon Center for Therapeutic Oncology Research</td>
</tr>
<tr>
<td>University of Texas Southwestern Medical Center</td>
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<tr>
<td><strong>Philip Beachy, PhD</strong></td>
</tr>
<tr>
<td>Professor of Developmental Biology</td>
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<tr>
<td>Howard Hughes Medical Institute</td>
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<tr>
<td>Stanford University School of Medicine</td>
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<tr>
<td><strong>Garrett Brodeur, MD</strong></td>
</tr>
<tr>
<td>Professor of Pediatrics; Associate Chair for Research</td>
</tr>
<tr>
<td>Associate Director, Abramson Cancer Center</td>
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<tr>
<td>The Children’s Hospital of Philadelphia</td>
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</table>
**Process.** The EAB formally meets for one day once a year followed by an informal dinner. There have been four EAB meetings since 2009 at the time of this submission (there will be a fifth meeting in April 2014). Individual EAB members may be called upon during the year to provide additional guidance. The annual agenda for EAB meetings typically includes the director’s overview of scientific and institutional accomplishments, followed by focused sessions on one or more thematic areas in which the EAB’s counsel is sought. Written EAB reports (available at site visit) are reviewed by the Director and Senior Leaders and a course for action is implemented.

**EAB recommendations and actions.** EAB comments have been highly laudatory during the project period. In particular, the EAB has noted the considerable progress made in achieving the organizational and scientific goals of the center. In recent years, clinical research support services, global oncology, health economics and biomedical informatics were among the topics discussed. The EAB has also provided valuable guidance on our scientific development and evolution and has reviewed and approved the programmatic structure presented in this application. In addition, the EAB has counseled senior leaders on scientific areas in which the Consortium is well poised to make major contributions or areas in need of development.

EAB recommendations are highly influential and all of its major recommendations have been addressed. Key recommendations and actions taken are summarized below.

<table>
<thead>
<tr>
<th>Year</th>
<th>EAB Recommendation</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>• Expand global oncology research.</td>
<td>• Conducted assessment of global oncology program “readiness,” new program is presented in this application.</td>
</tr>
<tr>
<td></td>
<td>• Consider developing a comparative effectiveness research as program.</td>
<td>• Dr. Corey created Hutchinson Institute for Cancer Outcomes Research; recruited new faculty.</td>
</tr>
<tr>
<td></td>
<td>• Continue to invest in cancer immunotherapy.</td>
<td>• Raised &gt;$20M in philanthropic funds for immunotherapy and launched new Seattle company for cellular therapy.</td>
</tr>
<tr>
<td></td>
<td>• Articulate a plan for biomedical informatics.</td>
<td>• Hired new biomedical informatics leader; appointed special advisory board; new developing resource proposed in this application.</td>
</tr>
<tr>
<td>2011</td>
<td>• Support health disparities efforts.</td>
<td>• Established a new Health Disparities Research Center; appointed an Associate Director for</td>
</tr>
<tr>
<td>Year</td>
<td>EAB Recommendation</td>
<td>Response</td>
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<td></td>
<td>• Develop a Precision Oncology (molecular diagnostics) program.</td>
<td>Minority Health and Health Disparities, Dr. Beti Thompson; allocated pilot funds to health disparities research.</td>
</tr>
<tr>
<td>2012</td>
<td>• Recommended changes in program structure for 2014 competing renewal.</td>
<td>• Merged Transplantation Biology and Clinical Transplantation; merged Epidemiology and Cancer Prevention; eliminated Genome Instability and Stem Cell programs and realigned cancer relevant members into relevant programs; formed Cancer Basic Biology Program with increased cancer focus; eliminated Cancer Imaging program and realigned members into programs where they have natural alliances; launched new Global Oncology program; more prominently feature computational science in renamed Biostatistics and Computational Biology Program.</td>
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<tr>
<td>2013</td>
<td>• Further refinement of program structure and strategy for competing renewal (all programs presented to the EAB for review). • Increase oversight of clinical trials and implement clinical trials management system.</td>
<td>• As above. • Appointed new clinical research oversight committee that reports to the Director to oversee clinical trials. • Engaged consultant to advise on best practices for clinical research support. • Begun evaluation of clinical trials management system vendors.</td>
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*Ad hoc* external advisory committees that provide expert advice for specific initiatives. For major initiatives in highly specialized areas, the center has utilized external committees of nationally recognized figures with specialized expertise. For example, to seek expert guidance on the Biomedical Informatics developing resource (see Developmental Funds), Drs. Corey and Paul Fearn, the Biomedical Informatics Director, created an external advisory committee. Chaired by Dr. Warren Kibbe, formerly the leader of informatics at Northwestern University and now Director of the NCI Center for Biomedical Informatics and Information Technology, the committee includes national informatics experts Drs. Andrew Winter (Northwestern), Sorena Nadaf (University of California at San Francisco), and Dan Masys (University of Washington). CCSG funds partially supported the committee’s first planning meeting in September 2013. The committee has agreed to meet annually so that it can evaluate progress toward objectives and ensure that the project incorporates best practices. Copies of their first report will be available at the site visit.

The Consortium has used other advisors to provide counsel or evaluate specific issues, such as those noted in the last CCSG renewal or raised by our EAB. For example:

- In 2010, a former cancer center administrator, James Lynch, reviewed the Consortium’s clinical research support activities and made recommendations that were subsequently adopted, including increasing the level of effort for the Medical Director, appointment of a new senior administrator and consolidation of several previously disparate functions under this individual.
- Since 2012, Beverly Ginsburg-Cooper, now an EAB member, has been engaged to provide ongoing advice and assistance to senior leadership and Administration on CCSG guideline changes, planning and evaluation strategies, and clinical research support improvement. Her advice has been helpful as leaders assume new roles within the Cancer Center.
- In 2011, external advice was sought on the search for the new director of FHCRC’s Public Health Sciences, Division, who also serves as Consortium Associate Director for Population Sciences. Leaders in the field, including Dr. Harvey Fineberg, President of the Institute of Medicine, were invited.
to participate in three discussion forums with Consortium faculty and senior leaders on future opportunities in population sciences in order to inform the search process, which was conducted by an inter-institutional committee.

**Internal Planning and Evaluation Mechanisms**

Dr. Corey sets the scientific vision for the center and uses his leadership skills to create an inclusive and interactive environment in which creative planning, rigorous evaluation and targeted investments occur. Through his leadership, senior leaders have developed a shared vision, collaborative resource and program development, and resource commitment strategy.

Senior leaders are jointly responsible for identifying opportunities for growth and development of new investigative areas and resource requirements, as well as for identifying deficiencies that represent barriers to the cancer center’s strategic objectives. Dr. Corey and the senior leadership team rely on counsel from the External Advisory Board (EAB), which is valued for its candid evaluation of the Consortium’s ongoing activities and proposed new initiatives. Importantly, senior leaders share ultimate responsibility for building the cancer focus of the center, further integrating the Consortium structure, providing an exciting and productive forum for researchers of all disciplines to conduct transdisciplinary, translational team science, and ensuring that the resources of the center are used for maximum advantage to the growth and development of center and member cancer research.

Interdisciplinary, inter-institutional internal committees charged with planning and evaluation. The Institutional Planning Committee (IPC) is formally charged with center-wide Planning and Evaluation. During the project period, the strategic priorities for the center were identified by IPC; feedback was actively solicited from the External Advisory Board; and working groups were developed and implemented specific plans. The IPC oversees progress of initiatives and the overall effectiveness of the planning process. Specific topics addressed by the IPC during the project period included biospecimen banking, research program structure, and clinical trials issues including the need for a clinical trials management system, for example. Specific examples and outcomes of this process are described later in the section. The IPC formally meets as a group quarterly, however subgroups related to specific initiatives often meet more frequently. In addition to the Senior Leaders, the IPC also includes additional representatives to ensure appropriate institutional balance and effective communication. One IPC meeting each year is held jointly with the Clinical Oncology Oversight Committee (a subcommittee of the IPC that oversees clinical research planning across the Consortium). More detail on the structure and operations of the IPC, and other Consortium committees, is described in the Organizational Capabilities section, and minutes and membership rosters will be available at the site visit.

Directly after the CCSG renewal in 2008, the IPC launched a review of strategic directions for the new project period, and also assessed actions needed to respond to site visitor comments. Following his appointment as President of FHCRC and Consortium Director in 2011, Dr. Corey worked with the senior leaders and trustees at FHCRC, and with leaders of Consortium partner institutions, to review scientific priorities of FHCRC and the Consortium. The changes and adjustments of many of the programs outlined in this proposal are a direct result of these processes. Strategic objectives since Dr. Corey’s appointment were approved by the IPC in 2013 and are summarized in the Director’s Overview. Highlights of strategic accomplishments resulting from these planning activities are presented later in this section and in other sections of this proposal. The center’s planning documents will be available at the site visit.

The IPC sets the priorities for the allocation of CCSG Developmental Funds based on the strategic objectives of the project period. In the current project period, areas of allocation included solid tumor translational research, global oncology, new technology/shared resource applications, health disparities research, and new resources for computational biology and centralized biospecimen collection. Recipients of CCSG Developmental Funds (pilot projects and new investigator awards) are contacted each year by Administration regarding their scientific progress and outcomes. The information gathered is reviewed by the IPC near the end of the budget year; funding priorities may be redirected depending on overall progress toward achievement of strategic objectives or new opportunities that emerge. EAB comments and suggestions regarding future directions directly affect decisions regarding future Developmental Fund priorities.

The Scientific Steering Committee (SSC) contributes to the planning and evaluation process by conducting formal reviews of both Research Programs and Shared Resources. The SSC meets monthly and includes representation from all research programs and institutions; meeting minutes and membership roster will be available at the site visit. Chaired by Drs. Pete Nelson and Johanna Lampe, the SSC oversees internal
planning and conducts mid-grant-cycle evaluation of NCI-approved Established Programs; monitors burgeoning programs that may be considered for the next CCSG renewal; identifies the need for new core facilities and scientific infrastructure; annually reviews each CCSG Shared Resource; recommends changes in core facilities (expansion of services, termination); and advises on strategic scientific areas that should be considered for Developmental Funds. For example, the SSC recommended several of the targeted pilot project competitions described above.

SSC meetings also include presentations from Developmental Fund awardees, and from leaders of scientific initiatives in order to stimulate potential collaborative opportunities. For example, Dr. Mac Cheever presented on the NCI Cancer Immunotherapy Trials Network, which he directs, which has led to new collaborative clinical trials with Consortium members for Merkel cell carcinoma. The SSC also has responsibility for soliciting input from its members about themes and topics for potential scientific symposia. Center-wide symposia have a critical function in planning and evaluation. They serve as interactive forums for engaging leaders, members and external experts in assessing the strength of the scientific efforts at the center and in facilitating interest and interaction on planned or potential scientific areas. In addition to featuring internal faculty at symposia, there are presentations from, and discussion with, external experts. Attendance at Consortium-sponsored conferences is typically very high, reflecting the effectiveness of the SSC in selecting topics and speakers. A few recent symposia, including several (denoted with *) supported using CCSG funds, are:

- Exploring Opportunities to Extend the Application of Molecular Diagnostics to Cancer Care
- Small Nucleic Acids in Biology and Disease*
- Long Term Effects of Cancer Treatment: Surveillance, Mechanisms, and Interventions*
- Metabolism and Cancer*
- Improving the Health And Well-Being of Latinas: Tools for Public Health and Service Providers
- Will Genomics Revolutionize Cancer Therapy?*
- Aging at the Hutch*

Activities that inform and foster enhanced CCSG planning and evaluation. Senior Leaders and Administration regularly attend national meetings where they interact with other cancer center directors and administrators. They gain invaluable insight into best practices at NCI-designated Comprehensive Cancer Centers and incorporate these into their planning. These meetings include the American Association of Cancer Institutes and Cancer Center Administrators Forum. Of particularly value were meetings that included discussions of consortia-type centers, CTSA-CCSG interactions and clinical research support. Internally, planning and evaluation is informed by input from members, such as through Shared Resource surveys.

**Consortium Planning and Evaluation Governance**

**Consortium agreement.** All of the Consortium partners have signed a memorandum of understanding committing to a shared vision, joint planning and institutional support for the Cancer Center. A copy of this document will be available at the site visit.

**Inter-Institutional Planning and Support.** While a formal agreement among the partner institutions has been in place since the Consortium’s founding, personal relationships, collaboration, and joint planning have evolved significantly under Dr. Corey. It is noteworthy that Dr. Corey meets personally with the leaders of each partner institution at least monthly, and this has undoubtedly led to greater institutional understanding, engagement and proactive support for center initiatives. Such meetings have provided sufficient confidential time to address issues and concerns of partner institutions at the highest levels. They have also ensured that the vision and plans of the center are supported by the institutional leadership but is also bilateral, meaning that the center’s efforts support the goals of the institutional partner and the goals of the center will be helped by the commitment, energy, resources, and strategies of individual partner institutions. Under Dr. Corey the Consortium relationship has further been cemented, and institutional lines are not impediments.

**Accomplishments**

The strongest evidence of the Consortium’s planning and evaluation mechanisms is the number of successful accomplishments from the project period. Examples include:

**Development of a phase I clinical trials initiative.** During the latter part of the prior project period, the EAB recommended the development of a Phase I Clinical Trials Initiative. Dr. John Thompson, a UW-based melanoma medical oncologist with expertise in early phase trials, was asked to lead this effort. He formed a working group to oversee planning, and Dr. Mac Cheever, the prior Associate Director for Solid Tumor
Research (he has since stepped down to lead the NCI Cancer Immunotherapy Trials Network), served as the IPC representative/Senior Leader for this effort. The working group engaged an outside strategic advisor to assist its planning activities and Drs. Cheever and Thompson secured $2.2M in grant funding from WA State’s Life Sciences Discovery Fund; developed a sustainability plan to ensure the program’s durability beyond the grant funding period; and conducted a successful pilot project program to stimulate investigator-initiated trials. The SCCA also provided more than $1M in funding as well as space and facilities for a dedicated Phase I Clinical Unit which was opened in 2010 to support the initiative’s growth.

The Phase I initiative is open to and has participation from all disease groups and established CCSG disease programs. It provides experienced research support for conducting phase I studies, and, through two standing meetings each month, provides a forum for discussion and prioritization of new Phase I trial opportunities. During the project period, the total number of Consortium phase I trials has increased from 50 to 88, and the number of investigator-initiated phase I trials has increased from 2 to 13. Patient enrollment onto phase I therapeutic studies has nearly tripled, from 96 to 282.

Recruitment of a new Solid Tumor Translational Research director. Senior Leaders successfully recruited Eric Holland, a neurosurgeon and lab-based brain tumor researcher from Memorial-Sloan Kettering, following a national search led by Deputy Director Groudine and including broad representation and input from FHCRC- and UW-based members. Dr. Holland is fully integrated into the Consortium’s leadership and leads solid tumor translational research across the center. He has leadership appointments at both FHCRC and UW and leadership of a cross-institutional solid tumor translational research effort, and is the Consortium Associate Director of Solid Tumor Translational Research. He has also received significant institutional support from FHCRC and UW for additional faculty recruitment (6 lab based positions at FHCRC and 4 endowed chairs at UW) and research support to ensure his success. One of Dr. Holland’s first objectives has been to assess existing interdisciplinary, collaborative organ-specific research teams and to investigate methods to further strengthen them. In his relatively short tenure here, he and his team have conducted an extensive survey to identify existing strengths and gaps as a first step in strategic plan development (these activities are further described below in Future Plans).

Opening of a Consortium-wide adult biospecimen acquisition and distribution resource. The IPC appointed Drs. John Slattery (UW, and Consortium AD for Inter-Institutional Initiatives) and Peggy Porter (FHCRC, co-head of the Women’s Cancer Program and a pathologist who has established a successful breast biospecimen repository) to develop a plan for a centralized resource for biospecimen collection and distribution, called Northwest BioTrust. Drs. Slattery and Porter formed an inter-institutional working group that developed a plan to streamline our system and allow for: Web-based queries of existing biospecimen holdings; uniform consent of patients for contribution of research biospecimens; centralized collection of discarded clinical care biospecimens for use in research; and centralized prospective biospecimen collection for research studies. Drs. Slattery and Porter were successful in obtaining two grants totalling $6.75M from the WA State Life Sciences Discovery Fund for the initial phase of the resource’s development and implementation. A multi-disciplinary, inter-institutional governance committee has been created and includes representation from IPC members (Drs. Slattery and Holland). CCSG Developmental Funds were used to support the repository’s development. The resource is now operational and is proposed as an established Shared Resource in this application. To provide leadership for Northwest BioTrust, Stephen Schmechel was recruited from the University of Minnesota, where he led a successful biospecimen repository, with UW institutional and CCSG Developmental Funds.

Formation of a Program in Global Oncology. In 2010, Dr. Corey presented an overview of the Consortium’s global oncology research portfolio to the EAB, which encouraged Senior Leaders to develop a program in global oncology for the 2014 CCSG competing renewal application. Following his appointment as Consortium Director, Dr. Corey appointed Corey Casper (FHCRC), who leads the FHCRC’s infection related cancers collaboration with the Uganda Cancer Institute, and Chris Murray (UW), the Director of the Institute for Health Metrics and Evaluation and leader of the Global Burden of Disease Study, to assess member interests, create an inventory of ongoing and planned global oncology research projects, and identify scientific aims. These activities, which occurred through planning sessions including lab-based faculty, epidemiologists, and disease surveillance experts, identified potential areas for collaboration in the new program. The result has been the formation of a Global Oncology program, which is one of the few (perhaps only) such programs among NCI Comprehensive Cancer Centers and is presented in this application. The IPC will be responsible for evaluating the program’s progress toward goals. The program’s strategic plan will be made available at the site visit.
Restructuring of Research Programs. Dr. Corey and the senior leaders, with the advice and endorsement of the EAB, devoted significant effort to evaluating the CCSG program structure during the project period. In addition to the decision to present a new CCSG program in Global Oncology, several changes have resulted from these planning and evaluation activities such that we present in this application nine CCSG programs that most strongly support natural collaborations and promote new ones, minimize overlap of scientific aims and maximize cancer focus. The changes result from review and discussion by senior leaders of the 2008 CCSG reviewer comments, an internal program review process led by Deputy Director Groudine and Consortium Administration with the Scientific Steering Committee (all program heads were required to present to the SSC and address reviewer comments), presentation of SSC recommendations to IPC, discussion with research program leaders, and input from the EAB at the 2012 and 2013 meetings. These changes can be summarized as follows and are described further in the relevant program sections:

- Reflecting the extensive collaboration and synergy of goals in the Clinical Transplantation and Transplantation Biology programs, these have been melded into a new Hematologic Malignancies program. The new program also includes selected members of the former Stem and Progenitor Cell Biology Program who have natural alliances and collaborations.

- Similarly, the programs in Cancer Prevention and Epidemiology have been melded into the Cancer Epidemiology, Prevention and Control Program to better take advantage of the existing strong intraprogammatic interactions and to address reviewer comments about overlapping goals.

- The Cancer Basic Biology Program (CBB) is a reorganized Program created by merging portions of the previous programs in Basic Sciences, Genome Instability and Mutagenesis, and Stem and Progenitor Cell Biology, together with new faculty recruitment. CBB was created to provide a sharper focus on basic and translational cancer biology, and to advance inter-institutional collaboration in basic research relevant to cancer. Concerns (2008 review) about low intra-programmatic interactions have been addressed; the restructured program has greater than 10 percent intra- and inter-institutional collaborative publications.

- The Cancer Imaging Program has been eliminated as a separate program and, instead, most members are listed in those programs where they have active research activities. This restructuring was prompted by the departure of a prior program leader as well as a need to further expand our imaging research portfolio. Cancer imaging remains a major priority of the Consortium, and will now undergo a formal review. This review will be led by Drs. Appelbaum and Holland, Nina Mayr (the recently recruited chair of the UW Dept. of Radiation Oncology) and Norman Beauchamp (Chair of the UW Dept. of Radiology). We anticipate increased investment in this area, including CCSG Early Phase Clinical Research Support funds. In the meantime, Center leaders are facilitating more active engagement of imaging researchers in multidisciplinary research, and working to create new collaborations among imaging and radiation researchers.

Strengthening of cellular immunotherapy research activities. Cellular immunotherapy has long been an area of strength of the Consortium and members have developed novel methods for adoptive T-cell therapy. There are substantial resource requirements required to move these therapies from the laboratory through the translational pipeline, including the need for GMP-grade reagent manufacturing and regulatory support. The IPC appointed Stan Riddell, co-associate program head of the Immunology and Vaccine Development Program, to chair a working group to identify resource needs and, following a successful fundraising effort that garnered more than $20M during the project period, a plan to develop or augment existing shared resources to support successful clinical translation. During the project period this working group successfully orchestrated the development of new cores for process development and vector production, regulatory support and clinical trials support, as well as a new fellowship program for training junior immunotherapy investigators. Dr. Appelbaum also serves as an immunotherapy working group member, ensuring the IPC is apprised of progress and obstacles. In 2013, FHCRC led the development of a new Seattle company, Juno Therapeutics, Inc., which will accelerate the translation of Consortium adoptive T cell therapy technology to clinical practice. Memorial Sloan-Kettering Cancer Center is a partner in this venture.

Development of a biomedical informatics resource. At the time of the last CCSG application, Consortium leaders were encouraged to devote effort to develop a robust biomedical informatics resource to support translational research. This recommendation was strongly supported by the Consortium EAB. Under Dr. Corey’s leadership, an outstanding bioinformatics leader, Paul Fearn, was appointed to lead a new Developing
Shared Resource in Bioinformatics. Mr. Fearn has led the development of a strategic plan for a clinical research data warehouse (the Hutchinson Informatics Data Repository and Archive, or HIDRA), engaged all partner institutions in this effort and established a cross-institutional governance structure. As described earlier, an external advisory board of experts has been appointed to provide counsel on the resource’s development. Implementation of the project is underway and is described in more detail in the Developmental Funds section. The strategic plan for the resource will be available at the site visit.

Development and implementation of a plan to enhance clinical research services and support. At our last CCSG review, senior leaders were encouraged to devote more attention to the administrative support for clinical trial development and conduct. In response, a working group was formed that conducted a faculty survey to identify the most significant gaps in service, and external advisors have been engaged to provide a review of existing services. As a result, the Clinical Research Support Office has been reorganized, including appointment of a new medical director with 40% effort devoted to this role and consolidation of several previously separately managed functions under one office and a senior administrator appointed to oversee these services. Many other improvements have been made to improve quality and efficiency, and an implementation plan for a clinical trials management system is underway. Additional progress and further plans are discussed in more detail in the Clinical Protocol and Data Management section.

Future Plans
In consultation with the EAB, senior leaders have identified areas that present opportunities or that demand additional attention during the next grant cycle, including:

- **Continuing to build multi-disciplinary solid tumor translational research across institutions.** Dr. Holland has recently completed an assessment of current member expertise in all disciplines and has begun to define approaches that can further strengthen solid tumor translational organ-site centers. These approaches should allow us to better integrate and expand the breadth of research for a particular tumor site, including more basic scientists and faculty from a broad range of clinical subspecialties (such as imaging and radiation science). Several of these organ-site centers are well developed, with established CCSG programs in Prostate Cancer, GI Cancer, and Women’s Cancer that have been well reviewed. There are also NCI Specialized Program of Research Excellence Awards in prostate, ovary and, newly awarded during the project period, breast. Other disease groups are poised for national leadership and established CCSG program development, and will benefit from additional resource investment and strategic planning. Through his assessment Dr. Holland has already begun to identify areas of opportunity and gaps, and use this information to develop a strategic plan in collaboration with disease group leaders. Initial strategic plans will concentrate on eight diseases groups that include the established CCSG solid tumor programs as well as lung, brain, and head and neck cancers. He is assembling a comprehensive database of metrics on publications, grants and collaborations in order to track progress over time and will provide regular reports to the IPC. In addition, Dr. Holland will devote effort to building new collaborations among imaging and radiation scientists and solid tumor investigators. CCSG Developmental and Early Phase Clinical Research Support funds will be allocated to all of the above strategies.

- **Strengthening the Consortium’s focus on health disparities and inclusion of minorities in research.** Consortium senior leaders are strongly committed to strengthening our research portfolio in the catchment area and with underserved populations in the next project period. As a result of discussion among senior leaders, culminating in a presentation at the 2011 EAB meeting by Dr. Beti Thompson on health disparities research, Dr. Corey appointed Dr. Thompson (FHCRC) in 2013 to a newly created position of Associate Director for Minority Health and Health Disparities. Dr. Thompson, who leads several successful NCI projects with Latino populations and whose background is described in more detail in the Senior Leaders section, recently established a new Consortium Health Disparities Research Center and has engaged Hannah Linden (UW) and Jason Mendoza (Children’s), two other Consortium members experienced in research with special populations, as co-directors of this center. Developmental funds are requested in this application to support Drs. Linden and Mendoza as Special Populations Staff Investigators. Together, they have used the three-year planning tool described above to map out strategic objectives and resource needs. Their plan for increasing minority participation in Consortium research will be available at the site visit; elements of the plan include appointment of a committee to evaluate minority participation in research studies, engagement of strategic advisors and allocation of CCSG pilot funds to support research studies aimed at inclusion of minorities in research.
• Ensuring that Consortium clinical research support infrastructure is well organized, integrated, effective, and efficient. Medical Director for Clinical Research Services, Paul Martin, and Director of Clinical Research Support, Ulrich Mueller, jointly lead a working group responsible for reviewing and reorganizing the clinical trials operation, improving protocol review quality and timeliness, and achieving better integration and consistency of the clinical trials platform across the Consortium. In addition to its focus on organization, process, and resources, the group will also secure needed technology that relieves faculty burden, enhances compliance, streamlines operations, assures adherence with CCSG guidelines, and adopts best practice. This includes a commitment to implement a clinical trials management system, with the vendor selection process initiated in 2013. Drs. Martin and Mueller will report regularly to the IPC and will apprise the Director and EAB on a regular basis of their progress. In addition, in 2013 Dr. Corey has appointed a new Clinical Research Oversight Committee to assure oversight of all Consortium clinical trials and compliance with all Consortium, institutional and NCI policies and procedures as related to clinical trials. Deputy Director Appelbaum chairs the inter-institutional committee; meeting roster and minutes will be available at the site visit.

• Completing the development and implementation of the biomedical informatics and cancer molecular diagnostics efforts initiated during the current project period. One of Dr. Corey’s major objectives has been for the Consortium to be well positioned to apply advances in cancer genome analysis. The specific goal is to improve patient outcomes through the development of more accurate diagnostic and prognostic tests. In 2012, reflecting a shared commitment to building a robust translational research infrastructure, Dr. Corey and Dr. Ramsey, Dean of the UW School of Medicine, appointed a planning committee to establish an adult clinical cancer molecular diagnostics initiative. The purpose is to better intergrate existing molecular diagnostics services across the cancer center into a single program to improve efficiency and effectiveness, as well as to expand the Consortium’s computational and laboratory capabilities to discover new actionable targets for therapy and create a robust pipeline to develop these into CLIA-approved tests. Deputy Director Dr. Fred Appelbaum, and Dr. Tom Montine, the Chair of the Pathology Department at UW School of Medicine, chair this group. FHCRC and UW provided funding for a project manager and have committed to joint fundraising for this initiative, which will require the continued development of the Biomedical Informatics Resource, described above.

• Strengthening the research platform in health economics and outcomes, global oncology and obesity research. These scientific programmatic areas will be further developed during the project period with the engagement of the IPC and EAB (see Director’s Overview for greater detail). In 2012, Dr. Corey appointed Scott Ramsey (FHCRC) to lead a new Hutchinson Institute for Cancer Outcomes Research (HICOR) which involves both FHCRC and UW-based members. Dr. Ramsey, a nationally recognized physician and healthcare economist, has formed an advisory board that will provide counsel on faculty recruitment, resource development, fundraising activities and strategic partnerships with government agencies, academic collaborators and insurance companies. Global Oncology planning is led by program heads Corey Casper (FHCRC), who directs the FHCRC/Uganda Cancer Institute alliance, and Chris Murray (UW), Director of the UW Institute for Health Metrics and Evaluation and leader of the Global Burden of Disease Study. A strategic plan has been developed, metrics of progress such as grants and publications will be tracked, and progress will be monitored by the IPC. Garnet Anderson, Associate Director for Population Sciences, is responsible for leading planning to expand Consortium research in the Cancer Epidemiology, Prevention and Control Program on the mechanistic links between obesity, physical activity and cancer. An initial recruitment for an FHCRC-based member, conducted jointly with the UW Department of Health Services, is underway.

CCSG Budget Request

Allocation of CCSG Funds During the Project Period. CCSG funds have been very valuable for the Consortium’s planning and evaluation activities. During the current project period, CCSG funds were used for each annual EAB meeting and related travel expenses; special advisor visits including the biomedical informatics advisory board; and Consortium-wide scientific symposia. The Consortium augments CCSG funds with institutional funds for planning and evaluation activities, including consultation with strategic advisors and scientific symposia.

Proposed budget. As described in the accompanying budget justification, we are requesting a total of $34,250 in CCSG Planning and Evaluation funds, starting in Year 1 of the renewal, for annual EAB meetings and scientific symposia and retreats.
DEVELOPMENTAL FUNDS

Overview and Specific Aims

Developmental funds play several critical roles in furthering the Consortium’s strategic objectives. Several outstanding investigators who received recruitment funds during the project period would not have come to Seattle without the extra support that was offered through the availability of CCSG new investigator funds. The availability of CCSG pilot project funding provides investigators a very tangible benefit of cancer center membership, and, as described later in this section, has stimulated new collaborations that would otherwise not have occurred. And, funds to catalyze new shared resource development have afforded Consortium members access to technologies and expertise that would otherwise not be sustainable on an individual laboratory or even in many cases an institutional basis.

During the past grant period, developmental funds supported the recruitment of 28 productive Consortium faculty members in areas of strategic growth; 47 pilot projects resulting in the acquisition of 26 grants and the publication of 32 papers; and four developing shared resources for Bioinformatics, Tissue Bank, Tumor Models, and High Throughput Screening. In this application, developmental funds are requested for these three types of high impact activities as well as two Special Populations Staff Investigators. Clearly defined, longstanding Consortium processes for allocating these funds are described in each subsection below.

The Specific Aims of Developmental Funds are to:

1. Provide critical research support for up to 9 new Consortium investigators per year in areas of high strategic importance to the Consortium, including solid tumor translational research, immunotherapy, health disparities research, health economics and obesity research. The Consortium typically recruits 10 to 15 new members per year.

2. Provide pilot funding to stimulate 5-7 of the most innovative Consortium cancer research projects annually. Awards will be targeted to areas of strategic growth (see specific aim 1) as well as to encourage new avenues of research to support the most promising projects in cancer diagnosis, treatment or prevention, with emphasis placed on likelihood of stimulating follow-on funding and potential impact in the catchment area.

3. Develop a new Biomedical Informatics shared resource. This resource has been strongly endorsed by senior leaders and our External Advisory Board, and will integrate data on all Consortium patients, specimens, clinical trials and studies, and associated genomics or other assay data, and efficiently support the further development of Consortium solid tumor translational research.

4. Support two Special Populations Staff Investigators who will advance our strategic objective to increase research in the catchment area and enhance inclusion of minorities in Consortium research.

Use of New Investigator Funds During the Project Period

28 faculty members were recruited during the project period and have been highly productive. The attached table (Research & Related Other Project Information) summarizes each investigator's funding, publications and leadership of clinical trials or other activities since their appointment. Each new recruit was awarded $50,000 to $100,000 direct costs; three to nine CCSG-supported awards were made each year. Because the leveraging potential of CCSG funds increases over time, in this table we have also included data on recipients of new investigator funds from the last two years of the prior project period (2007-2008), all of whom have garnered follow on funding. In distributing these funds, the committee considers where they will have the biggest impact. For example, high priority is given to situations where a relatively small amount of funding can make the difference in a successful recruitment or not, and to situations, such as the case with recruitment of clinical researchers, where opportunities for grant-based awards are more difficult.

Awardees are responsible for providing annual updates on progress. The Consortium Recruitment Subcommittee of the Institutional Planning Committee (IPC) makes recommendations for allocation of CCSG funds that reflect the strategic priorities determined by the Director and the IPC in consultation with the EAB. Recruitments were targeted to areas designated for expansion at the last competing renewal (clinical translational research, particularly in solid-tumor cancers, immunotherapy and computational biology) or that emerged as strategic directions during the project period (health economics, cancer disparities). The list below summarizes the research focus of the recipients of new investigator funds.
Clinical/Translational Research

Eli Estey, MD (UW, Medicine/Hematology) is an expert in treatment of acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). He was recruited to strengthen the Hematologic Malignancies Program’s clinical research on non-transplant therapies for leukemia. His research focuses on novel clinical trial design, particularly methodology that simultaneously monitors multiple endpoints and involves small randomized trials to select a therapy to move to a later stage of testing.

Venu Pillarisetty, MD (UW/Surgery) is a surgical oncologist with a focus on the multidisciplinary management of neoplasms of the pancreas, liver, biliary tract, and upper gastrointestinal tract using both open and minimally invasive techniques. He was recruited to build the Consortium’s pancreatic research portfolio, particularly in immunotherapy. His research interests include basic and translational studies of the role of immune dysregulation in facilitating progression of pancreatic cancer, with a goal of developing novel immunotherapies.

Laura Chow, MD (UW/Medicine/Oncology) is a medical oncologist specializing in lung, head and neck, thyroid and esophageal cancers. Dr. Chow’s research interests focus on early phase clinical trials for advanced lung cancer patients, including studies of drugs that prevent T-cell inhibition and promote programmed cell death, as well therapies targeted to specific tumor genomic abnormalities. She has recently been named Associate Director of the Consortium’s Phase I Clinical Trials initiative.

Michael Jensen, MD (Seattle Children’s) is a pediatric oncologist and leader in adoptive T-cell therapy, and was recruited to lead Seattle Children’s Ben Towne Center for Childhood Cancers. Dr. Jensen develops and implements immunotherapeutic approaches for pediatric and adult malignancies, including clinical trials of adoptive T cell immunotherapy for B cell malignancies. He is the Consortium Associate Director for Childhood Cancer Research and a co-associate head of the Immunology and Vaccine Development Program.

Eve Rodler, MD (UW/Medicine/Oncology) is a medical oncologist specializing in the treatment of breast cancer. Her research focuses on early stage clinical trials of breast cancer therapies, with particular interest in BRCA-mutation associated cancers. Dr. Rodler joined the faculty of University of California, Davis, in 2013, for family reasons. She remains a Consortium affiliate investigator and collaborator on two clinical trials.

Larissa Korde, MD, MPH (UW/Medicine/Oncology) is a medical oncologist specializing in breast cancer. Her research focuses on breast cancer prevention, including studies assessing lifestyle interventions and chemoprevention in women at increased risk of breast cancer. She is also interested in assessing new modalities for the treatment of patients with early stage breast cancer. Dr. Korde is faculty director of the Prevention Center Shared Resource.

Jonathan Grim, MD, PhD (FHCRC/Clinical Research) is a laboratory researcher and hematologist/oncologist. He conducts a translational research program in gastrointestinal malignancies with a specific focus on the development of novel targeted therapies in colorectal and associated cancers. He has developed mouse models of colorectal cancer that lack tumor suppressors involved in the ubiquitin pathway that serve as a novel tool for studies of advanced colorectal cancer as well as carcinogenesis associated with ubiquitin pathway mutations.

Ed Libby, MD (UW/Medicine/Oncology) is a hematologist specializing in clinical trials to advance the diagnosis and treatment of patients with lymphoma and plasma cell diseases including multiple myeloma, Waldenstroms macroglobulinemia and amyloidosis.

Cecilia Yeung, MD (FHCRC/Clinical Research) is a hematopathologist and a molecular genetics pathologist. She uses whole genome interrogation methods to study novel molecular markers in lymphomas and leukemias to improve diagnosis and prognosis and guide future therapies.

Shailander Bhatia, MD (UW/Medicine/Oncology) is a medical oncologist who leads clinical trials that aim to improve outcomes in skin cancers, especially melanoma and Merkel cell carcinoma, and kidney cancers. He is particularly interested in novel therapeutic approaches that stimulate the immune system against cancer and those that target therapy to the tumors to spare unnecessary toxicity.

Brian Till, MD (FHCRC/Clinical Research) is a medical oncologist who specializes in autologous stem cell transplantation to treat lymphoma and multiple myeloma. His research focuses on development of genetically modified T cells for adoptive T cell therapy clinical trials for lymphoma, work for which he was awarded a Damon Runyon Clinical Investigator Award.
Elena Chiorean, MD (UW/Medicine/Oncology) is a newly recruited medical oncologist specializing in colorectal, gastrointestinal, hepatobiliary, and pancreatic cancers. She will lead early stage clinical trials in the treatment of GI malignancies.

Eirini Papapetrou, MD, PhD (UW/Medicine/Hematology) is a laboratory investigator whose research focuses on understanding normal and abnormal hematopoiesis with the goals of identifying new therapeutic targets and developing novel cell and gene therapies. Her major focus is the investigation of the mechanisms and genetic basis of myelodysplasia, using genetic and chemical screens to identify candidate genes and pathways responsible for the disease phenotype(s) and further study their role in hematopoiesis.

Stephen Schmechel, MD, PhD (UW/Pathology) specializes in cytopathology and genitourinary pathology. His research program involves identifying and validating biomarkers (typically protein products of genes assayed by immunohistochemistry) of aggressive biological behavior of prostate cancer. Dr. Schmechel has extensive experience in developing biospecimen repositories and was recruited to provide leadership for the Consortium biospecimen resource (Northwest BioTrust) presented in this application.

Christina Baik, MD (UW/Medicine/Oncology) has a clinical focus on the care of patients with lung, head and neck cancer, and a research interest in the development of new therapeutics in this patient population and the use of novel biomarkers to guide that development.

Eleanor Chen, MD, PhD (UW/Medicine/Pathology) is a pathologist whose research focuses on dissecting cellular and molecular mechanisms underlying pediatric embryonal rhabdomyosarcoma, in particular the key events driving relapse and metastasis. She utilizes high-throughput chemical genetic and genomic approaches to identify key driver events of embryonal rhabdomyosarcoma. In addition, by imaging cellular processes in transgenic zebrafish tumor models, she seeks to dissect key cellular events leading to relapse and metastasis.

Andrew Covelar, MD (UW/Medicine/Oncology) is a medical oncologist specializing in gastrointestinal cancers. His research focuses on early phase clinical trials, particularly immunotherapeutic approaches, and immunologic biomarkers to predict vaccine efficacy.

Edgardo Castellar, MD, PhD (UW/Medicine/Pathology) is a pathologist whose research focuses on the study of the molecular changes leading up to pathway dysregulation in ovarian neoplasia using massively parallel next generation sequencing and mass spectroscopic approaches for diagnostic, therapeutic, and biomarker discovery applications. His research seeks to contribute more broadly to the development of high-throughput molecular genetic and precision diagnostics for personalized care within oncology.

William Harris, MD (UW/Medicine/Oncology) is a medical oncologist specializing in gastrointestinal cancers, with a particular focus on hepatocellular carcinoma and cholangiocarcinoma. His research interests focus on clinical trials combining chemotherapy and biologic therapies.

Health Economics

Veena Shankaran, MD (UW/Medicine/Oncology) is a medical oncologist specializing in gastrointestinal cancer whose research focuses on health outcomes, comparative effectiveness and cost-effectiveness of cancer therapies. She has recently completed a study to assess financial hardship of patients undergoing adjuvant chemotherapy for stage III colon cancer, finding that many experience hardship despite having health insurance coverage. These and related studies may inform strategies to help at-risk patients early on during therapy to prevent long-term financial adverse effects.

Anirban Basu, PhD (UW/Health Services) focuses on methods and applications that study observed and unobserved heterogeneity in clinical and economic outcomes and attempts to establish the value of individualized care. Using micro-econometric theory and models, Dr. Basu conducts health economic evaluations that are in line with public policy decision making.

Janie Lee, MD (UW/Radiology) is a newly recruited breast imaging specialist focused on improving breast cancer screening outcomes. Her research involves evaluating the comparative effectiveness and cost-effectiveness of MRI screening in women at increased genetic risk of breast cancer. She has developed a computer simulation model which integrates available data and surrogate endpoints to project long-term health and economic outcomes of various screening strategies using MRI and mammography. The results of this project will provide additional data for developing standardized guidelines for the role of MRI in breast cancer screening.

Computational Biology
Timothy Thornton, PhD (UW/Biostatistics) is a statistical geneticist and was recruited to strengthen the Consortium’s computational biology research. His research focuses on statistical methodology for case-control genome-wide association studies (GWAS) in samples with related individuals and/or hidden population structure, methods that he is applying to studies of cancer.

Robert Bradley, PhD (FHCRC/Public Health Sciences) is a computational biologist and laboratory investigator who studies alternative RNA splicing, a process that increases the complexity of eukaryotic genomes, and plays important roles in many human diseases including cancer. He uses high-throughput genomics, sequence analysis, and molecular genetics to study the mechanistic origins and phenotypic consequences of alternative splicing and other RNA processing.

Ying Huang, PhD (FHCRC/Public Health Sciences) develops statistical methods in biomarker evaluation for cancer screening, surrogate endpoint identification, and treatment selection. She is actively involved in studies that examine interactions between high-dimensional SNPs and clinical trial intervention effects on breast cancer, and in studies of dietary biomarkers and related calibrated consumption estimates in association with the risk of major cancers and other chronic diseases.

Health Disparities Research and Cancer Prevention

India Ornelas, PhD, MPH (UW/Health Services) is a cancer prevention researcher who studies how social factors, including discrimination, contribute to Latino health disparities and is designing interventions to reduce these disparities. Her research has focused on how immigration-related stressors influence the health behaviors of Latino men as well as on discrimination, coping and health among Latinos, the results of which have informed the development of a more valid and reliable measure of perceived discrimination for Latinos.

Rachel Ceballos, PhD (FHCRC/Public Health Sciences) is a cancer prevention scientist who focuses on addressing minority population health disparities. She is working with local service organizations and advocates of African-American breast cancer survivors in King County, WA, to conduct a qualitative assessment to identify gaps in the provision of information or services to African-American breast cancer survivors in the county, with the goal of developing strategies to improve care and outcomes in this population.

Parveen Bhatti, PhD (FHCRC/Public Health Sciences) studies occupational and environmental epidemiology of cancer. The bulk of his epidemiologic research has focused on genetic susceptibility to cancer following low dose exposure to occupational or medical ionizing radiation. He is particularly interested in incorporating biomarkers of exposure and susceptibility to get better exposure estimates and identify subpopulations that may be particularly harmed by certain exposures.

Planned Uses of New Investigator Funds

The Director annually reviews Consortium strategic objectives with Consortium senior leaders and the External Advisory Board. The Recruitment subcommittee of the Institutional Planning Committee (IPC) selects future areas of recruitment emphasis from the resulting future objectives, and uses this information to encourage and provide a financial incentive to department chairs and division directors of the partner institutions to recruit candidates with an emphasis in the targeted areas. This tactic has proven to be highly effective in encouraging search committee chairs to focus their energy on candidates whose research is in strong alignment with Consortium goals. This is evidenced by our successful recruitments during this project period. The Recruitment Subcommittee also keeps abreast of newly recruited Consortium faculty in strategic areas of focus and may allocate funds to catalyze the research programs of these investigators.

The Clinical Oncology Oversight Committee, which includes all of the chairs of UW School of Medicine-based departments, is the group where recruitment needs for clinical investigators across the Consortium are vetted and where opportunities to recruit specific clinical candidates are discussed. Deputy Director Fred Appelbaum (FHCRC) chairs this committee, and Bill Bremner, MD (UW), Bruder Stapleton, MD (Children’s), Associate Director for Solid Tumor Translational Research Eric Holland, MD, PhD (FHCRC), and Deputy Director Mark Groudine (FHCRC) from the Institutional Planning Committee are participants. Recommendations concerning CCSG funding for clinical new investigators are made as a result of these deliberations.

As described in the Planning and Evaluation and Director’s Overview sections, several areas of scientific focus have been designated as areas of strategic focus for the new project period and as such, will become the priorities for faculty recruitment. These areas include health disparities research, global oncology, solid tumor translational research, healthcare economics, immunotherapy, and obesity research.
The Recruitment subcommittee generally allocates funds of $50,000 to $100,000 for each supported recruit, to be spent on staff and/or research support to establish research activities within the Consortium. In this application, we are requesting $450,000 annually to support funding for up to nine new recruits per year through this mechanism; this is the same as current funding. Using CCSG and institutional funds, the Consortium typically recruits 10 to 15 new members per year. The CCSG recruitment funds are invaluable to the Consortium not only for their ability to attract new cancer researchers but for catalyzing a spirit of collaboration with departments where the recruit is based, which has led chairs and others to jointly recruit individuals to the benefit of the cancer center.

**Use of Pilot Funds During the Grant Period**

Pilot funding is awarded annually. The process includes announcement of an RFA to all Consortium members. Senior leaders and program leaders are encouraged to reach out to members and actively encourage applications. The Scientific Review Committee, in conjunction with Consortium Administration, implements the process. The peer-review process is achieved through a committee chaired by an appointee of Deputy Director Appelbaum and that has institutional balance and scientific expertise relevant to the RFA focus and proposals submitted. Consortium senior leaders strike a balance between targeted pilot competitions to catalyze research in areas designated for strategic growth with open competitions to ensure that novel, highly promising studies in any area of cancer research have the opportunity to be pursued. Regardless of the focus of the RFA, all proposals are evaluated based on scientific merit; potential to impact cancer diagnosis, treatment and prevention; likelihood of leading to follow-on funding; and potential impact to the catchment area.

Examples of targeted pilot competitions during the project period were three RFAs targeted to solid tumor translational research that required a laboratory-based and a clinical co-investigator, small awards to stimulate the use of shared resources or newly acquired shared resource technologies, global oncology research and health disparities research. This approach has led to successes; for example, a $40,000 targeted solid tumor translational pilot grant to Patrick Paddison and Jim Olson for “Identification of synergistic combination therapies for glioblastoma” stimulated a collaboration that would not otherwise have happened and provided preliminary data leading to three follow-on grants totalling $2.4M, including an NCI Provocative Questions R21 Award (CA170722).

During the current project period, 47 pilot grants were awarded. Awardees report on progress, including publications and follow-on funding, annually. To date, 21 of these awards have resulted in publications; 17 have resulted in follow-on funding. The attached table (in Research & Related Other Project Information) provides detail on these outcomes. Since the leverage of CCSG pilot funds increases with time, we have also included in the table the last two years of the prior project period, which includes 19 additional pilots awarded in 2007-2008. In total (current project period to date plus two additional years), ~$2.75M (direct costs) in pilot funding was awarded during this time and has leveraged ~$35.5M (total costs) in follow-on funding.

**Proposed Uses of Pilot Project Funds**

During the current project period, Consortium has funded 6 to 11 pilot projects a year in amounts that range from $10,000 for shared resource/new technology grants to typically from $50,000-$100,000 for other projects. For the new project period, we request $450,000 annually to support 5 to 10 projects. As described above, senior leaders will strike a balance between targeted awards to areas of strategic growth and open competitions to stimulate new research directions. However, all award competitions will prioritize applications based on their potential to make a significant impact on cancer treatment, diagnosis or prevention; likelihood to stimulate follow-on funding; and impact in the catchment area. At least one pilot award annually will continue to be dedicated to stimulating inclusion of minorities in research.

**Use of Developing Shared Resources Funds During the Project Period**

Developmental funds were used during the last grant period to support four resources and technologies: Bioinformatics, Tissue Bank, Tumor Models and High-Throughput Screening.

The Bioinformatics resource was successfully established under a prominent leader, Martin McIntosh, co-head of the Biostatistics and Computational Biology Program, to provide analysis of high-throughput data on a genome-wide and/or proteome-wide basis. The three services provided by this resource (drop-in consulting, project-based consulting and training and outreach) each had 28, 37 and 50 unique users during the project period (some with multiple visits), representing all partner institutions. Based on the maturity of this resource
and increasing demand for these services, this resource is proposed as a full Shared Resource renamed Computational Biology in this application.

The Tissue Bank resource was established to provide centralized, Consortium-wide biospecimen acquisition and distribution. This resource has undergone extensive inter-institutional planning and development during the project period and is fully operational. CCSG developmental funds leveraged more than $6M in follow-on funding from the WA State Life Sciences Discovery Fund (via two grants to Drs. John Slattery and Peggy Porter) to establish the resource. In addition, FHCRC and UW collaborated on the recruitment of a co-leader for this resource, Stephen Schmechel, who received CCSG new investigator funds. The resource is part of the critical translational research infrastructure for expanding solid tumor translational research and is presented in this application as a full resource renamed Northwest BioTrust, with examples of how the resource has supported Consortium peer-reviewed research projects.

A pre-clinical Tumor Models resource was established to provide mouse models for understanding the biology of human cancers, particularly focusing on prostate and hematopoietic cancers. During the project period, 12 unique members have used this resource and these activities have been well supported by research grants. To continue expanding access to mouse xenograft models for a wide range of tumors, Consortium members recently established a collaboration with the Jackson Laboratories Patient Derived Xenograft (PDX) Consortium. These tumor model activities have been combined with the Comparative Medicine Shared Resource (see Shared Resources) and are described further in that section, with CCSG funds requested there.

The High-Throughput Screening Facility was established to provide scientists the ability to access commercially available libraries for high-throughput screens using cell- and animal-based assays consisting of small molecules to modulate protein function, short interfering RNAs (siRNAs), and targeted collections of small molecule libraries. High-throughput screens have been well used by Consortium members during the project period; 10 unique members used the facility in FY13. Over time, however, we have recognized that many scientists at partner institutions who are not part of the the cancer center wanted access to this critical capability. Center leaders concluded that it was more beneficial and practical for each institution to have its own dedicated facility, rather than continuing the Consortium core. A facility performing needed services is now based at the University of Washington’s Quellos Center at South Lake Union and at FHCRC. CCSG funds are therefore not requested in this application, but the impact of previously used CCSG funds to enable our investigators to have immediate access to high-throughput screening has been achieved beyond expectations.

Developing resources operate in accordance with CCSG, Consortium and institutional policies on Shared Resources. During the project period, additional funding for personnel, equipment and associated start up costs for the last four developing resources proposed was provided through institutional and other grant funding.

**Planned Uses of Developing Shared Resource Funds**

$298,896 is requested annually for one new resource during the next project period: Biomedical Informatics. Development of this resource emerged from the Consortium’s planning and evaluation process that determined strategic objectives for the new project period, including recommendations from our External Advisory Board and from the IPC (see also Planning and Evaluation). This resource is expected to be extensively utilized across the Consortium; based on a survey of programmatic needs, we project usage by members in all nine of the proposed research programs.

**Biomedical Informatics Resource (BMI)**

Access to high quality, richly annotated clinical and biospecimen data is critical to our cancer center’s translational research objectives. Historically, transplant data collection and distribution at FHCRC has been a centralized activity, with a comprehensive database now of over 16,000 transplants performed on FHCRC protocols that is used routinely by all Consortium members engaged in clinical transplant research. Our progress in establishing a similar integrated data warehouse and associated expertise to support solid-tumor translational research has been more limited, and at the time of our last CCSG review Consortium senior leaders were strongly encouraged to devote attention to this area, a recommendation that was supported by our EAB.

The objectives of the Biomedical Informatics (BMI) resource are to 1) integrate data on all Consortium patients, specimens, clinical trials and studies, and associated genomics or other assay data from laboratories; and 2) make these data readily available to Consortium investigators.
Since 2008, we have made significant institutional investment and progress in biomedical informatics, which form the basis for the proposed BMI resource.

- The University of Washington has purchased and implemented the Amalga software platform and has aggregated electronic clinical data from over 35 source systems into a unified data warehouse. UW has invested $75 million in capital expenditures during the project period to strengthen its clinical informatics infrastructure and electronic medical record. The Amalga resource now contains 15 billion observations about 3.8 million individuals.

- The Consortium engaged Paul Fearn, previously Manager of Surgery Informatics at Memorial Sloan Kettering Cancer Center and inventor of the Caisis Database System, to conduct a review of Consortium solid-tumor database activities. Mr. Fearn relocated to Seattle and has been appointed Consortium Director of Biomedical Informatics Strategy.

- With endorsement of the Institutional Planning Committee, Mr. Fearn has surveyed requirements of all Consortium disease programs and assessed best practices from other NCI-designated cancer centers to develop a strategic plan for the resource. Central to this plan is the development of “HIDRA” – the Hutch Integrated Data Repository and Archive. HIDRA is a resource to centralize clinical, biospecimen and study data on all cancer types from Amalga and the NW BioTrust Shared Resource for biospecimen acquisition, augment it with molecular assay data, implement tools for data exploration, extraction and analysis, and support clinical and translational studies. FHCRC has committed $4.3 million to HIDRA in the past 18 months to launch the resource and is committed to further ongoing support. The resource now contains information on 10,928 patients, including 88 tables from 11 data sources (e.g. laboratory, pathology, appointments) that supplement the Amalga data warehouse described above.

- Staff and existing tools for study management have been consolidated to provide centralized coordination and to allocate sufficient FTEs to HIDRA implementation. This also ensures that HIDRA implementation is and will be coordinated with other Consortium informatics projects, such as implementation of a clinical trials management system (CTMS) during the next project period and the Northwest BioTrust (biospecimen) shared resource.

- A memorandum of understanding for data sharing has been signed by all Consortium partners, which will facilitate data flow.

- Institutional Review Board approval has been obtained for HIDRA-related activities.

- A special external advisory board for biomedical informatics was convened in September 2013, partially supported by CCSG funds. The committee’s first meeting was chaired by Warren Kibbe, formerly the leader of informatics at Northwestern University and now the Director of the NCI Center for Biomedical Informatics and Information Technology. The board will be convened annually to evaluate strategy and progress toward objectives, and to ensure the project leaders incorporate best practices. The report from the committee’s first meeting will be available at the site visit.

- A governance structure has been established with representation from all Consortium partners.

Proposed Activities of the Resource

As noted above, HIDRA is a resource that is central to many of BMI Resource’s services, and functions as an oncology data warehouse that complements two other major resources: UW Amalga, which is a UW clinical and administrative data repository; and the Seattle Cancer Care Alliance’s Oncology Alliance Select Integrated System (OASIS) which supports SCCA’s business operations. HIDRA has the following strategic goals: supporting a Learning Healthcare System via rapid secondary use of clinical data for research, operations and quality improvement; integrating data of many types and organizational sources; automating data abstraction that is currently done manually; and complying with current and future security and regulatory requirements, such as HIPAA/HITECH and WA state laws. Its development is planned as a core data integration platform (using the open source LabKey Server) that supports a coordinated set of informatics applications providing end-user tools and ‘value added’ services (figure below). In a systematic requirements analysis across disease programs from June through October 2013, Mr. Fearn and colleagues found most investigators and staff are often constrained by the costs of manual data abstraction and data manipulation. Based on an associated analysis of ~15,000 data elements across existing and desired databases from all disease programs (about 150,000 historical cases and 5000-6000 new per year), they have created a map to clinical source systems.
and have prioritized candidates for natural language processing (NLP) and computation. BMI is developing an enterprise-wide clinical data model and designing a clinical NLP pipeline to facilitate and automate current manual data acquisition and manual data processing activities. Next steps include parallel migration of current databases to the new data model and pilot NLP projects to inform and drive the automated clinical data pipeline. To date, HIDRA contains data on 10,928 patients, including 88 tables from 11 data source (e.g. laboratory, pathology, appointments), more than 600 million records, more than 6,000 fields, and more than 38 billion data points.

The CTMS will be integrated to draw data from and provide data to HIDRA. Mr. Fearn is on the steering committees for HIDRA and CTMS implementation, as well on the NW BioTrust (the Consortium biospecimen shared resource presented in this application) operations committee to ensure these efforts are complementary and part of an overall vision for Consortium informatics.

**Services that will be provided to Consortium investigators**

The estimated initial content of HIDRA is 150,000 historical Consortium patients and subjects from existing systems (~5000-6000 new patients per year coming through Seattle Cancer Care Alliance.) These data will be linked to over 70,000 historical specimens, new specimens acquired through the NW BioTrust shared resource, Consortium studies and clinical trials. This foundation will enable the Center to learn from every new patient who comes through the door, to use data from historical cases and specimens to test hypotheses or determine feasibility for grants or trials, and to more rapidly translate and integrate that knowledge back into the clinical care through trials and care pathways. Moreover, the platform and services developed in the BMI resource are designed for extensibility to include additional patient cohorts, organizations and types of data.

Specific services will include:

- Provide clinical data for feasibility for grants and studies, such an easy to use tool for investigators to directly query counts of patients with specified diagnostic or treatment characteristics, and graph them over time to estimate accrual.

- Provide data for retrospective studies and find associated samples.

- Provide self-service tools and training for investigators. In our analysis, the most commonly needed information is simple (e.g. how many patients do we have with a specific treatment or diagnosis?) With a unified platform, a simplified user interface, training, and a coordinated support team, we aim to make investigative teams largely self sufficient.

- To provide support to initiatives in solid tumor translational research and cancer molecular diagnostics, we are developing a pilot application to browse and select cohorts by their molecular profiles in addition to or instead of clinical data points.

- Enhance Consortium efforts to increase research in the catchment area by improving collection of long-term follow up care of patients as they return to their primary care provider.

Mr. Fearn is well qualified to lead this resource. He is Director of Biomedical Informatics at FHCRC, where he has led the development of HIDRA for the FHCRC/UW Cancer Consortium. Previously, he was the Informatics Manager for the Department of Surgery and the Office of Strategic Planning and Innovation at Memorial Sloan-Kettering Cancer Center (MSKCC), where he initiated and led the Caisis project, an open-source system that is currently used at over 25 centers. Mr. Fearn is a PhD Candidate at University of Washington Department of Biomedical Informatics and Medical Education (expected degree date June 2014), where his research focuses on developing text mining and natural language processing tools to extract and evaluate provenance of biospecimen data from publications. He has over 15 years of experience in cancer research informatics at Baylor College of Medicine, MSKCC and FHCRC. He serves on the NCI’s National Cancer Advisory Board.
Informatics Working Group, and was a member of the caBIG Oversight ad hoc Working Group of NCI’s Board of Scientific Advisors (2011).

**Planned Uses of Staff Investigator Funds**

Funding is requested (10% effort each) for two Special Populations Staff Investigators, Hannah Linden and Jason Mendoza. Consortium senior leaders are strongly committed to strengthening our research portfolio in the catchment area and with underserved populations in the next project period as one of our major strategic objectives. In 2013, Dr. Corey appointed Dr. Beti Thompson as Associate Director for Minority Health and Health Disparities. Dr. Thompson (FHCRC) serves as director of a recently established Health Disparities Research Center, for which Drs. Linden (UW) and Mendoza (Children’s) serve as co-directors. A major focus of this center is to continually evaluate, and develop strategies to increase, accrual to Consortium research studies by working with Consortium members in all applicable research programs. As noted above, CCSG pilot funds will also be allocated to health disparities research.

Drs. Linden and Mendoza have strong track records working with special populations and are highly collaborative. Descriptions of their qualifications can be found in the accompanying budget justification and in their attached biosketches.
Biostatistics and Computational Biology Program

1. Program Overview

1A. Program Focus

Investigators in the Biostatistics and Computational Biology program have doctoral-level training in biostatistics, statistics, mathematics, and physics, and their research program portfolio spans a broad range of activities from the development of statistical methods to leading biological research programs that include experimental methods alongside computational methods. Statistical methods research includes emphases in the quantitative analysis of genome-scale data sets, the analysis of data for molecular diagnostics, and other areas. The biological research programs include activities in immunology, infectious disease/microbiome, and basic molecular biology. The activities of program members have lead to the development of new statistical methodologies, new experimental approaches and methods, and several high-impact biological discoveries. A hallmark of the program is the strong commitment of its members to collaborative research with other CCSG programs, and with researchers at other institutions whose mission is to prevent and treat cancer. This is demonstrated in part through our activities leading several large-scale coordinating centers nationwide that project our impact in areas such as biomarker validation studies, intervention studies, and clinical trial management. These collaborations and also our activities in U01s allow our researchers to disseminate or translate our research in order to maximize its impact. Our specific aims are to:

**Aim 1:** Develop rigorous statistical and mathematical methods relevant to predictive and personalized medicine. An emphasis will be placed on the quantitative analysis of genome-scale data sets, the evaluation of molecular diagnostic biomarkers, and other predictive methods relevant to cancer risk stratification.

**Aim 2:** Develop and use experimental, technological, and companion computational or mathematical methods to gain understanding of the natural history of cancer. An emphasis is placed on understanding the natural history of the host immune response to cancer, and mechanisms of translation control and applications to methods to diagnose, prevent and treat cancer.

**Aim 3:** Promote the development, dissemination and use of statistical and computational methods in cancer research. An emphasis is placed on development of methods in our broadly adopted biostatistical and bioinformatics computing platforms.

1B. Program Structure

The Biostatistics and Biomathematics Program received a score of Outstanding in 2008, without any specific critiques, and the Computational Biology was presented as a Developing Program. The Consortium Program in Biostatistics and Computational Biology unites the two research areas. The Biostatistics program was founded in 1983 when the FHCRC Program in Epidemiology and Biostatistics became the Division of Public Health Sciences. Dr. John Crowley (1983-1994) and Steven Self (1994-2011) served as program heads. Dr. Kooperberg became co-Head in 2007. In 2008 it was renamed Biostatistics and Biomathematics Program to reflect the expansion in mathematical modeling. The Computational Biology Developing Program began with recruitments in the Biostatistics and Biomathematics Program, so the combination of these two programs was a natural evolution. A hallmark of the Biostatistics and Biomathematics component is its strong commitment to both collaborative and statistical methodologic research, and the now mature Computational Biology component of the combined program emphasizes a focus on specific biological problems that can be addressed in novel ways by computational approaches, novel technology development, and experimentation. The CCSG program has computational and mathematical faculty whose research spans the range of activities including technological methods and biological research.

The rationale for melding biostatistics and computational biology research groups derived initially from the ubiquity of genome scale molecular assays and its impact on the population and biological sciences, and the need for the CCSG to foster their use in applied cancer research. Today, the CCSG program supports this premise and has fostered a number of strategic collaborative recruitments across the cancer center, including Robert Bradley (who is also a lab-based basic scientist) and others.

Together, program members have the expertise to develop a wide range of core computational/mathematical methods that are critical to cancer research – statistical methods research and computational biology, including analysis of large-scale sequence data – but to also lead substantive research in a variety of relevant high-impact areas; some statisticians lead population science research and computational biologists lead programs.
in cancer molecular biology or immunology. Program faculty exchange ideas and expertise across different research domains, including both population and biological science that often share a common core of technical challenges. The program promotes the sharing of ideas and complementary expertise – quantitative analysis versus analysis of sequences -- and intellectual exchange through jointly run meetings and strategic planning sessions.

The program sponsors several different seminar series that spans the range of interests of the CCSG program faculty, including a series that emphasizes advanced statistical methods, especially in genomic data, and another that focuses on the substantive research areas that are commonly using a variety of genome-scale assays and advanced modeling tools. The program also sponsors a variety of workshops including regular research conferences focused on computational methods in genomics, as part of Bioconductor workshops, a variety of basic and advanced classes using the UCSG genome browser or the related functions in Bioconductor, and other basic tools to train members of other programs in core data analysis methods useful in biological research; some are conducted in collaboration with the Computational Biology Shared Resources. In October 2011 the program sponsored a conference on topics in Chronic Disease Research, co-organized by Drs. Kooperberg and Hsu from our program. In November 2013 the program sponsored a conference on the Impact of Large-Scale Genomic Data on Statistical and Quantitative Genetics, organized by Drs. Thornton and Weir from our program.

1C. Program Leadership and Qualifications

The Biostatistics and Computational Biology Program heads are Dr. Charles Kooperberg, appointed as co-Head of the Biostatistics and Biomathematics Program in 2007 and Dr. Martin McIntosh, appointed as co-Head in 2013. Dr. Bruce Weir, appointed in 2013, serves as Associate Program Head. The three program leaders have distinct responsibilities. Dr. Kooperberg, who also serves as head of the administrative FHCRC Biostatistics group, focuses on the biostatistics component of the program, including statistical methodology research. Dr. Kooperberg led the recruitment of Drs. Di (statistical methodologist), Othus (clinical trial methodologist), and He and Wu (both methods for genome-scale data) and is actively involved in the mentoring of these junior faculty. Dr. Kooperberg also functions as the sponsor of an active working group of postdoctoral fellows at the FHCRC. Dr. McIntosh, who also heads the administrative Computational Biology group at the FHCRC, focuses on the activities of the computational biology group. The mission of computational biology faculty is to advance their biological research area, which largely but not exclusively requires work that spans the experimentation and computation areas. Dr. McIntosh was responsible for the recruitment of Drs. Matsen (microbiome), R. Bradley (transcription control), Edlefsen (viral and host genome sequence analysis), and R. Gottardo (immune-assay/flow cytometry development). Dr. McIntosh serves as mentor for junior computational biology faculty. Dr. Weir is chair of the University of Washington Department of Biostatistics and he led the recruitment of Dr. Timothy Thornton. Members of the CCSG Biostatistics and Computational Biology Program span both the FHCRC and UW, and Dr. Weir’s position in the leadership assures that the CCSG can operate effectively across these institutional boundaries. There is a historical and existing close relation between program faculty at the FHCRC and the University of Washington (UW), with many faculty having joint appointments across the two institutes; for example, Dr. Kooperberg has an appointment in the Department of Biostatistics at UW and Dr. Weir has an appointment at the FHCRC. Drs. Weir and Kooperberg interact closely on issues involving both institutions, including recruitments.

1D. Program Membership

The Biostatistics and Computational Biology Program currently has 42 members from 2 Institutions, 3 schools and 7 departments. 32 Members (93%) have peer-reviewed funding for independent research, are leading coordinating centers, or are newly recruited, totaling over $12.4M in grant funding (direct dollars) of which $10.9M (88%) is peer-reviewed. 49% of peer reviewed funding, $5.4M, is from NCI and. Funded program activities may be used to categorize our faculty in 11 distinct areas of expertise, as reflected in the following broad categories:

- **Statistical Methods Research for Medical Studies** (Drs. Dai, Di, Feng, Heagerty, Hsu, Huang, Kooperberg, Pepe, Prentice, CY Wang, P Wang, Zheng). In addition to statistical methods R01 grants to each of these (and other) named individuals, all are also supported by a long-standing NCI P01 award (PI: Prentice), which has three projects focusing on development of statistical methodologies for a in population research in chronic diseases, the design and analysis of genetic/genomic studies, and biomarker development and validation.
• **Biomathematical (multiscale) Modeling** (Drs. Etzioni, Luebeck, Moolgavkar). The central theme of this work is the use of multiscale models to combine experimental and population-level data to address important problems in cancer trends, and to predict the effect of potential interventions, and early detection. This work is supported by NCI R01 grants (Etzioni, Leubeck), two CISNET U01 grants (the NCI CISNET program; Cancer Intervention and Surveillance Modeling Network), and Dr. Luebeck is also PI of a U01 grant focused on multi-scale modeling in esophagus cancer.

• **Statistical Genetics** (Drs. Dai, Emond, He, Hsu, Huang, Kooperberg, LeBlanc, Prentice, Thornton, Weir, Zhao). This program has a substantial number of investigators working in this area, both at the UW (centered around the NHGRI funded GENEVA coordinating center), and at FHRC. Investigators both develop methodologies and work with colleagues in other programs in leading GWAS and sequencing studies. This work is supported by several NIH U01 grants (Kooperberg, Weir), a P01 project grant (Weir) and a number of R01 grants (Dai, Hsu, Kooperberg, Weir, Zhao).

• **Cancer Immunology** (Drs. Robins and McIntosh): The central theme of this work is to understand the evolution of the adaptive immune response to cancer, including humoral (B-Cell) and cellular (T-Cell) response. Dr. Robins studies, largely through the use of T-Cell and B-Cell repertoire profiling technologies he has developed, the natural history of the T-Cell and B-Cell repertoire before and during cancer, and after therapy. Dr. McIntosh’s work focuses on identifying tumor antigens (proteins) that give rise to the immune response, and then further develop these antigens as therapeutic targets for adoptive T Cell therapy, antibody therapy, or for prevention by prophylactic tumor vaccines, or as novel targets for imaging. This work is supported by a Keck foundation grant (Robins), a U01 supported by the NCI CTDD (cancer target discovery and development) program (McIntosh), and a Department of Defense Innovation Award for Ovarian Cancer (McIntosh).

• **Infectious Disease/Microbiome Research in Cancer** (Drs. Matsen, Edlefsen, Gottardo, McIntosh, Gilbert): This work focuses on studying the role of infectious agents and/or the microbiome on the host, including an emphasis on the role of measuring and characterizing phylogeny, exposure and the immune response to pathogens, especially in infection associated cancer. This work has been supported by several NCI R01 grants (Matsen, Gottardo), the NSF (Matsen, Gottardo), and the Seattle Center For Aids Research (CFAR) and funded by the NHGRI (McIntosh).

• **Molecular and Cellular Biology** (Drs. Philip Bradley and Robert Bradley): A recent emphasis in the computational biology program recruitments has been in investigators engaged in functional and structural molecular/cellular biology. Currently program members Drs. P and R Bradley represent this growing area. Dr. P. Bradley (supported by an R01 grant) studies DNA and protein binding, especially in relation to the design of proteins or drugs, and he is also a leading developer of methods for macromolecular modeling. Dr. R Bradley studies translation control and the role of disruption in translation has in cancer.

• **Design and Evaluation of Biomarker Studies** (Drs. Etzioni, Feng, Huang, Janes, McIntosh, Pepe, Zheng). Methodology for rigorous statistical evaluation of candidate biomarkers, including methods to combine and use biomarkers in screening programs, is a research focus of the Biostatistics and Computational Biology Program. Local collaborations that motivate this work especially with faculty in a developing program in molecular diagnostics include biomarker investigations using the Women’s Health Initiative and Carotene and Retinol Efficacy Trial specimen repositories, the Specialized Programs of Research Excellence (SPORE). The NCI Early Detection Research Network (EDRN) leverages national leadership of our faculty. The statistical methods work in this area is supported by a number of independent R01 grants (Etzioni, Huang, Janes, Pepe, Zheng), the NCI SPORE programs, and the EDRN Data Management and Coordinating Center, based at FHRC.

• **Long-term Intervention and Observational Studies:**
  - **The National Wilms’ Tumor Study** (Dr. Breslow) is a part of the Children’s Oncology Group (COG) designed to eliminate the personal, family and societal burden of cancer in children and adolescents. Dr. Leisenring (based in Cancer Prevention and Epidemiology) has replaced Dr. Breslow as the PI of this project (R01 CA055498). The NWTS Data and Statistical Center collects detailed information on registered patients from over 100 participating institutions. The NWTS collaborates with several groups of molecular biologists in studies of the genetic etiology of Wilms’ tumor and of the role of genetic markers in prognosis.
Women’s Health Initiative (WHI) Clinical Coordinating Center (Drs. Prentice, Kooperberg). The WHI is a long-term national health study that has focused on strategies for preventing heart disease, breast and colorectal cancer, and osteoporotic fractures in postmenopausal women. The WHI Coordinating Center is based in the Cancer Prevention and Epidemiology program, but several key faculty are based in the Biostatistics and Computational Biology Program.

**Coordinating Therapeutic Clinical Trials at the National and Local Level:**

- **Southwest Oncology Group (SWOG) Coordinating Center** (Drs. Guthrie, Othus, Wu) conducts cancer clinical trials in all types of adult cancers, and is coordinating prostate cancer prevention trials. Other investigators in the SWOG coordinating center are affiliated with the Cancer Epidemiology, Prevention and Control program.

- **The CCSG Clinical Statistics Support for Clinical Research Division** (Drs. Storer, Guthrie, Gooley) provides statistical, data collection, and data management support for almost all of the clinical research initiatives undertaken within the Consortium. The faculty provide statistical collaboration in experimental design, data collection, and interim and final analyses of clinical trials, retrospective studies, and laboratory studies.

**Coordinating National Research Consortia:**

- **The Data Monitoring Coordinating Center (DMCC) of the Early Detection Research Network (EDRN)** (Drs. Feng, Huang, Pepe, Zheng). The EDRN is an initiative of the NCI, bringing together dozens of institutions to accelerate the translation of biomarker information into clinical applications and to evaluate new ways of testing for cancer in its earliest stages and for cancer risk. The DMCC provides coordination and data management for the EDRN and develops statistical and analytical methods in response to the scientific needs of the Network. Dr. Feng relocated to M.D. Anderson Cancer Center in 2013, however the EDRN DMCC remains based at FHCRC with Drs. Pepe and Mark Thornquist (Cancer Epi, Prev and Control) as local PIs.

- **The Statistical Center for HIV/AIDS Research & Prevention (SCHARP)** (Drs. Dai, Fleming, Fong, Gilbert, Gottardo, Halloran, Huang, Janes, Magaret, Richardson, Self) provides statistical collaboration to HIV/AIDS researchers around the world and conducts a complementary program of statistical methodology and mathematical modeling research. SCHARP currently serves the Statistical and Data Management Center for the HIV Prevention Trials Network (HPTN), the HIV Vaccine Trials Network (HVTN), and the Microbicide Trials Network (MTN). The Division of AIDS (DAIDS) of the National Institute of Allergy and Infectious Diseases (NIAID), a component of the National Institutes of Health (NIH), funds the HVTN, HPTN, and MTN. Researchers in this group are having a variety of “methods grants”, that develop quantitative methods that are also relevant for other diseases, including cancer (Gilbert, Gottardo, Halloran, Janes, Self).

- Statistical assessment of immune correlates/surrogate endpoints from efficacy trial data (Drs. Self, Gilbert, Fong). Through R03 (R03 AI104370 Fong), UM1 (UM1 AI068635 Self/Gilbert) and R37 (R37 AI054165 Gilbert) funding, program faculty members developed a novel framework for statistical assessment of immune correlates/surrogate endpoints from efficacy trial data, with a series of more than 30 papers published on this topic since 2008. Included in this novel framework is the “sieve analysis” of HIV-1 sequences sampled from infected trial participants, which evaluates if and how vaccine efficacy depends on genotypic and phenotypic characteristics of exposing HIV-1s, which can shed light on the potential protective determinants and thus guide insert sequence selection to increase VE against a broader range of HIVs. Program faculty pioneered sieve analysis of pathogen sequences as an important complement to assessing immune response biomarkers as surrogate endpoints (more than 10 papers since 2008 additionally to those referenced above). Sieve analysis complements immune correlates assessment because (1) It directly assesses a causal effect of vaccine by leveraging randomized treatment assignments; (2) It can identify vaccine-induced selective pressures not detectable by employed immunological assays; (3) It can help validate putative immune correlates (e.g., Rolland et al., Nature, 2012); (4) It motivates further analysis (e.g., to assess whether measured vaccine-induced immune responses explain observed sieve effects); and (5) It generates specific hypotheses to test experimentally. Notably, this immune correlates research is highly complementary to biomarker research conducted by Biostatistics and Computational Biology faculty focusing on cancer applications, with several faculty publishing related methods in both cancer prevention studies and HIV vaccine trials (e.g., Drs. Ying Huang...
and Holly Janes contributed to the “biomarker development” achievement as well as being core members of the RV144 Correlates Team.

- **Developing and extending statistical and bioinformatics compute-platforms** (Drs. M. Morgan, P. Bradley, C. Kooperberg, M. McIntosh, P. Gilbert, and E. Matsen): The primary goal of this work is to establish de-facto standards for sharing methods and data sources. Many of these platforms are world leading and serve as the de-facto standard platforms for research in the computational biology and bio statistical community. In addition to a number of specific tools for the statistical analysis (e.g., ROC curve analysis software [Pepe et al., Stat A, 2009; Janes et al., Stat A, 2009]) the analysis of molecular sequence data, (e.g., proteomics analysis (see proteomics.fhcrc.org), and phylogenetic analysis (https://github.com/fhcrc), the most comprehensive platforms include, Bio-Conductor (Dr. Martin Morgan, Principal Staff Scientist, PI), the leading platform for the statistical analysis of molecular profiling data sets, Rosetta (resettacommons.org; co-PI Dr. P Bradley (contact PI Dr. Baker UW), and initially co-developed by Dr. Kooperberg), the leading platform for macromolecular modeling (e.g., protein structure prediction), and LabKey, (www.labkey.com/www.labkey.org) an open-source platform for data integration and biological data management and analysis, including components for analysis of proteomics (Dr. McIntosh), Flow Cytometry and immune-assay management, (Gottardo/Gilbert) and a variety of other molecular data types (contributed by the research community). Of note, the Bioconductor project reached significant milestones this past year, making available more than 650 software ‘packages’ downloaded to more than 20,000 distinct IP addresses each month. The project, funded by a 5-year multi-million dollar NHGRI grant renewed in 2011 (PI: Dr. M. Morgan) serves the research and training needs of a truly global statistical and bioinformatics community, with recent growth driven by the research opportunities of next generation sequence analysis.

2. **Scientific Accomplishments**

The development of a framework to identify interactions in Genome-Wide Association Studies

Researchers in the Biostatistics and Computational Biology Program have established a novel framework for the identification of gene × gene and gene × environment interactions in Genome-Wide Association Studies (GWAS), and they have deployed this framework in a number of international studies. Program members leading this project are Drs. James Dai, Li Hsu, Michael LeBlanc, Ross Prentice and Charles Kooperberg and include collaborators in other CCSG programs, including other consortium members involved are Drs. Huang, LaCroix, Newcomb, Peters, Potter, Ulrich, and White (Cancer Epi, Prev and Control Program). Research support was provided by a large number of NIH grants to Drs. Hsu (R01 AD014358), Prentice (P01 CA053996), Peters (Cancer Epi, Prev and Control Program), Kooperberg (R01 HG006124, U01 HG004790), Dai (R01 HL114901), and Reiner.

There is a strong assumption that interactions between single nucleotide polymorphisms (SNPs) (or genes) and interactions between SNPs and environmental factors substantially contribute to the genetic risk of a disease. Identification of such interactions could potentially lead to increased understanding about disease mechanisms; drug × gene interactions could have profound applications for personalized medicine; strong interaction effects would be beneficial for risk prediction models that involve both genetic and environmental factors. Since the odds ratios in GWAS are typically very small, and the number of potential interactions in GWAS is at least an order larger than the number of SNPs, which can already be about a million, innovative multistage approaches are needed to identify interactions, as the power for a direct search is very limited. The basic idea of two-stage procedures is very simple: rather than testing every single interaction, we first “screen” SNPs. We select those SNPs that are likely candidates for interaction, for example, because they show a marginal association with the disease phenotype (say, colorectal cancer), or because they show a marginal correlation with an environmental factor, ignoring disease state. Those selected SNPs are then tested for interaction. Statistically this is advantageous if and only if we can ignore the selection in the interaction testing — since then we can correct for a much smaller number of tests for interaction than when all possible interactions are tested, seriously increasing the power of a search for interactions.

In Kooperberg & LeBlanc (Kooperberg & LeBlanc, Gen Epidemiol, 2008) an initial two-stage procedure that controls the Type 1 error, in which only marginally associated variants are tested for interactions, was proposed. Dai et al. (Dai et al., Biometrika, 2012) formalized this procedure, and identified conditions that the screening procedures and the tests for interaction need to satisfy to allow ignoring of the screening when testing for interactions. Building on these conditions, Hsu et al. (Hsu et al., Gen Epidemiol, 2012) developed a
comprehensive procedure that is among the most powerful approaches currently available to identify interactions in GWAS. The method combines a variety of different screening procedures, and the subsequent test for interaction depends on which screening procedure was used for a particular SNP to pass the screening. These procedures are currently state of the art for identifying interactions in GWAS. Each of these papers includes a number of simulation studies identifying situations when these procedures are and are not more powerful than alternatives. The conclusion is that while situations exist when other procedures are more powerful, in all reasonable situations the procedure of Hsu et al. (Hsu et al., Gen Epidemiol, 2012) is close to the most powerful procedure.

Within the GWAS studies that consortium members are involved in, these procedures are now typically used for identifying gene × environment interactions. For example, Hutter et al. (Hutter et al., Cancer Res, 2011) identified an interaction between vegetable consumption and a variant on chromosome 8 on colorectal cancer. A series of additional papers from the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) (Lead by Dr. Peters from the Cancer Epidemiology & Prevention Program, also involving Biostatistics and Computational Biology faculty) that use this approach are currently under review.

**The development and use of biotechnologies profiling the T Cell Repertoire to establish the natural history of the adaptive immune system in cancer.**

Over the past five years, Dr. Robins has lead a group of collaborators, including Drs. Christopher Carlson and Edus Warren in the CCSG, to develop a technology (including computational algorithms and biochemistry) that utilize the power of high-throughput sequencing to measure the dynamics and properties of the adaptive immune system (Robins et al., Blood, 2009). Pilot funding from the Cancer Consortium supported the initial pilot proposal that developed these methods. An entire new field of immune profiling has sprung up around the technology, including biochemistry and their companion computational methods, and the Robins group is leading their application in a variety of areas, including cancer. A total of 5 patents pending exist on the fundamental technology and applications. This technology has been spun off to Adaptive Biotechnologies, Inc., and is presently used for clinical decision-making, and as a research resource used by many faculty in the CCSG and world-wide.

In brief, the DNA loci in the human genome that encode the B and T cell receptor (BCR or TCR) genes rearrange somatically in adaptive immune cells to produce an enormous variety of receptors in order to recognize the vast array of potential pathogens. The team has created a multiplex PCR technology that quantitatively amplifies every possible rearrangement and a procedure to sequence these specific molecules at high-throughput (Robins et al., J Imm Methods, 2012; Larimore et al., J Immunol, 2012; Sherwood et al., Sci Transl Med., 201, Robins et al., Sci Transl Med, 2010; Emerson et al., J Immunol Method, 2013). Although the set of applications being pursued with collaborators is large (e.g., see Zhu et al., Nature, 2013), Dr. Robins has primarily focused our cancer-related efforts on cancer diagnostics, or predictive medicine. There are three areas where this technique is actively being applied. First is diagnosis and monitoring of minimal residual disease for hematological malignancies. If the original cancerous cell is a B or T cell, a lymphoid malignancy, then most or all of the cancerous cells have the same BCR or TCR rearrangement -- cancer is clonal, usually with the entire cancer mass derived from a single cell. These rearranged sequences act as a unique tag of the cancer cells. Given a bone marrow sample at diagnosis for leukemia or lymphoma, our technology is readily able to identify the TCR or BCR sequence in the cancer clone and then track it after treatment below one cell in a million. He has shown in Acute Lymphoblastic Leukemia that his technology is far more sensitive and more accurate than the state of the art flow cytometry (Wu et al., Sci Transl Med, 2012). The second area is the study of tumor infiltrating lymphocytes (TILs), the study of which is a central component of nearly all immunotherapy research for cancer. Using his TCR sequencing technology, Dr. Robins and colleagues can directly assess T cell quantity and clonal expansion in TIL (Sherwood et al., Cancer Immunol Immunotherapy, 2013). We have completed studies in colorectal cancer, ovarian carcinoma, and melanoma that all show clonal expansion in TIL is an independent and informative prognostic biomarker for disease free survival. Additionally, TIL count and clonality is highly predictive of response to immunotherapy in melanoma. Third, they have hypothesized that diversity of the T cell repertoire is a marker for immunocompetence. To test this, they have multiple studies of immune reconstitution after hematopoietic stem transplant. The studies all show that higher diversity reduces risk of mortality and morbidity from infection. Most recently Dr. Robins and colleagues have developed a method for using this technology to precisely quantify the number, or percentage, of cells in a solid tumor which are T Cells and showed that one can use these to make improved predictions of ovarian cancer prognosis (Robins, et. al. Sci Trans. Med, 2013).
**Defining the standards of practice for rigorous biomarker research.**

The FHCRC has become an internationally renowned center for statistical expertise in methodology for biomarker evaluation – together our program members hold over a dozen grants that support research on developing pertinent new statistical and/or biotechnological methodologies for diagnostics and predictive medicine, including in areas such as cancer early detection, evaluation of biomarkers for risk prediction (Wang, R01 GM082802), for prognostic research (Zheng, R01 GM085047), and most recently for treatment selection (Janes, R01 CA152089; Huang, R01 GM 106177). The work is motivated by a variety questions that arise in discovery research (Wang, R01 GM082802; Randolph, R01 CA126205; Feng, Thornquist, Pepe U24 CA086368) and validation research (Janes et al., Ann Int Med, 2011; Pepe et al., Am J Epidem, 2008; Pepe & Janes, JNCI, 2008; Janes et al., Ann In Med 2008; Kerr et al., Am J Epidem, 2012).

Developing biomarkers for detecting subclinical cancer has been lead initially by advances in biotechnology, but practices for using these technologies in a sound study design has lagged. Unlike the common practices in therapeutic trials, there were no design standards or even commonly used terms to discuss the state of biomarker translational research (e.g., comparable to Phase I, II, III trials, etc.). Biostatisticians at the FHCRC took the leadership to begin developing these standards. The team helps lay the foundation for rigorous biomarker research, and then by example demonstrate to the biomarker research community how they can be used in practice. Two foundational manuscripts helped establish the baseline of the filed. The first landmark paper (Pepe et al., J Nat Cancer Inst, 2001) provided a roadmap to define a phased sequence of studies that could lead to a successful clinically useful biomarker for early detection. In addition to outlining basic design of studies at each phase this work importantly provided a common language for biomarker researchers to communicate with each other and to the world. The nomenclature provided in this first set of papers has not become as standard as the phased therapeutic trials. Subsequently the group provided a prototype design that should lead to improved quality for biomarker validation studies, called the PRoBE design – Prospective sample collection, retrospective blinded evaluation. The basic concept is straightforward: prospective collection of samples and outcome ascertaining in the clinical context of interest with biomarker assays of random subsets of cases and controls. The emphasis of the work is on the collection of samples in a specific clinical context, and establishment of meaningful effect sizes in that context. The PRoBE design has been used as a framework for designing a coherent and clinically meaningful biomarker validation study (Pepe et al., J Nat Cancer Inst, 2008). These two contributions are now commonly adopted by the NCI and others. Several RFAs (National Institutes of Health) issued by the NCI refer to these frameworks.

Our program members have been demonstrating the use of this framework in a variety of research programs, including in in NCI Funded SPORE programs, in foundation-funded research, and through leadership of the EDRN coordinating Center, to a number of research sites across the nation. Of note has been our rigorous studies (funded by the EDRN) that lead to approved for use by the FDA for %proPSA in 2012 for reducing numbers of unnecessary prostate biopsies (Sokoll et al., J Urol, 2008; Sokoll et al., Cancer Epidem Biom & Prev, 2010). Other examples influencing local CCSG programs may be found in a number of studies that have been completed or underway throughout our Center, including in the prostate SPORE (Dr. Yingye Zheng), the Ovarian Cancer SPORE (Dr. Martin McIntosh), the Breast Cancer SPORE (Dr. Pei Wang), with the Women’s Health Initiative (e.g., for triple negative breast cancer [Li et al., Br Cancer Res Treat, 2012]) -- McIntosh and Pepe with Dr Chris Li -- and colon cancer [Ladd et al., Cancer Prev Res, 2012] -- Feng with Hanash and Prentice), and other examples using specimens derived from large national biorepositories to validate ovarian cancer biomarkers in the Prostate Lung Colon and Ovarian screening study (Cramer et al., Cancer Prev Res, 2011) and evaluation of biomarkers for ovarian and lung cancers with samples from the CARET study (Anderson et al., J Nat Cancer Inst, 2010, Pass et al., N Engl J Med, 2012).

**Identified Vulnerabilities in glioblastoma.**

Glioblastoma multiforme (GBM) is a malignant brain tumor that is resistant to existing drug and radiation-based therapies. As a result of this resistance, 90% of patients diagnosed with GBM succumb within two years, highlighting the urgent need for new treatment strategies. Dr. Robert Bradley, co-first author with graduate student Christopher Hubert, and CCSG collaborators James Olson and Patrick Paddison, reported in *Genes & Development* a genome-wide shRNA study and identified a novel viability requirement for glioblastoma stem cells (GSCs) -- a spliceosome component PHF5A. This is now being pursued as a putative therapeutic target for GBM. This was identified as a major finding by other journals (No Authors Listed, Cancer Disc, 2013).

Hubert, et al. (Hubert, et al., Genes Dev, 2013) infected GSC and normal neural stem cells (NSC) with pools of shRNA-expressing viruses and then assessed the cells for differences in shRNA content over time. Most of the
tested shRNAs either caused no difference or were underrepresented in the NSCs more than the GSCs; however, the authors identified 27 candidate genes which preferentially inhibited GSCs. Seven of these candidate genes were validated by other criteria and in multiple cell lines; the strongest hit was PHF5A.

Dr. Robert Bradley, a functional genomics expert who focuses on RNA splicing, used computational and experimental techniques to find that PHF5A is a core component of the U2 snRNP spliceosome, a nucleoprotein complex necessary for the removal of introns from pre-mRNA after transcription. Deep RNA sequencing (RNA-seq) experiments identified exon skipping or intron retention in hundreds of genes in PHF5A k/d GSCs but not NSCs. These aberrant splicing phenotypes correlated with a subset of exons encoding characteristic sequences in the 3’ splice site, leading to severe RNA processing defects in many cell cycle progression genes. Furthermore, this phenotype was replicated with three different small molecule inhibitors of the U2 snRNP complex of the spliceosome or by knocking down known PHF5A binding partners in the spliceosome. Before PHF5A k/d caused GSC cell death, the authors also noticed dramatic G2/M phase cell cycle arrest. Taken together, these data suggest that PHF5A functions to recognize a specific class of exons with distinctive 3’ splice sites that are critical for cell cycle progression in GSC.

To evaluate this altered splicing phenotype in vivo a competition experiment was deployed in a xenograft GBM model. PHF5A-shRNA expressing GSCs were unable to proliferate and engraft in vivo and exhibited characteristics of cell cycle arrest two days post implantation. The authors also established GBM tumors expressing a doxycycline-inducible PHF5A-specific shRNA diminished to near undetectable levels after doxycycline administration, while control shRNA transduced tumors grew normally. These findings confirm that PHF5A is necessary for both GBM formation and maintenance. Finally, normal NSCs, astrocytes, or fibroblasts immortalized or transformed with the oncogenes Myc or Ras became acutely sensitive to inhibitors that target the PHF5A-containing component of the spliceosome. This finding suggests that inhibition of PHF5A may be generalizable to a wide range of cancers that rely on these oncogenes. This work was supported by the CCSG genomics shared resources.

**Framing the debate regarding guidelines for prostate cancer screening**

The publication of apparently conflicting results from the two large prostate cancer screening trials intensified the debate about the benefits of PSA screening and culminated in a decision by the US Preventive Services Task Force to recommend against screening (Gulati et al., Cancer Epidem Biom Prev, 2011). Their perception is that the harms outweighed the benefits. In work funded by the population surveillance data was funded by the Cancer Intervention and Surveillance Modeling Network (CISNET) Dr. Ruth Etzioni was able to bring new insight into this debate by using her longstanding population models. Specifically, her models allow a deeper understanding of overdiagnosis due to PSA screening (Etzioni et al., Ann Intern Med, 2013; Telesca et al., Biometrics 2008) and the likely roles of treatment changes and screening in the sustained decline in mortality that has been observed since the early 1990s (Etzioni et al., Cancer, 2012; Etzioni et al., Cancer Causes Control, 2008). Modeling was necessary for this question because the absolute benefit (lives saved) and the ratio of benefit to harm (overdiagnoses relative to lives saved) cannot accurately estimated using short-term empirical data derived from trials, and Dr. Etzioni used her models to extrapolate from the trial setting to the population over larger time-scales (Gulati et al., J Clin Epidemiol, 2011). Further, although the trials appeared to be conflicting, the circumstances of their implementation were very different; models were needed to reconcile the results in terms of plausible values for the underlying screening efficacy (Gulati et al., Cancer Causes Control, 2012). Finally, the empirical results from the trials could not inform about overdiagnosis which is inherently unobservable; we had previously developed models for estimating overdiagnosis from incidence under screening (Gulati et al., Cancer Epidem Biom Prev, 2011; Telesca et al., Biometrics 2008).

This modeling work has questioned the evidence used by the Task Force (Etzioni, Evid Based Med, 2013; Etzioni et al., Med Care, 2013) and was used to propose approaches that mitigate the harms of screening rather than eliminating the opportunity for early detection. This work has been recognized by the clinical, public health, and statistical communities. They have used results of our models to inform the early detection guidelines panels for three national organizations, namely, the American Cancer Society (general early detection panel, chairing the subcommittee on cervical cancer screening and co-authored the 2010 guideline (Wolf et al., CA Cancer J Clin, 2010) on prostate cancer screening), the American Urology Association (prostate cancer early detection panel) (Carter et al., J Urol, 2013), and the National Comprehensive Cancer Network (prostate cancer early detection panel).

**Identification of the Three-Dimensional Structure of TAL-effector: DNA Interactions.**
The ability to target effector molecules (i.e., small molecules that can specifically bind a protein and regulate its activity) to specific sites in large genomes is critical for a wide range of molecular biology and biotechnology applications, including the development of targeted therapies. Examples include correction of disease mutations and creation of targeted gene knockouts. Recently, a new family of bacterial proteins, the TAL effectors, was discovered whose mode of DNA recognition has made them the molecule of choice for engineering proteins that recognize and bind to target sites of interest. Using the TAL effector platform, DNA binding proteins with a wide range of binding specificity can be constructed easily and with reasonable success rates. A wide range of targeted modifications to cellular state can be affected by fusing these DNA binding proteins to effector molecules, such as nuclease or transcriptional activators or repressors.

A key question to realize the potential of these effectors is, “What is the molecular basis/structural explanation for the unique DNA targeting ability of TAL effectors?” Knowledge of the three-dimensional structure of a TAL effector-DNA complex could provide tremendous insight into this emerging gene-targeting platform, and it might enable rational engineering of additional effectors to further enhance our ability to construct sequence-specific DNA binding proteins.

In a collaboration between Dr. P Bradley (funded by R01 GM082277) and Dr. Barry Stoddard’s group (Basic Sciences) a novel approach was used to identify the three-dimensional structure of the Tal Receptor (Mak et al., Science, 2012, Dr. P. Bradley co-lead and contact author). The work, published in February 2013, has already been cited dozens of times. Dr. Stoddard’s group applied the tools of X-ray crystallography to collect a large experimental (diffraction) dataset on the TAL effector PthXo1. These data on their own were unable to determine the 3D structure. Dr. Bradley used molecular modeling techniques he and others had originally developed for protein structure prediction to solve the structure. He generated predictions of the structure of the protein:DNA complex, and these predictions were accurate enough to enable determination of the structure by a technique called “molecular replacement.” This was one of the first examples using protein structure prediction, or macro-molecular modeling in general, to solve the structure of a protein that was not amenable to experimental approaches alone. This work represents collaboration across different CCSG programs. The computational biology work was made possible by CCSG support to Center scientific computing.

**Diet and Cancer Association Studies Using Biomarker-calibrated Exposure Estimates.**

Despite the most recent emphasis on molecular predictors for disease, it is exposure or environmental factors that contain the bulk of the information in predicting cancer risk. Our CCSG program retains a strong group dedicated to advancing this area, especially in the area of diet. In spite of some decades of study few clear cancer risk associations have emerged from nutritional epidemiology research (WHO Tech Report, 2003; WHO, 1997), even though there are established risk elevations for several prominent cancers among persons having excess body fat. Reports to date have relied almost exclusively on self-reported diet. For some aspects of diet, including total energy consumption and protein consumption, there is an established biomarker of short-term consumption. We have conducted biomarker sub-studies among 994 women from the Women’s Health Initiative. Regression of (log-transformed) biomarker energy on (log-transformed) food frequency questionnaire (FFQ) energy and other factors illustrated only a weak signal from the FFQ for both total energy and protein, and importantly, revealed strong systematic biases in the self-report data related to body mass index (BMI), age, and ethnicity. For example, overweight and obese women in WHI underreported total energy consumption on FFQs by 30–50%, while slim women tended not to underreport (Neuhauser et al., Am J Epidemiol, 2008; Prentice et al., Am J Epidemiol, 2011). However, the regression equations just mentioned led to calibrated consumption estimates from the self-report data and other characteristics (BMI, age, ethnicity, …) that could explain the majority of the consumption variation, especially after adjusting for temporal biomarker variation using data from reliability sub-studies that involved repeating the entire protocol about 6 months after the initial application for a 20% subsample (Prentice et al., Am J Epidemiol, 2011). When calibrated energy was associated with subsequent cancer incidence in WHI cohorts, strong positive associations emerged for total invasive cancer, and for breast, colon cancer, endometrial, and kidney cancer, none of which were evident without biomarker calibration of the self-report data (Prentice et al., Am J Epidemiol, 2009). The associations essentially disappear when BMI is added to the disease risk model, suggesting the energy associations to be mediated by body fat deposition over time. Similar energy association results were found for coronary heart disease, not for stroke (Prentice et al., Epidemiol, 2011), and for diabetes (Tinker et al., Am J Clin Nutr, 2011). Also, calibrated protein was found to relate inversely to frailty incidence (Beasley et al., Am Geriatr Soc, 2010), whereas the association was much weaker without calibration. The second biomarker study also included indirect calorimetry for resting energy expenditure (REE) assessment, thereby giving an objective measure of total activity-related energy expenditure (AREE) as the difference between total energy...
expenditure and resting energy expenditure (Neuhouser et al., Am J Epidemiol, 2013). These reveal systematic biases in AREE self-reports, and analyses are underway to jointly associate total energy, and AREE to the risk of cancer and other chronic diseases.

The rather few dietary components for which there is an established biomarker is the major limitation to a broad application of a biomarker calibration approach to nutritional epidemiology. For this reason, we are currently (2010-2014) conducting a human feeding study among 150 WHI women in Seattle where all food and drink is provided over a two-week period using an individualized diet that approximates each woman’s usual diet. Provided nutrients/foods over the two-week feeding period will be regressed on pertinent urine and blood measures, including metabolomic profiles, and study subject characteristics for the development of novel biomarkers, for subsequent application in chronic disease association studies in WHI and other cohorts. Research for this project is supported by The Nutrition Assessment Shared Resource.

**Identification of surrogate endpoint for vaccine trial efficacy, and its impact on the design of studies in infection associated cancer.**

The RV144 Phase 3 clinical trial provided an important milestone for the HIV-1 vaccine field – it was the first trial demonstrating partial efficacy of an HIV-1 vaccine to prevent HIV-1 infection (Roland et al., Nature 2012). Consortium faculty members Drs Gilbert and McElrath, and colleagues undertook an expansive biomarker study to generating hypotheses to explain the mechanism of action among those who were protected by the vaccine. Drs. Gilbert, Edlefsen and Gottardo provided analytic support to this effort. Putative immune response biomarkers were evaluated in vaccine recipients who became HIV-1 infected, in comparison with vaccine recipients who did not acquire infection, and six assays were selected for larger-scale case-control analysis. This work generated the hypothesis that antibodies to the V2 region of the HIV-1 Envelope were predictive of the protection and possibly part of a mechanism of protection (Haynes et al., N Engl J Med, 2012). To test this hypothesis, program faculty applied its “sieve analysis” methodology to the HIV-1 sequences of infected subjects, indicating that vaccine efficacy was significantly greater against HIVs with genetic signatures at sites 169 and 181 of V2 (Rolland et al., Nature, 2012). These results motivated fine mapping and structural biology experiments that further supported V2 antibodies as a potential mechanism of protection. Nature (Nature, 2012 end-of-year issue) selected Rolland et al. (Rolland et al., Nature, 2012) as one of eight ‘fast-paced discoveries’ of the year, and these results have guided the research plans of the FHCRC-based HIV Vaccine Trials Network to conduct novel efficacy trial designs of refined HIV-1 vaccine regimens (Gilbert et al., Stat Comm Infect Disease, 2011). Program faculty member Paul Edlefsen is co-first author of Rolland et al. (Rolland et al., Nature, 2012).

The RV144 Immune Correlates research has a fundamental relevance for the CCSG, including but not limited to the role HIV has in increasing the risk of a number of cancers. Most relevant is the larger role that infectious disease may play in cancer burden internationally and thus prevention of those infections – through vaccine research – can prevent many cancers in developing countries. The quantitative sciences group in our CCSG program includes members who span HIV vaccine and cancer prevention trials researchers, and the RV144 Immune Correlates study introduced a new paradigm that will be used to identify immune correlates in a variety of vaccine discovery work. The work has generated interest for broader application, including cancer vaccine efficacy trials conducted or planned by FHCRC (e.g., HPV and Burkitt’s lymphoma vaccine trials) as well as cancer prevention trials of general prevention interventions (e.g., WHI).

### 4. Future Plans

The Biostatistics and Computational Biology Program have identified several areas of strategic importance to develop in the coming years, and processes and procedures will be put in place to foster these areas. Emphasis Areas (EA) include EA1) developing methodologies for and analysis of moderate and high-throughput technologies, including the simultaneous analysis of multiple-omics technologies and biomarker data, EA2) multi-scale molecular modeling, and EA3) expanding efforts in the area functional genomics of cancer. These three areas of research build on the strengths of our program and expanding in areas with the largest opportunities and potential impact.

These three scientific areas are directly supportive to the Aims of our program – Aim 1 quantitative methods in molecular data analysis, Aim 2 functional genomics and tumor immunology, especially in diagnostics and therapy, and Aim 3 dissemination of these methods for use in other CCSG programs. Priorities for strategic recruitments will be in these areas for the next project period. In addition, program leaders will further expand institutional/programmatic efforts to build this expertise and collaborations in these areas locally. This will be
done through engagement with other CCSG programs by way of inter-program retreats/meetings and jointly sponsored programs based around those three themes to facilitate new collaborations and grant opportunities. Specifically, the program seminar series will emphasize EA1 by including both methodologists as well as substantive applied scientists; each will support dissemination of new techniques and/or new areas of potential impact. When selecting the speakers an emphasis is placed on speakers whose research most closely supports that of Aim 2, whether statistical methods or substantive experimentalists whose research relies on innovative techniques and methods. Aim 3 will be supported by a number of research grants whose aims include the development and dissemination of algorithms, and expanded outreach to invite program members to Bioconductor and Rosetta tutorials – over the past year alone over 250 CCSG members or their staff spanning every program have been trained in classes in a number of workshops. We intend to expand that work to emphasize use and development of new software packages in R and Bioconductor, and training in the use of these tools in the fields of virology, molecular biology, and personalized medicine.

Several new collaborative research initiatives are planned. Dr. Kooperberg and colleagues, including genome scientists Drs. Debbie Nickerson and Jay Shendure (Cancer Basic Biology) and Ulrike Peters (Cancer Epi, Prev and Control) have submitted a proposal for a U54 Big Data Center of Excellence, which would produce tools and resources to utilize large complex data sets.

To leverage his recently awarded NCI U01 Cancer Target Discovery and Development grant, Dr. McIntosh has initiated a new inter-programmatic working group that meets monthly to stimulate new translational research collaborations for development of immunotherapies and diagnostics for lung and head and neck cancers. Group members include immunotherapy researchers Drs. Stan Riddell (IVD) and Hootie Warren (IVD and Global Oncology); lung/head and neck cancer experts Drs. McGarry Houghton (Cancer Basic Biology) and Renato Martins (Cancer Epi, Prev and Control); and Dr. Robins (Biostat and Comp Bio).
Cancer Basic Biology Program

1. PROGRAM OVERVIEW

1A. Program focus

The Cancer Basic Biology (CBB) Program goal is to stimulate inter-disciplinary, inter-institutional, collaborative research into the genomic and cellular mechanisms that regulate the normal and transformed phenotype. Program members develop new molecular approaches and tools to advance disease diagnosis and therapy, and join with other Consortium program members to advance translational cancer research. Three CBB scientific themes are foci for program research:

1. Biology of the nucleus in normal and cancer cells.
   1A. Genetic and epigenetic mechanisms regulating gene expression in normal and tumor cells.
   Cancer is associated with mutations in epigenetic regulators, transcription factors, signaling proteins and cell cycle regulators. We are investigating the genetic and epigenetic mechanisms that regulate gene expression in normal and cancer cells. A highlight of the last funding period was the discovery that components of the basal machinery of RNA splicing are essential in cancer cells but not in normal cells, a discovery providing new opportunities for therapy.

   1B. Maintenance and loss of genome stability in normal and cancer cells. Genetic instability drives the origin and progression of cancer. It is thus critical to identify the mechanisms that maintain genomic integrity, and how they are disrupted in cancer. CBB members focus on the molecular determinants of nuclear structure and genomic stability, mutation mechanisms including the repair of therapeutic DNA damage, and mechanisms that ensure faithful genome replication and chromosome segregation. A major advance was an intra-program CBB collaboration that isolated and characterized the kinetochore, a key protein complex that regulates chromosome segregation to prevent aneuploidy.

   2A. Regulation of normal and cancer cell biology. A detailed molecular understanding of the signaling pathways and molecular mechanisms that regulate the cell cycle, cell differentiation, stem cell maintenance and cell migration provides the scientific basis for understanding ‘hallmarks’ of cancer such as cellular immortality and independence from growth-regulatory signals. A highlight of the last funding period was the exploitation of an elegant model system for uncovering causal relationships between events that occur in aging cells and that lead to genome instability.

   2B. Genetic, metabolic and high throughput screening strategies to improve cancer diagnosis and therapy. Many types of cancer have vulnerabilities that can be exploited for therapy. These vulnerabilities are being identified as part of the global effort to catalog genomic and metabolic abnormalities unique to, or shared among, different tumor types. These abnormalities are being linked to potential new therapies by both targeted and more global genetic and chemical screens. An important focus in the coming period will be to build on recent exciting progress with RNA interference screens applied to brain and neuroendocrine tumors.

3. Protein design and genome engineering as enabling technologies to advance basic and translational cancer biology.
   We have substantial accomplishments from the previous period in developing novel approaches and reagents for protein design and genome engineering. The refinement and application of these tools will facilitate science in themes 1 and 2 above. These powerful technologies will be used by CBB investigators to address unsolved problems in cancer diagnosis and therapy in the next period.

1B. Program structure

Background: CBB is a newly formed Program created by merging portions of the previous programs in Basic Biology (BB), Genome Instability and Mutagenesis (GIM), and Stem and Progenitor Cell Biology Program (SPC), together with new faculty recruitment at all levels. CBB was created to provide a program with a sharper focus on basic and translational cancer biology, while combining the strengths of the BB, GIM and SPC programs. All three preceding programs were highly accomplished, as outlined below.
In 2008 reviewers rated the Basic Biology Program as Outstanding. The site visit committee "unanimously judged .... that this program is clearly outstanding". However, reviewers were concerned that a portion of faculty was not working on cancer, that clear paths to translate basic science advances were not in place, and that the level of intra-programmatic collaboration was modest. The Genome Instability and Mutagenesis Program was assessed Excellent to Outstanding with strong translational research and good use of CCSG mechanisms to recruit new faculty and stimulate research. Weaknesses noted included poorly developed efforts focused on gene-environment interactions, and few successes in developing new tools and methods with translational potential. The Stem Cell Program was new in 2008, and was rated Very Good to Excellent, but with a limited focus on cancer.

CBB increases inter-institutional collaboration by bringing together Basic Biology, which was 90% FHCRC based, with Genome Instability and Mutagenesis and Stem and Progenitor Biology, where >90% of members were based at UW. This transition was planned by Consortium Leadership in 2011 after consultation with the new Program heads and advice from the EAB, and builds on combined Basic Biology and Genome Instability and Mutagenesis strengths while addressing weaknesses noted in the 2008 CCSG review. Inclusion criteria for CBB members and grants have been tightened to ensure cancer focus.

**Present structure:** The new program is jointly led by Drs. Jonathan Cooper and Ray Monnat. Both are united in fostering research in all areas of the basic biology of normal and cancer cells, together with the development of new molecular approaches and tools to improve cancer diagnosis and therapy. A subsidiary aim of CBB is to develop, with other Consortium programs, the intellectual and technical infrastructure to advance translational cancer research. The CBB leaders are based at the FHCRC (Cooper) and the UW (Monnat), where they are in continuous contact and discussion with CBB faculty to assess research progress and the adequacy of shared resources. Monthly meetings of the program leadership ensure coordination across the key areas of Program membership, recruitment, and strategic research directions. While developing CBB, the Program heads Cooper and Monnat jointly reviewed and revised the program membership, recruited new faculty, and eliminated faculty whose research was not relevant to cancer.

The Consortium structure fosters a high level of interaction through seminars and clubs and research groups. Scientists from Consortium partner institutions meet in cross-disciplinary groups such as the Northwest Genome Engineering Consortium (NGEC), Mitosis Club and Seattle Ubiquitin Research Group, and at CCSG-sponsored events such as the Small Nucleic Acids Symposium and Workshop (2010), a Cancer Genomics Symposium (2012), and postdoc-organized Seattle Genetic Instability Symposium (2013 and 2014). These meetings fueled new research in growth areas such as genome engineering, chromosome segregation, RNA interference, genomics and mutation research, as highlighted in Scientific Progress section.

Direct funding from the CCSG for Pilot Projects, targeted recruiting and Shared Resources has also been catalytic. Pilot Awards from the CCSG supported 18 new projects in CBB. Pilots from the Institute of Translational Health Sciences (the local CTSA) supported another 3 projects in CBB, with a further 9 pilots funded by the Ovarian, Prostate or Breast SPORE grants. Pilot awards supported new work on metabolic subtypes in breast cancer; telomerase effectors; HIF-induced cancer stem cells; monoallelic expression in myelodysplastic syndrome; synergetic therapies for glioblastoma; and the use of synthetic lethal RNAi screens to identify drug targets in cancers with Fbw7 mutations. These competitive awards speak to the success of CBB investigators in bridging basic and translational research.

CCSG Recruitment Awards helped bring Robert Bradley, Jonathan Grim and Eleanor Chen to the Consortium. Bradley uses computational and wet lab approaches to analyze the complexity of RNA splicing. One of his collaborations is highlighted in the Scientific Progress section. Grim is using marrow transplan-tation to accelerate leukemia gene discovery by transposon-based insertion mutagenesis. Chen is using a combination of zebrafish and mouse models to identify new treatment strategies for rhabdomyosarcoma.

A CURE (Continuing Umbrella of Research Excellence) supplement to K. Peichel from the CCSG is being utilized for a summer research training program aimed at undergraduates from under-represented minority groups, part of a larger effort to enhance research training diversity and participation.

CCSG Shared Resources play a critical role in enabling research in the small labs and groups that predominate in the Cancer Basic Biology Program. Consortium Shared Resources for Genomics, Proteomics & Metabolomics, Cell Imaging and Comparative Medicine are heavily utilized—and highly valued—by CBB Program faculty as an effective way for small labs to pursue instrumentation and facilities-intensive genomic, proteomic, imaging or rodent research.
1C. Program Leadership and Qualifications

Program Head Jonathan Cooper was Program Head of the previous Basic Biology Program from 2009, and Associate Head for 5 years before that. His research focuses on signal transduction in normal and cancer cells, with a primary interest in the roles of tyrosine phosphorylation and ubiquitylation in regulating cell migration during development and cell transformation. He has published 180 peer-reviewed research articles, 120 as first or senior author, and 26 book chapters and reviews. He is Senior Vice President and Director of the Basic Sciences Division of the FHCRC, which includes approximately half of the CBB membership. As a Senior Vice President of the FHCRC, Cooper meets biweekly with FHCRC leadership, and sits as a member of the FHCRC Appointments and Promotions committee. He serves as Consortium Associate Director for Basic Sciences, and is a member of the Institutional Planning Committee and Membership sub-committee. Between 1995 and 2000 he was the FHCRC Director of the Graduate Program in Molecular and Cellular Biology, which awards PhD degrees through the UW. Cooper is the P.I. of an NCI T32 training program on Chromosome Metabolism and Cancer, which currently has 6 postdoctoral and 2 predoctoral trainees focused on basic science related to cancer. He has been continuously funded by NCI grants since 1985 including a MERIT award (1998-2006). He has been a member and chair of an ACS and two NIH study sections, and an ad hoc reviewer for T32, F32 and P01 grants. Cooper, with Monnat, identifies new recruits for the CBB Program, sits on the Scientific Steering Committee of the CCSG, and is a member of the CCSG Appointments Committee. He is responsible for faculty recruiting, mentoring, evaluation and retention in the basic sciences at the FHCRC.

Program Head Ray Monnat developed the previous Genome Instability and Mutagenesis Program for inclusion in the CCSG in 2002. Monnat’s research has focused on RECQ helicase roles in DNA metabolism and cancer biology; and on developing tools and approaches for genome engineering. He has published 100 peer-reviewed research articles on these topics. Monnat is a Professor of Pathology and Genome Sciences (joint) at the University of WA; a founding member of the Northwest Genome Engineering Center; a member of the UW Molecular and Engineering Sciences Institute; and a founding member of the Center for Synthetic Biology. He participates in graduate training programs in Genome Sciences, Pathology, Molecular and Cellular Biology, Environmental Pathology/Toxicology, MSTP and Genetic Approaches to Aging. He is a founding member and on the steering committees of the Interdisciplinary Training Program in Cancer Research and the Molecular Medicine Training Program. Monnat has been the PI of an NCI-funded P01 grant focused on RECQ helicas in cancer for 15 years, and has had additional continuous funding from the NCI as well as other sources since 1986. He has been a member of the Fanconi Anemia Research Fund SAB since 1999, serves on the UW School of Medicine Appointments and Promotions Committee, and has been a member of the Chemical Pathology and the Biomedical Research Training Study Sections as well as an ad hoc reviewer for the NIGMS, NCI, NIA and NIEHS. Monnat coordinates with UW-based members of the CBB to ensure their interests are represented within the Consortium, and serves on the Consortium Scientific Steering Committee. He identifies new Consortium members and has recruited many highly-collaborative translational researchers to the CBB program.

Associate Program Head Sue Biggins is a mid-career basic researcher who studies chromosome segregation using yeast. The relevance of her work for cancer is evident from her characterization of the protein composition of the kinetochore (which links the chromosome to the mitotic spindle) and discovery that the large majority of kinetochore proteins are conserved in humans. Moreover, two major kinases that regulate chromosome segregation, Aurora B and Mps1 (TTK), are being investigated as chemotherapy targets since their inhibition leads to extreme aneuploidy and death of cancer cells. Biggins is highly collaborative: she has nucleated a core of mitosis researchers in the Consortium, and fostered a large number of collaborative, high-profile publications. She works with Cooper to recruit, mentor and retain CBB faculty and has been a member of the Consortium Scientific Steering Committee.

Associate Program Head Larry Loeb is best known for his measurements of mutation rates and his mutator hypothesis for cancer, first proposed 50 years ago (Loeb, Nature Rev. Cancer 2011). He is a past president of the AACR and of the Environmental Mutagen Society, been keynote speaker at over 17 international conferences, and was awarded the AACR Princess Takamatsu Award in 2008 and was elected in the first class of Fellows of the AACR Academy in 2013. Loeb’s present research is focused on mechanisms that ensure the fidelity of DNA replication; detecting and quantifying rare and subclonal mutations in human
1D. Program Membership and Inter-programmatic Collaborations

The program leadership uses stringent science and funding criteria to ensure a strong focus on cancer within the CBB program. The program currently has 73 members from 18 departments and 2 institutions; 42 members have primary appointments at FHCRC, and 31 at UW. This represents an increase in UW members to 42%. Approximately 93% of members have peer-reviewed funding, or are newly recruited and supported by institutional startup funding. Seventeen new members were added through targeted recruiting at the junior level. Examples include Robert Bradley, David MacPherson, Slobodan Beronja and Eleanor Chen. These researchers all add new energy to solid tumor translational research. Bradley has already played a leading role in research on glioblastoma, featured below in the Accomplishments section. MacPherson was recruited from an independent fellow position at the Carnegie Institution. Prior to that, he was a postdoctoral fellow with Tyler Jacks at MIT. He has used mouse models with deficiencies in Rb-related "pocket proteins" to develop a model for human retinoblastoma and demonstrate the importance of a miRNA and p19Arf interactions. MacPherson is now developing mouse models for lung cancer, a new area being targeted for growth in the next funding period. Beronja was recruited from Elaine Fuchs' laboratory at Rockefeller. He has used pooled-format lentiviral-mediated RNAi together with quantitative Illumina sequencing to perform rapid, relatively inexpensive genome-wide screens of gene function during embryonic development and in Ras-induced epidermal hyperplasia. He plans to extend this approach to identify in vivo enhancers of tumor initiation and progression in the oncogenic Ras animal model. Dr. Eleanor Chen, a new Assistant Professor of Pathology, started at the UW in mid-November 2013. Eleanor had M.D.-Ph.D. training at Minnesota, clinical training at Brigham & Women's-Harvard, and then a Fellowship in the lab of David Langenau at the Cancer Center/Harvard Stem Cell Institute. She is a Board-certified anatomic pathologist who brings a vigorous research program focused on zebrafish and mouse models of human cancer. More junior translational researcher hires are planned for the next funding period.

CBB program members have also been added at the senior level. A particularly important addition is Dr. Eric Holland, newly recruited to the Consortium as Associate Director of Solid Tumor Translational Research and member of CBB. His mission is to stimulate translational research into solid tumors, starting with brain cancer. His leadership will be instrumental in attracting additional translational researchers into CBB, as outlined in Section 3, Future Plans, below.

The program currently has $39.1M in research funding (direct), of which $32.7M is peer-reviewed and $7.1M is from the NCI. Baker, Eichler, Eisenman, Gottschling, Groudine and Henikoff are members of the National Academy. Six investigators (Baker, Malik, Moon, Henikoff, Zheng and Eichler) are HHMI Investigators. Eisenman, Gottschling and Groudine hold R37 MERIT awards. Other funding sources include DOD, DARPA, NSF, the Ellison Medical Foundation, Pew Charitable Trusts, Kimmel Foundation, Helen Hay Whitney Foundation, Susan B. Komen Foundation and W.M.Keck Foundation. Due to the local tradition of basic research in small laboratories led by independent investigators, most of this funding is in the form of independent research grants (R01s). However, several CBB Members are PIs on larger grants: Blau (P01), Eichler (P01), Monnat (P01), Tapscott (P01), Kemp (U01), Eaton (P30), Rabinovitch (P30), and Stamatoynopoulos (U01 and U54). Many of these Program grants have an explicit focus on cancer biology or translational science related to cancer.

CBB members play an important role training future generations of cancer researchers. Maizels, Cooper, Overbaugh and Linial/Stoddard are PIs of T32 training grants for pre- and postdoctoral trainees. Collaborative research and training are encouraged at all levels. The Interdisciplinary Training Grant T32 (Linial/Stoddard) has been instrumental in this regard, requiring all trainees to have two mentors in different disciplines (often different UW departments or different FHCRC divisions) together with a focus on cancer biology. These trainees often serve as catalysts for collaboration between their joint mentors’ labs.

Several lab-based basic cancer researchers are included in other CCSG Programs because their research is focused on specific cancer types, e.g., Vasioukhin (Prostate) and Taniguchi (Womens). These and additional tumor-focused researchers participate actively in inter-programmatic meetings to foster collaboration and
ensure the exchange of ideas. For example, cell biology researchers in the CBB (Cooper, Moens, Parkhurst, MacPherson) meet weekly with cell biologist Vasiukhin (Prostate); and CBB structural biologists Stoddard and Baker interact extensively with P. Bradley (Biostat-Comp) and Strong (IVD).

2. SCIENTIFIC ACCOMPLISHMENTS

The Cancer Basic Biology Program published a total of 1116 papers in the previous grant period: 12% were intra-programmatic, and 17% inter-programmatic with 11% of publications involved CCSG members from both the FHCRC and UW. As can be seen from the Publication List, a considerable fraction of CBB publications has appeared in high-impact research journals. The following section highlights examples of high-impact conceptual or technical achievements, inter- or intra-programmatic collaborations, and translational research that have been supported by CCSG shared resources, pilot grants or scientific meeting support.

2.1. Biology of the nucleus in normal and cancer cells.

2.1A. Mechanisms of genetic and epigenetic control of gene expression in normal and tumor cells.

Chromatin biology: CBB investigator Stamatoyannopoulos played a major role in mapping and functional interpretation of DNase I hypersensitive sites (DHSs) as part of the ENCODE Consortium (Thurman et al., Nature, 2012). DHSs in different cell types are correlated with the transcriptional activity of nearby genes. Stamatoyannopoulos, Heimfeld (Heme Malig) and others recently compared DNase I hypersensitive sites (DHSs) with nucleotide polymorphisms (SNPs) that have been associated with various diseases in GWAS studies. They found that 88% of DHSs are active during fetal development, and are enriched in variants associated with gestational exposure-related phenotypes. Disease-associated variants in these sites systematically perturb transcription factor binding and frequently alter allelic chromatin states, thus perturbing regulatory networks. These results suggest pervasive involvement of regulatory DNA variation in common human diseases, and provide pathogenetic insight into diverse disorders (Maurano et al., Science 2012). Consortium shared resources in Genomics supported this collaborative research.

Several CBB investigators study the molecular and structural biology of gene expression and DNA replication using model organisms. These studies provide the groundwork for drug design. Tsukiyama studies chromatin remodeling by factors that use the energy of ATP hydrolysis to slide nucleosomes along DNA. In an intra-programmatic collaboration, Tsukiyama and Henikoff showed that remodelers bind adjacent to transcription factors in non-transcribed regions, but affect nucleosome turnover at a distance (Zentner et al, PLoS Genet, 2013). Tsukiyama has also shown that remodelers can influence events at a distance through DNA looping (Yadon et al, Mol Cell 2013). He also found that chromatin accessibility is altered ahead of DNA replication forks in an ATR-dependent manner (Rodriguez, Genes Dev. 2013). This may promote successful replication under conditions of replication stress, while minimizing damage to the genome. Hahn has been investigating the basal transcription machinery (Grunberg, Nat Struct Mol Biol 2012; Knutson, Science 2011), and the mechanism of gene activation by acidic transcription activators (collaboration with Baker/CBB and Klevitt/Women's) (Brzovic, Mol Cell, 2011). Their studies were supported by the Genomics shared resource.

CBB member Henikoff developed new methods to isolate chromatin from different cell types in complex tissues, and to chemically label newly-synthesized histones to compare rates of nucleosome replacement at different genomic loci (Deal et al., Dev Cell, 2010 and Science 2010). These procedures allow measurement of nucleosome turnover under different conditions of normal and abnormal cell growth, or in response to damage. Methods were also developed for mapping nucleosome motility using salt fractionation of nucleosomes (Teves and Henikoff, Genes Dev, 2011; Henikoff et al., PNAS, 2011). These methods provide simple strategies to identify epigenetic and transcriptional changes associated with different cancer types, and revealed unexpected effects of anthracyclin chemotherapy on nucleosome turnover (Yang et al, Curr Biol 2013).

Genome structure and dynamics: New diagnostic assays for DNA alterations in cancer have been developed as a result of intra- and inter-programmatic collaborations in the CBB (Diede, Olson and Tapscott) and Women's Cancer (Porter). Diede et al. (PNAS, 2010) reported a new method for identifying methylated DNA in the genome of pediatric medulloblastomas. Guenthoer et al. (Genome Res, 2012) observed that DNA amplification is common in breast cancer, and correlates with increased tumorigenesis and poor prognosis. They coupled high-resolution palindrome profiling by the Genome-wide Analysis of Palindrome Formation (GAPF) assay with genome-wide copy-number analyses on a set of breast cancer cell lines and primary
tumors to spatially associate palindromes with copy-number gains. Their work implicates palindrome formation in the amplification of oncogenes, and provides a new prognostic marker for subtypes of breast cancer.

**RNA splicing, a new target for therapy:** As part of the growing focus on basic brain cancer research, CBB members R. Bradley, P. Paddison and J. Olson collaborated to identify genes required by glioblastoma but not normal neural stem cells. Glioma and normal neural stem cells were grown under identical, serum-free, conditions that preserve transcriptional profiles of the respective cell types in vitro. A lentivirus-based RNA interference screen revealed an unexpected requirement for PHF5a, a splicing factor (Hubert et al, Genes Dev 2013) that is required in cancer–but not normal–stem cells for the faithful splicing of thousands of genes. When PHF5a is inhibited, a large subset of alternatively spliced transcripts is affected, including mRNAs for other splicing factors to create a cascading series of changes This was a remarkable finding because PHF5a is a component of the basal splicing machinery, and was not thought to be involved in alternative splicing. Other inhibitors of the U2 snRNP that regulate the 3' splice junction also kill glioma cells with high specificity, and thus may represent the focus for developing novel approaches to treat glioblastoma, the most common primary adult brain tumor. This collaborative work was directly supported by the CCSG in the form of a Recruitment Award for R. Bradley, as well as the Consortium shared Genomics resource.

**2.1B. Maintenance and loss of genome stability in normal and cancer cells.**

**Structural characterization of the kinetochore that ensures fidelity of chromosome segregation to prevent aneuploidy:** A major highlight of the last funding period was the purification and characterization of the kinetochore: the link between the centromere and microtubules during mitosis, and a key player in chromosome segregation. CBB members Biggins (genetics), Asbury (biophysics), Ranish (proteomics) and former member Gonen (structure) have been involved in a highly productive intra-program, inter-institutional (FHcrc, UW and ISB) and interdisciplinary collaboration to characterize the kinetochore. Defects in chromosome segregation cause aneuploidy in cancer cells. Thus defining the composition and functioning of the kinetochore is of fundamental importance to both normal and cancer cell biology.

Initially, Biggins, in collaboration with Tsukiyama, developed the first robust method to purify kinetochores, then collaborated with Ranish to identify the full complement of kinetochore proteins (Akiyoshi et al, Genes Dev, 2009 and Genetics, 2009). Biggins then collaborated with Asbury to use sophisticated optical methods to detect kinetochore-microtubule interactions, and to measure the forces generated (Akiyoshi et al, Nature, 2010). She found that the kinetochore forms a "catch bond" which develops more strength under tension. The results explain the behavior of chromosomes at anaphase, and led in part to Biggins selection for the 2013 Molecular Biology Prize of the National Academy of Sciences. Supported by a CCSG Pilot award, Gonen and Biggins then took purified kinetochores for negative stain EM and 3D image reconstruction to develop a model of this megadalton-sized molecular machine to reveal its sliding collar and spider-like arms (Gonen et al, Nat Struct Biol., 2012).

Structures of kinetochores attached to microtubules are now being developed to determine where particular kinetochore proteins lie in the 3D structure. Biggins and Asbury are also working to understand how the kinetochore can slide from the side to the tip of a microtubule, yet remain attached to microtubules even as the microtubule end is de-polymerizing. Biggins is also interested in how the attachments are regulated by post-translational modifications, for example the phosphorylation catalyzed by the Aurora kinases which are targets of anti-cancer drugs (London et al., Curr Biol, 2012; Sarangapani et al., PNAS 2013). These fruitful collaborations were initiated through the inter-institutional Mitosis Club, and continue with the support of the CCSG through the Consortium Genomics, Proteomics and Cell Imaging resources.

**Centromere structure and evolution:** The Henikoff group has been characterizing the centromere, using the Genomics Resource. Henikoff has found that nucleosomes at the centromere are fundamentally different from nucleosomes located elsewhere on chromosomes, contain only four histones instead of eight, and have DNA wound in positive instead of negative supercoils (Furuyama et al, Cell, 2009). Nuclease digestion patterns point to an unusually short protected region of DNA (Krassovsky et al, PNAS, 2012). These results revealed a problem in that centromeric DNA can also form conventional (octameric) nucleosomes, as shown by many other investigators. A future collaboration between Biggins and Henikoff may help resolve this issue by creating octameric and tetrameric nucleosomes in vitro, followed by testing to determine which nucleosome form is preferentially bound by purified kinetochores.

A series of papers from the Malik laboratory demonstrate the importance of centromeric DNA and proteins in speciation (Bayes and Malik, Science 2009; Ross et al., Science, 2013; Roach et al., Dev Cell 2013).
Centromeric sequences evolve rapidly under selective pressure imposed by chromosome competition at meiosis. Altered centromere sequences drive correspondingly rapid changes in centromeric proteins to compensate. As a result, distantly related individuals become unable to form viable hybrids, allowing speciation to occur. Less extreme divergence occurs even within the human population. The implications for genetic instability in cancer are being investigated.

**Quantifying mutations and the mutator phenotype:** Understanding the mechanisms underlying mutator phenotypes in cancer cells, and their consequences for cancer, remains a major emphasis of a number of CBB researchers. Major strides made in DNA sequencing in the past few years have allowed the detection of specific gene signatures in cancer cells. However, a key problem in mutation research has been how to detect and determine the significance of subclonal mutations in mixed populations of cancer cells. With mutation rates below 10E-8 and PCR amplification and sequencing errors at 10E-2, true mutations could not be distinguished from a multitude of sequencing errors. Loeb's group developed a powerful Next-Gen sequencing protocol that reduces sequencing errors to below 10E-9 (Schmitt et al., PNAS 2012). The result is that low frequency mutations can now be identified reliably, allowing quantification of mutation rates and tumor genetic complexity as well as the tracking of cell lineages in heterogeneous tumors and normal tissues (Carlson et al, Nat Methods, 2011; Johnson et al Nature 2013). Loeb and colleagues are working now to determine whether mutational load—the sum of all clonal and subclonal mutations in a tumor—might provide a useful new metric for tumor genetic diversity and therapeutic responsiveness.

Other CBB researchers developed and studied mouse strains to assess the importance of mutations in checkpoint and DNA repair and replication genes such as pp53, Atm, DNA-PK, DNA polymerase ε and δ, and RECQ helicases in cancer phenotypes (Bailey, Mol Cancer Res 2008; Gurley et al., EMBO Rep 2009; Albertson et al, PNAS 2009; Dhillon et al, DNA Repair, 2010; Hsu et al, Mol Carcinog 2010; Thangavel et al., Mol Cell Biol 2010), and the regulation of DNA replication in the response to DNA damage (Duxin et al, J BiolChem 2012; Berti et al, Nature Struct Molec Biol 2013; Sidorova et al, DNA Repair, 2013 and Hughes et al., PNAS 2013). These studies utilize human tumors and mouse cancer models, and have been coordinated by CBB program leaders Monnat and Loeb in conjunction with members of other Programs.

**Nuclear structure, organization, function and variation:** Inter-program collaboration between Groudine (CBB) and Kooperberg (Biostat-Comp) led to new insights into cellular organization. Rajapakse et al (PNAS, 2009) investigated the interphase organization of genes in the nucleus. We know that individual genes are subject to regulation, but can be co-regulated with adjacent genes on the same chromosome. Computational analysis by Rajapakse et al shows that there are also patterns of co-regulation that span regions on different chromosomes. These patterns change as stem cells differentiate. Remarkably, there is a correlation between pairs of chromosomes bearing co-regulated genes and the pairs of chromosomes that lie close to each other at mitosis. This suggests that protein interactions that allow co-expression of genes may also tie chromosomes together in a functional—and perhaps physical—sense over long distances and time periods. The computational approach developed by Rajapakse required the expertise of Kooperberg in the Biostat-Comp. program.

Several studies by Eichler (CBB) (eg, Kidd et al, Nature 2008, Cell, 2010; Ng et al, Nature 2009) have revealed surprising variation in the genomes of apparently normal people, with numerous deletions, insertions and inversions relative to the reference genome. The landscape for acquired oncogenic mutations is very diverse, and the effects of these mutations may be further modulated by between-individual differences in genomic architecture that are heritable. Better understanding of this interplay between heritable and acquired genomic variation will be important in developing effective tumor type-specific therapies for individual patients.

### 2.2. Molecular pathways that regulate cancer cell phenotypes.

#### 2.2A. Regulation of normal and cancer cell biology.

**New mechanistic insights into aging:** Chronological age is universally the strongest risk factor for cancer, whereas "immortality" is one of the hallmarks of cancer cells. The Gottschling group has been studying replicative aging, that is, the aging that occurs with each transit of the cell cycle. Veatch et al (Cell, 2009) investigated the source of genome instability in aging yeast, and discovered an effect of aging mitochondria. The mitochondrial contribution is not energy, as might have been expected, but "iron-sulfur cluster" proteins which appear to be an evolutionary vestige of the archetype proto-symbiont, and an essential component in a diverse range of catalytic and non-catalytic proteins. The Gottschling lab developed a method for separating old from young cells (Lindstrom, Genetics, 2009), then used it to show that aged cells that retain mitochondria also have unstable genomes with increased recombination between repeat DNA arrays. The increased
recombination may be due to replication stress in the aged cells. Tracing the mechanism further, the initial defect that leads to mitochondrial dysfunction may be the loss of vacular (lysosomal) acidity (Hughes, Nature 2012). Through unknown mechanisms, this leads to fragmentation of mitochondria with a decrease in mitochondrial function. Lysosomes of human cells have also been shown to lose acidity as they age, but causal relationships between lysosome pH, mitochondrial malfunction, and genome instability have not been established in human or human tumor cells. The superior genetics of yeast, combined with the new biochemical approaches of the Gottschling group and Consortium Imaging and Proteomics resources, are leading to a better understanding of how aging affects cell biology and genome stability via lysosomes and mitochondria.

Research by CBB members Ladiges and Rabinovitch also points to aged mitochondria as a source of damage in mammalian cells. As noted above, tumors often have mutations in mitochondrial DNA, though surprisingly these correlate negatively with cancer (Ericson, PLoS Genet 2012). The lower mutation rate may result from the switch from oxidative phosphorylation to glycolysis, resulting in decreased reactive oxygen species and reduced mutagenesis. In related work, Rabinovitch, Ladiges and colleagues tested whether expressing catalase in mitochondria would protect cells from aging and cancer. Remarkably, membrane-targeted catalase slows aging in mice and suppresses invasive breast cancer (Treuting et al., J Gerontol A Biol Sci Med Sci, 2008; Goh et al., BMC Cancer 2011; Dai et al, Aging Cell 2010). These results validate antioxidant approaches to inhibit cancer.

Bedalov, using QTL mapping to identify loci that control lifespan (Kwan et al., PLoS Genetics 2011), identified a single nucleotide polymorphism in BUL2 controls chronological lifespan and telomere length. BUL2 is a component of a ubiquitin ligase complex involved in trafficking of amino acid permeases and regulating amino acid uptake. Inhibitors of this pathway might be exploited to inhibit tumor proliferation.

**Signaling pathways in cancer and development:** Research from CBB Head Cooper illustrates how basic research into cell migration during mouse development can lead to new understanding of fundamental mechanisms of cancer (Laszlo and Cooper, Current Biology, 2009). In this work, Laszlo and Cooper tested a novel hypothesis that malignant transformation by the Src tyrosine kinase may be inhibited by active turnover of Src substrates. This hypothesis was inspired by Cooper’s parallel studies of Src regulation in neural development. The results suggest that two events—loss of heterozygosity of Cul5 and high activity of Src, both of which occur frequently in human tumors—may cooperate for full transformation. The research was supported by the Proteomics, Genomics, Research Pathology, Scientific Imaging and Comparative Medicine shared resources, and pilot funding from the Breast Cancer SPORE.

Parkhurst and Moens also use model systems to study basic cell biology. Parkhurst uses *Drosophila* embryos to study cell migration during development and wound healing, and Moens uses zebrafish to study cell migration during development. Parkhurst found that Rho GTPases regulate the healing of wounds caused by laser injury to single cells by acting through some of the same signaling pathways that regulate migration of normal and cancer cells (Abreu-Blanco et al, J Cell Sci 2012). Moens used forward genetic screens in zebrafish to make the surprising finding that planar cell polarity (PCP) proteins regulate cell migration (Walsh et al, Development 2011). A role for PCP—which normally aligns cellular asymmetries in the plane of an epithelium—in migration was previously unknown.

### 2.2B. Genetic, metabolic and high throughput screening strategies to improve cancer diagnosis and therapy.

**Translational studies of brain cancer:** Paddison (CBB), a junior faculty member who developed shRNA technology while at Cold Spring Harbor, collaborated with Olson to search for genes that might be required in human brain tumors but not normal cells (Ding, Cancer Discov. 2012). Brain tumor initiating cells (BTICs) have been defined by their ability to form glioblastoma-type tumors with patient-specific histology and genetic signatures when orthotopically implanted into mice. BTICs may be maintained in culture under the same conditions as normal human neural stem cells while retaining BTIC potential. An shRNA screen revealed that BUB1B is essential for survival of BTICs but not normal neural stem cells. Removing BUB1B from BTICs but not normal neural stem cells causes loss of kinetochore-microtubule attachments and major defects in chromosome disjunction at anaphase, with lethal results. Synthetic lethal screens like this will continue to be a priority for the future. The research was initiated with a CCSG Pilot Award to Paddison. The Consortium structure also helped in a less tangible way: Paddison’s first reaction upon learning of the BUB1B hit was to visit Biggins to get a quick education on the spindle assembly checkpoint. Continued work by Paddison on BUB1B will occur in consultation with Biggins and involve other members of the Mitosis Club.
In an elegant use of mouse cancer models, Olson (CBB) and LeBlanc (CP-Epi) utilized the Consortium Comparative Medicine resource to study the role of Notch signaling in medulloblastoma (Hatton et al., Oncogene, 2010). Previous work had shown that Sonic hedgehog (Shh) signaling is activated in 15-30% of human medulloblastomas, and that gamma secretase inhibitors can kill medulloblastoma cells in vitro and in flank xenografts. However, Notch activity was not needed for Shh-driven tumor initiation or maintenance in vivo. These observations collectively suggested that gamma secretase inhibitors may not be helpful to patients. However, the same investigators collaborated to test the effects of Shh pathway inhibition in a mouse medulloblastoma model, and observed dramatic increases in survival even when the inhibitor was used after tumor onset (Lee et al., PNAS, 2012).

Olson also continues to develop labeled peptides as tracers for tumor cells during surgery. His use of Tumor Paint, a conjugate of a scorpion toxin with a dye that fluoresces when illuminated in the infrared, enables efficient resection of tumors while minimizing damage to normal tissue, which is critical for pediatric brain tumor patients (Akcan et al, J Med Chem, 2011). Conjugation of scorpion toxin to iron nanoparticles instead of dyes provides the possibility of vital imaging using NMR (Lee et al PLoS One, 2010).

Translational studies of GI cancer: Long term translational research collaborations between CBB and Gastrointestinal Program investigators has allowed the definition of genomic instability endpoints to assess the clinical/natural history of inflammatory bowel disease (IBD), and use of these endpoints to assess patient risk of progressing to colorectal cancer (Bronner et al, Am J Pathol 2008). Maggio-Price et al. (Am J Pathol 2009) set up a mouse model to mimic inflammation-associated colon cancer. Similar analyses of patients with ulcerative colitis led to the identification of protein and genetic markers indicating progression to neoplasia (Brentnall et al., Proteomics Clin Appl, 2009: Salk et al., PNAS, 2009; Bronner et al., Mod Pathol 2010; Risques et al, Gastroenterology 2008; Risques, Cancer Res. 2011). In related research, many of the same investigators have developed a parallel story for Barrett’s esophagus, a pre-malignant disease with high neoplastic transformation potential (Lai et al. Mol Cancer Res 2010).

Exploiting oncogene and tumor suppressor pathways for therapy: c-MYC is a well-understood nuclear oncogene that is activated by gene amplification or rearrangement in many cancers. MYC is highly expressed in embryonic stem cells, and was one of the original cocktail of transcription factors used by Yamanaka and colleagues to generate induce pluripotent stem cells (iPSCs). The Eisenman group (CBB) found that MYC also activates the expression of several miRNAs in stem cells but not in differentiated cells (Lin et al, PlosOne 2009 and Lin et al, EMBO J 2009). These miRNAs target various differentiation-specific genes to repress them and thus inhibit differentiation. Now Eisenman, working with the Proteomics Resource, has found a nicked form of Myc that has a novel function in the cytoplasm to stimulate differentiation (Conacci-Sorrell et al, Cell, 2010). Cleavage of Myc by calpain releases a fragment that regulates tubulin acetylation. This opens up a "moon-lighting" function of Myc that is pro-differentiation as opposed to pro-oncogenic. Clearly regulation of Myc cleavage could be a major control point in cancer cells.

In a study made possible by a CCSG Pilot Award, Grandori (CBB) collaborated with Park (Heme Malig) and used functional genomics to identify synthetic-lethal interactions with c-MYC overexpression (Toyoshima et al., PNAS, 2012). MYC onco-proteins are implicated in cancer, yet are considered "undruggable": inhibiting their roles in transcription and proliferation could have adverse side effects. Grandori and colleagues screened a collection of ~3,300 druggable genes to identify synthetic-lethal interactions. Using RNAi and available small-molecule inhibitors, they confirmed that inhibition of one of the genes they isolated, CSNK1e, halted growth of MYCN-amplified neuroblastoma xenografts. CSNK1e had previously been implicated in the regulation of developmental pathways and circadian rhythms. These new data identify a previously unknown link with oncogenic MYC. The study provides proof of principle that functional genomics is capable of identifying genes required for proliferation in specific tumor types, and thus may identify potential new targets for cancer therapy. Building on the pilot award, Kemp, Grandori, Mendez (CP-EPI), Gadi (Women's Cancer) and Margolin (SAGE Bionetworks, Seattle) successfully applied for a U01 grant under the NCI’s Cancer Target Discovery and Development (CTDD) Network and program. Kemp will use patient-derived tumor cultures grown under conditions discovered by Grandori for RNAi screens to discover new synthetic lethal interactions with therapeutic potential. The CTDD Network is focused on complementing large scale 'omics type approaches by using functional studies on patient-derived tumor cells, rather than cancer cell lines, to identify the most promising new therapeutic options.

In previous work, CBB Head Monnat together with Grandori and colleagues identified a synthetic lethal interaction between MYC over-expression and a requirement for continuous expression of the Werner
syndrome RECQ helicase. This led to current studies to identify second and third generation helicase inhibitors for the treatment of MYC-overexpressing tumors. A study by Grandori and Kemp (CBB), made possible by a Pilot Award from the CCSG and making use of the Computational Biology Core resource, followed up on this previous observation to demonstrate that WRN is required for SCLC cells (which over-express MYC) to form tumors upon xenotransplantation. Again, since WRN has both exonuclease and helicase activities that are potentially drugable, inhibitors are predicted to suppress epithelial as well as lymphoid malignancies in which MYC is activated (Moser et al., Mol.Cancer.Res. 2012).

Metabolism – a developing CBB focus area: Changes in tumor metabolism have been noted for the better part of a century, though the diagnostic and therapeutic import of these changes have only recently begun to be explored by CBB and by other investigators. Cell metabolic state may be a sensitive indicator of biochemical networks that are altered by tumor-associated mutations or changes in epigenetic or chromatin state. As noted above, mutations in tumor mitochondrial DNA are inversely correlated with cancer (Ericson, PLoS Genet 2012). One explanation for this is that the switch from oxidative phosphorylation to glycolysis, with corresponding reductions in reactive oxygen species generation and oxidative damage-induced mitochondrial (and perhaps nuclear) mutagenesis. In related work, Rabinovitch, Ladiges and colleagues tested whether expressing catalase in mitochondria would protect cells from aging and cancer by buffering the generation of mutagenic oxygen intermediates. Remarkably, as noted above, membrane-targeted catalase slows aging in mice and suppresses invasive breast cancer (Treuting et al., J Gerontol A Biol Sci Med Sci, 2008; Goh et al., BMC Cancer 2011).

Other efforts to modulate cellular metabolic state in tumor, normal and stem cells have been reported by CBB investigators. Ruhola-Baker, Ware, Hockenbery and colleagues demonstrated that HIF1α shifts stem cell metabolism to glycolysis during the ESC-to-EpiSC transition (Zhou et al, EMBO J, 2012). Eisenman, in research funded by a Pilot award from the ITHS, identified Mondo as a gene required by Myc-transformed but not normal cells, and demonstrated the importance of Mondo as a regulator of cancer cell metabolism and a partial explanation for the Warburg effect. Both Roth and Miller have been investigating the ability of simple small molecules to produce a state of suspended metabolic animation (Morrison et al J Trauma 2008). This ability may have practical utility in ‘resetting’ cell metabolic state or altering the response to conventional or metabolite-targeted therapies. New CBB member Raftery is expert in quantifying metabolites in esophageal cancer using LC-MS and NMR. Rabinovitch has an active genetically driven research program to investigate the role of cell signaling pathways in the biology of aging (Johnson et al Nature 2013). This work, focused on key growth regulatory pathways (e.g., mTOR and IGF-driven signaling), has emphasized the interplay between yeast genetics and mouse models while providing a complement to the work by Gottschling on the role of key proteins in maintaining genomic integrity (see above).

2.3. Protein design and genome engineering as enabling technologies to advance basic and translational cancer biology.

Genome engineering: Genome engineering is being pursued by CBB Members throughout the Consortium, including Monnat, Stoddard (protein structure), Baker and P. Bradley (protein computational design), with HemeMalig and IVD Members Jerome, Kiern and Scharenberg. Their collaboration has been supported by Consortium Genomics and Proteomics cores and CCSG-funded administrative support, and by an NIH Director’s Initiative U54 NW Genome Engineering Consortium grant.

One of their approaches is to develop homing endonuclease proteins to cleave animal or human DNA at unique sites for genome engineering. Homing endonucleases are small (~300-residue), and hence easy to package and transfer. They recognize long DNA target sites (~20 bp), and are likely more site-specific than the competing engineering nucleases such as zinc-finger nucleases, CRISPR/Cas and TALENs. The CBB team has used structure-based design to alter the DNA sequence specificity of natural homing endonucleases (Li et al, Nucl Acids Res 2012; Baxter et al, Nucl Acids Res, 2012; Ulge et al., Nucl. Acids Res., 2011; Ashworth et al, Nucl. Acids Res., 2010). One important study reveals that a homing endonuclease, I-Anil, achieves DNA sequence specificity two ways: it binds specific sequences and it only stabilizes transition states with the correct sequence (Thyme et al, Nature, 2009). Another study emphasized the potentially large natural reservoir of additional homing endonuclease proteins with different target specificities (Takeuchi et al, PNAS 2011). Investigators also collaborated to generate cleaving and nicking versions of the same protein that can exert either activity at the same target site (McConnell-Smith et al., PNAS, 2009). One goal is to use gene-targeting approaches together with patient-derived lymphocytes to integrate chimeric antigen receptors (CARs) for cancer immunotherapy. Ongoing studies show that a modified homing endonuclease can efficiently and
specifically cleave the T cell receptor alpha chain gene, which will be useful for generating patient-derived T cell clones with novel antigen reactivity. Shared Resources that played important roles in this work at several levels include Cell Processing, Computational Biology, Flow Cytometry, Genomics and Scientific Imaging. These, together with Biologics Production, Blood Cell Analysis, Genotype Tracking, Hematopoietic Cell Processing and Vector Production, will play key roles in clinical implementation of this technology.

TALENs (TAL-effector nucleases) are one of the highly sequence-specific DNA binding proteins being developed for genome engineering within the Consortium. TALENs are derived from plant pathogenic bacteria, and contain virtually identical repeats of 34 residues in which just two residues determine the recognition of single target site DNA base pairs. In 2012, two groups simultaneously reported the first TALE structures. The Seattle structure was the fruit of a collaboration between Stoddard (CBB) and P. Bradley (Biostat-Comp). A researcher in the Stoddard lab was able to grow crystals and obtain X ray diffraction patterns of a TALE binding module on its DNA target site. However, without a structural model it was not possible to phase the data and build a structural model. Bradley identified protein folds that might be adopted by the TALE repeats, and computationally fitted these to DNA. Thousands of models were compared for predicted binding affinity, and the selected models were then used to fit the diffraction data. This creative use of computational structure prediction was key to solving the first complete structure for a natural TALE (Mak et al, Science, 2012). This collaborative effort, aided by Consortium Genomics and Proteomics cores, helped make TALENs a runner up "Breakthrough of the Year 2012" (see Science, 21 Dec 2012). The continued structural characterization and development of homing endonucleases, hybrid homing endonuclease-TALEN proteins, and variants of the Cas9/CRISPR system for genome engineering will be a major focus in future work.

**Protein computational design and prediction:** The TALEN structural determination project mentioned immediately above, the engineering of homing endonuclease proteins, and an increasing number of CBB-related basic and translational projects depend on the twin technologies of protein design and engineering together with genome engineering. The Baker group at the UW has played a key role in developing one of the premier design engines for protein engineering, termed Rosetta, that was utilized for the preceding projects. The potential of expanding this design suite in the form of a publicly accessible web engineering interface was demonstrated by the Baker group in conjunction with UW Computer Science and Engineering colleagues as ‘Fold-it’ (Cooper et al, Nature 2010). This software allows thousands of participants worldwide to contribute to protein computation and structural determination challenges, while providing a powerful stimulus and data source for investigators interested in how people visualize and tackle intrinsically complex problems. An elegant example of the ability of this approach to do challenging real science was the recent success of Fold-it players to generate a crystal structure for a monomeric retroviral protease that had been refractory to more direct and conventional approaches to structure determination (Khatib et al, Nat. Struct. Mol. Biol., 2011).

New directions have been opened up by the continued Stoddard/Baker intra-program CBB collaboration. Baker has developed robust computational methods that permit the design of completely artificial proteins with predetermined binding specificities, and these specificities have been validated by Stoddard (Tinberg et al, Nature 2013) using structural approaches. The test case was a novel digoxigenin-binding protein, but the principle applies to other small molecules that may be of interest as biosensors, diagnostics or therapeutics. Design started by arranging amino acid side chains in empty space to maximize hydrophobic, Van der Waals and hydrogen bonding interactions with a molecule of digoxigenin. Different protein shells were then modeled around the desired side chains. Several designs were produced and tested, and the best one optimized. The result was a protein that bound digoxigenin with subnanomolar affinity and high stereospecificity. This is the first time that a completely synthetic protein-ligand pair have been constructed and validated. It opens the door for design of other small, stable proteins with unique binding or catalytic activities that could be used to target chemotherapy to cancer cells, detect cancer antigens, or illuminate cancer cells during surgery. The recent application of a stabilized enzyme, previously published by Baker/Stoddard (Korkegian et al 2005, Science 308:857), to convert the 5-fluorocytosine pro-drug to chemotherapy agent 5-fluorouracil in tumor cells of glioblastoma patients injected with a replication-competent retroviral vector (clinicaltrials.gov, NCT01156584), underlines the importance of protein engineering for therapeutic uses.

**Progress summary:** In the prior grant period CBB and its predecessor programs and investigators made substantial discoveries in three key areas: understanding the basic mechanisms that control the structure, expression, replication and segregation of genes and chromosomes; how these mechanisms are altered to promote the hallmarks by which we recognize cancer as a disease process; and the development of key enabling technologies to aid these efforts by the design and engineering of proteins and genes.
3. FUTURE PLANS

In the coming period CBB will focus on deepening our understanding of the biology that underlies cancer as a disease process, with the goal of combining new knowledge and technical expertise to foster cancer translational science. This effort will have three major components.

1. **Develop new research directions:** Two focus areas for the coming period are tumor metabolism and brain tumor biology and therapy. New recruit Raftery, an expert in metabolomics, will join with current CBB members Hockenbery and Ruohola-Baker to expand research in tumor metabolism. Both basic and translational research focused on brain tumors will become a major focus for CBB. Dr. Eric Holland, a neurosurgeon with a clinical and basic research program focused on glioblastoma, was recently recruited from Sloan Kettering to become the new head of the Human Biology Division at the FHCRC, Consortium Associate Director and head of the UW Alvord Brain Tumor Center (ABTC). Holland also is leading the new Solid Tumor Translational Research (STTR) initiative across the cancer center. Both the ABTC and STTR program share the goal of developing both SPORE- and P01-funded basic and translational research focused on brain and other pediatric and adult malignancies. The STTR will also expand solid tumor translational research within CBB and other Consortium Programs. For example, CBB is home to Beronja and Houghton, two investigators with a focus on lung cancer.

2. **Recruit key new faculty:** Recruiting efforts will focus on adding strength in existing areas of excellence, and in bringing new ideas, approaches, technology and investigators into CBB to foster translational research. Cancer genomics, molecular diagnostics and direct human tumor therapeutic profiling and modeling are examples of areas where key hires in conjunction with the development of solid tumor translational research could have a high scientific and programmatic ‘multiplier’ effect.

3. **Develop translational science within CBB:** Successful translational oncology requires strong cancer-oriented basic science, together with an effective way to bring basic science knowledge and tools to the clinic. Throughout the current grant cycle, Consortium and CBB leaders together with CBB members have created new resources to move scientific discoveries from the bench to the clinic. Examples include powerful synergies between the newly developed patient-derived xenograft (PDX) program within Comparative Medicine, NW BioTrust, the Alvord Brain Tumor Center; the CTDD U01 award for cancer therapeutic target identification and development; and translationally-focused drug/small molecule and RNAi screens. The CBB Program is also well-positioned to expand translational research by leveraging the considerable local expertise in genome engineering and protein computational design, two strongly synergistic and complementary technology development areas with manifold applications in translational research. Examples include the engineering of patient-specific, chimeric antigen receptor T-cells for immunotherapy; the identification of genetic and epigenetic drivers of cancer pathogenesis that will serve as new targets for therapy; and the identification of new biomarkers for cancer detection and disease progression or therapeutic response monitoring.
1. Program Overview

1A. Program focus
The Cancer Epidemiology, Prevention, and Control Program (CEPC) is a large, highly interdisciplinary program with sizeable breadth and depth of expertise. Program goals are to reduce cancer incidence and mortality through research on environmental and genetic causes of cancer, risk reduction, early detection, and improved outcomes and quality of life among both general and targeted populations. An important aspect of this research is the translation of findings into practice in the community and clinic.

The scientific goals of the CEPC Program are to

1. Discover and characterize environmental and genetic causes of human cancer and its progression, with an emphasis on the identification of underlying mechanisms.
2. Identify and evaluate cancer screening and surveillance methods that can be readily translated into clinical practice and health policy, with an emphasis on underserved populations.
3. Develop and test strategies to enhance cancer survivorship and improve cancer treatment effectiveness.
4. Conduct rigorous clinical and community-based intervention studies in targeted and general populations to identify ways to reduce cancer morbidity and mortality.

1B. Program structure
The CEPC Program is a new program that includes a diverse and multidisciplinary membership of scientists and clinicians drawn primarily from the former Cancer Prevention and Epidemiology programs. Members hold appointments in a total 15 departments and all Consortium partner institutions are represented. CEPC’s origins date back to 1973 when the FHCRC established its first population science research program, the Program in Epidemiology and Biostatistics. Ensuing growth in population science research and faculty led to the formation in 1983 of the FHCRC Division of Public Health Sciences and the establishment of separate programs in Epidemiology and Biostatistics. The Epidemiology Program has long been recognized for its research accomplishments in the identification of causes of cancer and cancer progression. The Cancer Prevention Program was established in 1983 with the funding of the nation’s first Program Project in cancer prevention. Since then, the program has been a model of multidisciplinary cancer control research for U.S. cancer centers and academic institutions the world over, and is recognized for contributing directly to national and worldwide reductions in cancer incidence and mortality. In the 2008 CCSG review, the Epidemiology Program received an assessment of excellent to outstanding merit, and the Cancer Prevention Program received an assessment of outstanding merit.

Much of the etiologic and mechanistic work of the Epidemiology Program has had direct relevance to the development and evaluation of primary and secondary prevention strategies, resulting in shared goals, natural affinities, and increasing collaborations with Cancer Prevention faculty. These mutual research interests over the years have led increasingly to combined program activities including, for example, the Epidemiology and Cancer Prevention Seminar Series and weekly grant review and critique brownbag meetings. Building on both programs’ strengths and exploiting common goals and close faculty collaborations, the programs elected to create a combined program in Cancer Epidemiology, Prevention and Control, a move enthusiastically endorsed by the External Advisory Board in 2012. The new program structure has facilitated opportunities for collaboration, and introduced efficiencies through joint planning and evaluation of program needs. Another positive result has been focused recruitments, such as in screening and cancer survivorship. We believe that the new combined program will result in enhanced team science across our diverse faculty.

1C. Program leadership and qualifications
The CEPC is co-led by program heads Dr. Polly Newcomb and Dr. Kathleen Malone. Drs. Beti Thompson and Johanna Lampe serve as Associate Program Heads. Dr. Newcomb focuses her research on genetics, cancer epidemiology, screening and survival for colorectal, breast, and other common cancers. She has served as Head of the Consortium Cancer Prevention Program for nearly 10 years, and also heads the FHCRC’s Cancer Prevention Program. Dr. Newcomb is also a Professor of Epidemiology at the University of Washington School of Public Health (UWSPH), and serves on the Steering Committees for two University of Washington pre-doctoral and post-doctoral fellowship training programs. Dr. Newcomb has participated in the training of over 40 individuals for the next generation of cancer control scientists, including actively mentoring pre-doctoral and post-doctoral fellows, as well as junior faculty in this large program. In 2010, Dr. Newcomb received the
Dr. Newcomb serves on NIH standing and ad-hoc study sections, including a current term on NIH/NCI Subcommittee F-Institutional Training and Education, and consults with NCI Comprehensive Cancer Centers. She actively participates in major national professional organizations and research consortia; she is the President-Elect of the American Society of Preventive Oncology (ASPO) and in March 2013 received that organization’s Distinguished Achievement Award.

Dr. Malone is an epidemiologist whose research is focused on environmental and heritable determinants of breast cancer incidence and mortality. She has served as Head of the Consortium Program in Epidemiology, as well as the FHCRC Program in Epidemiology, for 1.5 years, assuming these roles after nearly a decade as the Associate Program Head. She is a Professor of Epidemiology at the UWSPH, serves on the steering committee for the Cancer Epidemiology and Biostatistics pre- and post-doctoral training program, and has mentored 29 pre-doctoral students and post-doctoral fellows. Previously, Dr. Malone served as a Faculty Consultant to the FHCRC Scientific Ombuds Office. She actively mentors junior faculty and co-authored the guidelines for faculty mentoring committees. Dr. Malone has served on NIH standing and ad-hoc study sections, and recently completed a four year term as member of the standing NIH/NCI Epidemiology of Cancer Study Section.

Dr. Thompson, a sociologist and Full Member, founded the Consortium Health Disparities Research Center and was recently named the Consortium’s Associate Director for Minority Health and Health Disparities Research. She is also a Professor in the Department of Health Services, UWSPH, where she has mentored 35 students and five junior faculty; she has been nationally recognized for this mentoring excellence. Dr. Thompson has 25 years’ experience conducting research aimed at reducing health disparities among underserved populations, with a focus on Latinos. Using a community-based participatory research approach, she has forged close relationships with Latino communities throughout Washington State. Her research in these communities has increased screening and early detection of cancer and other diseases, as well as addressed lifestyle behaviors associated with cancer risk, e.g., diet, physical activity and smoking. Dr. Thompson recently received the 2013 AACR Distinguished Lectureship on the Science of Cancer Health Disparities.

Dr. Johanna Lampe is a Full Member and Associate Director of the Division of Public Health Sciences, FHCRC, and is on the core faculty of the UW Interdisciplinary Program in Nutritional Sciences and a Professor in the Department of Epidemiology, UWSPH. Dr. Lampe also co-chairs the Consortium Scientific Steering Committee. Dr. Lampe is an experienced nutritional biochemist with a nearly 20 year history studying the effects of diet and other risk factors for cancer primarily in the context of intervention studies. Her current research includes intervention studies on the effects of dietary bioactives on colonic epithelium and the gut microbiota. She has participated in numerous national and institutional programs with training components, and chairs the Steering Committee of the American Association for Cancer Research Molecular Epidemiology Working Group. She has received numerous awards for mentoring, including the 2009 FHCRC McDougall Mentorship Award and in 2013 completed a 4-year term as member and chair of NIH/NCI, Subcommittee J-Population and Patient-Oriented Training.

As national experts in their fields, the CEPC leadership team brings broad and highly complementary experiences to bear on furthering the goals of the program and ensuring that its faculty has the scientific, fiscal, and administrative resources to conduct their research. As an example, CEPC leaders strongly support and often participate in multi-investigator grants, large collaborative studies, and successful coordinating centers. In addition, mentoring young scientists is a priority for the Program leaders. The Program leadership team meets monthly and is responsible for advising the Center Director on all issues related to the CEPC, e.g., serving on review committees for pilot funding and assessment of shared resources and development of future research directions. The Program leadership is well positioned to advise and act on these and other issues.

1D. Program membership and inter-programmatic interactions

Program Membership

This program has 76 faculty members from 15 departments and 3 Consortium member institutions, representing multiple scientific disciplines. 93% of members have peer-reviewed cancer related research funding, totaling over $26M in grant funding (direct dollars), of which 83% is peer reviewed (49% from NCI).

To facilitate interactions across the Program, the CEPC includes six Affinity Groups (Cancer Policy Research, Clinical Trials, Genetic and Molecular Epidemiology, Long Term Effects and Survivorship, Nutrition/Energy Balance and Physical Activity) focused on specific research areas of shared interest. These Affinity Groups
meet monthly and include working group sessions and scientific presentations by local, national, and international leaders in the groups’ primary areas of research focus. Program members also actively participate in the CCSG Biobehavioral and Outcomes Research (BORG) Affinity Group. This Affinity Group brings together multidisciplinary faculty from all Consortium institutions, with a focus on biobehavioral and patient-centered outcomes research. Finally, the Program sponsors a monthly seminar series, inviting internal and external speakers to present on a wide variety of topics relevant to population sciences. See “Programmatic Activities Table” for details of these entities. All of these activities serve to facilitate intra- and inter-programmatic research collaborations and identify areas of new research and opportunities to exploit existing resources to advance population science. Program faculty meetings are well attended and held monthly; the agenda includes a brief scientific presentation, in addition to the business of the program, i.e., prioritizing Program goals, assessing opportunities and challenges, and developing strategic research priorities. Also, in response to the current challenging research funding environment, the CEPC launched full faculty weekly meetings, held each Tuesday, to discuss and develop new areas of research, and review and strengthen new and resubmission applications.

Since the last grant period, a number of strategic CEPC faculty recruitments were completed to build research capacity, including in areas of health disparities, survivorship, and health economics:

**Assistant Member/Professor level:**

- Dr. Christina Baik (UW) is a practicing oncologist whose research interests, in addition to cancer treatment trials, include investigations of molecular biomarkers for detection of cancer from blood.
- Dr. Parveen Bhatti (FHCRC), recruited from NCI, expands CEPC activities in molecular epidemiology with an emphasis on environmental and occupational causes of cancer.
- Dr. Rachel Ceballos (FHCRC) researches biobehavioral mechanisms contributing to health disparities, with a primary interest in cancer survival among Latino and African-American populations.
- Dr. Linda Ko’s (FHCRC) primary research areas are health communication, health literacy and cancer screening, and reducing health disparities in Hispanic and Korean immigrant populations.
- Dr. Margaret Madeleine (FHCRC) adds experience in the epidemiology of HPV in relation to cancer risk and the molecular epidemiology of pathogens and the immune response to them.
- Dr. India Ornelas (UW) works on cancer prevention activities in underserved populations and the effects of discrimination on health.
- Dr. Amanda Phipps (UW) brings experience in molecular subtypes of tumors and has strong interests in genetic determinants of colorectal cancer survival.
- Dr. Kerryn Reding (UW) is an epidemiologist with a research focus on the development and assessment of the biologic impact of physical activity, diet and obesity interventions for cancer risk reduction.
- Dr. John Scott (UW) is an internist and infectious disease specialist who has developed an innovative telemedicine program to improve health care access in underserved communities.

Each of these new junior recruits has obtained independent extramural research funding. Recruitment of Drs. Baik, Bhatti, Ceballos and Ornelas was facilitated by CCSG New Investigator funds.

**Associate Member/Professor level:**

- Dr. Jason Mendoza (UW/Children’s) is a pediatrician whose primary research focus is on the development and evaluation of interventions aimed at reducing childhood obesity in underserved populations.

**Member/Professor level:**

- Dr. Joann Elmore (UW) is a clinical epidemiologist and Professor, Department of Medicine, who brings expertise in cancer screening, diagnostic tests, pathology, and evaluation of pathology diagnoses.
- Dr. Sean Sullivan (UW) is a Professor in the School of Pharmacy and the Department of Health Services, and is Director of the Pharmaceutical Outcomes Research and Policy Program.
- Dr. David Veenstra (UW) is a Professor, School of Pharmacy, and Director of the Graduate Program in the Pharmaceutical Outcomes Research and Policy Program.
- Dr. Larry Kessler (UW) is Chair and Professor in the Department of Health Services and holds an adjunct appointment in the School of Pharmacy.
• Dr. Gary Lyman (FHCR) is national and international leader in comparative effectiveness and outcomes research. A medical oncologist, he co-directs the Hutchinson Institute for Cancer Outcomes Research (HICOR).

Inter-programmatic Interactions:
Many CEPC faculty members are actively involved in inter-programmatic research. One-third of all CEPC Program publications are joint with other Consortium programs and some members are also dually appointed in other Consortium programs (e.g., Li in Women’s Cancer, Neuhouser in Prostate, Prentice in Biostat-Comp, and Schwartz/Taylor in Global Oncology). Some of this work is highlighted elsewhere in this application. Inter-programmatic contributions also include participation in seminar/retreat planning and faculty search committees, and development of large multi-project grants such as SPORES and P01s. Many members also lead or collaborate on national and international research consortia (e.g., Colon Cancer Family Registry (CCFR), Barrett’s and Esophageal Adenocarcinoma Consortium (BEACON), the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO)); additional details are presented in the Programmatic Activities Table, Section 2. Selected examples of CEPC inter-programmatic work follow.

• Dr. Peters, with Dr. Kooperberg and others in Biostatistics & Computational Biology (Biostat-Comp), has conducted GWAS for multiple solid tumors (e.g., Jiao et al., PLoS One, 2012) and performed fine-mapping in African Americans as a means for narrowing in on the functional candidate(s) underlying initial GWAS findings in European populations (e.g., Peters et al., PLoS Genet, 2013).

• Dr. Neuhouser (CEPC/Prostate) with Dr. Prentice (CEPC/Biostat-Comp) has conducted studies on diet and cancer association using biomarker-calibrated exposure estimates (e.g., Neuhouser et al., Am J Epidemiol, 2013).

• Drs. Carlson (CEPC), Robins (Biostat-Comp) and Warren (Immunology and Vaccine Development [IVD]) developed new technology for measuring adaptive immunity via massive parallel sequencing of T cell receptors, generating significant publications (e.g., Robins et al., Blood, 2009) and a Keck Foundation award.

• Drs. C. Li (CEPC/Women’s Cancer) and Malone have collaborated with colleagues in Women’s Cancer on studies of breast cancer risk, for example in relation to hypertension (e.g., Li et al., JAMA Intern Med, 2013), as well as risk factors for breast cancer subtypes (e.g., Phipps et al., Cancer Causes Control, 2011).

• Dr. Kopecky has long collaborated with colleagues in Hematologic Malignancies ([Heme-Malig] e.g., Petersdorf et al., Blood 2013) on leukemia and in Global Oncology on radiation effects on humans (Grant et al., Radiat Res 2012).

• Dr. Newcomb’s inter-programmatic activities include work with Dr. Grady (Gastrointestinal [GI] Oncology) related to the Colon Cancer Family Registry (e.g., Burnett-Hartman et al., Cancer Res, 2013), and on HIV and colon cancer with Global Oncology (Coghill et al., AIDS, 2013).

• Drs. Lampe and Eaton have a long-standing collaboration studying the impact of dietary constituents on biotransformation enzyme activity in humans (e.g., Peterson et al., Cancer Epidemiol Biomarkers Prev, 2009; Poulton et al., Toxicol Appl Pharmacol, 2013).

• Drs. Schwartz, Madeleine, and Galloway (Cancer Basic Biology) have continued their collaborative studies of the infectious and immune underpinnings of anogenital and other cancers, for which they received the 2011 AACR Team Science Award.

• Dr. Ramsey’s health economics and cancer outcomes work encompasses multiple Consortium programs, e.g., Heme-Malig (McCune et al., Pharmacotherapy, 2012) and GI Oncology (Shankaran et al., J Clin Oncol, 2012).

2. Scientific Accomplishments
With 1655 publications during the last grant period, there are a large number of scientific accomplishments that illustrate the diversity of research in the program. Below we present selected examples from our extensive research portfolio that represent our work to expand knowledge of cancer etiology and risk factors (e.g., medications, genomics, and diet); develop and test behavioral interventions designed to reduce cancer risk in populations (e.g., smoking and diet); evaluate and translate early detection strategies directed to populations at heightened risk because of race, ethnicity and income; and identify factors that enhance survival after cancer diagnosis. Selected projects also illustrate the inter-programmatic inclusion of our program’s research.

2A. Identification of new genetic risk loci through broader and deeper interrogation of the genome
Colorectal cancer (CRC) is the second leading cause of cancer death in developed countries, with the lifetime risk estimated to be 5-6%. Linkage studies have identified important rare germline mutations, such as those in the APC gene and DNA mismatch repair genes, leading to hereditary syndromes, e.g. familial adenomatous polyposis and Lynch syndrome. However, these high-penetrance mutations explain only a small fraction of the total genetic risk. To date, genome-wide association studies (GWAS) have identified almost 20 low-penetrance genetic variants that, together, explain approximately 8% of disease heritability. Based on a recent method by Chatterjee and Park that estimates the amount of familial association explained by common genetic variants, it is expected that about 60-70 common variants would explain approximately 20% of CRC heritability. Accordingly, the majority of common colorectal cancer susceptibility loci have yet to be identified.

Peters et al. developed the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO). Funded in 2009, GECCO is comprised of a coordinating center at the FHCRC and investigators from 18 different clinical trials, cohorts, and case-control studies conducted in North America and Europe. This consortium aims to both accelerate the discovery of CRC-related variants and perform thorough epidemiologic evaluations of new susceptibility loci via gene-environment interaction (GxE) analyses. A key strength of GECCO is the large sample size of nearly 40,000 participants (>20,000 with GWAS and ExomeChip data). In addition to confirming established loci, Peters identified a new loci in nucleic acid binding protein 1 (NABP1), a key regulator of genomic stability, that reached the conventional genome-wide significance level at $P<5.0 \times 10^{-8}$ (Peters et al., Gastroenterology, 2013). GECCO has led or contributed to the identification of eight novel CRC loci and has published several findings for CRC survival, GxE and GxG interactions, pleiotropic effects, and imputation methods among others, with several additional papers submitted. Of the known colorectal genetic loci, significant GxE interactions were observed by Newcomb, Peters and colleagues for diet (Hutter et al., Cancer Res, 2010).

The GECCO infrastructure and expertise has also been expanded into other populations and outcomes. For example, using genetic data from the Women’s Health Initiative (WHI), Carlson and colleagues found that loci previously identified as associated with age at menarche and menopause in women of European ancestry were also associated with length of reproductive lifespan in Hispanic women (Chen et al., Hum Mol Genet, 2012). Phipps et al. examined 16 GWAS-derived CRC susceptibility loci for their association with survival and found a significant association with a SNP in SMAD7 (Phipps et al., Gastroenterology, 2012). Newcomb and Peters showed that SNPs in the promoter of ERβ were statistically significant predictors of colorectal and overall survival (Passarelli et al., Cancer Res, 2013). Such studies often require and stimulate new statistical methods. For instance, Peters and biostatistical colleagues developed a new powerful “cocktail method” for detecting GxE interactions and a new method for using imputed values in meta-analyses of genome wide association (Hsu et al., Genet Epidemiol, 2012).

Esophageal adenocarcinoma is associated with poor survival and incidence continues to rise. Vaughan et al. formed the international Barrett’s and Esophageal Adenocarcinoma Consortium (BEACON) and pooled data and specimens from 15 studies to assess heritability and identify genetic variants associated with increased risk of these conditions. They established for the first time a substantial role for heritability in both Barrett’s esophagus and esophageal adenocarcinoma and demonstrated substantial genetic correlation and polygenic overlap between the two phenotypes (Ek et al., J Natl Cancer Inst, 2013). These results indicate that the impact of inherited factors lies largely in the development of Barrett’s esophagus, and that environmental and lifestyle factors, which are manageable and/or modifiable, likely underlie most of the variability in neoplastic progression to cancer. Further, four novel loci were found to be associated with these conditions (Su et al., Nat Genet 2012; Levine et al., Nat Genet, 2013). Ultimately, these findings will contribute to the development of new screening tools to identify individuals at highest risk for esophageal adenocarcinoma and Barrett’s.

Genomics will continue to contribute to future etiologic and treatment studies (Fullerton et al., Public Health Genomics, 2012), and may play an important role in understanding health disparities and in directing screening decisions that impact quality of life (Ramsey et al., Public Health Genomics, 2010). Use of a formal quantitative risk benefit framework will provide valuable tools for evaluating and prioritizing the use of genomic tests in clinical practice (Veenstra et al., Genet Med, 2010). The Consortium is a leader in the detection of new variants and gene-environment interactions; future efforts aim to use genomic data to understand health disparities, direct screening decisions, and understand survival differences.

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2B. Modification of cancer risk markers using diet and exercise

Obesity and sedentary lifestyle are associated with many chronic diseases, including cancers, and multiple metabolic and endocrine pathways are dysregulated in obesity. Inflammation and disordered metabolism are some of the many metabolic disturbances in obese individuals. Generally, weight loss improves the health profile, but it has been unclear whether specific dietary patterns, macronutrient distributions or diet quality improve health through beneficial changes in inflammation profiles.

Neuhouser et al conducted a randomized double cross-over feeding study testing low v. high glycemic load experimental diets on biomarkers of inflammation and obesity in 80 normal, overweight, and obese healthy adults. Among participants with high-body fat mass (>32% for males and >25% for females), the low-GL diet reduced C-reactive protein (CRP) \( (P = 0.02) \) and marginally increased adiponectin \( (P = 0.06) \). This study demonstrates carbohydrate quality, independent of energy, is important and dietary patterns emphasizing low-GL foods may improve the inflammatory and adiponectin profiles of overweight and obese individuals (Neuhouser et al., J Nutr, 2012). McTiernan and colleagues also studied the effects of energy intake and expenditure. In their study of exercise and caloric restriction on inflammatory profiles in a yearlong randomized trial, 439 overweight or obese postmenopausal women were assigned to diet (10% weight loss goal), moderate to vigorous physical activity, diet + physical activity or a control intervention (Imayama et al., Cancer Res, 2012). After 12 months, the diet and diet + exercise groups had reduced CRP levels overall and in subgroups defined by baseline BMI, waist circumference, CRP level, and fasting glucose. These findings indicate that a calorie restricted weight loss diet with or without exercise reduces biomarkers of inflammation. In an ancillary study within this trial, Kratz, Ulrich and colleagues examined the impact of weight loss on adipose tissue gene expression, finding that weight loss was associated with changes in adipose tissue gene expression after 6 months, particularly in pathways postulated to link obesity and cancer: steroid hormone metabolism and IGF signaling (Campbell et al., Cancer Prev Res, 2013). Lampe and colleagues have conducted studies that suggest that the composition of the gut microbiome may influence metabolism and energy homeostasis and contribute to chronic inflammation (Hullar et al., Cancer Treat Res, 2014).

Unfortunately, high quality diets and physical activity are difficult to promote and maintain in the presence of socio-economic disparities, so that obesity is often endemic (Aggarwal et al., PLoS One, 2012). An ongoing feeding study by Neuhouser is focusing on understanding the relationship between dietary patterns and risk of inflammation and metabolic disorders in Hispanic women (P50 CA148143, PI: Thompson) to aid in designing effective, acceptable programs for cancer prevention. Dietary patterns, weight reduction and physical activity modifications may have clinical significance for cancer risk reduction, if widely adopted. Further study may also provide insights into the biology of this relationship.

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Shared Resources: Prevention Center, Nutrition Assessment, Cellular Imaging

2C. Identification of environmental determinants of cancer and interventions to reduce such risks

There is a continuing public health need to monitor and intervene on environmental factors that affect cancer risk. CEPC faculty members have considerable expertise in intervention research to reduce cancer risk from known environmental causes, particularly tobacco exposure. Tobacco use accounts for approximately 5 million deaths per year worldwide; access to effective smoking cessation treatment remains a critical need. In a landmark group-randomized trial for adolescent smoking cessation, Peterson et al. (J Natl Cancer Inst, 2009) tested a proactive, telephone counselor delivered, personalized intervention combining “motivational interviewing” and cognitive behavioral skills training. This randomized control trial was the first ever to demonstrate 6-month prolonged smoking cessation among a large population-based cohort of adolescent smokers. The intervention nearly doubled the percentage of daily smokers who achieved 6-month prolonged smoking abstinence \( (P = 0.02) \). This generalizable intervention provides a promising new foundation for youth tobacco cessation efforts that can serve as a catalyst for future research. [Additional tobacco intervention research is presented in section 3.]
Pharmacoepidemiology is one key focus area in our program with the potential for cancer prevention intervention. Pharmacosurveillance for cancer risk is motivated by the dual goals of identifying unforeseen adverse effects as well as preventive attributes. Following up on past findings of increased breast cancer risk in young women in relation to oral contraceptive (OC) use, Malone and colleagues (Dolle et al., Cancer Epidemiol Biomarkers Prev, 2009) investigated whether this association varied by triple negative receptor status (TNBC; ER-/PR-/HER2-), a subtype associated with high mortality. OC use was associated with 3-4 fold increases in risk of TNBC but was unrelated to risk of non-TNBC. These findings, if replicated, provide important clues regarding the biology of TNBC and could serve as another component of risk assessment. Newcomb and colleagues evaluated the use of bisphosphonates for osteoporosis prevention and treatment in relation to cancer risk, hypothesizing that because the most commonly used nitrogen-containing bisphosphonate compounds inhibit protein prenylation, they may also exert anti-tumor properties. They found bisphosphonates were associated with a 30% reduction in breast cancer (Newcomb et al., Br J Cancer, 2010); similarly, Li, Malone, and colleagues found bisphosphonate use to be associated with a 60% reduction in the risk of second primary breast cancer (Monesees et al., J Natl Cancer Inst, 2011). Another hormone related cancer, CRC, was unrelated to bisphosphonate use in women in the WHI (Passarelli et al., J Bone Miner Res, 2013). Vaughan and colleagues examined the effects of medications within the BEACON Consortium and a prospective cohort of Barrett’s esophagus patients. Regular users of non-steroidal anti-inflammatory drugs (NSAIDs) had a 30% reduction in risk of esophageal adenocarcinoma (Liao et al., Gastroenterology, 2012) and Barrett’s patients who used statins and aspirin had 30-40% reductions in risk of esophageal adenocarcinoma (Kantor et al., Cancer Epidemiol Biomarkers Prev, 2012). These medication-related risk reductions suggest potentially powerful strategies for future cancer prevention.

Another environmental exposure of interest is shift work that disrupts the body’s normal circadian rhythm. CEPC faculty have assessed shift work associations with specific cancers, such as a recent investigation of epithelial ovarian cancer in which Bhatti, Davis, and Rossing found that working night shifts was associated with a 24% increased risk of invasive epithelial ovarian cancer and a 48% increased risk of borderline ovarian cancer compared with working daytime hours (Bhatti et al., Occup Environ Med, 2013). Davis and colleagues have also conducted studies designed to identify mechanisms underlying the carcinogenic effects of shift work. In a study of exclusive night-shift and day-shift workers, the night shift workers had substantially reduced 6-sulfatoxymelatonin levels that persisted whether working or sleeping at night (Davis et al., Cancer Epidemiol Biomarkers Prev, 2012). This work can inform development of interventions to reduce circadian disruption associated with shift work. We will continue to use our well-characterized population resources to rigorously assess potential risk factors and translate findings through the development and testing of cancer risk reduction interventions.

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**Shared Resources:** Prevention Center, Cellular Imaging, Collaborative Data Services

**2D. Resources of the WHI and other multicenter studies produce practice-changing results and form the basis of additional local and national research efforts**

The CEPC Program is home to coordinating centers that provide outstanding interdisciplinary leadership and service to multicenter studies in cancer prevention, including those for the WHI, the Translational Research for Energetics and Cancer (TREC) network, two prostate cancer prevention trials conducted through SWOG – the Selenium and Vitamin E Trial (SELECT), and the Prostate Cancer Prevention Trial (PCPT) testing finasteride, the Colon Cancer Family Registry (CCFR), and the Carotene and Retinol Efficacy Trial (CARET) testing beta-carotene and vitamin A for lung cancer prevention in heavy smokers and asbestos exposed men. These efforts have yielded practice changing results and created databases and specimen repositories that form the foundation of many additional efforts, both local and national.

The WHI, the largest individually randomized controlled disease prevention trial, is a key example of these efforts. Since publication of the first trial findings in 2002 showing that health risks exceeded benefits of combined estrogen/progestin therapy, world-wide hormone use declined dramatically and national breast cancer rates declined for the very first time, by around 8%. Subsequent work has sought to better understand and refine initial findings and examine longer-term and post-intervention effects (Manson et al., JAMA, 2013). Recent WHI reports include analyses of the temporal trends in breast cancer diagnoses in the WHI,
In addition to studies based upon the clinical trials, the success of WHI is in its more than 1800 projects and publications supported by investigators worldwide, including reports on the major disease end points as well as recruitment, compliance, genetics, and other factors such as breast density, that have practical implications for health in women as they age. An important contribution has been the substantial methodological work to improve dietary assessment by Prentice, Neuhaus and colleagues (e.g., Prentice et al., Am J Epidemiol, 2009; see work highlighted in Biostat-Comp). Prentice et al. reported on a biomarker adjusted approach to evaluating dietary intake; such an approach will permit a more accurate assessment of diet by correcting self-reported intake from food frequency questionnaires using objective measures. The WHI cohort’s rich longitudinal database and vast biospecimen repository have been the source for multiple funded projects by CEPC and other consortium investigators. These include an EDRN-sponsored study by C. Li, examining biomarkers for early detection of triple negative breast cancers (Li C et al., Breast Cancer Res Treat, 2012), and two studies led by Newcomb and McTiernan demonstrating beneficial associations between physical activity and colon cancer mortality (Kuiper et al., Cancer Causes Control, 2012) and breast cancer survival and survival overall (Irwin et al., Cancer Prev Res, 2011). CEPC investigators continue to leverage this resource extensively. WHI has been a major contributor to the GECCO GWAS described in section 2E and participates in numerous other international cancer consortia focused on genetic discovery. Recently Anderson and colleagues were funded to create the WHI Cancer Survivor Cohort, augmenting the WHI database and biorepository with cancer treatment and outcomes data as well as tumor tissue for selected WHI participants with breast, lung, colorectal, endometrial, ovarian and other cancers. The WHI remains one of the great local and national public health resources for the study of health in women. Its value for cancer research, and that of these other large, well-maintained cohorts, continues to develop with the investment in additional data and well annotated biospecimens made widely available to investigators worldwide.

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Shared Resources: Collaborative Data Services

2E. Tailored interventions for cancer early detection and improved screening in at-risk populations.

Cervical cancer is one of the most preventable cancers but is associated with, with high mortality if diagnosed at later stages. Some high risk populations such as Latinas, Southeast Asian women, and those with low incomes often are not compliant with cervical cancer screening guidelines, and often fail to complete recommended diagnostic follow-up after an abnormal pap test. In a multi-centered randomized trial led by Dr. Thompson and colleagues, “Ayudando a las Mujeres con Informacion, Guia, y Amor para su Salud” (Helping Women with Information, Guidance, and Love for their Health), 613 women of Mexican origin were randomized to a lay health worker-delivered intervention that included an informational session, a video, or both, vs. usual care (Duggan et al., BMC Cancer, 2012). After 6 months they showed about a doubling of uptake (from 25%) that was generally comparable for all intervention types. These findings suggest that any of the interventions may significantly increase cervical screening among previously unscreened women. From a practical perspective this flexibility facilitates the dissemination and adoption of this intervention. The success of this program may be its cultural appropriateness rather than the specific intervention. Taylor and colleagues have conducted multiple studies promoting cervical cancer screening in Cambodian and Vietnamese immigrants. For example, in their study evaluating a culturally- and linguistically-appropriate cervical cancer control intervention for Vietnamese immigrants using lay health workers, the intervention proved effective and cost-
effective in increasing Pap testing (Taylor et al., Am J Public Health, 2010). A similar observation was made in trials that developed and tested different language appropriate screening messages, where screening was doubled when language appropriate screening messages were used compared to usual care, whether among Chinese immigrants or Native American men (Muus et al., J Rural Health, 2009; Tu et al., Medical Care, 2008). Identifying the language and cultural barriers to screening can increase screening uptake.

Identifying early high risk lesions may have important effects on surveillance intervals. In a colonoscopy-based screening study, Newcomb and colleagues conducted research to identify aggressive colorectal polyps. This research suggested that in addition to advanced adenomas, sessile serrated polyps may be important precursors to colorectal cancer (Burnett-Hartman et al., Cancer Res, 2013). Weiss and colleagues showed that older women still obtain a mortality benefit from Pap testing, even though current clinical practice truncates screening after mid-life (Kamineni et al., Cancer Causes Control, 2013) [Additional research on screening is presented in section 3.] Cancer screening is an effective prevention tool, if utilized. Improving cancer screening uptake in at-risk populations is an essential public health challenge that we continue to prioritize through innovative and tailored strategies.

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Shared Resources: Collaborative Data Services, Biostatistics, Research Pathology

2F. Determination and modification of risk factors can improve prognosis and quality of life of cancer survivors

The numbers of cancer survivors in the U.S. have risen steadily in recent decades, reaching nearly 14 million in 2012. Survivors are at increased risk of a variety of adverse outcomes including recurrence, second primary cancers, long-term treatment effects, reduced quality of life, and deleterious financial impacts. The CEPC pursues research in relation to all of these outcomes. Below, we highlight selected advances in a few areas, primarily regarding the identification of modifiable exposures that can reduce the risk of disease progression.

The high mortality burden of CRC points to the critical need for new strategies to improve survival. Research by Newcomb and colleagues (Coghill et al., Gut, 2011) in both the Seattle CCFR and the WHI showed prediagnostic use of NSAIDs to be associated with a 20% reduction in the risk of CRC death overall and a 45% reduction for those with CRC in the proximal colon. These new findings of reduced CRC mortality expand the known preventive impacts of NSAIDs. Using data from a phase III CRC therapeutic trial, Phipps and colleagues found smoking to be associated with significantly shorter disease-free survival (Phipps et al., J Clin Oncol, 2013), and used SEER data to show that CRC anatomic subsite is associated with second primary risk (Phipps et al., Cancer, 2013). An index CRC between the transverse and descending colon was associated with the greatest risk of developing any second primary cancer and particularly a second primary CRC, while CRC in the proximal colon was associated with elevated risk of second primary endometrial cancer. These latter two findings will be critical components in crafting clinical tools for risk assessment and tailored surveillance for cancer survivors.

Breast cancer survivors have an estimated two to six times greater risk of developing a contralateral breast primary compared to the risk of a first breast cancer in the general population. Yet, breast cancer survivors receive little guidance on second primary cancer risk and/or potential risk modifiers. Malone and colleagues (Malone et al., J Clin Oncol, 2010) demonstrated 5-fold and 3-fold increased risks of contralateral breast cancer (CBC) in breast cancer survivors who carried BRCA1 and BRCA2 mutations, respectively. C. Li and colleagues (Li et al., J Clin Oncol, 2009) conducted a population-based study of the risk of a second primary CBC among women with a first primary invasive breast cancer and identified three potentially modifiable lifestyle factors that were positively related to risk of subsequent CBC. Specifically, 40%, 90%, and 120% increases in the risk of CBC were observed in relation to obesity, consumption of alcohol and current smoking, respectively. These finding suggest promising avenues for prevention in cancer survivors.

Our faculty are identifying new biomarkers to more effectively target treatment. Chen, Schwartz, and colleagues identified gene expression profiles that may advance the prognostic assessment of oral cancer patients. These signatures can distinguish between invasive cancer, oral dysplasia and normal mucosa (Chen et al., Cancer Epidemiol Biomarkers Prev, 2008; Lohavanichbutr et al., PLoS One, 2012), predict better than tumor size who may harbor occult nodal metastasis (Mendez et al., Clin Cancer Res, 2011), and identify patients at highest risk of poor survival (Mendez et al., Clin Cancer Res, 2009; Lohavanichbutr et al., Clin
Quality of life is now included as an essential outcome in observational and clinical trials based upon work nationally led by CEPC faculty. For example, in a SWOG two-arm study for pancreatic cancer, Moinpour et al. reported that the addition of a second chemotherapeutic agent did not improve clinical or quality of life outcomes (Moinpour et al., J Clin Oncol, 2010). Andersen et al. showed in an observational study that involvement in decision making about ovarian cancer treatment, including surgery and follow-up care after treatment, was associated with better quality of life for cancer survivors (Andersen et al., Gynecol Oncol, 2012).

There is mounting interest in scrutinizing new medical interventions not only for their impact on clinical outcomes, but additionally in the broader context of individual and societal benefits and harms. Drs. Ramsey, Veenstra, and colleagues are leading national efforts in this area. For example, in the RxPONDER SWOG trial of Oncotype DX (a 21-gene expression profile) and chemotherapy assignment in early stage node-positive breast cancer, they recently described the benefits of and strategies for integrating comparative effectiveness features and outcomes into such clinical trials (Ramsey et al., Contemp Clin Trials, 2013) and issued a preliminary assessment of the return on investment of this trial (Wong et al., Contemp Clin Trials, 2012).

The economic impacts of a cancer diagnosis on the individual can be extensive and long-lasting. Leisenring and colleagues showed that childhood cancer survivors experience high rates of unemployment as adults (Kirchhoff et al., Med Care, 2010). In a retrospective cohort study of medical, personal, legal and bankruptcy sources in Washington State, Ramsey and colleagues found that cancer patients were three times more likely to go bankrupt than individuals without cancer (Ramsey et al., Health Aff, 2013). Bankruptcy rates were far greater in younger individuals. The biology of prognosis and other issues facing cancer survivors will continue to benefit from the extensive expertise and resources of our program.

3. Research that relates to health problems in the catchment area

Research serving the needs of our catchment area is a priority in the CEPC program, particularly with regard to underserved populations; below we highlight selected examples of projects serving the catchment area.

Lung cancer is the leading cause of cancer deaths in Washington State, the Pacific Northwest, and in the U.S. The primary cause of lung cancer is cigarette smoking. In Washington State, 15% of adults are smokers; smoking rates are higher among different demographic groups, e.g., 29% of adults with household incomes <25,000 are smokers, as are 26% of those with ≤ 12 years of schooling and 33% of Native Americans/Alaskan Natives. The CEPC has a strong tobacco use reduction research program recruiting participants in Washington and throughout the WAMI (Washington, Alaska, Montana, Idaho) region. Bricker and colleagues currently have three active cessation trials testing multiple delivery modes (web-based, telephone, small group counseling, and individual counseling) of an innovative intervention, Acceptance and Commitment Therapy (ACT) for smoking cessation. One of these studies, a CCSG-funded pilot-test of the WebQuit.org ACT intervention demonstrated a doubling of the quit rate in the ACT intervention arm, compared to standard care using Smokefree.org (P = 0.05). An additional ACT intervention trial focuses on one-to-one delivery of ACT to smokers with bipolar disorder. Buchwald et al. are conducting targeted cessation and prevention research using culturally-appropriate interventions among Native Alaskan populations in Eskimo villages in Alaska, and among American Indian youth (Bowen et al., J Med Internet Res, 2012).

Colorectal cancer is the third most common cancer, and the second leading cause of cancer death for men and women combined, in Washington State. CEPC research focuses on increasing screening rates among populations for whom screening is traditionally low and cancer morbidity and mortality is high. One example is
a Thompson et al. project involving rural Hispanics, Native Americans and other low SES populations in Yakima, Benton, and Franklin counties. A series of health fairs were conducted using a giant (L20’xW12’xH10’) walk-through inflatable colon with physical depictions of polyps and cancers to educate the population about CRC and early detection through regular screening. More than 2000 community members (76% Hispanic, 8% AI/AN; 46% did not complete high school) walked through the colon; participant pre- and post-testing showed significant increases in knowledge gain and screening intention (P<0.05). Partnering with a local community hospital, fecal occult blood test (FOBT) kits were distributed to participants aged 50 and older. Attendees returned 75% of kits for free analysis. The partnering hospital provided complimentary colonoscopy to those participants with abnormal FOBTs.

**Funding:** U54 CA153502, P30 CA015704-37S5, and a supplement from the CCSG

**Shared Resources:** Collaborative Data Services, Biostatistics

**Breast cancer** incidence rates in Washington State have been higher than the national rate since 1992. CEPC investigators have multiple projects in the field to improve both the cancer survivorship experience and screening rates. One ongoing study uses a community-based participatory research (CBPR) to assist African-American women diagnosed with breast cancer as they transition from treatment to post-treatment survivorship. Supported by CCSG pilot funding, Ceballos is conducting key informant interviews and focus groups to assess the experience of African-American breast cancer survivors in King, Pierce and Snohomish counties with the medical and psychosocial transition from cancer patient to post-treatment cancer survivor. In another study among Hispanic women in Washington, Ceballos is adapting a culturally-appropriate psycho-educational cancer survival support group she developed and tested for rural Hispanic women with breast cancer to the needs of urban Hispanic breast cancer survivors. Regarding breast cancer screening, Thompson and colleagues are conducting large CBPR projects using culturally-appropriate multi-level interventions to increase screening and improve cancer outcomes among Latinas.

**Funding:** CCSG pilot funding (Ceballos); K01 CA154938; P50 CA148143

**Shared Resources:** Collaborative Data Services, Biostatistics

**Invasive cervical cancer** incidence and mortality rates, both in Washington and nationally, have been higher in vulnerable populations, including immigrants. As noted in Section 2E, CEPC faculty members have actively developed and investigated new culturally suitable strategies to increase screening in immigrant and other under-served populations with successful outcomes. In addition, Taylor et al. have demonstrated the efficacy and cost effectiveness of tailoring cervical cancer screening for Southeast Asian immigrant women (Scoggins et al., Asian Pacific J Cancer Prev, 2010). A randomized trial by Thompson et al., aimed at increasing cervical cancer screening among Hispanic women, tested three intervention arms, all delivered by trained lay health workers (“promotoras”). The primary endpoint was self-reported cervical cancer screening validated through medical records review. All three arms showed a significant increase in Pap testing at the 6 month follow-up, compared to the control arm (P<0.001; Byrd et al., Cancer, 2013).

**Funding:** R01 CA115564, U01 CA114640, U48 DP000050, subaward to U48-DP000057

**Shared Resources:** Collaborative Data Services, Biostatistics

**4. Future Plans**

The future of our program will be shaped by the emerging need for collaborative translational studies. We have been fortunate to have received four NCI Cancer Epidemiology Cohort (CEC) infrastructure grants that will be used to support molecular cancer epidemiology, early detection and surveillance, and survivorship studies. These CECs constitute large, well-characterized cohorts based upon the PCPT/SELECT, CARET, WHI trials and the CCFR (UM1 CA182883, UM1 CA167462, UM1 CA173642, UM1 CA167551, respectively). These grants will leverage and enrich the carefully annotated data and rich biologic repositories in these cohorts, allowing pursuit of a deeper understanding of the many outcomes that occur in the CEPC coordinated cohorts. This latter activity will benefit from the expansion and maintenance of a strong and dedicated public health laboratory; new laboratory based collaborations will also facilitate the translational and interventional portfolio of the CEPC Program. We are also fortunate to have the Seattle Puget-Sound CSS, our population-based SEER cancer registry, which has been essential to much of our etiologic work and has increasingly become a platform for studies of cancer outcomes and comparative effectiveness.
Several new scientific initiatives will expand the CEPC program priorities over the next five years: obesity, aging, health outcomes and survivorship. Each new priority area has dedicated new recruitments; in some instances, several high level positions have been committed for this growth (e.g., appointment of Dr. Lyman as Co-director of the new Hutchinson Institute for Cancer Outcomes Research [HICOR], and a recruitment for an obesity research is underway). In addition, expansion will occur through building new and extending existing inter- and intra-programmatic collaborations, for example, in the area of pediatric obesity and physical activity, Dr. Jason Mendoza (UW/Seattle Children’s), in survivorship, Drs. Scott Baker, Karen Syrjala, and Eric Chow (all Heme-Malig), in community outreach, Dr. John Scott (UW), and in the evaluation of outcomes through screening and improved diagnoses, Dr. Joanne Elmore (UW). We anticipate that these activities will benefit from partnership across FHCRC, UW, Children’s Hospital and Group Health Research Institute in Seattle to develop community-based interventions and evaluate programs. Synergy around these new initiatives will lead to enhanced team science with opportunities for program projects or other multi-project awards.

Reducing cancer morbidity and mortality has been a challenge. Achieving and sustaining behavior change for major risk factors such as diet, physical activity, obesity, smoking cessation and screening uptake have shown only limited success. Major goals in the next grant cycle will be to understand the basis for certain behaviors, identify ways to change them and, importantly, rigorously test specific tailored interventions. Our program will continue to direct and support research in the biological basis for risk factors such as genes, gene-environment interactions, diet, and other lifestyle factors. Working more closely with laboratory and clinical scientists throughout the Consortium will move these areas forward. Together, we hope to direct the development of new hypotheses to be tested in future observational, small intervention studies, and full intervention trials. The CEPC program has the expertise to be involved at all levels of etiology, cancer prevention, and control.
1. Program Overview

1A. Program focus

The primary objective of the GI Cancer Program is to reduce the morbidity and mortality caused by GI cancers. The GI cancers that are the major causes of suffering in the US are colorectal cancer (143,000 cases/year), upper GI cancers (17,000 esophageal cancers and 21,000 stomach cancers annually), liver cancer (29,000 cases/year), and pancreatic cancer (44,000 cases/year). Thus, the GI Cancer Program has focused its efforts on esophageal adenocarcinoma, pancreatic cancer, liver cancer, and colorectal cancer. To achieve our goals we have developed integrative teams to advance our understanding of the molecular pathology and biology of these cancers and to translate those advances into the clinical care of GI cancer patients. Research themes of the GI cancer program are focused on: 1) investigation of the molecular features that drive the initiation and progression of upper and lower GI cancers; 2) investigation of the host and tumor factors that govern the behavior of GI cancers; 3) development of novel therapies based on new insights into the behavior of GI cancers; and 4) development of novel molecular diagnostics for the early detection and treatment of GI cancers. The specific aims of the Gastrointestinal Oncology Program are to:

1) Develop novel biomarker assays that can be used for the prevention and/or early detection of colorectal, esophageal, and pancreatic cancers and for risk-stratification for these cancers and liver cancer.

2) Develop novel therapeutic strategies for the treatment of pancreatic cancers directed at the tumor microenvironment.

3) Determine the molecular alterations in the major GI cancers (esophagus, stomach, pancreas, liver, and colon) and use the molecular profiles to inform and effectively treat the cancers.

1B. Program structure

The GI Cancer Program was formed in 2004 under the leadership of Dr. John Potter with a strong emphasis on the etiology and epidemiology of GI Cancer. At that time, there were no multidisciplinary care teams for the management of patients with GI Cancer. Since then, through CCSG and institutional support, the program has substantially expanded to include basic and translational investigators and clinicians whose disciplines cover the spectrum of fields needed to advance the prevention and management of GI cancer. Program members are based at the UW, FHCRC, VA Puget Sound Health Care System, and the SCCA, and have appointments in 14 different Departments and Divisions. The program functions as an integrated unit on two levels: 1) clinical/translational research teams that are oriented towards specific organ sites, and 2) research groups that are focused on the investigation and translation of the molecular pathology of GI cancers into innovative methods for cancer prevention and management. These functions have, in turn, led to the formation of the following integrated programmatic units:

1) Molecular Diagnostics Unit: The investigators in this unit collaborate to identify molecular alterations present in GI cancers that have the potential 1) to provide insights into the pathogenesis of GI cancers, 2) to be used as therapeutic targets for novel treatments, and 3) to be used as novel molecular diagnostics for the prevention or management of GI cancers. Support for these studies is provided by the CCSG and other grants: 1) the Early Detection Research Network (EDRN, U01CA152756 (PI: Grady), U01CA152746 (PI: Lampe), U01CA086042 (PI: Thompson-subcontract to Grady), 2) the Barretts Esophagus Translational Research Network (BTRNet, U54 CA163060 (PI: Grady)), 3) Physical Sciences-Oncology Center (PS-OC, U54CA14368 (PI: Davies, SI: Grady, co-I: Henikoff), 4) NCI (Chen PI 1R21CA164548), (Pan: 5K25CA137222-03).

2) Colorectal Cancer (CRC) Precision Medicine Development Unit: This unit studies: 1) the environmental and genetic causes of colorectal cancer, 2) the development of epigenetic, genetic and proteomic markers for screening, early detection and diagnosis using both clinical and epidemiologic approaches; 3) building economic cost-effectiveness models for population screening for colorectal cancer; 4) studies of the molecular mechanisms of cancer progression; 5) studies of pharmacogenetics in the prevention and treatment of colorectal cancer; and 6) novel therapeutics for colorectal cancer. Grant support includes the Early Detection Research Network (EDRN, U01CA152756 (PI: Grady), U01CA152746 (PI: Lampe), the Burroughs Wellcome Research Fund and philanthropy. Collaborators include Consortium investigators outside the program (Lampe, Newcomb, Burnett-Hartman, Peters) and outside of the Consortium (Markowitz, CWRU; Leibler, Leibler, Leibler).
This unit is notable for having members who coordinate national colon cancer screening studies (CONFIRM, PI: Dominitz, site PI: Kaz) or local operations of national studies (GLNE010: site PI: Grady). CONFIRM is a national VA sponsored study (N=50,000) comparing colonoscopy to fecal immunochemical testing (FIT) that has as its primary study endpoint CRC mortality within 10 years of enrollment. The secondary endpoints are (1) the incidence of CRC within 10 years of enrollment and (2) major complications of colonoscopy. This study will provide critical information needed to determine the true value of colonoscopy for CRC mortality reduction. The GLNE 010, funded by the EDRN, will assess the performance of a panel of novel early detection molecular markers through a case/control study of 5000 individuals undergoing screening colonoscopy.

3) Esophageal Cancer Prevention Unit: The focus of this unit is to identify innovative methods for the prevention of EAC based on insights into the molecular pathogenesis of Barretts Esophagus (BE). These studies are supported by the Barretts Esophagus Translational Research Network (BTRNet) (U54CA163060, PI: Grady), Early Detection Research Network (U01CA086402: PI-Thompson, subcontract Grady), and Multiscale Esophageal Adenocarcinoma Model (MEMO) study (1U01CA182940-01, co-PI: Luebeck, Inadomi, co-I: Grady), and a RO1 funded through the Provocative Questions RFA (PI: Reid) and employ resources from BEACON as well as the BTRNet. This unit encompasses clinicians, translational researchers, bioengineers, and epidemiologists in the study of Barrett’s esophagus and esophageal cancer. Our members and collaborators at Case Western Reserve University and the University of Michigan have identified many of the most promising biological and epidemiologic risk factors for esophageal adenocarcinoma (e.g. (Galipeau et al. PLoS Med, 2007; Paulson, Reid. Cancer Cell 2004)) and have characterized epigenetic alterations in Barretts esophagus and esophageal adenocarcinoma (Kaz et al. Genes Chromosomes Cancer, 2012; Kaz et al. Epigenetics, 2011). They are also developing novel imaging modalities for the upper GI tract. Lastly, Drs Grady, Inadomi, and Seibel are principal or co-investigators in the NCI sponsored Barretts Esophagus Translational Research Network (BTRNet), and Dr. Vaughn is the lead PI in BEACON (International Barretts and Esophageal Adenocarcinoma Consortium) consortium.

4) Center for Accelerated Translation in Pancreas Cancer (CATPAC): CATPAC is a cross-disciplinary program with a mission to transform the “state of the art” for pancreas cancer care by making molecular diagnoses of pancreas cancer subtypes at the earliest possible stages and treating with disease-specific therapies. Our ability to translate our most compelling findings to the clinic has been greatly enhanced by the development of the Pancreas Cancer Specialty Clinic (PCSC), a real-time multidisciplinary clinic, in which we see ~180 new cases of pancreas cancer each year resulting in approximately 70 pancreaticoduodenectomies per year. Patients receive a comprehensive care plan and are also given the opportunity to participate in our clinically annotated biorepository by providing biospecimens. This clinic is a core component of our Center for Accelerated Translation in Pancreatic Cancer (CATPAC), which catalyzes the bi-directional flow of information between research studies and clinical care on a number of levels: epidemiological; longitudinal; biomarkers for disease detection and response to therapy; chemoprevention; targeted therapies for early and advanced disease; and studies of familial disease. CATPAC has sponsored pilot projects and biospecimen repository development with philanthropic funds.

5) Northwest Liver Research Program (NWLRP): The Northwest Liver Research Program serves to integrate the clinical activities of the multi-disciplinary Liver Tumor Clinic, the first multi-disciplinary GI cancer clinic established in the Northwest, with the translational research programs being run under the leadership of Dr. Ray Yeung, Jim Park, Robert Carithers, and Jean Campbell. The Program meets monthly with meetings alternating between clinical seminars and research presentations. Since the time of the last CCSG renewal, the NWLRP has increased research activity in the areas of signal transduction in liver cancer through the recruitment of new faculty (Rhiele) and initiation of 6 clinical trials that include targeted therapies directed at a variety of tyrosine kinases (lavnatinib, cabozatinib, sorafenib, and tivantinib), and 2) therapeutic use of nanoparticles including initiation of a clinical trial using Theraspheres.

In the last program review, the program was rated Excellent. We have devoted considerable attention to strengthen all of the areas noted by reviewers, as follows.

1) “An issue with this program is that it mostly functions as independent sections rather than a fully integrated program. This is certainly somewhat expected in view of the breadth and depth of the program and its relative short time in place.”

The GI cancer program includes investigators who have areas of investigation focused on disease processes...
as well as on specific cancer types (e.g. colorectal cancer, esophageal cancer, pancreatic cancer, and liver cancer). We have made a substantial effort to integrate the program based on common thematic areas as well as on areas where synergy can be achieved through consolidation of efforts. Program members have integrative research programs in: 1) signal network deregulation (Liver: Yeung, Campbell; Pancreas: Hingorani, Colorectal: Grady, Grim) and 2) biomarkers (Hingorani, Reid, Grady, Brentnall, Kaz). These groups meet quarterly to plan collaborative studies that have resulted in a large number of collaborative publications such as (Baek et al. Int J Cancer, 2010; Kenerson et al. Gastroenterology, 2013; Wright et al. Int J Cancer, 2014; Izeradjene, et al. Cancer Cell, 2007; Lai, 2012; and Pan et al. Mol Biosyst, 2012). In addition, to facilitate Program interactions, prioritize Program goals, and accelerate discovery and translation, the Program members meet on an approximately monthly basis.

2) “The development of this goal [protocols for GI cancer management that seamlessly link clinical and research objectives] is not well outlined and there is little or no specific treatment research ongoing or proposed. Similarly, the trials recruitment of the program was somewhat lower than would be expected.”

We have made substantial gains in our clinical and translational research activities. Jennifer Yahne was hired as Program Manager in 2010 and has played a critical role in developing multidisciplinary clinical and research units for the upper GI tract, lower GI tract, and pancreas. To foster the development of a translational research program, the Program has recruited three cancer surgeons, 4 medical oncologists, 2 radiation oncologists, a GI pathologist, and molecular pathologist. Effective clinical trials units have been developed at both the SCCA (leader: Chiorean) and UW (leader: Grady). This has led to the initiation of an innovative phase I clinical trial using stroma-targeted therapy for pancreatic cancer (PI: Hingorani) and a phase II study employing stem cell directed therapy as maintenance therapy in patients with metastatic colorectal cancer (PI: Lin). The percentage of new patients on clinical trials has increased from 4% in 2008 to 9% in 2013.

As a result of concentrated efforts across a number of departments, divisions and programs, we have increased clinical trial participation of patients with pancreatic ductal adenocarcinoma (PDA) from 8% five years ago to 40% now, and the numbers continue to rise. Several Consortium investigators lead pancreas cancer trials at SCCA, including Dr. Gabriela Chiorean, Dr. Andrew Coveler and Dr. William Harris. CCSG recruitment funds have supported the work of Dr. Chiorean, Dr. Shankaran and Dr. Pillarisetty.

3) “Another issue of the program includes a recent change of leadership.”

Since the last CCSG renewal, Drs. Grady and Yeung have provided strong joint leadership, including coordinating programmatic activities such as seminars and leadership meetings, annual meetings with faculty regarding their progress, and meeting with Consortium senior leaders regarding programs needs. This has yielded recruitment of cancer surgeons (Park, Fichera, Pillarisetty), medical oncologists (Shankaran, Chiorean, Harris, Coveler), gastroenterologists (Inadomi, Kaz, Chatthadi), radiation oncologists (Apisarnthanarax, Kim), GI pathologist (Westerhoff, Dintzis) and molecular pathologist (Pritchard). In addition, Dr. Hingorani became an Associate Head in 2010 and has played a key role with Dr. Chiorean in developing the clinical trials infrastructure of the Program.

1C. Program Leadership and Qualifications

Program leadership is composed of co-heads Dr. William Grady (upper and lower GI tract), Dr. Ray Yeung (hepatobiliary), and associate head Dr. Sunil Hingorani (pancreatic). The leaders provide representation for the organ sites in the GI Oncology Program as well as the Consortium member institutions. They are all internationally recognized physician-scientists with successful NCI-funded research programs. Dr. Grady, Yeung and Hingorani have been Co-leaders of the Program since 2008 and have directed the substantial expansion in basic and translational research that has occurred in this program over the last 5 years.

Dr. Grady is a board-certified gastroenterologist and an independent NIH funded PI with >15 years of experience in translational research related to gastrointestinal cancer. He has been elected Vice-Chair for the American Gastroenterological Association (AGA) GI Oncology Section, Chair of the Gastroenterology Research Group, and is Deputy Editor for Gut, the flagship journal of the British Medical Association. His research has been recognized by multiple awards including a Mallinckrodt Scholar Award, Damon Runyon Lilly Clinical Investigator Award, Burroughs Wellcome Translational Research Award for Clinician Scientists, and a Presidential Early Career Award for Scientists and Engineers (PECASE). His research focuses on the role of epigenetic alterations and DNA repair enzymes as biomarkers for esophageal and colon cancer, respectively. Dr. Grady is a practicing gastroenterologist and is the Medical Director of the GI Cancer Prevention Program Clinic at the Seattle Cancer Care Alliance, which specializes in the care of individuals who
Dr. Yeung is a board-certified surgical oncologist with 20 years of R01 funding. He is the founder and director of the Liver Tumor Clinic at the University of Washington Medical Center and the Seattle Cancer Care Alliance. Dr. Yeung was Chair of DOD TSCRP Integration Panel (2007-2008) and Chair of DOD TSCRP Scientific Review Panel (2012). He also serves on the Scientific Advisory Boards of the Tuberous Sclerosis Alliance and the LAM Foundation. He is known internationally for his work related to tuberous sclerosis stemming from the characterization of the first animal model of TSC to the first pre-clinical demonstration of the efficacy of rapamycin in the treatment of TSC-related disorders. He also has an active research program in the pathogenesis of liver cancer, and has recently created the Northwest Liver Research Program to accelerate liver-related research through a collaborative network of investigators.

Dr. Hingorani is a gastrointestinal medical oncologist and a cancer biologist whose investigative program is focused on pancreatic cancer. He is an internationally recognized leader in pancreas cancer biology and pathogenesis and has 15 years of experience in translational research; he is currently PI of four active NIH grants (two R01s and two R21s). Dr. Hingorani led the seminal development of murine models of pre-invasive, invasive and metastatic pancreatic ductal adenocarcinoma (PDA) by introducing tissue specific mutations in key oncogene and select tumor suppressor genes in the pancreatic ductal cells. Dr. Hingorani is a member of the Scientific Advisory Board of the Pancreatic Cancer Action Network and of the Scientific Review Board of the Lustgarten Foundation. He is the founding Director of the Pancreas Cancer Specialty Clinic (PCSC) at the Seattle Cancer Care Alliance (SCCA), a multi-disciplinary clinic that is the focal point for a comprehensive translational research program in pancreas cancer, the Center for Accelerated Translation in Pancreas Cancer (CATPAC), which he also directs.

The Program Leaders interact extensively, collaborate on research projects, co-mentor junior faculty, and organize regular Program clinical and research meetings. The Program Heads also meet quarterly with the GI Leadership Committee, composed of members from Pathology, Radiology, Radiation Oncology, Nursing, Medicine, and Surgery who broadly represent the domains of GI cancer research and clinical care within the Consortium. The Program Heads advise the Center Director and Head of the Solid Tumor Translational Research Program on all issues related to GI Cancer concerning faculty recruitment and retention, space, and other research support.

1D. Program membership

The GI Oncology Program is comprised of 32 members who represent a spectrum of disciplines, including molecular biology, cell biology, epidemiology, genetics, clinical research, bioengineering, and others. The Program includes faculty in 14 FHCRC scientific divisions and UW departments. Key recruitments have been made to optimize the clinical and translational research in the Program, including medical oncologists (Shankaran, Harris, Coveler, Grim, Chiorean), surgeons (Fichera, Pillarisety, Park), radiation oncologists (Kim, Apisarnthanarax), gastroenterologists (Kaz, Inadomi, Chathadi), pathologists (Westerhoff), as well as basic scientists with research programs with a focus in translational research (Chen, Pang). These recruitments have had a dramatic impact on the program’s clinical and translational studies, including an innovative stroma-oriented phase I therapy trial that has borne out of the CATPAC. In addition, these recruitments have led to the establishment of multidisciplinary care teams for management of patients with upper GI tract cancers, lower GI tract cancers, hepatobiliary cancers, and pancreatic cancer, which both optimize patient care and provide a structure to facilitate translational studies. The amount of peer reviewed funding for the last budget year is $3,737,242 (direct dollars.) Within the last grant period, the total of 470 publications by Program members includes 12% intra-programmatic, 44% inter-programmatic and 17% inter-institutional manuscripts.

Interdisciplinary interactions are facilitated by the inclusion of members from diverse disciplines who interact extensively with each other as well as with other Consortium programs and institutions. The leadership group provides vision and works with members to identify and refine program goals, development, and progress. The four disease-specific sections foster interdisciplinary discussion and collaboration, with several faculty members participating in more than one section. The seminar series provides a forum for the exchange of ideas, methods and data in GI oncology research among consortium members and institutions. Prominent examples of just a few of these collaborative projects include 1) studies to identify Barretts Esophagus early detection and risk markers, which range from fluorescent probes to epigenetic biomarkers, being conducted at the FHCRC (Grady, Kaz, Luebeck), UWSOM (Inadomi, Seibet), and VA Puget Sound Health Care System (Dominitz); 2) molecular marker studies for colon adenomas and cancer (FHCRC: Grady, P. Lampe, Chris Li, Makar) and UWSOM (Sinanan, Pritchard, Mann, Upton); and 3) studies to determine key elements of deregulated growth factor biology and signal
pathway deregulation in liver cancer (FHCRC: Grady, UWSOM: Yeung, Yeh, Campbell). As demonstrated by the review of scientific accomplishments outlined below and the pattern of publications (Cancer Cell, Gastroenterology, Oncogene, PLoS Genetics, etc.), and multi-investigator funded awards (e.g. BTRNet (U54), EDRN (UO1), MEMO (U54), PS-OC (U54)), GI program members have a history of working collaboratively to address specific research problems through interdisciplinary and inter-institutional scientific communication.

2. Scientific Accomplishments

The Program has active research programs in basic, translational, and clinical research as well as in outcomes and epidemiological research. These programs are highly integrated not only within the Program but perhaps most notably with investigators in other programs in the Consortium and externally. Several CCSG Shared Resources have been critical for these accomplishments, in particular Research Pathology, Comparative Medicine, Animal Bioimaging, Genomics, Computational Biology, and Northwest BioTrust. Selected accomplishments are summarized below.

2A. COLORECTAL CANCER

1) The colorectal cancer epigenome and its use in directing clinical care

A. Advances in our understanding of the CRC epigenome: Substantial advances have been made in our understanding of the genetic and epigenetic alterations present in colorectal cancer (CRC) over the last 3 decades. Initial insights into the molecular pathogenesis of CRC revealed that the accumulation of gene mutations in oncogenes and tumor suppressor genes led the initiation and progression of normal colon epithelium to benign neoplasia and then to adenocarcinoma. More recently, epigenetic alterations have been found to occur commonly in CRCs. Initial skepticism of the functional significance of these alterations was only resolved through studies from a variety of laboratories including the Grady lab that revealed the equivalence of aberrant DNA methylation, the most commonly studied epigenetic alteration in cancers, to mutations in inactivating tumor suppressor genes (Grady et al. Nat Genet, 2000; Herman et al. Proc Natl Acad Sci, 1998; Veigl et al. Proc Natl Acad Sci, 1998). Controversy also marked the observation that a subset of CRCs showed an excessive frequency of aberrant methylation, termed the CpG Island Methylator Phenotype (CIMP), which was eventually resolved by the discovery of unique associated mutation patterns and clinicopathological features in CIMP CRCs, which provided substantial support for their unique pathogenesis (Toyota et al. Proc Natl Acad Sci, 1999; Weisenberger et al. Nucleic Acids Res, 2005). The discovery of CIMP and other discrete molecular subgroups of CRC that are recognized by their patterns of epigenetic alterations and by the form of genomic instability that they display has provided insight into the substantial heterogeneity of CRCs. Indeed, as with other tumor types, the molecular features of CRCs and colon adenomas and serrated polyps appear to have great potential to improve our accuracy to identify aggressive from indolent CRCs and polyps and to identify effective therapies for individual patients.

As CRCs are nearly universally derived from colon polyps, investigators in the GI Cancer Program have invested substantial effort into investigating the role of both the epigenetic alterations and gene mutations present in colon adenomas as well as in serrated polyps, which are now believed to have malignant transformation potential (Huang et al. Am J Gastroenterol, 2011). These studies have been carried out through the support of the EDRN and by a team of PIs including Dr’s Newcomb (CEPC program), Grady, Paul Lampe, Kaz, and Upton. These studies have revealed that aberrant DNA methylation arises early in the polyp→CRC progression sequence and that it can even be found in the normal colon mucosa of individuals with adjacent CRC, who are at increased risk of developing metachronous CRC (Grady et al. Oncogene, 2008; Kim et al. Genes Chromosomes Cancer, 2006). Moreover, Burnett-Hartman and colleagues have found that serrated polyps share the same molecular features as CIMP CRCs (e.g. mutant BRAF, CIMP) providing substantial evidence that serrated polyps are the precursors to this class of CRCs (Burnett-Hartman et al. Am J Gastroenterol, 2012; Burnett-Hartman et al. Cancer Res, 2013).

In an extension of these studies by Burnett-Hartman, Newcomb and Grady, the Grady lab has conducted genome-wide array-based studies and comprehensive data analyses of aberrantly methylated loci in normal colon, colon adenomas, and colorectal cancer. They have found that genome-wide alterations in DNA methylation are present in the normal colon mucosa adjacent to colorectal cancer, tubular adenomas, and colorectal cancer. Three subgroups of CRCs and two subgroups of adenomas were identified on the basis of their DNA methylation patterns. The adenomas separated into a high-frequency methylation class (Adenoma-H) and a low-frequency methylation class (Adenoma-L). The adenoma-H polyps have a methylated DNA signature similar to non-CIMP CRCs, whereas those of the Adenoma-L class have a similar methylation
pattern to normal colon mucosa. The CpGs that account for these signatures are located in intragenic/intergenic regions, suggesting that these two groups of adenomas arise from different stem cell populations. These findings and those of Burnett-Hartman and colleagues suggest that the different CRC molecular subgroups (CIN, MSI, and CIMP) are derived from unique polyp subgroups and have implications for chemoprevention strategies. (Luo, et al. Gastroenterology, revised manuscript under review).

B. Epigenetic alterations effect “driver genes” in CRC: In addition to characterizing alterations in the polyp→CRC progression sequence, investigators in the GI Cancer Program have revealed a number of epigenetically altered genes that appear to be functioning as driver genes in CRC formation. These genes include RET and NTRK3, which appear to be conditional tumor suppressor genes secondary to their function as dependence receptors, and TSP1, which regulates transforming growth factor β signaling. RET and NTRK3 were discovered to be aberrantly methylated in colon adenomas and CRCs through genome-wide scans and were unexpected, given their known functions as oncogenes in thyroid cancer and breast cancer, respectively (Luo et al. PLoS Genet., 2013; Luo et al. Oncogene, 2013). Dependence receptors are a class of receptors that are defined by their function to induce proliferation when they are activated by their ligands but to also be active in the ligand-free state and to cause apoptosis in this state (Goldschnieder, Mehlen. Oncogene, 2010). Through a careful series of studies, Luo et al determined that both RET and NTRK3 function as conditional tumor suppressor genes that presumably are selected for epigenetic silencing when the expression of these receptors is lost during CRC formation (Luo et al. PLoS Genet, 2013; Luo et al. Oncogene, 2013). These results suggest that ligand-trap therapy (i.e. soluble traps for GDNF and NT-3) may have potential for CRC prevention. This type of therapy has been effective in pre-clinical studies for other dependence receptors (Luchino et al. Cancer Cell, 2013). In addition to demonstrating that epigenetic alterations disrupt dependence receptor induced apoptosis in CRC, Rojas et al have demonstrated that epigenetic alterations can also suppress the tumor suppressive TGF-β signaling pathway providing evidence that this pathway is inactivated by both mutations and aberrant gene methylation in CRC (Rojas et al. Int J Cancer, 2008).

C. Epigenetic alterations, biomarkers, and advances in CRC screening: The discovery that aberrantly methylated genes are common in adenomas and CRCs and the availability of PCR-based assays for detecting methylated loci suggested that methylated loci could be used as colon polyp and CRC biomarkers. A number of pioneering studies, including those by the Grady lab demonstrated the feasibility for methylated genes to be used as serum-based and stool-based early detection molecular markers (Ausch et al. Clin Chem, 2009; Grady et al. Cancer Res, 2001; Laird. Nat Rev Cancer, 2003; Petkov et al. Hepatology, 2004). Since the publication of these initial studies, 100’s of studies have been published assessing the use of methylated genes as early detection, prognostic and predictive markers in tissue, blood, and stool based assays (Laird. Nat Rev Cancer, 2003; Lao, Grady. Nat Rev Gastroenterol Hepatology, 2011). In fact, the methylated MLH1 molecular marker assay developed by Grady and Markowitz is commonly used in clinical laboratories to assess the methylation status of this gene in CRC samples. (A patent application is under review.) The Grady laboratory, through the support of the Early Detection Research Network (EDRN) and in collaboration with Dr’s Upton, Makar, Ulrich, P. Lampe, J. Lampe, Kaz, Newcomb, and Inadomi is conducting genome wide DNA methylation studies to identify other methylated gene early detection biomarkers.

1) Phase III studies of epigenetic biomarkers for the early detection of colon adenomas and CRCs: In collaboration with CCSG members (Ulrich, Makar, Sinanan, Fichera, Mann, Horvath, Billingham, Coveler, Harris, Lin, Upton), Dr. Grady has carried out studies assessing the methylome of colon adenomas and adenocarcinomas. These studies have identified unique molecular subclasses of colon adenomas that appear to have low and high-risk for progressing to CRC as well as a number of promising aberrantly methylated genes for use as early detection markers and risk markers for colorectal cancer. In addition, Dr. Grady is the site PI at the University of Washington for a large prospective case-control study (GLNE010) that is enrolling 6000 participants undergoing screening colonoscopy in order to assess the clinical performance of a panel of novel biomarkers assays. Markers discovered and validated in the Grady lab have a high probability of being included in the final panel of assays that will be run as part of the GLNE010 study. Preliminary data for this EDRN BDL grant was generated with support from the CCSG (pilot project “Methylated Genes as Risk Stratification and Early Detection Markers for Colon Cancer “, PI: W. Grady), and results from these studies have been published in Clinical Chemistry, Clinical Cancer Research, Oncogene, and PLoS Genetics. (Ausch et al. Clin Chem, 2009; Kim et al. Genes Chromosomes Cancer 45:781-789, 2006; Luo et al. PLoS Genet, 2013; Luo et al. Oncogene, 2013).

D. State of the art colon cancer screening tests and assessment of current approaches: In addition to
the novel screening molecular markers described above, there are additional studies being run by investigators in the consortium to identify novel approaches to CRC screening. These studies are part of a larger colon cancer prevention program in the consortium that includes members outside of the GI Cancer Program who interact with GI cancer program members. Dr. Paul Lampe has an active research program funded by an EDRN BDL grant to identify protein biomarkers in blood for colorectal neoplasms. Using state of the art reverse phase protein antibody arrays (RRPA), he identified and validated protein biomarkers that predict an increased risk of developing CRC. Proteomic analysis of Women’s Health Initiative (WHI) samples collected before diagnosis of CRC resulted in the identification of six proteins with significantly (P < 0.05) elevated concentrations in cases compared with controls. (MAPRE1, IGFBP2, LRG1, and CEA: 57% sensitivity at 95% specificity), which was validated in an independent set of WHI samples collected within 7 months before diagnosis (41% sensitivity at 95% specificity). (Ladd et al. Cancer Prev Res, 2012).

In addition, Dr. Jason Dominitz is the PI of an ambitious VA Cooperative Study that will compare screening colonoscopy to annual fecal occult blood testing (with a fecal immunochemical test) for reduction in colorectal cancer mortality. This study is notable because it is the first study to determine the effect of colonoscopy based screening on colon cancer related deaths, which has not been directly assessed to date, and because it will generate data that will allow a direct comparison of the efficacy of the two most common colon cancer screening modalities being used in the US currently. This study will recruit 50,000 average risk adults from 40 facilities around the US and randomize them to one of these two strategies. The participants will be followed for 10 years to determine colorectal cancer incidence and mortality, as well as complications of screening colonoscopy. This study is on track to begin accruing study subjects this year. The study is sponsored by the Department of Veterans Affairs (NCT01239082) (PI: Dominitz, site PI: A. Kaz).

E. Precision medicine and CRC: There is tremendous potential for use of molecular features to improve our ability to manage cancer by improving diagnostic accuracy, prognostication, and prediction of therapeutic response to individual agents, as well as in developing novel targeted therapies directed at specific molecular features of individual tumors. The GI Cancer program (Grady, Inadomi, Brentnall, MacDonald, Lin, Chiorean, Harris, Coveler, Shankaran, Back) and other members of the consortium (Ulrich, Makar, J. Lampe, Warren) have developed an infrastructure, named ColoCare, for precision medicine studies through the support of the consortium and its Shared Resources (Collaborative Data Services, Specimen Processing, Biospecimen Repository). The ColoCare cohort study is a unique resource for Center investigators that has generated a clinically annotated biorepository of colon cancer patients. The registry has extensive clinical annotation, which includes health behavior, drug, and relevant clinical and pathological information, as well as serial follow-up information and follow-up biological samples. These elements distinguish it from other NIH sponsored projects, like the TCGA, which lacks the extensive clinical annotation and follow-up data that is part of the ColoCare study. Furthermore, the ColoCare study has served as the core resource for a number of funded grants at the Center (Grady, 5U01CA152756-02; Lampe, 5U01CA152746-02; Makar, R03 CA165153-01) as well for many pilot projects. It is also one of the repositories being used to establish the principles for the Consortium Biorepository project being run by Dr. Peggy Porter, which is funded by an LSDF grant, and the NW BioTrust biorepository being established by Dr. Steven Schmechel (Pathology Dept, UWMC).

In conjunction with the ColoCare study, GI Cancer Program member, Colin Pritchard has developed a suite of cutting-edge molecular assays for colorectal cancer as well as other cancer types that are in near-clinical and clinical use. In collaboration with Dr. Tait and Grady, he has developed enhanced assays for mutant KRAS, which is improving the management of patients with metastatic colorectal cancer (Pritchard and Grady). He has also developed a next-generation sequencing based assay, named OncoPlex, that assesses for mutations in >200 genes for which there are clinically actionable consequences (Pritchard et al. J Mol Diagn, 2014). The Oncoplex assay provides state of the art molecular characterization of solid tumors. It has been run on over 220 cancers to date, with >30% of these tumors being colorectal, stomach, and liver cancer. Furthermore, he also developed one of the first multi-gene hereditary GI cancer syndrome assays that has made the GI Cancer Prevention Program Clinic at the SCCA a one of a kind resource for patients with hereditary cancer syndromes (e.g. Lynch syndrome, Familial Adenomatous Polyposis, Cowdens syndrome, etc.) (Pritchard et al. J Mol Diagn, 2012). These assays were developed in collaboration with members of the GI Cancer Program (Grady, Steinbach, Brentnall).

2B. PANCREATIC CANCER

1) Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma: Dr. Hingorani led the development of the first genetically engineered mouse (GEM) models
of preinvasive, (Hingorani et al. Cancer Cell, 2003) invasive, and metastatic (Hingorani et al. Cancer Cell, 2005; Izeradjene, et al. Cancer Cell, 2007) PDA that faithfully recapitulate the clinical, histopathological, and genomic features of the human disease. These GEM models were developed in part to address the growing awareness that cancer cells arising and progressing spontaneously in a native organ are functionally distinct from the same cells growing on plastic or under the skin of immune compromised animals, particularly with respect to mechanisms of disease resistance and the attendant and potentially novel therapeutic vulnerabilities (Bissell, Radisky. Nat Rev Cancer, 2001). Targeted endogenous expression of oncogenic Kras<sup>G12D</sup> and Trp53<sup>R172H</sup> to tissue progenitor cells of the developing murine pancreas leads to the stochastic development and spontaneous progression of preinvasive pancreatic intraepithelial neoplasms (PanIN) to invasive and metastatic disease that faithfully models human PDA (Hingorani et al. Cancer Cell, 2005). The PDAs that develop in these Kras<sup>LSL-G12D</sup>+, Trp53<sup>LSL-R172H</sup>+, Cre (KPC) mice also manifest a complex and evolving fibroinflammatory, or desmoplastic, response that is essentially pathognomonic for human pancreatic cancer (Mahadevan, Von Hoff. Molecular Cancer Therapeutics, 2007) and includes stromal fibroblasts, immune cells and endothelial cells in a dense extracellular matrix. Studies in these mice have revealed unexpected properties of tumor progression, including a profound hypovascularity (Olive et al. Science, 2009) and the infiltration of multiple components of immune suppression beginning at the earliest stages of preinvasive disease (Clark et al. Cancer Res, 2007). These studies, in turn, have also helped identify previously underappreciated and unexplored mechanisms of therapeutic resistance in PDA (reviewed in Hingorani. Drug Discovery in Pancreatic Cancer, 2010).

These GEM model systems serve as primary platforms in the Murine Clinical Trials Program (MCTP), itself an essential component of the Center for Accelerated Translation in Pancreas Cancer (CATPAC), both of which Dr. Hingorani directs. Stringent criteria must be met in order for a GEM model of PDA to be included in the MCTP. Specifically, the model must:1) incorporate signature genetic events implicated in the human disease; 2) recapitulate the clinical syndrome of disease; 3) recapitulate the histopathology from preinvasive to invasive to metastatic disease (with metastases to the same sites and at the same frequencies as human PDA); 4) recapitulate the genetic progression and genomic instability implicated in human PDA; 5) recapitulate the treatment response and resistance to therapeutic agents already tested in patients.

One example of a strategy developed and advanced into the clinic through CATPAC is described next. To further investigate the basis for vascular collapse and impact on treatment in PDA, we studied the thermodynamics and biophysics of solute delivery and fluid flux in KPC mice and discovered inordinately high interstitial fluid pressures (IFP) in the primary tumors. These IFP ranged from 70 – 130 mm Hg (mean ~100 mm Hg), which rivals mean arterial pressure and would therefore be expected to significantly limit drug delivery, diffusion and convection into the tumor bed (Provenzano et al. Cancer Cell, 2012). Detailed analyses of the composition of the extracellular matrix revealed unusually high concentrations of hyaluronic acid (HA), or hyaluronan. HA is a megadalton polymer comprised of repeating units of N-acetyl glucosamine (NAG) and D-glucuronic acid. It imbibes and immobilizes large amounts of water due to a combination of Donnan and van’t Hoff forces, together with electrostatic repulsion of negative charges along its length. We hypothesized that degradation of interstitial HA would liberate this fluid phase, decrease IFP and allow for vascular re-expansion and perfusion. We showed that systemic administration of a pegylated form of hyaluronidase (PEGPH20) could effectively degrade intratumoral HA, normalizing pressures and enabling high concentrations of chemotherapeutics to penetrate the tumor bed. When combined with a conventional cytotoxic, gemcitabine, the tumor stroma was permanently remodeled and resulted in high objective response rates and an approximately 70% increase in survival (Provenzano et al. Cancer Cell, 2012). These results prompted a recently completed Phase 1b trial, for which Dr. Hingorani served as Global PI. This trial demonstrated a high tolerability profile for the combination arm, an objective response rate of 42% (compared with a historical rate for gemcitabine monotherapy of 7 -13%), and a median survival that has not yet been reached (>320 days at this point) (Hingorani et al. J Clin Oncol, 2013). These data, in turn, have led to the launch of two randomized Phase 2 trials currently underway testing the two new, recently approved standards for cytotoxic chemotherapy of PDA, namely nab-paclitaxel + gemcitabine (NCT01839487) and FOLFIRINOX (NCT01959139), respectively (the latter trial is being conducted by SWOG). Dr. Hingorani serves as a co-national PI on both trials. Additional trials in the planning stages include investigating the role of PEGPH20 as a radiosensitizing agent in PDA by increasing blood flow and local oxygen delivery and, more generally, as part of a strategy in locally advanced (Stage III) disease to try to achieve resectability.
selenium, and certain medications, such as NSAIDs can affect the risk of developing EAC

resource to establish our current understanding of the molecular clonal evolution of BE and EAC

1996; Li et al. clonal

prognostic markers for BE progression to EAC (aneuploidy, tetraploidy, 17p LOH) and then later showed that

Nat Genet

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The Seattle Barrett’s Esophagus Study, in 1983, which is a unique cohort of patients with BE who have been

ongoing studies of genetic alterations in BE and EAC and their assessment as biomarkers for BE, there is a

expanded in response to the dramatically increasing incidence of EAC in the US population. In addition to

2) Pancreatic cancer and stromal fibroblasts: Dr. Teri Brentnall’s laboratory has uncovered a new

mechanism through which the pancreatic oncogene palladin, which was discovered by the Brentnall lab, promotes pancreatic cancer formation (Brentnall et al. PLoS One, 2012). Cancer-associated fibroblasts (CAF), comprised of activated fibroblasts or myofibroblasts, are found in stroma surrounding solid tumors, such as pancreatic cancer. These myofibroblasts promote invasion and metastasis of cancer cells. Activation of stromal fibroblasts into myofibroblasts is induced by expression of cytoskeleton protein, palladin, at early stages in tumorigenesis and increases with neoplastic progression. Expression of palladin in fibroblasts is triggered by paracrine signaling from adjacent KRAS-expressing epithelial cells. Three-dimensional co-cultures of palladin-expressing fibroblasts and pancreatic cancer cells reveals that the activated fibroblasts lead the invasion by creating tunnels through the extracellular matrix through which the cancer cells follow.

Invasive tunneling occurs as a result of the development of invadopodia-like cellular protrusions in the palladin-activated fibroblasts and the addition of a wounding/inflammatory trigger. Abrogation of palladin reduces the invasive capacity of these cells. CAF also play a role in cancer resistance and immune privilege, making the targeting of activators of these cells of interest for oncologists. Funding sources include the Gene and Mary Ann Walters Fund for Pancreatic Cancer Research.

2C. ESOPHAGEAL CANCER

Barrett’s esophagus (BE) is a metaplastic process whereby the normal stratified, squamous esophageal epithelium is replaced by specialized intestinal epithelium. Barrett’s is the only accepted precursor lesion for esophageal adenocarcinoma (EAC), a solid tumor that is rapidly increasing in incidence in western countries. BE evolves into EAC through intermediate steps that involve increasing degrees of dysplasia. Current histologic criteria are quite subjective and the clinical behavior of BE is highly variable and difficult to predict using these standards. It is widely believed that molecular alterations present in BE and EAC will provide more precise prognostic and predictive markers for these conditions than the current clinical and histologic features in use.

The investigation of the molecular pathogenesis of esophageal adenocarcinoma has been an area of strength for the GI Cancer Program for many years. The seminal studies of Reid, Haggitt, and Rabinovitch (Blount et al. Cancer Res, 1991; Rabinovitch et al. Lab Invest, 1989; Reid et al. Gastroenterology, 1987) revealed the role that molecular alterations played in the progression of Barretts esophagus (BE) to esophageal adenocarcinoma (EAC). Since that time, the Reid lab in collaboration with other members of the GI Cancer Program (Rabinovitch, Blount) has continued to be one of the leading investigative teams in the study of the clonal evolution of esophageal adenocarcinoma and in the identification of BE risk markers for EAC (Galipeau et al. PLoS Med, 2007; Reid. Cancer Biomark, 2010). The activity of the GI Cancer Program in this area has expanded in response to the dramatically increasing incidence of EAC in the US population. In addition to ongoing studies of genetic alterations in BE and EAC and their assessment as biomarkers for BE, there is a collaborative team of investigators studying a variety of approaches to enhance our ability to identify BE at high-risk of progressing to EAC.

1) Clonal evolution and disease progression of Barretts esophagus. The research team composed of GI Cancer Program members Reid, Blount, Maley, Paulson, and Kaz as well as Vaughan, Maley, and others is internationally recognized for their work on the molecular genetics of Barretts esophagus. They established the Seattle Barrett’s Esophagus Study, in 1983, which is a unique cohort of patients with BE who have been followed with serial standardized endoscopy examinations for over a mean of 12 years. They have used this resource to establish our current understanding of the molecular clonal evolution of BE and EAC (Barrett et al. Nat Genet, 1999; Reid. Cancer Biomark, 2010). Based on their work in cancer genetics, they identified the first prognostic markers for BE progression to EAC (aneuploidy, tetraploidy, 17p LOH) and then later showed that clonal diversity of BE predicts an increased risk of progression to EAC (Galipeau et al. Proc Natl Acad Sci, 1996; Li et al. Cancer Prev Res, 2013).

More recently, they have assessed the affect of host genetic factors and environmental factors (including NSAIDs and micronutrients) on the formation of BE and its progression to EAC (Reid et al., 2011) In collaboration with members in the Cancer Prevention Program and with support from the Genomics Shared Resource, this team of investigators have shown that host factors, including BMI, tobacco use, as well as, selenium, and certain medications, such as NSAIDs can affect the risk of developing EAC (Duggan et al. Clin

Furthermore, through the efforts of a consortium-wide group of investigators, including Drs Reid and Blount in the GI Cancer Program, a number of host genetic factors have been recently identified that affect the risk of developing BE and/or EAC. These studies have been carried out in collaboration with investigators in BEACON (PI: T. Vaughan) and the international Esophageal Adenocarcinoma Genetics Consortium. The studies have shown that there is a polygenic contribution to BE and EAC (Ek et al. J Natl Cancer Inst, 2013), and that these loci include CRTC1, BARX1, FOXP1, and FOXF1 (Levine et al. Nat Genet, 2013; Su et al. Nat Genet, 2012). These studies have provided insights into host factors that have potential to improve the accuracy of current risk stratification methods being used in the clinic.

2) Epigenetic alterations and Barretts esophagus: Dr. William Grady, Dr. John Inadomi, Dr. Andrew Kaz, and Dr. Eric Seibel are all investigators in the Barretts Esophagus Translational Research Network (BTRNet) grant. Drs. Grady and Kaz are conducting studies to identify and validate aberrantly methylated genes for use as early detection markers and risk markers for Barretts Esophagus. This work is being carried out in collaboration with investigators at Columbia Medical College (Timothy Wang), University of Pennsylvania (Anil Rustgi), Case Western Reserve University (Amitabh Chak and Sanford Markowitz), University of Michigan (Tom Wang), and the Mayo Clinic (Ken Wang). The collaborative team of Grady, Kaz, Inadomi, and Luebeck, has been focused on studying the process of epigenetic alterations in the formation and progression of Barretts esophagus to esophageal adenocarcinoma and conducting these studies through the support of the consortium (Shared Resources: Genomics, Experimental Histopathology, Biospecimen Repository) and funding through the BTRNet and MEMO U01 grants. In order to further define molecular alterations that can classify unique groups of BE and EAC, the Grady lab has utilized methylation microarrays to compare the global gene methylation status of a collection of normal squamous, BE, BE + high-grade dysplasia (HGD) and EAC cases. They found distinct global methylation signatures, as well as differential methylation of specific genes, that discriminated these histological groups. Importantly, they noted high and low methylation epigenotypes among the BE and EAC cases. Additional validation of those CpG sites that distinguished BE from BE + HGD and EAC in phase II biomarker studies has led to the identification of a potential clinical applications in the diagnosis and prognosis of BE and EAC. These studies have resulted in publications in Epigenetics, Cancer Letters, and Genes, Chromosomes, and Cancer (Kaz et al. Genes Chromosomes Cancer, 2012; Kaz et al. Epigenetics, 2011).

2D. HEPATOBLIARY CANCER:

The NW Liver Research Program is composed of a multi-disciplinary group of investigators who study mechanisms that affect liver cancer formation and translate their findings into the clinical care of patients with liver cancer. The investigators in this section rely on the Comparative Medicine, Experimental Histopathology, Specimen Processing, and Collaborative Data Services Shared Resources for their studies. Two areas of research focus are highlighted below.

1) Insulin signaling and HCC: Using animal models with up-regulated insulin signaling in the liver, investigators in the Hepatobiliary section led by Ray Yeung have made the novel discovery of a functional interplay between AKT and mTORC1 activities in lipid metabolism and tumorigenesis in the liver. Contrary to the existing paradigm, mTORC1 hyperactivity in hepatocytes was found to protect against steatosis (Kenerson et al. PLoS One, 2011). They have also found that AKT and mTORC1 synergize in tumorigenesis and play a role in determining tumor differentiation (Kenerson et al. Gastroenterology, 2013). These findings have important implications for the use of mTOR inhibitors for the treatment of HCC as they suggest that the activation status of AKT in HCCs will modify the effect of these drugs on the cancer cells. These studies come at a time when the Hepatobiliary Cancer Section has dramatically increased the number of clinical trials being run by investigators in this section. Drs William Harris and Ray Yeung are currently running 6 clinical trials that include targeted therapies directed at a variety of tyrosine kinases (lavnatinib, cabozatinib, sorafenib, and tivantinib) as well as novel agents, including TheraspHERES. In addition, clinical trials for patients with cholangiocarcinoma are accruing patients, including a phase II trial of SP-1620 + docataxel.

2) Nano-material applications in HCC: The development of glypican-3-based nano-particles by Dr. James Park’s research team, which includes physician-scientists and bioengineers at the University of Washington, has provided a platform for functional imaging and therapy for GPC-3-expressing tumors, which include HCC (Veiseh O et al. Biomaterials, 2010; Park JO et al. Mol Imaging, 2011). This work is currently in a pre-clinical
phase in which the particles are being evaluated in animal models. This team has also refined a siRNA delivery system that can target specific genes in vivo (Mok H et al. Mol Pharm, 2010; Veiseh O et al. Biomaterials, 2011).

3. Research that relates to health problems in the catchment area

In WA state, colorectal cancer (CRC) and pancreatic cancer (PCA) are among the five most common causes of cancer deaths (924 for CRC and 650 for PCA) (Washington State Comprehensive Cancer Control Plan, 2005-2009 v4; WA, 2010). Indeed, amongst all cancer mortality, gastrointestinal (GI) cancers are numerically among the most common, are expensive to treat, especially when advanced, and equally affect the races and sexes. For example, CRC is the second leading cause of cancer-related death in the USA and affects ~3000 people in Washington each year. In addition to CRC, other GI cancers are becoming important health issues for Washington residents; the incidence of liver cancer in Washington is increasing rapidly, with a 30% increase in cases in the last 10 years.

To address the unique regional needs in the area GI cancer care, the Consortium has created outreach programs directed at high-risk populations in the catchment area-indigenous Alaskans and Asian immigrants and colorectal cancer screening interventional education programs in Yakima Valley, which has a large Hispanic population. In addition, the Consortium has supported the development of the GI Cancer Prevention Program Clinic, which is a multi-disciplinary clinic that provides care for individuals with hereditary cancer syndromes (e.g. Lynch Syndrome, Familial Adenomatous Polyposis, etc.). This clinic was started in 2004 and provides comprehensive genetic, medical, and surgical to these patients and their families. The clinic is the only one of its kind in the Northwest region and manages 120-150 patients each year. It has provided the basis for a number of studies that have advanced the clinical use of molecular genetics, including the NEXT study (PI Gail Jarvis, Division of Medical Genetics), which is a study that assesses the impact of whole exome sequencing on the management of patients with cancer syndromes.

The University of Washington Medical Center (UWMC)/Seattle Cancer Care Alliance (SCCA)/Fred Hutchinson Cancer Research Center (FHCRC)/Seattle Children’s Hospital are staffed by nationally and internationally renowned clinicians who function in multidisciplinary teams to provide cutting edge care to patients with GI cancers. Many GI cancers require coordinated care from surgical oncologists, medical oncologists, and radiation oncologists as well as from gastroenterologists and interventional radiologists. As a consequence of this need for multidisciplinary care, the catchment area for esophageal cancer, liver cancer, pancreatic cancer, and rectal cancer is regional. The majority of the patients seen at the UWMC/SCCA/SCH are from the state of Washington, but patients from Alaska, Idaho, Montana, Oregon and Wyoming are routinely seen. In 2012, the hepatobiliary program cared for 290 new patients, the colorectal cancer program cared for 142 new patients, the upper GI tract cancer program cared for 66 new patients, and the pancreatic cancer program cared for 102 patients. There has been a 5% growth in new patient visits each year over the last 5 years.

The GI Oncology Program has developed cutting-edge multi-disciplinary care for patients in the Pacific Northwest. These multi-disciplinary clinics are unique in the region and include clinics focused on: 1) pancreatic cancer, 2) esophageal cancer, 3) liver cancer, and 4) colorectal cancer. The multi-disciplinary clinics have increased the volume of patients with these cancers being seen at the SCCA/UWMC, which has increased enrollment in clinical trials, and have been the forum for studies in the molecular genetics and molecular pathology of cancer. Furthermore, a number of innovative clinical therapy studies are being offered to GI cancer patients in the Northwest. Two examples include: 1) a national randomized phase 2 study of PEGPH20 (PEGylated Recombinant Human Hyaluronidase) combined with nab-paclitaxel plus gemcitabine vs. nab-paclitaxel plus gemcitabine in subjects with stage IV previously untreated pancreatic cancer (N=130 patients will be treated on study with the primary endpoint being overall survival and secondary endpoints involve tumor biopsies and assessment of tumor hyaluronic acid content and correlation with outcomes.;) and 2) a multi-center study of BIBW2992, an irreversible ERGFR/HER2 kinase inhibitor, in combination with capecitabine for patients with refractory solid tumors and pancreatico-biliary cancers, which has pharmacokinetic (Dr J. McCune) and pharmacodynamic (Colin Pritchard) correlative studies and will assess the predictive value of OncoPlex mutation analysis.

4. Future Plans

The GI Leadership Committee have identified several areas for development over the next 5 years:
1) Recruitment of research and clinical faculty: The bacterial flora that live in the colon have been shown to affect a variety of diseases, including colorectal cancer, gastric cancer, and liver cancer. Recruitment of a physician scientist with a research program in this area will lead to the development of a number of collaborations among members of the GI Oncology Program.

The colorectal surgery program has developed substantially over the last 5 years, particularly with the recruitment of Alessandro Fichera to the University of Washington/SCCA, which has led to the development of the multidisciplinary colorectal cancer program. The recruitment of two additional board-certified colorectal surgeons is needed to develop the translational research program in biomarker research and innovative therapies guided by molecular diagnostics (e.g. Oncoplex).

2) Further development of GI cancer biospecimen resources: The ColoCare cohort study has successfully recruited 287 study subjects and has collected samples on these subjects. Continued development of the ColoCare colon cancer cohort study for identifying behavioral, genetic, and molecular prognostic factors will take place with the integration of laboratory assay results from expression array, methylation array, and RPA arrays though the use of LabMatrix biorepository software. The ColoCare study includes clinical information related to treatment, response to treatment, medication and supplement use, and diet and collects tissue and blood samples. (PI’s: N. Ulrich, WM Grady).

In addition to the repository developed through ColoCare, the Pancreatic Cancer Section has established a pancreatic cancer biorepository (PI: Hingorani). The next phase of development of these programs will be to extensively clinically annotate the samples in these biorepositories and to harmonize the management of the biorepositories through the use of LabMatrix biorepository management software (Biofortis) and the Hutchinson Integrated Data Repository and Archive (HIDRA, described in the Developmental Funds section), which will integrate biorepositories in the UWMC/SCCA/FHCRC system. In addition, Dr. Ray Yeung, Robert Carithers, Matthew Yeh and James Park have ongoing efforts to build a liver cancer biorepository. These biorepository efforts will be leveraged by support from Northwest BioTrust shared resource. Expansion of the liver tumor biorepository (PI: R. Yeung) with a prospective clinical database to develop in-depth genotype-phenotype analyses using NextGen sequencing data will be developed as well.

3) Development of investigator initiated clinical trials programs to advance translational research: Dr. Hingorani has developed a novel therapeutic approach for managing pancreatic cancer through the use of PEGPH20 (hyaluronidase) to enhance the delivery of chemotherapy to pancreatic cancer and this approach will be assessed in other GI cancers. In conjunction with the stroma-directed research program, Dr. Chiorean plans to develop clinical trials in pancreatic cancer targeting chemoresistance pathways and in immune checkpoints modulation in combination with chemotherapy. These studies will also employ the innovative molecular diagnostic assays being developed by Dr. Colin Pritchard.

Other areas that will be developed include an early phase combination therapy trials in rare tumors such as carcinoid neuroendocrine cancers, which will employ targeted therapy against the PI3K/mTOR pathway and somatostatin receptor blockade. The selection of agents will be directed by mutation and proteomic profiling studies. These efforts will be led by Drs. Chiorean and Yeung. Furthermore, a multi-institutional early and phase II/III trials of novel antiangiogenic agents, and multidisciplinary concepts integrating interventional radiotherapeutics and biological agents will be developed under the leadership of Dr. Harris.

With regard to luminal GI cancers, the colorectal group has already launched and plans to continue developing groundbreaking studies in colon and rectal cancers (e.g. Dr. Fichera-national PI for the PROSPECT study), that promise to change the landscape of standard of care treatment for these tumors. The Gastroesophageal cancer section plans to develop its program by leading several RTOG/cooperative group studies and initiating phase I trial using agents directed at relevant targets including HER2, MET, VEGFR2, and the immune checkpoints PD1/PD-L1.

Overall, the goals of the GI Oncology Clinical Trials program are to develop novel collaborative investigator-initiated trials and multi-institutional efforts incorporating the science and personalized therapeutics approach existent in our institutions, in the context of robust novel cooperative group and industry sponsored trials for a variety of tumors.
Program in Global Oncology

1. Program Overview

1A. Program focus

Once largely associated with resource-rich regions of the world, cancer is increasingly recognized as one of the major threats to the health of populations across the globe. As the world’s populations age, the impact of cancer on morbidity and mortality continues to increase in many regions. Globally, the number of cancer deaths has increased from 5.8 million to 8.0 million in the two decades spanning 1990 and 2010 (Lozano et al.,Lancet, 2012). This increase is largely the result of a growing burden of cancers in developing countries. Cancers in low- and middle- income countries are both increasing in number and also taking an increasing toll on the health of the population in these regions; nearly 130 million years of life were estimated to be lost due to cancer in 2010 alone. Further, the World Health Organization (WHO) predicts that by 2020, 70% of new cancer cases will arise in low- and middle-income countries (World Health Organization, Fact Sheets, 2009).

Drivers of these statistics include increasing life spans due to overall health and reductions in childhood and adult mortality; increasing obesity; higher smoking rates; and, in Africa, increasing rates of cancer associated with HIV therapy. These trends are likely to continue. Cancer mortality rates are also higher in developing economies. New strategies are needed for cancer prevention and treatment in regions where resources for healthcare are limited. At the National Cancer Institute, Global Health has become an important area of focus for cancer research, with the founding of a new Center for Global Health in 2011 and the definition of global cancer research as an area of research priority for the NCI (Goldberg,The Cancer Letter, 2013).

Over the past several years, Consortium members have developed projects related to cancer epidemiology, etiology, biology, treatment and prevention across the globe. Through these investigations, as well as those by others, it has become clear that the study of malignancies outside the United States may lead to more rapid gains in the understanding of cancer biology, prevention and treatment than simply continuing to work domestically. One example may be seen in the field of infection-related cancers. Cancers caused by infectious diseases comprise nearly 25% of the total global cancer burden (Parkin,International Journal of Cancer, 2006), but these cancers are not equally distributed throughout the world. In sub-Saharan Africa (SSA), more than 33% of cancers are attributable to infections, contrasted with ~9% in North America (de Martel et al.,Lancet Oncol, 2012). To study infection-related malignancies, we have developed a robust collaboration with the Uganda Cancer Institute (UCI), where six of the 10 most common cancers are attributable to viral or bacterial pathogens. This collaboration, known as the UCI / Hutchinson Center Cancer Alliance (UCI/HCCA), has allowed for efficient studies of Kaposi sarcoma (KS), lymphoma, and anogenital malignancies.

The Program in Global Oncology (PiGO) serves to capitalize on Consortium global oncology research, leverage the gains made in translational cancer research from the U.S. to studies of cancer in other regions, and enable interdisciplinary research by Consortium members in this field. PiGO’s Specific Aims are to:

1) Leverage data systems, methods and visualization to support global surveillance of cancer. This will be achieved through program interactions between the internationally recognized scientists and resources of the University of Washington’s (UW) Institute for Health Metrics and Evaluation (IHME) and the cancer expertise of the faculty from FHCRC, UW and SCH.

2) Expand our studies of tumors from HIV-infected and non-HIV-infected individuals to determine how and whether these cancers differ, utilizing the human and physical infrastructure we have developed in Uganda, South Africa and select areas in China. This work will extend current molecular profiling studies of HIV and non-HIV associated lung, cervical and Burkitt lymphoma to other common cancers in the developing world including breast, liver and prostate cancer. These experiments will inform understanding of the role of immune suppression and activation in oncogenesis.

3) Continue to build a robust multidisciplinary research program to discover novel infection-related cancers, with particular emphasis on HIV-infected individuals including women and children, and develop novel therapies for known and newly discovered cancer-related infections, including determination of whether early modification of Epstein-Barr virus infection can reduce the subsequent incidence of Burkitt lymphoma.

4) Develop effective in-country guidelines to improve the detection, potential prevention and treatment of common cancers found in resource poor settings.
1B. Program structure

The genesis of PiGO stems from a recognition by our External Advisory Board (EAB) that the Consortium was developing a major leadership role in international cancer research. The global oncology programs that Drs. Larry Corey and Corey Casper initiated in 2004 have been increasingly recognized by NCI and other global health leaders as important to the field of cancer research both nationally and internationally, and the EAB members encouraged us to make this an area of growth and focus for the next CCSG project period. As the active and growing membership from all Consortium institutions attests to, the work is interdisciplinary and inter-institutional and has potential to make a significant impact on cancer.

PiGO builds on longstanding Consortium studies in both infection-related cancers and international research. Since the late 1980s, Dr. Denise Galloway’s lab has been a leader in the study of the human papillomavirus (HPV), and significant contributions were made to knowledge of the virology of the infection that allowed for the development of the HPV vaccine (Garland et al., N Engl J Med, 2007; Hagensee et al., J Virol, 1993). Dr. Corey initiated the program in Kaposi sarcoma herpes virus (KSHV) biology in 1998, and with Dr. Casper extended these studies into Uganda in 2003. Studies were also initiated by a growing group of investigators into the epidemiology, pathology and clinical manifestations of HPV-associated anogenital and head and neck malignancies. At the same time, research in other infection-related cancers, such as Helicobacter pylori-associated gastric cancer, liver cancer and lymphoma continued to grow among Consortium investigators.

Consortium faculty have many years of experience leading international research projects. The Breast Health Global Initiative, led by Dr. Ben Anderson, has developed resource-stratified guidelines for the detection and management of breast cancer in low- and middle-income countries. Dr. Julie Gralow has been an international advocate for breast cancer awareness and treatment, and helped establish the Global Task Force on Cancer Care and Control, that has published consensus recommendations on ways to address gaps in ability to diagnose and care for patients with cancer in low-resource settings (Farmer et al., The Lancet, 2010). Work on occupational exposures and cancer development, conducted largely in collaboration with investigators in China, has been led by Dr. David Thomas (Agalliu et al., Cancer causes & control: CCC, 2011).

A training program for Uganda physician-scientists, led by Dr. Casper, was started in 2008 and has been a catalyst for interaction among the laboratory-based programs described above and several clinical and population scientists conducting international research. A strong example of synergy between the HIV-related malignancy program and population science research has been the breast cancer detection program in Uganda initiated by Dr. Constance Lehman (Cancer Epidemiology, Prevention and Control), which focuses on evaluating strategies for earlier detection of breast cancer using low-cost solutions to improve breast cancer diagnosis in the developing world.

Over the past three years, interactions among these and other investigators have expanded to include regular seminars, working groups and an annual symposium, initiated in 2010 with "The Global Health in Cancer: A Seattle Perspective." More recently, collaborative discussions were initiated with Dr. Christopher Murray, Director of the UW Institute of Health Metrics and Evaluation (IMHE), with the goal of marrying the knowledge gained from the Global Burden of Disease Study (GBD) with the cancer expertise of Consortium members.

Drs. Murray and Garnet Anderson (Consortium Associate Director for Population Sciences) convened a group of Consortium epidemiologists, clinical oncologists, biostatisticians and public health experts to discuss areas of common interest for further study with subsequent GBD analyses. This last group has started collaborations to develop specific health metrics around HIV-associated malignancies, lymphoma, dietary and environmental risk factors for cancer, and the contributors to poor cancer survival in low- and middle-income countries.

1C. Program Leadership and Qualifications

PiGO is co-directed by Drs. Corey Casper (FHCRC) and Christopher Murray (UW). Dr. Casper is a Member in the Vaccine and Infectious Disease and Public Health Sciences Divisions and an Associate Member in the Clinical Research Division at FHCRC. His research focuses on viral oncogenesis, including the epidemiology, natural history, virology, immunology, treatment and prevention of viral-associated cancers. He is the founder and director of the UCI / HCCA research and training program in Global Oncology based in Kampala, Uganda (described below); the Associate Director of the UW/FHCRC Center for AIDS Research, a member of the National Comprehensive Cancer Network’s International Oncology Committee, and advisor to the National Cancer Advisory Board’s Subcommittee on Global Cancer Research. Dr. Murray is a Professor of Global Health at the University of Washington and Director of IHME. He is a physician and health economist, and is a member of the Institute of Medicine. His work has led to the development of a range of new methods and
empirical studies to strengthen the basis for population health measurement, assessment of the performance of public health and medical care systems, and estimation of the cost effectiveness of health technologies. Dr. Murray is a founder of the Global Burden of Disease (GBD) approach, a systematic effort to quantify the comparative magnitude of health loss due to diseases, injuries, and risk factors by age, sex, and geography over time. From 1998 to 2003, Dr. Murray worked at the World Health Organization (WHO), where he served as the Executive Director of the Evidence and Information for Policy Cluster.

They are assisted by associate heads Denise Galloway and Nina Salama, both of whom lead NIH-funded research projects on pathogen associated cancers. Dr. Galloway is a Member of FHCRC’s Human Biology Division and a leading expert in human papillomavirus. She is a MERIT award recipient, and has been elected a Fellow of the Infectious Disease Society, the Academy of Microbiology and the American Association for the Advancement of Sciences. In 2011 she was the leader of the Seattle HPV Team that won the American Association of Cancer Research Team Science Award. Dr. Salama, also a Member of FHCRC’s Human Biology Division, studies the pathogenesis of Helicobacter pylori. Her research has focused on how H. pylori DNA metabolism and cell shape contribute to stomach colonization. She is an Associate Editor for PLoS Pathogens, and a member of the NIH peer review committee on Bacterial Pathogenesis.

Program leaders coordinate overall programmatic activities, and provide leadership for their areas of expertise through collaborative grants and working groups (see Membership and Activities section below). They are responsible for communicating with the Center Director on issues related to faculty recruitment; support for existing faculty; space; pilot funding; creation of shared resources; and training and mentoring.

1D. Program membership

PiGO has 35 members drawn from 3 schools and 18 departments of FHCRC, UW and Children’s. As noted in a number of the Scientific Accomplishments described below, this membership structure has yielded a number of collaborative, interdisciplinary projects and publications. Members have $4.5M in peer-reviewed funding (direct dollars) in fiscal year 2013, of which $2.6M (49%) is from NCI. Total program funding is $29.9M, which includes $21.4M (cancer-relevant portion of total) from the Bill & Melinda Gates Foundation. Members have published 322 papers, of which 10% are intra-programmatic, 33% are intra-programmatic and 18% are inter-institutional.

Members interact through multiple activities. For example, Dr. Casper leads a working group on International Translational and Clinical Oncology. Several other groups promote intra- and inter-programmatic interaction on the topic of infection-related cancers, including a monthly HPV meeting organized by Rachel Winer (Women’s Cancer), a monthly Merkel cell polyoma virus (MCPyV) meeting organized by Paul Nghiem, and a monthly DNA virus group meeting that includes cancer relevant topics, organized by Dr. Galloway and PiGO members Michael Lagunoff and Timothy Rose. A weekly research in progress meeting on Global Oncology led by Dr. Casper occurs by videoconference between the UCI and the FHCRC. These groups have stimulated collaborative research and peer reviewed funding, including a Provocative Questions R01 on pathogen associated cancers (CA170386, PI Galloway with collaborators Margaret Madeline and Dr. Casper), an R01 to Dr. Galloway on (CA183435) on the role of ALTO in the MCPyV Lifecycle and Tumorigenicity, and an NCI contract to establish a Burkitt lymphoma network in Central America, South America, and Africa. Program leaders initiated quarterly meetings in 2013 to assess the productivity and relevance of programmatic activities, review strategic plans, identify grant opportunities and recruitment and resource needs and bring these to the attention of Consortium leadership. These activities inform the annual Global Oncology Symposium, which is open to the entire Consortium community. Symposia highlight program activities and foster exchange of ideas to stimulate new intra- and inter-programmatic collaborations. Dr. Edward Trimble of NCI’s Center for Global Health will be the keynote speaker in 2014. In 2012, Dr. Julie Gralow initiated a monthly Global Oncology seminar series. Speakers have included PiGO and other Consortium members, and external speakers from local institutions (PATH, Bill and Melinda Gates Foundation) and from Uganda. The seminars are well attended and have stimulated discussions that have attracted new program members and led to at least 3 new grants. The UW Dept. of Global Health has a weekly seminar series on a wide range of global health topics.

Targeted recruitments to further build the membership base will be based on the strategic priorities described in the section below. Immediate priorities include infection-related cancers and pediatric cancers. Consortium leadership is highly supportive of these recruitments; a search for an infection-related cancer translational scientist was opened in late 2013; a search for a pediatric oncologist with experience international clinical and translational trials will open in early 2014.
1E. Strategic Planning

As a relatively new program, strategic planning has been a major focus of program leadership. Several planning sessions have been convened which, in addition to PiGO leaders, included Dr. Julie McElrath (co-head, Immunology and Vaccine Development), Dr. Garnet Anderson (Associate Director of Population Sciences), Dr. Ollie Press (Heme Malignancies), and Consortium Director Larry Corey. The following strategic foci have been identified:

1) Global Cancer Surveillance: A recent NCI Advisory Board noted that one of the major unmet needs in the area of global oncology, and especially HIV-associated cancers, was to better define the impact of these diseases in resource-limited settings. Our center has the unique ability to help define these issues globally through the IHME GBD program, which has altered the landscape of the macro-epidemiology of a variety of illnesses including cancer. Our goal is to leverage this resource to increase understanding of the environmental, genetic and epidemiologic risk factors associated with cancer, especially as they relate to breast cancer, hematologic malignancies, cervical cancer, lymphoma and HIV infections in the GBD dataset.

2) Leverage the infrastructure we have created in low and middle income countries to increase understanding of the biology of cancer in international settings: A) Expand ongoing studies of the genetics of HIV- and non-HIV associated malignancies in lung cancer, cervical cancer and Burkitt lymphoma to other common malignancies found in African men and women such as breast and prostate cancer; B) develop an international clinical trial network for the study of Burkitt Lymphoma in low- and middle-income countries, which could be leveraged for studies of other cancers of importance to low- and middle-income countries (LMICs).

Over the past five years, the Consortium has developed a relationship with the China Center for Disease Control. A joint venture is under development to provide a platform for Consortium members to complete research in China, giving them access to both unique populations of cancer patients and funding from the Chinese government. Led by Steven Self (Biostatistics and Computational Biology), initial collaborations were in the area of infectious disease. Since 2011, oncology projects have been established and will be the focus of further development, including those focused on HPV and cervical cancer and esophageal cancer. In 2013, we opened a 10,000 sq. ft., $4M state-of-the-art cellular immunology facility in Capetown, South Africa, to support FHCRC’s HIV and TB vaccine research programs. Discussions are underway to utilize this lab for studies associated with our Uganda program and other new cancer research programs that are being initiated in South Africa.

3) Infection-Related Cancer Research: A) Seek to identify new infectious etiologies of cancers predicted to be plausibly associated with infectious agents; B) Develop strategies for preventing either the acquisition of infectious oncogens or the progression from infection to malignancy through vaccines or chemo-prevention.

2. Scientific Accomplishments

Despite its new CCSG program status, PiGO has a solid track record of achievements. Selected highlights, many that are intra- or inter-programmatic, are described below.

2A. Program Innovations and Impact

2A.i. Global Cancer Surveillance


Cancer incidence is carefully tracked in many high-income countries through population-based cancer registries, though data on the cancer burden in low- and middle-income countries is often lacking (International Agency for Research and Cancer et al., IARC Sci Publ, 2007). Less than 1% of the population of sub-Saharan Africa is covered by a comprehensive cancer registry (Parkin et al., Cancer Causes Control, 2001), and even in high-resource regions there are few resources to examine the contributing factors to cancer incidence and mortality. PiGO investigators published the Global Burden of Disease Study 2010 (GBD 2010) in the Lancet in December 2012 (Lozano et al., Lancet, 2012) to alleviate data gaps such as this one. This landmark study represents a collaboration of 488 scientists from 303 institutions in 50 countries and was led by IHME as the coordinating center. The GBD 2010 collated, standardized, and synthesized data from 1990 to 2010 across 187 countries, including for 28 major classes of cancers. In total, the study generated nearly 1 billion estimates of health outcomes, including information on the trends in the years of life lost due to premature death and/or
disability, and the risk factors associated with these outcomes. The GBD 2010 estimated that 8.0 million lives were lost to cancer worldwide, an increase of 38% since 1990. Although ~25% of years of life lost globally were attributable to cancer in developed countries, up to 9% of years of life lost were due to cancer in developing regions. In developed countries, cancer deaths have remained relatively steady in the past two decades - 2.58 million deaths in 1990 increased to 3.08 million in 2010. However, during the same time, cancer deaths in developing countries increased from 3.19 million to 4.90 million, a 65% increase over two decades. Although cancer deaths in the developing world have been increasing for most cancer types, the largest increases have been seen for lung (increase from 1.35% to 2.23% of total deaths from 1990 to 2010), colon (0.53% to 0.83%), breast (0.38% to 0.59%), ovarian (0.14% to 0.22%), and prostate (0.12% to 0.25%). Importantly, the increase of breast and cervical cancer in developing nations among women of under age 50 is likely to result in these cancers becoming the leading causes of death in women of child-bearing age. As the populations of developing countries continue to age, resulting from improved maternal and child health and a reduced impact of nutritional deficiencies and infectious diseases, cancer will continue to grow in significance.

The GBD 2010 Study not only sets a benchmark to understand the current burden of malignancies in countries around the world, it also measures the impact of different risk factors on malignancies around the world. In developed countries, tobacco smoking has been the leading risk factor since 1990, contributing to 26% of all cancer-related DALYS (years of life lost due to poor health or premature death) in 2010. This is followed by dietary risks (12%), physical inactivity and high BMI (6% each). By contrast, in developing countries diet and tobacco each account for 13-14% of cancer-related DALYS, with excess alcohol use the third most critical risk factor, contributing to 4.4% of DALYs. Also more significant in developing countries is the impact of air pollution – both indoor household air pollution from use of solid fuels and ambient particulate pollution, each contributing to 2-3% of cancer-related DALYS. The impact of infectious agents such as H. pylori and hepatitis virus has also been noted in international studies involving PIGO members (Ikeda et al., 2012). In Japan H. pylori and Hepatitis B and C accounted for 31,000 deaths from gastric cancer (95% CI: 27,000–34,000) and 23,000 deaths from liver cancer (95% CI: 21,000–24,000) in 2007, primarily in men over 70. Salt intake accounted for 15,000 deaths from stomach cancer (95% CI: 9,000–20,000); alcohol use contributed to liver cancer (6,000 deaths, 95% CI: 4,000–8,000), esophageal cancer (5,000 deaths, 95% CI: 4,000–5,000), and colon cancer (4,000 deaths, 95% CI: 4,000–5,000). Further national and subnational analysis in other countries will surely identify other key risk factors in other settings. These studies have been supported through the Bill & Melinda Gates Foundation (No. 43650 and OPP1070441), Susan G. Komen Foundation, Japanese Ministry of Health, Labour and Welfare (H22-seisaku-shitei-033), and Japan Society for the Promotion of Science (No. 2239013).


The Consortium has long been an integral part of the Surveillance Epidemiology and End Results (SEER) program, with Dr. Stephen Schwartz (Cancer Epi, Prev and Control Program) serving as the PI of the Seattle-Puget Sound Cancer Registry. Through an inter-programmatic collaboration, Dr. Schwartz assisted researchers in Uganda to enhance the utility of the well-established Kampala Cancer Registry (Parkin et al.,Cancer Causes Control, 2001) for global oncology research. A more comprehensive set of data fields is now captured by the Kampala registry, which was adapted from the SEER data instruments. Dr. Schwartz taught a course on cancer registration to allow cancer registries to expand throughout the country of Uganda (sponsored by Dr. Casper’s NCI/Fogarty International Center D43 training grant). One practical application of this work has been to examine the burden of HIV-associated malignancies in sub-Saharan Africa. PIGO brought together experts in HIV medicine (Drs. Casper and Wald), epidemiology (Drs. Kristal, Casper and Wald as well as the Cancer, Epi, Prev and Control Program co-head, Dr. Polly Newcomb), and clinical oncology (Drs. Harlan, Press and Warren) in a series of projects that have attempted to measure how HIV and its treatment affects cancer incidence and survival (Coghill et al., Aids, 2013; Goldman et al., Lancet, 2011). This work began in Uganda, but has grown to include cancer registries from 8 other sub-Saharan African countries. A key outcome was to determine that among patients with five common cancers in Uganda (breast, cervical, esophageal, non-Hodgkin lymphoma [NHL] and Hodgkin Disease), persons with cancer and HIV infection were more than 2-fold more likely to die compared with those with cancer in the absence of HIV (Coghill et al., Aids, 2013). Finally, PIGO investigators sought to determine whether the introduction of highly active ART (HAART) for HIV treatment in Uganda would reduce the incidence of AIDS-defining malignancies, which in the US dropped more than 10-fold in the one-year period after HAART was introduced. It was found that each 10% increase in the availability of HAART in Uganda was associated with a modest decrease in KS...
incidence (6%), an increase in NHL incidence (4%), and no change in cervical cancer (Goldman et al., Lancet, 2011). These studies have allowed PIGO investigators to present the first data of its kind to policymakers at the World Health Organization and the United States Department of State (President’s Emergency Plan for AIDS Relief, PEPFAR) to guide the care of patients with both HIV infection and cancer in low-resource settings.

2.A.ii. Determining the Impact of HIV Infection on the Pathogenesis of Cancer

Kaposi Sarcoma


Kaposi Sarcoma (KS) is the most common cancer in many countries in sub-Saharan Africa (Ferlay J et al., IARC CancerBase, 2010). HHV-8 infection is necessary, but not sufficient, for the development of KS (Sullivan et al., Clin Infect Dis, 2008). Consortium members Drs. Lawrence Corey, Anna Wald, David Koelle, Michael Lagunoff, Timothy Rose, and Corey Casper have long studied the natural history of HHV-8 infection in the US. Their findings included that HHV-8 replicates in the oropharynx (Pauk et al., N Engl J Med, 2000) and is most likely transmitted through contact with saliva among high-risk populations in the U.S. (Casper et al., Sex Transm Infect, 2006; Casper et al., J Infect Dis, 2007; Casper et al., J Acquir Immune Defic Syndr, 2004; Casper et al., J Infect Dis, 2002). Consortium members were the first to intensively investigate humoral and cellular immunity to KS, demonstrating that neutralizing antibodies to HHV-8 may help control progression from asymptomatic infection to KS (Kimball et al., J Infect Dis, 2004) and gamma-delta T-cells may be an important component of the mucosal cellular immune response to HHV-8 infection (Barcy et al., J Immunol, 2008). Few studies, however, had examined the natural history of HHV-8 infection in African cohorts to determine the virologic, immunologic and epidemiologic factors that favor the progression from asymptomatic infection to KS.

The collaboration with the UCI was initiated to answer questions about KS pathogenesis and the virology and immunology of HHV-8 infection. In our first longitudinal cohort study, more than 10,000 biospecimens were collected from over 100 individuals with HHV-8 infection, and with and without KS to understand how viral replication differs in persons with asymptomatic infection, KS, and HIV co-infection. We found: 80% of the general population in Uganda to be infected with HHV-8; persons with KS exhibited poor control of HHV-8 replication both at mucosal sites and in the peripheral blood; and that HIV infection allowed for wider dissemination of HHV-8 to mucosal sites compared with HIV-negative persons (Johnston et al., PLoS One, 2009). Poor control of HHV-8 replication has been implicated as one of the strongest predictors of progression to KS (Engels et al., AIDS, 2003), and thus we believe that identification of individuals with frequent detection of HHV-8 in plasma or saliva could prove a valuable biomarker for incident cancer.

The variability we have described in the control of HHV-8 replication in both Seattle and Uganda could be attributable to host, viral or environmental factors. A collaboration between the FHCRC and NCI revealed that in a population-based serosurvey conducted among more than 20,000 random Ugandans, the prevalence of HHV-8 viremia was highest in regions of Uganda where the incidence of KS has been elevated since prior to the HIV pandemic (Shebl et al., J Med Virol, 2013). Of note, our prior HHV-8 natural history study found that individuals from tribes in regions where HHV-8 viremia was highly prevalent in the serosurvey and where KS has long been endemic exhibited poor control of HHV-8 replication. This work led to a supplement to Dr. Fred Appelbaum’s (Heme Malignancies) program project grant (P01 18029), through which fine HLA and KIR typing was conducted on over 100 Ugandans with and without KS to determine if there was an association between immunogenetics and the control of viral replication. Novel observations included: 1) substantial genetic diversity among Ugandans, leading to the discovery of previously unidentified HLA alleles; 2) the alleles HLA-C*06:02:01G and HLA-C*04:01:01G were overrepresented in both KS-positive persons and those with frequent HHV-8 viremia. Larger follow-up studies are planned. A CCSG supplement has allowed us to examine diversity in the HHV-8 genome, using deep sequencing to assemble full HHV-8 genomes from patients with HHV-8 associated disease (KS and Castleman Disease). Work is underway with the Computational Biology Shared Resource to relate genomic diversity to the clinical manifestation of HHV-8 infection.

Finally, evidence generated from the aforementioned clinical, epidemiologic and translational science has allowed PIGO members to more finely examine HHV-8 biology in the laboratory. Consortium investigators from FHCRC, UW, and SCH were recently awarded a P01 from NIDCR (P01 DE021954) to evaluate the biologic mechanisms by which HHV-8 infects the oral epithelium, as well as the local and systemic immune responses against this pathogen. This work utilizes patient-derived biospecimens from both the UW and the UCI / HCCA, and benefits from the new Northwest Biotrust shared resource. The work was catalyzed by a pilot award to
P01 investigators from an HIV-Related Malignancies supplement to the CCSG. Similarly, pilot funding helped PIGO member Michael Lagunoff to determine that subsequent to infection of endothelial cells, HHV-8 infection enters latency and induced the Warburg effect (alternation in the cellular metabolic pathways favoring a glycolytic / anaerobic state, a common characteristic of malignant cells) (Delgado et al., Proceedings of the National Academy of Sciences of the United States of America, 2010). These results show that a continuum exists between PIGO investigators where observations can be shared between the bench and the bedside.

Clinical manifestations of Kaposi Sarcoma (Bateganya et al., J Acquir Immune Defic Syndr, 2011; Chung et al., AIDS, 2013; Gantt et al., Pediatr Blood Cancer, 2010; Mwanda et al., J Clin Oncol, 2009; Slyker et al., J Infect Dis, 2013)

Growing from the UCI / HCCA initial scientific focus on KS, PIGO members have conducted the largest studies to date characterizing the clinical manifestation of KS in children and women. Children with KS most commonly present with lymphatic involvement (Gantt et al., Pediatr Blood Cancer, 2010), a finding that may be attributable to the disease onset being shortly after primary infection (analogous to the relationship between infectious mononucleosis and Hodgkin disease). Among children with access to ART and/or chemotherapy, nearly 2/3 of patients responded to treatment. In the US, KS overwhelmingly affects men, but in sub-Saharan Africa nearly equal numbers of men and women are afflicted with the disease. PIGO investigators found that women in Uganda were more likely to present with disease involving the face and less likely to have involvement of the lower limbs, had a lower median CD4 T-cell count at presentation, and were nearly half as likely to respond to treatment with ART and/or chemotherapy (Phipps et al., PLoS One, 2010). These observations have allowed clinicians in sub-Saharan Africa to develop programs for the earlier identification of KS (Amerson et al., Infectious Agents and Cancer, 2012), and informed studies of KS tumor genomics in this subgroup.

Non-Hodgkin Lymphoma

NHL is one of the cancers in sub-Saharan Africa whose incidence is increasing most rapidly (Parkin et al., Int J Cancer, 2010), and continues to rise in HIV-infected individuals despite the increasing availability of antiretroviral therapy (Goldman et al., Lancet, 2011). For these reasons, PIGO investigators have extensively studied the biology, epidemiology, and treatment of NHL for several years.

Virology and Natural History of NHL (Slyker et al., Clin Infect Dis, 2014; Slyker et al., J Infect Dis, 2013)

A large proportion of NHL cases in sub-Saharan Africa are associated with Epstein Barr Virus (EBV) infection, but little is known about the natural history of the infection and why the incidence of progression to cancer is so much higher in that region or in HIV-infected individuals. PIGO investigators, funded by NCI HIV-associated Malignancy Supplements to the CCSG, have established birth cohorts of children born in Uganda and Kenya to characterize primary infection with human herpesviruses (Slyker et al., J Infect Dis, 2013), where it was observed that acquisition of human herpesvirus is nearly universal before age 2 in this region and that the clinical manifestations of infection at this age can be severe. Poor control of viral replication, as evidenced by persistent detection of virus in plasma after primary infection, was seen in a subset of participants. These findings support the hypothesis that some children progress quickly from primary infection to cancer, and further work on the immunology and virology of these cohorts is ongoing. Also of note, it was observed that consistent with basic science studies described below, the use of protease inhibitor-based antiretroviral therapy was associated with a faster clearance of EBV in HIV-infected infants when compared to non-protease inhibitor-based therapy (Slyker et al., Clin Infect Dis, 2014). These results suggest that the choice of specific HIV treatment regimens in sub-Saharan Africa could impact the risk of subsequent cancer development.

Treatment of NHL in Africa and Predictors of Mortality (Bateganya et al., J Acquir Immune Defic Syndr, 2011; Mwanda et al., J Clin Oncol, 2009)

In reviewing the care of nearly 200 patients at the UCI with NHL, Drs. Casper and Orem found that survival after a diagnosis of NHL in Uganda was poor, and that many of the factors that predict survival of patients with NHL in resource-rich settings failed to predict outcomes in Uganda (Bateganya et al., J Acquir Immune Defic Syndr, 2011). Access to antiretroviral treatment and the severity of anemia at diagnosis were two of the strongest predictors of survival among patients with HIV-associated NHL. Dr. Orem has also shown that in resource-poor regions where access to cancer services is minimal, oral chemotherapy may be a viable alternative for the treatment of NHL (Mwanda et al., J Clin Oncol, 2009). These findings have led to the initiation of an NCI-funded international, multisite clinical trial of dose-adjusted oral chemotherapy for the treatment of AIDS-related lymphoma (National Institutes of Health, 2013).
Cervical Cancer (Chung et al., AIDS, 2013)

Invasive cervical cancer (ICC) is the most common cancer in women in many parts of sub-Saharan Africa (SSA). As noted earlier, Consortium investigators have been studying HPV-associated malignancies for many years, and recently have begun to study cervical cancer in SSA. Drs. Casper and Orem have been working with investigators at NCI’s Office of Cancer Genomics to evaluate similarities and differences between tumor genomes of women in Uganda vs. the US (described below). In 2009, with funding from the Centers for Disease Control (PHE KE.09.0238), Dr. Michael Chung began a study of HIV-positive women at the Hope Center in Nairobi to compare Pap smear, visual inspection with acetic acid (VIA), and HPV DNA testing against the gold standard of colposcopy-directed biopsy. Five hundred women were enrolled and of these 498 underwent successful visual inspection and sample collection, including biopsy (Chung et al., AIDS, 2013). Investigators found: 1) the most sensitive test was Pap; 2) the specificity of HPV DNA testing significantly decreased among women age <40 years, CD4 count ≤350 cells/mm³, and with short-term ART use; 3) VIA sensitivity was significantly decreased among women ≥40 years of age and specificity was decreased among those on ART <2 years; and 4) the sensitivity and specificity of Pap smear did not differ by ART duration, CD4 count, or age. These data are especially important as countries in sub-Saharan Africa scale up screening programs for ICC. The Consortium just awarded Dr. Chung pilot funding to test whether molecular assays for p16 and Ki67 increase the sensitivity / specificity of HPV DNA testing enough to replace VIA or Pap smears.

Tumor Genomics Reveal Factors that May Account for Aggressive Clinical Phenotypes of Cancer in Sub-Saharan Africa (Amon et al., Infectious Agents and Cancer, 2010; Phipps et al., Infectious Agents and Cancer, 2010)

Little is known of the genomic similarities or differences between HIV-associated and HIV-negative cancers, especially in regions such as Africa with a high HIV incidence. HIV infection is perhaps the most common experiment of nature that selectively increases the incidence of cancer. Defining the biology of these malignancies and the underlying role of immune activation and/or immunosuppression in the genesis of cancer is of major interest and importance. Our center has over the last 2 years developed a collaboration with NCI investigators to determine whether the differences in the clinical manifestations of cancer observed in sub-Saharan Africa (different presenting symptoms, morphology, and response to therapy, as outlined above) may be associated or attributable to differences in the tumor genome. Dr. Casper has obtained funds to study the genomics of 5 malignancies in Uganda (KS, lymphoma, cervical cancer, lung cancer, and ovarian cancer). To date, more than 300 participants have contributed biologic specimens to these projects. Analyses are ongoing, but PiGO investigators have already found that in the first whole-genome interrogations of KS tumors (using a combination of deep sequencing, proteomics, and array analyses), differences in the aggressive clinical manifestations of KS seen in Uganda could be attributable to higher frequencies of detection of both HHV-8 lytic gene products and tumor-derived inflammation mapping back to the interferon gamma pathway (Amon et al., Infectious Agents and Cancer, 2010; Phipps et al., Infectious Agents and Cancer, 2010).

2.A.iii Multidisciplinary research on novel infection-related cancers

The Consortium is well-situated among US cancer centers to explore the relationship between infectious diseases and cancers. Our clinical scientists have long examined the relationship between immunity, malignancy and infection. Established CCSG Programs in Immunology and Vaccine Development and Cancer Basic Biology provide unique expertise to understand how chronic infectious diseases lead to cancer and how to both prevent and treat these malignancies.


In the last two decades, two new tumor viruses have been identified as the causes of cancers not previously attributed to infection (HHV-8 as the cause of KS and Merkel Cell Polyomavirus (MCPyV) as the cause of Merkel Cell Carcinoma (MCC)). Consortium members have been at the forefront of defining the biology, clinical manifestations and treatment of these diseases. The Seattle MCC Program, led by Dr. Paul Nghiem, has played critical roles in improving the understanding and management of this cancer and developing clinical trials and therapy. The group discovered that antibodies to the MCPyV oncoprotein (small t antigen) can be used to track disease burden in Merkel cell carcinoma patients. These studies (Carter et al., J Natl Cancer Inst, 2009; Paulson et al., Cancer Research, 2010) were carried out in collaboration with Dr. Denise Galloway and
Observations serve as the foundation for a novel apoptosis and tumor regression in HIV of protease inhibitors in the inhibition of HHV. Epidemiologic observations on the impact of ART on KS incidence led to benefits for other antiherpetic antiviral medications and ganciclovir both reduced HHV. A related study (Iyer et al., Clin Cancer Res, 2011) was the first to define T cell epitopes derived from MCPyV that are recognized by patients and controls. Using MHC-peptide tetramer reagents created using these peptides, we have now begun a Phase I/II adoptive T cell therapy trial treating 16 patients with metastatic Merkel cell carcinoma. This study is funded by NCI (http://clinicaltrial.gov/show/NCT01758458). A recent study (Afanasiev et al., Clin Cancer Res, 2013) found evidence of T cell exhaustion in MCC patients among MCPyV-specific T cells (as compared to T cells specific for other viruses such as EBV or CMV). This finding has laid the groundwork for an anti-PD1 trial in Merkel cell carcinoma that is being planned in conjunction with the NCI funded Cancer Immune Therapy Trials Network led by Dr. Martin Cheever. Thirty-six papers have been published since 2009 and >$6 million in grants including two R01s and an RC2 'Challenge' grant has been received by team members. The research has been supported by the CCSG through a EPCRS award to Dr Shailender Bhatia, and the Research Pathology, Immune Monitoring, and Therapeutic Manufacturing shared resources.

**Discovery of Novel Infectious Oncogens**

It is widely believed that additional cancers may be attributable to chronic infectious diseases. Support for this hypothesis comes from epidemiologic data showing an increased incidence of certain cancers not currently attributed to infection in persons who are severely immunocompromised (lung cancer, EBV-negative lymphomas, squamous cell carcinoma of the conjunctiva, etc.), the high incidence of cancers such as epithelial and lung cancer among persons with HIV infections or the attribution of a cancer in animals to a virus that does not currently have a human analogue (i.e. lung cancer in sheep caused by an ovine retrovirus). PiGO members including Drs. Corey Casper, Denise Galloway and Margaret Madeleine received a “Provocative Questions” grant from NCI in 2012 (R01 CA170386) which will apply the latest molecular and computational biologic techniques to identify novel infectious causes of cancer from tumor specimens procured from patients both at the UCI / HCCA and a cohort of North American solid organ transplant recipients with cancer. Investigators are using deep sequencing and computational analyses (through the Genomics and Computational Biology Shared Resources) to look for both novel genomic viral signatures, or evidence of cancers developing in the absence of known tumor suppressors. This study will focus on lung cancer, HPV-negative anogenital cancers, EBV-negative lymphomas, and lip cancers. To date, more than 75 participants with HIV-associated cancer in Uganda have contributed tumor specimens to the project, and these samples are currently being analyzed in laboratories at the Hutchinson Center. While no novel pathogens have been identified to date, one example of interesting preliminary findings include determining a dominant sequence of T cell disease (Casper et al., Blood, 2004; Gantt et al., Antimicrob Agents Chemother, 2011; Gantt et al., J Clin Virol, 2013)

PiGO faculty have made observations over the last five years to lay the groundwork for studies of antiviral therapy for the prevention and/or treatment of infection-related cancers. Drs. Casper, Wald and Corey conducted the first randomized controlled trial of an antiviral medication inhibiting HHV-8 replication, and found that ganciclovir both reduced HHV-8 replication in Seattle men (Casper et al., J Infect Dis, 2008) and also abrogated the symptoms of the HHV-8-associated lymphoproliferative disorder, Multicentric Castleman Disease (Casper et al., Blood, 2004). Retrospective analyses of other antimicrobial trials have shown modest benefits for other antiherpetic antiviral medications (Cattamanchi et al., Journal of Medical Virology, 2011). Epidemiologic observations on the impact of ART on KS incidence led to *in vitro* studies showing the efficacy of protease inhibitors in the inhibition of HHV-8 replication (Gantt et al., Antimicrob Agents Chemother, 2011). Taken together with growing evidence supporting the ability of the protease inhibitor, nelfinavir, to induce apoptosis and tumor regression in HIV-negative solid tumors (Gantt et al., Curr Opin Oncol, 2013), these observations serve as the foundation for a novel trial of nelfinavir for the prevention and treatment of KS...

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Margaret Madeline (Cancer Epi, Prev and Control) and have led to early detection of dozens of recurrent cancers and other patients receiving reassuring data that their tumor is not staging a comeback. This antibody assay is being developed for routine clinical use. An unbiased mRNA expression study (Paulson et al., Journal of Clinical Oncology, 2011) demonstrated that the biological processes that were most associated with favorable outcome in MCC were related to Th1-type immune responses. Working with several collaborators, including Drs. Disis and Koelle (Immunology and Vaccine Development Program), this study demonstrated that infiltration of CD8+ lymphocytes into the tumor was associated with 100% disease-specific survival (even among patients presenting with nodal or metastatic disease), providing strong evidence for the role of the immune system in controlling this cancer. A related study (Iyer et al., Clin Cancer Res, 2011) was the first to define T cell epitopes derived from MCPyV that are recognized by patients and controls. Using MHC-peptide tetramer reagents created using these peptides, we have now begun a Phase I/II adoptive T cell therapy trial treating 16 patients with metastatic Merkel cell carcinoma. This study is funded by NCI (http://clinicaltrial.gov/show/NCT01758458). A recent study (Afanasiev et al., Clin Cancer Res, 2013) found evidence of T cell exhaustion in MCC patients among MCPyV-specific T cells (as compared to T cells specific for other viruses such as EBV or CMV). This finding has laid the groundwork for an anti-PD1 trial in Merkel cell carcinoma that is being planned in conjunction with the NCI funded Cancer Immune Therapy Trials Network led by Dr. Martin Cheever. Thirty-six papers have been published since 2009 and >$6 million in grants including two R01s and an RC2 'Challenge' grant has been received by team members. The research has been supported by the CCSG through a EPCRS award to Dr Shailender Bhatia, and the Research Pathology, Immune Monitoring, and Therapeutic Manufacturing shared resources.

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among HIV-infected individuals in the United States and SSA that will open in 2014 in collaboration with the NCI-funded AIDS Malignancy Consortium.

2.A.iv. Detection, potential prevention and treatment of common cancers found in resource poor settings.


In 2004, Drs. Larry Corey and Corey Casper sought to establish a collaboration to study KS and other infection-related cancers in regions where these diseases are endemic. Eastern Africa was a logical place for this endeavor; KS was endemic even before HIV, Uganda was an early adopter and member of the PEPFAR ART program, and 6 of the 10 most common cancers in Uganda are attributable to infectious diseases. Importantly, the country has been the home to a preeminent cancer center for over four decades and it was affiliated with a superb independent medical school and training center, Makerere University. The Uganda Cancer Institute (UCI) was founded in 1967 with a grant from the United States National Cancer Institute. It is the site of the first description of Burkitt Lymphoma (BL) and the first use of combination chemotherapy to treat cancer anywhere in the world (*Savage*, *J Natl Cancer Inst*, 2007). Discussions with the former (Dr Edward Mbidde) and current (Dr. Jackson Savage) Directors of the UCI led to an expansion of the program from a single research focus on HIV-related malignancies to a larger platform involving the entire spectrum of cancer.

Dr. Casper worked with colleagues at the UW and Hutchinson Center to develop a unique training program in oncology and research skills. The Principal of the Makerere University College of Health Sciences along with all four College Deans and the Chair of the UW Department of Medicine worked with Drs. Casper and Orem to select Ugandan physicians enrolled in the medical sciences program to come to Seattle for 13-18 months to enroll in this program, which started in 2006. Initial funding of the program came from Hutchinson Center. A formal Memorandum of Collaboration between FHRC and the UCI was signed in 2007. This collaboration (now known as the UCI / Hutchinson Center Cancer Alliance or “UCI / HCCA”), has yielded a strong foundation for cancer research and care. At the initiation of the collaboration, Dr. Orem was the sole oncologist working in Uganda (as well as 5 surrounding countries which also referred patients to the UCI). He cared for nearly 10,000 patients annually in a hospital and clinic that lacked an intact roof, running water or consistent electricity, and medications were rarely available. Our center, though PIGO, built the human and physical capacity at the UCI to enable quality research, patient care and training at the UCI under the UCI / HCCA collaboration (*Kingham et al.*, *Lancet Oncol*, 2013b). The training programs have drawn collaborating faculty from several Consortium programs including Drs. Ollie Press, Julie Gralow, Connie Lehman, Michael Linenberger, Polly Newcomb, Steve Schwartz, and Alan Kristal, and led to cross-country travel, mentorship and the development of conferences and focus groups in wide areas such as nutrition, tolerance to chemotherapy, novel strategies for early detection, and how to develop country-specific guidelines for cancer care. PIGO catalyzed successful acquisition of a series of training grants (5D43CA153720) that have resulted in the training of 15 Ugandan physician-scientists in Seattle over the past 5 years through a program of didactic coursework in public health, cancer biology, and infectious disease sciences at UW, clinical rotations at the Seattle Cancer Care Alliance, and research internships with Consortium faculty. Six of these trainees either have received or will receive advanced degrees, including 4 doctoral degrees and two Masters of Public Health; all are now back in Uganda engaged in cancer research and care. Two hundred additional persons at all levels have received training in cancer research with the PIGO through the aforementioned training grants.

Today, the UCI / HCCA employs a staff of more than 50 research personnel in Uganda based in a recently renovated clinical trial facility on the UCI campus. The UCI now has the capacity to see more than 35,000 patients annually. In the last three years alone, more than 7,000 participants have been seen in translational research studies and have contributed nearly 200,000 biologic samples (including tumor biopsies, peripheral blood mononuclear cells, plasma, serum, and mucosal secretions) to a specimen repository that is funded by awards from NIH (HHSN27520090087U, U01 CA066535). Twenty-three clinical trials are either ongoing or have recently been completed at the UCI / HCCA site, including a "Pilot Study to Evaluate the Feasibility of a Randomized Trial of Omega-3 Fatty Acid Supplementation in HIV-Positive Ugandan Adults with and without Kaposi Sarcoma" and “Predictors of Late Presentation of Cervical Cancer in HIV-Positive Ugandan Women.” Laboratories, staffed by Ugandan colleagues who receive training and continuous quality improvement from Consortium collaborators, currently operate in molecular virology, pathology, clinical chemistry and hematology, and immunology. Furthermore, a ~80°C cold chain has been established to return samples to Seattle and these specimens have proven viable for RNA microarray analysis, proteomics, DNA sequencing,
and cytokine expression profiling. In October 2011, construction began on a new $9M clinic, training center and research institute funded jointly by the US Agency for International Development and nearly $8M in institutional support from the Hutchinson Center, which will be complete in 2014 and will enhance the capacity to conduct state-of-the-art work in infection-related cancers.

The collaboration between the Hutchinson Center and the UCI has allowed clinicians from both sites to work together to developing new models for cancer care and research in low- and middle-resource settings. These models have been disseminated to the scientific community and many are being adopted in other low- and middle-income settings. Examples include a set of recommendations for improving research and care in sub-Saharan Africa in hematologic malignancies in general(Gopal et al.,Blood, 2012), specific hematologic malignancies such as cutaneous T-cell lymphoma(Ulrickson et al.,J Nati Compr Canc Netw, 2013), the approach to building capacity in surgical oncology(Kingham et al.,Lancet Oncol, 2013a), and HIV-associated malignancies(Casper,Annu Rev Med, 2011; Ulrickson et al.,Advances in Hematology, 2012). These studies illustrate that the foundation that has been built in Uganda provides an excellent platform for implementation science and operational research on cancer care delivery in low- and middle-income countries.

**Approach to the Diagnosis and Management of Breast Cancer In Low- and Middle-Income Countries**

*Anderson et al., The Lancet Oncology, 2011; Cleary et al., Breast, 2013*

The Breast Health Global Initiative (BHGI), led by Dr. Ben Anderson (Global Oncology, Women’s Cancer Programs) has convened several international summits to create resource-stratified guidelines for the detection and management of breast cancer in low- and middle-income countries (Anderson et al., The Lancet Oncology, 2011). These guidelines have subsequently been validated to improve both diagnosis and survival among cancer patients in Latin America, and are being widely adopted or modified for other settings around the world (Cleary et al., Breast, 2013). Breast Cancer is among the most rapidly increasing cancers in resource-limited settings, where some studies suggest the disease is significantly more aggressive (occurs at earlier ages and may be more refractory to treatment).

Drs. Connie Lehman (Cancer Epi, Prev and Control Program) and Peggy Porter (Women’s Cancer Program co-head) have been developing innovative strategies for breast cancer diagnosis in resource-limited settings (in collaboration with Dr. Casper’s UCI / HCCA). PiGO organized a summit in Kampala that brought Consortium breast cancer leaders to Uganda to assess feasibility and establish a plan for a research grant. This work led to an award from the General Electric Foundation through which Dr. Lehman developed a pilot screening program for women with palpable breast masses which utilizes field-rugged, portable/handheld ultrasound machines to evaluate the masses. In pilot data for this proposal, Dr. Lehman showed that radiologists in Uganda could be taught to use ultrasound objectively and accurately evaluate palpable breast masses that would require further evaluation through evidence-based guidelines and teaching modules. Together Drs. Lehman and Porter are working with PATH in Seattle to develop a flow cytometric assay that could be performed on fine needle aspirates of these breast masses to determine the estrogen and progesterone receptor (ER/PR) status of presumed breast tumors on equipment that is available in most low-resource settings due to international investments in HIV infrastructure (CD4/CD8 counts). These projects could have impact on breast cancer diagnosis and care in many low-resource settings, where neither mammography nor pathologic detection of ER / PR status are currently possible.

### 3. Research Relevant to Health Problems in Our Catchment Area

Despite its global focus, PiGO’s research is strongly relevant to health problems in the catchment area. PiGO’s focus on infection related cancer will benefit the ~10% of cancer cases in Western WA state attributable to these infections. Our center has the nation’s largest cohort of Merkel’s and Castleman Disease patients, with novel therapeutic trials being developed from Consortium laboratory research. Other diseases program members are studying in developing countries, including NHL and triple-negative breast cancer, will impact the global burden of cancer and provide novel cancer biology insights into cancers of relevance to the U.S.

### 4. Future Plans

**Specific Aim 1: Optimize and Utilize Global Disease Surveillance Systems for Oncology Research**

Going forward, annual updates of GBD will begin in 2014. Over the coming months, scientists at IHME will release the next iteration of the GBD study, which will add specific estimations for mesothelioma, new methodological updates in correction procedures for raw data, and a number of new Cancer Incidence in Five Continents, Volume X (CI5-X) data from the International Agency for Research on Cancer. Specific to the
PiGO program, the GBD 2013 release will benefit from the valuable insight of GBD cancer experts, including 17 who are (or are eligible to be) Consortium members. These investigators will review and provide timely feedback and suggestions related to the interpretation of results, data sources, and/or methodological approaches pertaining to their area of cancer expertise. The collaboration started by PiGO will allow for this and future revisions of data to also include information about cancer etiology, diagnosis, treatment and survival, and therefore greatly improve the ability to assess the global burden of cancer. PiGO program members have also begun to look at several specific questions using GBD 2010 data, including an examination of the availability of accurate histologic diagnoses of cancer by geographic region and the impact of this availability on cancer outcomes; an exploration of how HIV infection and its treatment modifies cancer incidence and survival by region; and an evaluation of uncertainties in the population-level assessment of diet, physical activity and obesity and how these affect the ability to model the relative importance of these factors in cancer development and survival.

Specific Aim 2: Biology of HIV-Associated Malignancies

PiGO has brought together over a dozen investigators in the Consortium to compete for an NIH U54 award to understand virologic and immunologic factors that govern the natural history of AIDS-Defining Cancers in Uganda. If funded, this grant, submitted in January 2014, will leverage the Genomics and Computational Biology Shared Resources, the UCI / HCCA clinical trial site, and the Program in Immunology and Vaccine Development. Work will continue in this field in collaboration with NCI’s AIDS Malignancy Consortium, where Dr. Casper Chairs the KS Working Group, and through individual investigators’ research awards.

Specific Aim 3: Infection-Related Cancers

In many regions of sub-Saharan Africa, lymphoma is the most common cancer among children and one of the most common cancers in adults. In contrast to lymphomas in the United States, the majority of lymphomas in this region are attributable to infection with Epstein Barr Virus (EBV). Over the last 2 years, members of PiGO have received funding from a private foundation (Burkitt Lymphoma Fund for Africa) and NCI to conduct operational and translational research in the field of endemic Burkitt Lymphoma (eBL). Drs. Oliver Press (Heme Malignancy), Lawrence Corey (Cancer Center Director), Holly Janes (Biostatistics and Computational Biology), and John Harlan (PiGO) have developed a comprehensive treatment project where every one of the >250 children presenting to the UCI with BL each year are provided without charge care from oncologists trained in the US, chemotherapy, nutrition and infection prevention supportive care, case management, and pain control. One-year and 3-year overall and event-free survival are being compared to historical controls at the UCI, and the economics of the intervention are being rigorously studied. Through a partnership with the NCI Office of Cancer Genomics, Dr. Casper’s team in Uganda is working to contribute tumor tissue, blood, and medical information to the Tumor Genome Atlas while working with NCI’s Dr. Louis Staudt (Deputy Director, NCI Center for Cancer Research) to characterize unique tumor pathways that may differentiate sporadic from eBL. Finally, the Consortium recently awarded pilot funding to Dr. Edus Warren (Immunology and Vaccine Development) to evaluate EBV gene expression in endemic Burkitt lymphoma tumors, and to characterize the host immune response to EBV in patients with BL and their first-degree relatives in Uganda. The projects will leverage the CCSG core services, including Computational Biology, Genomics, and Biostatistics and the local SEER program. We hope to bring all of this work together in an international Burkitt Lymphoma clinical and translational clinical trial network, funded by the NCI and its strategic partners. Dr. Casper and colleagues were awarded an NCI contract to evaluate the feasibility of establishing a multi-site clinical and translational BL trial network. More than 50 sites where cancer research and care sit side by side in LMIC on 3 continents were evaluated, focusing on those with a high burden of eBL. From these site evaluations, we have developed a proposal to bring together eight clinical research sites in Central America, South America, and Africa, build capacity for cancer clinical / translational research and care, and develop a series of protocols to study the biology and treatment of eBL in these regions, which is currently under review at NCI.

Specific Aim 4: Guidelines for Cancer Prevention and Treatment in Resource-Poor Settings

The aforementioned efforts in breast cancer and KS are examples of how a multimodal approach can be used to identify cancers earlier and more accurately. In the coming award period, we hope to recruit additional Consortium investigators to the problems of cancer diagnosis and early detection in LMIC. Examples include ongoing work with pathologists (Dr. Peggy Porter) and Computational Biologists (Dr. Martin McIntosh) to develop rapid, inexpensive molecular tests for diagnosis of breast cancer, lung cancer, and KS from bedside biopsies, and improving alternatives to the pap smear for the diagnosis of cervical cancer using molecular methods widely available in HIV care settings across LMICs.
Hematologic Malignancy Program

1. Program Overview

1A. Program focus

The goal of the Hematologic (Heme) Malignancy Program is to develop a better understanding of, and treatments for hematological malignancies. Four areas of focus predominate: (1) Leukemia Biology; (2) Developmental Therapeutics; (3) Preclinical Transplantation Biology; and (4) Clinical Hematopoietic Cell Transplantation. The Program has 75 members, 74 of whom have peer-reviewed funding, are the Principal Investigator on a clinical trial, or are newly recruited and have institutional support. The Program has $24.3M in grant funding (direct dollars) of which $6.9M (28%) is from the NCI and $16.9M (70%) is peer-reviewed. Members of the program published a total of 1218 papers in the previous grant period, 27% of which were intra-programmatic, 35% were inter-programmatic and 19% were inter-institutional. Specific scientific achievements are described below in Section 2.

The program has 4 Specific Aims:
1. Developing a deeper understanding of the biologic basis of hematologic malignancies;
2. Using this understanding to develop better non-transplant therapies;
3. Discovering novel methods to overcome the current limitations of hematopoietic cell transplantation;
4. Using these discoveries to improve the actual practice of hematopoietic cell transplantation.

1B. Program structure

The Heme Malignancy Program combines members from our previous Clinical Transplant and Transplant Biology Programs. At the time of the last competitive renewal, the Clinical Transplant Program was rated as “Outstanding” with the comment that “the program is moving nicely towards more non-BMT translational research, and the leadership is encouraged to increase non-transplant molecularly-targeted therapeutic trials, playing on the strengths of the described research.” The Transplantation Biology Program was rated as excellent to outstanding but the relatively small size of the Program was noted. Thus, following the suggestions of the reviewers and our external advisory board (EAB), in an effort to better coordinate our activities in non-transplant molecularly targeted therapies, transplantation biology and clinical transplantation, we have combined the previous Clinical Transplant and Transplant Biology Programs and have added selected individuals from the previous Stem/Progenitor Cell Biology Program to form this new Heme Malignancy Program.

1C. Program Leadership and Qualifications

Dr. Fred Appelbaum is the overall Program Leader, serving to help coordinate the activities of the overall Program membership, but with particular emphasis on the Clinical Transplant activities. He is assisted by two Associate Program Directors, Dr. Jan Abkowitz who pays special attention to activities in Leukemia Biology, and Dr. Hans-Peter Kiem whose focus is Transplantation Biology. The Program Leadership is responsible for advising the Center Director on all issues related to the Heme Malignancies Program concerning: (1) new faculty recruitment; (2) support for existing faculty; (3) allocation of space; (4) use of pilot funding; (5) selection and organization of grant applications; (6) creation and use of shared resources; and (7) development and support of training programs. The Program leadership group is well positioned to advise and act on these issues. All three Program leaders have their own active research programs, and have extensive administrative experience at both the local and national level. Dr. Appelbaum headed the previous Clinical Transplant Program and currently serves as the Deputy Director of the FHCRC and the President of the Seattle Cancer Care Alliance. He is a member of the NCI’s Adult Leukemia Steering Committee and the Pediatric Leukemia and Lymphoma Steering Committee, and is the chair of the NCI/NHLBI-funded Bone Marrow Transplant Clinical Trials Network Steering Committee. His grant funded research focuses on the science of human
hematopoietic cell transplantation. Dr. Abkowitz was the associate head of the prior Stem/Progenitor Cell Biology Program and is Head of the Hematology Division at the UW. She is the immediate-past President of the American Society of Hematology. Her grant-funded research program focuses on myeloid stem cell biology. Dr. Kiem was the associate head of the prior Transplant Biology Program. His grant-funded research program focuses predominantly of applications of gene therapy. He is currently a member of the NIH Recombinant DNA Advisory Committee.

1D. Program membership

This is a large program with 75 members. In order to efficiently conduct the research and care missions of the Program, the membership is organized in several ways. First, members with direct clinical interests join disease- or modality- specific groups with a designated chair and membership. Each group holds weekly or bi-weekly meetings at which translational research issues are presented, protocol development is reviewed, actual protocol prioritization occurs, and protocol conduct is summarized. The chairs have the responsibility of reporting results back to the Program Leadership. These groups include: (a) Acute Leukemia, Dr. Eli Estey chair; (b) Myeloma, Dr. William Bensinger chair; (c) Myelodysplasia, Dr. Bart Scott chair; (d) Lymphoma, Dr. Ajay Gopal chair; (e) Adult Transplant, Dr. Fred Appelbaum, chair; (f) Pediatric Transplant, Dr. Scott Baker, chair. Program members are also organized around specific research topics, usually as the result of a Program Project Grant, a U19, U54, or other efforts with multiple cooperating investigators. Like the disease and clinical modality specific groups, each research group has a chair, holds regular meetings and reports back to the Program Leadership. These subgroups include: (a) Myeloid stem cell biology, Dr. Akiko Shimamura, chair; (b) Radioimmunotherapy, Dr. Ollie Press, chair; (c) Cord blood transplantation, Dr. Colleen Delaney, chair; (d) Gene therapy, Dr. Hans-Peter Kiem, chair; (e) Transplantation biology, Dr. Rainer Storb, chair; (f) Long-term Follow-up, Dr. Stephanie Lee, chair. All members of the Program attend a Monday noon-time research seminar and a Tuesday afternoon investigators meeting at which research directions are discussed and new protocols reviewed. The leaders of the subgroups noted above participate as a group in the annual Seattle Cancer Care Alliance strategic planning retreat.

As a direct result of the coordinated planning of Heme Malignancy Program members, over the last grant period, a number of key areas for recruitment were identified and subsequent searches completed. Drs. Erini Papetrou, Vivian Oehler and Roland Walter all were recruited to enhance our studies of leukemia stem cell biology. Dr. Eli Estey moved from MD Anderson to Seattle to enhance our non-transplant leukemia clinical trials activity. Dr. Brian Till was promoted to faculty level to enhance our immunotherapy activities, particularly our studies of chimeric antigen receptor T cells. And Leslie Kean was recruited from Emory to expand our pre-clinical and clinical studies of tolerance induction following allogeneic HCT.

Additionally, as a result of joint planning, members of the Heme Malignancy Program have greatly benefitted from Center support. Examples directly related to the CCSG, in addition to support for new faculty recruitment, include expansion of those shared resources most used by Program members and pilot funding for early phase clinical trials. Other examples of Center support for the Heme Malignancy Program includes support for the development and maintenance of HemeBase, a research data base focused on patients with hematological malignancies. In addition, the Center has been instrumental in providing support for the development of a Leukemia/Myelodysplasia tumor bank, which now has well annotated samples from over 2000 patients with AML/MDS, and a developing bank for myeloma as well. Also, the Center has long provided support for a cell bank storing lymphocytes from every donor/recipient pair transplanted in Seattle, a resource that has been invaluable for our extensive studies of factors predicting transplant outcomes. Additionally, the Center has generously supported our Long-Term Follow-up Office, a facility that provides clinical support but also valuable research data to many of our investigators. These are but a few of many examples of resources that have been made available to members of the Heme Malignancy Program through our joint planning efforts.

2. Scientific Accomplishments

With over 1200 publications over the last grant period, there are a large number of scientific accomplishments that could be listed here. We have selected two examples (2A – Identification of Genetic Etiologies and 2B-
Clonal Diversity of Leukemia) as illustrations of our work in the general area of leukemia biology. Example 2C (Pretargeted Radioimmunotherapy) is representative of our efforts in developmental therapeutics. Two examples (2D – Determination of Novel MHC Genes and 2E – Cord Blood Expansion) are selected to represent our efforts to broaden and improve donor availability. Example 2F (Gene Therapy) describes a unique application of genetic manipulation of stem cells in the transplant setting. Example 2G (Improved Outcomes after Transplantation) summarizes the overall advances that have been made in allogeneic hematopoietic cell transplantation, many of which were supported in part, or in whole by this grant. In Example 2H, we describe several contributions illustrating the collaborative efforts of investigators within this program focused on non-transplant and transplant approaches. 2I (Therapy of AML with WT1 Clones) is included as an important example of inter-programmatic activities.


Inherited bone marrow failure syndromes and inherited myelodysplastic syndromes (iBMF/MDS) require specific treatment and medical management that are distinct from those for acquired marrow failure or MDS. Identification of iBMF/MDS is critical for diagnosis, prognosis, medical management, donor choice for hematopoietic stem cell transplant, family counseling, and therapeutic decision-making. A significant number of patients with iBMF/MDS lack the typical clinical stigmata associated with these syndromes. These cryptic presentations of inherited iBMF/MDS pose difficult diagnostic challenges with profound ramifications for treatment and clinical outcomes. Members of our Program have worked to identify constitutional mutations that drive the pathogenesis of marrow failure/MDS presenting both in families with previously unexplained syndromes and in seemingly sporadic cases presenting at a young age.

We performed genetic studies of families with marrow failure/MDS to identify novel genes causing iBMFS/MDS. Using classical genetic methodologies to study 4 large kindreds with familial MDS/AML, Dr. Marshall Horwitz from Cancer Biology and colleagues from our Program identified GATA-2 as a novel MDS/AML predisposition gene (Hahn et al. Nature Genetics, 2011). GATA-2 was subsequently shown by other groups to be responsible for MonoMac and Emberger syndromes. Mutated GATA-2 was identified in a concurrent study by Dr. Akiko Shimamura and Dr. Mary-Claire King utilizing whole exome sequencing of 4 members of a single kindred with cytopenias and clonal cytogenetic abnormalities without other clinical stigmata of MonoMac or Emberger syndromes (Kazenwadel et al, Blood, 2012). A subsequent screen of young patients with marrow failure/MDS without other clinical stigmata identified GATA-2 mutations in a significant subset. We have subsequently identified another novel iBMF/MDS gene by whole exome sequencing and performed functional validation studies (manuscript in preparation). The availability of shared resources including the hematopoietic cell processing lab, flow cytometry, scientific imaging, and virus vector production at FHCRC have been instrumental for the cellular and biochemical assays required for functional validation of these new iBMF/MDS genes. The identification of new genes has broadened our diagnostic and therapeutic armamentarium and yielded novel insights into the molecular pathogenesis of these disorders.

Members of the Program have also developed a comprehensive unbiased genetic screen for iBMF/MDS. In collaboration with Dr. Mary-Claire King, Shimamura’s lab utilized cutting edge multiplexed targeted gene capture coupled with massively parallel sequencing to screen for mutations in 161 genes associated with iBMF/MDS. Oligonucleotides targeting all genes, including coding regions, non-coding intronic sequences flanking each exon, and 5 kb genomic sequences flanking each gene, were designed. Analysis yields all mutations of all classes (point mutations, small indels, copy number variants, and genomic rearrangements). Both germline and somatic mutations were detected, depending on the source of patient DNA. They successfully identified all genes in a blinded test of a panel of patients with a variety of known genetic mutations. They identified marrow failure/MDS germline gene mutations in 10% of patients presenting with idiopathic marrow failure or MDS. Some patients had phenotypes previously not reported for those genes. Thus, this comprehensive screening approach revealed constitutional mutations in genes that had not been suspected a priori based on clinical phenotype (manuscript in preparation). They are currently testing whether this screen might predict which patients are unlikely to benefit from standard medical therapies and should therefore proceed to transplant upfront. This rapid and comprehensive workup for marrow failure and MDS is more economical, more rapid,
and more comprehensive than the current approach of sequentially testing individual genes based on clinical suspicion, and thus offers a novel approach to the diagnostic workup of marrow failure and MDS that should inform treatment decisions. This test will be made available to the general medical community. Like the GATA-2 studies described above, these studies could not have been performed without the support of the CCSG Cellular Imaging Shared Resources, as well as institutionally supported resources for Specimen Processing and Flow Cytometry. This work was supported in part by DK099808 and DK058161.

2B. Clonal Evolution in Leukemia (Paguirigan et al, Science Trans Med, in revision)

The focus of the Radich lab has long been to understand the genetics of response and relapse in leukemia. Working initially in chronic myeloid leukemia (CML), he and his colleagues were among the first to show the utility of PCR monitoring of BCR-ABL to guide therapy following allogeneic HCT (Radich et al, Blood, 1995) and, more recently, following therapy of CML with first and second generation tyrosine kinase inhibitors (Hughes et al, Blood, 2010 and Stein et al, BMC Cancer, 2013). His group also described the gene expression changes associated with progression and response in CML (Radich et al, Proc Natl Acad Sci, 2006), and then used Bayesian model averaging to identify a 6-gene signature that is able to discriminate early from late chronic phase, i.e. predict impending disease evolution (Oehler et al, Blood, 2009). Radich and colleagues also demonstrated that altered gene expression precedes development of therapy-related myelodysplasia/acute myeloid leukemia and thus could be used to identify patients at risk (Li et al, Cancer Cell, 2011).

The Radich lab is currently studying clonal heterogeneity, natural selection, and relapse in AML by performing genotyping of flow cytometry isolated single cells from AML samples. In a recent publication, his group identified concurrent mutations and corresponding zygosities in each of three genes (FLT3, NPM1 and WT1) in individual AML patients. Surprisingly, they found all possible combinations of mutations and zygosities for the genes analyzed at the single cell level in each of the samples analyzed (Paguirigan et al, Science Trans Med, in press). This finding is in contrast to the commonly accepted model of step-wise accumulation of mutations with outgrowth of a dominant or resistant clone. These data suggest that the clonal structure of AML is far more complex than previously assumed, and further make it clear that genotyping the bulk leukemia sample cannot reveal the complexity of the clonal structure of the neoplasm. The studies conducted by the Radich lab could not have been conducted without the cooperation of his clinical colleagues at the Center who provided the clinical samples, as well as our leukemia tumor bank, and institutionally supported resources for Specimen Processing and Flow Cytometry. This work was supported in part by CA018029, CA149566 and CA140371.

2C. Clinical Translation of Pretargeted Radioimmunotherapy for Advanced Hematologic Malignancies

High dose chemoradiotherapy with hematopoietic cell transplantation (HCT) is potentially curative for patients who have failed conventional chemotherapy, however, HCT produces a 5-year survival rate of only 20-50% in relapsed hematologic malignancies as a result of treatment-related mortality and disease recurrence. Prior studies have shown that increasing the dose of total body irradiation (TBI) in transplant conditioning regimens significantly reduces the relapse rate, but increases treatment-related toxicity, nullifying the advantage of the lower relapse rate. Chemotherapy and external radiation therapy expose normal and neoplastic cells to identical doses of cytotoxic agents and depend upon the enhanced sensitivity of rapidly dividing cancer cells to achieve preferential killing. Therapeutic efficacy should be markedly enhanced and toxicity diminished if tumoricidal agents can be selectively focused on malignant cells. Therefore, Abs directed against tumor-associated antigens and conjugated to toxins, drugs, or radionuclides have been developed. Radiolabeled antibodies (RAbs) appear particularly attractive for hematologic malignancies because 1) their surface antigens are well delineated, 2) multiple high quality Abs are available, 3) leukemias and lymphomas are exquisitely sensitive to radiation therapy, and 4) human anti-mouse Abs are less likely to form than in solid tumor settings. We have pioneered the use of myeloablative radioimmunotherapy (RIT) as a component of HCT conditioning regimens for leukemia, lymphoma, and myeloma and documented the safety and efficacy of this approach in curing patients who have failed conventional therapies (P01CA044991). As one example, Drs. Appelbaum,
Eary, Pagel and colleagues developed an anti-CD45 radiolabelled conjugate and demonstrated its safety and potential efficacy when used as part of a transplant preparative regimen for patients with acute leukemia (Pagel et al., Blood, 2009). Actinium Pharmaceuticals Inc., is now collaborating with FHCRC investigators to initiate a phase III multi-center randomized trial formally testing this therapeutic. Despite the effectiveness of this approach, the slow clearance of unbound RAbs from the circulation and the resultant high levels of background radioactivity are significant obstacles to the optimal implementation of RIT since these pharmacokinetic features limit the tumor-to-normal organ ratios of absorbed radiation that can be achieved. One approach to reduce the toxicity of RAb in conventional RIT involves multi-step "pretargeting" methods (PRIT) to disassociate the slow distribution phase of the Ab molecule from the administration of the therapeutic radionuclide. PRIT strategies administrate tumor-reactive Ab in a non-radioactive form, allowing it to localize to tumor sites and accumulate without subjecting the rest of the body to non-specific irradiation from circulating RAbs. After maximal accumulation of Ab in the tumor, a small molecular weight radioactive moiety with high affinity for the tumor-reactive Ab is administered. Because of its small size, this second reagent penetrates tumors rapidly where the “pretargeted” Ab traps it. Furthermore, unbound molecules of the second (radioactive) reagent are small enough to be rapidly cleared from the blood and excreted in the urine. Central to the PRIT concept is the premise that high affinity binding can be achieved between the Ab and the subsequently administered radiolabeled small molecule. Several strategies have been proposed to accomplish this, but one of the most successful exploits the extraordinarily high affinity of streptavidin (or SA) for biotin. We and others have convincingly documented in preclinical studies that SA-biotin PRIT protocols effectively circumvent the major pharmacokinetic limitations of conventional “one-step” RIT. Striking tumor-to-blood ratios are obtained with SA-biotin PRIT (>10:1 at 4 hr and up to 1000:1 at 144 hr). Treatment of lymphoma, leukemia, and myeloma xenografts with SA-Ab targeting CD20 (for B-NHL), CD45 (for AML), or CD38 for MM) followed by ⁸⁹Ytrium-DOTA-biotin (0.8-1.2 mCi) led to durable, complete remissions, long term disease-free survival and negligible toxicity in multiple murine models of AML (R01CA109663), B-NHL (R01CA076287) and MM (R01CA154897). In contrast, directly-labeled ⁹⁰Y-Ab exhibited fatal toxicity above 0.4 mCi and tumor/blood ratios of no greater than 5:1 by 144 hr and cured <10% of mice. These successes in preclinical mouse xenograft models have now been translated into an ongoing Phase I clinical trial of anti-CD45 PRIT using the SA-biotin approach in patients with relapsed AML and MDS (P01CA044991). Preliminary results in 7 patients with AML or MDS demonstrate the feasibility, safety, and promise of this approach though further dose-escalation is necessary to optimize efficacy. A similar PRIT trial is planned to open for patients with relapsed B-NHL in 2014.

Although the merits of the SA-biotin system for PRIT have been well demonstrated and merit the ongoing clinical evaluation, some limitations exist including the immunogenicity of SA and the presence of “endogenous biotin” which may partially block binding of therapeutic ⁸⁹Y-DOTA-biotin. To circumvent these obstacles, we have recently synthesized and purified genetically engineered bispecific antibodies recognizing both tumor cell antigens (CD20, CD45, or CD38) as well as radiolabeled ligands (⁹⁰Y-DOTA) that achieve effective pretargeting and eliminate the reliance of PRIT on SA-biotin binding (R01_CA136639). Further animal studies are ongoing and human clinical trials are planned in the future. These studies have depended heavily on the CCSG Therapeutic Manufacturing Shared Resource. This work was supported in part by grants CA044991, CA136639, CA109663, CA154897, CA138720 and CA155911.

2D. Determination of Novel MHC Genes Determining Hematopoietic Cell Transplant Outcome

The Major Histocompatibility Complex (MHC) on chromosome 6 is the most gene-dense region of the entire human genome. The MHC is best known for the HLA genes that govern histocompatibility. Nowhere is the role of HLA more prominent than in the setting of unrelated donor hematopoietic cell transplantation (HCT), where DNA-based methods for precise HLA matching are used to approximate the MHC identity that is achieved between siblings who are identical-by-descent. Although HLA matching lowers the overall risks to recipients of unrelated donor transplants, such transplants remain hazardous. Given the extreme density of genes with immune function, Petersdorf et al. hypothesized that untyped genetic variation within the MHC contributes to
GVHD and mortality after HLA-matched unrelated donor HCT. If this were true, then efforts to lower risks for future patients can be envisioned, through pre-transplant risk-assessment of patients seeking an unrelated donor transplant, as well as optimal matching of donors.

To test these hypotheses, she employed a classic discovery-validation study design and probed the MHC with a high-density SNP genotyping platform for associations to clinical outcome (Petersdorf et al, Science Translational Medicine, 2012). Her group confirmed 1 SNP marker strongly predictive of survival and a second marker of acute GVHD, demonstrating that novel MHC genes have significance in transplantation but are not currently tested in clinical practice. The SNP associated with survival is also a marker for type 1 diabetes, and the GVHD-associated SNP is a risk marker for rheumatoid arthritis, asthma and lymphoma. The discovery of these two new transplantation determinants sheds new light on shared pathways between autoimmunity, inflammation and transplantation.

If the MHC harbors novel transplantation determinants, how can these results improve the success of future transplant patients? In a retrospective study of 230 patients referred to the Seattle Transplant Program with at least two HLA-matched donors identified on their search, we genotyped the GVHD-associated SNP and showed that most patients have SNP-matched donors. These unique data from the Seattle Transplant Program demonstrate the portability of the SNP mapping data to prospective donor assessment and the potential to lower GVHD for future patients in need of a transplant. A new prospective clinical protocol is currently being designed to offer SNP genotyping and matching for patients and their unrelated donors. This collaboration between the Seattle Transplant Program and the National Marrow Donor Program is the first of its kind to integrate the findings from a large-scale genetic association study into prospective donor evaluation and selection. Current efforts in the laboratory are focused on identifying the true causative genes that are tagged by the SNPs.

Beyond the MHC, genetic variation in cytokine and immune response genes also influence risks after related and unrelated donor hematopoietic cell transplantation. In a retrospective analysis of SNPs with previously described associations to acute GVHD, Chien et al. (Blood, 2012) confirmed the correlation of CTLA4, HSPE, IL6 and IL10 variants with clinical outcome. These data suggest that complex pathways are involved in graft-versus-host alloreactivity, and provide a platform for understanding the mechanisms leading to clinical GVHD.

These studies would not have been possible without the support of the Heme Malignancy Program to maintain a large cell bank of samples from all donors and recipients transplanted in Seattle and support from our LTFU. Both the cell bank and the LTFU office depend heavily of Center support. This work was supported in part by grants AI069197, CA018029, AI033484 and HL105914.


Delayed myeloid engraftment is a known risk factor for cord blood transplant (CBT) recipients and is associated with the low total nucleated cell (TNC) and CD34+ cell doses provided in a single or double cord blood (CB) graft. In fact, a recent analysis of adult single unit CBT recipients demonstrated that infused CD34+ cell dose is the most important predictor of myeloid engraftment. Furthermore, as we demonstrated, non-relapse mortality (NRM) is highest in double CBT recipients when compared to matched and mismatched unrelated donor recipients, with the majority of NRM occurring within the first 100 days post-transplant and infection being the most common cause of death (Brunstein et al, Blood, 2010). Thus, the significant delay in myeloid recovery that is observed in CBT recipients remains a critical barrier to successful outcomes, and there exists a great need for methods to avoid the prolonged neutropenia that occurs in CBT recipients. One such strategy is the ex vivo expansion of hematopoietic stem and progenitor cells (HSPC). However, prior to our proof-of-concept studies, no strategies had been shown to enhance engraftment or shorten the duration of neutrophil recovery in the clinical setting.

In 2010, our group published the methodologies and preliminary clinical results using a novel and clinically feasible ex vivo expansion strategy in which the absolute number of marrow repopulating CB HSPC can be increased by culture with the Notch ligand Delta1 (Delaney et al, Nature Medicine 2010). This work
represented the successful culmination of translational work that began more than a decade prior by Dr. Irv Bernstein and colleagues with detection of the human Notch1 gene in CD34+ or CD34+lin human hematopoietic precursors and the demonstration of enhanced self-renewal of repopulating cells by retrovirus-mediated expression of a constitutively active form of Notch1. In subsequent studies by our group, activation of endogenous Notch receptors using soluble Notch ligand forms revealed profound effects on the growth and differentiation of isolated murine marrow precursors with a multi-log increase in the number of Sca-1+Gr-1+ cells with short-term lymphoid and myeloid repopulating ability. Similarly, for human cells, incubation of CB HSPC in the presence of immobilized ligand generated an approximate 100-fold increase in CD34+ cell numbers with enhanced repopulating ability when transplanted into immunodeficient mice (Delaney et al. Blood, 2005). These observations demonstrated the feasibility of using extrinsic regulators of stem cell fate to manipulate cell fate decisions ex vivo and led to development of a clinically feasible methodology for generating cord blood stem/progenitor cells for clinical use.

Our report of the first 10 patients treated with Notch-mediated ex vivo expanded cells was the first clear demonstration of rapid hematopoietic engraftment derived from ex vivo expanded HSPC. This clinical trial has recently closed to accrual after enrollment of 23 patients at four institutions. Infusion of the partially HLA-matched expanded CB product along with a second non-manipulated CB graft resulted in a median time to neutrophil recovery (500/mm3) of just 12 days as compared to a median time of 25 days (p<0.0001) in a concurrent cohort of 40 patients undergoing identical treatment but with two non-manipulated CB units (updated data). We have identified a cell dose relationship between CD34+ cell dose/kg and time to rapid neutrophil recovery in recipients of partially-HLA matched expanded CB products, where 8 out of 11 patients who received greater than 8x106 CD34+ cells/kg achieved an ANC ≥ 500/mm3 within 10 days.

Our current work is aimed at developing an economically feasible “off-the-shelf” source of expanded HSPC capable of providing rapid neutrophil recovery. To this end, we are generating a bank of pre-expanded, cryopreserved hematopoietic progenitor cell products (each derived from a single CB unit) that can be held for future clinical use. We hypothesize that this expanded cell product, which is devoid of T cells, can be infused as an off-the-shelf cellular therapy to provide rapid but temporary myeloid engraftment and to potentially facilitate hematopoietic recovery in both CB stem cell transplant and non-transplant settings, thereby reducing the infectious complications and increased risk of early mortality that is associated with these intensive therapies. We recently obtained funding (NHLBI P50 110787) to support the conduct of a randomized trial comparing standard of care cord blood transplantation with or without the addition of an expanded cord using the technology developed at our Center. Our group will serve as the coordinating center and will be joined by investigators at Harvard, Duke, Vanderbilt, University of Colorado, and City of Hope. Without the CCSG GMP Therapeutic Manufacturing and Immune Monitoring Shared Resources and the Center-supported Specimen Processing resource, and close collaboration of our clinical transplant colleagues, these studies of cord blood expansion would not have been possible. This work was supported in part by grants HL110787, LLS-6407, R24HL74445 and RO1HL080245.


Although hematopoietic cell transplantation using genetically modified autologous cells is a potentially attractive approach for various diseases, the current efficiency of gene transfer to hematopoietic stem cells is a barrier to successful application. The ability to selectively increase the percentage of gene-modified cells following transplantation might overcome this obstacle. Accordingly, we tested whether ex vivo transfection of bone marrow cells using a gammaretrovirus with mutant methylguanine methyltransferase (MGMTP140K) followed by treatment with O6-benzylguanine (O6BG) and/or bis-(2-chloroethyl)-N-nitroso-urea (BCNU) would allow for the selective expansion of gene modified hematopoietic progenitors. In both macaque and baboon nonhuman primate models, we found bone marrow progenitor cells could be transfected with modest efficiency, and that subsequent treatment with O6BG and BCNU led to in vivo selection of gene-modified cells with the proportion of modified cells rising above 50%, with all three cell lineages involved and gene modified...
cells persisting with the longest follow-up over 2.2 years (Beard et al, JCI, 2010). Retrovirus integration site analysis before and after drug therapy treatments confirmed the presences of multiple clones.

Following this successful demonstration in non-human primates, we then tested a similar strategy in patients with glioblastoma, the most common primary brain tumor diagnosed in adults. Standard treatment of such patients includes surgery, combination radiation and chemotherapy with the alkylating agent temozolomide, followed by maintenance chemotherapy with temozolomide. Despite this aggressive strategy, median overall survival remains less than two years from diagnosis. Moreover, for the approximately 60% of patients whose tumors overexpress the MGMT gene (MGMThigh), median survival with treatment is only one year, owing to the ability of MGMThigh tumor cells to resist the cell killing effects of chemotherapy with alkylating agents, such as temozolomide. O6BG has been combined with temozolomide for recurrent glioblastoma patients in hopes that MGMT in tumor cells would be inhibited and thus, temozolomide sensitivity would be restored. However, dose-limiting myelosuppression occurred after a single dose of 472 mg/m² temozolomide, which was defined as the maximum tolerated dose when given in combination with O6BG. This was thought to be caused by a lack of MGMT expression in normal bone and blood marrow cells, thus rendering them highly sensitive to this chemotherapy regimen.

Thus, we tested whether we could genetically modify autologous hematopoietic stem cells with a mutant version of the MGMTPT140K, re-infuse these chemotherapy-resistant bone marrow cells back into MGMThigh GBM patients and treat those patients with O6BG and 472 mg/m² temozolomide. In this study, we found that autologous P140K-gene modified hematopoietic cells engraft efficiently after chemotherapy conditioning with single-agent BCNU. Gene modified cells of multiple blood cell lineages persisted and expanded through multiple rounds of combination chemotherapy. O6BG + temozolomide chemotherapy was well-tolerated, with acceptable hematopoietic toxicity and no significant extramedullary toxicity observed (Adair et al, Science Translational Medicine, 2012). This study is currently still enrolling and has now treated a total of seven patients. Of these, six patients have surpassed the median survival for MGMThigh patients and the seventh patient is currently doing well but is at an early stage of treatment too soon to be evaluable for response. Most encouragingly, the first patient treated in this study has survived 4 years since diagnosis without evidence for disease progression. This study thus demonstrated the ability to gene modify hematopoietic progenitors, allowing for their in vivo selection and substantially reducing hematopoietic toxicity. The Therapeutic Manufacturing Shared Resource and the Center’s Vector Core Laboratory were both instrumental in translating preclinical gene modification conducted in Dr. Kiem’s laboratory to patient hematopoietic stem cells in this study. The CCGS Genomics Shared Resource was also used in the conduct of this research. This work was supported in part by CA114218, DK056465 and HL098489.


Over the past decades, multiple studies have been conducted that individually have gradually changed the practice of hematopoietic cell transplantation. We therefore conducted a study to determine whether and to what degree these changes have improved the outcome of transplantation. Our group analyzed the overall mortality, transplanted related mortality, malignant disease recurrence, and the frequency and severity of major complications, including graft-versus-host disease (GVHD) and hepatic, renal, pulmonary, and infectious complications, among 1418 patients transplanted at our center between 1993 and 1997, comparing these results with those seen in 1148 patients transplanted at our center a decade later, between 2003 and 2007 (Gooley et al, NEJM, 2010). The Pretransplant Assessment of Mortality (PAM) score was used in regression models to adjust for the severity of disease and co-morbidities at the time of transplant.

Compared to the results seen in the 1993-1997 period, we observed significant drops in transplant-related mortality (by 60%), malignant disease recurrence (by 21%) and overall mortality (by 41%). We also found significant decreases in the risk of severe GVHD, disease caused by viral, bacterial, and fungal infections; and damage to the liver, kidneys, and lungs. These improvements were not simply due to better HLA-typing technology nor the application of reduced-intensity preparative regimens, since the same magnitude of improvement was seen in matched siblings (where typing methodologies are rarely an issue) and unrelated
transplants, and when the analysis was limited to those receiving myeloablative conditioning regimens. Nor is the improvement due to better selection of patients to undergo transplantation, since those transplanted during the more recent era actually had significantly higher, not lower, PAM scores. There are several changes in our transplant practice, based on prior studies conducted by our team in Seattle that may have contributed to these results. We now avoid the most intensive preparative regimens and have adopted individualized dosing of busulfan. We use a topically active glucocorticoid and reduced dose systemic prednisone to treat GVHD restricted to the skin and GI tract, resulting in fewer systemic infections. Prophylactic use of ursodiol results in reduced liver dysfunction. And the availability of better anti-bacterial, antiviral, and especially antifungal therapies has had profound effects on our outcome.

This study (and many others like it) are the cooperative work of multiple members of the Program in Heme Malignancy, with contributions from members of the Programs in Immunology and Vaccine Development and Biostatistics and Computational Biology. This work was supported by the CCSG Clinical Research Support and Biostatistics Shared Resource. It was funded, in part, by grants CA018029, CA078902, PO1HL36444 and RO1HL088203.

2H. Integration of Non-transplant and Transplant Approaches to the Treatment of Acute Leukemia


Although the outcome of transplantation appears superior to chemotherapy for older patients with AML in first remission, prior studies have suggested that only a small minority (<15%) of patients who achieve a first CR actually proceed to transplant. These studies were not able to define the reasons limiting transplantation, but they did cast a pall on the likelihood of ever completing a controlled study to determine the true value of this approach. We hypothesized that with greater donor availability, a single center where induction chemotherapy and transplantation are more seamlessly connected should be able to transplant the majority of older patients with AML in CR1. Accordingly, we studied 244 consecutive newly diagnosed AML referred to our center over a two year period (Mawad, JCO, in press). Among them, 135 were less than age 75, and had intermediate or high risk disease. Seventy-nine (68%) were transplanted in first CR, including 67% of those over age 50. These results demonstrate that given the broader availability of donors and greater acceptance of transplantation as a treatment modality for older patients, a majority of patients can be transplanted, which also means that a study comparing transplantation in first CR with conventional chemotherapy is possible.

In the course of this and other studies, we have been mindful of the fact that there may be subsets of patients based on cytogenetic and molecular studies for which transplant is of more or less benefit. An alternative or additional approach to the pre-transplant evaluation of patients undergoing transplant is the use of multiparametric flow cytometry (MFC) to assay for the presence of minimal residual disease (MRD) before transplant. A 10-color flow cytometry assay has been developed by Dr. Brent Wood at our center. This assay has the potential advantages of being broadly applicable (AML-specific immunophenotypes can be detected in ~95% of cases) and sensitive, being able to detect leukemia cells at a level of 10^{-3} to 10^{-4}. Using this assay, we studied the impact of the presence or absence of MRD as measured by MFC on the outcome of allogeneic HCT in 253 consecutive patients with AML transplanted while in remission (Walter et al, Blood, in press). Three year estimates of overall survival were 73% for the MRD^{neg} patients and 32% for the MRD^{pos} population. Multivariable analysis was conducted taking into account patient age, cytogenetics, leukemia molecular subtype, and primary versus secondary disease. After multivariable adjustment, the risk of relapse and death were 4.90-times and 2.61-times higher for MRD^{pos} patients, demonstrating that measurement of pre-transplant MRD by MFC is an independent predictor of outcome. In the recently published AML trial S0106, we used the same 10-color flow assay to measure MRD after induction therapy in 583 patients who were subsequently treated without transplantation. These results are now undergoing analysis and, combined with the results of the impact of MRD prior to transplant, should be able to give us additional information, above and beyond that available from cytogenetic and molecular testing, about the best form of therapy to recommend for patients. These studies benefited from the FHCRC LTFU Office and the Leukemia Sample Repository. This work was supported, in part, by grants CA018029 and CA138720.
Chapuis et al have recently described a clinical trial in which patients that have either relapsed or were at very high risk of relapsing post-transplant received cytotoxic T cell (CTL) clones specific for the Wilms tumor antigen (WT1) from their HLA-matched donors following transplantation. The last four patients treated on this trial received cells exposed to IL-21 as a means to prolong in vivo survival after transfer. The cell infusions were well tolerated, and transferred cells exhibited direct anti-leukemic activity in two patients with active AML, one transient and the other sustained. Additionally, three treated patients in remission at the time of cell infusion but at high risk for relapse (probability of DFS at 2 years <10%) have survival more for >3 years without leukemia relapse, all with detectable evidence of the T cell clones. These studies are described in much more detail in the Immunology and Vaccine Development Program section, but are mentioned here because they are an important example of inter-programmatic activities, and represent a major future direction of our program. These studies are also a great example of the benefits of the Center’s cores including our Therapeutic Manufacturing Shared Resource. This work was supported in part by grants AI107776, CA169485 and CA18029.

2J. Accrual to Clinical Trials and Participation in the National Clinical Trials Network

Members of the Hematologic Malignancy Program are deeply committed to the concept of clinical trials development and participation both locally and nationally. Between 10/30/2012 – 9/30/2013, there were 802 new reportable cases of hematologic malignancies treated at our cancer center, and 466 enrollments on therapeutic trials. This high level of clinical trials activity is made possible by the Clinical Research Support provided by the Cancer Center, including Protocol Review Coordination, Regulatory Affairs and the Protocol Review and Monitoring System.

In addition to the advances noted above, prior clinical trials initiated at our institution have provided the basis for national trials. Work from the laboratory of Irwin Bernstein led to the development of gemtuzumab ozogamicin, which led to phase III trials both in adults (Blood, 121:4854-4860, 2013) and children (ASH, 2013). Results of laboratory studies conducted by Fred Appelbaum on lipid metabolism led to a SWOG clinical trial in AML (S0919) which in November, 2012, was stopped early because the positive boundary for success was crossed before full accrual was achieved. Dr. Brent Wood’s studies of minimal residual disease have led his laboratory to become the reference laboratory for SWOG’s and COG’s myeloid leukemia studies, and Jerry Radich’s studies in CML have resulted in his laboratory’s leadership in national studies of molecular responses in CML. Dr. Oliver Press’s early studies on the use of radiolabelled antibody therapies for lymphoma resulted in his leadership of SWOG 0016, a randomized trial comparing CHOP+rituximab with CHOP+131-I-tositumomab. Members of this program have leadership roles in the National Clinical Trials Network. Dr. Radich co-chairs the NCI Leukemia Steering Committee, which also has Drs. Appelbaum, and Kopecky as members. Dr. Oliver Press co-chairs the NCI Lymphoma Steering Committee. Drs. Estey and Appelbaum also serve on the NCI Pediatric Leukemia/Lymphoma Steering Committee. Finally, Dr. Appelbaum is the chair-elect of the Bone Marrow Transplant Clinical Trials Network Steering Committee. While not a major focus of our Program, we also effectively partner with industry; for example we helped lead the pivotal trials of brentuximab vedotin for recurrent Hodgkin disease (Younes, JCO, 2012), and most recently, idelalisib (Gopal, NEJM, in press) for relapsed indolent lymphoma.

3. Research Relevant to Health Problems in Our Catchment Area

Unlike many other forms of cancer, there is relatively little data that prevention or early detection plays a role in the hematologic malignancies. Thus, the major contributions of our center to our region come in the form of therapy. As the only comprehensive cancer center in Washington State, we see and treat a substantial proportion of patients with the most difficult forms of hematologic malignancies. As one example, we treat about 150 new cases of AML each year at our center. According to the Leukemia and Lymphoma Society, this translates into about 50% of all new cases of AML in Washington State. As noted above, a large majority of these patients are treated on clinical research trials.
We are the only FACT-approved transplant center in the entire Pacific Northwest (Alaska, Idaho, Montana, Wyoming and Washington) and thus the only provider of this complex form of therapy. In order to allow patients from throughout the Pacific Northwest to come to Seattle for transplant, the FHCRC built and operates two residential housing units, one of which (the Pete Gross House) is strictly for transplant patients and their families. We have also created and support a long-term follow-up unit (LTFU) that follows all transplant patients after they leave Seattle. The LTFU-unit carefully collects data on all post transplant patients and also provides these patients and their physicians immediate access to transplant experts if any problems or concerns develop.

In an effort to allow patients with less complex hematologic malignancies to be treated closer to home, we have developed a network of participating institutions. These network participants are offered selected protocols, treatment pathways, and accelerated second opinions. In addition, members of our program frequently give regional talks and each year representatives from these Network sites come to Seattle for a day-long summit at which new protocols and treatment directions are discussed.

4. Future Plans

A major development over the last grant period that will shape the future direction of our program is the emergence of T cell therapy as a therapeutic advance. Using both chimeric antigen receptor T cells (CARTs) and T cells with modified T-cell receptors (TCRs), our group has documented dramatic and persistent responses in both myeloid and lymphoid malignancies. These studies have been conducted in collaboration with members of the Program in Immunology and Vaccine Development. While results have been encouraging, a number of challenges remain including the identification of additional target antigens in the hematologic malignancies, development of methods to enhance the persistence and potency of transferred T-cells, and techniques to avoid toxicities. In order to expand our activities in these areas, we currently have two open searches, one for a basic immunologist interested in antigen discovery and a second search for a more clinically oriented individual, again in collaboration with the Immunology and Vaccine Development Program.

The two major limitations to successful allogeneic hematopoietic cell transplantation are the development of graft-versus-host disease, and therefore the need for persistent immunosuppression, and malignant disease recurrence. The adoptive transfer of tumor specific T-cells is an attractive approach to prevent relapse following allogeneic hematopoietic cell transplant, but this approach will likely be unsuccessful in patients with persistent graft-versus-host disease requiring substantial continued immunosuppressive therapy. Thus, a second major direction of our program will be the search for methods to enhance the development of tolerance. The recent recruitment of Leslie Kean and the promotion of Marie Bleakley are key investments in this effort.

Finally, our non-transplant clinical trials program continues to grow and two additional recruits are planned here.
Immunology and Vaccine Development Program

1. Program Overview

1A. Program focus and Specific Aims

The Immunology and Vaccine Development (IVD) Program was created in 2008 to bring together researchers and clinicians engaged in the study of cancer immunobiology, basic immunology, immunotherapy, vaccinology, and infectious diseases who shared a vision of developing immunologic strategies that could be deployed to harness the immune system for targeting malignancies as well as infectious diseases that develop and progress in immuno-compromised individuals. This has proven to be a highly successful effort, as substantial progress has been made not only in our understanding of the immunobiology of these diseases, but in translating these insights into new treatment strategies. Modulating the immune system with vaccines for the prevention of human infections has had many very dramatic successes, but the paradigms and strategies for reagent development to prevent diseases such as polio or diphtheria have proven neither adequate nor readily translatable to infections such as HIV and tuberculosis or to the treatment of cancer. The IVD program was created to strengthen the existing collaborative interactions, provide opportunities for new collaborations, and promote a synergy of research efforts that will accelerate progress in cancer immunology, immunotherapeutics, and vaccine development.

Our specific aims for the next cycle, which build on current efforts and expand programs horizons, are to:

1. Develop a greater breadth of cellular therapy interventional clinical trials, including initiating trials to advance cellular therapy to become an approved standard therapy for leukemia and solid tumors.
2. Define the immunological obstacles in the host and tumor microenvironment that interfere with effective immunotherapeutic targeting of tumors so that strategies can be developed to effectively treat cancers not currently responsive to therapy.
3. Identify, test, and validate improved strategies for infection control in immune compromised cancer patients.
4. Adapt and translate insights from our basic, preclinical, and clinical studies in vaccine biology to enhance immune responses to cancer antigens and improve the efficacy of adoptive T cell transfer.

1B. Program Structure and Interactive Activities

Most of the original members of the IVD program were from two previously existing programs, the Program in Immunology and the Program in Infectious Diseases. At the last review, the IVD program was rated as "Outstanding." It was noted that the Program was: "integrating groups doing premier basic immunology research with clinical translational research, building upon the premier work by members of the program in adoptive T cell transfer of antigen-specific T cells for viral diseases, cancer, and minor histocompatibility antigens expressed by tumors," and that "the addition of a strong group of investigators focused on viral vaccine development should facilitate new collaborative efforts that cross over between cancer and viral immunity and immunotherapy." The program is highly interactive, with members having the opportunity to attend multiple seminar series, including a weekly Immunology Seminar Series, which focuses mostly on basic immunology, a monthly Immunotherapy Seminar series, which focuses on translational bench to bedside studies, and the weekly Vaccine and Infectious Disease Seminar Series, which includes a broad range of basic, preclinical, and clinical presentations. Program leaders also foster interactions among members through collaborative grants, and leaders facilitate collaborative prioritization of recruitment and resource needs. For example, an Immunotherapy Steering Committee, chaired by Stanley Riddell, was established during the project period to identify new opportunities for collaborative science, and advise on resource allocation for immunotherapy, which as described in the Director’s Overview is a strategic priority of the cancer center. The members of the program have continued to be individually productive and interactive, with 994 peer-reviewed
publications during this granting period, of which 22% were intra-programmatic, 26% were inter-programmatic, and 22% were inter-institutional.

It was noted in the previous review that: “the program is now poised to accelerate at the clinical level, but this will require significant resources, particularly to translate the efforts in genetically engineered T cells. If there is one group in the world to invest in based on yield in knowledge, this Program is the one.” The program has a total of $20.5M in grant support (direct dollars), including $16.8M in peer-reviewed support, $4.8M from the NCI and substantial support from prestigious foundations, such as from AACR/SU2C for our role as part of a multi-institutional Dream Team in Immunotherapy of Cancer. HIV-related grants formerly included in the program’s funding base have been excluded in this application, except for the portion of some HIV grants that is relevant to cancer. Program leaders have, with the aid of CCSG leadership, expanded essential existing center shared resources in immune monitoring and developed new shared resources in process development and lentiviral vector development/production, and initiated multiple clinical trials. More than $20M in philanthropic funds was raised during the project period to support these activities.

1C. Program Leadership and Qualifications

Leadership: The Program is co-headed by Philip Greenberg, MD and M. Juliana McElrath, MD, PhD, with two co-Associate Directors, Stanley Riddell, MD and Michael Jensen, MD. The leaders coordinate the activities of the overall program, oversee seminar series and multi-investigator research-in-progress meetings, review applications of potential members in the program, oversee recruitment of new investigators, mentor junior faculty and trainees, and evaluate and pursue initiatives identified by members of the program that have the potential to enhance the goals of the program, such as creation and expansion of core facilities. Since the last review, Larry Corey, who was co-head of the IVD program, has succeeded Lee Hartwell as President and Director of the FHCRC and Consortium Director. Dr. McElrath now fills his role as program co-head who was an Associate Director of the IVD program at the time of the last renewal. Dr. Jensen was appointed Associate Head and, as described below, brings new expertise in pediatric oncology to the program and greatly expands our translational efforts in childhood malignancies.

Dr. Greenberg is an internationally recognized cancer immunologist whose research focuses on both basic immunology and cancer immunobiology as well as translational studies in adoptive T cell therapy of human malignancies and chronic infections using antigen-specific T cells. He is a UW Professor in the Oncology Division in the Department of Medicine and Professor in the Department of Immunology, and Member in the Clinical Research Division at FHCRC. He has been elected to several honorary societies, including the American Society of Clinical Investigation, the American Association of Physicians, the American Association for the Advancement of Science, and the American College of Physicians, and is the recipient of two NIH MERIT awards. In 2010, he, along with past and present members of his research group, received the International Society for Immunotherapy of Cancer (SITC) Team Science Award for Career Achievements (2010), and in 2011 he shared, with Steve Rosenberg from the NCI, the Cancer Research Institute’s William B. Coley Award for Distinguished Research in Tumor Immunology for their independent studies to develop and translate adoptive T cell therapy of cancer.

Dr. McElrath is a Senior Vice President at the FHCRC and Director and Member of the Vaccine and Infectious Disease Division (VIDD), and a Professor in the Department of Medicine at the UW. As a physician scientist board certified in internal medicine and infectious disease, she attends on the Infectious Diseases consult service for cancer and immuno-compromised patients at the SCCA/ UW Medical Center. Dr. McElrath is the Director and Principal Investigator of the HIV Vaccine Trials Network (HVTN) Laboratory Program, which, under her leadership, has become a highly recognized resource for the HIV vaccine field and for research in vaccine and immunotherapeutic approaches of other diseases, including cancer. Dr. McElrath has served as a principal investigator of many independent research projects including NIH RO1 and program project funding for infectious diseases and immuno-pathogenesis studies, has been the recipient of an NIH R37 merit award, a Burroughs Wellcome Clinical Scientist Award in Translational Research, and the Gaia Vaccine Award, and was...
elected to the Association for American Physicians. As Director of VID, her expertise encompasses an integrated approach to preventing infections in cancer and immuno-compromised patients.

Dr. Riddell is a Member of the Clinical Research Division at FHCRC and Professor in the Department of Medicine at UW. He has been an Associate Director of the IVD Program since its inception. Dr. Riddell’s research focuses on understanding the contributions of distinct human T cell subsets to protective immunity to pathogens and tumors and on the development and clinical application of adoptive T cell therapy for viral diseases and cancer using unmodified and genetically modified antigen-specific T cells of defined composition. He was principal investigator on the first human trial to adoptively transfer T cell clones to prevent cytomegalovirus infection after allogeneic bone marrow transplantation and on three subsequent FDA approved human trials of T cell therapy, including the first efforts to treat relapsed leukemia after hematopoietic stem cell transplantation with selected leukemia-reactive T cells. Many of these methods are now employed broadly in the field of adoptive immunotherapy for cancer. Dr. Riddell has been elected to the American College of Physicians and the American Association of Physicians, and was awarded a Hans Fischer Senior Fellowship at the Institute for Advanced Study at the Technical University of Munich to advance technologies for clinical cell processing and purification.

Dr. Jensen was recruited to Seattle Children’s in 2012 to direct the Ben Towne Center for Childhood Cancer Research from the Beckman Research Institute at City of Hope (COH), where he established a translational research program integrating synthetic antigen receptor design and T cell gene transfer as a strategy for cancer immunotherapy. He initiated the first trials of T cells transfected/transduced with a chimeric antigen receptor specific for CD20 or CD19, as well as first in human trials for pediatric neuroblastoma. His research is highly translational; he has acquired FDA approval of five Investigational New Drug Applications covering first-in-human applications of adoptive transfer of genetically engineered T cells with re-directed tumor specificity for lymphoma, leukemia, neuroblastoma, and malignant gliomas. Though new to Seattle, Dr. Jensen has a long history of collaboration with Consortium members, having completed post-doctoral training with Dr. Greenberg and collaborated with Dr. Riddell. Dr. Jensen has been continuously funded by NCI grants, including RO1’s and R21’s, and is Project Leader on PPG and SPORE projects. He received the Society for Pediatric Research Young Investigator Award and the Stop Cancer Foundation 20th Anniversary Armand Hammer Research Career Recognition Award. Dr. Jensen is also the Sinegal Endowed Professor of Pediatrics and Adjunct Professor of Bioengineering at UW, and Member of the FHCRC’s Clinical Research Division.

1D. Program membership

Membership has grown during the project period from 34 to 50, with most growth reflecting recruitment after national searches. Program members, 96% who have peer-reviewed funding or are PI on a clinical trial, draw from all Consortium research partner institutions. New recruits, who are all operating independent funded laboratories, include:

Matthias Stephan, MD, PhD, received his MD at the Medical University of Luebeck (Germany), and his PhD in Immunology at Cornell University with Michel Sadelain, a world’s leader in T cell engineering. He pursued postdoctoral training at the Koch Institute for Integrative Cancer Research at the Massachusetts Institute of Technology with Darrell J. Irvine, where he developed strategies to modulate the function of adoptively transferred T lymphocytes with synthetic nanoscale biomaterials (Stephan, Nat Med, 2010). He is the recipient of a Future Leader in Translational Medicine Award from the American Association for Cancer Research and a National Research Service Award from the National Institute of Biomedical Imaging and Bioengineering. He has initiated collaborations to test a novel biomaterial implant to deliver and functionally support encapsulated tumor-reactive T cells as a new immunotherapy to prevent tumor relapse after surgery, and is testing a new class of nanoparticles that can be delivered in vivo to reprogram T cells to recognize and destroy cancer cells. He has been notified that his first R01 application was enthusiastically reviewed and will be funded.

Martin Prlic, PhD, pursued his graduate training in the Microbiology, Immunology and Cancer Biology Program at the University of Minnesota with Stephen Jameson, with his thesis focused on unraveling the
mechanisms that control T cell and natural killer (NK) cell homeostasis. He subsequently was a postdoctoral fellow in the lab of Dr. Michael Bevan at the UW, where he studied the signaling requirements for generation and maintenance of CD8 memory responses (Prlic, J Exp Med, 2006; Prlic, PNAS, 2008; Prlic, PLoS One, 2012). During his postdoctoral training he received a K99/R00 transition award from the NIH to elucidate how the transition of CD8 T cells from the effector to the memory stage is regulated and how a fit memory T cell pool is generated. He was recruited to the FHCRC in 2011 to perform the R00 phase of his award and provide depth in our program for the development of strategies to generate “better” T cell responses, and has published two first author publications and a senior author publication thus far. He has broadened his efforts, for which he has already gained additional funding, to include an analysis of the mechanisms and consequences of CD8 T-cell mediated elimination of target cells (Chu, Cell Rep, 2013).

Cameron Turtle, MD, PhD, received his MD and PhD degrees and training in oncology in Australia and pursued postdoctoral training at the FHCRC with Dr. Riddell, studying the nature and function of CD8 memory T cells. He developed expertise in the isolation, culture, genetic modification, and propagation of T cells, and became proficient in the phenotypic, transcriptional, and functional analysis of human T cell subsets. He characterized high expression of ABCB1 as a mediator of drug efflux in antigen-experienced CD161<sup>hi</sup>CD8<sup>+</sup> T cells, which rendered them resistant to chemotherapy and a source of persistent and restored memory T cell responses after therapy (Turtle, Immunity, 2009), and elucidated the regulatory mechanisms that maintain the quiescence of innate-like CD161<sup>hi</sup>CD8<sup>+</sup> T cells during encounter with bacterial and fungal antigens as well as conditions by which this regulated TCR signaling are naturally overcome (Turtle, Blood, 2011). He is recipient of a K99/R00 transition award, and was recruited at the end of 2011 after a national search to remain at the FHCRC and join the IVD program during the R00 phase of this award. He is the recipient of a Damon Runyon Clinical Investigator Award and, in addition to more basic and pre-clinical research, is currently directing clinical cGMP-compliant cell manufacturing and monitoring of two phase I/II clinical trials of adoptive T cell therapy.

Jennifer Lund, PhD, performed her graduate work at Yale University with Akiko Iwasaki studying innate immune recognition and signaling (Carlsson, J Exp Med, 2003; Lee, Science, 2007) and joined UW in 2006 for postdoctoral training in Sasha Rudensky’s lab. Her postdoctoral work led to the surprising discovery that CD4+ regulatory T cells (T<sub>reg</sub>), rather than interfere with the development of effective immune responses to pathogens, actually facilitate early protective responses to local viral infection by allowing a timely entry of immune cells into infected tissue (Lund, Science, 2008). She was recruited in 2009 to the FHCRC and IVD Program to broaden our efforts to define the function and develop strategies to modulate CD4+ T<sub>reg</sub> cells. Her current work focuses largely on the role of T<sub>reg</sub> cells in anti-viral immune responses and in regulating mucosal immunity. She received a 5-year Cancer Research Institute Investigator Award, and has been successful in garnering NIH support, including 1 R01 as PI, 1 R01 as a co-PI, and as a project leader on two U19 grants.

Three national searches are underway for a basic tumor immunobiologist to provide the scientific underpinnings for future directions of our program; translational oncologist and immunotherapist to enhance capacity to expand our investigator-initiated clinical trials portfolio; and B cell biologist to provide insights for generating and utilizing protective and therapeutic antibodies. There has also been some attrition from our program, including Sasha Rudensky, who left to join MSKCC where he is now the Head of Immunology, and Cassian Yee, who left to become the Director of Solid Tumor Cell Therapy at MD Anderson. Fortunately, we have been able to retain/recruit junior investigators, who are expected to provide some of this lost expertise: in addition to Dr. Lund, Seth Pollack and Aude Chapuis, two “instructor level” investigators mentored by Dr. Yee, performing cell therapy for sarcoma and melanoma respectively, are now supervised by Drs. Riddell and Greenberg respectively, and are progressing towards faculty appointments as translational immunologists.

2. Scientific Accomplishments

Program members have published 994 peer-reviewed papers during this grant period, many of which provide essential insights for the generation of immune responses and the future development of more effective cancer immunotherapies. Several examples of our notable contributions are highlighted below.
a) Impact of quality and characteristics of dendritic cells on stimulation of CD8 T cell responses.

The generation of memory and effector T cells from primary T cell responses in vivo relies on antigen presentation by dendritic cells (DCs), a population of highly specialized antigen presenting cells (APCs). In addition to providing T cells with recognizable antigens by processing and presenting acquired proteins in the form of peptide-MHC complexes, activated DCs express costimulatory ligands and produce the cytokines necessary for the initiation of functional T cell responses. Triggering of costimulatory molecules by ligands present on DCs can influence T cell expansion, generation of effector functions, and T cell survival, although the exact contribution of each ligand alone and together in mediating these outcomes is not explicitly clear. In addition, cytokines produced by activated DCs during priming provide a necessary third signal that further influences T-cell expansion, development of effector functions, and response duration. Modulating the overall signal strength during activation, such as by reducing the duration of antigens, failing to provide costimulation through CD28, and/or diminishing the inflammatory environment, influences the magnitude and kinetics of the memory response, and each of these signals are impacted by the status of the antigen-presenting DC. Toll-like receptors (TLRs) expressed on DCs differentially activate DCs either alone or in combination, inducing distinct cytokines and costimulatory accessory molecules that influence T cell responses. Using an in vitro system to assess the influence of DC maturation signals on priming naive human CD8 T cells, we demonstrated (Greenberg, McElrath et al, Blood, 2011) that maturation of DCs with a TLR4 agonist (LPS) concurrently with a TLR7/8 agonist (R848) induced a heterogeneous population of DCs. Priming T cells with these DCs matured with both TLR4 and TLR7/8 signals resulted in not only larger responses but also the enhanced generation of responding CD8 T cells retaining CD28 expression, which contain the precursors of central memory cells, compared with DCs matured via either TLR pathway alone. The results suggest that it is possible to select adjuvants that can induce both larger magnitude responses as well as a greater percentage of antigen (Ag)-specific cells retaining central memory markers and acquiring reduced effector differentiation, which should be advantageous for future vaccine and immunotherapy strategies.

CTL precursors proliferate and become effector cells by recognizing foreign peptides in the groove of MHC class I molecules expressed by APCs. Professional APCs specialized for T-cell activation can either directly express the Ag (direct presentation) or can phagocytose target cells, followed by transfer of Ag to the cytosol, processing and MHC class I loading in a process called cross-presentation. It has been hypothesized an alternative pathway might exist, referred to as “cross-dressing,” in which an APC could present Ag following transfer of preformed peptide/MHC complexes from the surface of an infected cell to the APC without further processing. The Bevan lab demonstrated that this indeed does occur naturally in vivo following viral infection (Bevan et al, Nature, 2011), and that cross-dressed APCs do not acquire peptide/MHC complexes in the form of exosomes released by donor cells but rather that contact between the APCs and donor cells must occur for the transfer to be achieved. Such cross-dressed APCs can selectively promote the expansion of resting memory CD8 T cells, but cannot induce naive T cells to respond. The differential response of naive and memory T cells may reflect a disparity in their epitope density requirements for activation in vivo, particularly since cross-dressed Ag presentation is likely to be extremely low density. Thus, cross-dressing is a mechanism of Ag presentation used by DC that may be specifically harnessed for activating previously primed CD8 T cells.

b) Formation and persistence of memory CD8 T cells

The cell intrinsic properties of CD8 T cells contribute to the magnitude and quality of a T cell response, and the ability to form and maintain memory. Defining the properties that contribute to survival/expansion in responding cells and that facilitate persistence of memory in the potentially hostile environment encountered in cancer patients can provide insights not only for strategies to enhance responses but also for genetic modifications that might be introduced into T cells used for adoptive therapy to promote therapeutic activity. Pathogen recognition and signaling of cell-intrinsic innate immunity is a crucial process for initiation of the immune response to virus infection. Early recognition of RNA viruses and the induction of innate antiviral immunity are in large part dependent on the RIG-I-like receptors (RLRs). Members of the RLR family of cytosolic RNA
conidia that can simultaneously report phagocytic uptake and fungal viability during cellular interactions with microbial tissue burden or host survival, measuring aggregate processes rather than individual cellular approaches to better prevent aspergillosis. By creating mice lacking LGP2 expression, LGP2 was demonstrated to not be essential for induction of innate immune defenses (Clark, Bevan, Gale et al, Immunity, 2012). By contrast, adoptive transfer experiments revealed that LGP2, which is induced in T cells in response to TCR signaling, was required for controlling antigen-specific CD8 T cell survival and fitness during peripheral T cell expansion in response to virus infection, as reflected by lower peak responses of T cells lacking LGP2 despite no impact on proliferation, and this was followed by more extensive contraction during formation of memory. This did not reflect changes in T cell differentiation or expression of anti- or pro-apoptotic molecules in the responding T cells, but rather regulation of expression of death receptors involved in the extrinsic apoptosis signaling pathways. In particular, CD95 expression was increased in the absence of LGP2, and the cells exhibited increased susceptibility to CD95L (FasL)-mediated cell death. Thus, strategies that engage LGP2 or its downstream signaling pathways could enhance T cell survival and effector function for the control of virus infection or potentially antitumor responses. The mechanisms that maintain human T cell memory during normal and perturbed homeostasis are not fully understood. The repeated induction of profound lymphocytopenia in patients undergoing multiple cycles of cytotoxic chemotherapy infrequently results in severe infections with viruses controlled by memory CD8 T cells, suggesting that some memory T cells survive chemotherapy and restore immunity. We identified a phenotypically distinct subpopulation of memory CD8 T cells that were IL-18Ra^hi^CD161^hi^ that, similar to chemotherapy resistant hematopoietic stem cells, were quiescent and over-expressed the ATP-binding cassette (ABC)-superfamily multidrug efflux proteins that impart the cells with the ability to rapidly efflux and survive exposure to chemotherapy drugs in vitro and in vivo (Turtle, Riddell et al, Immunity, 2009). T cells with high efflux capacity were induced to proliferate in patients rendered lymphopenic after chemotherapy, and effluxing T cells that responded to Ag stimulation and inflammatory signals differentiated into non-effluxing subsets, thereby contributing to repopulation of the classical memory cell pool after chemotherapy. Thus, distinct CD8 memory T cells employ conserved resistance mechanisms utilized by classical stem cells and exhibit a stem cell-like capacity for self-renewal and differentiation, which has implications for vaccination and adoptive therapy for infectious disease and cancer in which one goal is induction of long-lived memory T cells.

c) Developing strategies to prevent/treat opportunistic Aspergillus infection

Invasive aspergillosis has become increasingly frequent among recipients of allogeneic hematopoietic-cell transplants (HCT), with an incidence rate of up to 12%. Despite the availability of new antifungal drugs, the outcome remains poor (1-year mortality of 50-80%), making invasive aspergillosis one of the leading infection-related causes of death after HCT. Identification of patients who are at increased risk for infection before HCT could facilitate development/testing of prevention strategies. Aspergillus activates innate immune cells through both TLR2 and TLR4, and polymorphisms in TLR genes have been associated with susceptibility to several infections. We analyzed a cohort of 336 recipients of HCT and their unrelated donors for single-nucleotide polymorphisms (SNPs) in TLR2, TLR3, TLR4, and TLR9 for associations with risk of invasive aspergillosis and validated outcomes with data from 103 case patients and 263 matched controls (Hansen, Aderem, Boeckh et al, N Engl J Med, 2008). Two donor TLR4 haplotypes, including one known to be associated with modified TLR4 function, increased the risk of invasive aspergillosis. The identification of donors with an increased risk of severe infection has implications for donor selection and prevention strategies in recipients of allogeneic HCT.

Designing approaches to better prevent or treat aspergillosis would greatly benefit from more informative animal models. Studies with purified immune cells do not model the complexity and context of intact tissues, and in vivo studies of host-pathogen encounters have often had to rely on surrogate endpoints, such as microbial tissue burden or host survival, measuring aggregate processes rather than individual cellular encounters. Former member Tobias Hohl and colleagues developed fluorescent Aspergillus reporter (FLARE) conidia that can simultaneously report phagocytic uptake and fungal viability during cellular interactions with
the intact murine respiratory innate immune system (Hohl et al, Cell Reports, 2012). Defects in neutrophil trafficking, number, or function predispose humans to invasive disease. Although the oxidative burst, degranulation, nutrient sequestration, and antimicrobial peptides all contribute to neutrophil antifungal activity, the mechanisms controlling neutrophil conidiacidal activity in vivo remains unclear. Our studies using FLARE conidia revealed stepwise and cell-type-specific requirements for CARD9 and Syk, transducers of C-type lectin receptor and integrin signals, in neutrophil recruitment, conidial uptake, and conidial killing in the lung. By achieving single-event resolution in defined leukocyte populations, the FLARE strain has provided a means to interrogate molecular and cellular elements that control phagocytic and cytotoxic responses to this fungus in the lung. This approach should now allow us and other researchers to reconstruct the molecular events essential for conidial clearance in vivo. Improved understanding of these mechanisms has the potential to lead to prophylactic or therapeutic strategies for invasive aspergillosis in at-risk patient populations.

d) T cell molecular profiling to understand failed or effective responses

To gain insights into requirements for generating and sustaining effective T cell responses, we have explored in depth phenotypic, functional, and molecular profiling of Ag-specific CD8 T cells in settings of successful protective responses to viral reactivation and in settings of failed responses to candidate tumor Ags that are also detectable at low levels in normal tissues because of tolerance induction. Clinical studies have shown that 50–80% of HSV reactivations are subclinical and of short duration (<6h), and that CD8 T cells not only infiltrate selectively to the site of viral reactivation, but also persist locally at the dermal–epidermal junction (DEJ), the portal of neuronal release of reactivated virus, for months after resolution of herpes lesions. Most herpes simplex virus 2 (HSV-2) reactivations in humans are subclinical and associated with rapid expansion and containment of virus, suggesting a poised protective response. Using cell-type-specific laser capture microdissection, transcriptional profiling and TCR-β chain genotyping on sequential genital skin biopsies, we showed that CD8αα+ T cells are the dominant persisting resident population of DEJ CD8 T cells at sites of previous HSV-2 reactivation (Koelle, Wald, Robins, Corey et al, Nature, 2013). CD8αα+ T cells located at the DEJ lacked expression of chemokine receptors required for lymphocyte egress and recirculation, expressed gene signatures of T cell activation and antiviral activity, and produced cytolytic granules during clinical and virological quiescent time periods. Sequencing of the TCR-β chain repertoire revealed that the DEJ CD8αα+ T cells are oligoclonal with diverse usage of TCR Vβ genes, which make these cells differ from those commonly described for mucosa-associated invariant T cells and natural killer T cells. Dominant TCR clonotypes overlapped among multiple recurrences over a period of two-and-a-half years. Episodes of rapid asymptomatic HSV-2 containment were also associated with a high CD8 effector-to-target ratio and focal enrichment of CD8αα+ T cells. The observed prompt CD8 antiviral response at the site of virus release during asymptomatic HSV reactivation is in sharp contrast to the delayed CD8 T cell infiltration during a lesion-forming herpes recurrence, in which CD8 T cell infiltration occurs 2 to 3 days after initial infection, and follows arrival of NKT cells and CD4 T cells. Thus, developing vaccination and/or cell transfer strategies to enhance the quantity and the function of tissue-resident CD8αα+ T cells may potentially be a mechanism for improved immunotherapeutic treatment and prevention of not only HSV-2 reactivation and other mucosal infections in humans including HIV, but also for tumors that arise in mucosal surfaces.

Tolerant self Ag-specific CD8 T cells fail to proliferate in response to Ag, thereby preventing autoimmune disease. However, many cancer antigens are self-Ags, and tolerance to these proteins can impede antitumor T cell responses. A critical challenge in tumor immunology is to develop strategies that break T cell tolerance to tumor/self-Ags without causing unacceptable autoimmune injury. We developed a genetically modified mouse model in which a candidate tumor Ag is expressed at low levels in a normal tissue and T cells expressing a TCR specific for the Ag can be tracked and isolated. By transferring tolerant T cells into manipulatable secondary hosts, we demonstrated that tolerant CD8 T cells could be induced to proliferate and become functional in the tolerogenic as well as in a normal host under conditions in which the host was rendered lymphopenic (Blattman, Greenberg et al, Science, 2012). However, T cell rescue was only transient, lasting through the phase of homeostatic proliferation, but with tolerance re-imposed upon repletion of the lymphoid
component even in the normal host not expressing the tolerogen (self-Ag), which challenges the prevailing paradigm that continuous Ag exposure is critical to maintain tolerance. Genome-wide mRNA and microRNA profiling revealed that tolerant T cells have a distinct tolerance-specific gene profile that can be temporarily overridden under lymphopenic conditions but is inevitably re-imposed, revealing tolerance to be a distinct cell fate that is epigenetically regulated. These insights into the mechanisms that maintain or break self-tolerance have the potential to lead to new strategies for the treatment of cancer and autoimmunity. Permanent rescue of tolerant CD8 T cells for cancer immunotherapy will require strategies to either erase tolerance-specific epigenetic memory, or alternatively, to achieve transient cyclical therapy by repeated induction of lymphopenia leading to re-rescue of tolerant T cells. The molecular nature of the epigenetic program is now being characterized in collaboration with members of the ENCODE project to determine if selective sites might alternatively be targeted.

e) T cell therapy of leukemia

Our group has been at the forefront of developing adoptive T cell therapy with cloned or polyclonal tumor-reactive T cells as a treatment modality for human malignancies, and this is increasingly the centerpiece of our translational efforts. We have reported therapeutic benefits in melanoma, will soon report therapeutic activity in sarcoma and Merkel Cell Carcinoma, and continue to develop next generation reagents and technologies that will simplify the process of generating cells, enhance therapeutic efficacy, and broaden the range of tumors that can be treated. Since the last renewal, we have made major inroads in developing T cell therapy for leukemia, including 2 completed Phase I/II clinical trials described below.

The elimination of leukemia after allogeneic HCT results in part from a graft-versus-leukemia (GVL) effect mediated by lymphocytes contained in the donor hematopoietic cell graft. Although the GVL effect is associated with GVHD, GVHD is neither necessary nor sufficient for GVL activity. In HCT in which the donor and recipient are matched at MHC, minor histocompatibility Ags (mHAgs) encoded by polymorphic genes are presented as peptides bound to MHC molecules on recipient cells that can be recognized by donor T cells. Some of these polymorphic genes are lineage restricted, and donor T cells that recognize such mHAgs expressed on recipient hematopoietic cells, including leukemic stem cells, but not on tissues affected by GVHD, have the potential to mediate GVL without causing GVHD. However, at the present time, few patients would be eligible for such T cell therapy because only a small number of mHAgs have been molecularly defined, and treatment could only be given to Ag-positive patients who have an Ag-negative donor and express the appropriate MHC-restricting allele. We previously demonstrated that CD8 CTL clones specific for mHAgs preferentially but not necessarily only expressed on hematopoietic cells can be isolated from most patients after myeloablative allogeneic HCT from an MHC-matched, related donor. Therefore, we performed a phase 1 clinical trial in which we evaluated the safety of transferring donor-derived CD8 CTL clones recognizing mHAgs expressed in recipient hematopoietic cells but not recipient dermal fibroblasts to patients with relapsed acute leukemia after myeloablative allogeneic HCT (Warren, Gooley, Appelbaum, Riddell et al, Blood, 2010).

More detailed molecular characterization of the mHAgs recognized by the CD8 clones administered to 3 patients in this study who experienced antileukemic activity and/or toxicity was performed to provide insight into the mechanism of the antitumor activity or toxicity. Adoptively transferred CTLs persisted in the blood up to 21 days after infusion, and 5 patients achieved complete but transient remissions after therapy. Pulmonary toxicity was seen in 3 patients, was severe in 1 patient, and correlated with the level of expression of the targeted mHAg-encoding genes in lung tissue. The clone administered to a patient who achieved a CR recognized an epitope in the gene P2RX7 on chromosome 12q, which is expressed at high levels in hematopoietic cells, including the patients leukemia, and low levels in the lung (patient experienced mild reversible pulmonary toxicity). The patient eventually relapsed, and the recurrent leukemia was found to have down-regulated expression of the gene. This study illustrates the potential to selectively enhance GVL activity by the adoptive transfer of mHAg-specific T-cell clones as well as the challenges for the broad application of this approach in allogeneic HCT.
A more broadly useful strategy for enhancing the GVL effect without promoting GVHD in post-HCT patients is to target leukemia-associated antigens that are predictably expressed in most/all patients with leukemia with Ag-specific CD8 CTL clones. Although the most ideal target Ags would be unique mutated proteins that are also obligate for the leukemic phenotype, T cell responses to common mutations such as epitopes created by TEL-AML1 or BCR-abl fusions have been hampered, in part due to limited processing and/or few unique epitopes that bind to human HLA alleles. Therefore, we have focused on non-polymorphic proteins overexpressed by leukemic cells that contribute to the oncogenic phenotype. The zinc finger transcription factor Wilms tumor antigen 1 (WT1) is expressed at 10- to 1000-fold higher levels in leukemic cells compared to normal CD34+ cells, and the magnitude of expression correlates with clinical aggressiveness. Because WT1 promotes proliferation and oncogenicity, loss of its expression is disadvantageous for the tumor, making outgrowth of Ag-loss variants less likely. WT1 is essential during embryogenesis, but after birth expression is limited to low levels predominantly in kidney podocytes and CD34+ HSC. We performed a Phase I/II clinical trial in which HLA-A*0201-restricted WT1-specific donor-derived CD8+ CTL clones were administered after HCT to 11 relapsed or high-risk leukemia patients (Radich, Greenberg et al, Sci Transl Med, 2013). The therapy appeared safe, with no evidence of on-target toxicity. The last four treated patients received CTL clones generated with exposure to interleukin-21 (IL-21) to prolong in vivo CTL survival, because IL-21 can limit terminal differentiation of Ag-specific T cells generated in vitro. Transferred cells exhibited direct evidence of anti-leukemic activity in two patients: a transient response in one patient with advanced progressive disease and the induction of a prolonged remission in a patient with minimal residual disease (MRD). Additionally, three treated patients at high risk for relapse after HCT (predicted median survival of ~6 months and 2 year survival <10%) continue to survive (for now >4 years) without leukemia relapse, GVHD, or additional anti-leukemic treatment. CTLs generated in the presence of IL-21, which were transferred in these latter three patients and the patient with MRD, all remained detectable long term and maintained or acquired in vivo phenotypic and functional characteristics associated with long-lived memory CD8 T cells. This study has provided the support for our now expanded efforts to immunologically target WT1.

f) Antigen discovery to identify proteins that can be targeted immunologically

Identifying Ags that can be safely and effectively targeted is essential for the broad application of T cell therapy. To achieve maximal efficacy against leukemia with minimal toxicity, the selected leukemia-associated Ags (LAAs) need to have not only high expression in and presentation by leukemic cells but also lack significant expression in healthy tissues. Moreover, as it is well established that AML is organized hierarchically and is initiated and maintained by a small population of phenotypically distinct leukemia stem cells (LSCs), eradication of leukemia will likely require the targeted LAA to be expressed by LSC. Several AML LAAs have been described, but only WT1, which we are currently targeting in clinical trials, has been shown to be expressed in LSCs of the majority of AML patients at levels significantly higher than the physiologic levels in hematopoietic stem cells (HSC). In collaboration with Irv Weisman’s group at Stanford, we used microarray expression analysis to assess differential gene expression of highly purified LSCs, hematopoietic cell subpopulations, and peripheral tissues (Bleakley, Warren, Greenberg et al, Blood, 2012). Only 7 genes, which included WT1, appeared as viable targets. The most promising was CCNA1, which encodes cyclin A1 and was detected in normal tissues only in spermatagonia, where it is known to regulate progression of male germ cells through meiosis I. By contrast, the related cyclin family member, cyclin A2, is ubiquitously expressed in all dividing cells and is essential for mitosis. CCNA1+ mice are viable and phenotypically normal, with the exception of male infertility. Cyclin A1 is aberrantly expressed in AML, as well as other malignancies, and can sustain the malignant phenotype through its pro-proliferative and anti-apoptotic activities. Overexpression of cyclin A1 in mice causes dysplastic myelopoiesis, and ~15% of these mice proceed to develop transplantable myeloid leukemias. Using dendritic cells pulsed with a cyclin A1 peptide library, we generated CD8 T cells against several cyclin A1 oligopeptides. Two HLA A*0201-restricted epitopes were further characterized, and specific CD8 T cell clones recognized peptide-pulsed target cells, and the HLA A*0201-positive AML line THP-1, which expresses cyclin A1. Furthermore, cyclin A1-specific CD8 T cells lysed
primary AML cells from patients. Thus, cyclin A1 is the first prototypic leukemia-testis Ag shown to be expressed in AML LSCs. The pro-oncogenic activity, high expression levels, and multitude of immunogenic epitopes make it a viable target for pursuing with our planned T cell-based therapy approaches.

We have also been developing chimeric antigen receptors (CARs) as a strategy for introducing genes into T cells that take advantage of the biologic activity of T cells and the recognition specificity of Abs. CARs consist of a single-chain Ab fragment (scFv) derived from the variable heavy (V\text{H}) and variable light (V\text{L}) chains of a mAb linked to the TCR CD3\text{ξ} chain that mediates T cell activation and cytotoxicity. Costimulatory signals can also be provided through the CAR by fusing the costimulatory domain of CD28 and/or 4-1BB to the CD3\text{ξ} chain. As CARs are specific for cell surface molecules expressed independent from HLA, this strategy overcomes limitations of TCR recognition, including HLA-restriction and low levels of HLA-expression on some tumor cells. MAbs and T cells modified to express CARs specific for B-cell lineage surface molecules such as CD20 or CD19 have exhibited very promising antitumor activity in B-cell malignancies, but also deplete normal B cells. The receptor tyrosine kinase-like orphan receptor 1 (ROR1) was identified as a highly expressed gene in B-cell chronic lymphocytic leukemia (B-CLL), but not normal B cells, suggesting it may serve as a tumor-selective target for therapy. We analyzed ROR1-expression in normal nonhematopoietic and hematopoietic cells including B-cell precursors, and in hematopoietic malignancies (Bleakley, Turtle, Maloney, Jensen, Riddell et al, Blood, 2010). ROR1 has characteristics of an oncofetal gene, as it is expressed in undifferentiated embryonic stem cells, B-CLL and mantle cell lymphoma, but not in major adult tissues apart from low levels in adipose tissue and at an early stage of B-cell development. We constructed a ROR1-specific CAR that when expressed in T cells from healthy donors or CLL patients conferred specific recognition of primary B-CLL and mantle cell lymphoma, including the rare drug effluxing, chemotherapy resistant, tumor cells implicated in maintaining the malignancy, but not mature normal B cells. Thus, T cell therapies targeting ROR1 may be effective in B-CLL and other ROR1-positive tumors, and we are aggressively pursuing this in preclinical studies with plans to advance to clinical trials after more safety and efficacy data is acquired.

g) Generation/Expression of high affinity tumor-reactive receptors

One obstacle in developing T cell therapy as a treatment modality has been the variability in the cell product that is administered to each patient. This includes the affinity of the receptor on the T cells for the targeted antigen, and the quality and functional capacity of the infused cells. Such variability greatly impedes efforts to elucidate the basis for successes and the reasons for failures. Therefore, we have pursued strategies to create well-defined cell products that can reproducibly be delivered to patients. In particular, this has involved creating high affinity receptors that can be predictably expressed at high levels in recipient T cells, and developing methods to isolate, for transduction with these receptors, phenotypically defined, purified T cell subsets with known functional properties.

TCR gene transfer as a strategy to create tumor-reactive T cells has the potential to overcome many of the obstacles associated with conventional T cell adoptive immunotherapy. With TCR gene therapy, a single, well-characterized, high-affinity TCR can be used as an “off the shelf” reagent for treatment of all patients with tumors expressing the target Ag, so long as the patient expresses the appropriate HLA allele. However, many promising tumor Ags are overexpressed self-proteins, and, when targeting these Ags, even the highest affinity naturally occurring TCRs that can be isolated from peripheral T cells may not possess adequate affinity to efficiently lyse target cells because of the elimination of self-reactive T cells with higher affinity TCRs by negative selection in the thymus. Strategies now exist to enhance the affinity of such naturally occurring TCRs through in vitro directed evolution as a means to increase the anti-tumor efficacy of the transduced cells. Approaches to increase the affinity of tumor-reactive TCRs are predicated on the assumption that the thymus to some degree overprotects against self-reactivity, such that T cells expressing higher affinity variants will be tolerated when transferred in vivo or that the extent of tissue injury or T-cell dysfunction resulting from recognition of normal tissues will be acceptable. Many tumor Ags that are candidates for therapeutic targeting, such as WT1, are expressed at high levels during embryogenesis, but are found at very much lower levels in
adult tissues. We have already isolated the highest affinity WT-1 specific TCR that we could detect in ~70 normal repertoires, have initiated a clinical trial in AML with CD8 T cells transduced with this TCR, and will soon initiate a similar trial targeting WT1 in NSCLC. However, based on the hypothesis that thymic selection may frequently be overprotective for such tumor Ags and that increasing the affinity of TCRs specific for naturally occurring tumor/self-Ags beyond the affinity threshold necessary for negative selection or other tolerance mechanisms operative during development in the thymus will not necessarily lead to autoimmunity in the periphery, we generated and tested enhanced affinity TCRs (Greenberg et al, Blood, 2013). The experiments were performed targeting WT1 in B6 mice as a model, since mice express similar levels of WT1 in the same tissues as humans during development and adult life (as well as over-expression in tumors). We screened B6 mice and isolated the highest affinity TCR detectable in the normal repertoire. Enhanced-affinity variants were then generated by saturation mutagenesis of the CDR3 region of Vα using a T cell display system followed by selection with a WT1/Dβ dimer. Two enhanced affinity CDR3α mutants were identified that bound the peptide/major histocompatibility complex (MHC) dimer independent of CD8, raising affinity ~100 and 500 fold respectively. Peripheral CD8 T cells transduced with these enhanced affinity TCRs functioned normally after transfer into B6 mice, responded to immunization and formed memory cells with no evidence of activation by or recognition of normal tissues, and were safe, with no evidence of infiltration into or injury of normal tissues that express low levels of WT1. However, if these same TCRs were expressed in HSC that must undergo thymic development and are thus subjected to thymic selection mechanisms, the developing T cells expressing the same enhanced-affinity TCRs experienced tolerizing events in the thymus, resulting in deletion of many of the T cells and downregulation of expression of the TCR and CD8 in cells that escaped deletion- these cells then exhibited attenuated Ag sensitivity in the periphery. Thus, TCRs for WT1 that are of higher affinity and potentially safe are being deleted during thymic development, suggesting that bypassing such thymic selection could provide a window of opportunity and allow the use of enhanced affinity TCRs that safely enhance the anti-tumor response of TCR gene-modified T cells.

We have also been developing technologies to express chimeric Ag receptors (CARs) in T cells to provide a high affinity receptor for recognition of tumor Ags. CARs typically consist of a single-chain variable fragment (scFv) derived from a mAb specific for a tumor cell-surface molecule linked to one or more T cell signaling moieties to activate effector function. Most B cell malignancies including B-ALL typically express CD19 on the cell surface and several groups, including our own, have developed CD19-specific CARs that are being tested in clinical trials in patients with advanced B cell malignancies. We previously identified a role for cell intrinsic properties of distinct memory T cell subsets in determining cell fate after adoptive transfer and showed that effector cells for therapy derived from central memory T cells (Tcm) but not from effector memory T cells (Tem) are capable of persisting long-term after transfer. Therefore, we have developed a strategy for clinical selection with GMP reagents for purifying Tcm from peripheral blood and deriving and genetically modifying CMV- and EBV-specific T cells to express a CD19-specific CAR in the Tcm subset (Turtle, Jensen, Riddell et al, Blood, 2012). Functional analysis of signaling through either the CD19-CAR or the endogenous TCR on Tcm-derived bi-specific effector T cells demonstrated nearly equivalent activation of intracellular signaling pathways and activation of effector functions, as well as induction of T cell proliferation. Preclinical studies in immune-deficient mice have revealed that transduced T cells derived from Tcm exhibit vastly improved T cell function and persistence. These findings have highlighted the importance of and provided a strategy for performing adoptive T cell therapy with T cells of defined specificity and subset derivation. Transduction of bulk populations of autologous T cells, as being performed by some groups, will likely not provide cell products with uniform capacity to survive, mediate desired antitumor effector function, and migrate in vivo. The approach of purifying defined subsets of T cells, including those with a defined TCR specificity before genetic modification, should provide cell products that have more predictable activity after adoptive transfer.

3. Research Relevant to Health Problems in Our Catchment Area

Although the IVD program is a program with a strong foundation in basic and preclinical research, we are increasingly moving our work from the bench to the bedside. This is reflected not only in the increasing number
of disease categories in which we are enrolling cancer patients in innovative investigator-initiated trials, but also in the very large number of vaccine trials, especially in the context of prevention of viral diseases, that have been designed and are being run by our group. As our institution is a well-recognized referral center, our trials have national and international outreach. However, we are also considered an invaluable resource for our surrounding community. For example, we treat ~150 new cases of AML each year at our center, which represents about 50% of all new cases of AML in Washington State. This in large part reflects the recognition by our community that we offer innovative therapeutic options, such as the T cell therapy trials described above, which are not presently available at other institutions in our catchment area.

4. Future Plans

The IVD program plans to maintain its strong basic research program into the immunobiology of effective and ineffective immune responses, as this has proved critical for providing insights and leads that have driven translational efforts. However, as many of our basic and preclinical efforts have matured since the last review, and are poised for translation, we anticipate having a much larger footprint in translational clinical trials. This is particularly true in the arena of adoptive T cell therapy, which is a major strength and focus of many of the members of our group. We already have ongoing T cell therapy trials in myeloid leukemia, lymphocytic leukemia, lymphoma, melanoma, sarcoma, Merkel cell carcinoma, breast cancer, and glioblastoma, and will be meeting with the FDA in the next few months to initiate a trial in non-small cell lung cancer (NSCLC) supported by a grant from the AACR/CRI as a component of an Immunotherapy Dream Team Award. Our trial in NSCLC will also build our experience combining checkpoint blockade reagents with T cell transfer as a strategy to achieve enhanced therapeutic activity. Many of these trials are relatively small Phase I/II trials, but we are hoping to advance our trials in AML with T cells expressing a high affinity WT1-specific TCR and ALL/CLL/B-cell lymphoma with central memory T cells expressing a CD19-specific CAR fused to a co-stimulatory domain to larger therapy trials. The funding of Phase 2 trials for cellular immunotherapy appears to require resources beyond what NIH will approve, even for “orphan diseases”, and as such we are seeking to leverage our positive results with sufficient resources from philanthropy and commercial partners to enable us to perform trials adequately powered to prove efficacy. As such, FHCRC and Children’s, together with Memorial Sloan-Kettering Cancer Center, has recently led the development of Seattle-based Juno Therapeutics, Inc., with three members of the IVD program as founding scientists, to accelerate translation of adoptive T cell therapy.

We are also pursuing preclinical models that will help us broaden the types of tumors we can treat, as well as make our therapeutic strategies more effective. For example, we are actively collaborating with Sunil Hingorani’s lab (GI Program), which has developed a genetically engineered mouse model of pancreatic cancer that faithfully recapitulates the biology and histopathology of the human disease, and have already developed TCRs specific for an Ag expressed by mouse and human pancreatic tumors that can impart antitumor activity to transduced T cells. However, this model has highlighted the fact that for many solid tumors additional obstacles will need to be addressed/resolved, including the presence of myeloid-derived suppressor cells (MDSC) and production of immunosuppressive factors such as TGFβ in the tumor microenvironment, and our collaborations provide unique opportunities to pre-clinically elucidate modulations that impact efficacy.

Finally, we hope to employ new technologies to enhance what can currently be achieved with our current immunotherapy approaches. For example, the recruitment to our program of Matthias Stephan, who is trained in bioengineering and nanotechnology, has provided new opportunities, such as the delivery of bioactive molecules to sites of T cell infiltration into tumors to overcome obstacles in the tumor microenvironment or the implantation into resected tumor beds of impregnated scaffolds that can modulate T cell function for prolonged time periods. Additionally, our vaccine development group is at the forefront of vaccine design for humans. We have already initiated T cell therapy trials in which vaccines are administered after T cell infusion to promote T cell expansion, survival, and function, and our plan is to expand this effort to achieve greater efficacy and prevent tolerance induction.
Prostate Cancer Program

1. Program Overview

1.A. Program focus

Carcinoma of the prostate is an extraordinarily common malignancy that exhibits a remarkable spectrum of behavior ranging from indolence to rapid progression and resultant cancer-specific lethality. When examining the state of clinical treatment, it is quite clear that current ‘optimal’ strategies for risk assessment, secondary prevention, and treatment of advanced prostate cancer are poor: survival rates of metastatic prostate cancer are dismal with substantial treatment-related side-effects and costs. As a field, we lack a fundamental understanding of the critical pathways that distinguish aggressive versus indolent tumor behavior, a feature of prostate cancer that has led to overdiagnosis, overtreatment, and profound confusion among clinicians and the lay public with regards to screening, early detection and primary therapy. These issues continue to reshape and refine our ideas resulting in the evolution of Program goals over time that have emphasized host- and tumor-directed studies, where quantifiable measures of risk, response, and resistance can be obtained.

The primary objective of the Prostate Cancer Program (PCP) is to advance and exploit scientific knowledge that will lead to a reduction in the morbidity and mortality attributed to this common and complex disease and to an improvement in patients’ quality of life. To achieve this goal, we collectively endorse integrated approaches involving basic scientists, population scientists and clinical investigators devoted to exploiting a fundamental understanding of cancer (and host) biology. Thematically, the PCP has three primary areas of focus where cooperative efforts (allocation of resources; faculty recruitments; scientific collaborations) have been coordinated to make substantive advancements: 1) understanding the heritable and environmental factors contributing to prostate cancer incidence, progression and lethality; 2) targeting mechanisms contributing to castration-resistant prostate cancer progression; 3) distinguishing lethal from indolent prostate cancer through discovery and validation of prognostic biomarkers and a treatment plan that affords longitudinal risk assessments.

The Prostate Cancer Program scientific goals are to:

1. Discover and validate genetic, genomic, and epigenomic biomarkers capable of distinguishing indolent from aggressive prostate cancers.
2. Identify genetic, environmental and lifestyle factors contributing to prostate cancer incidence and progression and implement clinical strategies for primary and secondary prevention.
3. Develop therapeutic approaches for the treatment of prostate cancers directed toward inhibiting key oncogenic (intrinsic) drivers, and modulating components of the tumor microenvironment.
4. Develop a molecular understanding of the androgen receptor (AR) signaling program to inform the rational design of new therapeutic strategies for treating metastatic prostate cancer.

1.B. Program structure

The Prostate Cancer Program was initiated in 1998 and comprises a diverse membership of scientists and clinicians that encompass the breadth of disciplines that impact our understanding of prostate cancer development, behavior, and treatment (see Program Membership). Program members are based at both the UW and the FHCRC, practice clinically at the UW, SCCA and VA Puget Sound Health Care System, and represent 10 distinct Departments and Divisions.

In the previous competitive renewal in 2008, the Prostate Cancer Program received a score of Outstanding to Excellent. When describing the many strengths, the reviewers noted “Clearly, there has been a substantial response to previous criticism of the limited involvement of clinical investigators in the program.” Over the present period of support, we have continued to recruit clinical investigators into the program including 3 new urologists (Bruce Dalkin, John Gore, Jonathan Wright), 1 medical oncologist (Elahe Mostaghel), and 2 pathologists (Steve Schmechel, Maria Tretiakova). Each of these investigators has a clinical and research focus on prostate cancer. Importantly, the addition of Drs. Schmechel and Tretiakova allowed the Department of Pathology to develop a subspecialty GU oncology service with four GU pathology experts; a major attribute not only for research, but for providing consultation to referrals from throughout the Pacific Northwest.

In addition to the Program strengths, the reviewers commented on three areas for attention:

i) “With such strength, one would expect an even more robust program of clinical trial accrual, and this should be a major focus of the upcoming grant cycle”. To address this issue, we established a GU Clinical Trials Core that provides organizational resources for budgets, contracts, coordinator support, and a protocol assessment system to ensure that the most scientifically important studies move forward rapidly. In this support period we
have enrolled 16% of patients onto clinical trials, opened 14 investigator-initiated trials, advanced 6 agents to Phase III studies, including 2 with Program investigators as the overall PI.

ii) “…Given that most patients with prostate cancer present with localized disease, it would be highly desirable for this team to engage personnel who can develop improved therapeutic strategies in the domain of localized disease management. While this is not a strength of the current program, it does not currently weaken the many other very strong elements.” We concur that localized disease is a key area in prostate cancer management. To address this, we have emphasized two areas: First, we developed an Active Surveillance program, the Prostate cancer Active Surveillance Study (PASS) that now includes 9 institutions throughout the US, with Dr. Daniel Lin as overall study PI. PASS is supported in part through the NCI EDRN program and has enrolled 1020 patients of which >260 were enrolled through our Consortium sites. This study will provide much needed information concerning optimal management strategies for men with newly diagnosed clinically localized prostate cancer. Second, we have now designed and conducted four neoadjuvant therapeutic trials for men with high-risk localized prostate cancer. The recently completed trial of Abiraterone/Zytiga prior to prostatectomy, conducted in conjunction with the Dana Farber Cancer Institute and MD Anderson, produced complete response (CR) or near CR rates of 20%. We are building on this result through a neoadjuvant study of MDV3100/Enzalutamide (Bruce Montgomery PI).

iii) “One aspect that should be considered for the future is the placement of publications -- this program has some very robust goals and strong science. The paucity of manuscripts in Nature, Science, NEJM, etc. will perhaps become a problem for the program to continue to be seen as outstanding as it matures.” Our group has endeavored to engage in meritorious high-gain basic, population and clinical research studies. During the present period of support, we have published high-impact findings in Nature Medicine, Science, NEJM, Nature Genetics, Cell, PNAS, and other highly regarded journals. While many noteworthy publications originate from Program members, we are also highly collaborative, and feel a strong obligation to provide intellectual input and physical resources to other investigators advancing the field. Accordingly, Program members participate in numerous large consortia and have played essential supporting roles on publications reporting many of the major advances in the field over the past 10 years. We anticipate a continued high level of impact.

The PCP is structured around three major ‘hubs’ that serve as focal points for advancing research.

**HUB 1: The Pacific Northwest Prostate Cancer SPORE (Pete Nelson/Janet Stanford PI).** This NCI SPORE grant was recently renewed for a 3rd 5-year cycle of funding (9/2013-8/2018) based on a priority score of 11. The SPORE provides key prostate-focused resources that include support for pilot projects and recruitment of new faculty. The SPORE supports a robust biospecimen collection core that comprises one of 2 active prostate cancer rapid autopsy programs in the world. This SPORE has been catalytic in fostering translational research within the Consortium environment, and broadening inter-institutional collaborative studies across the United States and Canada (the University of British Columbia is a formal component of the PNW Prostate SPORE).

**HUB 2: The Department of Defense Prostate Cancer Clinical Trials Consortium (PCCTC) (Tia Higano PI).** This DOD-funded consortium comprises 13 clinical research sites and a central coordinating center. The UW PCCTC site provides key infrastructure for the conduct of clinical research, providing early access for patients in our catchment area to Phase 1 and Phase 2 clinical studies, and a venue for investigator-initiated trials emerging from our research programs to be rapidly translated and completed across other PCCTC sites.

**HUB 3: NCI Program Project Support: 3a) ‘P01 Mechanisms and Markers of Prostate Cancer Metastasis’ (Bob Vessella PI); 3b) ‘Androgen Receptor Action in CRPC’ (Pete Nelson Co-PI).** These NCI-supported program grants support basic and translational studies focused on two critical areas: bone metastasis and resistance to AR-targeted therapeutics. The projects focus on basic mechanisms with translational relevance supported by cores that integrate findings with human biospecimens (e.g. rapid autopsy) and clinical trials.
To facilitate Program interactions, prioritize Program goals, and accelerate discovery and translation, the Program members convene twice each week. One scheduled meeting per week focuses on clinical trials with agendas that alternate between planned and ongoing studies of localized disease, advanced disease, prevention, and multimodality interventions. The second scheduled meeting per week alternates between basic science and translational topics of risk, prevention, screening, metastasis, tumor microenvironment, genomics, therapeutics, and androgen receptor biology. Once per month an outside speaker is invited. The Consortium provides support for this seminar series. Trainees, early career investigators, and developmental project (pilot grant) awardees also present at this venue. Meeting topics are posted on the Program and SPORE website and videos of presentations are archived for viewing. These meetings are live video cast to Oregon Health and Science University and the University of British Columbia; sites where our Program has strong collaborative studies underway. These conferences are ideal conduits for identifying areas of research that would benefit from Program resources that include pathology support, biospecimens, biostatistical input and financial support to move a nascent idea forward. Twice yearly the Program organizes a research retreat held on the FHCRC campus where trainees, faculty, and patient advocates share recent data and plan collaborative studies.

1.C. Program leadership and qualifications
The Prostate Cancer Program has been continually guided by Dr. Janet Stanford who has served as Program Head since the Program’s inception in 1998. Dr. Nelson was appointed Associate Head in 2003 and Co-Head in 2007. Dr. Dan Lin was appointed as Associate Head in 2012, assuming this role from Dr. Paul Lange, former Chair of the Department of Urology, who remains active in the Program.

Dr. Stanford is an epidemiologist with a research focus centered on population- and family-based studies of heritable and environmental factors that contribute to prostate cancer development and progression. She is a Full Member of the Division of Public Health Sciences, FHCRC, and holds leadership positions with Dr. Nelson as co-PI of the Prostate SPORE and the Executive Committee of the Institute for Prostate Cancer Research (IPCR), a joint UW and FHCRC organization. She is a Professor of Epidemiology in the UW School of Public Health and holds an Adjunct appointment in the UW Department of Urology. She is internationally known for her expertise in prostate cancer epidemiology and is a founding member of the International Consortium for Prostate Cancer Genetics. She is co-Chair of the Prostate inter-SPORE Genetic Working Group, and a member of several international prostate cancer consortia, including PRACTICAL (prostate cancer association group to investigate cancer associated alterations in the genome), COGS (collaborative oncological gene-environment study), ELLIPSE (elucidating loci for prostate cancer susceptibility), MADCaP (men of African descent and carcinoma of the prostate) and a multicenter GWAS of prostate cancer in African American men. She has served on numerous grant review panels for the NIH and DOD. Dr. Stanford directs the PNW Prostate SPORE Career Development Program.

Dr. Nelson is a medical oncologist with a research focus on cancer genomics, androgen receptor biology, and clinical trials of new therapeutics. He is a Full Member of the FHCRC in the Human Biology and Clinical Research Divisions. He is also a Professor in the Division of Medical Oncology at the UW with Adjunct status in the Departments of Genome Sciences, Pathology, and Urology. Dr. Nelson has an active clinical practice in genitourinary (GU) medical oncology through the Seattle Cancer Care Alliance (SCCA) and is the Clinical Research Director of the GU Oncology group where he oversees the portfolio of clinical trials. He is the recipient of a Damon Runyon Scholar Award, the UW Medical Center (UWMC) Teamwork, Leadership, and Caring Award, and awards from the Prostate Cancer Foundation. He served on the National Academy of Sciences Institute of Medicine Committee on assessing Testosterone Replacement Therapy, and has been a member of several NIH and Department of Defense (DOD) study sections including NIH TME standing study section (Chair from 2008-2010). He is the Leader of the Canary Foundation Prostate Cancer Program, a member of the AACR and ASCO Educational Program Committees and a member of the CDMRP DOD Prostate Cancer Integration and Vision Setting Panel. Dr. Nelson is co-leader of the Consortium’s Scientific Steering Committee, and is on the Internal Advisory Boards of the FHCRC/UWMC Breast and Ovarian Cancer SPOREs. Dr. Nelson is the overall PI of the PNW Prostate SPORE and directs the Developmental Research Program.

Dr. Lin, Associate Program Head, is a urologist with research interests involving screening, active surveillance, and management of high-risk localized disease. Dr. Lin is Professor and Chief of Urological Oncology at UW, and a Full Member, Division of Public Health Sciences, FHCRC. He directs the Urological Oncology Fellowship Program, is a member of the Prostate Cancer Biorepository Network (PCBN) Scientific Advisory Committee and the GU Cancers (GU ASCO) Symposium Program Committee, and serves as PI of the multi-center Prostate cancer Active Surveillance Study (PASS). Dr. Lin has long-standing scientific and administrative interac-
tions with Dr. Stanford and Dr. Nelson and numerous other members of the Prostate Cancer Program.

Collectively, the diverse backgrounds of the Program leadership provide highly complementary areas of expertise and their participation in major national organizations and consortia that promote prostate cancer research and policy provide bi-directional conduits for information flow and access for Program Members. The Program Leaders interact extensively, share research grants, co-mentor junior faculty, and organize the weekly Program clinical and research meetings. The Program Heads also meet monthly with an ‘Executive Committee’ comprised of 6 faculty (Nelson, Stanford, Lange, Vessella, True, Montgomery) who broadly represent the domains of prostate cancer research and clinical care within the Consortium. The Program Leadership are also responsible for advising the Center Director on issues related to Prostate Cancer concerning: (1) new faculty recruitment; (2) faculty support; (3) allocation of space; (4) use of pilot funding; (5) selection and organization of grant applications; (6) creation and use of shared resources; and (7) development and support of training programs.

1.D. Program membership and inter-programmatic interactions
The Prostate Cancer Program comprises 32 members in 10 distinct academic Divisions and Departments across the Consortium Institutions. The members of the Program represent key areas of research that impact a basic understanding of prostate cancer development and behavior, and clinical aspects of prevention and treatment. Members have primary appointments in Pathology, Urology, Endocrinology, Geriatrics, Medical Oncology, Radiation Oncology, Genome Sciences, Epidemiology and Public Health Sciences.

During the present interval of support, we recognized several critical areas for Program expansion and consequently recruited 3 Urologists (Dalkin, Gore, Wright), 2 Prostate Pathologists (Schmechel, Tretiakova), 1 Medical Oncologist (Mostaghel) and 1 basic science faculty member (Lam). Each of these clinicians/scientists has expertise and research interests focused on prostate cancer. Further, their recruitments provided substantial programmatic depth that has been leveraged to successfully attain several large team-oriented grants upon which Program interactions are based. These grants currently serve as Hubs (see 1B. Program structure, above) for the organization of research activity and deployment of resources. The leaders of these Hubs (e.g. Nelson and Stanford for the PNW Prostate SPORE Hub) have designated slots for the weekly research and clinical meetings and they set topic priorities, select speakers, and lead discussions.

The Prostate Cancer Program continually seeks to engage scientists without a primary interest in prostate cancer, but with key expertise that could impact the field and further the Program’s scientific goals. We invite scientists from other programs to present original research in our weekly Program meetings and provide Career Development and Pilot Project funding to a wide-range of clinicians and scientists through our SPORE and philanthropic resources. For example, Robert Bradley, a junior faculty member in the Biostatistics and Computational Biology Program received pilot funding from the prostate program for studies on alternative splicing of the androgen receptor. Key investigators involved in prostate cancer research studies have primary affiliations with other Consortium Programs and thus serve to link inter-Programmatic research efforts. Examples include Dr. Etzioni’s studies of PSA screening (Biostatistics & Biomathematics Program), Dr. Neuhausen’s studies of dietary contributions to prostate cancer progression (Cancer Epi, Prevention and Control Program) and Dr. Pritchard’s work in molecular diagnostics to direct prostate cancer therapeutics (GI Cancer). The Prostate Program members also engage in periodic joint meetings with other Programs where there are clear overlapping interests. Examples include symposia conducted jointly with the Women’s Health Program on bone metastasis, endocrine therapy, and animal models.

2. Scientific Accomplishments


Prostate cancer is the most frequent solid tumor in US men, with 233,000 new patients expected in 2014. Even though 1 in 7 (15%) US men will be diagnosed with the disease, there is continued uncertainty about its causes and this has limited efforts in primary prevention. Up to 60% of prostate cancer incidence is attributed to environmental/lifestyle factors, which if changed could have a major impact on reducing disease incidence and mortality. Program members are working to find such modifiable exposures.

The role of widely used nutritional supplements in altering prostate cancer risk has been a major research focus. Based on suggestive evidence, selenium and vitamin E were hypothesized to reduce prostate cancer incidence. Drs. Alan Kristal, Cathy Tangen (Biostatistics program) and colleagues recently completed a large
already changed clinical pr
and Collaborative Data Services were instrumental in
gram. The shared resources of Specimen Processing, Experimental Histopathology,
Cancer Program, the Program in Biostatistics, and members of the Epidemiology and Cancer
Collectively, these studies were developed and completed through extensive interactions between the Prostate

fatty acids was associated with increased risk, and high intakes of ω-6 and trans fatty acids were associated with reduced risk of high-grade cancer. The finding for ω-3 fatty acids was recently replicated using data from SELECT (Brasky et al., J Natl Cancer Inst, 2013). These results suggest caution regarding the use of ω-3 fatty acid (fish oil) supplements for prostate cancer prevention. Vitamin D supplements are another frequent exposure for which some evidence supports anti-cancer effects. Dr. Ulrike Peters (EPI/CP program) and coworkers investigated the association between vitamin D status, as determined by serum 25-hydroxyvitamin D [25(OH)D] level, and risk of prostate cancer in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial and reported that vitamin D does not decrease risk of prostate cancer (Ahn et al., Carcinogenesis, 2009).

Dietary exposures in relation to prostate cancer risk were evaluated in a number of recent studies. Drs. Marian Neuhaus, Janet Stanford, and colleagues found that tea intake significantly reduced risk for prostate cancer. Compared to men who consumed ≤1 cup/week, those who drank ≥2 cups/day had almost a 40% lower risk. The biological effects of tea have been attributed to its polyphenols, which have potent antioxidant and anti-inflammatory activities. Another collaborative study by these investigators showed that intake of deep-fried foods elevates risk. Compared with <1/month, men with ≥1/week intake of French fries, fried chicken, fried fish or doughnuts had up to a 37% higher risk of prostate cancer. This study is the first to link consumption of deep-fried foods with prostate cancer, which may be due to carcinogenic compounds produced when foods are cooked at high temperatures (Stott-Miller et al., Prostate 2013).

High caloric intake contributes to obesity, and Drs. Ruth Etzioni (Biostatistics program) and Kristal used simulation models to examine the effects of obesity trends since 1980 on prostate cancer incidence and mortality. Results show that obesity has increased the incidence of high-grade tumors and prostate cancer mortality (Fesinmeyer et al., Cancer Epidemiol Biomarkers Prev, 2009). Through inter-programmatic collaborations, Drs. Jonathan Wright, Anne McTiernan (EPI/CP program) and coworkers recently completed a pilot randomized trial of a 6-week caloric restriction diet in men newly diagnosed prostate cancer. The study found that men in the intervention group changed their diet, lost weight, and had changes in serum proteins predicted to reduce risk. This group recently submitted an R01 grant for a larger trial of the calorie reduction dietary intervention for prostate cancer prevention (Wright et al., Prostate, 2013).

The association between commonly used medications and prostate cancer risk is also a research topic of interest to Program members. Drs. Stanford, Peters (EPI/CP program), Nelson and colleagues found a 21% significant reduction in risk associated with regular aspirin use; and the inverse association was stronger for long-term (>5 yrs) or daily, low-dose use (Salinas et al., Am J Epidemiol, 2010). A subsequent study by Dr. Peters using data from the PCLO trial confirmed that daily aspirin use was associated with lower prostate cancer incidence. Drs. Wright, Lin and colleagues recently completed a study showing that aspirin use is specifically associated with a reduced risk of TMPRSS2:ERG fusion positive prostate cancer (Manuscript submitted). This suggests that TMPRSS2:ERG fusion status may define tumors with distinct etiologies. Using data from a large population-based study, Drs. Wright and Stanford found that men taking the diabetic drug metformin had a significantly lower risk of prostate cancer (Wright and Stanford, Cancer Causes Control, 2009), which has also been reported by other groups. New studies have recently been initiated by Dr. Wright and colleagues to address the potential use of metformin as a chemoprevention agent.

Collectively, these studies were developed and completed through extensive interactions between the Prostate Cancer Program, the Program in Biostatistics, and members of the Epidemiology and Cancer Prevention Program. The shared resources of Specimen Processing, Experimental Histopathology, the Prevention Center and Collaborative Data Services were instrumental in efficiently generating high quality data. The results have already changed clinical practice in providing clinicians with evidence to counsel patients against Vitamin E
and selenium supplementation, and have generated key data to support cause-and-effect clinical studies of dietary modifications.


Treatment of clinically localized prostate cancer (>85% of new diagnoses) is curative for some patients, but over time up to a third will experience recurrence or progression. When prostate cancer reaches an advanced stage, current therapies have limited efficacy; the 5-year relative survival rate for distant disease has hovered around 30% for decades. There is a critical need for translational research aimed at identifying and characterizing genetic (germline and somatic) and environmental factors that drive prostate cancer toward its lethal phenotype. Program members are working to identify factors associated with aggressive prostate cancer, which could lead to development of more effective secondary prevention and therapy strategies.

Prognostic biomarkers for lethal prostate cancer that could be used at diagnosis to distinguish high-risk patients could have a major impact on reducing overtreatment and focusing aggressive treatment on patients who are most likely to benefit. Drs. Lin, Stanford and colleagues recently identified a panel of 22 genetic variants (SNPs) that were significantly (p ≤ 0.01) associated with prostate cancer-specific mortality (PCSM) in a cohort of over 1,300 patients diagnosed in 1993-1996 or 2002-2005 who are under long-term follow-up. In collaboration with colleagues from the Karolinska Institute, they subsequently completed a validation study in a large Swedish patient cohort in which 5 of the 22 SNPs were confirmed to be significantly associated with PCSM (Lin et al., Cancer Epidemiol Biomarkers Prev, 2011) (work funded by P50 CA097186). Based on this promising evidence, further validation efforts are underway in both US- and international-based prostate cancer cohorts (i.e., Physicians’ Health Study, UK, Australia, and Finland). This validation work is funded ($400K) by awards to Dr. Stanford from the Prostate Cancer Foundation and the Movember Foundation.

Drs. Wright, Stanford and collaborators recently showed that a commonly used class of medications to lower serum cholesterol, i.e., statins, is associated with a substantial reduction in prostate cancer-specific mortality (Geybels et al., Prostate. 2013). A cohort of 1,001 incident prostate cancer patients diagnosed in 2002-2005 was interviewed in person concerning details of use of specific classes of medications. During an average follow-up period of 8 years post-diagnosis, only 1% of patients who used statins compared to 5% of non-users (p <0.01) died of prostate cancer. These results add to the growing body of evidence that statins could play an important role in secondary prevention. Statins have minimal adverse side-effects, are widely prescribed clinically to reduce LDL cholesterol and improve cardiovascular health, and are currently used by up to a third of US men in the general population. The biological mechanisms that may explain a beneficial effect of statins on slowing tumor progression and reducing its aggressiveness may relate to the drug’s ability to reduce intratumoral steroidogenesis, reduce inflammation, reduce proliferation, and alter lipid rafts involved in cell signaling. In support of these concepts, intra-programmatic basic science work conducted by Dr. Montgomery and Mostaghel found that elevated circulating cholesterol levels were associated with elevated intratumoral androgen levels in preclinical models of prostate cancer (Mostaghel et al., PLoS One, 2012). It has been suggested that the widespread use of statins at the population level has contributed to recent declines in the US prostate cancer mortality rate. Although in the current funding climate it would be difficult to launch a clinical trial of statins for secondary prevention of prostate cancer, available data from established patient cohorts under long-term follow-up for mortality may provide more evidence in the future.

Obesity is linked to higher risks for prostate cancer progression and mortality, but the underlying mechanisms are unclear. As mentioned above, Drs. Wright, Lin and colleagues completed a pilot study of a calorie restricted diet and found that the intervention resulted in weight loss and favorable changes in biomarkers predicted to reduce recurrence. An R01 grant for a larger randomized trial of the dietary intervention is pending review, and will focus on understanding biological effects of obesity/weight loss on biochemical (PSA) recurrence. Another recent dietary study by Drs. Neuhouser, Wright, and Stanford provides evidence that coffee consumption could improve patient outcomes. Compared to ≤1 cup/week, men who drank ≥4 cups/day of coffee had almost a 60% lower risk for prostate cancer recurrence/progression (Geybels et al., Cancer Causes Control, 2013).

Several studies have focused on assessment of germline genetic variants in pathways of interest in relation to prostate cancer recurrence/progression (patient follow-up is funded by P50 CA097186). Dr. Stanford and numerous colleagues (Drs. Wright, Lin, Mostaghel, Nelson) have evaluated the association between genetic vari-
genetics of affected men from 400 HPC families. To identify causal mutations for HPC, Dr. Stanford and colleagues launched the Prostate Cancer Genetic Research Study (PROGRESS) in 1995 (Prostate Cancer Foundation; NCI/NIH R01 CA080122) and have enrolled 307 HPC families, with 1,069 prostate cancer patients, 649 unaffected male relatives, and 574 female relatives participating. A recently completed targeted SNP scan identified multiple linkage regions of interest, and the strongest evidence was for a locus at 15q that was highlighted in families with early onset disease and in families with colon cancer (Stanford et al., Hum Mol Genet, 2009). To follow up these results, Drs. Stanford, Shendure (Cancer Basic Biology program) and colleagues recently initiated two next-generation sequencing projects: 1) targeted sequencing of the linkage region on chr. 15q in HPC families with colon cancer; and, 2) whole-exome sequencing (WES) of multiple kindreds (n=91) in 19 families with aggressive and/or early onset prostate cancer. The biospecimens for this large study were handled through the Specimen Processing and Collaborative Data Services shared resources. Bioinformatics- and family-based filtering of WES data identified 196 candidate mutations, which were then genotyped in an independent set of 270 HPC families (n=1,315 men) for validation. Two missense mutations (Asp336Asn, rs41441651; Gly454Cys, rs28362675) in the butyrophilin-like 2 (BTNL2) gene segregated with disease in 2 of the sequenced families and were significantly associated with HPC in the 270 confirmation families. In the 270 families, these SNVs were carried by 1.5% (p=0.003) and 1.2% (p=0.007) of 819 affected men, respectively, but none of the 496 unaffected men were carriers. For further confirmation, the two rare BTNL2 mutations were genotyped in a population-based study (n=1,155 incident cases; n=1,060 controls). Over 2% of cases and 0.9% of controls carried one of the SNVs, and both missense changes were associated with significant elevations in risk: rs4144651, OR= 2.73 (95% CI 1.3-5.9, p=0.01), and rs28362675, OR= 2.52 (95% CI 1.2-5.5, p=0.02) (FitzGerald et al., Cancer Epidemiol Biomarkers Prevent, 2013). Interestingly, BTNL proteins play a role in immune regulation and in vitro studies indicate that BTNL2 is a negative regulator of both T-cell proliferation and cytokine production. Dr. Larry True of the Dept. of Pathology is working with Dr. Stanford’s team on a study to examine BTNL2 protein expression in tumor tissue from patients that carry the BTNL2 germline mutations compared to patients who are non-carriers with support from the Experimental Histopathology resource.

In 2012, colleagues in the International Consortium for Prostate Cancer Genetics (ICPCG) completed targeted sequencing of a linkage region on 17q to find a rare HPC germline mutation (G84E, rs138213197) in the HOXB13 gene. A large ICPCG follow-up study that included PROGRESS families found that 2.4% of prostate cancer patients from 1,892 HPC families carried the G84E mutation. In a population-based study, Dr. Stanford and colleagues confirmed that the G84E mutation was more frequent in cases (1.3%) than controls (0.4%), and carriers had a 3.3-fold higher risk for prostate cancer compared to non-carriers. Based on success to date in finding rare HPC mutations in two genes (HOXB13, BTNL2) not previously suspected to play a role in prostate cancer, the ICPCG collaborative group was recently funded (U01 CA089600) to initiate a large WES effort of affected men from 400 HPC families.
Our group has also participated in numerous candidate gene and GWAS studies of sporadic prostate cancer. Dr. Stanford and colleagues have carried out population-based studies of candidate genes in biological pathways of interest, including androgen, estrogen, DNA repair, and inflammation; numerous risk-associated SNPs were identified, including some for aggressive prostate cancer (Fitzgerald et al., Cancer Epidemiol Biomarkers Prev, 2011) (Al Olama et al., Hum Mol Genet, 2013). We have also contributed to collaborative projects that have led to the discovery and confirmation of over 80 common SNPs from GWAS of both European and African ancestry men. (Eeles et al., Nat Genet, 2009), (Haiman et al., Nat Genet, 2011), (Kote-Jarai et al., Nat Genet, 2011), (Eeles et al., Nat Genet, 2013). The most recent paper defined 23 new susceptibility loci, which taken together with previously reported SNPs are predicted to explain up to 30% of the genetic risk for sporadic prostate cancer in Europeans (Eeles et al., Nat Genet, 2013). Because African American men have a higher incidence of the disease, Dr. Stanford and colleagues are also working on studies in this high-risk population. A recent GWAS of African Americans led by our colleagues at USC found a novel locus on chromosome 17q21 (Haiman et al., Nat Genet, 2011), and confirmed that many of the previously defined GWAS risk-SNPs in men of European descent are also associated with risk in African Americans. To further characterize genetic susceptibility, a new international collaborative effort (U19, GAME-On) has been launched and will genotype over 40K prostate cancer cases and 20K controls on a new “OncoArray” chip developed to interrogate >600K common and rare variants. The 196 rare candidate mutations from our WES project described above are included on the chip, as well as our panel of 22 SNPs associated with PCSM. In addition, we are contributing cases and controls (data and germline DNA) to the project. Data are expected by the end of 2014.


A major recognized impediment to effective cancer treatment is the development of resistance to cytotoxic and cytostatic agents. Mechanisms that enhance damage repair, efflux drugs, or modify cell death programs are recognized contributors to de novo or acquired tolerance to anti-neoplastic therapies. However, the finding that ex vivo assays of chemotherapy sensitivity are poor predictors of tumor responses in vivo indicate that micro-environments also contribute substantially to tumor cell survival. In this context, cancer treatments also affect benign cells, and can disrupt the normal function and physiology of host tissues and organs. Responses to genotoxic agents include the activation of damage-sensing programs that culminate in powerful intrinsic tumor suppressor mechanisms.

To evaluate the effect of genotoxic chemotherapy on the prostate microenvironment, Drs. Pete Nelson, Larry True and colleagues quantitated gene expression changes in benign prostate stroma using a well-annotated collection of biospecimens from patients enrolled on a phase 2 clinical trial, led by Dr. Tia Higano, of neoadjuvant mitoxantrone and docetaxel chemotherapy for men with high-risk localized prostate cancer. Striking changes were observed including the induction of a diverse spectrum of growth factors and cytokines, many of which have known roles in promoting tumor cell proliferation and attenuating apoptotic responses. This clinical observation was further evaluated in the laboratory where collectively, this DNA damage secretory program (DDSP) promoted the resistance of prostate cancer cells to further rounds of chemotherapy (Sun et al., Nat Med, 2012). We also identified several novel components of the DDSP, including a member of the Wnt family, WNT16B, which was upregulated 30-fold following genotoxic treatment, and contributed ~30% of the protective effect exerted by the microenvironment DDSP toward tumor cell survival. Translating this work back to the clinic, we found that WNT16B upregulation in the tumor microenvironment following chemotherapy was associated with a significantly higher risk of disease recurrence following primary therapy. Collaborating with Drs. Peggy Porter and Nicole Urban in the Women’s Cancer Program, we confirmed that this damage response involving upregulation of WNT16B occurred in both breast and ovarian cancers.

In subsequent unpublished studies, we have focused on defining upstream master regulators of the DDSP in order to develop treatment strategies to suppress this response and potentially enhance the effectiveness of standard genotoxic therapies. We have found that NFkB and mTOR regulate a substantial fraction of the DDSP and that blocking mTOR activity with rapamycin or RAD001 substantially enhances the effects of mitoxantrone chemotherapy in vivo. These results spawned two clinical trials, developed by Bruce Montgomery and Jonathan Wright that exploit targeting the tumor microenvironment damage response in prostate and bladder cancer, respectively. The tumor microenvironment studies are funded through a major project in the PNW Prostate Cancer SPORE (2P50CA097186), support through the NCI Tumor Microenvironment Network (TMEN) (1U01CA164188-01), and a R01 (1R01CA165573). Consortium shared resources were used extensively in these studies including the Genomics resource for transcriptional profiling, Imaging resource for as-
sessions DNA/chromosomal damage; Histopathology for laser capture microdissection and immunohistochemistry; and Animal Health for xenograft and drug treatment studies.


Two key developments have fueled opportunities for providing treatments specifically directed toward vulnerabilities present in individual tumors, rather than more generic ‘one-size-fits-all’ interventions that remain the standard of care for most malignancies. The first is the recognition that there are discrete molecular pathways comprised of signaling cascades, responsible for cell survival and proliferation, and often altered in neoplasms. The second is the evolution of high-throughput technologies capable of comprehensively assessing the mutation and activity status of the entire genome. Other than therapeutics directed toward the Androgen Receptor (AR) axis – which, along with endocrine therapy for breast cancer represents the first striking success of ‘precision medicine’, pathway-directed individualized treatments have not been advanced in prostate cancer. In part, this is due to a lack of knowledge concerning the key molecular alterations that occur in metastatic disease.

In 2011, an inter-programmatic collaboration between members of the Prostate Cancer Program, Nelson, Vessella, Morrissey, and True, and Dr. Shendure in the Cancer Basic Biology Program, published the first genome wide-analyses of coding mutations in advanced prostate cancers (Kumar et al.,Proc Natl Acad Sci U S A 2011). We capitalized on Dr. Shendure’s work with colleagues in Genome Sciences in developing deep catalogs of human genetic variation to distinguish germline variants from somatic mutations. On average, each advanced prostate cancer contained ~200 novel nonsynonymous variants, of which the vast majority was specific or personal to individual carcinomas. However, a subset of genes was recurrently altered across tumors derived from different individuals, including TP53, DLK2, GPC6, SPOP, and SDF4. Unexpectedly, three prostate cancer genomes exhibited substantially higher mutation frequencies, with 2,000-4,000 novel coding variants per exome. Overall, these results indicated that: (i) point mutations arising in coding regions of advanced prostate cancers are common; (ii) with notable exceptions, few genes are mutated in a substantial fraction of tumors; (iii) a previously undescribed subtype of prostate cancers exists with "hypermutated" genomes with potential implications for resistance to cancer therapeutics; and (iv) increasingly deep catalogs of human germline variation challenge the necessity of sequencing matched tumor-normal pairs, thus substantially reducing the costs of tumor genome analyses. This study was supported through a DOD Synergy grant between Dr. Shendure and Dr. Nelson with additional support from the PNW Prostate SPORE and Consortium shared resources (e.g. Genomics; Histopathology). We have advanced the findings from this study in several ways:

(i) **Confirmation of SPOP as a recurrent mutation in prostate cancer:** Drs. Morrissey and Nelson collaborated in a multi-institutional study to determine the frequency of somatic mutations in primary prostate cancers. We confirmed that the SPOP mutations also occur in a substantial fraction (10-14%) of primary tumors. The mutation sites, which cluster in the ubiquitin ligase binding pocket, strongly suggest a functional role and the potential for drug development (Barbieri et al.,Nat Genet, 2012).

(ii) **Preclinical models of hypermutated prostate cancers for drug testing.** Drs. Robert Vessella and Eva Corey have developed preclinical models of the hyper-mutation phenotype in the form of three patient-derived xenografts, and initiated therapeutic studies to determine if they have distinct responses to therapeutics targeting DNA repair pathways (e.g., PARP inhibitors).

(iii) **Clinical grade assays for research and precision medicine.** Through an inter-programmatic collaboration with members of the Prostate Cancer Program, Dr. Colin Pritchard (GI Oncology Program) employed two CLIA and CAP-approved molecular diagnostics assays (co-developed by Mary-Claire King of the Women’s Cancer Program) to identify a series of structural rearrangements in mismatch repair-family genes in advanced prostate cancers that provide a mechanistic understanding for the hyper-mutation tumors. Assay versions 3.0 have been developed to incorporate new structural variants in key prostate cancer genes and are in use to assess for actionable variants in men with high-risk localized disease and advanced metastatic cancer.
(iv) Testing precision medicine. To determine the practical outcome of identifying potential tumor vulnerabilities and directing specific therapies, several members of the Prostate Cancer Program (Drs. Nelson, Montgomery, True, Vessella, Corey, Morrissey, Yu) are collaborating in a multi-institutional project supported by a Stand-Up to Cancer AACR/PCF award that is designed to comprehensively define the spectrum of molecular changes in advanced prostate cancer and determine the effectiveness of molecularly-directed treatment. In addition to the FHCRC/UW Consortium site, collaborating institutions include Memorial Sloan Kettering, University of Michigan, Dana Farber Cancer Institute, Weill-Cornell, and the Royal Marsden Hospital. The major clinical studies embedded within this effort that have been activated are shown below as well as our current accrual to these studies:

<table>
<thead>
<tr>
<th>Patient Subset (Characteristics: Clinical/Molecular)</th>
<th>Mechanism Supporting Actionable Precision Target</th>
<th>Agent/Intervention</th>
<th>Program Enrollment 2012-2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rising PSA and Tumor Progression on Androgen Deprivation (ADT)</td>
<td>AR Activity (PSA Expression)</td>
<td>Enzalutamide/Abiraterone</td>
<td>40</td>
</tr>
<tr>
<td>AR Activation in the setting of castrate serum androgens</td>
<td>CYP17-Androgen Synthesis</td>
<td>Abiraterone + Dolutegrade</td>
<td>10</td>
</tr>
<tr>
<td>AR Activation and tumor progression on Abiraterone</td>
<td>CYP17-Androgen Synthesis</td>
<td>Abiraterone: Dose Escalation</td>
<td>20</td>
</tr>
<tr>
<td>T2: ERG Rearrangement</td>
<td>ERG-Mediated DNA Damage</td>
<td>ABT888 (PARP)</td>
<td>5</td>
</tr>
<tr>
<td>Hyper-mutation</td>
<td>Loss of DNA repair (BRCA/other)</td>
<td>ABT888 (PARP)</td>
<td>5</td>
</tr>
<tr>
<td>Neuroendocrine/Small Cell Carcinoma (Progression without rising PSA)</td>
<td>Aurora Kinase activation in NECO</td>
<td>MLN8237</td>
<td>3</td>
</tr>
</tbody>
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The androgen receptor (AR) is considered a prostate cancer lineage oncogene: a master regulator to which cells of prostate epithelial origin are dependent (Nelson, J Clin Oncol, 2012). Despite dramatic initial clinical responses to AR pathway suppression, essentially all patients with metastatic prostate cancer progress over time to a castration-resistant state that is uniformly lethal. A key question in the field concerns determining how the AR program is reactivated in prostate cancer cells despite undetectable levels of circulating testosterone. To address this problem, investigators in our group have exploited two unique resources developed and maintained by Robert Vessella and colleagues and supported by the Consortium: (i) a series of patient-derived xenograft lines that recapitulate the phenotype of response and resistance to androgen treatments; (ii) metastatic tumor biospecimens obtained from men with lethal prostate cancer collected through a rapid autopsy tissue collection program. Two important findings resulted from these studies:

(i) Dr. Steve Plymate and colleagues identified a splice variant of the AR that retained the N-terminal DNA-binding domain, but no longer encodes the ligand-binding C-terminus of the receptor. This ARv567es variant is constitutively active, and is upregulated following androgen suppression or treatment with strong AR C-terminal antagonists and promotes the growth of prostate cancers in a castrate environment (Sun et al., J Clin Invest, 2010). This work has led to productive collaborations with academic and pharmaceutical groups developing new classes of agents designed to interrupt n-terminal AR activity and a multi-institutional, multi-national DOD “Transformative Impact Award” led by Dr. Plymate.

(ii) Drs. Mostaghel, Montgomery, and colleagues determined that a substantial subset of metastatic prostate cancers have concentrations of intratumoral testosterone and/or dihydrotestosterone (DHT) that far exceeds levels found in the bloodstream. This work was made possible through novel highly sensitive and specific mass spectrometry-based assays for steroid hormone measurements developed by Dr. Matsumoto and colleagues. Our group also determined that a substantial number of advanced prostate cancers express the full complement of enzymes required to synthesize testosterone from cholesterol or adrenal androgen precursors such as DHEA. These findings foreshadowed and provided a mechanistic understanding for the success of CYP17 inhibitors such as Abiraterone in extending survival in advanced prostate cancer. Our recent studies have identified mechanisms leading to Abiraterone resistance including the upregulation of CYP17 and the induction of AR splice variants (Mostaghel et al., Clin Cancer Res, 2011), and advanced the development of several clinical trials designed to further evaluate resistance to potent AR antagonists such as MDV3100/Enzalutamide and ARN509.

The studies involving AR pathway therapeutics represent highly collaborative multidisciplinary interactions between basic and clinical scientists and link medical oncology, urology, endocrinology and radiation oncology. CCSG pilot grants to Dr. Mostaghel supported early studies involving androgen transporters and cooperative/collaborative projects supported by the PNW Prostate Cancer SPORE, two NCI P01s (P01CA85859,
The Prostate Cancer Foundation, and the Department of Defense Clinical Trials Consortium continue to sustain these research directions and integrate our local work with collaborators at the Dana Farber Cancer Center, the University of British Columbia, and the University of Pennsylvania. Consortium shared resources were used extensively in these studies including the Biospecimen Resource (for metastatic tumor tissue collection through the rapid autopsy program), Research Pathology (for immunohistochemical assays of androgen metabolic enzymes), Genomics (for sequencing of AR splice variants and AR mutations) and Comparative Medicine (for studies of drugs targeting androgen metabolism).

3. Research that relates to health problems in the catchment area

3.A. Therapeutic catchment area

Prostate cancer is the most commonly diagnosed solid tumor in the therapeutic catchment area of Western Washington and Washington State with an excess of 150 new cases per 100,000 men identified yearly. The vast majority of these diagnoses are localized cancers, and the majority currently undergo treatment with curative intent. We have ongoing efforts to address key areas of relevance to prostate cancer in the region:

Prevention: The primary prevention of prostate cancer is a key objective for reducing the burden of prostate cancer in the catchment region. We have substantial efforts devoted toward understanding the environmental influences that act to increase or decrease prostate cancer incidence. The work of Alan Kristal, Cathy Tangen and others in the Program have evaluated nutritional supplements such as selenium and vitamin E (SELECT trial) in reducing incidence rates, and found that these supplements did not reduce rates, but vitamin E actually increased prostate cancer risk. Providing this information and encouraging men to discontinue (or not initiate) these supplements could have long-term impact. Recent work also indicates that high intake of ω-3 fatty acids is associated with increased risk of high-grade cancer, and suggest caution regarding the use of ω-3 fatty acid (fish oil) supplements for prostate cancer prevention.

Over-detection and Clarification of PSA Screening Risks/Benefits. It is now readily apparent that over-diagnosis of prostate cancer is a major problem. A major component of over-diagnosis can be attributed to PSA screening and there remains substantial controversy regarding actual benefit and risk due to problems encountered in the major screening trials and the interpretation of results. Dr. Etzioni and colleagues have focused on understanding the benefits of screening and interventions, and emphasize that subgroups of the population could greatly benefit from thoughtfully applied early detection approaches.

Over-treatment (PASS). It is clear that a large number of men diagnosed with prostate cancer will never be impacted by their disease if left untreated. However, accurately determining indolent from non-indolent disease remains a challenge. Drs. Lin, Ellis, Dalkin, Wright, Nelson, and colleagues lead a multi-institutional study of active surveillance that has now enrolled more than 250 men from the Cancer Center catchment area within the last 5 years. In addition to providing a surveillance roadmap for patients and their providers to follow, the study is designed to identify tissue, blood and urine-based markers that could aid in discriminating disease progression and consequently trigger points for curative intervention.

Prostate Cancer Disparities. Prostate cancer disproportionately affects men of African ancestry. Genetic and environmental contributions to this observation remain poorly defined. Though the Pacific Northwest does not have a large African American population, we have endeavored to emphasize the recruitment of African Americans into research studies and provide education pertinent to known lifestyle factors that influence prostate cancer development and behavior. For example, we targeted the recruitment of African American Hereditary Prostate Cancer (HPC) families through local barber shops, beauty shops (developed a special study brochure); we also participated in local African American health fairs, talked to local fire stations about prostate cancer, etc. The SU2C ‘Testing Precision Medicine’ research study of tumor genome sequencing has an outreach arm specifically intended to inform and recruit under-represented populations into this program using the Prostate Health Education Network (PHEN) [http://prostatehealthed.org/].

3.B. Pacific Northwest (PNW)

We anticipate that efforts directed toward key issues in the Consortium catchment area will substantially impact prostate cancer in the Pacific Northwest (and beyond). In addition, we have specific efforts that, by design, go beyond the catchment area to reach further into Washington State and the Washington, Wyoming, Alaska, Montana, Idaho (WWAMI) region.

Education. Members of the Prostate Cancer Program are committed to enhancing the awareness and understanding of key aspects of prostate cancer that spans current knowledge of prevention, screening and treatment of early and advanced stage prostate cancer. Drs. Lange, Nelson, Lin and others lead a bi-annual educational symposium which is free to the public and recorded for dissemination broadly via YouTube. Program members regularly develop curriculum for the ‘Mini-Medical School’—targeted to the lay public, and
these lectures are broadcast nation-wide on the UW TV network. Program members travel throughout the WWAMI region to deliver CME courses to providers.

**Quality of Care and Treatment Outcomes.** Studies have documented that prostate cancer treatment outcomes vary widely in terms of disease control, side-effects, and costs. Dr. John Gore and colleagues have active research efforts devoted to understanding and improving the quality of care and patient satisfaction in several domains of prostate cancer care delivery. A particular focus is integrated into the Surgical Care and Outcomes Assessment Program (SCOAP) that tracks variation in care, develops guidelines for improving outcomes, and determines the effectiveness of these interventions. To date, 40 hospitals throughout Washington State are participating in the program (http://www.scoap.org/hospitals).

**SCCA Network:** The Seattle Cancer Care Alliance (SCCA) Network comprising 9 cancer centers including sites in Montana and Alaska, provides community-based physicians throughout the PNW with access to the latest prostate cancer diagnostic and treatment information. The objective is to offer selected clinical trials through these sites to provide local access to new treatments and avoid the burden of travel to Seattle. The Prostate Cancer Program has initiated two trials through this Network and additional studies are planned.

### 4. Future Plans

The Prostate Cancer Program encompasses a diverse spectrum of basic, population, and clinical research. We have emphasized several areas for investment and infrastructure development that will serve to advance the major scientific goals of the Program.

**Prevention Center.** We plan to open a Prostate Cancer Prevention Center that will serve several functions relevant to risk-based screening, the identification and validation of germ-line and somatic biomarkers of risk, and the coordination of intervention studies to modulate behavioral, dietary, and environmental exposures.

**Tumor Microenvironment/Immunotherapy.** A key area of research and treatment involves understanding and modulating host variation and host reactions to prostate cancer. In alignment with the strategic goals of the Consortium, we plan to enhance collaborations and recruit translational investigators focused on prostate cancer immune responses in the context prostate cancer initiation and therapeutics.

**Tracking Natural History and Treatment Outcomes.** Prostate cancer exhibits a wide range of behavior that spans indolent disease to a highly-aggressive lethal phenotype. Understanding critical determinants of behavior will provide better risk-based indicators to guide therapy and potentially identify factors that can be modified or therapeutically targeted. To advance research in this area, we will further develop approaches that: (i) facilitate the tracking of patients treated within our system over multi-year time spans, (ii) provide mechanisms for future contact for research, and (iii) link outcomes to biospecimen resources.

**Precision Medicine.** We plan to continue our focus on individualizing approaches for prostate cancer screening, prevention and the treatment of early and advanced disease. A substantial component of these efforts will center on host and tumor genomics, and we plan investments in bioinformatics, genetics and medical oncology. Importantly, advanced metastatic prostate cancer is plagued by the reality of tumor heterogeneity which currently is challenging to assess in a quantitative manner to predict outcomes. To address this, we plan to encourage faculty recruitments in functional imaging and molecular diagnostics that involve assessment of circulating tumor cells/cell-free nucleic acid analysis technologies.
Women’s Cancer Research Program

1. Program Overview

1A. Program focus

The Women’s Cancer Research Program (WCRP) brings together a highly cross-disciplinary group of investigators dedicated to reducing the incidence and subsequent mortality of breast and gynecologic cancers. The program fosters interdisciplinary research among faculty at the FHCRC, the UW, and in the clinical community to improve cancer prevention, detection, diagnosis, and treatment. It has 52 members; 96% have peer-reviewed grant funding or are PI on a clinical trial. The program holds $11.2M in peer-reviewed funding (direct dollars), of which $9.0 (80%) is from NCI. Program members have published 583 papers in the last 5 years, including 16% inter-institutional, 19% intra-programmatic and 35% inter-programmatic manuscripts.

The Program goals are to:

1. Improve strategies for identifying women at high risk for breast and gynecological cancer
2. Develop and validate assays and imaging modalities to diagnose breast and gynecological cancer early
3. Improve the efficacy and safety of adoptive T-cell transfer for breast and gynecological cancer
4. Improve response and lower resistance to various forms of chemotherapy for patients with breast and gynecological cancer

1B. Program structure

The program is structured to inform the leadership about members’ needs for new recruits, faculty support, shared resources, and support for pilot studies, and to ensure that the value of the program as a whole is greater than that of its individual members separately. Within the Consortium, communication is the key to effective integration of research on cancers specifically affecting women with research on other solid tumors. At the time of the last competitive renewal, the WCRP was a new program formed by merging the Breast and Gynecological Cancer Programs to increase their scientific contributions to the Consortium. The program was assessed as ‘Outstanding to Excellent’ and leadership was encouraged to facilitate the combined goals of the new program and identify and exploit potential parallel avenues of breast and gynecological cancer research. The program leaders and associate leaders have made special efforts to work together to promote interaction and research development primarily through combined seminars and meetings, and through SPORE activities and pilot funding. Their efforts have supported research relevant to both breast and ovarian cancer and yielded NCI funding for a large grant in biomarker research (NCI EDRN Clinical Validation; NCI U01 CA152637), described below, which focuses on both breast and ovarian cancers.

Three large multidisciplinary grants, described below, have strengthened and expanded many WCRP activities, including research, mentoring, project development and inter-and intra-programmatic interaction. In addition, the program has a broad portfolio of outstanding interdisciplinary projects including those in imaging, immunotherapy and genetics (see Scientific Accomplishments section).

The Pacific Ovarian Cancer Research Consortium SPORE, led by Dr. Nicole Urban, has been continuously funded since 1999; it was renewed in 2009 for a 3rd 5-year cycle of funding (7/2009-6/2014) based on a priority score of 131. The SPORE provides key ovarian-focused resources that include support for Developmental (Pilot) Projects and recruitment of new faculty. The SPORE supports a robust biospecimen collection core that provides blood and tissue samples to investigators locally and throughout the country. Its five projects focus on risk and early detection, immunotherapy, and improving response to therapy. Project 1 (Nicole Urban, WCRP; Beth Karlan, CSMC) is a randomized control trial (RCT) in high-risk women to compare two ovarian cancer-screening strategies. The first strategy (Arm 1) uses both CA125 and HE4 in a first-line screen to select women for imaging (Urban, CEBP, 2012; Anderson, JNCI, 2010; Urban, Annals of Onc, 2011; Cramer, Ca Prev Res, 2011; Zhu, Ca Prev Res, 2011; Shah, CEBP, 2009). The second (Arm 2) uses CA125 alone as a first-line screen to select women for HE4 and imaging, introducing HE4 as a second-line screen (Urban, JNCI, 2011). Enrollment goals have been met: 1200 women have been enrolled at five study sites. Publications (1-7 below) describe sensitivity and lead time of CA125 and HE4 when used in a longitudinal algorithm. The goal of Project 2 (Sanjiv Gambhir, Stanford University; Charles Drescher, WCRP) is to validate and refine molecularly
targeted microbubble contrast enhanced ultrasound (CEUS) for non-invasive, in-vivo imaging of the ovarian cancer vascular network, to develop a targeted microbubble CEUS for use as a second-line screen in a multimodal ovarian cancer screening strategy such as those in Project 1 (Drescher, Ca Prev Res, 2012) as well as in diagnosis and for monitoring the response of ovarian cancer to anti-angiogenic therapy. Project 3 (Andre Lieber, WCRP; Charles Drescher, WCRP) evaluates in a series of clinical trials a small recombinant protein (JO-1) that can transiently open tight junctions between epithelial tumor cells to enhance the efficacy of chemotherapeutics (Beyer, Clin Ca Res, 2011) and monoclonal antibodies (Beyer, Ca Res, 2012) by increasing intratumoral drug penetration and unmasking of target receptors (Wang, Nat Med, 2011; Wang, J Virol, 2011). The administration of JO-1 combined therapy was shown to be safe in adequate transgenic mouse models (Liu, Ca Gene Ther, 2011) and in non-human primates. A Phase I clinical trial to test the safety of combined Doxorubicin and JO-1 has begun in non-human primates and the approach appears to be safe in experiments conducted to date. Project 4 (Toshi Taniguchi, WCRP; Elizabeth Swisher, WCRP) addresses the role of genes (Walsh, PNAS, 2011) for inherited ovarian, fallopian tube, and peritoneal carcinoma (Wickramanyake, Gyn Onc, 2012; Pennington, Gyn Onc, 2013) in risk (Pennington, Gyn Onc, 2012; Swisher, JNCI, 2012) and response to chemotherapy (Sakai, Ca Res, 2009; Dhillon, Ca Sci, 2011; Norquist, J Clin Oncol 2011). Such genes affect survival (Wurz, Genes Chromosomes Cancer, 2010) and are not always signaled by pedigree (Norquist, Gynecol Oncol, 2013). Project 5 (Nora Disis, WCRP/Immunology and Vaccine Development; Lupe Salazar, WCRP) is a Phase I trial active immunization (Liao, Gynecol Oncol, 2013) with an IGFBP-2 Class II polyepitope plasmid DNA vaccine (Dang, Clin Ca Res, 2012) in patients with advanced stage ovarian cancer in the adjuvant setting. Of 52 vaccinations given to 25 participants there was only one acute post vaccine toxicity, suggesting a good safety profile. This SPORE has been catalytic in fostering translational research within the Consortium environment, and broadening inter-institutional collaborative studies along the west coast and across the United States more generally.

The Seattle Cancer Consortium Breast SPORE, led by Drs. Peggy Porter and Martin “Mac” Cheever (Immunology and Vaccine Development), received funding in 2010. It brings together clinical and laboratory researchers from the FHCRC and UW and supports strategic research in highly translational projects, the development of new research directions, and sponsorship of new investigators—those starting their careers and those with established careers newly focusing on breast cancer. The four projects of the SPORE focus on targeted approaches to specific breast tumor types. Two of the SPORE projects have initiated clinical trials and three of the projects are focused on gaining insight into resistance to therapy and eventually defining what targeted therapies are needed to treat resistant tumors. Project 1 (James Roberts, Cancer Basic Biology; Peggy Porter, WCRP) applies the basic discovery of p27kip1 cell cycle regulation in breast cancer to predict mortality and response to therapy, particularly in HER2-expressing tumors. Project 2 (Stan Riddell, Immunology and Vaccine Development; Lupe Salazar, WCRP) uses exquisitely specific and engineered central memory T cells to target abnormally expressed tumor-associated proteins with vaccines and therapy (Nauerth, Sci Transl Med, 2013; Hudecek Clin Cancer Res, 2013; Turtle, Curr Opin Immunol, 2012). Project 2 is initiating a clinical trial to perform a phase I trial of adoptive T cell therapy with TCM-derived HER-2/neu (HER-2)-specific T cells following in vivo priming with a HER-2 peptide vaccine in patients with advanced HER-2+ breast cancer. Project 3 (Jennifer Specht, WCRP; David Hockenbery, Cancer Basic Biology) is designed to determine the biological basis and discover new therapeutic targets for a breast imaging metabolism/perfusion mismatch profile that predicts poor prognosis and poor response to systemic therapy. They are currently enrolling patients into an imaging trial designed to compare imaging features of primary breast cancer to gene expression profiles, and delineate changes in the tumor metabolic profile over the course of chemotherapy. Data from the study will be used to address their hypothesis that “metabolic flexibility” underlies resistance to standard chemotherapy. Project 4 (Kathi Malone, CEPC; Amanda Paulovich, Cancer Basic Biology) draws on a well-characterized population-based cohort to identify specific DNA-damage pathway biomarkers that could prevent the over, or under, treatment of women with breast cancer. Together, these four projects afford both short- and long-term translational potential for advances in breast cancer care. As in the Ovarian SPORE, the breast SPORE maintains an active repository with tissue and blood specimens for over 3000 individuals. These samples have been critical for investigators designing new breast cancer studies. Additionally, the breast and ovarian repositories have provided samples to investigators studying both breast and ovarian cancer and have facilitated projects that are or will be included in SPORE renewal applications (Andre Leiber, WCRP; Nora Disis, WCRP; Elizabeth Swisher, WCRP).

NCI EDRN Clinical Validation Center (Chris Li, PI; co-investigator Urban). This U01 grant (NCI U01 CA152637) was funded by NCI in 2010 and represents a new collaboration between breast and ovarian cancer
researchers at the Center. It is a clinical biomarker validation center in breast and ovarian cancer representing collaboration with over ten institutions in the U.S. It includes five local studies, two in breast cancer and three in ovarian cancer, as well as three collaborative studies. Local studies include a Phase 3 Validation Study of Breast Cancer Early Detection Biomarker Candidates from our WHI Discovery Project (Chris Li, WCRP; Paul Lampe, CEPC), which involves evaluation of promising candidates from our initial discovery work using a customized antibody microarray; a Phase 3 retrospective validation of ovarian cancer early detection markers in serial preclinical samples from the PLCO trial (Urban) that uses preclinical PLCO proximate samples to evaluate the roles of candidate markers HE4, MSLN, MMP7 and SLPI in ovarian cancer screening strategies; a Phase 3 Validation of screening decision rules in preclinical UKCTOCS serial samples in which we will evaluate HE4 as a 2nd line screen using approximately 3 serial serum samples each from 50 cases and 250 matched control women who participated in the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS); a Phase 3 Validation of Ovarian Cancer Serum Markers in Preclinical WHI Samples focused on determining the impact of using a longitudinal algorithm rather than a single threshold rule when evaluating biomarker positivity; and Phase 2 and 3 Validations of Putative Breast Cancer Early Detection Candidates in the clinically relevant setting of mammography screening (Chris Li, WCRP; Buist, WCRP; Porter, WCRP). Collaborative studies include Ovary Cancer Biomarker Validation for which Dr. Urban has identified a serum set consisting of 50 high grade serous ovarian cancer cases and 50 benign serous controls and lists of our most promising candidate biomarkers; Triple Negative Breast Cancer Biomarkers for which Dr. Li has contributed a list of his most promising triple negative breast cancer biomarkers; and Ductal Carcinoma in Situ (DCIS) Biomarkers Predictive of Risk of Subsequent Breast Cancer, which is led by Dr. Li. The work of the FHCRC Breast and Ovarian Cancer Clinical Validation Center will lead to better breast and ovarian cancer screening methods. For breast cancer, we hope to validate promising early detection biomarkers identified in our discovery experiments in high quality preclinical samples. For ovary cancer, use of a longitudinal algorithm with multiple biomarkers to determine whether an individual should be referred for a surgical consult will help improve the cancer diagnosis process while reducing the number of unnecessary surgeries resulting from false positive biomarker and ultrasound results.

Clinical trials. Emphasis across all programs is on interventional clinical trials that can make a difference, either by advancing the field or changing medical practice. Strong examples in the WCRP are the PARP inhibitor and vaccine trials. Phase I trials are activated primarily by clinical scientists, some within the SPOREs, and Phase II/III trials are conducted primarily in collaboration with clinical cooperative groups such as the GOG and SWOG, or with industry. Accrual of patients to interventional clinical trials is assured by frequent meetings among the clinical disease site groups to review accrual to protocols and to decide on new protocols to open. Formal review is performed semi-annually with more frequent phone conferences with collaborators at community sites to activate new protocols. Medical and radiation oncologists from UW, Swedish, Multicare, and Northwest attend as well as study coordinators from the different sites and nursing. Our partners in the community participate to decide which trials we will open only at SCCA versus which can be opened through cooperative groups or our network sites so that we can improve accrual to trials and provide access to clinical trials throughout the Pacific Northwest. Program intervention trial accrual by type of trial (national, institutional, externally peer-reviewed, and industry) is summarized in the attachment for this narrative. In FY13, 1010 women were enrolled in interventional trials, including 85 patients placed in therapeutic clinical trials (10%).

Programmatic interaction. Program members convene twice monthly to discuss progress of translational research—one standing meeting is focused on breast cancer and one on ovarian and other gynecological cancers. To facilitate Program interactions, prioritize Program goals, and accelerate discovery and translation, the program hosts twice yearly research retreats held on the FHCRC campus where all WCRP trainees, faculty, and patient advocates share recent data and plan collaborative studies.

Drs. Urban and Porter serve on each other’s SPORE Advisory Board, actively advising and promoting new research that is relevant to both breast and ovarian cancer. Through pilot funds from their SPORE grants and donor support over the past grant period, they have funded 35 pilot projects totaling $1.5 million. Program members with strong disease overlap, including Drs. Disis, Urban, Swisher, Taniguchi, and Lieber, have been specifically supported through pilot funding. Developmental research funds have been awarded from both the Ovarian and Breast SPORE programs to Dr. Taniguchi for the analysis of the Fanconi Anemia pathway in breast and ovarian cancer and to Dr. Lieber for study of his recombinant tight junction opener for enhancement of breast and ovarian cancer therapy. In 2011, developmental research funds were awarded to Dr. Lieber to support research on a combination therapy of JO-1 and chemotherapy, leading to a full-scale project in the Ovarian SPORE. Additional pilot funding for Dr. Leiber through Breast SPORE developmental funds has
supported JO-1 studies in breast cancer. Career development funds from the Ovarian SPORE and pilot funds from the Breast SPORE have been provided to Matthias Stephan, M.D., Ph.D. (IVD), Assistant Member in the Clinical Research Division at FHCRC and Assistant Professor in the Department of Medicine, Division of Medical Oncology at the UW to develop bioengineered scaffolding techniques to deliver therapy for ovarian and breast cancer. Dr. Stephan recently was awarded the OCRF Liz Tilberis Early Career Award.

**New faculty** with expertise in tumor biology and cancer imaging have been recruited to the WCRP in the past grant period. Cyrus Ghajar, Ph.D., Assistant Member Public Health Sciences Division, joined the FHCRC from Dr. Mina Bissell’s lab in San Francisco. His research focuses on the relationship of small blood vessels and the maintenance of disseminated tumor cell (DTC) dormancy at potential metastatic sites in the body. Dr. Ghajar has found that dormant DTCs reside on microvasculature of lung, bone marrow and brain, and that maintaining microvascular homeostasis is key to maintaining the dormant cell niche. He has been awarded pilot funding to investigate tumor-vascular Interactions to develop therapies that eradicate dormant tumor cells. His recruitment helped achieve a strategic goal set by Drs. Porter and Urban to strengthen tumor biology expertise in the program.

Dr. Christoph Lee, M.D., MSHS, UW Assistant Professor, Department of Radiology, Breast Imaging was recruited in 2012. He has an exceptional background in radiology health services research. He completed his diagnostic radiology residency at Stanford University and his fellowship as a Robert Wood Johnson Foundation Clinical Scholar at UCLA. As an assistant professor of radiology at UW Medicine, with additional appointments at Fred Hutchinson Cancer Research Center, the UW Comparative Effectiveness, Cost and Outcomes Center (CECORC), and RAND Health, Dr. Lee bridges clinical radiology and health services research.

His expertise on breast density legislation outreach has shaped the national narrative on this important issue. His recent reviews of the legislation have significantly contributed to the debate as to the most appropriate way to partner with patients and legislators so that scientific and clinical data lead to the development of legislation and protocols for appropriately managing breast cancer screening.

**Biospecimen resources** are priorities for the breast and gynecological cancer research and Drs. Porter and Urban have configured their respective repositories to promote inter-and intra-programmatic interaction. Through the NWBioTrust ([www.nwbiotrust.org](http://www.nwbiotrust.org), and see Shared Resources section), a Consortium shared resource that Dr. Porter co-directs with Dr. Stephen Schmechel (UW); the Virtual Biospecimen Discovery (VBD) tool provides a searchable database of biospecimens available in the ovarian, breast and other institutional solid tumor repositories. The database is updated each month to reflect current holdings in the repositories and investigators can search across repositories to identify biospecimens of multiple tumor types for their research.

Clinical care for both breast and gynecological cancer patients is centered at the SCCA Women’s Clinic along with the Breast and Ovarian Cancer Prevention Clinic. This provides an opportunity for program clinicians to develop and conduct clinical treatment trials, genetic testing and survivorship strategies for both breast and ovarian cancer patients. Collaborative PARP inhibitor trials for breast and ovarian cancers are ongoing (Julie Gralow, WCRP; Jennifer Specht WCRP; Elizabeth Swisher, WCRP).

**1C. Program Leadership and Qualifications**

For over a decade, Dr. Peggy Porter and Dr. Nicole Urban have led the Program along with Associate Program leaders, Dr. Julie Gralow and Dr. Barbara Goff. Dr. Porter is a Member in the Divisions of Human Biology and Public Health Sciences at FHCRC, a Professor of Pathology at UW, and co-Director of the newly established NWBioTrust, a resource for annotated research biospecimens ([https://www.nwbiotrust.org/en.html](https://www.nwbiotrust.org/en.html)). She is board certified in Anatomic Pathology and in Cytopathology. Dr. Porter’s research is focused on identifying and understanding the molecular events associated with the initiation and progression of breast cancer. Her leadership and participation in collaborative research provides a unique opportunity to test the clinical importance of basic science discoveries in large clinical and population-based studies. She is the P.I. of the Seattle Breast Cancer SPORE (NCI P50 CA138293). Dr. Porter organizes the monthly Breast Seminar Series, manages the announcement, review and funding of breast pilot projects, oversees the Thomsen Family Fellowship in Breast Cancer Research, and directs the Breast Specimen Repository.

Dr. Nicole Urban is a Member in the Division of Public Health Sciences at FHCRC and a Research Professor of Health Services in the School of Public Health and Community Medicine at UW. She trained in Health Services and Biostatistics at the Harvard School of Public Health, and has been at the Center for 29 years. She has studied breast cancer for over 25 years and ovarian cancer for over 15 years. She has led the Pacific
Ovarian Cancer Research Consortium SPORE (NCI P50 CA083636) since 1999. Her group has developed a biomarker pipeline that has produced HE4 and Mesothelin, ovarian cancer markers that performed well in Phase III validation. HE4 is FDA approved for use in post-treatment surveillance and is being evaluated prospectively in the Ovarian SPORE for use in early detection. Dr. Urban is Principal Investigator of a study using stored serum samples and epidemiologic risk factor data from several large trial cohorts to develop and validate a risk classifier for ovarian cancer (NCI R21 CA3534178), and co-investigator in the EDRN CVC (NCI U01 CA152637, PI Li). Dr. Urban organizes the monthly Translational Working Group and Gynecologic Cancer Research seminars, manages the announcement, review and funding of ovarian Career Development and Developmental Research projects, and directs the Translational and Outcomes Research (TOR) Specimen Repository.

Drs. Gralow and Goff are nationally recognized for their breast and gynecological cancer expertise and leadership in clinical trials. Dr. Gralow is the Director of Breast Medical Oncology at SCCA and is an Executive Officer of the Southwest Oncology Group (SWOG) and in this role develops, coordinates and helps oversee the SWOG breast committee’s clinical trials portfolio and participates in the North American Breast Cancer Intergroup. She and Dr. Porter are members of the Translational Breast Cancer Research Consortium (TBCRC), a national clinical trial group dedicated to innovative, high impact and biologically driven clinical research in breast cancer. Dr. Gralow leads the Clinical Core for the Breast SPORE and breast clinical trials at SCCA. She is responsible for the quarterly Clinical Breast Faculty Retreat. Dr. Goff developed an ovarian cancer symptom index that influenced the adoption of guidelines urging women and physicians to heed the early warning signs of ovarian cancer. Her work contributed importantly to a decision by the American Cancer Society (ACS), the Society of Gynecologic Oncologists (SGO) and the Gynecologic Cancer Foundation (GCF) to issue a consensus statement about symptoms and early detection of ovarian cancer. Dr. Goff is the Division Director of Gynecologic Oncology at UW and SCCA and currently serves as president of the national Society of Gynecologic Oncology. She directs the Gynecologic Oncology fellowship and is the Co-PI under Dr. Appelbaum for the Gynecologic Oncology portion of the T-32 training grant in oncology at FHCRC. She has served as the Chair of the Puget Sound Oncology Consortium Gynecologic Cancer Division and is responsible for the oversight of all the regional clinical trials in gynecologic cancer. She is very active in the Phase I working group and is the PI of numerous phase I and II trials.

1D. Program membership and Inter-programmatic interactions

The WCRP is a large program with 51 members having a research focus in breast cancer, gynecologic cancer, or both. Members come from ten departments at the University of Washington (Medical Oncology, Gynecological Oncology, Surgery, Pathology, Radiology, Radiation Oncology, Genetics, Immunology, Health Services, Medical Genetics), and three divisions (Clinical Research, Human Biology, Public Health Sciences) at the Fred Hutchinson. Ninety-six percent of the members have peer-reviewed funding.

The broad expertise of the membership and strong collaborations between members of the WCRP and other programs including Heme Malignancy, IVD and CEPC, promotes a cross-disciplinary research environment that addresses the central themes of the program and effectively supports the new research directions. Longstanding interdisciplinary collaborations with the cancer imaging group are now part of WCRP and make up an important portion of the intra-programmatic translational research being conducted. Specific examples of intra- and inter-programmatic collaborations across the institutions include ovarian and breast clinical trials (Swisher WCRP/UW) based on findings from basic research in Fanconi Anemia genes (Taniguchi WCRP/FHCRC); targeted adoptive T-cell immunotherapy in HER2 vaccinated breast cancer patients (Salazar WCRP/UW with Disis IVD/UW and Riddell IVD/FHCRC); evaluation of quantitative FDG PET/MRI as predictors of response to therapy in breast cancer (Linden WCRP/UW and Partridge WCRP/UW); and identification of risk factors for primary and second primary breast cancers (Li WCRP/FHCRC and Malone CEPC/FHCRC). Vaccinating against IGFBP-2 to prevent ovarian cancer relapse (Salazar WCRP with Disis IVD) is a project in the Ovarian SPORE.

The promotion of new inter-programmatic collaborations is a high priority for the WCRP. The very robust pilot project funding for both ovarian and breast cancer research and career development funds from the SPORE grants have been especially effective in promoting the initiation of studies by investigators that did not have previous research in women’s cancers. Examples include Heme Malignancy members Turtle and Spies who have respectively developed methods for TcR gene transfer and programming of central memory cells for breast cancer (Turtle, Curr Opin Immunol, 2012) and found that NKG2D acts as a stimulatory receptor on breast, ovarian, colon and prostate carcinoma cells where it exploits the presence of its ligands for autocrine
activation of major oncogenic pathways and stimulation of tumor growth (Benitez, Proc Natl Acad Sci USA 2011). Robert Bradley (Biostatistics and Computational Biology) received breast pilot funding for a project to discover synthetic interactions between spliceosomal RNAs and breast cancer therapeutics. Heidi Divinge in his lab has been recently awarded a DoD fellowship (DoD BC130666) to carry on these studies (Dvinge, Nature, 2013). Key investigators leading breast cancer research studies have primary affiliations with other Consortium Programs and thus serve to link inter-Programmatic research efforts. Examples include Dr. Beti Thompson’s (CEPC) P50 Center for Population Health and Health Disparities (CPHHD; NIH/NCI P50 CA148143) that includes four projects addressing breast cancer screening, dietary and reproductive risk factors, and ancestry in Hispanic women (Neuhauser, CEPC; Porter, WCRP; Li, WCRP); Dr. Anne McTiernan’s (CEPC) intervention-based research to evaluate physical activity, diet, and chemoprevention strategies for prevention of breast cancer; and the Women’s Health Initiative (WHI), led by Garnet Anderson (CEPC). Drs. Anderson and Porter recently received funding for a Women’s Health Initiative Cancer Survivor Cohort (Core Infrastructure & Methodological Research for Cancer Epidemiology Cohorts (UM1CA173642) that will establish a resource of tumor specimens from the WHI cohort at the FHCRC. Dr. Mary Claire King’s group is collaborating with Dr. Swisher and Dr. Pritchard (GI Oncology) at UW Laboratory Medicine to implement molecular diagnostics and expanded genetic screening to assess risk for breast and ovarian cancer (Walsh, PNAS, 2011). Dr. Drescher is nurturing an important translational project aimed at measurement of tumor infiltrating lymphocytes in ovarian cancer by Drs. Bielas (Cancer Basic Biology) and Robins (Biostatistics and Computational Biology) through provision of specimens and clinical guidance (W Emerson, J Pathol, 2013; Robins and Bielas, Sci Transl Med, Dec 2013).

WCRP members also engage in periodic joint meetings with other Programs where there are clear overlapping interests. Examples include symposia conducted jointly with the Prostate Program on bone metastasis, endocrine therapy, and animal models.

2. Scientific Accomplishments

Below are highlights of selected research accomplishments from the previous funding period.

**Elucidation of the role of viral load and variants in the persistence and progression of HPV infections**
(Winer et al., Sex Transm Dis, 2012; Martin et al, J Clin Virol, 2013; Xi et al, J Infect Dis, 2011; Xi et al, Int J Cancer, 2013; Xi et al, J Infect Dis, 2009). WCRP members Dr. Nancy Kiviat, Professor, Pathology, UW, with Dr. Rachel Winer (Asstistant Professor, Epidemiology, UW) reported that both recent and cumulative sexual history are associated with prevalent HPV infection in high-risk mid-adult women. Dr. Kiviat also reported that novel HPV types can be isolated from oral rinse samples collected from healthy individuals. These findings have important implications for timely detection of HPV infection. Using an assay developed in the previous funding cycle (Feng et al, J Clin Microbiol, 2009), she has also determined that HPV viral load at detection predicts progression to CIN3, which has implications for the control of cervical cancer in the U.S. and worldwide. Working with Dr. Denise Galloway (Global Oncol/FHCRC), she conducted a nested case-control study, reporting that among those with a persistent HPV-16 infection, changes in viral load predicted subsequent and/or underlying CIN3. In related work, she reported that prevalent infection associated with a higher HPV-16 or HPV-18 viral load was associated with short-term but not long-term persistence, and recently she reported that variant C of HPV-31 is more likely to be associated with persistent infection than is variant B, and that C variants were less likely to clear than A variants in African-American women. Measurement of viral load and variants in newly detected HPV infection promises to guide clinical decisions in the control of cervical cancer. Dr. Kiviat has a related grant (NCI R01 CA157469) to continue her work in detection and diagnosis of HPV infection as it relates to prevention of cervical cancer.

**Development of a small recombinant protein that has the potential to enhance the efficacy of monoclonal and chemotherapeutic agents** (Wang et al., Nature Medicine, 2011; Beyer et al., Cancer Research, 2011; Beyer et al., Clinical Cancer Research, 2012). Dr. Andre Lieber, Professor, Medical Genetics UW, has developed a small recombinant protein (JO-1) that can transiently open tight junctions between epithelial tumor cells. JO-1 co-therapy has the potential to enhance the efficacy of chemotherapeutics and monoclonal antibodies in breast and ovarian cancer patients by increasing intratumoral drug penetration and unmasking of target receptors. His group has shown in animal models that JO-1 co-therapy allowed for lowering the effective dose of drugs, which in turn reduced adverse side effects associated with monoclonal antibodies and chemotherapeutics. In a number of xenograft tumor models including orthotopic triple-negative breast and high-grade serous ovarian cancer models, intravenous injection of JO-1 improved the efficacy of Herceptin, Erlitux, Abraxane, and Doxil. The administration of JO-1 combined therapy was shown to be safe in
adequate transgenic mouse models and in non-human primates. He is currently developing Phase I clinical trials to test the safety of combined Doxorubicin and JO-1 in ovarian and breast cancer. He has begun such a trial in non-human primates in the Ovarian SPORE and plans a Phase I trial in ovarian cancer patients in collaboration with Dr. Charles Dresher (WCRP) next cycle (competing renewal application was submitted in September, 2013). Dr. Lieber has used and will continue to use the Northwest BioTrust shared resource, and will use the Therapeutic Manufacturing shared resource to produce clinical grade drug for use in human trials. He has several related grants (NCI R01CA136487; R01CA144057-08S1A1; R01 HLA078836) to complete the translational work required to make this exciting new agent available to patients.

**Comprehensive genetic testing to identify women with inherited mutations beyond those determined as BRCA1/2.** (Walsh et al, PNAS, 2011; Wickramanayake, Gynecol Oncol, 2012). Dr. Elizabeth Swisher has reported compelling evidence that comprehensive genetic testing for inherited carcinoma is warranted for all women with ovarian, peritoneal, or fallopian tube carcinoma, regardless of age or family history. Using the BROCA assay, developed by Dr. Mary Claire King's lab and based on targeted capture and massively parallel genomic sequencing, her group evaluated inherited mutations in 360 women with primary ovarian, peritoneal, or fallopian tube carcinoma, unselected for age or family history. Of 360 subjects, 24% carried germ-line loss-of-function mutations: 18% in BRCA1 or BRCA2 and 6% in BARD1, BRIP1, CHEK2, MRE11A, MSH6, NBN, PALB2, RAD51C, or TP53. Subsequently, her group identified an additional 1% of cases with inherited RAD51D mutations. She recently extended these analyses to 1412 cases of ovarian carcinoma, with similar findings (ASHG annual meeting October 2013), demonstrating that 28% of clinically significant inherited mutations occurred in genes other than BRCA1/2. Furthermore, Lynch syndrome was rare (0.4%) and is not the next most common contributor after BRCA1/2 to hereditary ovarian cancer as has been widely accepted. The next most common contributors to hereditary ovarian cancer include BRIP1 (present in nearly 2% of unselected cases), RAD51C, RAD51D, and PALB2The known relative risks for ovarian cancers for mutations in these genes are clinically actionable. For example, RAD51D and BRIP1 confer a 6-8 fold relative risk (i.e. 10-15% lifetime risk), a risk level that should be managed by age appropriate risk reducing salpingo-oophorectomy. Therefore, more comprehensive genetic testing for all women with ovarian, peritoneal or fallopian tube carcinoma would provide information that could be used in at least three ways for clinical benefit: 1. inform the patient about risk of other cancers. 2. influence the choice of therapy, including PARP inhibitors and repeat use of platinum chemotherapy and 3. inform unaffected family members who could then be tested for inherited risk and adopt appropriate risk reducing strategies when indicated.

In their project in the Ovarian SPORE, Dr. Swisher and colleagues demonstrated that both somatic and germ line mutations in ovarian carcinomas in genes in the Fanconi anemia-BRCA DNA repair pathway strongly correlate with improved primary response to platinum chemotherapy and longer overall survival (Pennington et al, Clinical Cancer Research, 2013). In the SPORE collaboration with Dr. Taniguchi’s group at FHRC, the group also demonstrated that secondary mutations of BRCA1/2 that cancel the effect of the initial BRCA1/2 mutations and restore BRCA1/2 protein expression occur in about 40% of platinum-resistant recurrent ovarian carcinomas in BRCA1/2 mutations carriers, suggesting that this is one of the major mechanisms of clinical acquired platinum resistance (Norquist et al, J Clin Oncol, 2011). The popular dogma has emphasized that defects in this DNA repair pathway are more common in the subset of ovarian carcinomas with high-grade serous histology. However, Dr. Swisher found Fanconi anemia-BRCA mutations equally often in serous and non-serous ovarian carcinomas. These data have influenced design of current PARP inhibitor trials; Clovis Oncology used these data to justify broadening entry criteria for the Ariel 2 and Ariel 3 international clinical trials beyond high-grade serous ovarian carcinomas. Drs. Swisher and Taniguchi have used and will continue to use the Northwest BioTrust shared resource in their work.

**HE4 outperforms imaging in screening for epithelial ovarian cancer.** Dr. Nicole Urban has recently reported that, because of a strong effect of age on levels of serum marker human epididymis protein 4 (HE4), HE4 positivity thresholds are best defined for specific ages (Urban et al, CEBP, 2012). She has also reported that HE4 outperforms imaging in screening for epithelial ovarian cancer. Unnecessary surgery can be reduced by limiting use of transvaginal ultrasound (TVU) to women with increasing CA125 serum levels; replacing or augmenting TVU with measurement of HE4 further improves screening performance. Serum samples from 112 invasive ovarian cancer patients and 706 matched control subjects from the Prostate, Lung, Colon, and Ovary trial were used to evaluate HE4 for its potential use in screening. TVU results were available for a subset of 84 patients and 516 control subjects used to compare HE4 with TVU. HE4 was found to perform better than TVU as a second-line screen, confirming 27 of 39 cancers with increasing CA125 serum levels compared with 17
cancers confirmed by TVU \((P = .03)\). Serum HE4 levels were found to increase with age and smoking status, suggesting that a longitudinal algorithm might improve its performance (Urban et al, JNCI, 2011). This approach is currently being evaluated in a Phase I trial in the Ovarian SPORE (NCI P50 CA083636) led by Dr. Urban, who contributes to the Northwest BioTrust shared resource as part of this work.

**Contraceptive depo-medroxyprogesterone acetate, antihypertensives and lipid lowering medications increase and bisphosphonates affect risk of breast cancer.** Dr. Christopher Li (WCRP) in collaboration with Drs. Malone (CEPC) and Porter (WCRP) reported that current use of the injectable contraceptive depo-medroxyprogesterone acetate for a year or longer is associated with a 2.2-fold increased risk of breast cancer among premenopausal women in the first U.S. based study to evaluate this relationship. (Li, Cancer Research, 2012) In another study Dr. Li, Dr. Malone, and their colleagues reported that use of bisphosphonates reduces risk of second primary contralateral breast cancer among breast cancer survivors. (Monsees, JNCI, 2011) Most recently this team has reported that use of particular types of antihypertensives (Li, JAMA Internal Medicine, 2013) and lipid lowering medications (McDougall, CEBP, 2013) are associated with risk of postmenopausal breast cancer. Continuing work on breast cancer early detection biomarker discovery, Dr. Li and colleagues observed that the proteins involved in the glycolytic pathway are as a group more abundant in preclinical plasma of women who subsequently developed ER+ breast cancer compared to controls (Amon, Cancer Research, 2012). Further, in experiments focused on triple-negative cancer he and his colleagues reported on a set of 29 novel candidate biomarkers that distinguished between women who went on to develop triple-negative breast cancer from controls (Li, Breast Cancer Res Treat, 2012). Dr. Li has used and will continue to use the Northwest BioTrust shared resource for this work. Evaluation of these markers is ongoing in the clinical biomarker validation center (NCI U01 CA152637).


A highly translational research effort funded by NCI Breast SPORE grant involves close collaboration between investigators from the Program in Immunology and Vaccine Development (Drs. Salazar and Riddell), the Women’s Cancer Program (Drs. Gadi and Gralow). Dr. Riddell and Dr. Salazar are co-PI’s on the project and Dr. Gralow is the Core Leader for the Clinical Core of the Breast SPORE. This interdisciplinary group initiated a clinical trial of a Her2/neu vaccine in patients with advanced Her-2 positive breast cancer with the objective of determining the phenotype, function, and qualitative properties of CD8+ T cells elicited by vaccination. The patients received their vaccinations and leukapheresis utilizing resources provided by the ITHS (CTSA; P.I. Dr. Nora Disis). Rigorous cell selection methods were used to demonstrate that robust CD8+ central memory T cell responses develop after vaccination and the quality of these T cells is now being examined using a novel \(K_{\text{off}}\) rate assay to provide a measure of T cell receptor avidity. These studies may provide rationale for combining vaccination with tumor-specific antigens to elicit T cell responses that can be expanded ex vivo for adoptive T cell transfer, and have the capacity to persist long term after transfer and mediate potent tumor recognition.

A second focus of this project is the identification of novel targets for adoptive immunotherapy of breast cancer using genetically modified T cells. We have developed chimeric antigen receptors (CARs) that recognize the orphan tyrosine kinase receptor ROR1, which we had previously identified as being on the surface of B cell malignancies, and has now been shown to be expressed on many epithelial malignancies including triple negative breast cancer. CAR-modified T cells recognize tumor cells independent from HLA, and can be utilized to treat all of the patients with a tumor type that expresses the target molecule. We have evaluated ROR1 CARs of different epitope specificities, affinities, and with distinct intracellular signaling domains, and demonstrated efficient recognition of ROR1+ breast cancers in vitro and in vivo in immunodeficient mice. CARs constructed from a high affinity scFv (R12) were superior for tumor elimination to CARs constructed from a lower affinity scFv (2A2). Preliminary safety studies in mouse and non-human primate models have not shown toxicity to normal tissues, and if confirmed we will conduct a phase 1 clinical trial of ROR1 CAR T cells in patients with advanced ROR1+ malignancies. This effort involves CCSG Shared Resources for Research Pathology and Therapeutic Manufacturing, institutional resources for flow cytometry, and other resources for clinical research through the ITHS (local CTSA).

**Breast Imaging.** Members of the imaging group and Women’s Program have long-standing collaborative efforts that support the program aims. The breast-imaging group is exploring improvements in breast cancer diagnosis and response to treatment through standard clinical breast imaging, MR and PET. The MR group
evaluates new imaging techniques to reduce false-positive results and unnecessary biopsies. A project in the molecular imaging P01 (5P01CA042045; P.I. Ken Krohn) is testing the use of 18F-FES PET to choose therapy in patients with a history of ER+ breast cancer who have failed prior regimens and are being considered for salvage endocrine therapy (see accomplishment below). The project is also imaging androgen receptor function in prostate cancer to identify heterogeneous AR expression.

**Quantitative FDG positron emission tomography (PET) predicts response to aromatase inhibitor in breast cancer** (Linden, Clin Cancer Res, 2011). Dr. Hannah Linden, Associate Professor Medical Oncology UW, has worked closely with Dr. Ken Krohn (WCRP) and the nuclear imaging group to advance the clinical use of PET imaging. They have shown that quantitative FDG PET predicts response to aromatase inhibitor and correlates with Ki-67 in early breast cancer; a similar trial using 3'-[18F]fluoro-3'-deoxythymidine (FLT) is underway, given the potential for this tracer to more tightly correlate with tumor proliferation. They have developed 18F-fluorostradiol (FES) under IND and shown it predicts response to untreated metastatic breast cancer, correlates with ER expression by IHC, and effectively demonstrates physiologic blockade of the ER by targeted endocrine agents. They have shown that ER expression, measured by FES, is modulated by HDAC inhibition and have open an investigator initiated clinical trial of vorinostat, an HDAC inhibitor, to restore sensitivity to endocrine therapy partnered with an imaging biomarker study using serial FES as part of a P01 (P.I. Dr. Kenneth Krohn) in molecular imaging. Dr. Linden is the PI for a multicenter FES biomarker study with Farrokh Dehdashti (Wash U) through ECOG ACRIN, having completed a single institution study IND in the Consortium (Peterson, Mol Imaging Biol, 2013).

In additional collaborations between WCRP oncology and imaging members Dr. Jennifer Specht and Dr. Mankoff (former) found that tumor metabolism and blood flow assessed by PET varies by tumor subtype in locally advanced breast cancer and that a metabolism and blood flow mismatch predicts resistance to chemotherapy (Specht et al., Clin Cancer Res, 2010). These imaging findings, led to the hypothesis that metabolism/perfusion patterns associated with therapeutic resistance are manifestations of metabolic flexibility, defined as the ability to alter energy metabolism pathway utilization in response to cellular stress. This hypothesis is being tested in one of the breast SPORE projects led now by Dr. Specht and Dr. David Hockenbery (Cancer Basic Biology).

### 3. Research that relates to health problems in the catchment area

**Therapeutic catchment area**

According to data provided by the Centers for Disease Control, incidence of ovarian and breast cancer is relatively high in Washington State: In 2010, Washington State had the third highest ovarian cancer incidence rate in the U.S., 13.3 cases per 100,000 women compared to an average of 11.4 in the U.S. overall, and the sixth highest invasive breast cancer incidence rate, 129.0 cases per 100,000 women compared to an average of 118.7 in the U.S. overall. Mortality rate rankings were much better, at 12th for ovarian cancer and 35th for breast cancer, hopefully reflecting early detection and exemplary care provided by the Consortium. The therapeutic catchment area is defined as the 13 counties of Western Washington, because nearly 70% of SCCA treated patients come from this area. The program makes sure that both treatment trials and screening trials reach patients in the catchment area. To facilitate access to treatment trials, the Puget Sound Oncology Consortium (PSOC), based at FHCRC, has affiliate sites throughout the region that can enroll patients to breast and gynecologic oncology clinical trials. The PSOC Gynecologic Committee, including academic and private practice physicians, meets twice a year to review potential trials and accrual to ongoing studies. The SCCA Network also makes trials available in breast and ovarian cancer, and PHS coordinates screening trials in collaboration with the Marsha Rivkin Center. For example, to facilitate access to early detection and prevention trials, the Ovarian SPORE reaches out to all of Western Washington in recruitment for its Novel Markers Trial (Project 1). Western Washington residents account for 778 of the 829 participants at the Seattle clinical site for this Phase I screening trial. An advocate makes special efforts in Bellingham. Enrollment in this screening trial by county is reported in Table 1.

### Table 1. Participation in the Novel Markers Trial by Residents of Western WA:
<table>
<thead>
<tr>
<th>COUNTY</th>
<th>RESIDENTS</th>
<th>COUNTY</th>
<th>RESIDENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clallam</td>
<td>4</td>
<td>Mason</td>
<td>1</td>
</tr>
<tr>
<td>Grays Harbor</td>
<td>2</td>
<td>Pierce</td>
<td>21</td>
</tr>
<tr>
<td>Island</td>
<td>10</td>
<td>San Juan</td>
<td>5</td>
</tr>
<tr>
<td>Jefferson</td>
<td>5</td>
<td>Skagit</td>
<td>5</td>
</tr>
<tr>
<td>King</td>
<td>605</td>
<td>Snohomish</td>
<td>69</td>
</tr>
<tr>
<td>Kitsap</td>
<td>24</td>
<td>Thurston</td>
<td>11</td>
</tr>
<tr>
<td>Lewis</td>
<td>3</td>
<td>Whatcom</td>
<td>13</td>
</tr>
</tbody>
</table>

The Safeway/Seattle Cancer Care Alliance Mobile Mammography Van, directed by Dr. Constance Lehman (CEPC), is a key inter-programmatic resource that provides screening to more than 4,000 women per year, especially to underserved women and in underserved neighborhoods in our catchment area. Our state-of-the-art digital mammography van provides a convenient way for many women to gain needed access to high-quality mammograms at local Safeway stores, healthcare facilities and other convenient community locations. In the first two quarters of 2013, 2271 women were screened, including those in underserved communities at Harborview Medical Center, NeighborCare High Point Community Health Center, NeighborCare Rainier Park Community Health Center, Sea Mar CHC Seattle, Sea Mar CHC Burien, Ethiopian Cultural Center, Center for Multicultural Health, St. Elizabeth Seton Catholic Church and Safe Harbor Free Clinic. Improvements in screening rates of Hispanic women at the SeaMar clinics is the focus of one of the projects in Beti Thompson’s Center for Population Health and Health Disparities grant (CPHHD; NIH/NCI P50 CA148143).

The SCCA is recognized as a national leader in the delivery of cancer survivorship care, and its Women’s Wellness Clinic helps incorporate women’s experiences as cancer patients — and as cancer survivors — into their post-cancer treatment regimen. The clinic provides follow-up, with a focus on total health and wellness, for breast cancer and gynecologic oncology patients. This follow-up care includes screening for cancer recurrence, supporting patients through the long-term complications of treatment, and dealing with other health issues affecting cancer survivors. It also includes nutritional advice, physical therapy, psychiatry/therapy services and rehabilitation therapy. Many investigator-initiated and multi-institutional studies are being conducted in the survivor population including: SWOG (limited institution) S1200: “Acupuncture vs sham acupuncture for aromatase inhibitor-induced arthralgia” (Columbia/Gralow); SWOG (limited institution) S1008 “Curves weight loss intervention study” (Columbia/Gralow); SWOG S0812 “Phase IIb randomized controlled biomarker modulation study of vitamin D in premenopausal women at high risk for breast cancer” (Gralow); “Randomized trial of cognitive rehabilitation in cancer survivors” (Cherrier); “Hypnosis for symptom management in breast cancer survivors” (Jensen); “Young and Strong: An education and supportive care intervention study for young women with breast cancer” (Dana Farber/Korde); “Pregnancy after breast cancer: randomized trial of timing of tamoxifen in young women desiring fertility” (Farber/IBCSG/Korde); “Low Dose tamoxifen in Hodgkin lymphoma survivors for breast cancer risk reduction: a randomized phase Ib placebo-controlled study” (COH/Korde); “Flax/lignan in breast cancer prevention” (U Kansas/Korde); HEAL study (Healthy Eating, Activity and Lifestyle) in breast cancer survivors (McTiernan, CEPC).

The SCCA Women’s Wellness Program is a nationally recognized model for post-cancer care that provides cancer patients with regular newsletters and lectures, as well as access to weekend wellness retreats. We currently partner with Harmony Hill Retreat Center on Hood Canal in Kitsap County in a series of retreats at their facility and are hosting several one-day mini-retreats at SCCA House to provide more local opportunities for cancer survivors to participate.

4. Future Plans

The Ovarian SPORE was submitted for competitive renewal in September 2013. The new portfolio includes a project to examine the role of salpingectomy in ovarian cancer prevention (Urban). To intervene as early as possible in high-risk women, and to apply a successful prevention intervention more widely, a Phase I/II RCT that compares intensive and conventional risk assessment, prevention and surveillance strategies will be conducted. The portfolio also includes Dr. Lieber’s project to conduct a Phase I clinical trial of combined PEGylated liposomal doxorubicin and JO1 in ovarian cancer, Drs. Swisher and Taniguchi’s project to investigate the relationship between newly identified inherited susceptibility genes and response to PARPi, and Dr. Drescher’s collaboration with Dr. Gambhir (Stanford University) to evaluate use of photoacoustic imaging in diagnosis of ovarian cancer.
The breast SPORE competing renewal will be submitted for competitive renewal in September 2014. It is already in the planning stages and is expected to include a continuation of the very innovative immunotherapy trials to test oncofetal orphan tyrosine kinase receptor ROR1 as a candidate target for CAR T-cell therapy in triple negative breast cancer and NY-BR-1 T cell receptor for treatment of ER-positive breast cancer. New translational projects are being considered including a breast cancer trial of combined PEGylated liposomal doxorubicin and JO1 that will be complementary to the planned ovarian SPORE project.

Dr. Eric Holland was recently recruited from Memorial Sloan Kettering Cancer Center to lead Solid Tumor Translational Research across the Consortium, with leadership positions at FHCRC and UW. Dr. Holland has begun working with solid tumor program leaders, including Drs. Porter and Urban, to identify recruitment and resource needs, and opportunities for increasing collaborative research within and among solid tumor programs.

Program leadership will continue an active agenda to sponsor seminar series and workshops that promote integration of Women’s Cancer activities and scientific aims as well as collaboration among all WCRP members and with members of other programs. The breast and ovarian SPORE mechanisms, along with philanthropic funds, will continue to provide support for innovative pilot projects that have potential for developing into multi-investigator translational breast cancer research. The program leaders and co-leaders will continue to build biospecimen resources, to participate together in both breast and ovarian review committees for pilot and career development awards and serve on advisory boards for the SPORE grants.
Population Sciences

Biostatistics Shared Resource

Introduction
Within the Cancer Consortium, approximately 100 biostatisticians (approximately half at the Ph.D. level and half at the MS level) are involved full-time in ongoing Consortium-associated projects. Most of these statisticians are engaged in large-scale studies such as the Southwest Oncology Group (SWOG), the Women’s Health Initiative (WHI), the Early Detection Research Network (EDRN) and the Statistical Center for HIV/AIDS Research and Prevention (SCHARP), and are not directly available to investigators outside of these projects. The Biostatistics Shared Resource (BSR) provides no-charge statistical support for smaller projects that are unable to engage full time dedicated statisticians. The resource is not used to support research in statistical methodology. The BSR received an outstanding assessment in the 2008 competitive renewal. Barry Storer, Ph.D., the resource director, now heads only one Shared Resource (2008 critique).

The staff is divided between statisticians based in both the Fred Hutchinson Cancer Research Center (FHCRC) Clinical Research (CRD) and Public Health Sciences (PHS) divisions. Dr. Storer oversees the Clinical Statistics group within the CRD. Sarah Holte, Ph.D. coordinates the activities of the statisticians based in PHS; however, the BSR provides support for members from all Consortium institutions.

The CCSG support for this shared resource ensures that a stable biostatistics staff is available to Consortium investigators to support projects that require only a short-term level of support, and to provide assistance to investigators developing new or continuing proposals.

Nearly all of the faculty who are part of the BSR are also part of the Biostatistics and Computational Biology Program and pursue research interests in statistical methodology. These research interests are frequently stimulated by collaborative interactions (e.g., in the evaluation of medical diagnostic tests, the design of Phase I trials, or the analysis of biomarkers and genomic array data). Although this methodological research is not considered part of the shared resource effort, the interactive collaboration often provides the impetus for methodological development which, in turn, enhances the support provided to other scientists.

Major Services

Facilities and Equipment
The BSR employs seven PhD and four MS level statisticians who jointly provide approximately 10 FTEs of collaborative statistical support to the Consortium. Five of these individuals (Storer, Gooley, Leisenring, Redman, and Xie) are primarily affiliated with the FHCRC CRD; the remaining staff members (Holte, Randolph, Wang, Copeland, Xiao, Zheng) are affiliated with the FHCRC PHS, and all statisticians have offices at FHCRC.

Each statistician can connect via local and FHCRC data networks to UNIX workstations. Statisticians based in the FHCRC CRD are connected to the ALPHA cluster housing the transplant database. Available statistical software includes: SAS, Splus, R, Minitab, Stata, MatLab, NQuery and StatExact. A statistical library is available at FHCRC as well as at the University of Washington.

Technologies and Expertise
The BSR provides no-charge collaborative statistical support to Consortium members in all of the Consortium research programs outside of Biostatistics and Computational Biology, including Hematologic Malignancies, Immunology and Vaccine Development, Prostate, Women’s and GI Cancer, Global Oncology and Cancer Epidemiology Prevention and Control. Such support may include any or all of the following: selection of primary and secondary endpoints, study design, sample size and power calculations, randomization procedures, design of data collection instruments, design of early stopping criteria, interim monitoring, data retrieval and analysis and manuscript preparation and review. The resource emphasizes the importance of establishing ongoing and continuing collaboration with biostatisticians during the entire research effort, rather than one-time consultation without appropriate context. Most of the funding for this collaborative effort comes from research grants and contracts. The qualifications and expertise of the seven Ph.D. staff are described in greater detail below. The four MS level statisticians work in conjunction with and are supervised by the Ph.D. staff members.
It is important to note that the staff of the BSR work within and have access to a much larger community of highly productive and creative statisticians, both in the Biostatistics and Computational Biology Program of the Consortium, and in the University of Washington Department of Biostatistics.

**Importance to Scientific Programs**
The BSR interacts with scores of different investigators, representing almost all of the Consortium programs. Each year they co-author 80-100 collaborative publications and assist with the development of numerous peer-reviewed grant proposals. Below we describe some specific examples of interactions with Consortium investigators. These are selected to illustrate interactions for which statistical support has been possible solely through CCGS support for the shared resource.

**Paul Nghiem, MD, PhD, UW Department of Medicine, Global Oncology**


A comprehensive review of staging criteria for Merkel cell carcinoma was undertaken, based on over 5000 cases extracted from the National Cancer Data Base. Dr. Storer performed all of the statistical analysis for this project. Patients with clinically local-only disease and pathologically proven negative nodes had better outcome than those who were node negative based only on clinical nodal evaluation. More routine pathologic nodal evaluation may be indicated in many cases as it improves prognostic accuracy and has important treatment implications for those found to have microscopic nodal involvement.

**Thomas Spies, PhD, FHCRC Clinical Research Division, Hematologic Malignancies**


The stimulatory natural killer group 2 member D (NKG2D) lymphocyte receptor and its tumor-associated ligands are important mediators in the immune surveillance of cancer. With advanced human tumors, however, persistent NKG2D ligand expression may favor tumor progression. Working with Dr. Gooley, the potential association was examined among 60 women with breast or ovarian cancer, and found statistically significant correlations between mean percentages of NKG2D+ cancer cells and tumor stage, tumor size/spread, and lymph node status. Together, these results provide ex vivo correlative evidence associating NKG2D expression with criteria of tumor progression, thereby lending support to its tumor growth factor receptor-like stimulatory functions.

**Steven Pergam, MD, MPH, FHCRC VID Division, Immunology and Vaccine Development**


A cohort of umbilical cord blood transplant (UCBT) patients who were CMV seropositive prior to transplant was studied to evaluate the outcomes of a new intensive preemptive ganciclovir prophylactic therapy protocol. Dr. Leisenring performed the statistical analysis for this project. Hazard rates and cumulative incidence of CMV complications along with days treated were compared in high-risk CMV seropositive UCBT recipients who received the new intensive strategy and a historical cohort who received a standard strategy. The intensive strategy resulted in reduced CMV reactivation and CMV disease rates. In addition, among those who reactivated, the intensive strategy led to fewer days on CMV-specific antiviral therapy.

**Jon Cooper, PhD, FHCRC Basic Sciences Division, Cancer Basic Biology**


Dr. Randolph worked with members of the Cooper lab on this project that established new aspects of the mechanisms of endocytosis. Endocytic mechanisms play a role in tumor cell migration, and endocytic adaptor proteins facilitate cargo recruitment and clathrin-coated pit nucleation. This study showed that Dab2, an endocytic adaptor, plays an important role and suggests that Dab2-mediated recruitment of EH domain proteins selectively drives the internalization of integrin β1.
Rachel Ceballos, PhD, FHCRC PHS Division, Cancer Epidemiology, Prevention and Control
Dr. Holte worked with Dr. Ceballos to develop a successfully funded grant proposal (NIH/NCI K01CA154938) to address a significant gap in levels of distress and quality of life experienced by Hispanic cancer survivors living in rural communities using a biopsychosocial approach. The project includes development of a culturally-appropriate support program for post-treatment cancer survivors, followed by, a randomized control trial in which the program is implemented and evaluated. This grant also supports the training and career development of Dr. Ceballos as an independent junior investigator.

Eric Chow, MD, MPH, Seattle Children’s, Hematologic Malignancies
Dr. Leisenring collaborated with Dr. Chow to develop a successfully funded grant proposal in cancer survivorship (Leukemia and Lymphoma Society 6243-13). Given the critical role anthracyclines have in many effective cancer treatments and the risk for subsequent cardiotoxicity associated with this class of agents, development of an effective cardioprotective strategy is of great importance. Although adult studies have shown that dexrazoxane (DRZ) is effective in minimizing cardiomyopathy/heart failure after anthracycline therapy, short and long-term data in children are much more limited. To address these gaps in knowledge, using a cross-sectional study design, we propose to prospectively ascertain echocardiographic and serum biomarkers of cardiac injury in a cohort of long-term pediatric T-cell leukemia and Hodgkin lymphoma survivors enrolled on 3 front-line Children’s Oncology Group) clinical trials that featured upfront DRZ randomization and a range of anthracycline exposures commonly used in contemporary. The primary aim of this research is to determine whether patients randomized to the experimental DRZ arms have decreased markers of myocardial injury compared with patients treated without DRZ.

Betty Thompson, PhD, FHCRC PHS Division, Cancer Epidemiology, Prevention and Control
Dr. Holte provided statistical support for a proposal involving collaboration between New Mexico State University (NMSU), a minority-serving institution, and the Fred Hutchinson Cancer Research Center (FHCRC), a comprehensive cancer center, to expand the current regional cancer program at NMSU and to increase knowledge and attention to cancer related health disparities at FHCRC and NMSU. This proposal was successfully funded (NIH/NCI U54CA153502). Dr Holte provides statistical guidance and support for all proposed and new projects. Since one of the primary goals of the program is to provide a mentorship mechanism for junior investigators, Dr. Holte will mentor these junior investigators in the process of establishing collaborative relationships with trained statisticians.

Elizabeth Swisher, MD, UW Department of Medicine, Women’s Cancer
Dr. Storer worked with Dr. Swisher to develop a successfully funded grant proposal (DOD OC120312) evaluating the role of BRCA mutation status in the treatment of patients with ovarian cancer. Preliminary data from other studies have suggested that maintenance therapy with bevacizumab does not prolong progression-free survival in patients with the BRCA mutation, in contrast to those with the wild-type gene. This proposal will more formally evaluate this hypothesis in a large study of 950 women being treated with and without bevacizumab maintenance.

Johanna Lampe, PhD, FHCRC PHS Division, Cancer Epidemiology, Prevention and Control
Dr. Randolph worked with Drs. Lampe and Hullar in developing a large, multi-institutional (Harvard, USC, U Hawaii, FHCRC) proposal that was successfully funded (NIH/NCI P01CA168530). This study measures body fat and aims to identify blood biomarkers and lifestyle behaviors that predict body fat distribution in a multiethnic population in order to test their associations with risks of breast and colorectal cancers. Project 4 (FHCRC) focuses on “Associations of Gut Microbiome Predictors of Body Fat Amount and Distribution with Intermediate Cancer Phenotypes”. Dr Randolph’s expertise in multivariate and high-dimensional statistical methods was a key contribution to both Project 4 and the Data Analysis Core (U Hawaii).

Mary Anne Rossing, PhD, DVM, FHCRC PHS Division, Cancer Epidemiology, Prevention and Control
Dr. Randolph collaborated with Drs. Rossing and Doherty in preparing a successfully funded grant application (NIH/NCI R01CA168758) to study distinct molecular subtypes of epithelial ovarian cancer. Classification models will be developed to examine epidemiologic risk and survival differences among ovarian cancer subtypes, including four newly recognized subgroups of high-grade serous ovarian cancer.
Cost Effectiveness
The CCSG budget for the BSR provides salary support for eleven biostatisticians (7 Ph.D. and 4 M.S.) that assist with statistical support to Consortium investigators. The remainder of the effort is supported by grants and contracts for which the staff member is providing dedicated effort.

The CCSG support for the shared resource comprises only a small fraction (less than 5%) of the overall statistical effort available within the Consortium; however, the leveraged CCSG funds shared play a critical role in supporting projects and programs that cannot hire and provide long-term support to one or more full-time statisticians. The CCSG support ensures that a stable biostatistical staff is available to all Consortium investigators, and in particular provides a resource to support projects that require only a small level of biostatistical support or support on an occasional basis, and to provide assistance to investigators developing new or continuing proposals.

One measure of the effectiveness and productivity of the shared resource is in publications where a biostatistician is included as a co-author. It is only an approximate measure of activity, as the number of publications resulting from an interaction does not necessarily correlate with the amount of effort entailed. Also, the inclusion of a statistical collaborator as a co-author is at the discretion of the primary author, and policies vary. Current and past shared resource members were named as co-authors on 83 cancer-related collaborative publications with Consortium members, published or in press from 2012-2013. This total excludes publications related to statistical methodology, publications related to large national projects with which the member was involved, or publications with collaborators entirely from outside the Consortium institutions. The same set of publications involved co-authorship with 93 different members of the Consortium’s research programs, representing all of the Consortium research programs outside of Biostatistics and Computational Biology. Consortium members based outside the FHCRC accounted for approximately one third of the collaborations. The table below summarizes this interaction by tabulating the number of members from each program who were co-authors with BSR members, and the number of publications involved.

Co-authorship of BSR members with other Consortium members during 2012-2003

<table>
<thead>
<tr>
<th>Research Program</th>
<th># of members</th>
<th># of pubs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Epidemiology, Prevention and Control</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Cancer Basic Biology</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>GI Cancer</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Global Oncology</td>
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<td>12</td>
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<tr>
<td>Hematologic Malignancies</td>
<td>44</td>
<td>59</td>
</tr>
<tr>
<td>Immunology and Vaccine Development</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Unaligned</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Women’s Cancer</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

sum of 124 exceeds 83 because many publications involved co-authors from more than one program

Usage of Resource

<table>
<thead>
<tr>
<th>Service</th>
<th>Consortium Users</th>
<th>Peer-Reviewed</th>
<th>Non-Peer Reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-authored Collaboration</td>
<td>93</td>
<td>72 (77.4%)</td>
<td>21 (22.6%)</td>
</tr>
</tbody>
</table>

Management Structure, Policies and Operations
Administration
Dr. Storer has overall responsibility for the functioning of the BSR, and formally supervises the members who are part of Clinical Statistics in consultation with Paul Woloshin, MBA, Ph.D., Consortium Shared Resources Director. Dr. Holte serves as a liaison and manager for the shared resource members within the PHS group.
However, all faculty of the shared resource may receive direct requests for collaboration and may use their own discretion in responding. Once a week, the respective shared resource staffs gather for a meeting where they exchange information about new requests for support that have been received and discuss continuing projects. This communication ensures that effort is allocated fairly among the staff, taking into account other project and shared resource assignments. The meetings also provide a useful forum for brainstorming statistical problems and sharing ideas. Drs. Storer and Holte work closely together to ensure that effort is balanced between the two groups, and that there are no gaps in support for Consortium members.

The BSR has an advisory committee comprised of the following faculty: Paul Martin, M.D., Hematologic Malignancies, Kim Margolin, M.D., not programmatically aligned, Peggy Porter, M.D., Women’s Cancer, Michael LeBlanc, Ph.D., Cancer Epidemiology, Prevention and Control. The advisory committee meets annually to discuss overall BSR direction and progress.

Access and Usage Policy
The BSR is available to all Consortium members. Members seeking statistical support may contact either Dr. Storer or Dr. Holte, who will refer them to the faculty or staff member best suited to the project in terms of needs and availability of effort. Members are also free to contact individual faculty and staff within the shared resource, particularly if a prior or ongoing collaborative relationship has been established. The BSR is not available to external customers.

Billing
No fees are charged to Consortium members; however, whenever the statistical support required for a project is substantial and continuing, every effort is made to secure committed funding from that project. Shared resource staff will assist members in the preparation of grant proposals and projects with the expectation that committed effort for biostatistical collaboration that exceeds a minimal level will be budgeted in such proposals. The success of this approach is reflected in the fact that over 80% of the collaborative effort of the shared resource personnel is funded by research grants and contracts and less than 20% through the CCSG.

Education and Outreach
Users and potential users are kept up to date on changing technologies and services offered by the facility through the FHCRC and Consortium websites, Shared Resource Newsletter, and special memo distributions. Outreach to the broader Consortium community, particularly those within the UW and Seattle Children’s Hospital, will be enhanced through the activities of the Institute of Translational Health Sciences (ITHS). As an ITHS approved facility, it is anticipated that the Resource will play an ongoing and expanded role in support of translational research activities.

Priorities and New Initiatives
Priority is given to Consortium members working on cancer-related projects, who have or are seeking peer-reviewed funding. In particular, junior faculty seeking research funding are a priority. Support for non-cancer projects or for unfunded projects may be provided as time permits. Historically, the shared resource has been able to respond to virtually all requests, and formal prioritization has been unnecessary.

Future priorities for the resource itself are to make sure that the faculty and staffs funded via this mechanism maintain an ongoing interest in collaborative science, and that the combined expertise among the shared resource staff is sufficiently diverse to support all of the needs of Consortium members. In particular, there is a need to maintain expertise and training in the design and analysis of “omics” studies, and the use of electronic medical records in comparative effectiveness research.

Personnel
Key staff qualifications
Barry Storer Ph.D., Resource Director, joined the FHCRC in 1995 as Director of Clinical Statistics for the Clinical Research division. He is a Member of the FHCRC and an Affiliate Professor at the University of Washington. Dr. Storer received his Ph.D. in Biostatistics from the University of Washington in 1984 and served for 11 years on the faculty of the University of Wisconsin-Madison and as a member of the University of Wisconsin Comprehensive Cancer Center. Dr. Storer is an author or co-author on nearly 300 publications. He
will devote half of his allocated effort to this resource as core leader and half as a biostatistician. **Expertise:** clinical trial design and analysis, survival analysis with competing risks, analysis of transplant studies.

_Sarah Holte, Ph.D. Manager_, received her Ph.D in Mathematics from the University of Oregon in 1990. After serving for 3 years on the faculty of the University of Missouri-Rolla Department of Mathematics she completed post-doctoral training in Biostatistics at the University of Washington in 1995. Since then she has served as a statistical collaborator on a variety of projects in both HIV/AIDS and infectious diseases as well as cancer and cancer prevention with investigators at the University of Washington and FHCRC. Dr. Holte is head of the Biometrics Core for the Center for AIDS Research at the University of Washington and has primary responsibility for the portion of the Biostatistics Shared Resource which supports investigators in the Public Health Sciences Division at FHCRC. Dr. Holte devotes half her time to administrative oversight of the PHS portion of the Biostatistics Shared Resource and half her time as a consulting statistician. **Expertise:** Functional and longitudinal data analysis, statistical and mathematical modeling of nonlinear biological processes.

Nine additional biostatisticians devote effort to the shared resource, serving as collaborative biostatisticians in support of Consortium research activities.
Basic Sciences/Translational Research

CELLULAR IMAGING SHARED RESOURCE

Introduction
The Cellular Imaging Shared Resource (CISR) provides Consortium researchers with a comprehensive set of advanced high resolution imaging techniques, quantitative gel and blot imaging, and quantitative image analysis. The resource is comprised of two service-based laboratories, Electron Microscopy (EM) and Scientific Imaging (SI). The EM laboratory offers sample preparation, access to microtomy, cryo- and immuno- EM technologies, and training in transmission and scanning EM, and atomic force microscopy. The SI laboratory provides access to advanced imaging systems for confocal, deconvolution, multi photon, time lapse, total internal reflection fluorescence, high content analysis, whole slide scanning, and other light microscopy techniques, along with powerful software for visualization and quantitative analysis of microscopy data. As research needs and priorities have evolved, CI has expanded into new areas to provide support for a broader range of investigator and research programs. Examples of new services include: high content analysis and plate screening; whole slide scanning and analysis; and Cryo and Immuno-EM. Overall, all Consortium research programs currently use the resource and both components provide essential services and technologies for member research. The resource constantly evaluates new technologies and the benefits they can bring to the Consortium, and actively promotes the use of such technologies through classes, workshops, seminars, and one-on-one discussions with individual researchers. The CI received an excellent merit assessment in the 2008 competitive renewal. In response to reviewer comments, the percentage of Consortium users outside of the Hutchinson Center has increased from an average of 5% to 14%. Cancer focus of users has also increased, as is indicated in the examples presented below.

Major Services

Facilities and Equipment
The CI resource is located at the Fred Hutchinson Cancer Research Center campus. Total facility space is 3,300 square feet, with 1,900 square feet devoted to the EM and 1,400 square feet to the SI Laboratory. The two laboratories are located close to each other, and in close proximity to other shared resources. The resource is in a central location, close to the main lobby and visitor parking, for easy access by all FHCRC and outside Consortium researchers. Data generated within the resource are transferred through automated pipelines to systems supported by the FHCRC’s IT group, providing Consortium researchers with centralized data storage, backup and archival services, and allowing investigators immediate access to data created and data sharing. Services and instruments can be booked in person, by phone, email, or online, and access to the resource outside of normal working hours is granted to trained users only, and is controlled through programmable key card readers. Major instrumentation available in the resource is listed below:

Electron Microscopy

JEOL JEM 1400 Transmission Electron Microscope (TEM)
A 120 kV instrument with 0.20nm resolution (lattice image), and a magnification range of 50X - 2,000,000X. The microscope is equipped with a Gatan Ultrascan 1000XP 4 MP (megapixel) bottom mount CCD camera and 11 MP Gatan side mount CCD camera for digital acquisition of images.

JEOL JSM 6610LV Scanning Electron Microscope (SEM)
High-performance SEM for fast characterization and imaging of fine structures on both small and large samples and offers a magnification range from 5X to 300,000X and a resolution of 3.0nm at 30KV in the high vacuum mode.

Agilent 5500 Atomic Force Microscope (AFM)
Provides high-resolution and three-dimensional information and can resolve features as small as an atomic lattice, for either conductive or non-conductive samples. Imaging modes include: Mac, Contact, and Acoustic AC Mode, phase imaging and force modulation.

Cryo Equipment
Includes a Leica EMPact2 High Pressure Freezing (HPF) apparatus, Leica EM AFS2 freeze substitution system (AFS), and Leica EM FC6 cryochamber for cryo-ultramicrotomy. A Leica VT 1200S Vibratome is also available to provide support with HPF of tissue. The HPF apparatus has the benefit of freezing down to 200um into the specimen without significant ice crystal damage, and is ideal for correlative light/EM microscopy.

**Scientific Imaging**

*Zeiss LSM 780 NLO*
Offers laser scanning confocal and two-photon microscope. Advanced, state-of-the-art system for fluorescence confocal imaging, transmitted and reflected light imaging, time-lapse microscopy, spectral imaging, photobleaching (FRAP and FLIP), and fluorescence resonance energy transfer imaging (FRET). Includes a Coherent Chameleon Vision II multi photon laser with pre compensation, and Zeiss BiG GaAsP non-descanned detector for sensitive multi photon imaging.

*Applied Precision DeltaVision Elite*
Optical sectioning and image restoration system for high resolution, high contrast quantitative fluorescence imaging in seven channels from the near-UV to far-red. Dedicated software for post-acquisition image processing, including deconvolution, 3-D modeling, and data analysis, is available on two separate computer workstations.

*Cellomics/Thermofisher Arrayscan VTI*
A dedicated microscope for the automated imaging and analysis of samples in multi-well plate format for high content analysis and for image-based screening applications. The system includes a robotic arm and automation software for unattended sample loading and imaging of up to 45 plates, a server with 2 TB of data storage and the Cellomics High Content Informatics suite.

*Perkin Elmer Ultraview Vox*
A high performance spinning disk confocal microscope system for fast imaging of live specimens. System is equipped with four lasers (405, 488, 561 and 640 nm), and two sensitive Hamamatsu ImagEM EMCCD cameras for simultaneous acquisition of green and red channels. The system includes a Photokinesis module for photoactivation and photobleaching experiments, and a Photonic Instruments Micro-Point nitrogen laser for precise cell ablation and other localized photo-induced damage.

*Nikon Total Internal Reflection Fluorescence (TIRF) and STORM*
Advanced system for the detection of faint signals at or near the cell surface, for the detection of molecules in *in vitro* reconstituted systems down to single molecule sensitivity, and for single molecule detection and super-resolution imaging. Equipped with the latest EMCCD technology (Andor iXon X3 EMCCD camera), and a four-laser launch with 405, 488, 561 and 640 nm laser lines.

*Nikon Live and Prairie Technologies FRAP*
Dedicated system for live cell imaging (time lapse) in transmitted light (Phase, DIC), conventional widefield), and confocal fluorescence (swept field) modes. Equipped with a Photometrics QuantEM 512x512 pixel EMCCD camera for confocal, and a high resolution Photometrics CoolSnap HQ2 scientific CCD camera for widefield imaging. Includes a Prairie Technologies fluorescence recovery after photoactivation (FRAP) system for photobleaching, photoactivation, and cell ablation with 405 nm, 488 nm, and 355 nm (UV) light. The FRAP system was custom-built to meet specific requirements of Consortium users.

*Tissuegnostics Tissuefaxes*
Includes a motorized Zeiss Imager Z2 stand, motorized 8-slide Marzhauser stage, a Pixelink color camera for true color transmitted light imaging (immunohistochemistry), and a PCO monochrome camera for immunofluorescence imaging of whole slides, including large tissue sections and tissue micro arrays. Image acquisition is highly automated for higher throughput and image consistency. Includes two software packages, TissueQuest and HistoQuest, for the analysis and scoring of IHC and IF slides.

*GE Typhoon Trio*
Versatile, three-laser (488, 532, 640 nm) multi-mode scanner for the acquisition of quantitative images of
radioactive (through Phosphor screen technology), fluorescent, or chemiluminescent samples. Can scan gels, blots, multi-well plates, and various other sample formats, at resolutions down to 25 microns. System includes ImageQuant software for quantitative analysis of the acquired images.

**Li-Cor Odyssey**
Sensitive far red/near infrared two-color fluorescence scanner for the imaging and quantitation of gels, blots, 96-well plates and a variety of other applications, including tissues and whole animals. The instrument has two lasers and two detection channels at 680 nm and 800 nm. System includes Odyssey software for data analysis.

**Other equipment**
The resource includes a number of ancillary equipment (microscopes, accessories for tissue culture, ultramicrotomes, etc.) to support all imaging needs.

**Technologies and Expertise**
The CISR is headed jointly by Julio Vazquez, Ph.D., director of the SI lab, and Ms. Bobbie Schneider, manager of the EM lab. Both have more than 15 years of experience and broad expertise in their respective fields. Dr. Vazquez and Ms. Schneider assist Consortium researchers by providing introductory classes and advanced workshops on a variety of microscopy and quantitative image analysis topics, by providing guidance with experiment design and data analysis, and by introducing or implementing new imaging techniques, and analysis of protocols as needed. Under their leadership, CI has added several previously unavailable capabilities, such as high content analysis and screening, total internal reflection fluorescence microscopy, cell ablation, and high pressure freezing. Dr. Vazquez and Ms. Schneider have made major contributions to a number of projects, and have been co-authors on several publications by Consortium and other investigators. Three imaging specialists with more than 20 years of combined experience further contribute essential skills. Mr. David McDonald used his expertise in clinical cytology to set-up a karyotyping service for several Consortium laboratories, providing results several weeks faster than expected, and at a small fraction of the cost compared to outside cytogenetics labs. In summary, CISR staff strives to provide state of the art technologies, along with the needed expertise to make advanced, cost-effective services accessible to all Consortium researchers, where they can be used productively for the advancement of research.

**Atomic Force Microscopy**
Provides high-resolution and three-dimensional information. With this technique it is possible to image in-situ, in fluid, under controlled temperature and in other controlled environments.

**Cryotechniques**
EM owns several pieces of Leica cryo equipment to produce superior cellular preservation for morphological studies and better antigen retention for immunolabeling work.

**Immunoelectron Microscopy**
IEM uses antibodies to detect the intracellular location of structures of particular proteins by electron microscopy. Ultra-thin sections are labeled with antibodies against the required antigen and then with gold particles. Gold particles of different diameters enable two or more proteins to be studied.

**Scanning Electron Microscopy**
SEM is primarily useful for providing a three-dimensional image of the surface of the specimen and for viewing large objects such as fruit flies. Additional supportive services offered include fixation and dehydration, critical point drying, sputter coating, and training.

**Transmission Electron Microscopy**
TEM provides information on internal structures in thin-sections (70-100nm) from specimens. Cellular and subcellular structures can be viewed in great detail. TEM is also useful for viewing suspensions of microscopic particles such as bacteria or virus using negative staining techniques. Supportive services include specimen preparation and sectioning, staining, particle quantification and training.

**Gel and Blot Imaging**
The resource provides instrumentation and expertise for imaging and quantification of radioactive, fluorescent, and chemiluminescent samples in gels, blots, plates, and other sample formats. Staff provide training on the various instruments, analysis, software and data analysis techniques. Staff can provide data analysis for researchers as well.

**Image Processing and Quantitation workstations**

The Scientific Imaging core facility provides software for the deconvolution of images acquired on the DeltaVision and other 3-D sectioning microscopes, and several image analysis software packages for the processing, quantitation, analysis, and display of microscopy image data, including 3-D volume rendering, geometric and intensity measurements, colocalization analysis, high content analysis (image based high throughput image analysis and plate screening), tissue section and tissue micro-array scoring. The resource will also work with the researchers on developing new analysis tools when appropriate.

The laboratory maintains and operates several high performance imaging workstations for the visualization and quantitative analysis of data generated by the microscopes and scanners. The different software suites are critical for the accurate measurement of fluorescence intensities, shapes, spatial distributions, colocalization, and for the quantitative measurement of changes in cellular or sub-cellular architecture. Available software includes Volocity (Improvision), Imaris (Bitplane), Zeiss ZEN, SoftWoRx (Applied Precision), Metamorph, Cellomics high content informatics suite, TissueQuest, HistoQuest, ImageQuant, Odyssey, ImageJ, and more. To maintain these analytical capabilities state-of-the-art, three new high performance 64-bit workstations were purchased in the last year, along with upgrades to several of the software suites.

**Other services:** Karyotyping and plate screening.

**Importance to Scientific Programs**

A centralized, shared imaging facility is critical to advancing cancer research due to the cost and complexity of instrumentation. Modern microscopes are highly specialized instruments that require a great deal of expertise to maintain, operate and use in the most efficient and scientifically relevant manner. By providing a broad range of instruments along with the required expertise to use them, and by providing one-on-one training and assistance tailored to each researcher’s needs, CI makes it possible for all Consortium labs, even those with little or no experience with microscopy, to get access to powerful and sophisticated imaging techniques and to use them to benefit their own research. The resource also offers valuable consultation services, advises researchers on experiment design and data analysis, and often takes a more involved role by collaborating with researchers on specific projects, as attested by several co-authored publications. For example, the resource has made projects possible by developing analysis tools (such as high content screening protocols for the Eisenman, Emerman, Paddison, Galloway, Taniguchi and other laboratories), and by providing highly customized instruments, such as a UV photoactivation device for the Taniguchi lab. In the last two years, approximately one hundred Consortium laboratories have used CI to support their research from all but one of the Consortium’s research programs. Over the period 2008-2012, the resource had contributed to an estimated 200 publications by consortium researchers. A small sample of research projects from various research programs supported or made possible by Cellular Imaging is listed below.

**Mark Groudine, MD, PhD, and Susan Parkhurst, PhD. Cancer Basic Biology**

**Epigenetic control of gene expression, and mechanisms of wound repair.**

Research in the Groudine laboratory focuses on the role of chromatin and nuclear organization on the regulation of gene expression. Recent work from this and Dr Parkhurst’s lab used a combination of biochemical, genetic, and microscopy approaches, including use of the CI resource’s Deltavision microscope, to identify a new set of transcriptional regulators that act by preventing the spreading of active chromatin. Current research in Dr. Parkhurst’s lab also focuses on the mechanisms of small (single cell) and large wound repair and normal development. Basic mechanisms of cell migration during wound repair and development are relevant to the migration of metastatic cells in cancer. These mechanisms are being addressed through a combination of genetic, molecular and microscopy approaches. These, and other studies from these two labs, make extensive use of equipment available in the CI resource, including the PerkinElmer spinning disk microscope system and Micro-Point high power nitrogen laser, confocal, and deltavision microscopes.


Steven Henikoff, PhD. Cancer Basic Biology
The Henikoff lab uses the Agilent Atomic Force Microscope (AFM) and the Deltavision deconvolution microscope in the CI Shared Resource for his studies of centromeric chromatin. Centromeres are loci responsible for attaching chromosomes to the mitotic spindle for segregation to the poles at mitosis and meiosis. Segregation defects, sometimes caused by defective centromere function, are common in cancer. Accordingly, understanding the basic principles of centromere specification and function is an important long-term goal for the Henikoff lab. The laboratory had previously shown that the chromatin of centromeres, defined as consisting of nucleosomes containing the CenH3 histone variant in place of canonical H3, is configured as half-nucleosomes or “hemisomes” in Drosophila. This and subsequent in vivo studies of human CenH3 hemisomes used AFM to distinguish hemisomes containing one each of the four core histones from bulk octameric nucleosomes based on their shorter y-axis dimension when imaged on a flat mica surface. More recently, the lab applied an alternative nucleosome reconstitution protocol to assemble stable hemisomes in vitro, and used the AFM instrument as a key method to distinguish hemisomes from octameric nucleosomes. The lab will continue these in vitro reconstitution studies using AFM to probe fine differences between CenH3 and H3 octameric nucleosomes and hemisomes, for example using different DNA sequences and mutant CenH3 forms for reconstitution.


Patrick Paddison, PhD. Cancer Basic Biology
Functional genomics of stem cell and cancer cell biology
The Paddison Lab uses functional genomics to probe the underlying biology of mammalian stem and progenitor cells. Their primary goal is to define the biological units of self-renewal, expansion, and lineage commitment in model stem cell systems, including: embryonic stem cells, hematopoietic stem cells, neural progenitor cells, and brain tumor initiating cells (i.e., brain tumor stem cells). Three research projects are currently underway in the lab. One specific project is aimed at identifying potential therapeutic targets for glioblastoma multiforme, a common and aggressive form of brain cancer. These studies relied on functional genomic approaches using RNA interference by small hairpin RNAs and high content screening on multi-well plates. For this project, and in combination with the genomics resource, the CI resource developed and optimized high content analysis protocols utilizing the Cellomics system. The resulting screens, the first of this type to be conducted at the FHCRC, led to the discovery of BUB1B/BUB1R, a mitotic spindle checkpoint protein, as the top scoring glioblastoma lethal kinase. These results, co-authored by members of the CI and Genomics resources, offer opportunities for better understanding the mechanisms of, and developing therapeutic agents for the treatment of brain cancer.


Daniel Raftery, PhD, and David Hockenbery, PhD. Cancer Basic Biology
Mitochondrial metabolism and cancer
Collaboration between the Hockenbery and Raftery laboratories is directed towards a comprehensive analysis of mitochondrial metabolism in breast cancer cells. Cancer cells have altered bioenergetic metabolism and mitochondrial function. Many studies have indicated that understanding the metabolic changes in mitochondria is critical to insights into mechanisms that support cancer growth and drug resistance. One specific project of the Raftery group addresses the role of peroxisome proliferator-activated receptor gamma co-activator 1 alpha
(PGC1α) in controlling mitochondrial structure and function in mouse cardiac tissue, and whether changes in PGC1α in the heart can maintain mitochondrial biogenesis and improve contractile function in heart failure. These studies require EM analysis of samples of cardiac tissue from PGC1α transgenic and control mice at baseline and after cardiac pressure overload to determine changes in the morphology, number and size of the mitochondria. The Hockenbery lab studies programmed cell death (apoptosis) pathways that are defective in many cancer cells, and the role of cancer-cell metabolism in apoptosis, oncogene functions, and environmental/dietary risk factors. These studies rely extensively on confocal, multiphoton, and electron microscopy available in the resource.


Toshiyasu Taniguchi, MD, PhD. Women's Cancer
DNA damage response pathways and cancer
Dr Taniguchi’s research focuses on the molecular mechanisms of DNA damage response pathways, with the long term goal of developing better diagnostics tools and safer, more effective drugs for the treatment of cancer. The DNA molecules that constitute the genetic material of chromosomes are very sensitive to damage by a variety of chemical and physical agents. Such damage can cause genetic mutations or chromosomal abnormalities, and when severe may lead to cell death or uncontrolled growth and cancer. To keep adverse effects to a minimum, DNA damage repair molecules are constantly monitoring and repairing chromosomal DNA. Defects in the repair pathway can promote cancer formation. On the other hand, certain types of cancer cells are defective in the repair process, and therefore are more sensitive than normal cells to DNA damaging agents. This enhanced sensitivity can be exploited for developing more effective and safer therapeutic agents. One specific project in the lab aims to identify and characterize novel genes involved in the general DNA repair pathway, and the FA-BRAC pathway in particular. The studies involve sophisticated experiments utilizing instrumentation available in the CI resource. A highly focused UV or near-UV laser beam is used to induce lesions on chromosomal DNA. Subsequently, GFP-tagged proteins involved in the repair process are visualized using time lapse microscopy on a fast spinning disk confocal microscope, as they accumulate at the lesion sites. Furthermore, fluorescence recovery after photobleaching (FRAP) is used to address the dynamics of protein accumulation, and a variety of mutations or drugs can be assessed for their ability to prevent or disrupt the accumulation of DNA repair proteins at the lesion sites, or alter the kinetics of accumulation. The laboratory is also using the Cellomics Arrayscan high content reader and associated image analysis software to identify small molecules that interfere with the DNA damage repair response. Candidates thus identified in high throughput screens can be further characterized and evaluated for their potential as therapeutic agents. A similar approach is also being used in the lab to identify MicroRNAs that regulate the DNA damage repair response.


Nina Salama, PhD. Global Oncology
Pathogenicity of Helicobacter pylori
The Salama laboratory studies the bacterial pathogen Helicobacter pylori which infects the human stomach. Infection with this bacterium causes inflammation in the stomach that can progress to peptic ulcer and/or gastric cancer. This bacterium has a spiral shape and its shape is thought to facilitate colonization of the mucus layer
overlying the gastric epithelium. A major focus of the lab’s research is towards discovering the determinants of H. pylori cell shape and the role shape plays in motility, as well as the genetic factors that determine host selectivity. The laboratory uses electron microscopy to characterize shape mutants, monitor cell envelope structure and query proper localization of cell surface structures, such as the polar localized flagella. These studies absolutely require the sensitivity and resolution of the electron microscope. This lab also uses high resolution 3-D fluorescence deconvolution microscopy and particle analysis with the resource’s advanced imaging software to address bacterial structure and to measure the rate of motility of spiral and straight bacterial cells in media of varying viscosity. They expect to expand this work to include immunolocalization of bacterial proteins on the cell, which will require electron microscopy and cryo-EM to preserve delicate structures on the bacterium. The resource is also evaluating new, super resolution light microscopy techniques such as structured illumination to apply to this project.


Suzie Pun, PhD, Immunology and Vaccine Development
Cancer drug delivery
The Pun lab develops polymeric delivery vehicles for various biomedical applications including cancer treatment. CI has been a critical core facility for characterizing drug delivery materials such as nanoparticles. The lab uses TEM in conjunction with dynamic light scattering analysis to determine the average size and morphology of particles. They have also recently investigated intracellular trafficking of delivery particles by electron microscopy of fixed cell sections. This method allows them to better assess particle morphology in physiologically relevant environments, and to visualize intracellular distribution of particles. The lab has published two articles in 2013, and has another republication in revision, that acknowledge work completed using the CI Resource.


Brian Iritani, PhD. GI Cancer
Lymphocyte development, signaling, and transformation
The Iritani laboratory is particularly interested in understanding the role of a novel metabolic regulating protein called Fnip1 in the development, activation, metabolism, and transformation on lymphocytes. They have previously shown that fnip1 is essential for metabolic homeostasis in developing and activated lymphocytes, in part by regulating the ability of AMPK to inhibit mTOR. They have further shown using the electron microscopy capability provided by the CI resource, that mitophagy and autophagy are inhibited. They hypothesize that AMPK requires Fnip1 to stimulate autophagy and inhibit mTOR in response to nutrient and energy stress. They propose a series of experiments in primary lymphocytes and lymphoma cells to define the mechanism of autophagy induction by Fnip1, using immuno blotting and electron microscopy as the primary experimental methods. Another project from this lab is aimed at understanding the role of Hematopietic protein-1 (Hem-1) in red blood cell formation and stability. These studies take advantage of confocal microscopy provided by the CI resource to reveal changes in red blood cell morphology in Hem-1 mutant mice (Park et al., Immunity, 2012; Chan et al., PLoS ONE, 2013).


**Beverly Torok-Storb. Hematologic Malignancies**

Hematopoietic stem cells and blood cell production  

The Torok-Storb lab research centers around studies of stem cells, blood cell production. These studies are of utmost clinical importance, as they directly relate to the treatment of blood cancers through bone marrow transplantation, and other clinical applications. One of the projects from this laboratory uses confocal and time lapse microscopy available at the CI resource to investigate the mechanisms of blood cell communication and migration in a three-dimensional experimental system. This system, developed in collaboration with the University of Washington's bioengineering department, incorporates vasculature and flow, to better approximate the in vivo conditions in bone marrow. A second project that addresses the signaling pathways important for blood cell production rely extensively on the analysis by immunohistochemical methods of marrow biopsies. These studies greatly benefit from the availability of a versatile whole slide scanner (Tissuefax) for the automated acquisition of high resolution images of large areas of the specimens, and subsequent analysis with HistoQuest software. Finally, the laboratory also makes extensive use of the resource’s karyotyping service for the characterization of frozen stem cell lines used in their studies, and the development of methods to derive primary marrow stromal cells from bone marrow for clinical use.


**Paul Lampe, PhD. Cancer Epidemiology, Prevention and Control**

Cancer, connexin, and cellular communication  

The Lampe laboratory investigates the control of cell growth at the cell biological level to mechanistically connect gap junction regulation with wound repair responses in skin, hypoxic events in heart, the cell cycle, the control of cell growth, and carcinogenesis. Ongoing research involves the regulation of gap junction assembly and function. Gap junctions allow diffusion of small molecules (<1000 MW) between adjacent cells via matched cell-to-cell membrane channels. Results from this lab indicate that gap junction formation and degradation are highly regulated via protein kinases at various stages of the assembly process and the cell cycle. Gap junctions can be readily examined in a fluorescence microscope, and the lab makes extensive use of the confocal and DeltaVision microscopes and imaging software in the CI resource. The dynamics of gap junctions is also investigated through the use of protein fusions to green fluorescent proteins and time lapse microscopy. Current studies include determination of the cellular localization of different connexin phosphorylation events and the specific serine substrates that are phosphorylated within connexins in different tissues in response to insults such as skin wounding or cardiac hypoxia. Such detailed structural studies are prime candidates for new super resolution techniques, and the resource is considering the acquisition of a dedicated microscope to help advance the research of this, and other laboratories who need molecular-level resolution in a light microscope.


**Cost Effectiveness**

The CI shared resource operates in a cost effective manner while maintaining a high level of service to
investigators within the Consortium. Appropriate adjustments are made with respect to staffing levels and operations as needed. By thoroughly training of all users and daily maintenance of the instruments, the resource can keep maintenance costs to a minimum. For example, maintenance costs for all the scientific imaging laboratory's instruments (ten major instruments, six high performance computers, and several accessories) in the last fiscal year, excluding costs of software upgrades, were approximately $36,000, or roughly the cost of a service contract for one single typical instrument. These low operating costs are passed down to users in the form of low user fees. Because the costs are shared by many users, individual labs can get access to a broad range of sophisticated technologies at a small fraction of the cost they would incur if they had to use their own instruments. In fact, by using the resource, most labs can get access to nearly all major microscopy techniques for an entire year for less than the cost of a single instrument repair service visit. While most of the services provided by the resource cannot readily be outsourced, in those cases where they could be outsourced (such as karyotyping, high content screening, and whole slide scanning), utilizing outside instruments and services would cost users an estimated three to ten times more, and would delay results by weeks. In addition to significantly lower costs, the benefit of having virtually instantaneous access to instruments and support (including assistance with experiment design and troubleshooting) at all times is invaluable.

Use of Services

<table>
<thead>
<tr>
<th>CI Service</th>
<th>Total Users</th>
<th>Peer Reviewed</th>
<th>Non-Peer Reviewed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electron Microscopy</td>
<td>22</td>
<td>20 (91%)</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Light Microscopy</td>
<td>71</td>
<td>68 (96%)</td>
<td>3 (4%)</td>
</tr>
</tbody>
</table>

Management Structure, Policies and Operations

Administration
The Cellular Imaging resource operates in accordance with Consortium and institutional polices for Shared Resources. Individual resources are managed by a specific director or manager. For the CI resource, leadership is provided jointly by Julio Vazquez, Ph.D. (SI lab) and Ms. Bobbie Schneider (EM lab) in consultation with the Paul Woloshin, MBA, PhD, Consortium Shared Resources Director. The resource directors supervise their technical staff, and ensure they fulfill their responsibilities. Staff performance is evaluated at least once a year. Staff development is ensured through in-house training sessions and discussions, hands-on experience, seminars, and technical workshops. Resource managers and staff receive assistance from the Shared Resources administrative team and other FHCRC administrative departments for tasks such as billing and purchasing.

Faculty oversight of the resource is provided by faculty advisory committees (two in the case of the CI resource, i.e. one for each of the resource’s laboratories). Advisory committees are responsible for reviewing shared resource operation on an annual basis, providing review of user fee changes, evaluating annual capital budget requests and providing guidance on future goals and objectives. Committee members for 2013 include Nina Salama and Jais Lingappa (Global Oncology), and Susan Parkhurst (Cancer Basic Biology) for the EM lab, and Beverly Torok-Storb (Hematological Malignancies), and Steven Henikoff, James Olson, Jonathan Cooper, and James Priess (Cancer Basic Biology) for SI. The Consortium’s Scientific Steering Committee ensures that all Consortium resources are aligned with the Consortium’s strategic goals and assesses their continued value to the Cancer Center.

Access and Usage Policy
Services are available to all members of the Consortium, on a first-come, first served basis. Support is provided to external users as time permits. Costs are charged directly to applicable awards based on actual usage. Rates are based on projected operating costs net of CCSG and institutional support. Rate schedules are evaluated and revised as required on an annual basis. External user fees reflect the full cost (both direct and indirect) of rendering service according to the most recent rate revision. No benefit of institutional or federal funding received by the resource is considered in the establishment of outside rates.

Billing
Standardized service request forms provide authorization of service and requested information for each respective transaction. Services are billed upon completion and information is entered into a Shared Resource billing system which provides the ability to track resource use at the project level by activity. Ongoing review is
conducted to monitor activity levels and observe usage trends to ensure appropriate adjustments are made in operations to adapt to changing demand. Usage is assessed and summary reports are developed by institution, by investigator, and by program for each service provided by the resource. Ongoing evaluation of resource operations is conducted through implementation of appropriate analyses, benchmarking studies, surveys and other tools.

Education and Outreach

Users are kept up to date on changing technologies and services offered by the facility through the FHCRC and Consortium websites, Share Resources Newsletter, and special memo distributions. Outreach to the broader Consortium community, particularly those within the UW and Children’s Hospital and Regional Medical Center (Children’s), will be enhanced through the activities of the Institute of Translational Health Sciences (ITHS) and the eagle-I web portal. As an ITHS approved facility, it is anticipated that the Resource will play an ongoing and expanded role in support of translational research activities. The eagle-I consortium website makes available a nationwide listing of shared resources searchable by institution.

Priorities and New Initiatives

The resource is well equipped to meet the immediate imaging needs of Consortium members in the areas of light and electron microscopy and quantitative image analysis. The future development of the facility will be the acquisition of technologies that expand resource capabilities to address extended needs of Consortium members. New services such as high content analysis, whole slide scanning, total internal reflection fluorescence microscopy, karyotyping, correlative microscopy, and Electron Tomography have been recently added, or are currently being developed. Other services, primarily in the area of super resolution light microscopy, are under consideration for the coming years.

Correlative Microscopy

Correlative Microscopy allows users to combine light and EM microscopy techniques to obtain valuable information that is difficult or impossible to obtain through each individual approach alone. For instance, users can look at both the global distribution of specific antigens within a cell, and the high resolution mapping of such antigens to specific cellular structures. Users can also use fluorescence light microscopy to identify suitable rare cells, tissue regions, and/or developmental stages for further analysis at the EM level. This approach will be of great benefit to investigators who need to identify rare events (light microscopy) for further high-resolution (EM) analysis, such as in viral research (McElrath and Corey; Immunology/Vaccine), or high-resolution studies of nuclear and/or cellular architecture (Groudie; Cancer Basic Biology) and wound studies in Drosophila embryos (Susan Parkhurst; Cancer Basic Biology program).

Electron Tomography (ET)

Electron Tomography is a technique for obtaining detailed 3D structures of subcellular macromolecular objects at the electron microscopy level. It uses the resource’s JEOL JEM 1400 transmission electron microscope at 120KV to collect data. In the process, a beam is passed through the sample at incremental degrees of rotation around the center of the target sample. This information is collected and used to assemble a three dimensional image of the target. Current resolutions are in the 5-20 nm range, suitable for examining supra-molecular multi-protein structures such as sites of exocytosis and endocytosis (Jihong Bai, of the Cancer Basic Biology program) centrioles (Jim Priess of the Cancer Basic Biology program) and kinetochores (Sue Biggins, Cancer Basic Biology).

Super resolution microscopy

A variety of so-called “super resolution” techniques have been developed in recent years. These techniques extend the resolution limit achievable on a light microscope from the classical value of approximately 200 nanometers, down to 10-20 nanometers. This increase in resolution will allow to take advantage of many existing benefits of light microscopy (such as the ability to use fluorescence to label and visualize multiple targets in the same specimen), but with a ten-fold or higher resolution, allowing researchers to visualize single molecules, map molecular interactions, measure colocalization, and reconstruct cellular architecture with unprecedented accuracy. Super resolution techniques are the next frontier in microscopy, and are likely to be of tremendous importance for fundamental and cancer research.

Other techniques
Resource Surveys indicate that workshops in AFM and immunogold will be beneficial to increase awareness, and possibly greater usage by Consortium members, of these techniques. Jihong Bai, of the Cancer Biology program; Nina Salama, and Tim Rose, both of the Global Oncology program would be a few of the consortium members that would benefit.

**iLab online scheduling/management system**
Implementation of iLab Solutions Software for core facility management will be launched for eleven resources, anticipated January 2014. This system will allow Consortium researchers and Shared Resource staff to manage service requests, equipment reservations, usage tracking and billing online.

**Personnel**
**Key Staff Qualifications**
Electron and fluorescence microscopy are highly specialized, yet complementary techniques; their implementation requires advanced and specialized skills and knowledge. The staffing of the CIR reflects the various needs of specialization and interdisciplinary collaboration.

**Julio Vazquez PhD, Staff Scientist and Director** of the Scientific Imaging Laboratory was hired in March 2003. He oversees the operations of the SI laboratory, evaluates and purchases new instruments, implements new techniques, and trains and supervises SI staff. His leadership responsibilities also include consulting with researchers to enable them to take advantage of modern microscopy techniques to address important biomedical questions in their specific fields, and introducing new technologies deemed critical for achieving the Consortium’s research goals. Dr. Vazquez earned a PhD in Molecular Biology in Geneva (Switzerland) and performed postdoctoral work in Genetics, Cell Biology, and Microscopy at Princeton University and UCSF. His postdoctoral work included five years in the laboratory of Dr. John Sedat, at UCSF, a pioneer of deconvolution and super-resolution microscopy. He has 15 publications in peer-reviewed journals, and continues to pursue his research interests through collaborations with Consortium scientists.

**Bobbie L. Schneider, Manager** of the Electron Microscopy Laboratory was hired in 2001 and oversees the general operations of the EM laboratory, equipment maintenance, the evaluation and implementation of new technology and the supervision of resource staff. Ms. Schneider earned a B.A. degree in Biological Sciences from California State Univ., Fresno, and a specialty degree in Electron Microscopy from San Joaquin Delta Community College. She has 28 years of experience in Electron Microscopy and can work proficiently with a wide array of instruments and sample types, and is familiar with many different research areas. She has co-authored several publications in the field of electron microscopy.

In addition to managing their respective labs, Dr. Vazquez and Ms. Schneider work closely on an ongoing basis to establish strategic directions for the resource, coordinate training and outreach efforts in support of evolving research needs within the Consortium, and facilitate implementation of cross-platform technologies such as correlative microscopy.

Additional technical support is provided by three imaging specialists (2.65 combined FTE). Dave McDonald, a Scientific Imaging Specialist, earned a BA in Zoology from the University of Washington (UW), is a licensed Clinical Laboratory Specialist in Cytogenetics, and has over ten years of experience in light microscopy and image analysis. Sharmo Knecht, a Scientific Imaging Specialist, earned a M.S. in Biology from Ball State University, Muncie, IN. She maintains a shared position between the Scientific Imaging and EM labs. She has nine years of experience with light and electron microscopy, and image analysis. Steven MacFarlane, Electron Microscopy Specialist III, earned a BA in Biology from Grinnell College, Grinnell, IA and has 29 years of experience in electron microscopy. Mr. McDonald, Mr. MacFarlane and Ms. Knecht are responsible for everyday lab operation, instrument maintenance, user training and assistance, and for providing all other imaging and analysis services. Mr McDonald also provides additional support with cytogenetics sample preparation. They stay current in their fields through meetings, training classes, and seminars.
Population Science

COLLABORATIVE DATA SERVICES SHARED RESOURCE

Introduction
CDS was created almost 25 years ago as a survey science shared resource, specializing in the design, management, and execution of survey-related projects. At that time, their clients were primarily involved in cancer prevention and epidemiology studies. CDS has diversified its client base, which now includes clinical research and laboratory-based projects, and supports researchers in the Biostatistics and Computational Biology, Global Oncology, Hematologic Malignancies and Immunology and Vaccine Development programs, in addition to Cancer Epidemiology, Prevention and Control.

The Collaborative Data Services Shared Resource provides a broad range of specialized services to support the collection, storage and analysis of complex datasets for Fred Hutchinson/University of Washington Cancer Consortium (Consortium) investigators. CDS provides data acquisition, data management and database and software development services to over eighty projects each year. As Consortium projects have become more data-driven and computationally intensive, CDS’ expertise has is increasingly necessary to the success of a diverse array of studies. The CDS received an outstanding merit assessment in the 2008 competitive renewal with no major criticisms.

Major Services
Facilities and Equipment
CDS is located in the Arnold Public Health Sciences Building at the Hutchinson Center at the South Lake Union site. The space occupies a total of 5,248 sq. ft. of space on the first floor of the building and is readily accessible to both investigators and research project staff. This square footage includes 21 offices or shared spaces for managers and staff:

- The Data Operations group has two offices for full-time staff, four workstations for part-time employees, a meeting area and a workroom for high-speed scanning, label printing, color printing, and mail assembly space for customized participant mailings.

- The Interviewing group has a telephone call center with nineteen privacy cubicles for interviewing and a work and storage area. CDS has six lead interviewer offices set-up for monitoring interviewer telephones and computers for quality control.

- The Programming group has six offices equipped with programming workstations, and a meeting area with a conference table. The Management/Administrative Team has two management offices and an office with workstations for two interns.

- CDS has access to several other shared spaces, including a secure short-term records storage room, a library/conference room, a break-room, a mail and copy room, and two full computer racks in a secure server room. All spaces are in the same general area of the building.

CDS utilizes a state-of-the-art computerized call center for their interviewers who have access to a custom call management software application that is fully integrated with the DatStat Illume survey research system developed. The systems are maintained by CDS programmers to address the complexity and volume of research for the consortium and launch projects in days instead of weeks. Surveys are easily adapted and expanded without additional cost. Reducing lag between survey design, data collection and analysis by at least 75%, researchers now have faster access to actionable findings for their critical mission. The system ensures compliance, supports complex survey design, allows changes over time without affecting data integrity, with sophisticated requirements—IRB and HIPAA compliance, multiple users, time periods, and languages, and integration across multiple methods, databases, and projects. The programming team has created databases and applications for hundreds of projects and has developed a software toolbox that they can draw upon to quickly provide custom yet affordable solutions.
CDS has a diverse mix of databases and custom applications hosted on a server infrastructure maintained by Center IT to provide hosting services for Cancer Consortium clients. The department has a number of web and database servers all hosted on the VMWare virtual server system. CDS maintains primary and redundant systems, with separate servers for internal and externally accessible applications.

The CDS has access to the following equipment to provide services to Cancer Consortium projects: Brady Label Printer 360X (for freezer labels); Epson 4800 Color Printer and three high-throughput scanners.

Technologies and Expertise
CDS provides technical support to Consortium projects and scientists in the areas of data management, interviewing, and database and software development. CDS actively enquires about and assesses the data collection needs of studies, providing convenient, efficient and comprehensive methods to be used to collect and manage data. Specific tasks carried out on behalf of projects are outlined within the following.

CDS has expertise in fielding and monitoring data collection activities for case-control, cohort and prevention studies, and other trials. The Data Operations group provides technical support for recruitment and participant tracking, survey implementation, data quality control, data management and project management. Specific tasks carried out on behalf of projects by the Data Operations group include: data editing/coding; data entry and data cleaning; data acquisition through high-speed scanning of completed forms; mailing and tracking of mailed questionnaires; respondent tracking; informed consent tracking; questionnaire design and testing; web-based survey design and deployment; scheduling biospecimen collections; project documentation; response/refusal rate reporting; and bar code label printing for tracking paper or biological samples.

The participant tracking resource uses state of the art resources and techniques for locating participants crucial to quality research within the Consortium. One of the most valuable resources provided is consultation with investigators before research begins to advise staff on the kind of information to request from participants and IRB concerns regarding privacy and confidentiality as they affect future attempts to locate participants. The resources and techniques used can be categorized into three distinct groups: 1) Consortium Owned-Licensed Public Databases and Directories; 2) Use of Public Records and 3) Online Database Services. Because of the sensitive nature of tracking human subjects the resource has worked closely with the IRB to protect the privacy and confidentiality of individuals participating in Consortium research. All studies requesting services must first receive approval from the IRB, and all procedures performed by the resource undergo full review by the IRB.

Services provided by the Interview group include: multilingual in-person and telephone interviewing; participant recruitment, including random digit dialing recruitment; interview design and testing; interview project management, including budgeting and planning, and formal interviewer training.

The CDS Programming group offers a variety of programming capabilities on a number of different programming platforms. Specific services include: application, database and web site design and development; database management and secure application hosting; technology project specification, estimation, planning and management and technology training.

CDS has four programmers with extensive experience building software on the Microsoft .NET platform using the C# language, and using the Microsoft SQL Server database management system. Two programmers are familiar with statistical software packages including SAS, SPSS, and R.

Importance to Scientific Programs
CDS supports the researchers of Consortium programs by providing technical expertise in areas including data collection, participant tracking and development of datasets.

CDS provides data collection, processing and programming services to a wide variety of Consortium research projects. Supporting case control, cohort and prevention and other non-therapeutic trials, the resource has provided services including the development and maintenance of biospecimen tracking systems and web-
based systems for the delivery of questionnaires, data results and administrative services. Programming support is provided in areas such as database modeling and design and database programming and consulting. Selected descriptions of projects being supported by the resource are outlined below.

**Jonathan Bricker, PhD, Cancer Epidemiology and Prevention Control**

The PATH study is a 5-year, two-arm randomized controlled trial comparing Acceptance-Commitment Therapy (ACT) vs. the current standard Cognitive-Behavioral Therapy (CBT) counseling program for cigarette smoking cessation. CDS conducts all the data entry from study forms, performs follow-up data collection (via phone, mail, email), manages the mailing and results of the saliva cotinine kits, and generates the datasets for this study. This research has not yet been published.

The TALK study was a pilot collaboration with Alere studying the efficacy of telephone counseling in cigarette smoking cessation. Approximately 150 participants were enrolled. CDS screened potential participants for eligibility, conducted all the data entry from study forms, performed follow-up data collection (via phone, mail, email), managed the mailing of study provided NRT, and generated the datasets for this study. Dr. Bricker will submit an RO1 for approval this year. If funded, the study will enroll 980 participants. This research has not yet been published.

The WebQuit study, funded by pilot funds from the Cancer Center Support Grant, studied the effectiveness of online smoking cessation programs with the goal of improving them. CDS developed the recruitment, intervention, and control websites, created the accompanying videos, performed mailings, managed follow-up data collection through telephone interviews and paper surveys, and generated the datasets for this study. Webquit was a CCSG funded pilot study.


**Scott Ramsey, MD, PhD, Cancer Epidemiology and Prevention Control**

**Family And Cancer Treatment Selection (FACTS) study**

SIP 25-04 1-U48-DP-000050 - CDCP, PRCP

The FACTS study goal is to obtain information about the prostate cancer treatment decision process, and relate this to quality of life and satisfaction with care following the treatment decision. This prospective study contacted approximately 338 patients with localized prostate cancer recruited, their physicians (approximately 25 total), and 338 close family members. CDS created the framework for data collection, provided coding procedures and data entry and verification for surveys. In addition, CDS prepared survey mailings and is currently providing data entry and verification, and will prepare the final data set for analysis once all survey work is completed.


**Karen Syrjala, PhD, Hematologic Malignancies**

**Internet studies to enhance long term survivorship after hematologic malignancy.**

NIH 5R01CA160684-03

This project's goal is to use an internet-based program, called INSPIRE, to reduce depression and transplant-related emotional distress, and to improve health behaviors among adult hematopoietic stem cell
transplantation (HCST) survivors. The CDS Programming group has built intervention and control web sites for the project that include sophisticated logging of all views and clicks. The Programming group has also built a system for sending emails and text messages to participants.

**Vicky Taylor, MD, MPH, Cancer Epidemiology and Prevention Control**

For Hepatitis B ESL Education, CDS provided data management and quality control. Specifically, for the follow-up survey phase, CDS reviewed the questionnaire for data entry purposes and prepared coding procedures for staff to follow. CDS provided routine data entry for follow-up surveys, prepared data sets for analysis and archived completed questionnaires.


For Cervical Cancer Control in Vietnamese Women, CDS created the baseline survey sampling frame and randomly selected households for survey participation, provided coding procedures and data entry and verification for surveys and trained baseline interviewers on general and project-specific interviewing procedures. In addition, CDS prepared baseline survey mailings and interviewer packets and provided a final baseline dataset for analysis. For the follow-up survey phase, CDS provided data entry and verification and prepared the final dataset for analysis after all the survey work was completed. CDS also archived all baseline and follow-up surveys.


Garnet Anderson, PhD, Cancer Epidemiology and Prevention Control
The Women’s Health Initiative (WHI) Medications and Supplements Inventory
WHI Extension HHSN268201100046C
The Women’s Health Initiative (WHI) Medications and Supplements Inventory. This aspect of the WHI Extension study collects participant’s medication and supplement self-report. Medication use is being tracked, in part, to study the effectiveness of statins and other drugs on cancer risk. The CDS Data Operations group provided key entry for over 10,000 surveys and the Interviewing group has made calls to 17,925 women.

WHI Long Life Study. CDS Interviewing group made calls to 4,382 non-responders and the Data Operations group printed over 350,000 barcoded sample labels for blood samples. Specimens and information collected by the study are available to cancer researchers studying early detection and cancer risk.

WHI Life and Longevity After Cancer Study (LILAC) UM1CA173642. The CDS Data Operations group is providing phone follow-up to mailings. The study examines factors that may affect life and longevity among women who have been diagnosed with cancer.

Cornelia Ulrich, PhD, Cancer Epidemiology and Prevention Control
ColoCare. Ongoing data collection of general health and wellness of colon cancer survivors including an inventory of medications, supplements and level of activity. The Data Operations group has data entered over 500 surveys.


Ruth Etzioni, PhD, Biostatistics and Computational Biology
CANTRANce (Cancer Translation for Comparative Effectiveness: A Tool to Translate Intermediate Endpoints to Mortality in CE Studies)
1RC4CA155806-01
CANTRANce (Cancer Translation for Comparative Effectiveness) is a suite of micro-simulation models to quantify how the impact of several cancer control interventions on the specified intermediate endpoints translates to impact on cancer-specific mortality. CDS has designed a download, self-installing software to implement the models. The interface allow investigators to enter their comparative effectiveness study results, choose from a variety of assumptions, set values for key parameters and specify how to display model results.


Cost Effectiveness
CDS adds value to researchers in a number of areas. (1) CDS has attracted and retained experienced staff that can be deployed at varying levels of involvement, across a variety of studies, to meet specific study requirements. (2) CDS has made a long-term investment in well-crafted processes, procedures, tool and technologies. Projects can purchase ‘percentages’ of this expertise, which is less expensive than hiring extra personnel on their study to perform the same task. (3) Having a repository of these skills within the Consortium saves researcher and staff time in researching and obtaining bids from outside vendors.

For example, a project may have a cyclical need for a programmer or data manager. Without CDS, the project would have to hire to meet requirements for their peaks in usage, and either find work for the staff during periods of low activity, or assign staff temporarily to another project in an ad hoc manner. By working with CDS a project can receive the experienced help they need, when they need it and without the difficulty of maintaining those employees during non-peak times. In addition, CDS is often called upon to help projects catch-up with data entry or interviewing tasks and can then hand the work back to the project once it is back on track.

Additionally, long-term investment in hardware, software and process and procedures has given CDS a number of assets that projects would otherwise have to purchase or develop for themselves. Not having to create standard operating procedures or a tracking database from scratch not only means lower costs and more rapid start-up for a project, but it directly influences the quality of the data collected. CDS can apply their experience with many previous studies to avoid common pitfalls and help structure the data acquisition and management in the best possible manner.

Use of Services Table

<table>
<thead>
<tr>
<th>CI Service</th>
<th>Total Users</th>
<th>Peer Reviewed</th>
<th>Non-Peer Reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data Operations</td>
<td>20</td>
<td>18 (90%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Programming</td>
<td>36</td>
<td>31 (86.1%)</td>
<td>5 (13.9%)</td>
</tr>
</tbody>
</table>

Management Structure, Policies and Operations
Administration
The Prevention Center resource operates in accordance with Consortium and institutional polices for Shared Resources. Catherine Duggan, PhD, is Senior Staff Scientist and resource Director of the Prevention Center and works in consultation with Paul Woloshin, MBA, PhD, Consortium Director of Shared Resources. The resource director supervises the technical staff, and ensures they fulfill their responsibilities. Operational oversight is provided by Rosemarie Keenan, Public Health Sciences Division Administrator. Staff performance is evaluated at least once a year. Staff development is ensured through in-house training sessions and discussions, hands-on experience, seminars, and technical workshops. Resource managers and staff receive assistance from the Shared Resources administrative team and other FHCRC administrative departments for tasks such as billing and purchasing.

Faculty oversight of the resource is provided by an advisory committee and is responsible for reviewing shared resource operation on an annual basis, providing review of user fee changes, evaluating annual capital budget requests and providing guidance on future goals and objectives. Faculty Advisory Committee members for 2013 include Mary Ann Rossing (Chair, Cancer Epidemiology, Prevention and Control), Kathi Malone, Polly Newcomb, Steve Schwartz (CEPC), and Georg Luebeck (Biostat-Comp). The Consortium’s Scientific Steering Committee ensures that all Consortium resources are aligned with the Consortium’s strategic goals and assesses their continued value to the Cancer Center.
Access and Usage Policy
Services are available to all members of the Consortium, on a first-come, first served basis. Support is provided to external users as time permits. Costs are charged directly to applicable awards based on actual usage. Rates are based on projected operating costs net of CCSG and institutional support. Rate schedules are evaluated and revised as required on an annual basis. External user fees reflect the full cost (both direct and indirect) of rendering service according to the most recent rate revision. No benefit of institutional or federal funding received by the resource is considered in the establishment of outside rates.

Billing
Standardized service request forms provide authorization of service and requested information for each respective transaction. Services are billed upon completion and information is entered into a Shared Resource billing system which provides the ability to track resource use at the project level by activity. Ongoing review is conducted to monitor activity levels and observe usage trends to ensure appropriate adjustments are made in operations to adapt to changing demand. Usage is assessed and summary reports are develop by institution, by investigator, and by program for each service provided by the resource. Ongoing evaluation of resource operations is conducted through implementation of appropriate analyses, benchmarking studies, surveys and other tools.

Education and Outreach
Users are kept up to date on changing technologies and services offered by the facility through the FHCRC and Consortium websites, Share Resource Newsletter, and special memo distributions. Outreach to the broader Consortium community, particularly those within the UW and Children’s Hospital and Regional Medical Center (children’s) will be enhanced through the activities of the Institute of Translational Health Sciences (ITHS). As an ITHS approved facility, it is anticipated that the Resource will play an ongoing and expanded role in support of translational research activities. The eagle-l consortium website makes available a nationwide listing of shared resources searchable by institution.

Priorities and New Initiatives
The first priority of CDS is to provide high-quality support to the researchers of the Cancer Consortium. The resource strives to do this through continued commitment to excellence in our offerings and by investing in development of new services and expertise to meet changing research approaches, priorities and technology. New initiatives include the following: (1) Developing expertise in new data collection methods such as collection of data through smart phone applications and web-based surveys that can be quickly deployed to study participants. (2) Increasing service level to smaller studies, or those who have limited funds. This may involve development of alternatives to custom database will include re-scaling of services to provide access to more ‘low-level’ basic database development, such as Access, versus more sophisticated programming requirements for larger scale, more data-intensive studies. (3) A number of researchers have expressed interest in database templates for data entry and study tracking that can be easily modified by study staff. CDS programmers will provide a solution that will benefit a large number of smaller Consortium studies. (4) CDS currently acts as the Clinical Coordination and Data Management Center for the multi-center NIH funded study on the development of Salivary Biomarkers for Sjögren’s Syndrome Detection. CDS expects to expand this useful service and to make it available to Consortium researchers. (5) CDS is working on a system to measure client satisfaction throughout the progress of the study, to continue to refine and improve services. (6) CDS will start to maintain a higher profile among Consortium researchers via information sessions, and an increased presence on center websites. CDS would like to encourage researchers with any data needs to contact CDS, regardless of project size.

Personnel
Key Staff Qualifications
Catherine Duggan, PhD, Senior Staff Scientist and Director, was hired in November of 2013 to manage a department of twenty-five employees specializing in software development, data management, and survey research. Dr. Duggan provides scientific oversight of resource operations, oversees general operations, develops the strategic direction of the resource and provides a leadership role in the implementation of new
technologies and services. She plays a key role in guiding the development of the resource to ensure its ability to address the needs of peer-reviewed Consortium research. Dr. Duggan has extensive experience in project management and study design, data and biospecimen management, and in statistical analyses. She was responsible for management of a statistical research core, as part of the Transdisciplinary Research on Energetics and Cancer (TREC) initiative, which provided programming, database and data entry services to a number of studies. She has worked on studies that have been multi-center and international in nature, utilizing skills in decision making, flexibility and team-work. She currently directs a variety of projects including intervention studies, randomized controlled trials and breast cancer survivor cohorts. These studies have required a variety of skills including data management, statistical analyses, development and implementation of new research projects, and supervision of study staff.

Paul Litwin, Programming Manager, manages a team of three programmers and two project managers. He has served as project lead on a number of technology development projects. Mr. Litwin works with the staff in the data operations and interviewing groups to develop an efficient and easily maintained flow of materials along with establishing protocols to insure accuracy and standards reflective of HIPAA requirements for confidentiality. Mr. Litwin’s main duties are to oversee a variety of complex projects in an organized, cooperative and timely way, and to establish new and more efficient protocols as needed. He is also world-renowned expert in the development of information systems using Microsoft’s .NET platform, SQL Server, and Microsoft Access. Mr. Litwin has authored over ten technical books, dozens of articles, and courseware for a number of classes on software development. Mr. Litwin previously worked as a biostatistician for the University of Washington.

Star Dirette, Data Operations Manager, supervises workflow and staffing for the data center and the interviewing center. Ms. Dirette is responsible for assigning workflow to 20 people in both units along with developing and maintaining standards for processing and quality control of data collection. She currently supervises data collection for eight different projects. In addition, Ms. Dirette works in collaboration with database programmers to ensure timely and accurate data for analysis.
COMPARATIVE MEDICINE SHARED RESOURCE

Introduction
Animal models have a long history in Consortium research and played a critical role in our Nobel Prize winning research in bone marrow transplantation and hematopoietic cancers. The Comparative Medicine Shared Resource (CMSR) provides a broad variety of animal housing, veterinary, and research support services, and, new to this application, patient-derived-xenografts from the Consortium Xenograft Resource (CCXR) for Consortium members. The facility is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) and complies with all United States Department of Agriculture (USDA), Public Health Service (PHS), Washington State and local area animal welfare regulations. Comprehensive animal husbandry services are provided for all vertebrate animals used in the Consortium’s programs of research. CMSR works closely with the Institutional Animal Care and Use Committee (IACUC) to assure regulatory compliance and welfare of the animals used in research. The CM Director/Attending Veterinarian is a permanent member of the IACUC. For any researcher, an IACUC approved research protocol as well as IACUC and CMSR required training programs need to be completed for gaining access to the facility and working with research animals. The CMSR was rated “Outstanding to excellent merit” assessment in 2008, and resource staff have continued to seek opportunities to strengthen or expand services as necessary to further advance the research of the Consortium Programs. For example, the new CCXR service was developed to support the maturation of the Tumor Models developing shared resource, which was was established during the current roject period to provide mouse models for understanding the biology of human cancers, particularly focusing on prostate and hematopoietic cancers. To continue expanding access to mouse xenograft models for a wide range of tumors, we recently established a collaboration with the Jackson Laboratories Patient Derived Xenograft (PDX) Consortium, and these activities have been integrated with the CMSR (see below).

Major Services
Facilities and Equipment
The CMSR occupies a total space of approximately 36,200 net square feet at FHCRC with the CCXR occupying 240 square feet of primary space at the University of Washington and additional housing for 120 dogs at our South Snohomish Facility (SSF). All housing and use of vertebrate animals is done in CMSR’s centralized facilities spread over two locations. Species capabilities include laboratory rodents, dogs, and fish. The facility can accommodate more than 10,000 rodent cages, fish tanks that can hold more than 30,000 fish (zebra fish and stickleback fish) and kennels that can house more than 200 dogs. CMSR manages all animal care, veterinary care, research support services and maintenance issues at the FHCRC facility. CMSR manages and provides veterinary care and research support services at the SSF location and daily animal care is provided as a contract services. Heating, cooling, and ventilation systems of all building areas are constantly monitored and air supply is 100% fresh from the outside with no recirculation. Both animal facilities have stringent card-key controlled access, video surveillance, and are under direct daily patrol by trained security officers. Collectively, these facilities offer the high quality environments and professional expertise necessary to support a broad variety of program areas in translational research. Research projects are developed in collaboration with veterinary staff for the best possible standards of care, and investigators work alongside resource staff in daily evaluations and treatments.

Small Animal Unit
The small animal facility of CMSR (approx. 29,000 square feet) is located at FHCRC and includes entry airlocks, administrative and staff support rooms, locker rooms, a centralized cage wash and autoclave facility, four ABSL-2 rooms, a radiation hazard suite, quarantine, necropsy facility, multiple rodent surgery/procedure rooms, imaging rooms and 45 dedicated housing rooms for rodents and fish. All facilities are operated under specific pathogen-free barrier conditions with equipment and procedures intended to maintain the animal colonies free of adventitious diseases. Mice and rats are monitored utilizing the sentinel health monitoring program. Rodent health diagnostic testing includes broad-panel serology, plus whole-health monitoring including pathology screening, bacteriology and parasitology assessments, on at least a quarterly basis for all rodent rooms. The FHCRC veterinary pathologist is also available to perform necropsy and histopathology examinations and screening of individual clinical cases.
A broad variety of rodent models, many with genetic modifications including strains with immune deficiencies, are housed in HEPA filtered individually ventilated micro-isolator cage environments. A central cage wash facility equipped with BetterBuilt rack wash, tunnel wash, bedding dispenser, garb-el, and multiple autoclaves provide wash facilities and sterilize all housing equipment prior to use. All animal feed and cage enrichment materials are irradiated and only purified water is provided. Husbandry is performed in HEPA filtered laminar flow cabinets using high-level disinfectants by gowned technicians. Procedure and surgical areas contain class II biosafety cabinets, downdraft and necropsy stations, Isoflurane vaporizers, glass bead sterilizers and warm water circulation pads.

The small animal facility also houses multiple imaging platforms utilized by the Translational Bio-imaging Core resource which are discussed in the TBIC narrative. The location of these imaging instruments within the small animal facility enables rodents to move between technologies while maintaining protection from environmental variables, adventitious disease, and minimizing physiologic stress. Collaborative studies occasionally require rodents to use imaging platforms located at the University of Washington (UW) and then later on platforms located at the FHCRC. Accommodation of these studies is met through a dedicated quarantine housing room with negatively pressurized HEPA filtered individually ventilated cages. This housing, disinfection procedures, and husbandry procedures allow the maintenance of separation between these higher risk imaging colonies and all other colonies located in the facility. UW and FHCRC have a standing inter institutional agreement which facilitates transfer of animals between the institutions.

Other equipment includes - Mark I Cesium irradiator, Mopec Necropsy Station, multiple Allentown IVCs, multiple Tecniplast IVCs, 2 Innovive IVCs with disposable cages for quarantine, 2 Backdraft stations, multiple Class II Biosafety cabinets, multiple HEPA Filtered laminar Flow Hoods, multiple Isoflurane vaporizers and warm water circulation pads for surgical support, updated cage wash systems (tunnel, rack washer) and multiple autoclaves.

Large Animal Unit
The CMSR Canine Facility is managed at two locations; One at FHCRC (approximately 7,200 net square feet) where animal preconditioning and hematopoietic cell transplants are done as well as major and minor operative procedures, and the SSF facility which is used principally for breeding, short and long term animal housing, and research-related treatments following experimental manipulations done in the FHCRC facility. These facilities are used for housing, care, and experimental use of laboratory beagles, beagle crosses and other breeds of dogs with naturally occurring heritable disorders. The FHCRC facility holds approximately 45 dogs and includes eight animal holding rooms with hose-down kennels, two of which have BioBubble containment units, an animal diet kitchen, administrative and staff support rooms, a large chamber autoclave and laundry facility, a treatment/procedure room with self-contained intensive care unit, a dedicated sterile surgery facility with adjacent surgeon’s scrub sinks, two operational I-Stat handheld clinical analyzers, two COBE spectra apheresis systems, and a recently upgraded 6 MeV 600 CD (Varian) linear accelerator which is used for total body irradiation experiments in several of the animal-based research programs. A dedicated room for clinical trials in pet canine cancer patients was recently developed. This room has high biocontainment standards, including a HEPA filtered biobubble entry, highly restricted traffic and air flow controls. A dedicated necropsy room fitted with down-draft table and ductless fume hood for post-mortem gross pathological evaluations.

The FHCRC-based canine sterile surgery suite contains two anesthesia machines with Isoflurane vaporizers and pediatric bellows. State-of-the-art intra-operative patient monitoring and support equipment in the surgery include two capnographs with pulseoximetry, a vital signs monitor with electrocardiography, and forced-air temperature management blankets. An I-Stat handheld clinical analyzer, programmable infusion pumps, several ultrasonic doppler flow detectors, and two clinical centrifuges help support care. Two COBE Spectra apheresis systems also sit within the resource. All dogs are provided high quality laboratory-grade chow with supplements as needed and drinking water is delivered ad libitum via automated lixit-type water systems. A diagnostic x-ray machine with automatic film processor and a portable high-resolution laptop ultrasound unit are also located conveniently in the same area for veterinary care and research support.

The canine population at the SSF facility recently moved to this facility in January, 2014. The South Snohomish Facility (SSF) is located in a building provided by the Shin Nippon Biomedical Laboratories (SNBL) USA at
Everett, WA, and is located approximately 30 miles from the FHCRC campus. CMSR will remain in charge of care for this breeding colony. Husbandry services for the animals will be provided by SNBL under a contract agreement. The facility includes 12 animal housing rooms with new flexible kennel systems to house dogs. The maximum capacity of the facility will be around 120 dogs. The housing capacity for dogs will be restricted to 175 after moving to SSF which is lower than the previous capacity of 225 dogs, however, we expect this to be adequate to support the existing research programs as the dog population has decreased in the last 2 years. The SSF location is AAALAC accredited (through SNBL) and complies with all federal and state regulations on use of animals for research. While FHCRC IACUC will maintain primary responsibility for these animals, there is a Memorandum of Understanding (MOU) between the IACUC’s of FHCRC and SNBL to share some of the responsibilities. In addition to the office space for CMSR employees, there will be a procedure/treatment room and cage wash facility. Access to imaging and surgical facilities is available within the building. The two dedicated USDA complaint vans will be used for transportation of dogs between SSF and main campus.

The Comparative Pathology Service occupies a separate office and lab at the FHCRC facility. Major equipment includes a Nikon Eclipse 50i microscope with teaching head and a Nikon DS camera head and control Unit DS-L1. The Consortium Experimental Histopathology Shared Resource provides the processed and stained slides to the pathologist for evaluation.

**CCXR**
The CCXR, located within the K-wing vivarium at the University of Washington’s Magnuson Health Sciences Complex, maintains the highest level of Specific Pathogen Free (SPF) within the UW system. The Core has a dedicated room (20’ x 12’) for housing mice and performing xenograft and surgical procedures. The mice are housed in BSL-2 individually ventilated cages with filtered air, and cage changing is performed in a laminar flow hood. The CCXR maintains a breeding colony of NSG immune deficient mice used to generate recipient stock mice for human tumor fragments. The room also contains a dedicated isoflurane anesthesia machine (Euthanex EZ-7000) designed specifically for use with small laboratory animals. Xenograft tissue samples are stored in a Panasonic Ultra-low chest freezer (model #MDFC2156VANCPA) which is hooked up to a LN2 back-up tank in case of power failure. The CCXR utilizes imaging, histology and pathology services available in other core resources.

**Technologies and expertise**

**Animal Husbandry and Care**
CMSR provides daily husbandry and care services of large and small animals that include housing, feeding, watering and enrichment of animals in accordance with the recommendations of the ‘Guide for Care and Use of Laboratory Animals’. In addition to the standard practices, the special housing, husbandry and care requirements of many small and large animals that have specific requirements are also met. These animals include mice with genetic modifications, immune deficiencies of varying severity, and rodent models of infectious diseases. Canine models that need special husbandry requirements include models of immunotherapy, radiation therapy, graft versus host disease (GVHD), Lymphoma and gastrointestinal (GI) toxicity as well as canine models of genetic diseases such as Duchene Muscular Dystrophy, Severe Combined Immune Deficiency and Pyruvate Kinase Deficiency. CMSR provides daily care for more than 20,000 mice, 130 dogs and other species of animals.

**Veterinary Services**
Veterinary Services provided by CMSR involve preventive medicine including vaccinations for dogs, disease surveillance, quarantine programs, health management/monitoring programs, daily observation of animals for illness, veterinary care of all sick animals and maintenance of medical records. Veterinary services also include providing researchers with veterinary consultation for research protocol preparation (Pre-veterinary review), providing advice regarding selection of agents for sedation, analgesia, and anesthesia during development of protocols and considering revisions to ongoing protocols. Pre-veterinary review includes assessment of the pain/distress category assigned by the investigator completing the application or revision. Additionally, all FHCRC clinical veterinarians are involved with protocol review and attend the IACUC meetings.

**Research Support/Technical Services**
A number of research-driven technical support services are provided by the resource, including anesthesia, test article injections, blood and tissue sampling, animal identification, rodent colony breeding and
management, animal shipping, major and minor surgeries and bone marrow harvests. Services offered by the large animal facility to investigators include clinical pathology, ante-mortem tissue biopsies, ultrasound and x-ray evaluations, normal breeding as well as artificial insemination of dogs, administration of medications and test articles, total body or regional irradiations, blood and bone marrow sampling, catheterizations, surgeries, general anesthesia and post-operative supportive care, blood transfusions, necropsy services, and carcass disposal.

**Imaging Support**
CMSR works closely with Consortium Translational Bioimaging Core Shared Resource (TBIC) to support rodent and large animal imaging to ensure appropriate methods of handling, anesthesia, infection control, and anatomic/physiologic interpretation of findings. CMSR works case-by-case with faculty investigators and the TBIC so that housing, transportation, veterinary care, and regulatory approvals meet institutional standards and federal requirements through all project stages, including those involving TBIC resources located at the UW. Advance communications between the veterinary care personnel and the IACUC of consortium partners sites assure that all aspects of these studies proceed uneventfully. CMSR’s animal transportation cargo vans are scheduled so that these highly valuable research rodents can move between sites in accordance with regulatory requirements and without significant risk.

**Pathology Services**
A board certified veterinary pathologist, provides comparative pathology services to consortium investigators, including necropsy and hands-on mouse necropsy instruction, consultation and evaluation of histopathology slides, description and interpretation of gross and microscopic lesions, assistance or collaboration in manuscript and grant preparation (lesion description, data summary and interpretation, image production). In addition, Comparative Pathology also provides valuable assistance with interpretation of experimentation with genetically-engineered mice and phenotyping of genetically engineered mice.

**Patient-Derived Xenografts (PDX)**
A pre-clinical Tumor Models developing shared resource was established during the current project period to provide models for understanding the biology of human cancers, particularly focusing on prostate and hematopoietic cancers. During the project period, 12 unique members have used this resource and these activities have been well supported by research grants. To continue expanding access to mouse xenograft models for a wide range of tumors, Consortium members recently established a collaboration with the Jackson Laboratories Patient Derived Xenograft (PDX) Consortium. These tumor model activities have been combined with the CMSR.

The Cancer Consortium Xenograft Resource (CCXR) which makes available PDX for cancer research. CCXR has three major components: 1) Tissue acquisition through the Consortium Northwest BioTrust Shared Resource (NWBT) 2) Distribution of tissue to the Jackson Laboratory who develops xenografts in immune deficient mice (NSG strain); and 3) The receipt and management of xenografts and mice following which they are distributed to investigators, or carry out in-house treatment protocols by request. The expertise is thus available for collection of patient tumor fragments, the initial engraftment, and the subsequent performance of experimental protocols. The NWBT works with repositories throughout the Cancer Consortium to coordinate solid tumor specimen acquisition and distribution efforts in conjunction with the UWMIC Depts. of Surgery and Pathology, and in accordance with all applicable human subject rules and regulations.

**Importance to Scientific Programs**
CMSR plays an important role in a variety of research projects that are critical to the mission of the Consortium, which include cutting edge research in cancer and cancer-related infectious diseases. Selected descriptions of projects being conducted within the facility are outlined below, emphasizing the importance of the resource to peer reviewed research.

**Small Animal**

**Jonathan A. Cooper, PhD, Cancer Basic Biology**
Four publications from the Cooper laboratory, supported by R01’s from the NCI and NINDS, supported the investigation of signaling pathways that regulate cell migrations during embryonic brain development. CM staff assisted in the preparation of "knock-in" mutant mice by performing blastocyst injections and embryo transfers,
and the Vivarium was used to maintain mutant mouse strains, prepared at FHCRC or imported from other investigators, and breed the mice through various crosses. In some cases, new strains were imported as frozen embryos or ES cells, and blastocyst injections/embryo transfers were performed in-house. CM also provided and maintained the procedure rooms that were used for in utero surgery to transfer DNA into cells in the developing brain. The papers demonstrated (i) the importance of different phosphorylation sites in the Src substrate protein Dab1 for different aspects of cell migration in the developing brain; (ii) the importance of a phosphotyrosine-specific ubiquitin ligase (the Cullin5-RING ligase) in development of the fore- and hind-brain; and (iii) unexpected roles for N-cadherin in Src signaling during migration.


Mark Groudevne, MD,PhD, Cancer Basic Biology
Michael Bender, MD,PhD, Hematologic Malignancies
The β-globin locus control region (LCR) is necessary for high-level β-globin gene transcription and differentiation-dependent relocation of the β-globin locus from the nuclear periphery to the central nucleoplasm and to foci of hyper-phosphorylated Pol II “transcription factories” (TFs). To determine the contribution of individual LCR DNaseI hypersensitive sites (HSs) to transcription and nuclear location, we compared β-globin gene activity and location in erythroid cells derived from mice with deletions of individual HSs, deletions of two HSs and deletion of the whole LCR. We found that each HS has a similar spectrum of activities, albeit to different degrees. Each HS acts as an independent module to activate expression in an additive manner, and this correlates with relocation away from the nuclear periphery. In contrast, HSs have redundant activities with respect to association with TFs and the probability that an allele is actively transcribed. The limiting effect on RNA levels occurs after β-globin genes associate with TFs, at which time HSs contribute to the amount of RNA arising from each burst of transcription by stimulating transcriptional elongation. CMSR was helpful in maintaining care for the numerous strains of mice essential for this work.


Robert N. Eisenman, Ph.D., Cancer Basic Biology
This laboratory studies molecular mechanisms underlying tumor initiation and progression with a strong focus on the myc oncogene family. A major event in Myc-driven lymphomagenesis (in mice bearing an Em-myc transgene) involves secondary mutations that bypass apoptosis in cells that express activated Myc genes. To identify novel genes involved in evasion of apoptosis during tumorogenesis, Mendrysa et al. increased the sensitivity to apoptosis by generating Em-myc-driven lymphomas in an mdm2 mutant background. We then performed a large-scale proviral insertional mutagenesis screen based on the hypothesis that in tumors appearing in these mice, the spectrum of retroviral insertions would be shifted toward loci encoding strong anti-apoptotic genes. Nine novel common insertion sites specific to mice with this sensitized genetic background were identified two of which were validated as novel oncogenes.

In the Conerly et al. study we examined changes in gene occupancy of the important histone variant H2A.Z during lymphoma progression in Em-Myc tumors. We found a progressive depletion of H2A.Z around transcriptional start sites (TSSs) during MYC-induced transformation of pre-B cells and, subsequently, during lymphomagenesis. Furthermore H2A.Z and DNA methylation were generally anticorrelated around TSSs in both wild-type and MYC-transformed cells. Our results indicate that antagonism between H2A.Z deposition and DNA methylation is a conserved feature of eukaryotic genes, and that transcription-coupled H2A.Z is likely to play a role in cancer initiation and progression. Both of these studies were highly dependent on the CMSR resource which permitted us to validate, maintain and breed our mouse models of human cancer.
William M. Grady, MD, Gastrointestinal Cancer

The accumulation of genetic and epigenetic alterations mediates colorectal cancer (CRC) formation by deregulating key signaling pathways in cancer cells. In CRC, one of the most commonly inactivated signaling pathways is the transforming growth factor-beta (TGF-β) signaling pathway, which is often inactivated by mutations of TGF-β type II receptor (TGFBR2). Another commonly deregulated pathway in CRC is the phosphoinositide-3-kinase (PI3K)-AKT pathway. Phosphatase and tensin homolog deleted on chromosome 10 (PTEN) is an important negative regulator of PI3K-AKT signaling and is silenced in approximately 30% of CRC. The combination of TGFBR2 inactivation and loss of PTEN is particularly common in microsatellite unstable CRCs. Consequently, Yu et al determined in vivo if deregulation of these two pathways cooperate to affect CRC formation by analyzing tumors arising in mice that lack Tgfbr2 and/or Pten specifically in the intestinal epithelium. We found that lack of Tgfbr2 (Tgfbr2<sup>IEKO</sup>) alone is not sufficient for intestinal tumor formation and lack of Pten (Pten<sup>IEKO</sup>) alone had a weak effect on intestinal tumor induction. However, the combination of Tgfbr2 inactivation with Pten loss (Pten<sup>IEKO</sup>;Tgfbr2<sup>IEKO</sup>) led to malignant tumors in both the small intestine and colon in 78% of the mice and to metastases in 10% of the mice. Moreover, these tumors arose via a β-catenin independent mechanism. Combined loss of Tgfbr2 and Pten in tumors led to increased cell proliferation, decreased apoptosis, and decreased expression of cyclin-dependent kinase inhibitors. Thus, TGF-β signaling inactivation and PTEN loss appear to cooperate to converge to drive intestinal cancer formation and progression by suppressing cell cycle inhibitors. The CM supported these studies through the use of the Vivarium to maintain mutant mouse strains, prepared at FHCRC and imported from other investigators and through cross-breeding multiple mouse strains. The CM also provided instruction in necropsy techniques.


Support for these studies was provided by the NIH (RO1CA115513, P30CA15704, UO1CA152756, U54CA143862, and P01CA077852 WMG), a Burroughs Wellcome Fund Translational Research Award for Clinician Scientist (WMG), and an Interdisciplinary Training in Cancer Research Grant (T32 CA080416, SMM).

Valeri Vasioukhin, PhD, Prostate Cancer

Our use of CMSR was critical in identification of a novel gene and a novel developmental mechanism involved in proper morphogenesis of mammalian lung. The lung is one of the best-studied examples of a developing organ that undergoes the highly coordinated process of branching morphogenesis coupled with timely progenitor cell differentiation. Together, these events result in the formation of an organ containing branched airways that terminate in millions of functional alveolar sacs enabling adequate lung function. Failure of proper lung development can result in neonatal death or chronic pulmonary disease. We used a gene knockout strategy in mice and found that Dlg5 is required for proper mammalian lung morphogenesis as Dlg5<sup>-/-</sup> mice developed completely penetrant emphysema-like phenotype. We showed that Dlg5 regulates apical cell polarity by binding to aPKC and maintaining its apical membrane localization. This study demonstrated a critical role of apical-basal cell polarity mechanisms in regulation of mammalian branching morphogenesis and differentiation of progenitor cells.


William M. Grady, MD, Gastrointestinal Cancer

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Amanda Paulovich, MD, PhD, Cancer Basic Biology, Women's Cancer

This study demonstrated that a staged, targeted mass spectrometry-based pipeline for discovery, triage, and quantitation of a significant number of biomarker candidates is a feasible approach for developing novel biomarkers of utility in plasma. The proof-of-principle experiments performed using a mouse model of breast cancer (a doxycycline-inducible, bitransgenic MMTV-tTA/TetO-NeuNT model) demonstrated sufficient sensitivity, precision, specificity, and multiplexability to be useful for large-scale implementation in human studies. All animal housing, breeding, treatments, and sample procurement were performed in the CMSR. This study was funded by grants from the Paul G. Allen Family Foundation (Cancer Biomarker Discovery and Validation, PI: Hartwell) and National Institutes of Health grant U24 CA126476 (Measuring Cancer Biomarker Candidates by Targeted MS and Ab Enrichment, PI: Paulovich, Carr, Anderson) from the National Cancer Institute Clinical Proteomic Technology Assessment Center (CPTAC).


David MacPherson, PhD, Cancer Basic Biology

Mouse Models of Human Cancers

My laboratory uses genetically engineered mice to understand major cancer genes. We focus on the RB-deleted cancers retinoblastoma and small cell lung carcinoma (SCLC). Our major recent effort has been to sequence human SCLC samples for mutations and then use sensitized mouse models of SCLC to interrogate roles for new potential driver genes. These models involve deleting the Rb and p53 tumor suppressors as well as mutating additional candidate driver genes in the lung epithelium. We have a number of ongoing studies that interrogate roles for genes newly implicated in SCLC. This unpublished work makes extensive use of the resources provided by CMSR - our animals are housed in the Vivarium maintained by CM. CM provides strong veterinary support to our mouse colony and CM staff maintain procedure and necropsy rooms that we use for our studies. Our studies are supported by R01CA148867, "Using mouse models to understand retinoblastoma initiation and progression"

Eduardo Mendez, MD, Cancer Epidemiology, Prevention and Control

This study characterized a metastatic gene set based on DNA copy number abnormalities (CNAs) of differentially expressed genes in oral cancer by comparing DNA and RNA of OSCC cells laser-microdissected from non-metastatic primary tumors with those from lymph node metastases. A 95-gene signature was identified and found to be prognostic of survival in patients. To identify potential therapeutic targets, candidate over-amplified/over-expressed genes where knock-down in a panel of head and neck cancer cell lines in a high-throughput format with RNAi screens. Cell lines were tested for tumorigenicity in an orthotopic mouse...
model of tongue cancer which recapitulates not only tumor growth in the tongue but the lymphotropism of squamous cell carcinoma. Top candidates with greatest effect on cell viability upon inhibition are being tested using inducible lentiviral knockdowns in vivo using this orthotopic model of tongue cancer. All experiments were done in Comparative Medicine with the assistance of experienced CMSR staff. Assistance was provided by CMSR staff when the mice where imaged and anesthetized for tongue injections and tumor monitoring. CMSR maintained the animals and monitored them daily performing euthanasia and other procedures when necessary.


Christopher Kemp, PhD, Cancer Basic Biology
Using a “systems biology” approach – which focuses on understanding the complex relationships between biological systems – to look under the hood of an aggressive form of breast cancer, researchers for the first time have identified a set of proteins in the blood that change in abundance long before the cancer is clinically detectable. CMSR maintained the animals and monitored their health daily performing additional procedures when necessary.


Slobodan Beronja, PhD, Cancer Basic Biology
Walsh, et al. are validating a set of genes identified as essential and specific to oncogenic Hras function in the mouse epidermal squamous carcinoma. This work heavily depends on the use of a transgenic mouse model of oncogenic hyperplasia that is housed by the CMSR. Moreover, candidate gene function analyses are performed in mice that are stably transduced with lentivirally-encoded RNAi constructs. This in vivo transduction is achieved through ultrasound-guided microinjections into mid-gestation embryos, and the procedure is performed using the space and equipment provided by the CMSR.


Elahé Mostaghel MD PhD, Prostate Cancer Research
Factors influencing the responses of prostate cancers to AR axis targeting are poorly understood and are critically needed as predictors of treatment efficacy. Using two patient-derived xenograft models of advanced prostate cancer, we find that molecular differences in basal steroidogenesis and expression of AR splice variants associate with response to ligand synthesis inhibition. Direct examination of metastatic human prostate tumors showed that in situ metastases demonstrate a patient-specific range of tumor androgen levels and differences in AR expression similar to that observed in the xenograft models. These data demonstrate that intrinsic differences in basal steroidogenesis and expression of ligand-independent AR variants associate with response and resistance to pre-receptor suppression of AR ligands, and may be relevant as biomarkers for optimizing treatment strategies that inhibit ligand-synthesis or target the AR directly. CMSR maintained the animals and provided daily monitoring and performed additional procedures as needed.


Large Animal
Rainer Storb, MD, Hematologic Malignancies
Inducible costimulatory (ICOS), a member of the CD28 family of costimulatory molecules, is expressed on the surface of CD4+ and CD8+ T cells after activation. The nature of ICOS up-regulation on activated T cells and the expression of the ligand Bh.7, make ICOS a potential candidate for therapeutic approaches to two major issues in allogeneic hematopoietic cell transplantation: graft rejection and graft-versus-host disease (GVHD). In this paper we described the production of the anti-ICOS monoclonal antibody, specificity of expression, and binding characteristics to lymphocytes isolated from dogs undergoing chronic GVHD or hematopoietic cell graft rejection. The kinetics of up-regulation and high expression levels of ICOS in the canine GVHD model suggest that an anti-human equivalent antibody may offer a potential therapeutic approach to the treatment of chronic GVHD in the clinic. The development and testing of anti-ICOS was made possible through the following Fred Hutchinson Cancer Research Centers’ shared resource facilities: Comparative Animal Medicine, Antibody Development, Biologics Production, Experimental Histopathology, and Flow Cytometry.


**George Georges, MD, Hematologic Malignancies**

CMSR supports Dr. Georges research to determine the biological significance of drugs used in preventing Acute Radiation Syndrome after treatment with high dose total body irradiation. This study is also critical for patients undergoing hematopoietic cell transplantation since this work will identify drugs that will reduce the effect of mucositis and complication of GI syndrome. Continuous and skilled support for the animals that underwent radiation and follow-up therapy is critical for success of this study. The CMSR large animal group provides 24-hour, intensive care support to the dogs assigned to this study.


**Brenda M. Sandmaier, MD, Hematologic Malignancies**

Yun, et al. investigated radioimmunotherapy with an anti-CD45 mAb labeled with the alpha-emitter astatine-211 (At-211) as a conditioning regimen in dog leukocyte antigen-identical hematopoietic cell transplantation (HCT) to reduce toxicity associated with external gamma beam radiation. Dose finding studies in 6 dogs treated with 100 to 618 microcurie/kg At-211 anti-CD45 mAb without HCT rescue demonstrated dose dependent myelosuppression with subsequent autologous recovery. Subsequently, 8 dogs conditioned with 155 to 625 microcurie/kg At-211 labeled anti-CD45 mAb before HCT followed by a short course of cyclosporine and mycophenolate motefill for immunosuppression had prompt recovery with long term donor chimerism. In conclusion, conditioning with At-211 labeled anti-CD45 mAb is safe and efficacious and provides a platform for future clinical trials of nonmyeloablative transplantation with radioimmunotherapy-based conditioning.

All the treatments and monitoring of the dogs under the study were done by the CMSR Staff and Clinical Veterinarians at the SELU and First Hill Facilities. The Clinical Veterinarian reviews and approves the experimental study protocol for CM staff to follow. The CM staff schedules the dog for treatment before and after the injection of the At-211 labeled anti-CD45 mAb. CM provides and prepares the room used for the injection of the At-211 labeled anti-CD45 mAb. The CM staff performs blood draws, bone marrow harvest, infusion of the bone marrow to the recipient dog, assists in injection of the At-211 labeled anti-CD45 mAb, administers the immunosuppressive drugs, supportive drugs, and blood for transfusion. CM staff performs kidney, lymph node and bone marrow biopsies when needed. The staff monitors the condition of the dogs twice daily and enters it on the DVMAX, which allows investigators access to the dogs clinical condition and serves as a source for documentation of clinical data. At the end of the study, the assigned CM staff will perform the necropsy. The necropsy samples are then sent to Experimental Histopathology by the CM staff.

The necropsy samples were processed in the Experimental Histopathology department for pathological examination. The anti-CD45 mAb was produced at the Biologics Production facility, blood samples stained with...
canine mAbs were analyzed using the Flow cytometry facility and donor chimerism analysis was done at the Genomics facility.

Yun Chen, Brian Kornblit, Donald K. Hamlin, George E. Sale, Erlinda B. Santos, D. Scott Wilbur, Barry E. Storer, Rainer Storb and Brenda M. Sandmaier. Published in Blood, 2 February 2012, Volume 119, Number 5.

PDX
The successful treatment of cancer is increasingly dependent on targeting therapy to specific tumor characteristics. Giving our scientists access to a broad “library” of tumor types in a living (mouse) model will enable them, for example, to determine which drugs are likely to work best in particular types of cancer patients, including whether specific sequences or combinations of drugs show more potential than a single drug alone, without having to expose patients to potentially ineffective and toxic drugs. Having a number of mice with identical tumors can also accelerate research progress by enabling researchers to test several different therapeutic approaches simultaneously. Building a repository representing a wide array of cancer types can enable research to proceed, even in the absence of access to patients with those particular types of cancer. Potential users of the service include the following CCSG programs and investigators:

Jim Olson, MD, PhD, Cancer Basic Biology
Hubert et al provide an example of how the Olson lab identifies, prioritizes, and advances therapeutics into clinical trials for children with brain cancer, with increasing focus on types of brain tumors that are uncommon and have the greatest need for translational research. CCXR staff will develop and manage PDX mouse models to be used to test hypotheses generated by the screening and validation programs, with anticipation of advancing the most effective combinations of drugs into the next generation of national clinical trials through the multiple clinical trial consortia.

Hubert CG et al., Genome-wide RNAi screens in human brain tumor isolates reveal a novel viability requirement for PHF5A. Genes Dev. 2013 May 1;27(9):1032-45.

Ray Monnat, MD, PhD, Cancer Basic Biology
Lauper et al describe how the Monnat lab is investigating the molecular mechanisms that insure genome stability, and how these modulate cancer or disease risk and the response to therapy. This work is focused on the human RECP helicases that play key roles in DNA metabolism. Loss of function of three RECP proteins, WRN, BLM and RECP4, cause the heritable genetic instability/cancer predisposition diseases Werner, Bloom and Rothmund-Thomson syndromes respectively. Loss or aberrant expression of several of these proteins may also be common in adult cancers, and may modulate the response to chemotherapy. CCXR staff will generate PDX mouse models to be used to test new or current drugs.


Bill Grady, MD, Gastrointestinal Cancer
Grady describes how his lab is pursuing discoveries that could revolutionize the way colorectal cancer is prevented, detected and treated. Colorectal cancer ranks as the third most commonly diagnosed, and second-deadliest form of cancer in the United States in men and women. The cancer develops from polyps, which are benign initially but transform into cancerous tumors. Those cancer cells invade and destroy nearby tissue, and can break away from the original tumor to form new tumors in other parts of the body. CCXR staff will assist in the development and management of PDX mouse models that will be used to test how these invasive tumor cells respond to drug combinations.


Cost Effectiveness
The CMSR shared resource operates in a cost effective manner while maintaining a high level of service to investigators within the Consortium. Appropriate adjustments are made with respect to staffing levels and operations as needed. By thoroughly training of all users and daily maintenance of the instruments, the
resource can keep maintenance costs to a minimum. Rodent and canine housing rates are lower than other size-comparable institutions in Seattle as well as within the Western AAALAS Region. The cost of services and housing are reviewed regularly by CMSR staff in order to update prices and accurately reflect current practice. The faculty advisory committee reviews any change in rates before. All the cost calculations are performed based on NCRR Cost Analysis and Rate Setting Manual for Animal Research Facilities.

### Use of Services

<table>
<thead>
<tr>
<th>Service</th>
<th>Total Users</th>
<th># Peer Reviewed</th>
<th># Non-Peer Reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large Animal Per Diem Days</td>
<td>15</td>
<td>13 (87%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Small Animal Per Diem Days</td>
<td>62</td>
<td>57 (92%)</td>
<td>5 (8%)</td>
</tr>
</tbody>
</table>

### Management Structure, Policies and Operations

**Administration**

CMSR operates in accordance with Consortium and institutional policies for Shared Resources. The resource is under the direction of the Attending Veterinarian, Rajesh Uthamanthil DVM, Ph.D., in consultation with the Consortium Director of Shared Resources, Paul Woloshin, MBA, Ph.D. Faculty oversight of the resource is provided by an advisory committee responsible for reviewing CMSR operations on annual basis, providing review of user fee changes, evaluating capital budget requests and providing guidance on future goals and objectives. The current advisory committee consists of: M. Bender, MD, Ph.D. (Hematologic Malignancies), Denny Liggitt, DVM, PhD (UW), Hans-Peter Kiem, M.D. (Hematologic Malignancies), David MacPherson, Ph.D. (Cancer Basic Biology), Valera Vasioukhin, Ph.D. (Prostate Cancer), Chris Kemp, Ph.D. (Cancer Basic Biology), and Ray Monnat, M.D. (Cancer Basic Biology). The Consortium’s Scientific Steering Committee ensures that this and other Consortium resources are aligned with the Consortiums strategic goals and its continued value to the Cancer Center.

**Access and Usage Policy**

Services are available to all members of the Consortium, on a first-come, first served basis. Support is provided to external users as time permits. Costs are charged directly to applicable awards based on actual usage. Rates are based on projected operating costs net of CCSG and institutional support. Rate schedules are revaluated and revised as required on an annual basis. External user fees reflect the full cost (both direct and indirect) of rendering service according to the most recent rate revision. No benefit of institutional or federal funding receive by the resource is considered in the establishment of outside rates.

**Billing**

Standardized service request forms provide authorization of service and requested information for each respective transaction. Services are billed upon completion in accordance with OMB policies and information is entered into a Shared Resources automated billing system which provides the ability to track resource use at the project level by activity. Ongoing review is conducted to monitor activity levels and observe usage trends to ensure appropriate adjustments are made in operations to adapt to changing demand. Usage is assessed and summary reports are develop by institution, by investigator, and by program for each service provided by the resource. Ongoing evaluation of resource operations is conducted through implementation of appropriate analyses, benchmarking studies, surveys and other tools.

**Education and Outreach**

Users are kept up to date on changing technologies and services offered by the facility through the FHCRC and Consortium websites, Shared Resource Newsletter, and special memo distributions. Outreach to the broader Consortium community, particularly those within the UW and Children's Hospital, will be enhanced through the activities of the UW Institute of Translational Health Sciences (ITHS). As an ITHS approved facility, it is anticipated that the Resource will play an ongoing and expanded role in support of translational research activities. Also, Consortium Shared Resources can be found through eagle-I, a web-based, searchable nationwide network of scientific services. Resource employees keep current in their field through scientific publications, seminars and national conferences.

**Priorities and New Initiatives**

The priorities for the CMSR are 1) Develop strategies for more efficient space utilization including high density animal housing, 2) Support TBIC through better coordinating transportation and movement of animals as well
as better work flow for sharing imaging equipment, 3) Develop increased ABSL2 and other containment housing systems to support projected increase in infectious disease research, 4) Further improve research support services to accommodate increase in animals and clinical procedures, 5) Work closely with CCXR resource to provide better support for Patient Derived Tumor Xenograft (Avatar) models 6) Develop more efficient training and communication strategies (that include development of a new CMSR website that provide latest news and other resources, new thrust in providing more hands on training, use of new animal management software that allow better communication etc., 7) Improve efficiency in managing animal protocols by the IACUC, tracking staff training, as well as animal inventory, ordering and billing through the implementation of new web-based software by Topaz Technologies.

Personnel

Key Staff Qualifications

Rajesh K. Uthamanthil, D.V.M., MVSc, Ph.D., DACLAM, Director and Attending Veterinarian. Dr. Uthamanthil received his clinical veterinary degree in 1997 from Kerala Agricultural University, Kerala, India followed by M.V.Sc. in veterinary surgery and radiology. He has a PhD in comparative Biomedical Sciences from the University of Wisconsin-Madison (2004) and worked as a Post-Doctoral fellow at William Marsh Rice University, Houston (2004-2006). He is a licensed veterinarian in the US (2005) and is a Diplomate ACLAM (2009). Dr. Uthamanthil has more than 14 years of experience in comparative medicine that include working with various laboratory animal species, ranging from mice to non-human primates.

Michele Spector, DVM, Clinical Veterinarian - Dr. Spector received her DVM degree in 1994 from the University of Wisconsin and participated in a post-doctoral residency program in laboratory animal medicine at the University of Washington (1994-1997). Dr. Spector is licensed to practice veterinary medicine in the State of Washington and has 18 years of clinical laboratory animal medicine experience. She also has extensive experience working in and training with the Biological Resources Laboratory of the University of Illinois at Chicago.

Jennifer Duncan, DVM, Clinical Veterinarian - Dr. Duncan received her DVM degree in 1995 from Washington State University and she is licensed to practice veterinary medicine in the State of Washington. Prior to joining FHCRC in 2008, Dr. Duncan was Medical Director for the Northwest Organization for Animal Help, a regionally renowned animal shelter with state-of-the-art veterinary clinic and spay/neuter surgical suite. Her specialty knowledge of shelter medicine contributes to her success in helping with the large FHCRC dog breeding/holding colonies.

Sue Knoblaugh, DVM, DACVP, Veterinary Pathologist - Dr. Knoblaugh has 14 years’ experience as a veterinarian, nine of which have been in comparative pathology. She received her post-graduate training in comparative pathology and laboratory animal pathology at the University of Washington in the Department of Comparative Medicine and received board certification by the American College of Veterinary Pathology in 2009. Dr. Knoblaugh is an active member of the ACVP. Dr. Knoblaugh presented and taught a mouse necropsy lecture and wet lab at the 9th Annual Workshop on the Pathology of Mouse Models of Human Disease in 2010.

Warren Ladiges, DVM, MSc, Professor, Department of Comparative Medicine, CCXR. Dr. Ladiges will be responsible for the overall operations of the CCXR. He has a broad and longstanding area of expertise in cancer research and tissue and marrow engraftment. His postdoctoral work was done at FHCRC under the mentorship of Dr. Rainer Storb, where he established protocols to enhance successful marrow engraftment in dogs. He then accepted an academic position in the Department of Comparative Medicine at the University of Washington and established his own independent research laboratory. For his own studies, he has developed and used a number of mouse tumor engraftment models including patient derived tumors in nude mice and human and mouse tumor cell lines in a variety of mouse backgrounds.

Robert Hunter, BS, Research Scientist IV, Manager, CCXR, Department of Comparative Medicine. Mr. Hunter is well qualified to perform his duties with extensive experience in creating mouse xenograft models at the University of Arizona, and management of the Transgenic Mouse Program cost center at the University of Washington. He and Dr. Ladiges have worked together for the last seven years.
COMPUTATIONAL BIOLOGY SHARED RESOURCE

Introduction
The Computational Biology Shared Resource (CBSR) provides analysis of high throughput data on a genome-wide and/or proteome-wide basis and assists in experimental design, preprocessing and quality assurance of data, choice of analysis methodology and consulting services on appropriate software tools for each of these steps. The shared resource provides regular training sessions aimed at best practices methodology for assays and experiments that are widely used by Consortium members. The broad goal of the CBSR is to enable Consortium investigators to include genome-scale assays in their research, especially for novel technologies.

The CBSR represents the maturation of the Bioinformatics Developing Shared Resource currently funded by the CCSG. The Bioinformatics resource was successfully established under a prominent leader, Martin McIntosh, co-head of the Biostatistics and Computational Biology Program, to provide analysis of high-throughput data on a genome-wide and/or proteome-wide basis. The three services provided by this resource (drop-in consulting, project-based consulting and training and outreach) each had 28, 37 and 50 unique users during the project period (some with multiple visits), representing all partner institutions. Based on the maturity of this resource and increasing demand for these services, this resource is presented here as a full Shared Resource renamed Computational Biology.

The CBSR cooperates closely with the Genomics (GSR) and Proteomics/Metabolomics (PMSR) shared resources that offer basic analytic tools, but which emphasize standardized workflows. The CBSR focuses on problems that are outside the capabilities or scope of the standardized pipelines offered by the GSR and PMSR. These problems routinely arise in a research environment and may require modification to existing steps of a pipeline, the generation of customized queries or data processing steps, or the integration of disparate data sets. The resource promotes the use of genome-scale assays in Consortium research through the following five distinct activities 1) Consulting and programming expertise for investigators who need the assistance of specialized programmers with domain knowledge in biological research, 2) One-on-one training of research staff to help them gain the skills needed to process their data and interpret their results, 3) Education for Consortium research scientists and/or their staff in the most widely utilized technologies to allow them to gain sufficient expertise to perform independent analysis of their own data, 4) Ongoing technical support to staff through drop-in consulting services, 5) Acquisition of emerging technologies to respond to anticipated new avenues of research, by providing access to methods published in the literature or by disseminating methods developed within the Consortium Biostatistics and Computational Biology program. In the past year alone we have supported investigators from 8 of 9 Consortium scientific programs.

Major Services
Facilities and Equipment
The resource includes primarily intellectual expertise in the area of bioinformatics computing, but also maintains an installation of a number of bioinformatics programs and databases for ready access by Center investigators and staff. Current staffing for the Resource is 2FTE. The staff has access to five offices, one dedicated conference room, and a workroom, totaling approximately 1,295 square feet.

For storage of centralized reference sequences, annotations, and public data derived from biological systems of broad interest, the Bioinformatics Resource has a dedicated 4TB disk volume available on all Center servers and cluster nodes. Software available for processing data, available both to end users and to Resource staff, includes: R/Bioconductor, FastQC, BWA, Bowtie, TopHat, Cufflinks, GMAP/GSNAP, Samtools, Bedtools, NCBI Blast, ClustalW.

To run workflows based on this software and conduct data-intensive analyses, the Resource relies on the Center's extensive computing infrastructure, including three generally available large-memory servers and over 80 high-performance cluster nodes under control of the Slurm resource manager. For accounting purposes, the Resource assigns specific Principal Investigator accounts when submitting jobs. For jobs that cannot be assigned to a single specific PI, such as development of new workflows, computing usage is charged to the...
Resource itself; in any given reporting period, our use does not exceed thresholds established for an average group at the Center.

Other than broadly used reference files stored in our own 4TB disk volume, data typically transits through our Resource. It originates with the end user or another Shared Resource (e.g., Genomics or Proteomics) and is processed by the Bioinformatics Resource to generate one or more analytic datasets that are copied back to disk space managed by the PI of record. This strategy limits the growth of storage required by the Bioinformatics Resource.

Technologies and Expertise
The services provided by our research fall under the following five categories. Activities in each of these areas are tracked as part of our management and oversight of the resource. The categories are:

Project-based Consulting and Programming/analysis services
CBSR provides one-on-one consulting and programming services to Consortium investigators on a project-by-project basis. Users include investigators who plan to use non-standardized genome-scale assays as part of their research, who have a need to analyze their data in novel ways or want to integrate their data with other data sets that they or others have developed. Consultations are intended to evaluate the user’s bioinformatics needs, assess feasibility, and to determine a plan of action, of which most often includes a plan for the bioinformatics resource to produce a data set amenable for downstream analysis by the expertise of the project staff or their less specialized collaborators. This service addresses the large number of investigators whose research is dependent on a relatively short-term computational need for data processing but where the remainder of their research is within their expertise or can be within their expertise with an appropriate amount of supervision (see consulting section below). During the previous year we supported 66 project specific requests from 37 individual investigators, and at least one from each of the CCSG scientific programs. This represents a 13% increase in both number of projects conducted and number of investigators supported over the prior year. Expertise is provided for analysis of microarrays, high-throughput sequencing, genomics, and proteomics data, and combining this data with public bioinformatics resources. The majority of the effort has been in analysis of high-throughput sequencing data. The projects supported by this service typically share the characteristic that by overcoming a small number of computing barriers the Consortium investigator can move forward using either on their own or with the minimal expertise of our resource. Ongoing staffing of their project is not provided as a service of this resource although short-term support beyond the ordinary service maybe arranged as long as investigator funding is available and staffing demands allow.

Individualized drop-in consulting and ongoing technical supervision of staff
Many Consortium investigators have access to their own research staff, or a collaborator’s research staff, who have computational training adequate to execute much of the analytic plan for their research, but the investigators lack specific technical skills required to supervise these staff members in this area. To encourage Consortium investigators to build and retain analytic expertise in their own lab we provide two pathways: First, we provide twice-weekly drop-in sessions for any Consortium staff member to meet with a resource expert to discuss their work and analytic plans, or even get help using an analytic tool (e.g., IGV, UCSC genome browser, R, Bioconductor). These first-come-first-served sessions provide a forum for researchers and their staff to solicit feedback on proposed analysis plans, approaches, and seek advice on a variety of miscellaneous computing questions related to their labs research: to clarify material presented in our formal training courses, and to receive individualized tutorials on methods and software. Second, we support specific research projects in which the investigator has requested that we provide technical oversight to their staff for specific funded research projects over a period of time. We arrange this supervision for investigators whose staff members are sufficiently skilled to perform the large majority of research tasks that are anticipated and who only require occasional support or guidance. A resource staff member may be invited to lab-presentations, engage in regular one-on-one meetings with the staff member with or without the investigator, or may respond by email. While we do not have formal rules to govern the effort at this time, this service is offered only to those investigators whose research staff can work somewhat independently for days at a time without the need for ongoing assistance. Over the most recent two-month period, the number of visitors to our drop-in service has averaged four distinct individuals (and an equal number of investigator’s) per week. We presently support supervision of analytic staff from four different research groups representing both basic and clinical projects.
Training & Outreach
Another goal of the resource is to train individuals at the Center in computational techniques that will help them more effectively utilize our resource or the Genomics resource, or enhance their collaborative activities with computational colleagues. We have a unique position given our perspective on the large number of investigators and their collaborators we work with to identify ways to improve the interactions among Consortium members; even researchers or their staff who are computationally oriented lack biologically relevant background in computing that compromises effective collaborations with their biologically trained staff. Thus, through our training activities for tools that interface with genome-scale data sets, the resource plays an important role in fostering transdisciplinary collaboration among Consortium members. Classes with hands-on computing labs are offered to introduce genomics and proteomics techniques and analysis tools to a wide range of Consortium investigators or their staff. The classes have two tracks – one for staff who are predominately biologically oriented and those that are predominately computationally oriented (e.g., statisticians and computer scientists or programmers). We offer progressive course series on the R statistical computing environment and a variety of Bioconductor packages (including Introductory, Intermediate, and Advanced sessions), and specifically for biologists, an introduction to the basics of the R language (getting data in and out and basic data manipulation) and a series of classes that progress to applications of Bioconductor for short-read sequence data analysis. Two sessions of each level (each including Introductory, Intermediate, and Advanced classes) are offered per year with each session attracting the maximum 25 registrants. In the past year we have also offered a series of classes focused on interpreting sequence data related to cancer, focusing on the use of the University of California Santa Cruz (UCSC) cancer genome browser with one series of classes intended for people with a background in molecular biology, and one focused on non-biologically trained researchers and their staff which includes a component of Bioconductor related to accessing cancer genome data. This series of classes was primarily intended to allow scientists access to derived annotations regarding specific genes of interest, especially annotations that are being derived from large-scale genome projects such as the Cancer Genome Atlas (TCGA). A total of 40 individuals have attended each of the classes in this series (the class limit).

Technology acquisition and transfer
In collaboration with the Genomics Shared Resource, we evaluate quarterly emerging technologies and/or workflows to develop areas that may benefit from a strategic investment from our resource staff. New technical development is sometimes necessary for these approaches since waiting for commercial or free software to implement the workflows is often not practical. Moreover, even when software is available, experience is needed in its use before it is deployed or used at the Center. The priority of our resource is described above, but a set of additional strategic initiatives are always identified so that personnel can work on these when time is available. The specific areas that are chosen are agreed upon between the Computational Biology and Genomics shared resources and then approved by the user committees. Much of this work is directed at translating tools or methods already published or used by experts in the field, or methods described in brief in publication then implanted locally, or that are identified as technologies developed by Biostat and Computational Biology Program faculty and ready for deployment as a fee-for-service activity. In the past year we have developed toolkits to support methods for viral sequencing in a complex background of human or macaque DNA, deployed pipelines and trained staff on methods to classify reads from microbiome sequencing, and investigated interpretation of electron-transfer dissociation (ETD) fragmentation spectra (mass spectrometry (MS) proteomics method useful for identifying modifications), and implemented an iTRAQ pipeline for quantitative MS in the Center.

Inter-Resource Activities with Genomics Shared Resources, Proteomics and Metabolomics and Scientific Computing
We work closely with the Genomics (GSR) and Proteomics/Metabolomics (PMSR) resources and meet regularly with their respective Directors to discuss upcoming projects, develop proposals for future resource needs and anticipate technology developments. Semi-weekly consulting and strategic planning meetings include staff from the GSR, PMSR and CBSR resource for coordination and to support information transfer. A member of the CBSR is designated as a representative to various Consortium committees that manage the scientific computing infrastructure and policies including defining essential supported software infrastructure, planning appropriate capacity for emerging methods and data and storage needs. We provide expertise in the area of the design and analysis of a large-class of genome-scale assays and their integration. The resource
staff have experience in parsing and processing a variety of data file formats (mzXML, fastq, BAM, MIAME, etc.), developing novel tools for processing or visualizing mass spectrometry and short-read data sets, and in integrating disparate data sets with bioinformatics data resources, such as the UCSC genome browser, KEGG, UCSC EST and TCGA databases. A key expertise of the resource is the design and analysis of a variety of RNA-seq experiments, including methods for the quantitative analysis of splice variation, ribosome profiling, and the identification of long-noncoding RNAs.

**Importance to Scientific Programs**
We support a broad range of research including almost all of the Consortium scientific programs. Selected examples, which include peer-reviewed research and support of newly recruited investigators, are provided below.

**Edus Warren, MD, PhD, Global Oncology, Immunology and Vaccine Development**
Dr. Warren studies tumor biology and immunotherapeutic strategies in cancer. Patient-derived xenografts (PDXs) are one important tool in these studies, but the degree to which PDXs maintain, after many passages, the phenotype and transcription profile of the parental tumor has been incompletely characterized. The Warren Lab undertook large-scale RNA-seq profiling of parental tumors and corresponding PDXs passaged for up to seven generations in immune-deficient mice. Because RNA consisted of a mixture of human and mouse, the standard analytic pipelines were not amenable to investigating the tumor component. Moreover, once the data were analyzed and available in analytic format, the Warren lab did not have the capacity on hand to perform the iterative steps to execute the analysis, or perform investigational graphical or analytic queries of the data. The Computational Biology Resource aligned over 1 billion read pairs and developed strategies to distinguish reads derived from human tumor from a background of mouse stroma, then calculated summaries by gene-level expression and splicing events across all samples, tracked SNVs from the parental tumor through many generations of engraftment, and compared expression of orthologous genes in the xenograft samples.

Concomitant with the execution of these experiments, to cope with the downstream analysis, the clinical fellow and other staff in Dr. Warren's lab attended the basic and advanced R class to learn skills to manipulate the resulting data, and executed the plan; during the analysis and manuscript development the staff made extensive use of our drop-in consulting hours and was able to complete the analysis largely without further data analysis efforts on our part. The scripts that were used to separate the mouse from human reads are available for future use, and have been used multiple times since this initial instance.


**Soheil Meshinchi, MD, PhD, Hematologic Malignancies**
Dr. Meshinchi studies pediatric leukemia, with emphasis on risk-stratification and identification of predictors of response to chemotherapy and of progression to relapse. The TARGET AML project, for which Dr. Meshinchi is co-investigator, has generated RNA-seq profiles of almost 70 pediatric AML malignancies. His interest was in identifying small subsets of genes that may be related to response, and our analysis plan focused on selecting candidates that were derived from un-annotated splicing events, with the hypothesis that these events may be more likely to be cancer specific and thus more functionally related to cancer progression. The Computational Biology Resource aligned and filtered all short reads from these samples and generated transcript expression and splice-junction level summaries using methods our faculty supervisor had previously developed to highlight cancer-selective novel splicing events; we then applied survival analysis methods on a splicing-event-by-splicing-event level to identify a set of genes that contained putative novel splice events that may be most related to clinical outcome. These data were provided back to the investigators who then used biological criteria to select candidates for further investigation. Among these analyses, selected and confirmed by the investigators, was a previously unreported splice variant of the adhesion molecule ITGA5, lacking the 2nd and 3rd exons. The relative expression of this variant was found to be a potential marker for adverse outcome in low-risk AML in confirmation studies in independent samples. Our Resource assisted in the writing of the methods section for publication.

Dan Gottschling, PhD, Cancer Basic Biology
Dr. Gottschling studies the relationship between cancer and aging using the replicative life span of yeast as a model system to examine the genetic and proteomic regulation of longevity. The development of his "Mother Enrichment Program" (MEP), which allows study of mother cells that normally would be lost in a sea of exponentially proliferating daughter cells, combined with metabolic labeling provide a foundation to study protein turnover throughout the replicative life span of a population of yeast cells. The Computational Biology Resource assisted the Gottschling Lab with the analysis of a "pulse chase" SILAC experiment to determine which proteins are selectively retained in the mother cells. These experiments, which are not entirely uncommon, are highly sensitive to the peculiarities of tandem mass spectrometry that may lead to frequent false-positives should one rely only on automated data analysis pipelines. We applied a variety of quantitative methods to these data, including our in-house-developed Q3 protein quantitation software that we tuned to eliminate a common type of false positive finding in proteomics data, then filtered results for quality, and combined them into analytical datasets showing which proteins, and portions of proteins, are retained in the mother cells or newly synthesized in the daughter cells. These data were transferred to a PhD student in the Gottschling Lab who, with our training and periodic advice and consulting was able to take over almost all day-to-day analysis – specifically, in order to eliminate a sufficient number of false positives the student was trained to visualize the events that lead to the quantitative summary for each protein so that he could identify situations that are most likely to be true or false positives. The Resource also provided training on which types of identifications can frequently yield overly high ratios. This student was able to largely independently carry out these with occasional support to answer specific questions by resource staff. These results now form the basis of a manuscript that is now in preparation, and work was supported by R37 AG023779.

Pete Nelson, MD, Prostate Cancer
Dr. Nelson sought our assistance for his study of the transcription profiles of established prostate cancer xenografts. We aligned RNA-seq reads from 23 xenografts, filtering human and mouse reads into separate files using the toolkit we described in the first example above. Then using the RNA-seq pipelines the faculty sponsor developed as part of his NIH funded research we summarized gene-level expression, splicing patterns, potential gene fusion events, potential RNA editing sites, and compared SNVs to corresponding exome-capture sequencing data. We also provided training to staff to visualize the splicing events using IGV and allow them to characterize the nature of the specific splicing events that were characterized; e.g., exon skip, alternate start. The Core faculty supervisors group developed the visualization functions of IGV. These analyses found several variations of interest that are now being investigated; they suggested the presence of androgen receptor 'exon 9' and documented several splice variants associated with splice-site polymorphisms. It also revealed a novel lincRNA that may be associated with the more aggressive small-cell cancer phenotype and was subject to extensive confirmation and follow-up by a graduate student in the Nelson Lab. This work was funded by DOD grant PC09337P1. Data from this work was used to support two publications.


Rainer Storb, MD, Hematologic Malignancies
Dr. Storb and Brad Stone, Ph.D. engaged in a study of minor histocompatibility antigens (mHAgs) and their role in graft-versus-leukemia and graft-versus-host-disease. They sought assistance of the Computational Biology Resource in identifying candidate mHAgs in canines and the design of minigenes to screen these candidates for T cell activity via multiplex ELISPOT assays. We began with a prospective survey of two breeding pairs, where the male and female in each pair were matched for MHC alleles, to look for loci that
might contain protein-coding differences in future offspring. Illumina DNA-seq was performed on PBMCs from each dog, and we trimmed, filtered, and aligned all reads. We analyzed the resulting alignments to call almost 25,000 coding variants found in only one parent, therefore potentially discordant in sibling offspring. To continue the work we began supervising a programmer to develop a software pipeline to automatically design minigenes suitable for microarray-based synthesis and high-throughput ELISPOT screening.

**Patrick Paddison, PhD, Cancer Basic Biology**

Dr. Patrick Paddison sought assistance with the analysis of a large-scale shRNA screen to search for genes that when suppressed are lethal to glioblastoma multiforme stem cells (GSCs). He used a lentiviral shRNA library, including 54,000 small hairpin RNAs representing approximately 15,000 human genes, to screen three GSC lines and a neural stem cell (NSCs) line. After several weeks of outgrowth, half-hairpin PCR products were sequenced on the Illumina HiSeq 2500. Hairpin sequences observed in the NSC line but underrepresented in the GSC lines suggest that corresponding genes might be involved in supporting tumor outgrowth. The Computational Biology Resource performed initial quality assessment of the resulting data, developed methods to trim and quantitate the half-hairpin sequences, and conducted differential profiling with edgeR and limma. Members of the Paddison Lab also made extensive use of the twice-weekly Computational Biology consulting sessions conducted by resource member Dr. Jerry Davison, who helped guide them in conducting more of the analyses on their own. Dr. Davison contributed to and is a co-author on a resulting manuscript.

**David Hockenbery, MD, Cancer Basic Biology**

Dr. Hockenbery sought assistance in analyzing mass spectrometry data profiling the effect on histone acetylation of metabolic control by the Myc oncogene, which is associated with a wide range of malignancies. Cell reprogramming from a quiescent to proliferative state requires coordinate activation of multiple -omic networks. These networks activate histones, increase cellular bioenergetics and the synthesis of macromolecules required for cell proliferation. However, mechanisms that coordinate the regulation of these interconnected networks are not fully understood. The metabolic labeling strategy used sought to compare, in histone H4, unacetylated lysines with those enriched in acetyl groups derived from two sources: heavy-labeled acetate and heavy-labeled glucose. Control peptides were also generated, labeled in vitro with acetylation of unmodified lysines by deuterated acetic anhydride. This produced complex mass spectra, with superimposed copies of the isotopic distribution of the target peptide shifted by zero, one, two, or three m/z units depending on the source of label. Matt Fitzgibbon of our Resource developed a procedure to deconvolute these overlapping isotopic distributions, conducted analyses, wrote a description of analysis steps for a resulting manuscript, and is a co-author on that manuscript. The data point to a key role for Myc in directing the interconnection of -omic networks, and in particular, epigenetic modification of proteins in response to proliferative signals.

**Corey Casper, MD, Global Oncology**

Dr. Casper sought the assistance of the Computational Biology Resource in the analysis of massively parallel next-generation RNA and DNA sequence data from clinical isolates of HHV8, the virus that causes Kaposis sarcoma (KS) and primary effusion lymphoma (PEL). We processed RNA-seq data from 39 KS tumor punch biopsies comprising over 3 billion paired-end reads (~163GB of aligned sequence data). The TopHat splice-aware alignment software was used to map all reads onto a combined human (GRCh37/hg19) and HHV8 (GQ994935.1) reference sequence. We performed initial quality assessment of the alignments, finding that more than half had sufficient coverage of HHV8 to warrant further consideration, not surprising given variability...
in the amount of virus, transcriptional activity of different kinds of tumors, and the expected dominance of human RNA. We have performed quantitative analyses, summarized SNVs and indels across the samples, looked in detail at problematic “repeat-rich” regions of the HHV8 genome, and developed methods to find larger variants such as a 15nt insertion relative to the HHV8 JSC1 reference sequence. We have also analyzed pilot DNA-seq data from two HHV8 clinical isolates, one blood sample and one oral swab. The overall yield of HHV8 from the blood sample was low, and analysis of the oral sample was complicated by presence of large amounts of bacterial DNA. We developed methods to filter the data, first aligning to a human reference supplemented with representatives of common oral, genital, and skin bacterial species. Reads that did not align to this reference collection of potential contaminants were the aligned to the HHV8 genome. We then removed likely PCR duplicates, realigned sequences near potential indels, and called potential variants. We have also explored de novo alignment of the candidate HHV8 reads, although this is hampered by the low-coverage (<4X in both samples). We are currently working with this group to identify viable enrichment strategies (e.g. custom capture reagents).

**Edgardo Castellar, MD, PhD, Women’s Cancer**

Dr. Castellar has recently received CCSG New Investigator Developmental funds and will use these to launch studies to apply a relatively new type of massively parallel sequencing to the search for clinically-relevant chromosomal rearrangements in small cell carcinoma of the ovary, hypercalcemic type (SCCOHT), an aggressive ovarian cancer with poor prognosis that affects primarily young women. Dr. Castellar will work the Resource on this new investigation which will employ massively-parallel mate pair sequencing. This approach allows sequencing of libraries with large insert sizes, up to several kilobases, which can better capture long-range structural variation in the genome. Because these inserts are too large to sequence directly on most next generation sequencers, such as the Illumina HiSeq 2500s available in the Genomics Resource, they are first circularized with a biotinylated junction adaptor joining the two ends. Circularized molecules are then fragmented, with those fragments containing the original junction adapter captured for sequencing. In the ideal case, this will result in a pair of reads, in outward-facing orientation, for each original insert with reads in each pair located several kilobases apart. In practice, the junction adapter may appear in any location within the original fragment. We are planning steps to support this workflow, detecting and removing the adaptor sequence while using its position within each pair to separate outward-facing (junction spanning) and inward-facing read pairs into groups to be aligned separately. We will report potential translocations and inversions in the resulting alignments using methods that we have applied successfully to acute myeloid leukemia, where we have worked with other Consortium members to find and confirm several gene fusions.

**Cost Effectiveness**

The CBSR is considered a specialized resource and does not have chargebacks for services, so direct comparisons with competing entities is not possible. The general cost-effectiveness of the resource comparing grants and programs supported to CCSG funding is exceptionally high. Due to the fact that CBSR staff are largely trained in research labs and from other NIH funding sources, the CCSG funds offset only the implementation costs of the service, and not the cost of training. For the majority of services we provide it is not possible to obtain expertise on short-term basis at all without committing to long-term collaborative relationships.

**Use of Services Table**

<table>
<thead>
<tr>
<th>Service</th>
<th>Consortium Users</th>
<th>Peer Reviewed</th>
<th>Non-Peer Reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drop-in Consulting</td>
<td>28</td>
<td>25 (89.3%)</td>
<td>3 (10.7%)</td>
</tr>
<tr>
<td>Project-based Consulting</td>
<td>37</td>
<td>34 (91.9%)</td>
<td>3 (8.1%)</td>
</tr>
<tr>
<td>Training &amp; Outreach</td>
<td>50</td>
<td>37 (74%)</td>
<td>3 (6%)</td>
</tr>
</tbody>
</table>

**Management Structure, Policies and Operations**

**Administration**

The CBSR operates in accordance with Consortium and institutional policies for Shared Resources. The Consortium’s Scientific Steering Committee ensures that this and other Consortium resources are aligned with the Consortium’s strategic goals and its continued value to the Cancer Center. The CBSR is led by Martin McIntosh, Ph.D. co-head of the Biostatistics and Computational Biology program, and by Executive Director, Matt Fitzgibbon, who is also part of Dr. McIntosh’s research program staff. Mr. Fitzgibbon provides day-to-day supervision of the resource, including tracking all resource projects, providing the bulk of the technical
supervision of the resource staff (many of whom are funded part-time by CCSG funds), leads the CBSR/GSR semi-weekly meetings, and is also responsible for assigning tasks to the resource staff. Dr. McIntosh is in charge of strategic planning, including the selection of which new pipelines to develop and balancing priorities of competing needs of the resource.

The CBSR operates in consultation with Paul Woloshin, MBA, Ph.D., Consortium Director of Shared Resources and under the guidance of a faculty advisory committee that is convened annually to review and update operating policies. The purpose of the CBSR advisory committee is to provide scientific and administrative direction to the CBSR Directors and staff, and to ensure optimal service. Current members are: Dan Gottchling, Ph.D. and David MacPherson, Ph.D. (Cancer Basic Biology), Akiko Shimamura, M.D., Ph.D. (Hematologic Malignancies), Chris Li, M.D., Ph.D. (Women’s Cancer), Raphael Gottardo, Ph.D. (Biostatistics and Comp. Biol.) and David Koelle, M.D. (Global Oncology).

Access and Usage Policy
Services are available to all members of the Consortium, on a first-come, first served basis. Support is not provided to external users – unlike fee-for-service assays all outside activities would consume personnel effort that would take away resources for use by Consortium activities. Resources are restricted to Consortium investigators. No costs are charged to the investigators as long as the need falls into the primary mission of the resource – to address barriers to progress that are short-term and require specialized support. Longer term support, when needed, is set by an hourly rate which is calculated as the average hourly rate of the resource staff after adjusting for the CCSG salary support. These policies are reevaluated and revised on an annual basis and are dependent on the relevant impact of the value of the service to the investigators.

Billing
Standardized service request procedures document information for each respective transaction. Services are tracked, although not billed, by their total time from initiation to completion based on staff hours. Reports of usage by investigators and staff are produced each month. Usage is assessed and summary reports are developed by institution, by investigator, and by program. This is intended to identify which programs may not be appropriately served by the resource but to also identify individual investigators whose usage is not compatible with a free resource at the Center.

Education and Outreach
Users are kept up to date on changing technologies and services offered by the facility through the FHCRC and Consortium websites, Shared Resource Newsletter, and special memo distributions. Outreach to the broader Consortium community, particularly those within the UW and Children’s Hospital and Regional Medical Center (Children’s) will be enhanced through the activities of the Institute of Translational Health Sciences (ITHS). As an ITHS approved facility, it is anticipated that the Resource will play an ongoing and expanded role in support of translational research activities.

Priorities and New Initiatives
New Initiatives will focus on (1) gathering and integrating public data resources to support multiple investigators across the Cancer Consortium, (2) configuration of local mirrors of key public bioinformatics analysis systems to provide greater access to established workflows and (3) development and implementation of newer, more specialized genomic and proteomic workflows.

Public Data Resources
As part of our ongoing activities, we provide expertise on accessing large-scale public data resources, including acquiring resources that are publicly available for readily available local access. Whenever the investigator has access permission to resources such as TCGA (we help them with the process to acquire permission) we will access the data on their behalf, and process and integrate it with their analysis plans or existing data. Core public data sources of particular interest are ENCODE, TCGA, GTEX (normal somatic tissue expression profiles). For our own local data we have established several local "shared biodata" directories to provide ready access to key public data resources across all major servers and cluster nodes at the Center. These directories currently include:
- **Blast databases** for local searches of human genomic, non-redundant protein (nr), comprehensive nucleotide (nt), and Transcriptome Shotgun Assembly (tsa_nt) sequences.
- **Illumina iGenomes** reference collections for human, mouse, Drosophila, C. elegans, and yeast. These collections include reference assembly sequence, abundant and contaminating sequence, and integrated annotations for many species formatted for direct use by popular short-read tools including BWA, Bowtie, Bowtie2, TopHat, and Cufflinks. We supplement the distributed iGenomes with derived genome and transcriptome indices for use with the GMAP/GSNAP software.
- **GATK Resource Bundle**, including 1000Genomes reference sequences, known indel coordinates for local realignment, and VCF files containing variants from dbSNP and genotypes from HapMap. This also includes a large-scale test BAM file and sample results for testing of local variant calling pipelines.
- **Illumina BodyMap 2.0 RNA-seq data** from 16 commercially acquired tissues. These data sets have been used by several Cancer Consortium groups both for methods development and for integration with and comparison to other large RNA-seq data sets.

Our next steps will be to automate, where appropriate, the update of these important data resources as well as to add new collections of data that would support the work of multiple Consortium investigators. In particular, we have had inquiries about staging a local subset of ENCODE data as well as RNA-seq and Exome sequencing from the NCI-60 cell lines.

**Local Mirrors of Public Bioinformatics Analysis Systems**
As microarrays, short-read sequencing, and other genomic technologies have become more commoditized, several research groups have developed and disseminated substantial data analysis platforms that make advanced workflows directly available to users without requiring specialized command-line or computing expertise. An ongoing task of the Resource is to evaluate these platforms to see which may bring significant benefit to Consortium members if deployed locally. Two platforms that we are investigating for local deployment include Galaxy and GenePattern.

**Galaxy:** The Galaxy Project provides a web-based environment for the navigation of genomic resources and embodies popular genomic workflows in a convenient web-based graphical user interface. Established Galaxy workflows include conversions between many common data file formats, matching genomic interval coordinates to features, converting coordinates between reference assembly versions, and encapsulation of next-generation sequence workflows (read mapping, splice detection, transcript isoform inference, various alignment file manipulations, genotyping tools).

Several research groups at the Center have been successfully using public Galaxy servers but have run into limitations that might be removed by establishing a local Galaxy instance for use within the Center. There are two principal impediments to using the public servers: 1) it is expensive and inconvenient to send and retrieve large datasets over the web, and 2) we have no ability to directly customize external Galaxy servers to better serve the particular needs of our Consortium members. The Galaxy source code, associated applications, and many related data sources are publicly available, and we have begun to establish local Galaxy instances to embody popular workflows.

**GenePattern:** We are also investigating a complementary analysis platform, GenePattern, from the Broad Institute. This platform provides a web-based interface for manipulation and analysis of microarray, next-generation sequencing, and flow-cytometry data. While there is some overlap between the analyses supported by GenePattern with those supported by pre-configured Galaxy workflows, there are also a number of complementary analysis modules. In particular, tools from the Broad are well supported within GenePattern. Specifically, we hope to use GenePattern to provide easy end-user access to the Picard tools for manipulating short-read alignment files, to the Scripture reference-guided transcriptome reconstruction software, and to various tools developed by the Broad for analyzing flow cytometry data.

**Specialized Workflows**
Our data analysis strategies for common workflows (e.g. RNA-seq, ChIP-seq, exome capture) are well established. However, we continue to receive more specialized requests through our automated request-tracking system. When we determine that a request points towards an emerging need, and is likely to benefit multiple Consortium members, we prioritize it for further investigation and development. It is difficult to predict
Variant calling in RNA-seq data sets: Several research groups have asked for assistance calling variants in RNA-seq data sets, both longer-range structural variation, such as gene fusions, as well as single-point changes, such as SNVs or RNA editing events. Variant calling is more challenging in this context than in DNA-seq or Exome capture data due to the wide dynamic range of the RNA-seq and the added complexity of handling superimposed splice variants. We have performed successful fusion detection with TopHat-Fusion, uncovering a number of PCR verified fusions in at least two cancer types, but the process generates a large number of false-positives and requires the attention of an experienced data curator. We intend to integrate several complementary fusion-aware tools to focus attention on candidates supported by more than one algorithm. For SNV calling we plan to adapt existing variant callers, modifying them as needed.

Small genome assembly: We have received requests for assistance assembling small (<250MB) microbial genomes from a number of Consortium members. We have piloted this work by working with one group to assemble a novel macacine herpesvirus. We began with over 200 million read pairs, 50nt from each end, from an infected pigtail macaque. We developed procedures to screen out reads from pigtail macaque DNA by using low-stringency matches to the closest available reference genome, rhesus macaque rheMac3. Remaining reads were assembled with Velvet, using various kmer and expected coverage settings, until contigs with homology to known herpesvirus sequences emerged. These were combined into a final assembly which, when compared to the closest human herpesvirus, revealed orthologous genes with the same order and orientation. We plan to formalize the procedures applied in this pilot and to apply them to agents of infection-driven cancers (EBV, HHV8, Merkel polyomavirus, etc).

De novo transcriptome assembly: Several groups have asked for assistance with transcriptome profiling of organisms that currently lack a usable finished genome assembly (pigtail macaque, camel, naked mole rat). Our conventional RNA-seq analysis pipelines depend on alignment to a well-annotated reference assembly, so exploration in the absence of an assembly has been limited. Newer methods of de novo transcriptome assembly provide one avenue to extend such exploration. Such methods may also be useful for studying structural variation, since some prevalent structural variants will be missing from even the best annotated genomes (e.g. see for example fosmid sequences from the NHGRI Structural Variation Project). We plan to implement the Trinity software for de novo transcriptome assembly.

Personnel
Key Staff Qualifications

Martin McIntosh, Ph.D. (CBSR Director) is Full Member and Resource Director in Computational Biology at Fred Hutchinson Cancer Research Center. He is also the co-Head of the Consortium’s Biostatistics and Computational Biology Program. In his various leadership roles Dr. McIntosh has working relationships with a large number of computational researchers at the cancer center. Much of the support of this research comes from tapping into the expertise of his staff, which is particularly well suited to support the mission of the resource. His research touches on several areas that are relevant to supporting Consortium programs, including an active program that includes broad expertise in bioinformatics, statistics, computation, and also translational research in early detection and therapy discovery. His group has published scientific manuscripts in each of these areas, and he currently has several research grants that support both computational biology technology development (primarily RNA-seq analysis) and translational research. In the past he has had a number of research grants that developed technologies for mass spectrometry data analysis largely for proteomics, but also metabolomics, and their use in a practical setting. He also has an active wet-lab component to his group, providing him with a unique perspective on the needs and practices of the Consortium laboratory researchers who are the primary users of the resource. His training in statistics provides him with a unique perspective on the role of the resource to help population scientists.

Matt Fitzgibbon, Executive Director, has nearly 20 years of experience designing software and analyzing data in various biological contexts including sequence analysis, microarrays, signal processing, development of syntenic maps, and peptide synthesis and sequencing. As a software engineer at Thinking Machines Corporation, he built molecular visualization software and explored protein sequence alignment on massively-
parallel computers. Joining Darwin Molecular Corporation in 1995, and after subsequent acquisition of the company by Celltech Group PLC, he worked on candidate-gene discovery projects based on expressed sequence tag (EST) profiling and on mouse mutagenesis. He built custom pipelines to search for novel, enriched genes in normalized EST libraries and participated in data analysis leading to two patents on which Mr. Fitzgibbon is co-inventor (US 7,879,982 and 7,585,954). To support candidate gene discovery by mouse mutagenesis, he designed and developed syntenic mapping software to combine information from mouse and human sources to greatly increase the number of candidate genes available in regions found by linkage mapping. In the Department of Microbiology at the University of Washington, he analyzed rhesus macaque ESTs, participated in the design of one of the first macaque microarrays, and analyzed experimental results from these arrays. For the past eight years, Mr. Fitzgibbon has been on the technical staff in the McIntosh Lab at FHCRC, developing methods and analyzing protein and nucleotide sequence data and more recently leading the RNA-seq analysis for common RNA-seq experiments and ribosome profiling, focusing on variation in sequences that arise in alternative splicing. He has led efforts to profile the transcriptomes of over 50 ovarian tumors and several dozen controls, developing methods to integrate public “normal” tissues data to identify potentially novel cancer-associated transcript isoforms. He has been involved in methods development for MS/MS proteomics including development of quantitative methods, search scoring algorithms, signal processing and database systems in Java, Python, and C++. He has been in his present position for three years.

Other resource staff include Qing Zhang, a bioinformatics analyst who works under the technical supervision of Mr. Fitzgibbon to provide consulting and data analysis services to researchers studying sequence-level variation and leads our development of proteomics workflows. Ms. Zhang has developed processes, based on industry best-practices, to align reads and perform variant calling in short-read exome-capture data sets, to call somatic mutations in matched tumor/normal pairs, and to search for evidence of structural variation in RNA-seq & DNA-seq datasets. She is working closely with our local Galaxy deployment process to make these workflows more-broadly available. Kavita Garg, Ph.D., is a staff scientist who consults on analysis of data that require integration of multiple genomics data sets, or integration of data sets of different types, research requiring the identification or study of noncoding RNAs, including long-noncoding RNAs and miRNAs, and splicing variation in RNA-seq datasets. She is also the lead on the infectious disease and cancer component; this augments her other role as the executive director of the Center for Aids Research (CFAR) computational biology core. Jerry Davison, Ph.D., is a data analyst who conducts much of the quantitative analysis for the Computational Biology Resource, assisting diverse research groups with analysis of microarray, RNA-seq, ChIP-seq, and large-scale RNAi screening data. He has extensive experience with R/Bioconductor, benefiting a wide audience of Consortium members through twice-weekly personalized drop-in consulting sessions and a well-received series of training courses introducing R for data analysis.
Basic Sciences/Translational Research

GENOMICS SHARED RESOURCE

Introduction
The GSR is an expansion of the highly successful Fred Hutchinson Cancer Research Center (FHCRC) DNA (deoxyribonucleic acid) Array Laboratory launched in 1998, which was one of the first microarray core laboratories in the country. Initially, the resource was instrumental in assisting researchers in the development of a number of novel microarray applications, including assays examining protein-DNA interactions, DNA methylation profiling, and DNA replication timing patterns. The resource then transitioned from primarily making custom spotted arrays to using several commercial array-based platforms. The DNA Array Lab was later incorporated into a new entity - the Consortium Genomics Shared Resource – along with a newly developed second laboratory, the Genetic Analysis Lab, which was developed to provide capillary-based sequencing services (and later, NextGen sequencing services). This expansion required new support infrastructure and instrumentation for the main service areas. A major component of this infrastructure is HutchBASE, an in-house developed Laboratory Information and Management System (LIMS) system that supports online ordering of services, sample tracking, data management and analysis, and billing. The GSR is heavily utilized by Cancer Consortium investigators and has a well-earned reputation for its highly experienced and dedicated staff and exceptional service. The GSR received an Outstanding merit score in the 2008 competitive renewal.

Major Services
Facilities and Equipment
The GSR is located at the FHCRC. Total facility space is 2500 square feet, with 1800 square feet devoted to the DNA Array Laboratory and 700 square feet to the Genetic Analysis Laboratory. The space is located in proximity to other Consortium shared resources including Proteomics, Cellular Imaging, Histopathology and Immune Monitoring. Computers within the GSR are connected to the FHCRC networked computer system allowing Consortium investigators immediate access to experimental data. The FHCRC central Scientific Computing department and the Shared Resources Research Computing resource support the GSR by providing the infrastructure to support data management and archiving activities.

DNA Array Laboratory
The DNA Array Laboratory consists of two unique areas designed to accommodate different functions and activities. The larger area constitutes a wet laboratory area and is used for reagent preparation, RNA and DNA sample QC analysis, implementation of microarray applications, and data generation (e.g., scanning) procedures. The second area consists of a limited-access room designed to house the facility’s 4°C and -80°C storage and provides space for other support equipment.

Laboratory equipment includes an Illumina BeadStation System, including an iScan Reader and additional supporting automation (chip autoloader and a Tecan liquid-handling robot), and a high-resolution Agilent Technologies DNA Microarray Scanner with a 48-slide autoloader carousel. The lab also has two Robbins Scientific Hybridization Incubators for use with Agilent Technologies arrays.

The lab houses general laboratory equipment (used to support all technologies) including a Covaris LE220 focused-ultrasonicator, two Sage Science Pippin Prep gel systems, two Agilent 2100 Bioanlyzers, an Agilent 2200 TapeStation, a Nanodrop ND-1000 spectrometer, a Caliper DropSense 96 spectrometer, an Invitrogen Qubit 2.0 fluorometer, and an ABI StepOne Real-Time PCR System.

Genetic Analysis Laboratory
The Genetic Analysis Laboratory includes instrumentation for capillary-based DNA sequencing and genotyping assays, NextGen sequencing, and quantitative PCR.

DNA sequencing and genotyping services are performed using two Applied Biosystems capillary 3730xl DNA Analyzers. NextGen sequencing technologies include two Illumina HiSeq 2500 sequencers, a Roche/454 GS Junior, and two Qiagen PyroMark targeted pyrosequencers - a PyroMark Q24 and a high-throughput PyroMark Q96 MD.
Quantitative polymerase chain reaction (qPCR) analysis is available on four ABI Prism 7900HT Sequence Detection Systems, one of which is interfaced with an ABI automatic plate loader and a 384-well block module for higher throughput needs. These instruments are located in a shared instrument room located in proximity to the Genetic Analysis Laboratory. Controlled access is provided 24x7, via the FHCRC security system. Instrument time is scheduled using the shared resource online instrument scheduler available on the FHCRC web site and is accessible by all Consortium users.

Technologies and Expertise
DNA Array Laboratory
The DNA Array Laboratory was one of the first microarray core facilities in the country, and with a combined total of more than 30 years of experience, the staff offers a high level of expertise. The laboratory provides Consortium members with an end-to-end solution, from assistance with experimental design to data generation, QC and, if needed, data analysis. Services include consultation on technology selection, assistance with experimental design, assessment of RNA and DNA quality, troubleshooting support, and assistance with reviewing data quality and implementation of data analysis strategies.

The laboratory currently has instrumentation to support two major commercial microarray platforms: Agilent Technologies Microarrays and Illumina BeadChips. Microarray assays supported through the GSR include differential gene expression, ChIP-chip, arrayCGH, miRNA analysis, CpG methylation profiling, genotyping, and CNV analysis.

Genetic Analysis Laboratory
Services for capillary-based sequencing include two sample submission options, researcher-provided DNA template or ready-to-sequence cocktails. In addition, the Resource offers services for Fragment Analysis and SNPlex assays. Staff provides pre- and post-data generation consultation, performs sample preparation and processing, performs data QC, assists investigators with troubleshooting, and maintains instrumentation.

Services for NextGen sequencing include WG sequencing, mRNA-Seq, small RNA-Seq, ChIP-Seq, exome sequencing, CpG methylation analysis, targeted resequencing, and numerous unique methodologies (e.g., see Teves and Henikoff and Robins, et al. below) to support researchers' needs. Staff provides extensive pre- and post-sequencing consultation, sample quality control (QC), library construction and QC, sequencing, troubleshooting assistance, and data processing, QC, and in some cases, data analysis.

PyroMark services include targeted mutation and (cytosine phosphate guanine) CpG methylation assays. Resource staff members work closely with researchers during the planning phase to ensure the best selection of target sequences to maximize data quality and assist with designing optimal template and sequencing primers. Resource staff perform all pyrosequencing runs and assess the quality before creating detailed reports for the end-user.

The lab also supports and provides access to equipment for real-time qPCR analysis. This includes maintaining routine instrument maintenance and calibration schedule, and working with vendors when onsite repairs are warranted.

Data Management
Most service requests to the GSR occur through various technology-themed modules of HutchBASE, a web-based LIMS that was developed, tested, and implemented by resource staff. HutchBASE was initially developed using the BASE v2.6 (BioArray Software Environment, Lund University, Sweden) microarray database framework. Over time, the Resource developers have overhauled and expanded this system into what is now a broad, highly customized LIMS suited to meet the administrative, technical, and scientific needs of the GSR and its end-users. In addition to facilitating service requests, HutchBASE captures sample annotation and QC, provides sample-tracking features, manages workflows, automatically triggers data processing protocols, produces data QC reports, affords data management capabilities, and initiates billing reports. The database also offers the end-user electronic lab notebook capabilities for their genomics projects, through the user-defined addition of project and sample annotation fields.
Additionally, staff supports the data analysis needs of the GSR’s end-users. The level of support can vary from providing programming advice and troubleshooting existing code, support and guidance using commercial and academic analysis tools, and (under the direct supervision and guidance of the Resource Director) a full range of data analysis strategies that encompass in-depth data QC, various statistical analyses, and bioinformatics (e.g., gene ontology (GO) enrichment, pathway analysis). Towards this goal, Resource staff members work closely with Computational Biology Shared Resource staff, including formal biweekly meetings to go over open projects and discuss data quality and analysis strategies. Surveying the last few years (January 2011 to August 2013), the GSR staff has independently supported the needs of Cancer Consortium members (comprising 9 of the 10 research programs) on over 110 individual research projects. This work is in addition to maintaining the day-to-day IT and informatics needs of the GSR and its used-base.

GSR staff also maintains an IP-restricted website where end-users can access technology specific analysis tools, as well as request access to commercial tools provided through the Resource (e.g., Ingenuity Pathway Analysis, Partek Genomics Suite).

Training Services
The GSR offers personalized instruction in the use of various software tools, as well as consultation on data analysis and visualization concepts. All software and instructional information, including supporting materials, are provided via a dedicated website. Furthermore, staff members provide training on the operation of the facility’s ABI 7900HT Real-Time PCR Systems, consultation on experimental design, and assistance with data analysis and troubleshooting.

Importance to Scientific Programs
The following are examples of projects supported by the expertise and services provided by the GSR. Examples provided include researchers that are experienced in the use of genomics-based tools, as well as those new to using such technologies. A main mission of the GSR is to provide support for experienced users to push the boundaries of a technology, while providing a broader range of support that is required for new users of a given technology. Below are a few examples selected from the more than 290 peer-reviewed research articles published since 2009 that have included work performed by GSR staff.

William Grady, MD, GI Cancer
Kaz, A, et al. “Patterns of DNA Methylation in the Normal Colon Vary by Anatomical Location, Gender, and Age. (Manuscript in preparation)
Kaz, et al., sought to characterize the DNA methylation state of the normal colon in order to provide a better understanding of the role of DNA methylation in field cancerization. Both whole-genome methylation analysis and targeted sequencing of specific loci were performed on normal colon biopsies. Although variability in methylation between biopsies and amongst different colon segments was minimal for repetitive elements, analyses of specific cancer-related genes as well as genome-wide methylation analysis demonstrated differential methylation based on colon location, individual age, and gender. GSR staff provided assay design consultations and performed Illumina BeadChip genome-wide CpG methylation analysis, as well as the pyrosequencing of candidate loci using Qiagen’s PyroMark technology.

Phillip Greenberg, MD, Immunology and Vaccine Development
By using an in vivo mouse model, Schietinger, et al., showed that tolerant T cells proliferate and become functional under lymphopenic conditions, even in a tolerogenic environment. However, T cell rescue is only transient, with tolerance reimposed upon lymphopoiesis even in the absence of tolerogen (self-antigen). Genome-wide messenger RNA (mRNA) and micro RNA (miRNA) expression profiling of naïve, memory, tolerant, rescued, and retolerized cluster of differentiation 8 (CD8) T cells were performed and gene signatures were identified. To assist with this study, the GSR staff provided consultation on experimental design, performed sample QC and troubleshooting, sample labeling, microarray processing and imaging services, as well as all gene expression data and bioinformatics analyses. Two of the co-authors on the published results of this study (J. J. Delrow and R. S. Basom) are GSR staff members.
Mark Groudine, MD, PhD and Susan Parkhurst, PhD, Cancer Basic Biology
Rincon-Arano, et al. identified the transcriptional regulator, UpSET, which encodes a SET domain-containing protein recruited to active and inducible genes in Drosophila. Unlike other Drosophila SET proteins associated with gene transcription, UpSET is part of an Rpd3/Sin3-containing complex that restricts chromatin accessibility and histone acetylation to promoter regions. The authors applied the DamID method to perform genome-wide mapping of UpSET binding sites, as well as expression profiling, to help characterize the protein’s role. To assist with this study, GSR staff provided consultation on technical and experimental design issues, performed sample QC, RNA labeling, microarray processing and imaging services, gene expression data analysis, and programming support. The GSR Director (J. J. Delrow) is a co-author on the published results from this study.

Steven Henikoff, PhD, Cancer Basic Biology
Teves and Henikoff developed a novel deep-sequencing method to characterize epigenomic changes in chromatin using the heat-shock response in Drosophila S2 cells as their test system. NextGen sequencing was employed to profile classical low-salt-soluble chromatin, RNA polymerase II (Pol II), and nucleosome turnover dynamics at single-base-pair resolution. GSR staff performed NextGen sequencing and also processed the raw sequencing data. Staff also worked with Center IT to provide additional support to facilitate data analysis.

Hermit Malik, PhD, Cancer Basic Biology
Ross, et al. characterized the function of an evolutionary young Drosophila gene and showed that it has surprisingly acquired an essential function in chromosome segregation. This work involved PCR and sequencing of the Umbrea gene from over 35 species of Drosophila and many strains of a couple of species, for evolutionary analyses. In addition, for characterization, they made over 40 chimeric proteins, each of which had to be sequence verified before analysis. Finally, they made transgene rescues, which needed to be validated by sequencing. All of these steps required the ABI capillary-based sequencing services provided by the GSR for discovery and validation.

Eirini Papapetrou, MD, PhD, Hematologic Malignancies
The loss of chromosome 7q is a characteristic cytogenetic abnormality in Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML). Dr. Papapetrou’s group has derived del(7q) induced pluripotent stem cell (iPSC) lines from hematoietic cells of MDS patients along with isogenic karyotypically normal iPSCs. They have shown disease-related cellular phenotypes in the del(7q)-iPSC lines that can be rescued by spontaneous dosage compensation and recapitulated by engineered hemizygosity of chromosome 7 region q32.3-q36.1. To assist with this study, GSR staff provided consultation of technical and experimental design issues, performed sample QC, RNA and DNA labeling, microarray processing and imaging services, and gene expression and arrayCGH data analysis support. A manuscript of this work has been submitted for publication and includes the GSR Director (J. J. Delrow) as a co-author.

Brian Reid, MD, PhD, GI Cancer
Thomas Vaughan, MD, MPH, Cancer Epidemiology, Prevention and Control
Kostadinov, et al. initiated a study aimed to determine if the use of non-steroidal anti-inflammatory drugs (NSAIDs) modulates clonal evolution by reducing the rate of acquisition of somatic genetic abnormalities (SGAs). An intensive longitudinal study of 13 individuals was employed, including 5-8 time points per individual, with 10-20 biopsies per individual, and 6.4-19 years of follow-up. The data showed that overall NSAID use is associated with an approximately 10-fold reduction in the rate of acquisition of SGAs. The GSR
performed the genotyping of all study samples, and also performed initial data QC and generated all the genotype call reports. A GSR staff member (C. L. Sather) is a coauthor on the published results from this study.

Harlan Robins, PhD, Biostatistics and Computational Biology
Christopher Carlson, PhD, Cancer Epidemiology, Prevention and Control
Edus “Hootie” Warren, MD, PhD, Immunology and Vaccine Development, Global Oncology
Stanley Riddell, MD, Immunology and Vaccine Development

Robins, et al., developed a novel experimental and computational approach to measure TCR CDR3 diversity based on deep sequencing technology, and used this approach to determine the CDR3 sequence in millions of rearranged TCRbeta genes from T cells of 2 adults. To assist with their study, GSR staff provided consultation, performed deep sequencing, and processed raw data. Staff also provided significant background information pertaining to the sequencing technology and data processing methodologies being employed so to assist the researchers in better understanding their data and how best to develop of their analytical tools.

Thomas Vaughan, MD, MPH, Cancer Epidemiology, Prevention and Control

This is the first reported genome-wide association study of esophageal adenocarcinoma, and the first to examine this cancer with its precancerous lesion, Barrett’s esophagus. In this study, 2390 esophageal adenocarcinoma cases and 3175 Barrett’s esophagus cases were compared with 10,120 controls. Three new genetic associations were identified. The GSR performed the genotyping of all BEAGESS specimens. The GSR also performed initial cohort QC and generated all the genotype call reports. A GSR staff member (C. Sather) is a coauthor on the published results from this study.

Cost Effectiveness
The GSR offers Consortium members open access to cutting-edge technologies with a commitment to a high-quality standard of service and with a focus on cost-effectiveness. Those new to using genomics-based approaches in their research benefit from the expertise of the Resource staff in several ways. Moreover, the staff works closely with investigators to monitor data quality and offer advice and provide (as part of the service) data analysis and visualization support. For those researchers with experience using genomics-based approaches, the Resource provides an additional opportunity for developing new techniques and applications that otherwise would not be feasible in an investigator’s lab or through a commercial vendor.

Price comparisons between core facilities at other institutions and commercial entities are often challenging to perform, as many service labs do not publically disclose their pricing structures. In an effort to gather some pricing information, we surveyed (verifiable) service fees as advertised on GenoHub, an online marketplace for accessing NGS core lab services, as well as fees published by a selection of facilities listed in Illumina’s Core Lab Program. As an example, we chose to compare service fees for a lane of PE50 sequencing on an Illumina HiSeq 2000/2500 system. Core facilities at 7 academic/non-profit research institutes had on average a fee of $1867 for this service. For the same service, the GSR fee was the lowest offered, coming in ~21% below the average value. Moreover, when considering the general pricing offered by 4 commercial NGS service providers, service fees were in excess of 1.8 times the fees offered through the GSR. An additional value provided thorough the GSR comes in the data analysis support provided by the staff, which is provided free of charge to those acquiring data through the facility.

In addition, the GSR offers a high-degree of flexibility and customized support in their services that are not typically provided by external service cores (or, if so, they come at a highly elevated fee-level). For example, Robins, et al. (see description under Importance to Programs heading) required a significant amount of consultation and the testing of several protocol iterations in order to optimize their custom library preparation protocol they used in their TCR CDR3 diversity sequencing work. The GSR staff also provided support to the Tsukiyama Lab and their use of the NimbleGen microarray platform to identify nucleosome-free regions
(NFRs) through a nucleosome position assay (Whitehouse, et al, Nature, 2007; Yadon, et al, Mol Cell Bio, 2010). The Tsukiyama Lab also used the NimbleGen microarray platform to develop a novel genome-wide method to measure chromosome accessibility to micrococcal nuclease (Rodriguez and Tsukiyama, Genes Dev, 2013). In both cases, the GSR staff consulted on protocol modifications, assisted with array processing, and provided insights into data analysis methodologies unique to the assays. These assays are currently being transferred to the Resource’s NextGen sequencing services. In addition, the GSR staff made reagent adjustments to facilitate a cost-effective, custom PE25 sequencing approach for several projects supporting the Henikoff Lab. For an example of where this was applied, please see the Henikoff project listed under the Importance to Scientific Programs heading.

It would also be very expensive for individual investigators to employ staff with the same level of experience and purchase and maintain the equipment necessary to produce high quality results. Additionally, the experimental design and data analysis provided by Genomics reduces the number and complexity of experiments resulting in lower cost. Shared Resources performs annual benchmarking analysis as well as customer satisfaction surveys to ensure cost competitiveness and quality of service.

<table>
<thead>
<tr>
<th>CI Service</th>
<th>Total Users</th>
<th>Peer Reviewed</th>
<th>Non-Peer Reviewed</th>
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<tr>
<td>NextGen</td>
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<td>40 (93%)</td>
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Management Structure, Policies and Operations

Administration

The Genomics Shared Resource operates in accordance with Consortium and institutional policies for Shared Resources. The Resource is directed by Jeff Delrow, PhD, who oversees the general operation of the resource, keeps abreast of the latest relevant technology advancements and ensures that the resource continues to meet the needs of investigators. Faculty oversight of the Resource is provided by an advisory committee responsible for reviewing Shared Resource operations on annual basis, providing review of user fee changes, evaluating capital budget requests and providing guidance on future goals and objectives. The Consortium’s Scientific Steering Committee ensures that this and other Consortium resources are aligned with the Consortium’s strategic goals and its continued value to the Cancer Center. The resource operates in consultation with Paul Woloshin, MBA, PhD, Consortium Shared Resources Director.

Faculty oversight is provided by an advisory committee responsible for annual review of the shared resource operation, providing review of user fee changes, evaluating annual capital budget requests and providing guidance on future goals and objectives. The Consortium’s Scientific Steering Committee ensures that this and other Consortium resources are aligned with the Consortium’s strategic goals and assesses its continued value to the Cancer Center. Current members include Drs. Steve Henikoff and Stephen Tapscott of the Cancer Basic Biology Program, Dr. Jerald Radich of the Hematologic Malignancies Program, Dr. David Fredricks of the Immunology and Vaccine Development Program, Dr. Martin McIntosh of the Biostats and Computational Biology Program, and Dr. Chu Chen of the Cancer Prevention and Epidemiology Program.

Access and Usage Policy

Services are available to all members of the Consortium, on a first-come, first served basis. Support is provided to external users as time permits. Costs are charged directly to applicable awards based on actual usage and rates are based on projected direct operating costs net of CCSG and institutional support. Rate schedules are reevaluated and revised as required on an annual basis. External user fees reflect the full cost (both direct and indirect) of rendering service according to the most recent rate revision. No benefit of institutional or federal funding received by the resource is considered in the establishment of outside rates.

Billing

Standardized service request forms provide authorization of service and requested information for each respective transaction. Services are billed upon completion and information is entered into a Shared Resources billing system which provides the ability to track resource use at the project level by activity.
Ongoing review is conducted to monitor activity levels and observe usage trends to ensure appropriate adjustments are made in operations to adapt to changing demand. Usage is assessed and summary reports are develop by institution, by investigator, and by program for each service provided by the resource. Ongoing evaluation of resource operations is conducted through implementation of appropriate analyses, benchmarking studies, surveys and other tools.

Education and Outreach
Users are kept up to date on changing technologies and services offered by the facility through the FHCRC and Consortium websites, Shared Resource Newsletter, and special memo distributions. Outreach to the broader Consortium community, particularly those within the UW and Children’s Hospital and Regional Medical Center (Children’s), will be enhanced through the activities of the Institute of Translational Health Sciences (ITHS). As an ITHS approved facility, the Resource is plays an ongoing and important role in support of translational research activities. Also, Consortium Shared Resources can be found through eagle-l, a web-based, searchable nationwide network of scientific services. Resource employees keep current in their field through scientific publications, seminars and national conferences.

Priorities and New Initiatives
Over the past several years, advancements in NextGen sequencing (NGS) technologies have resulted in the supplanting of many of the assays traditionally performed on microarray platforms. Most notably, differential expression analysis (DEA) and chromatin immuno precipitation (ChIP) assays have for the most part migrated to NGS platforms. As a result, the Resource has phased out the Affymetrix and NimbleGen services - the former the result of diminishing demand and the latter the result of the company terminating their microarray business. That said, microarray technology still has relevance in genomics-based research and as such the Resource has maintained its abilities to provide Illumina and Agilent microarray services. In many cases, cost issues and high sample throughput – especially large genotyping projects – still favor an array-based platform, and past usage and existing demand for these services are reflective of this fact. Moving forward, a major focus of the GSR will be to stay abreast of developments in NGS technologies and expand the Resource’s capabilities as this area continues to advance. The Resource is currently reviewing library prep automation systems in hopes of being able to reduce turnaround times, while building in the capacity to increase throughput. In addition, new methodologies to support extremely low sample input (e.g., single cell) are especially of interest and more efforts will be put in place to test and optimize new developments in library preparation methodologies. At the same time, the Resource will be monitoring microarray usage and take further actions on existing services related to this technology as warranted.

A second area of focus that is related to NGS advancements is the GSR’s continued development with data analysis and bioinformatics support, which continues to expand through the partnership with the Computational Biology Shared Resource. A common obstacle for a researcher considering NGS technology is the need for assistance with managing and analyzing NGS data. Through this joint partnership, the Genomics Shared Resource has taken great efforts to reduce such obstacles as researchers consider the best technologies to address their scientific questions. As the analysis of NGS data is a developing area of research, the Resource’s staff is dedicated to keeping abreast on the advancements in this ever-evolving area and implementing new data analysis methodologies to data generated in the Resource, as warranted.

A third area that the GSR will be developing is digital PCR technology services. This will likely occur in parallel with the needed upgrades the Resource’s existing four ABI Prism 7900HT Sequence Detection Systems that will not be supported by the vendor (Life Technologies, Inc.) in the next few years.

Personnel
Key Staff Qualifications
Jeffrey Delrow Ph.D., Staff Scientist and Director, was hired in 1998 to develop the DNA Array Facility. He subsequently assumed the responsibilities for leadership of the GSR in 2001. Dr. Delrow oversees the general operation of the facility, keeps abreast of the latest relevant technology advancements, and ensures that the Resource continues to meet the needs of investigators. One of his primary responsibilities includes consulting with researchers on issues ranging from technology selection and experimental design to data analysis. Dr. Delrow is an expert in the field of genomics and is a co-author on over 50 per-reviewed publications relating to genomics-based research. He received a Ph.D. in Physical Chemistry while studying in the in the laboratory of
Dr. J. Michael Schurr at the University of Washington, where he applied experimental and computational approaches to study the structure and dynamics of double-stranded DNA.

Ms. Cassandra Sather, Supervisor and Senior Specialist, has worked at FHCRC for 18 years, with 14 years of experience in the GSR. Ms. Sather directly supervises junior laboratory staff. She has a BS in Biochemistry and Molecular Biology from the University of Idaho. Among Ms. Sather’s many accomplishments, she has been instrumental in the successful completion of several large genotyping studies, including multiple GWAS totaling 44,537 samples genotyped in the past 6 years.

Four laboratory specialists provide technical support across a breadth of activities within the Resource. Ms. Elizabeth Jensen has a BS degree in Molecular and Cellular Biology from the University of Washington, Ms. Alyssa Dawson has a BS in Biochemistry from Western Washington University, Mr. Jerry (Andy) Marty has a BS in Biology with a minor in Chemistry from Western Washington University, and Ms. Crissa Bennett has a MS in Pharmaceutical Bioengineering and a BS in Cellular, Molecular, and Developmental Biology from the University of Washington. These staff members are highly experienced, with an average tenure in the Resource of approximately 8.5 years. Two additional staff members are responsible for maintaining the software infrastructure for the Resource and provided programming and data analysis support. Dr. David Waring received a Ph.D. in Biochemistry and Biophysics from the University of California, San Francisco. Dr. Waring originally honed his programming skills in the commercial sector, followed by 5 years as a bioinformatics programmer and lead database designer at the University of Washington’s Genome Center. He has been with the GSR since 2006. Mr. Ryan Basom has a BS in Molecular and Cell Biology from the University of Washington and has taken numerous courses in biostatistics, computer programming, UNIX support, and web development. He has been with the GSR since 2000.
Clinical/Translational
IMMUNE MONITORING SHARED RESOURCE

Introduction
The Immune Monitoring Shared Resource provides investigators with a broad range of services and expertise to perform human protein and other biological mediator analyses and to provide precise evaluation of immunologic responses for both preclinical and clinical studies. Resource services include the production of peptide-major histocompatibility complex Class-I tetramers, reagents useful for accessing antigen-specific T cells; molecular assays for interrogating T cell receptor usage and frequency, cellular assays for determining cell function, and high throughput analytical services using ELISA assay and Luminex microbead methodology. Support is provided for both single experiments as well as large long-term clinical studies. The IMSR works very closely with the Therapeutic Manufacturing Shared Resource to support clinical trials. The resource received an assessment of Outstanding in the 2008 renewal. Reviewers suggested that given the breadth and depth of immune therapy and vaccine programs, the facility seemed somewhat understaffed. The resource has added one additional full-time staff person during the project period and is adequately staffed for the current demand.

Major Services
Facilities and Equipment
The IMSR is located at the Fred Hutchinson Cancer Research Center (FHCRC). Total facility space is 800 square feet, of which 700 square feet is devoted to lab space and 100 square feet for office support. In addition, 100 square feet is provided in a shared equipment room for instrumentation available to users on a 24x7 basis. The resource is equipped with biosafety cabinets, carbon dioxide (CO₂) incubator, FPLC system, multiple mode Hybrid reader, ELISPOT reader, ELISA reader, xCELLigence System, luminometer, qPCR system, centrifuges, freezers, refrigerators, microscopes, water baths, pH meters, shaker incubator, balances, spectrophotometer, plate washer, and other small equipment. A robotic liquid handling system performs repetitive pipetting in the performance of ELISA assays. A Top-Count scintillation counter, harvester and microplate washer are in a shared equipment room located in proximity to the resource. A new Luminex 200 instrument was added this year for cytokine analysis using microbead technology.

Technologies and Expertise
Peptide-MHC Class I Tetramer Production
Tetramers are multimeric pMHC molecules, which are critical reagents for analyzing antigen-specific T cells. The multimeric nature of tetramers increases the affinity of pMHC molecules for the T cell receptor (TCR) molecules, enabling their usage as labeling reagents for identification of cells expressing a TCR of defined specificity. Labeling of antigen-specific T cells by tetramers makes possible the characterization of the phenotype and functionality of these cell populations, which are usually found at only low frequencies. In the production of tetramers, the desired MHC heavy chain protein and peptide epitope are refolded into an MHC complex with β2-microglobulin in vitro. The successfully refolded monomers are purified by gel-filtration and biotinylated. Tetramerization is achieved by binding to streptavidin, and a fluorescent dye is often added by using fluorochrome-conjugated streptavidin.

The resource produces investigator-defined pMHC monomers and tetramers with specific MHC alleles and peptide epitopes. We now have the following MHC alleles available: 2 mouse, 4 monkey and 37 human and offer the tetramers conjugated with Phycoerythrin (PE), Allophycocyanin (APC), AlexaFluor, Quantum dots and others detection molecules as needed for the assay to be performed.

The resource has added a clean room and developed standard operating procedures for the production of tetramers for clinical applications. We have also installed a dedicated FPLC system for the purification of these reagents. These tetramers are approved by the Food and Drug Administration (FDA) to sort anti-tumor T cells in several funded clinical trials.

Molecular Analysis of T cell Receptors
TCR Spectratyping - Spectratyping utilizes a set of multiplexed reverse transcription PCR (RT-PCR) reactions that amplify all T cell receptor Vβ chains to reveal the clonal length polymorphism in the CDR3 region. This technique is used to assess the clonal composition of T cell populations, and can be used to determine clonal
expansion, contraction and deletion during immune responses and reconstitution. TCR spectratyping can be provided for peripheral blood mononuclear cells (PBMC) samples or for fluorescence-activated cell sorted (FACS) subsets.

**Clonal TCR analysis** - The unique feature of each T cell clone is found in the recombined TCR sequences. IMSR can identify the clonal TCR Vβ chain sequence by RT-PCR and direct sequencing of the clonal cell sample. The clonal TCR beta (TCRB) sequence can be cloned and used for qPCR analysis. With knowledge of the clonal TCR sequence, specific primers and a probe for qPCR analysis can be designed, allowing the quantitation of the clonal T cells in a cell population. This analysis offers the possibility of analyzing and tracking T cells by their specific TCR.

**Real-time PCR analysis** – With knowledge of the clonal TCR sequence, specific primers and probes for quantitative real-time PCR analysis can be designed, which allow quantitation of the frequency of the clonal T cells in a cell population. This analysis has been used to support clinical immunotherapy trials of adoptive T cell transfer in cancer patients, making it possible to track the frequency of infused T cells among the peripheral blood mononuclear cells.

**TREC assay** – The T cell receptor excision circle (TREC) assay is a quantitative real-time PCR analysis of the TCR excision circle, a circular DNA fragment removed from the genome as a result of the TCR rearrangement in the thymus. As this circular DNA is not capable of replication and is therefore diluted as T cells divide in the periphery, monitoring the relative quantity and absolute number of cells containing the TREC DNA provides a dynamic measurement of thymic output of naïve T cells.

**Cellular Analysis of Immune Cells**

**Lymphoproliferation assay** - classic method for assessing lymphocyte response to stimulation. Lymphocytes proliferate after incubation in vitro with mitogens and specific antigens, or in a mixed lymphocyte reaction, which is then measured by ³H-thymidine incorporation. The magnitude of proliferation provides an indication for general lymphocyte activity or responsiveness to specific antigens.

**Chromium-51 release assay** – Cytotoxic T Lymphocytes (CTL) and Natural Killer (NK) cells function by killing their target cells, which can be measured by the Chromium-51 (⁵¹Cr) – release assay. Specific target cells are loaded with ⁵¹Cr, which is then released into the medium when the cells are lysed by the specific CTL or NK cells. This functional assay is widely used in studies of antigen-specific CTL and NK activity.

**Immune phenotyping by FACS analysis** – Analyzing cell surface and intracellular proteins by labeling with fluorochrome-conjugated antibodies and flow cytometry is a common method employed in immunology to characterize the nature and function of cells. Antigen-specific T cells can be analyzed by concurrent labeling or prior sorting with specific pMHC tetramer. The IMSR provides multi-parametric flow cytometric analysis in accordance to specific study requirements. For example, support has been provided for complete peripheral lymphocyte phenotyping of B cells, T cells, monocytes, NK and dendritic cells for evaluation of immune reconstitution and function after hematopoietic stem cell transplant.

**ELISPOT Assay** - The ELISPOT assay is a high-throughput procedure used to evaluate antigen-specific T cell responses based on the function of single responding cells. In this assay, cells that are responding to antigenic stimulation secrete cytokines that can be captured locally by antibodies, and visualized by staining in the form of spots which are quantified by computer-based imaging analysis tools. Thus the precise enumeration of responsive cells can be made. The IMSR provides training and technical support for investigators performing this assay and using the ELISPOT reader.

**ELISA and Luminex assay**

The resource provides analytical, consultative and development services including the use of ELISA and Luminex assay for cytokines and other biological mediators. Services include: consultations on ELISA and Luminex microbead methodology and trouble-shooting assays with unacceptable variance, performance of assays using commercial ELISA kits, development of ELISA and Luminex microbead methods for new parameters, and performance of standard assays. The IMSR's assay repertoire currently covers about 50 cytokines and other proteins. All these assays are validated and on line. Most of the assays were developed in
response to requests by investigators. Development services are provided in partnership with collaborating laboratories, often developing assays for which no commercial assay kit could be found.

Consulting
A significant proportion of the IMSR services are provided through ongoing consultation with Consortium users involving initial experimental design, data analysis and interpretation and follow-on tracking of specific immune responses. We are able to respond rapidly to investigator requirements especially within the context of just-in-time assay processing for clinical treatment protocols.

Importance to Programs
The IMSR supports several Consortium investigators in programs including Immunology and Vaccine Development and Hematologic Malignancies. These research and clinical programs focus on understanding the immunobiology of cancer and the obstacles to developing/sustaining effective T cell responses to malignancies; the immunobiology of viral and infectious disease derived cancers, and the requirements for developing effective vaccines to infections and cancers; and approaches to manipulate the cellular and molecular aspects of the immune system to prevent and treat malignancies and life-threatening infections. A major effort of this program is an elucidation of the reasons for success or failure of immunotherapeutic strategies by monitoring the persistence, localization and function of antigen-specific T cells following adoptive transfer or vaccination protocols. The Hematologic Malignancies program combines basic and translational research to investigate the immunobiology of blood borne cancers. Four areas of focus predominate: (1) Myeloid Leukemia Biology; (2) Developmental Therapeutics; (3) Preclinical Transplantation Biology; and (4) Clinical Hematopoietic Cell Transplantation. Several other Consortium programs rely on the specialized services provided by this resource to support peer reviewed research.

Selected descriptions of projects being conducted within the facility are outlined below, emphasizing the importance of the resource to peer reviewed research.

**Philip Greenberg MD, Immunology & Vaccine Development**

Relapse remains a leading cause of death after allogeneic hematopoietic cell transplantation (HCT) for patients with high-risk leukemias. As the potentially beneficial donor T cell-mediated graft-versus-leukemia (GVL) effect is often mitigated by concurrent graft-versus-host disease (GVHD), Dr. Greenberg’s laboratory investigates if providing T cells that can selectively target Wilms tumor antigen 1 (WT1), a transcription factor overexpressed in leukemias that contributes to the malignant phenotype, would promote antileukemic activity without inducing GVHD. HLA-A*0201-restricted WT1-specific donor-derived CD8 cytotoxic T cell (CTL) clones were administered after HCT to 11 relapsed or high-risk leukemia patients without evidence of on-target toxicity. Efforts were made to improve the quality of the transferred T cells, as reflected by phenotypic and functional analyses performed by the core, and the last four treated patients received CTL clones generated with exposure to interleukin-21 (IL-21), which was found to prolong in vivo CTL survival after transfer, because IL-21 can limit terminal differentiation of antigen-specific T cells generated in vitro. These improved qualities were reflected by multi-parametric analyses performed by flow cytometry on the cells prior to transfer, including retained expression of CD28 despite extensive cell expansion during in vitro culture. Transferred cells exhibited direct evidence of antileukemic activity in two patients: a transient response in one patient with advanced progressive disease and the induction of a prolonged remission in a patient with minimal residual disease (MRD). Additionally, three treated patients at high risk for relapse after HCT are surviving without leukemia relapse, GVHD, or additional antileukemic treatment. The CTLs generated in the presence of IL-21, which were transferred in these latter three patients and the patient with MRD, all remained detectable long-term (by flow cytometry and/or PCR for the unique rearranged TCR) and maintained or acquired in vivo phenotypic and functional characteristics associated with long-lived memory CD8 T cells, including expression of CD28 and the capacity to produce IL-2 following target recognition and use this cytokine as an autocrine proliferative signal. This study has supported studies now ongoing to expand efforts to immunologically target WT1, which are employing T cells transduced with a high affinity TCR specific for WT1, and are using tetramers to first isolate donor virus-specific T cells for transduction (to remove the risk of inducing GVHD) and sorting of transduced T cells expressing the WT1-specific TCR to limit the culture period and the extent of cell expansion required.
The IMSR is supporting Dr. Greenberg’s research and clinical trials with pMHC Class-I tetramers, which are used to identify and characterize tumor-specific T cells and to sort these cells for adoptive T cell therapy trials. The IMSR also provide qPCR service to analyze and track the transduced TCR genes in preparation of adoptive T cell infusion and follow-up studies.


Colleen Delaney MD, Hematologic Malignancies
A cord blood transplant is a hematopoietic stem cell transplant that uses umbilical cord blood instead of bone marrow or peripheral blood as the source of blood-producing stem cells for the transplant. In 2006, the Hutchinson Center launched its Cord Blood Program, which directed by Dr. Colleen Delaney and has performed more than 200 cord blood transplants through clinical trials aimed at improving and expanding this treatment. Clinical trials have shown that patients who receive transplants with an expanded number of cord blood stem cells regain their ability to fight infections faster. This may lead to more successful transplants and even possibly an off-the-shelf treatment that can be stored and used as needed to treat a variety of hematological diseases. The IMSR lab has supported these clinical trials since 2006 with the TREC assay and TCR spectratyping, which monitored patient’s thymic output of naïve T cells and T cell repertoires, respectively. Patients from 7 protocols of the cord blood transplant trials have been monitoring up to 2 years post-transplant. Manuscript is currently under preparation.

Stanley Riddell MD, Immunology and Vaccine Development
Cameron Turtle MBBS PhD, Immunology and Vaccine Development
The potential for immunotherapy to cure the most challenging human cancers has been demonstrated in small clinical trials. A promising advance is the adoptive transfer of T cells engineered to have tumor specificity by gene transfer, which has shown significant therapeutic activity in patients with incurable CD19+ B cell malignancies. This approach employs T cells that are modified to express a chimeric antigen receptor (CAR) consisting of an extracellular single chain variable fragment (scFv) of a CD19 specific monoclonal antibody fused to transmembrane and intracellular domains from one or more T cell signaling molecules. Lentiviral transduction is used to introduce the CD19-specific CAR (CD19 CAR) into distinct subsets of T cells, which can then be propagated in vitro before infusion into a patient with a CD19+ B cell malignancy. Drs. Riddell and Turtle’s team has initiated a phase I/II clinical trial (FHCRC Protocol 2639) to investigate the safety and preliminary efficacy of treatment of patients with B cell malignancies with autologous CD19 CAR-modified CD8+ central memory (T_CM) and CD4+ T cells. Prior to infusion, the genetically modified T cells undergo stringent release testing, as mandated by the IND application. The IMSR lab performs two of these release assays on both CD8+ T_CM and CD4+ T cell products, which are then formulated in a 1:1 ratio for infusion. QPCR for VSV-G is performed as a surrogate assay for the presence of replication competent lentivirus in the T cell product and qPCR for WPRE for VSVG is performed to determine the transgene copy number per cell. After T cell infusion, the IMSR lab assists with monitoring of the study participants. WPRE qPCR is performed determine the level of persistence of the genetically modified T cells. On recognition of tumor targets, effector function of CAR T cells is induced, which can cause a clinically severe cytokine release syndrome. For this reason, concentrations of serum cytokines (IFN-γ, TNF-α, MIP-1α, IL-2, IL-6, IL-8, IL-10, and GM-CSF) are closely monitored by the IMSR lab using Luminex assays before infusion and after infusion. In addition, during acute illness, serum cytokine levels and WPRE qPCR are performed to determine if there is evidence of CAR T cell-mediated toxicity. These assays are conducted by the IMSR lab in real-time, as clinically indicated. We have administered 8 infusions to 5 patients on this study. After the phase I portion is complete in January 2014, treatment of one patient each week is expected in the phase II study. Drs. Riddell and Turtle also have a second trial (FHCRC 2494) that is investigating the safety and preliminary efficacy of treatment of allogeneic hematopoietic stem cell transplant recipients with B cell malignancies with donor-derived CD19 CAR-modified CD8+ central memory (T_CM) cells. The IMSR lab performs VSVG and WPRE qPCR release assays on the engineered CD8+ T_CM cells, and WPRE qPCR and serum cytokine monitoring studies, as described above. We have enrolled one patient (one infusion).
Cameron Turtle MBBS PhD, Immunology and Vaccine Development

Low HCT graft content of NKT cells has been associated with an increased risk of acute GVHD after HCT, suggesting that strategies to improve NKT cell recovery might decrease the risk of GVHD after HCT. Dr. Turtle’s laboratory is analyzing how the composition of the colonic microbiota impacts recovery of NKT cells in blood after allogeneic HCT. Paired blood and stool samples from allogeneic HCT recipients are collected at distinct times after HCT and determine if the relative abundance of distinct bacterial species correlates with recovery of NKT cells. The relative abundance of distinct bacterial species in the stool microbiota at each time will be assessed by 16S rRNA gene PCR with high throughput sequencing followed by alignment and phylogenetic assignment of the amplified and sequenced fragments. In parallel, the fraction of NKT cells in a blood lymphocyte gate will be identified by flow cytometry by identifying events that co-express CD3 and a CD1d tetramer folded with alpha-galactosyl ceramide, and the absolute number of NKT cells calculated by performing a CBC at the same time. The CD1d tetramer will be made by the IMSR Lab. Identification of bacterial species that promote NKT cell recovery will provide insight into strategies to improve immune reconstitution after HCT.


**Edus Warren, MD, PhD, Immunology and Vaccine Development, Global Oncology**

Dr. Warren’s laboratory and clinical interest is the cellular and molecular dissection of antitumor immune responses, so that these immune responses can be exploited to clinical advantage. In particular, a major focus of the research in his laboratory is focused on the mechanisms and target molecules associated with the graft-versus-tumor (GVT) reaction that occurs after allogeneic hematopoietic cell transplantation for hematologic malignancies and selected solid tumors. The graft-versus-tumor (GVT) effect is one of the clearest examples of successful immunotherapy in humans. It is mediated primarily by CD8+ and CD4+ T lymphocytes contained in or derived from the donor hematopoietic cell graft, and the focus of one project in Dr. Warren’s lab is characterization of the T cells that mediate the GVT effect and identification of their target antigens. A major class of these target antigens comprises minor histocompatibility antigens, which are short peptides encoded by polymorphic genes that are presented on the cell surface by MHC class I and II molecules. The IMSR lab is supporting Dr. Warren’s research in the area of T cell responses to minor histocompatibility antigens with specific peptide MHC Class-I tetramers.


**Paul Nghiem, MD, PhD, Global Oncology**

Merkel cell carcinoma (MCC) is a rare but often lethal tumor of uncertain histogenesis. In 2008, the Merkel cell polyomavirus (MCPyV) was discovered and found to be integrated into the host genome in approximately 80% of MCC tumors(1). The host cellular immune system appears to be critical in preventing and controlling MCC(2, 3). Dr. Nghiem’s laboratory has shown that MCPyV-specific CD8 and CD4 T cells can localize to MCC tumors and reported novel MCPyV T cell epitopes(4). Some of epitopes are now serving as targets in on-going adoptive immune therapy trial.

The IMSR has provided tetramer/MHC/peptide reagents over the past couple of years for basic and clinical studies in Dr. Nghiem’s laboratory. The reagents have enabled tracking the virus-specific T-cell response in dozens of Merkel cell carcinoma patients with great specificity(5). These tools have provided insight into the disease process and have been used to isolate T-cells for therapeutic purposes. Based on preliminary data and an initial patient treated(6) using tetramers produced by the IMSR, Dr. Nghiem’s team successfully competed for NIH funding for a clinical trial of 16 patients to be treated with adoptive immune therapy with extensive immune monitoring. A second R01 characterizing the nature of the immune response in Merkel cell carcinoma also is heavily reliant on the technologies and services from the IMSR.


Cost Effectiveness
The IMSR provides the highest quality tetramer production and cellular assays for Consortium investigators at the lowest possible cost. Price comparisons between core facilities at other institutions and commercial entities revealed that the resource is the most cost effective option in Washington State. Furthermore, the resource offers custom services that are not available from other sources. It would also be very expensive for individual investigators to employ staff with the same level of experience and to purchase and maintain the equipment necessary to produce high quality results. Additionally, the experimental design and data analysis provided by IMSR reduces the number and complexity of experiments resulting in lower cost. Shared Resources performs annual benchmarking analysis as well as customer satisfaction surveys to ensure cost competitiveness and quality of service.

Use of Services Table

<table>
<thead>
<tr>
<th>IM Service</th>
<th>Total Users</th>
<th>Peer Reviewed</th>
<th>Non-Peer Reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELISA Assay</td>
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<td>0</td>
</tr>
<tr>
<td>Luminex Assay</td>
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<td>1 (5%)</td>
</tr>
<tr>
<td>Molecular &amp; Cellular Assay</td>
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<td>8 (89%)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Tetramers</td>
<td>18</td>
<td>17 (94%)</td>
<td>1 (6%)</td>
</tr>
</tbody>
</table>

Management Structure, Policies and Operations
Administration
The Immune Monitoring Lab operates in accordance with Consortium and institutional policies for Shared Resources. The IMSR is directed by Jianhong Cao, PhD, operates in consultation with Paul Woloshin, MBA, PhD, Consortium Director of Shared Resources. Dr. Cao oversees the general operation of the resource, keeps abreast of the latest relevant technology advances, and ensures that the resource continues to meet the needs of investigators. Dr. Cao has been managing the resource since 2003 and has experienced very little turnover of scientific staff. One of his primary responsibilities includes consulting with researchers on experimental design and the continuing development of new assays to address expanding research needs within the Consortium. Staff performance is evaluated at least once a year. Staff development is ensured through in-house training sessions and discussions, hands-on experience, seminars, and technical workshops. Resource managers and staff receive assistance from the Shared Resources administrative team and other FHCRC administrative departments for tasks such as billing and purchasing.

Faculty oversight is provided by an advisory committee responsible for annual review of the shared resource operation, providing review of user fee charges, evaluating annual capital budget requests, and providing guidance on future goals and objectives. Committee member for 2013 include Phil Greenberg and Cameron Turtle (Immunology and Vaccine Development), Bonnie McGregor (Cancer Epidemiology, Prevention and Control), and Marie Bleakley (Hematologic Malignancies) who are all faculty members at the FHCRC and University of Washington as well as consortium members. The Consortium’s Scientific Steering Committee ensures that this and other Consortium resources are aligned with the Consortium’s strategic goals and assesses its continued value to the Cancer Center.
**Access and Usage Policy**

Services are available to all members of the Consortium, on a first-come, first served basis. Support is provided to external users as time/reagents/staff permit. Costs are charged directly to applicable awards based on actual usage and rates are based on projected direct operating costs net of CCSG and institutional support. Rate schedules are revaluated and revised as required on an annual basis. External user fees reflect the full cost (both direct and indirect) of rendering services based on the current negotiated indirect cost rate. No benefit of institutional or federal funding received by the resource is considered in the establishment of outside rates.

**Billing**

Standardized service request forms provide authorization of service and requested information for each respective transaction. Services are billed upon completion in accordance with OMB policies and information is entered into a Shared Resources automated billing system which provides the ability to track resource use at the project level by activity. Ongoing review is conducted to monitor activity levels and observe usage trends to ensure appropriate adjustments are made in operations to adapt to changing demand. Usage is assessed and summary reports are develop by institution, by investigator, and by program for each service provided by the resource. Ongoing evaluation of resource operations is conducted through implementation of appropriate analyses, benchmarking studies, surveys and other tools.

**Education and Outreach**

Users are kept up to date on changing technologies and services offered by the facility through the FHCRC and Consortium websites, Shared Resource Newsletter, and special memo distributions. Outreach to the broader Consortium community, particularly those within the UW and Children’s Hospital and Regional Medical Center (Children’s), is being enhanced through the activities of the Institute of Translational Health Sciences (ITHS). As an ITHS approved facility, it is anticipated that the Resource will play an ongoing and expanded role in support of broader translational research activities.

**Priorities and New Initiatives**

We have expanded the services offered through the addition of a new Luminex instrument which: 1) provide users training and direct access to the Luminex instrument rather than have work performed by IMSR staff; 2) perform real-time Cytokine analysis which is required for the clinical immunotherapy studies being performed Stan Riddell, M.D. and Cameron Turtle, MD, Ph.D. Samples are often delivered as patients under protocol are at risk of experiencing “cytokine-storm” and specific treatments are now available targeting select cytokines that must be administered based on IMSR analysis; and 3) offer added instrument capacity to expand the Cytokine panel we currently offer.

**Develop a CD-1d tetramer**

A low content of Natural Killer T-cells (NKT) in hematopoietic cell transplantation (HCT) grafts has been associated with an increased risk of acute Graft vs. Host Disease (GVHD) after HCT, suggesting that strategies to improve early NKT cell generation/recovery might decrease the risk of GVHD. Investigators at the immunology program are analyzing how the composition of the colonic microbiota impacts recovery of NKT cells in blood after allogeneic HCT. The fraction of NKT cells in the blood will be identified by flow cytometry as reflected by detection of cells that co-express CD3 and a CD1d tetramer folded with alpha-galactosyl ceramide, and the absolute number of NKT cells calculated by performing a complete blood count (CBC) at the same time. The CD1d tetramer is being made by the IMSR. We are currently working on the CD1d expressing construct, and modifying our pMHC refolding protocol to produce the CD1d tetramer.

**Personnel**

**Key staff Qualifications**

**Jianhong Cao PhD Staff Scientist and Director** of the Immune Monitoring Lab was hired in 2003 to develop the resource. Dr. Cao oversees the general operation of the resource, keeps abreast of the latest relevant technology advances, and ensures that the resource continues to meet the needs of investigators. One of his primary responsibilities includes consulting with researchers on experimental design and continuing development of new assays to address expanding research needs within the consortium. Dr. Cao received his PhD in biology from the Technical University in Braunschweig, Germany in 1996. His expertise prior to joining
the shared resources was in molecular virology of HIV and human cytomegalovirus, and in assessing cellular immune responses during HIV infection.
NORTHWEST Biotrust Shared Resource

Introduction
NWBioTrust (NWBT) is a new Established Shared Resource that represents the maturation of the Developing Tissue Bank Shared Resource currently supported by CCSG Developmental Funds. The CCSG, as well as two major grants totaling $6.75M from Washington State’s Life Sciences Discovery Fund (LSDF), funded much of the early developmental work for this resource. NWBT is the result of a successful collaboration of the UW departments of Pathology, Laboratory Medicine, and Biomedical Informatics and Medical Education (BIME), the UW Institute of Translational Health Sciences (local CTSA), FHCRC, SCCA and Children’s. The mission of NWBT is to provide reliable and cost-effective access to high-quality human tissue, blood and other body fluid samples, and associated clinical and specimen annotation data, for innovative diagnostic, therapeutic and public health sciences research.

Major Services
Facilities and Equipment
NWBT operations staff has newly remodeled office space in the UW Health Sciences Building (HSB) room RR844, connected and adjacent to UW Medical Center. This 180 ft² space has computerized (auditable) keypad access, a private office for the Assistant Director and four additional workstations equipped with new PC computers. All computers listed are connected to an automated nightly network-based backup service.

NWBT tissue procurement activities occur either in the UW Pathology frozen section room or in the archival block room. The Pathology frozen section room is a 250 ft² room within the UW Medical Center adjacent to operating rooms, equipped with biosafety hood, gross photography stand with digital camera, dissecting platforms, scales, microtomes, PC computers connected to clinical and research barcoded label printers, equipment to snap-freeze and temporarily store (on dry ice) specimens prior to transport to researchers or biorepositories, a refrigerator, and an Olympus BX45 microscope with a Leitz digital camera. Paraffin embedded archival block handling occurs in a 95 ft² office space located 100 ft from the frozen section room, and equipped with an up-to-date PC computer. Histology functions are obtained from consulting laboratories including the UW Medical Center hospital pathology laboratory.

Technologies and Expertise
Biospecimen Procurement Supported by NWBT IT System to Track Studies, Consents, Patient- and Visit-Level Information, and Specimen Details
NWBT provides prospective collection of annotated research-only tissue, blood, and other specimens; high-throughput collections of annotated remnant diagnostic materials; and identification of existing annotated repository samples using the Virtual Biospecimen Discovery (VBD) system (described below).

NWBT operations are supported by the NWBT IT system which is described in detail later in this narrative. This system, which is primarily deployed in the LabKey (Seattle, WA) application server platform, functions to register studies and supporting regulatory (IRB, etc.) documentation, track study-specific consent management, identify patients who may be eligible for specific studies, and support the ordering, tracking, and reporting (delivery and invoicing) of research samples.

Specimens are accompanied by a standard data set including patient- and visit-level data extracted from the Amalga Clinical Data Repository (CDR) (Caradigm, Bellevue WA), a clinical data aggregation platform managed by UW Medicine that integrates information from multiple medical systems including various Epic applications (including the Epic electronic consent module), Cerner, Sunquest and source systems supporting surgical scheduling, radiology, and pathology operations. Additional study- and sample-level information is derived from information collected from the investigator through the NWBT portal. Consent and sample collection details (collection date/time, and for tissues anatomical site of origin, weight, size, storage location, clamp time, tissue removal time, etc.) are entered by NWBT staff who manage the collections.

Requests for NWBT services come through a single office, which responds to researcher requests via a single email address (nwbt@uw.edu). That office works with research users to develop a statement of work (SOW)
for each project, a project budget, a letter of support for grant applications if needed, and assists with IRB applications as needed. Researchers are then directed to the NWBT web portal Study Registration (SR) system to enter details about contact information for project staff, budget information, and sample request details, etc., and to upload IRB approvals and consents if appropriate. The system allows NWBT staff to assist researchers with entering this information. As specimens/data are delivered, delivery reports and invoices are indexed in the SR system.

The SR system consists of a customized LabKey application that is backed by a SQL Server database. A UW NetID is required to log in and submit study and sample request information. Study and sample request details entered by investigators are regularly imported into the NWBT SQL Server database over secure, SSL-encrypted network connections that require service-level authentication.

The system for prospective collection (PSC) of specimens consists of a set of custom developed user interface modules written in JavaScript and deployed to a separate LabKey application. The PSC system communicates with the NWBT SQL Server database through a custom-developed web services application running in a Tomcat servlet container. Web services (REST-based) require service-level authentication and are encrypted using SSL. The PSC system is intentionally separate from the SR system to maximally secure protected health information (PHI) and, unlike the SR system which is widely accessible by those with UW NetIDs, access to the PSC system is restricted to Honest Broker staff with LabKey user accounts accessible only from limited network addresses. Honest Broker staff maintain private information, such as patient identifiers and distribute de-identified material to other entities who do not have access to the entire set. The PSC system extracts EMR and other data from the Amalga CDR for the purposes of identifying patients eligible for studies, manages study-specific patient consent, and triggers orders for collection of tissue, blood and other specimens from upcoming surgical and clinic patient appointments. Upon collection, a barcoded label containing each sample’s coded identifier (a unique number generated in LabKey) is applied. The LabKey application also includes report modules to provide collection and distribution metrics.

The system for high-throughput identification of suitable remnant diagnostic blood, urine, and other fluids procured from UW Laboratory Medicine leverages a custom database utilizing SQL Server Integration Services (SSIS; Microsoft, Redmond WA), and stored procedures deployed in the Amalga CDR environment. Requests for discarded blood are created by matching highly specific study criteria, consent status, and sample data to create “pick lists” of specimens and associated labels with coded identifiers. The “pick lists” are sent to Lab Medicine using components running in the Amalga CDR and NWBT IT environments. The patient- and visit-level information (including consent information), sample-level information, and confirmation of successful “picks” are tracked in the NWBT database for auditing and reporting purposes.

The NWBT Virtual Biospecimen Discovery (VBD) portal (https://vbd.nwbiotrust.org/project/VBD/begin.view) has been developed as a customized LabKey application with fully de-identified sample data from Consortium biospecimen repositories. This system supports researcher queries for patient samples across disease types that may already be banked and available for study. Results of these queries are exported to the SR system to generate requests. This method maintains the central NWBT business office (nwbt@uw.edu) as a single point of researcher contact for biospecimens.

Consenting Services
Consent for use of specimens and clinical data, and for potential recontact for participation in clinical trials, is sought of UW Medicine and SCCA patients. Consent is obtained with IRB permission and oversight, is completely voluntary, and can be withdrawn at any time. A patient’s consent status is not revealed to clinical care providers and does not affect clinical care in any way. No specimens or data will be made available for research from patients who choose to “opt out.”

Consent is obtained either through a “front desk” system integrated into UW Medicine and SCCA clinic settings, through paper-based consents obtained by NWBT consenting staff, or through paper-based (often study-specific) consents obtained either by NWBT staff or other study coordinators, etc. As described above, paper consents may be uploaded into the NWBT IT system. The “front desk” electronic consent collection system uses a customized patient registration module in Epic along with Topaz signature e-readers to record patient consents for the use of leftover clinical specimens and existing medical data, as well as a patient’s
consent to be contacted in the future for research purposes. These consents are imported daily into an Epic Clarity database and subsequently into the Amalga CDR where back-end processes import the consent status into the NWBT database. Since UW Medicine and SCCA share the same Epic infrastructure, “front desk” IT methods are available to clinics in both institutions, and have been successfully rolled out at several UW Medicine clinics. As is very common among institutions, some research using coded biospecimen and data is done under IRB-exempt status. However, over time our institutional aspiration is that all research on human biospecimen and clinical data will be done with patient consent by leveraging the NWBT consenting services.

More Detailed Patient-, Visit-, and Specimen-Level Annotation Data Services
ITHS staffs a fee-for-service office whereby researchers may extract EMR-derived data (https://www.iths.org/BMI#/BMI/emr), which may be linked to specimens (either identified, or de-identified via NWBT sample codes, depending on IRB permissions). Further, NWBT staff work on a fee-for-service basis to manually extract information from EMRs if needed, utilizing their Honest Broker status.

Streamlined Billing Service
Although NWBT projects may involve various cooperating component laboratories, invoicing, billing, and accounting are handled by the NWBT office such that researchers receive comprehensive itemized quotes and correlated invoices by which they can track charges against each SOW and project budget. “Behind the scenes” from the researcher perspective, payments flow among component laboratories per standard rate schedules.

Importance to Scientific Programs
The following eight projects illustrate the expertise and services provided by NWBT. These examples include those in which NWBT facilitated efficient access to holdings of the existing Consortium cancer biorepositories, as well as those in which biospecimens were prospectively collected. Institutional and grant funds are used to ensure that the cancer repositories acquire and maintain sufficient biospecimens to support a wide range of research studies. Most of these examples represent peer-review-funded research. However, NWBT also plays an important role in establishing new biospecimen collections that provide preliminary data for Consortium members to obtain peer-reviewed funding.

Thomas Spies, PhD, Hematologic Malignancies
Ted Gooley, PhD, Biostatistics and Computational Biology
R01 CA174470-22A1

NKG2D is a T cell and natural killer (NK) cell activating receptor with well-established roles in protective tumor immunity owing to the presence of its ligands in essentially all types of cancers. Thomas Spies and colleagues discovered that NKG2D also moonlights as a stimulatory receptor on breast, ovarian, colon and prostate carcinoma cells where it exploits the presence of its ligands for autocrine activation of major oncogenic pathways and stimulation of tumor growth. Analysis of ex vivo isolated breast and ovarian carcinoma cells enabled them to show that NKG2D signaling has even more significant functional consequences as it promotes cancer cell plasticity with differentiation towards stem-cell like phenotypes, and migratory and tumor-initiating abilities (manuscript in preparation). For these studies, he received de-identified breast cancer specimens from the Breast Specimen Registry and Repository (BSRR) and de-identified ovarian cancer specimens from the Pacific Ovarian Cancer Research Consortium (POCRC) specimen core. The availability of NWBT-sourced cancer specimens were instrumental in these efforts to characterize the normally immune system-associated NKG2D receptor as a master regulator of cancer cell plasticity in human breast and ovarian cancer.

Paul Nghiem, MD, PhD, Global Oncology
Barry Storer, PhD, Biostatistics and Computational Biology
David Byrd, MD, Women’s Cancer
Merkel cell carcinoma (MCC) is an aggressive, neuroendocrine cancer of the skin with mortality of ~40%. There are approximately 1600 cases of MCC2 diagnosed in the United States each year, and this number continues to rise with an increase in the risk factors, including UV exposure and immune suppression, although more than 90% of MCC patients are not immune suppressed. 80% of MCC tumors are associated with the Merkel cell polyomavirus (MCPyV) and persistent expression of the viral small and large T antigen (T-ag) oncoproteins is required for tumor growth. MCPyV T-ag oncoproteins are non-self immunogenic proteins that can be targeted for immunotherapy. Paul Nghiem and colleagues lead MCC research to map MCPyV T antigen-specific T-cell epitopes to create MHC-peptide multimers, which will allow for isolating MCPyV specific T cells for adoptive T cell therapy as well as measure the functional characteristics of these cells in MCPyV-positive MCC tumors. The MCC tumor tissues received through NW Bio Trust are used to culture tumor-infiltrating lymphocytes (TIL) and identify antigen-specific T cells in these cultures. The investigators can also digest the tumor to study the functional characteristics of ex vivo TIL.

**Jason Bielas, PhD, Cancer Basic Biology**

**Harlan Robins, PhD, Biostatistics and Computational Biology**


R01 ES019319

Infiltrating T lymphocytes are frequently found in malignant tumors and are suggestive of a host cancer immune response. Studies have documented that the presence and quantity of tumor-infiltrating lymphocytes (TILs) are strongly correlated with increased survival. However, because of methodological factors, the exact effect of TILs on prognosis has remained unclear and inclusion of TILs in standard prognostic panels has been limited. To address this limitation, Jason Bielas, Harlan Robins and colleagues developed a digital DNA-based assay, termed QuanTILfy, to count TILs and assess T cell clonality in tissue samples, including tumors. They demonstrated the clonal specificity of this approach by the diagnosis of T cell acute lymphoblastic leukemia and the accurate, sensitive, and highly reproducible measurement of TILs in primary and metastatic ovarian cancer. Their experiments demonstrate an association between higher TIL counts and improved survival among women with ovarian cancer, and are consistent with previous observations that the immune response against ovarian cancer is a meaningful and independent prognostic factor. Because variability in the measurement and characterization of TILs has limited their clinical utility as biomarkers, these results highlight the significant translational potential of a robust, standardizable DNA-based assay to assess TILs in a variety of cancer types. These studies were facilitated by samples from the Consortium ovarian cancer repository through the Pacific Ovarian Cancer Research Consortium (SPORE, PI Nicole Urban.)

**Jennifer Specht, MD, Women’s Cancer**

1P50 CA-138293-03

In patients with locally advanced breast cancer, a mismatch between breast tumor metabolism assessed by dynamic FDG PET and tumor blood flow assessed by DCE-MRI has been consistently associated with poor response to neoadjuvant chemotherapy and poorer survival. The objective of the Seattle Cancer Consortium Breast SPORE project 3, Metabolic Alterations in Advanced Breast Cancer and Response to Systemic Therapy, is elucidation of the biologic underpinnings of this clinical observation. Aims for this project include prospective determination of associations between tumor metabolism assessed by dynamic FDG PET and blood flow assessed by DCE-MRI with breast cancer molecular subtypes assessed by genomic profiling, determination of the relationship of metabolism-blood flow mismatch with tumor hypoxia, and to identify genes and pathways which may be targeted to overcome the resistant phenotype conferred by metabolism-blood flow mismatch. To accomplish these goals, Jennifer Specht and colleagues are enrolling patients with newly diagnosed breast cancer to CCIRB # 7587, “Quantitative Dynamic PET and DCE-MRI in Breast Cancer Therapy. In this prospective imaging trial, patients consent to a research breast biopsy prior to neoadjuvant chemotherapy and collection of tissue at time of definitive breast surgery. This trial and project are dependent on collaboration with Peggy Porter, MD and NW BioTrust who assist with collection, routing and analysis of research tissue specimens.
“The ColoCare Study” includes a cohort of patients with colorectal cancer who have been cared for at the SCCA, UWMC, Swedish Medical Center, or Virginia Mason Medical Center. The intent of the study is to identify factors that determine both short-term and long-term survival in a prospective cohort of colorectal cancer patients. These factors will include inherited genetic and tumor characteristics that affect early detection, treatment response, and prognosis, as well as health behaviors patients adopt that may impact these health outcomes. The blood collection protocol, including collection prior to treatment/surgery and then at regular, 6-month intervals afterward, is a critical aspect of this study. This will enable the investigators to identify molecular markers unaffected by cancer treatment and surgery, as well as gaining an understanding of the prognostic significance of changes in these markers over time after treatment. Additionally, the biospecimens obtained from this patient cohort will provide an excellent resource for future investigation of serum, tumor, and urine markers that predict survival and recurrence.

Abundant evidence suggests that the adaptive immune system influences the natural history of colorectal cancer (CRC). The density of tumor infiltrating lymphocytes (TIL) in primary CRC tumors and liver metastases has been associated with improved survival, even in patients whose cancer has spread beyond the colon. However, the mechanism by which TIL interact with CRC tumors is still poorly understood, mainly due to the low numbers of TIL and CRC cells that can be obtained from each tumor for experimentation. Hootie Warren and colleagues devised methods to expand TIL and CRC cells in the laboratory with high fidelity and reliability, in order to facilitate studies characterizing the interaction between autologous TIL and CRC. The studies enrolled patients with CRC and collected from them samples of metastatic or primary colorectal tumors and uninvolved normal adjacent tissues, blood, and skin biopsies from surgical wounds (to generate cultured fibroblasts). Specimens were collected from 50 patients over the past 3 years, and been used to generate patient-derived xenograft and T cell lines. Enrollment of these patients and collection of the associated specimens was facilitated by the NWBio Trust. High throughput sequencing was used to characterize the xenografts with RNA-seq, and the T cells in CRC TIL with T cell receptor beta chain sequencing. In addition to the publication cited above, the investigators are currently preparing a second manuscript characterizing the T cell receptor repertoire of TIL in primary and metastatic colon tumors.

The Vessella laboratory received prostate cancer biospecimens from Genitourinary Cancer Biorepository during the past year for multiple studies. The most prominent study was the detection of disseminated tumor...
cells in the bone marrow of patients with prostate cancer and the gene expression profiling of these individually isolated cells in collaboration with Pete Nelson. This work revealed the tremendous heterogeneity of disseminated tumor cells isolated from the bone marrow. This work was supported by an NCI PO1 and data from this work were used to support an application to NIH (Morrissey as PI) which is pending review. A second study focused on the complexity of survival mechanisms in cancer cells from patients, which remains poorly understood. To obtain a comprehensive picture of tumour cell survival in lethal prostate cancer metastases, Dr. Vessella and colleagues examined five survival proteins that operate within three survival pathways in a cohort of 185 lethal metastatic prostate metastases obtained from 44 patients. These studies showed that bone and soft tissue metastases from the same patient differ significantly in expression of a panel of survival proteins and that with regard to survival protein expression, expression is associated with the metastatic site and not the patient. Altogether, this suggests that optimal therapeutic inhibition may require combinations of drugs that target both bone and soft tissue-specific survival pathways.

Scott Tykodi, MD, PhD, Immunology and Vaccine Development Program
Adaptive immune responses appear to influence the natural history of cancer progression as well as therapeutic outcomes in cancer patients. Although advanced renal cell carcinoma (RCC) is uniquely sensitive to immune-based therapies such as interleukin-2 and immune check point blocking monoclonal antibodies, the mechanisms by which tumor-infiltrating lymphocytes (TIL) detect RCC tumors and the basis for tumor escape from immune control are poorly understood. Scott Tykodi’s research group has used collected RCC tumor samples and paired normal renal cortex from 33 RCC patients undergoing nephrectomy surgery and established methods to propagate RCC tumor cells and normal renal epithelium in vitro. His current studies seek to develop methods to isolate, expand, and characterize the TIL population associated with RCC tumors. Recently, he has worked with the NWBio Trust to consent 3 additional RCC patients at the time of nephrectomy surgery for protocol FHCRC #1810 (IR #5594). We then collected viable RCC tumor specimens as the starting point for TIL isolation along with uninvolved renal cortex and peripheral blood as autologous sources for control lymphocyte populations. Ongoing pilot studies are planned to characterize purified T and B cell populations within TIL for immune receptor repertoire analyses by next-generation, high throughput sequence analysis. These analyses will provide essential preliminary data to support external grant applications in 2014 to extend their analyses of TIL-associated immune receptor repertoires.

Elizabeth Swisher, MD, Mary-Claire King, PhD, Women’s Cancer
Penington, KP et al., Germline and Somatic Mutations in Homologous Recombination Genes Predict Platinum Response and Survival in Ovarian, Fallopian Tube, and Peritoneal Carcinomas, Clin Cancer Res, In Press
P50CA083636

Hallmarks of germline BRCA1/2-associated ovarian carcinomas include chemosensitivity and improved survival. The therapeutic impact of somatic BRCA1/2 mutations and mutations in other homologous recombination (HR) DNA repair genes is uncertain. Using targeted capture and massively parallel genomic sequencing, Elizabeth Swisher and colleagues assessed 390 ovarian carcinomas for germline and somatic loss-of-function mutations in 30 genes, including BRCA1, BRCA2, and 11 other genes in the HR pathway. 31% of ovarian carcinomas had a deleterious germline (24%) and/or somatic (9%) mutation in one or more of the 13 HR genes: BRCA1, BRCA2, ATM, BARD1, BRIP1, CHEK1, CHEK2, FAM175A, MRE11A, NBN, PALB2, RAD51C, and RAD51D. Non-serous ovarian carcinomas had similar rates of HR mutations to serous carcinomas (28% vs. 31%, p=0.6), including clear cell, endometrioid, and carcinosarcoma. The presence of germline and somatic HR mutations was highly predictive of primary platinum sensitivity (p=0.0002) and improved overall survival (p=0.0006), with median overall survival 66 months in germline HR mutation carriers, months in cases with a somatic HR mutation, and 41 months for cases without an HR mutation. The investigators concluded that germline or somatic mutations in HR genes are present in almost one-third of ovarian carcinomas, including both serous and non-serous histologies. Somatic BRCA1/2 mutations and mutations in other HR genes have a similar positive impact on overall survival and platinum responsiveness as germline BRCA1/2 mutations. The similar rate of HR mutations in non-serous carcinomas supports their inclusion in PARP inhibitor clinical trials. These studies were facilitated by samples from the Consortium ovarian cancer repository through the Pacific Ovarian Cancer Research Consortium (SPORE, PI Nicole Urban.)
**Cost Effectiveness**

Biobanking operations are expensive, with conservative estimates of at least $2M to subsidize the estimated $800,000 annual operating cost during a ramp-up period, after which a blend of grant support and fee-for-service rates may recoup operating costs. Many biobanks often are not sustainable due to the absence of a well-developed business plan that, in addition to addressing regulatory, ethical, operational, and IT issues, also addresses business finance functions such as fee setting models that account for all costs.

NWBT operates under a detailed 5-year business plan that anticipates continued ramp-up of specimen and data distribution for research. This plan was developed by Dr. Schmechel, who ran an analogous, sustainable, and high volume biobank and annotation data service at UMN prior to his recruitment to UW. NWBT usage is expanding: currently 29 active studies are supported, and specimen shipments increased from 627 specimens in 2012 to 1195 specimens in 2013 (91% year-over-year volume growth). We anticipate specimen volumes to grow to 1800 specimens/year by 2015.

NWBT derives its support from multiple sources: CCSG support; other NWBT biobanking-related grants such as Dr. Porter’s LSDF grant mentioned above, and Dr. Schmechel’s recently funded CCSG Supplement entitled “NW BioTrust: Tissue Acquisition Site for NCI’s Patient-Derived Xenograft Repository”; other grants for which fractional FTEs of NWBT personnel are budgeted for specific activities; UW institutional support provided as part of Dr. Schmechel’s recruitment; and fees for NWBT services listed in the table below.

<table>
<thead>
<tr>
<th>Service</th>
<th>NWBT Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Internal</td>
</tr>
<tr>
<td>Biospecimen Aliquot</td>
<td>$136/aliquot</td>
</tr>
<tr>
<td>Coordinator/Scientist Consulting</td>
<td>$44/hour</td>
</tr>
<tr>
<td>Pathologist Consulting</td>
<td>$212/hour</td>
</tr>
<tr>
<td>Undergraduate Hourly Rate</td>
<td>$30/hour</td>
</tr>
<tr>
<td>Slide Scanning</td>
<td>$23/slide</td>
</tr>
<tr>
<td>Slide Scanning</td>
<td>$23/slide</td>
</tr>
</tbody>
</table>

External non-profit rates (for other collaborating academic investigators, etc.) are only 16% higher than Consortium rates since UW applies a 16% Goods & Services overhead rate on NWBT service rates. External for-profit rates (for a blend of projects including clinical trials work, work with external biorepositories, etc.) are substantially higher. Although external projects are accommodated only if schedules permit and other internal priorities are first met, higher rates for external projects promote NWBT sustainability.

It should be noted that without CCSG support, biospecimen costs for internal investigators would increase from $136/specimen to $306/specimen (a 125% increase of $170/specimen), external non-profit rates would increase by 125% to $354, and external for-profit rates would increase 125% to $532. The mission of NWBT would be impaired by such high rates, and thus CCSG support is crucial for this shared resource.

<table>
<thead>
<tr>
<th>Service</th>
<th>Total Users</th>
<th>Peer Reviewed</th>
<th>Non-Peer Reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collection</td>
<td>10</td>
<td>6 (60%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Consenting</td>
<td>9</td>
<td>5 (55.6%)</td>
<td>4 (44.4%)</td>
</tr>
<tr>
<td>Samples</td>
<td>9</td>
<td>7 (77.8%)</td>
<td>1 (22.2%)</td>
</tr>
</tbody>
</table>

**Management Structure, Policies and Operations**

The NWBT Governance Committee (GC) determines the types of services provided by NWBT to achieve its mission, outlines desired operational and financial plans, tasks the Director to achieve the operational and financial metrics, and reviews the Director’s performance. The GC has been structured to include: the UW
Chair of Pathology; the UW Vice Dean for Research and Graduate Education; the FHCRC Head of Human Biology and Director of Solid Tumor Translational Research; the Director of the Institute of Translational Health Sciences (the CTSA); the FHCRC Vice President for Shared Resources; faculty from bioethics, biomedical informatics, laboratory medicine, medical genetics, primary care; investigators who use biospecimens in research; and a patient representative.

<table>
<thead>
<tr>
<th>NWBT Governance Committee Member</th>
<th>Representing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tom Montine, Chair</td>
<td>Chair, Department of Pathology</td>
</tr>
<tr>
<td>John Slattery</td>
<td>UW Medicine Research, Consortium Associate Director for Inter-Institutional Initiatives</td>
</tr>
<tr>
<td>Eric Holland</td>
<td>Consortium Associate Director of Solid Tumor Translational Research</td>
</tr>
<tr>
<td>TBD</td>
<td>UW Bioethics</td>
</tr>
<tr>
<td>Nora Disis</td>
<td>ITHS, Women’s Cancer Research Program</td>
</tr>
<tr>
<td>Peter Tarczy-Hornoch</td>
<td>UW Biomedical Informatics, Biostatistics and Computational Biology</td>
</tr>
<tr>
<td>John Tait</td>
<td>UW Laboratory Medicine</td>
</tr>
<tr>
<td>Gail Jarvik</td>
<td>UW Medical Genetics, Cancer Epidemiology, Prevention, and Control</td>
</tr>
<tr>
<td>Laura-Mae Baldwin</td>
<td>Family Medicine</td>
</tr>
<tr>
<td>Karin Rodland</td>
<td>Research community (Eastern Washington)</td>
</tr>
<tr>
<td>Jay Heinecke</td>
<td>Research community (UW)</td>
</tr>
<tr>
<td>Paul Woloshin</td>
<td>Consortium Director of Shared Resources</td>
</tr>
<tr>
<td>Chris Li</td>
<td>Women’s Cancer Program</td>
</tr>
<tr>
<td>Rachel Cowan</td>
<td>Pathology Finance/Administration</td>
</tr>
<tr>
<td>TBD</td>
<td>Patient representative</td>
</tr>
<tr>
<td>Steve Schmechel (ex officio)</td>
<td>NWBT Director, Prostate Cancer Program</td>
</tr>
<tr>
<td>Peggy Porter (ex officio)</td>
<td>NWBT Co-Director, Women’s Cancer Program</td>
</tr>
</tbody>
</table>

Administration
NWBT operates in accordance with Consortium and institutional policies for Shared Resources. The resource is under Consortium Share Resources Director, Dr. Paul Woloshin. Faculty oversight of the resource is provided by an advisory committee responsible for reviewing Shared Resource operations on annual basis, providing review of user fee changes, evaluating capital budget requests and providing guidance on future goals and objectives. The Consortium’s Institutional Planning Committee ensures that this and other Consortium resources are aligned with the Consortiums strategic goals and its continued value to the Cancer Center.

Access and Usage Policy
Access to cancer specimens is granted with the advice of shared NWBT advisory committees composed of representatives from UW, FHCRC, and SCCA. The process is as follows: initially Dr. Schmechel or Dr. Porter determine if the study is clinically feasible (for example, conforms to clinical standards and requisite numbers of biospecimens are existing in biorepositories or anticipated to be procured in UW Medicine or SCCA laboratories). If so, the request is forwarded to the disease-relevant Cancer Specimen Priority Advisory Committee, which will approve or deny biospecimen requests and, if approved, assign a prioritization based on the scheme below. Cancer Center members are given priority for cancer specimens over non-members.

<table>
<thead>
<tr>
<th>Prioritization Scheme for Cancer Biospecimen Services: Highest (1) to Lowest (5) Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ongoing active project involving Cancer Center member</td>
</tr>
<tr>
<td>2. New project by a pilot awardee</td>
</tr>
<tr>
<td>3. New project from a member with peer-reviewed grant-funding specifically for the project</td>
</tr>
<tr>
<td>4. New project from a member with funding specific for the project other than peer-reviewed grant funding</td>
</tr>
<tr>
<td>5. New project that is not funded (such as for generating preliminary data), other than #2 above</td>
</tr>
<tr>
<td>6. Any project from a non-member</td>
</tr>
</tbody>
</table>

Services are available to all members of the Consortium. Support is provided to external users as time permits. Costs are charged directly to applicable awards based on actual usage. Rates are based on
projected operating costs net of CCSG and institutional support. Rate schedules are revaluated and revised as required on an annual basis. External user fees reflect the full cost (both direct and indirect) of rendering service according to the most recent rate revision. No benefit of institutional or federal funding received by the resource is considered in the establishment of outside rates.

Billing
Standardized service request forms provide authorization of service and requested information for each respective transaction. Services are billed upon completion and information is entered into a Shared Resource system which provides the ability to track resource use at the project level by activity. Ongoing review is conducted to monitor activity levels and observe usage trends to ensure appropriate adjustments are made in operations to adapt to changing demand. Usage is assessed and summary reports are developed by institution, by investigator, and by program for each service provided by the resource. Ongoing evaluation of resource operations is conducted through implementation of appropriate analyses, benchmarking studies, surveys and other tools.

Education and Outreach
Users are kept up to date on changing technologies and services offered by the facility through the FHCRC and Consortium websites, Share Resource Newsletter, and special memo distributions. Outreach to the broader Consortium community, particularly those within the UW and Children’s Hospital and Regional Medical Center (Children’s), will be enhanced through the activities of the Institute of Translational Health Sciences (ITHS). As an ITHS approved facility, it is anticipated that the Resource will play an ongoing and expanded role in support of translational research activities.

Priorities and New Initiatives
IT improvements to facilitate more detailed specimen annotation, derivatization and location tracking
The current NWBT IT system facilitates researcher and study registration, patient identification, consent tracking, and delivery of specimens annotated with Amalga CDR-derived patient- and visit-level data, and basic sample-level data including collection date/time, anatomical site of origin, weight, size, storage location, clamp time, tissue removal time, etc. However there is need for detailed pathology annotations. For example, it is desirable for a pathologist to examine “scout” slides (either surface frozen sections from frozen blocks, or sections from formalin-fixed paraffin-embedded blocks that “mirror” frozen blocks) and assign, on an aliquot-by-aliquot basis, a coded pathologic diagnosis using systems such as ICD-O (for oncology specimens), SNOMED, and/or NCI Thesaurus (http://ncit.nci.nih.gov/), as most appropriate for each diagnosis. There is also need to inventory aliquots and other derivatives (histologic slides, extracted nucleic acid, etc.) of samples. Lastly, detailed tracking of each derivative is desired, from its origin in a central NWBT facility (e.g., a freezer box in the frozen section room) throughout its distributions until final consumption in the research process. To record these specimen annotations, derivatizations and locations, NWBT has chosen to install a UW server-hosted, enterprise-wide instance of LabMatrix (BioFortis, Columbia MD), which is a robust biobanking and data annotation tool (http://www.biofortis.com/products/labmatrix/). LabMatrix was chosen by an ad hoc committee composed of NWBT IT and operations staff after rigorous review of proposals received through a formal Request for Proposals process, and recently installed (https://labmatrixtest.pathology.washington.edu/labmatrix/jsp/spring/login). Well documented Application Programmer Interfaces will facilitate integration of LabMatrix with other components of the NWBT IT system.

NWBT IT efforts will be focused on integrating the prospective collection (PSC) and high-throughput remnant specimen identification systems described above with LabMatrix. The operational workflow supported by these IT enhancements will be as follows: patient-, visit-, and initial sample-level data on research-only prospective specimens or remnant diagnostic specimens will flow from the LabKey system into LabMatrix. Within the LabMatrix system, aliquoting, derivatizations, and storage locations will be recorded. When pathologists review scout slides, coded diagnoses and other metrics (%neoplasia, %necrosis, etc.) will later be entered per specimen. When specimens are shipped to researchers or biorepositories, the shipping events and new locations will be recorded in LabMatrix. Specimens may pass into database sub-partitions which may be separately customized, such that research groups can develop highly customized forms to capture research assay results and other highly detailed annotations on materials within their subpartitions. Further, shipment events may be queries for efficient invoicing.
Further rollout of the “front desk” electronic consent collection system
Effort by operations and IT staff are needed to further roll out the “front desk” Epic consent collection system. This rollout, which requires substantial investment in terms of “front desk” staff training, IT linkages, and implementation, will ultimately make NWBT much more efficient by pre-consenting the vast majority of research subjects at the time of their check-in to clinics and other facilities of UW Medicine and SCCA.

**Personnel**

**Key Staff Qualifications**

The resource Director is Dr. Stephen Schmechel. Dr. Schmechel has 8 years’ experience in biobanking, including extensive experience running a self-sustaining biospecimen procurement, annotation, and distribution core facility at UMN (http://www.bionet.umn.edu/). Dr. Schmechel is a pathologist within the Department of Pathology’s CLIA laboratories and is board certified in clinical and anatomic pathology, cytopathology, and molecular diagnostics and a member of the Consortium Prostate Cancer Research Program. He has overall accountability for the success of NWBT.

The resource Co-Director, Dr. Peggy Porter, is also a board-certified Pathologist and a member of the FHCRC Divisions of Human Biology Division and Public Health Sciences, Co-Leader of the Women’s Cancer Program, Principal Investigator of an NCI Specialized Program of Research Excellence in breast cancer, and Professor in the UW Department of Pathology. She led a three-year initiative (2010-2013) to build the foundation for NWBT. Dr. Porter has established Cancer Specimen Priority Advisory Committee composed of cancer type-specific faculty who approve collection and distribution for studies based on research priorities and specimen availability. These committees are guided by NWBT priorities and business plan.

Drs. Schmechel and Porter provide scientific and pathology consultation for research projects, help researchers determine feasibility of projects based on part on the types and numbers of specimens in biorepositories and/or likely to come through UW Medicine and SCCA laboratory facilities, and provide high-level oversight of NWBT processes.

The Assistant Director is Ms. Sarah Bowell. Ms. Bowell has 15 years’ experience in biobanking, including 8 years’ experience working with Dr. Schmechel in day-to-day operations and finance activities of core facilities for patient consenting, and for biospecimen procurement, annotation, and distribution. Ms. Bowell moved from UMN as part of the Schmechel group recruitment to UW. Ms. Bowell will manage day-to-day activities of NWBT, including managing staff engaged in consenting, procurement, annotation and distribution of specimens and data; ensuring compliance with Honest Broker functions as allowed by UW IRB; serving as liaison with the NWBT IT developers to ensure that IT tools are optimized for NWBT functions; and overseeing finance staff in generating periodic reports of operational (numbers of specimens utilized, grants and papers resulting from specimen use, etc.) and financial (cash, income, and balance sheet statements) metrics.

The Research Coordinator is Ms. Melissa Shipley. She manages researcher applications and study registration, coordinates with the Director and Co-Director review of general feasibility of requests, compiles review materials for advisory committee reviews, and works with the Assistant Director to produce SOWs, budgets and letters of support. She performs the review of research cases and communicates with technicians and/or other consenters to ensure that patients are consented in a timely manner, specimen availability is monitored and specimens are brought to clinical staff for procurement. She oversees the scheduling and day-to-day activities of technicians and undergraduates (who cross-cover sites as needed), and trains technicians on study requirements for initial processing needs.

Technical IT Lead is Dr. Stefan Ponko who works in UW BIME Department where he provides technical leadership for NWBT software and database development. Dr. Ponko has over 13 years’ experience developing and leading the development of research applications and laboratory information systems in biotech companies including Immunex and Amgen. In addition to managing the NWBT IT team, his responsibilities also include architecting NWBT software components, and managing interactions with the Amalga, Lab Medicine, Pathology and the UW Epic IT teams as necessary to meet technical milestones.
Population Sciences

PREVENTION CENTER SHARED RESOURCE

INTRODUCTION
The Prevention Center Shared Resource (PCSR) functions as a staffed, full-service research facility and provides a physical space for research staff to perform clinical and epidemiologic studies. The resource includes a research clinic, exercise research center, and human nutrition lab. Resource staff encourage interdisciplinary, collaborative research within the Consortium by linking current faculty users with other Consortium members whose research may benefit from the resource’s services. The PCSR also provides training and certification for technical staff, and serves as a support resource and training facility for investigators, fellows and students.

In the 2008 competitive renewal evaluations, the PMSR was scored as Outstanding. In 2012, PMSR director Anne McTiernan was replaced by Larissa Korde, M.D., M.P.H., who is a well-funded and established investigator in nutrition-based cancer prevention research.

MAJOR SERVICES

Facilities and Equipment
Located at the Fred Hutchinson Cancer Research Center (FHCRC), the PCSR occupies a total of 12,560 square feet. Free underground parking is provided for all study participants. The facility has a full-time receptionist and reception waiting area, with spill-over waiting located in close proximity. It contains a 16-seat capacity classroom available for use by Consortium members. A bank of offices is available for administrative staff, with an office and computer access stations available for visiting faculty and client study contact personnel. Each of the three resources within the facility has dedicated office spaces for managers and a shared space for technical staff.

The RC (5,274 sf) includes 18 exam rooms, 4 interview rooms, and a DEXA scanner for measurement of bone density, body fat and total body composition, with a 450 pound load capacity. In addition there are three restrooms for volunteer use only, a pharmacy for storage and dispensing of intervention drugs, a specified phlebotomy area, a processing lab with hood capability and specimen pass-through from an attached private restroom. Two exam rooms are outfitted for gynecologic capabilities including an electronic adjustable table for volunteers with limited mobility.

The ERC (4,378 sf) houses state-of-the-art equipment for cardiovascular and strength training, and also contains a 400 square foot multi-purpose room designed for group activities related to health and wellness research. The MGC Diagnostics equipment was upgraded in 2012 with a new Pulmonary Exercise System and multi-user review software, which now interfaces with our internal server for data protection and direct-to-client reporting. The recently added Trackmaster Treadmill and Lode Corival Cycle Ergometer both interface directly with the Pulmonary Exercise System. The new Graded Exercise Testing (GXT) equipment allows for testing of individuals weighing up to 500 pounds. A code cart is present and fully supplied with medical response medications and supplies, and staff is trained regularly with code drills. The training resource includes 7 PRECOR treadmills, 2 Quinton treadmills, 5 PRECOR recumbent bikes, 2 PRECOR upright bikes, 9 PRECOR Elliptical Trainers, 3 Concept II rowing ergometers, one Monark upper/lower body ergometer and 6 CYBEX strength-training machines that work all of the major muscle groups. There are male and female shower facilities with built-in emergency response systems.

Both the training resource and the multi-purpose rooms are set up with audio-visual technology to enhance all activities with video and audio components. Certified exercise specialists provide testing oversight and create personalized exercise programs for study participants based upon study protocols and their testing results and individual capabilities. Twenty-four hour on-call medical personnel are available to respond to research volunteer emergencies.

The HNL measures 2,908 square feet and includes extensive food storage, preparation, and service areas. Over a third of the square footage is devoted to storage, allowing the purchase of food in lot size
amounts, and includes a walk-in freezer, refrigerator, and dry storage. The food preparation resource includes both cold and hot food preparation and production areas with a gas cook top, convection ovens, steamers, microwave oven, blast chiller, and a hand operated heat-sealing packaging system. The HNL uses Mettler-Toledo scientific balances for accurate food measuring with a range from 0.1mg to 32.2kg. The dining and service areas include a tray assembly/service area and dining room. The service area includes a serving station, double door pass-thru refrigerator, roll-in refrigerator, hot-holding cabinet, 4 microwaves for reheating meals, and beverage station. The dining room seats up to 36 at one time and can be used for classes and other group activities as necessary. A networked computer system, operated through the Division of Public Health Sciences, is used for data entry, diet development, and HNL food preparation documents. Available nutrition computer software includes ProNutra, ProNessy and NDS-R.

Technologies and Expertise
Most of the studies supported by the PCSR are in the areas of behavioral modification, nutritional assessment and community intervention. These disciplines are important approaches to better understanding the link between diet and exercise and cancer development and progression. In recent years, the PCSR has been increasingly used for intervention studies, including chemoprevention, vaccine, diet, and physical activity studies, with an aim toward understanding the impact of these factors on cancer development and progression.

Over the past decade, methods for measuring biochemical and physiologic changes in blood and other tissue samples have made it possible to assess the effect of numerous interventions on risk factors for cancer in healthy individuals. The PCSR supports this research by offering the services of three important and distinct intervention-focused facilities

The Research Clinic (RC) provides space, equipment and personnel to support the conduct of quality biologic research studies. Services provided include physical exams, gynecologic exams, collection of vital signs and anthropometric measurements, collection of biospecimens, quick turn-around specimen processing and short-term specimen storage and biospecimen tracking. RC staffs are also trained to perform minimally invasive procedures, including RPFNA (random periaereolar fine needle aspiration) of the breast and abdominal fat biopsies.

The Exercise Research Center (ERC) is a state-of-the-art resource that enables Consortium investigators to conduct studies in physical activity intervention research. The resource provides services to investigators at a lower cost than outside facilities, and also provides oversight for supervised exercise sessions, and research data collection, while maintaining privacy and convenient access to study participants. The ERC conducts exercise training, exercise testing that includes V02 max, submaximal exercise tolerance testing, spirometry, strength and flexibility assessment, and indirect calorimetry (REE) testing. Trained exercise physiologists are available to create tailored exercise programs for study participants and to oversee exercise sessions.

The Human Nutrition Laboratory (HNL) provides comprehensive support for the conduct of human feeding studies as well as the food component of behavioral and community nutrition intervention studies. Services provided include study diet design, food production and delivery, meal service, data collection, and study participant management and monitoring according to diet intake protocols. The HNL also provides nutritional support for participants in exercise or research intervention studies conducted in other components of the PCSR.

Importance to Scientific Programs
The Center provides expertise, services and facilities to PHS research studies and our Consortium partners. As our facility resources, capacity and reputation for thorough, quality work and exemplary expertise has grown we have expanded to provide services to other local research programs, including the Group Health Research Institution and the Veterans Administration Puget Sound Health Care System as newer users. Descriptions of selected projects being conducted within the facility are outlined below, emphasizing the importance of this shared resource facility to peer-reviewed research.

Ross Prentice, PhD, Cancer Epidemiology, Prevention and Control
Nutrition and Physical Activity Assessment Study (NPAAS)
This is the third ancillary study to the Women’s Health Initiative under the NPAAS umbrella to be conducted using PCSR facilities. Under this competing renewal of the “Nutrition and Physical Activity Assessment Study”, 150 post-menopausal women were recruited to provide biomarkers for additional nutrients and dietary components (i.e., urinary nitrogen, fructose, sucrose, alkylresorcinols, 1- and 3-methylhistidine, and blood-derived measures of carotenoids, tocopherols, phospholipid fatty acids, and folate) using a controlled feeding study. Study meals are designed, produced and served in the PCSR HNL and all measures and specimen will be taken and processed in the PCSR RC. The PCSR ERC conduct the resting energy expenditure for all NPAAS participants at the conclusion of their feeding periods.


Johanna Lampe, PhD, Cancer Epidemiology, Prevention and Control Broccoli and Bacteria Pilot Study (B & B)
Cruciferous vegetables are rich sources of glucosinolates, phytochemicals that give crucifers their distinctive odor and are of interest for their potential in cancer prevention and other beneficial health effects. Certain human gut bacteria are known to produce isothiocyanates (ITCs), a byproduct of glucosinolate hydrolysis, which have shown anticarcinogenic properties in vitro and in vivo. This study tested differences in fecal microbiota composition in high- and low- ITC excreters after controlled consumption of a broccoli meal. In addition, the study explored associations between habitual dietary cruciferous vegetable intake and fecal microbiota composition and urinary ITC-excretion status after the prescribed broccoli meal. The PCSR HNL procured, prepared, and served the broccoli meals.


Anne, McTiernan, MD, PhD, Cancer Epidemiology, Prevention and Control Nutrition and Exercise in Women (NEW) Study
Weight loss and physical activity are both associated with a reduced risk of breast cancer. However, the mechanisms for this association are not well understood, and the individual effects of diet and physical activity on weight changes and cancer risk reduction are an active topic of research. The NEW study randomized 437 post-menopausal, overweight women to one of four study arms: control, dietary weight loss, diet plus exercise and exercise alone, in order to determine the effect on body weight and cancer-related biomarkers of each
intervention. Clinical measures were taken by the staff of and in the PCSR RC and field exercise interventions were conducted and tracked by the PCSR ERC.


Vitamin D and Exercise (ViDA)
R03 CA162481 – NIH, Breast Cancer Research Foundation, Safeway Foundation
Vitamin D deficiency is related to obesity, but whether but whether vitamin D repletion supports weight loss and changes obesity-related biomarkers is unknown. In this study, 218 overweight or obese women (50-75 y) with serum 25-hydroxyvitamin D (25(OH)D) ≥10 ng/mL - <32 ng/mL were randomized (double-blinded) to: i) weight loss + 2000 IU/day oral vitamin D3 or ii) weight loss + daily placebo. The group-based weight loss intervention included a reduced-calorie diet (10% weight loss goal) and 225 mins/week of moderate-to-vigorous intensity aerobic activity. Weight, body composition, serum insulin, CRP and 25(OH)D were measured. Mean changes between baseline and 12 months were compared between groups (intent-to-treat) using generalized estimating equations. In a subset of patients, we collected breast and adipose tissue specimens before and after intervention to assess changes in cytology and gene expression from Vitamin D supplementation and exercise. Clinical measures were conducted by the staff of and in the PCSR RC. Data is currently being analyzed for manuscripts.


A Program Promoting Exercise and Active Lifestyle (APPEAL) Study
Regular exercise increases exercise self-efficacy and health-related quality of life (HRQOL); however, the mechanisms are unknown. We examined the associations of exercise adherence and physiological improvements with changes in exercise self-efficacy and HRQOL. Methods: Middle-aged adults (N = 202) were randomized to 12 months aerobic exercise (360 minutes/week) or control. Weight, waist circumference, percent body fat, cardiopulmonary fitness, HRQOL (SF-36), and exercise self-efficacy were assessed at baseline and 12 months. Adherence was measured in minutes/day from activity logs. The PCSR ERC provided exercise orientation, exercise training and session services and maintained participant logs and data collection for intervention analyses.


Kerryn Reding, PhD, Cancer Epidemiology, Prevention and Control

Investigating the Role of a Lifestyle Intervention on novel Estrogen Biomarkers (DEEM) R01 DK092568

This research study evaluates diet and exercise intervention aimed at reducing the ratio of genotoxic estrogen-DNA adduct (EDA) concentrations in comparison to their less reactive hydroxy estrogen (HE) counterparts. The Diet and Exercise Impact on Estrogen Markers (DEEM) intervention is designed to investigate the impact of diet and exercise intervention on biomarkers within the catechol estrogen metabolism pathway. Half of the 48 women recruited into this study are enrolled in an intervention aimed to help women improve their dietary intake and physical activity with attendance at weekly group sessions. All participants will be followed for a period of 6 months, completing questionnaires and attending clinic visits for blood and urine collections, DEXA scan and exercise testing in the PCSR RC. The PCSR ERC conducts the exercise testing and a 6 minute walking test for all participants. In addition, PCSR ERC staff lead group exercise education sessions at multiple time points throughout the intervention.

Marian Neuhausser, PhD, Cancer Epidemiology, Prevention and Control

Effect of Dietary Glycemic Index on Beta-Cell Function (DGI) R01 DK092568-NIH

This research study manipulate post-prandial glucose excursions using High Glycemic Load (HGL) and Low Glycemic Load (LGL) diets in a 4-week controlled dietary intervention during which changes in oxidative stress and beta-cell function will be measured. To determine whether oxidative stress is an important mechanism whereby a HGL diet and increased glycemic variability contribute to beta-cell dysfunction, a subset of subjects are treated with the anti-oxidant N-acetylcysteine (NAC) to determine whether NAC can prevent beta-cell dysfunction. Researchers enrolled subjects with Impaired Glucose Tolerance (IGT) as they already manifest defects in beta-cell function and therefore are more likely to demonstrate further deterioration on a HGL diet or improvement on a LGL diet. The PCSR HNL provides all study meals for participant pick-up and will monitor participant compliance and data.

Marian Neuhausser, PhD, Cancer Epidemiology, Prevention and Control

Carbohydrates And Related Biomarkers (CARB) Study

Low-glycemic load (GL) diets improve insulin resistance and glucose homeostasis in individuals with diabetes. Less is known about whether low-GL diets, independent of weight loss, improve the health profile for persons without diabetes or other preexisting conditions. Research staff conducted a randomized, cross-over feeding study testing low- compared to High-GL diets on biomarkers of inflammation and adiposity in healthy adults. Eighty participants (n = 40 with BMI 18.5-24.9 kg/m²; n = 40 with BMI 28.0-40.0 kg/m²) completed two 28-d feeding periods in random order where one period was a high-GL diet (mean GL/d = 250) and the other a low-GL diet (mean GL/d = 125). Diets were isocaloric with identical macronutrient content (as percent energy). All food was provided by PCSR HNL and participants maintained weight and usual physical activity. Physical measures and specimen were taken by the PCSR RC which included height, weight, and DXA measures at study entry and weight assessed again thrice per week. Blood was drawn from fasting participants at the beginning and end of each feeding period and serum concentrations of high-sensitivity CRP, serum amyloid A, IL-6, leptin, and adiponectin were measured.


**Mario Kratz, PhD, Cancer Epidemiology, Prevention and Control**

**Diet and Systemic Inflammation Study (DASI)**

**R21 HL108257-02 (Kratz)-NIH/NHLBI**

The objective of this project is to investigate whether fructose-sweetened beverages trigger low-grade systemic inflammation in healthy men and women. Low-grade systemic inflammation, specifically elevated plasma concentrations of C-reactive protein (CRP), is a risk factor for type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). Researchers recruited 12 obese (BMI 30-40 kg/m²) and 12 normal weight (BMI 20-25 kg/m²) men and women who were free of chronic inflammatory or metabolic disease. In a double-blind, randomized cross-over design, each subject completed three 8-day standardized dietary periods that differ only in the type of sweetened beverage administered. Specifically, subjects were asked to drink four servings of a beverage each day that were sweetened with glucose, fructose, or HFCS (55% fructose, 45% glucose). All solid food was provided for each of the three 8-day diet periods by the PCSR Human Nutrition Lab, and consumed ad libitum. Subjects were admitted to clinic on day one and day nine of each diet phase. During all clinic visits, the PCSR Research Clinic collected anthropometric data, fasting blood, and a stool sample. During day nine clinic visits researchers also performed the lactulose/mannitol-test to assess intestinal permeability. In individuals who were interested in participating in an optional ancillary portion of the study, a subcutaneous abdominal adipose tissue biopsy was also performed by the study physician using PC exam rooms on day nine clinic visits. Designated Human Nutrition Lab staff and DASI study staff worked with the Data Abstraction group in the Clinical Research office to randomize DASI participants. This collaboration is to ensure the double blind randomization requirement for the intervention. Data is currently being analyzed.

**Mario Kratz, PhD, Cancer Epidemiology, Prevention and Control**

**Feasibility, Efficacy and Mechanisms of Surgical vs Medical Diabetes Treatment (CROSSROADS)**

**R01 DK089528-03 (Cummings/Flum)-NIH/NIDDK**

The overall goal of this research study is to demonstrate the capacity to identify, recruit, and randomize 40 adult Group Health (GH) members identified as having Type 2 Diabetes Myelitis (T2DM) and a body mass index (BMI) between 30-40 kg/m² to a diet-and-exercise lifestyle intervention vs. bariatric surgery, and track outcomes. Twenty members will be randomly assigned to intensive behavioral/medical treatment, and twenty will be randomly assigned to receive gastric bypass surgery. Each treatment group will include 15 members with a BMI between 35 and 40 kg/m² and 5 members with a BMI between 30 and 35 kg/m². In the non-surgical
group, researchers will study the feasibility and resources needed to deploy a state-of-the-art intensive behavioral intervention to promote weight loss, which includes dietary and exercise components. Clinical measurements were taken and specimen collected in the PCSR RC and exercise testing was conducted and exercise sessions were held in the PCSR ERC. Data is currently being analyzed.

Cost Effectiveness
The Prevention Center staff serves as highly qualified and experienced staff for the various studies supported by our facility resources. The facility is able to provide the high-level expertise necessary to perform interventions in physical activity, diet development and production and clinic services so that individual studies do not have to incur the expense of hiring and training staff. Study investigators recognize the benefit of contracting and only paying for services necessary and used in the conduct of study protocols, which can be easily altered in response to changes in funding or inability to reach recruitment goals. Given the specialized and personal nature of the PMSR research and clientele there is no outsourcing alternative to the facilities.

Use of Services Table

<table>
<thead>
<tr>
<th>Service</th>
<th>Total Users</th>
<th>Peer Reviewed</th>
<th>Non-Peer Reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthopometrics</td>
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<td>2 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>DEXA Scans</td>
<td>2</td>
<td>2 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>Exercise Center</td>
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<td>3 (100%)</td>
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<tr>
<td>Human Nutrition</td>
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</tr>
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<td>Medical Staff</td>
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<td>18 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>Phlebotomy</td>
<td>12</td>
<td>12 (100%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Management Structure, Policies and Operations

Administration
The Prevention Center operates in accordance with Consortium and institutional policies for Shared Resources. The resource is under the direction of Lorissa Korde, MD, PhD, PCSR Director and Johanna Lampe, PhD, RD, Co-director. The directors are responsible for the overall operations of the resource including hiring staff, managing workflow, verifying billing, and management of large projects and operate in consultation with the Consortium Share Resources Director, Paul Woloshin, MBA, Ph.D. Resource managers and staff receive assistance from the Shared Resources administrative team and other FHCRC administrative departments for tasks such as billing and purchasing. The Prevention Center is managed by two co-directors and an Administrative Manager.

The facility operates under the guidance of an Oversight Committee that is convened annually to review and update operating policies; a subset of whom reviews applications for services throughout the year. The purpose of the PCSR Oversight Committee is to provide scientific and administrative direction to the PCSR Directors and staff, and to ensure optimal service and safety for studies and study participants. The PCSR Oversight Committee is composed of key scientists, clinicians, administrators, and key user representatives. Current members and their roles are as follows:

Larissa Korde, MD, PhD, PCSR Director and Medical Advisor; PHS Faculty, Women’s Cancer Johanna Lampe, PhD, RD, PCSR Co-director and Human Nutrition Lab supervisor; PHS Faculty, Cancer Prevention and Epidemiology Gerianne Sands, JD, Legal Advisor, Associate General Counsel, FHCRC Administration Kathleen Shannon-Dorcy, RN, PhD, Center Staff Representative, Clinical Research Nurse, FHCRC Clinical Research

Faculty Representatives:
Eric Chow, MD, Clinical advisor, Pediatric Oncology and Cancer Epi Res. Coop, Hematologic Malignancies Lesley Tinker, PhD, Principal Staff Scientist, Women’s Health Initiative Coordinating Center

Access and Usage Policy
Services are available to all members of the Consortium, on a first-come, first served basis. Support is provided to external users as time permits. Costs are charged directly to applicable awards based on actual usage and rates are based on projected direct operating costs net of CCSG and institutional support. Rate schedules are reevaluated and revised as required on an annual basis. External user fees reflect the full cost (both direct and indirect) of rendering services based on the current negotiated indirect cost rate. No benefit of institutional.

Billing
Standardized service request forms provide authorization of service and requested information for each respective transaction. Services are billed upon completion in accordance with OMB policies and information is entered into a Shared Resources automated billing system which provides the ability to track resource use at the project level by activity. Ongoing review is conducted to monitor activity levels and observe usage trends to ensure appropriate adjustments are made in operations to adapt to changing demand. Usage is assessed and summary reports are develop by institution, by investigator, and by program for each service provided by the resource. Ongoing evaluation of resource operations is conducted through implementation of appropriate analyses, benchmarking studies, surveys and other tools.

Education and Outreach
Users are kept up to date on changing technologies and services offered by the facility through the FHCRC and Consortium websites, Shared Resources Newsletter, and special memo distributions. Outreach to the broader Consortium community, particularly those within the UW and Children’s Hospital and Regional Medical Center (children’s) are done through a variety of communications channels.

Priorities and New Initiatives
The major priority of the Prevention Center is to continue to provide highly trained staff and state-of-the-art facilities to support population based research on the causes and prevention of cancer and its consequences with a particular emphasis on diet, physical activity, energy balance and obesity. To assure our ability to perform in this regard there have been upgrades to equipment over the years. However as we evolve with scientific research foci, some of the features of the various resources now require that we keep pace with changes in participant biological demography, changes in research trends toward more obesity studies and technologies that will keep us competitive as a high-quality, well-equipped and highly skilled Shared Resource facility. To maintain the quality service and appeal of our facility we intend to address the expressed needs of each component of the facility as identified by their managers’ review and desires for upgraded space and/or equipment. During the next project period, this will include upgrades to freezers for specimen storage in the research clinic, and replacing of aging equipment in the nutrition lab.

Several growing areas of Consortium research are expected increase usage of the facility in the next project period, and resource staff will work closely with faculty to support these activities. Areas include obesity research, for which additional faculty recruitment is underway; support for pharmokinetic analysis of acute responses to diet; and support for new projects in cancer survivorship. The expansion of metabolomics capabilities (see Proteomics and Metabolomics Shared Resource) at our center is expected to lead to increased use of the facility to investigate metabolic effects of diet and physical activity.

Key Personnel
Key Staff Qualifications
Larissa Korde, MD, PhD is an Assistant Member in the Clinical Research and Public Health Sciences divisions at FHCRC and Assistant Professor of Medicine in the UW Division of Medical Oncology. Dr. Korde serves as Director of the resource. Her research focuses on lifestyle and chemoprevention interventions in women at increased risk of breast cancer and on survivorship issues in young women with breast cancer.

Johanna Lampe, PhD, RD, is a Member in the Cancer Prevention Program at the FHCRC and a Research Professor of Epidemiology at the UW School of Public Health. Dr. Lampe serves as Co-director of the facility. She has extensive experience in conducting human dietary studies. Over the past 15 years, she has used controlled dietary interventions to address several research questions related to the effect of plant-based diets and plant food constituents on risk factors for cancer. These studies have also led to the development of biologic markers of plant food intake.
Jo Ann Henderson, MPH, serves as the operations, fiscal and client services officer for the three resources within the PCSR. Ms. Henderson interfaces with prospective clients to assess requests, reviews all cost estimates to assure appropriate revenue to cover all costs to perform the services, assesses the growth of the resources through services and staffing capacities to attract new business, writes the protocols for the PCSR SOP and oversees the billing for services. Ms. Henderson came to the Hutch with 10 years prior experience in public health. She served 6 years as the project manager with the Women’s Health Initiative Clinical Center at FHCRC, and five years as project coordinator for the TREC worksite health study (Move and Moderate in Balance). She has over 15 years in program administration experience with FHCRC, 10 years of which have been in her capacity as Administrative Manager of the PCSR. She received her MPH from the University of Washington.

Claudia Kumai, PA, oversees research clinic operations for the PCSR. She assures the continual training of staffs and maintains CEU training to recognize trends in research and faculty foci and assesses staff capabilities to grow services to meet client needs. She reviews requests for services from clients conducting behavioral and/or clinical prevention or therapeutic research. In addition she oversees and maintains the storage of clinical supplies, including those necessary for responding to emergencies that may arise as a result of unexpected participant sensitivities to clinical therapeutic protocols. Ms. Kumai was trained in Family Medicine in the Stanford Primary Care Physicians Assistant Program, in addition to having a BA in human biology from Stanford University. She has over 20 years of clinical experience in the private sector as well as over 15 years with FHCRC.

Kara Breymeyer, MPH, RD, coordinates research and administrative activities of controlled feeding studies associated with the HNL. In addition to a variety of undergraduate and graduate level food, nutrition, and dietetics student-interns, she has a highly skilled staff of five that produces the specialized meals of long- and short-term studies for approximately 20 participants per week, with varying specialized diets and menus, representing over 400 weekly meal days. Ms. Breymeyer has over 20 years’ experience in food preparation, menu and recipe design and production. She received her MPH, RD from the University of Washington and BS from Bastyr University and has been a managing or supervising member of the resource for over 8 years.

Matt VanDoren, BA, BS, oversees and coordinates daily operations, research protocols, and administrative activities in support of the ERC. As an experienced exercise physiologist Mr. VanDoren assists clients with the development of exercise research protocols. This is especially helpful to new investigators as well as experienced investigators who have little to no experience conducting research studies with an exercise component. Along with the development of the research protocols, Mr. VanDoren trains the clients’ research staff to ensure accurate and consistent execution of the interventions and research protocol. In addition to providing expertise as our ERC manager and as an experienced exercise physiologist he is responsible for attending to the maintenance of all the equipment and attendant computer interfaces housed in the resource. Mr. VanDoren has a BS in exercise physiology and a BA in physical education from Seattle Pacific University and over 12 years’ experience with FHCRC as an American College of Sports Medicine (ACSM) certified Health and Fitness Specialist.
**Basic Sciences/Translational Research**

**PROTEOMICS AND METABOLOMICS SHARED RESOURCE**

**Introduction**
The PMSR includes a Fred Hutchinson Cancer Research Center (FHCRC)-based Proteomics/Metabolomics laboratory and a University of Washington-South Lake Union (UW-SLU) laboratory. The Proteomics section of the PMSR was formed in November 2002 with the goal of providing cost-effective high performance liquid chromatography and mass spectrometry-based proteomics services to Cancer Consortium (Consortium) members. The Proteomics resource's mission is to provide high quality service in a timely manner for small- and large-scale qualitative and quantitative proteomics analyses, protein modification characterization, and targeted proteomic analyses. These services have evolved from small-scale identification of protein complexes in model systems and identifying modifications on highly purified proteins to large-scale biomarker discovery/validation experiments in serum samples and phosphoproteomics analysis of animal organs. The PMSR received an outstanding merit assessment in the 2008 competitive renewal with no major criticisms.

In 2010, the PMSR was expanded to include metabolomics research and related resources through the joint recruitment of Daniel Raftery, Ph.D., a recognized leader in metabolomics research, to FHCRC and the University of Washington (UW). Along with the proteomics services mentioned above, the resource now provides untargeted profiling of aqueous metabolites and lipids (lipidomics), targeted profiling of metabolites from numerous metabolic pathways via mass spectrometry and nuclear magnetic resonance spectroscopy, and isotope tracer capabilities. The PMSR is also rapidly developing mass spectrometry phospholipid analysis. The resource is committed to developing and implementing new proteomics and metabolomics tools in order to uncover the molecular details that influence cancer biology and to support development of diagnostic and clinical tests.

Scientific operations of the Proteomics and Metabolomics resource are divided between FHCRC and UW-medicine sites. Dr. Gafken oversees all operations at FHCRC and Dr. Raftery oversees those at UW. Drs. Gafken and Raftery meet on a monthly to coordinate activities, or more frequently if needed for specific projects. All proteomics-based projects are performed at FHCRC while metabolomics-based projects are divided between the two sites. Metabolomics projects for which established, routine assays are available are performed at FHCRC while those metabolomics projects that are non-routine and require significant development are performed at UW. As new metabolomics assays are developed and refined at the UW site, FHCRC-based staff will be trained on these protocols to make them more widely available as a service. All NMR capabilities and NMR-related projects will be conducted at UW-SLU.

**Major Services**

**Facilities and Equipment**
The Proteomics and Metabolomics Shared Resource (PMSR) is divided between two laboratory locations, one at FHCRC and one at the UW-SLU. At FHCRC, the total facility space is 2,400 square feet (sq. ft.) of which 1100 sq. ft. is devoted to instrumentation use, 970 sq. ft. is devoted to wet lab use, and 330 sq. ft. is devoted to office space for resource personnel. Proteomics and basic metabolomics services are provided at the FHCRC location. The UW-based laboratory, approximately 0.5 mile from FHCRC, is comprised of laboratory space and offices totaling 2,000 sq. ft., and contains rooms with a wet lab, fume hood, cell culture, instrument space, and offices. The 600 MHz Bruker NMR is located in an adjoining building at UW-South Lake Union, and is situated in 500 sq. ft. of lab space. Metabolomics research projects involving both MS and NMR are conducted at the UW location.

The FHCRC-based PMSR operates five liquid chromatography electrospray ionization (LC ESI) mass spectrometer systems. Eksigent NanoLC-2D autosamplers and HPLCs are connected to ThermoScientific LTQ, LTQ-OrbiTrapXL, and TSQ Vantage mass spectrometers while ThermoScientific nanoEasyLC autosampler and HPLCs are connected to a LTQ-OrbiTrap Elite and OrbiTrap Elite w/ETD mass spectrometers. All of the LC-ESI systems are automated for use 24 hours per day, 7 days per week. For proteomics experiments the HPLCs are configured for flow rates of less than 500 nanoliters per minute and
use columns that are less than 100 microns in internal diameter. In the proteomics configuration, the detection limits for peptides is about 200 attomoles for all systems, and, with the exception of the TSQ Vantage, these systems are primarily used for identifying proteins, characterizing post-translational modifications on proteins and peptides, and global quantitative experiments (SILAC, iTRAQ, TMT, and d0-d3 acrylamide labeling). The TSQ Vantage is used for highly selective (targeted) and highly sensitive qualitative and quantitative assays for peptides. The facility also operates a ThermoScientific Accela 600 HPLC with a PAL-HCT autosampler (installed Dec. 2011). This HPLC system is capable of ultra-high performance liquid chromatography and it is typically configured for flowrates of 100 to 1000 microliters per minute. The Accela system is a completely mobile HPLC that can be configured with any ESI instrument currently in the facility, and it is primarily used for metabolomics research. To date, the system has been used to develop assays on the LTQ, TSQ Vantage, and Orbitrap XL instruments.

The PMSR also operates a matrix-assisted laser-desorption ionization tandem time-of-flight mass spectrometer (MALDI TOF-TOF), along with a LC-MALDI spotting system. The MALDI TOF-TOF instrument is an Applied Biosystems 4800 Proteomics Analyzer capable of performing tandem MS (peptide sequencing) experiments. This instrument is used to support protein sequence mapping to determine sites of protein modifications, protein identification, partial de novo sequencing of peptides, protein profiling for biomarker discovery, and molecular weight measurements of proteins, peptide, and oligonucleotides. The 4800 mass spectrometer has a limit of detection for peptides of about 200 attomoles. The LC-MALDI system consists of an Eksigent NanoLC-2D HPLC coupled in-line with a LC Packings Probot spotting station. This system is primarily used to purify and separate peptide mixtures and then directly spot the separated peptides onto a 4800 MALDI target for analysis.

The UW-based facility contains four mass spectrometers for metabolomics projects, along with a 600 MHz NMR instrument. An AB-Sciex Qtrap 5500 MS LC-MS system is used for multiplexed targeted metabolite profiling and uses two Agilent 1260 UPLC pumps and columns that alternate between separation and regeneration. The AB-Sciex triple quad linear ion trap mass spectrometer is equipped with ESI Turbo Ionspray and APCI sources. This system is primarily used to detect and quantitate almost 170 known metabolites from 25 metabolic pathways using scheduled MRM transitions. An Agilent 6410 LC-MS/MS triple quad instrument is used for smaller targeted assays, such as glycolysis, TCA cycle intermediates, co-enzymes, and etc. This instrument is coupled to an Agilent 1260 UPLC system containing two pumps. An Agilent 6520 Q-TOF MS coupled to an Agilent 1200SL UPLC system is used primarily for untargeted global metabolite profiling, as the instrument has high sensitivity, high resolution, and high mass accuracy. It also can perform MS/MS using a quadrupole, a hexapole collision cell, and a time-of-flight analyzer to produce tandem spectra for unknown identification and verification. This instrument is used primarily for analyzing aqueous metabolites and lipidomic profiling. The instrument is also used for unknown identification and some isotope tracer work. Finally, an Agilent 7890A/5875C GC/MS system is used to analyze volatile, as well as semi-volatile or non-volatile metabolites after chemical derivatization. The Agilent GC-MS system can identify over 150 metabolites by comparing the spectra of samples against those from the commercial NIST and Fiehn libraries available in the laboratory. Derivatization using MTBSTFA and other silylation methods follow the corresponding standard operating procedures developed and validated by personnel at the UW-South Lake Union MS Facility.

The UW-South Lake Union Facility also contains a Bruker 600 MHz NMR spectrometer available for metabolomics studies. This widebore instrument is equipped with a Protasis microcoil NMR probe and automation system; a 3mm HRMAS for 1H, 13C and 15N NMR with 1H decoupling; 3 and 5 mm broadband probes covering nuclei between 15N and 31P with 1H decoupling; 10 and 20 mm broadband probes covering nuclei between 109Ag and 31P with 1H decoupling; a 30 mm volume-coil probe for 1H/19F/31P in vivo NMR/micro-imaging; a 25 mm surface coil probe for 1H/23Na in vivo NMR/micro-imaging. The instrument uses the separate software packages TOPSPIN and ParaVision for high-resolution NMR and in vivo NMR/micro-imaging experiments, respectively.

Technologies and Expertise
The resource provides a high-level of expertise in mass spectrometry, NMR and qualitative and quantitative proteomics and metabolomics. Additionally, the resource has a deep proficiency with performing HPLC
chromatographic separations. The PMSR makes it possible for consortium investigators to access state-of-the-art instrumentation through a cost-effective core facility and apply it to their research when necessary.

The major services offered by the Proteomics and Metabolomics Shared Resource are briefly described below:

Sample Preparation and Chromatography
The preparation of samples for proteomics analysis consists of enzymatic digestions of proteins in solution or gel slice, sample desalting, and purification/fractionation of proteins and peptides by high performance liquid chromatography (HPLC). Metabolomics sample preparation extracts either aqueous or lipid metabolites and reconstitutes them for analysis. Consultation with PMSR staff is available for experimental design considerations such as estimating sample quantity needs, optimal sample preparation methods for a particular analysis, and identifying contaminants that might inhibit analysis. Fractionation and purification of proteins, peptides, and small molecules by HPLC is offered by the resource. Multiple chromatography scales are available ranging from nanobore to preparative. Reverse phase, hydrophobic interaction chromatography (HILIC), and ion exchange are the most requested separation modes.

Molecular Weight Determination
The molecular weight of proteins, peptides, oligonucleotides, lipids, and small molecules can be determined by a variety of mass spectrometry techniques (e.g. electrospray ionization, matrix-assisted laser desorption ionization, liquid chromatography coupled to mass spectrometry, direct infusion). Mass spectrometry instrumentation with a resolving power of 240,000 and mass accuracy of less than 2 parts per million allows for highly accurate molecular weights to be determined and elemental compositions to be measured/estimated for many analytes (i.e. peptides, lipids, and small molecules).

Protein Identification and Quantification
Protein identifications are typically performed for purified proteins or complex mixtures of proteins via bottom-up proteomics; that is, proteins are enzymatically digested to peptides, the peptides are subjected to tandem mass spectrometry for “sequencing”, and the “sequenced” peptides are matched back to the protein(s) from which they originated. Tandem mass spectrometry data are utilized for protein database searching with X!Tandem or SEQUEST (Proteome Discoverer v1.4 software package) to identify proteins or sites of protein modifications. Quantitative experiments utilizing iTRAQ, TMT, SILAC, acrylamide, and dimethyl labeling are supported by the resource. Software used for analyzing quantitative data are EXPRESS (SILAC, dimethyl labeling), LIBRA (iTRAQ), Q3 (acrylamide labeling), and Proteome Discoverer v1.4 (iTRAQ, TMT, SILAC, and dimethyl labeling). Targeted protein quantification is performed by Selective Reaction Monitoring (SRM) methods utilizing isotopically-labeled reference peptides, with data analysis primarily being performed by the software SKYLINE.

Protein Modification Characterization
Numerous methods are used to identify, locate, and quantify post-translational modifications on proteins and peptides, most often characterizing methylation, acetylation, phosphorylation, and ubiquitylation. The resource has developed and extensively used novel quantitative assays for measuring histone acetylation and qualitative assays for protein ubiquitylation. The resource has also implemented large-scale phosphorylation analysis of cell lysates and tissues using a combination of extensive chromatographic fractionation and phosphopeptide enrichment with immobilized metal affinity chromatography (IMAC) followed by mass spectrometry analysis.

Metabolomic Profiling
Metabolites from cell lysates, biological fluids, and tissues can be analyzed by liquid chromatography coupled to mass spectrometry (LC-MS), gas chromatography mass spectrometry (GC-MS) and/or nuclear magnetic resonance spectrometry (NMR). Signal profiles from samples can be compared to compound libraries such as the METLIN and HMDB (Human Metabolite Database) to identify metabolites in the samples. Differentiation of biological or clinical conditions is typically made using univariate or multivariate statistical analysis. Currently, the resource is capable of profiling and identifying over 1000 aqueous metabolites and lipids from numerous classes.

Targeted Metabolite Analysis
Targeted metabolomics is a quantitative approach that measures a set of known metabolites using internal and external reference compounds. Data are used for pathway analysis or input variables for statistical models to distinguish sample classes. Approximately 170 identified metabolites emanating from 25 metabolic pathways are available for detection by LC-MS and approximately 30-50 metabolites are available for detection by NMR depending on sample type. The number of targeted metabolites is continually being increased as profiling experiments identify more metabolites of interest.

Consultation
Since experiments may require customization based on sample type and the goals of the investigators, the resource provides consultation services as needed. Typically, use of the resource begins with a meeting between research laboratory staff and one of the PMSR Directors. For most routine services, guidelines or protocols for sample preparation and purification are provided; while for other projects, more extensive consultation is necessary to provide guidance in experimental design. Often, the Computational Biology Shared Resource is contacted prior to starting a project to assist with design and identify potential computational and data analysis needs.

Data analysis and Informatics Support
Assistance with analyzing data generated by the resource is available. This includes assistance using software tools for analyzing results, reviewing raw data, and providing customized reports. Staff also aid with summarizing data for publications and assisting with grant applications that propose the use of proteomics and/or metabolomics. Computational infrastructure (i.e. hardware) for the storage and analysis of data is maintained by the FHCRC’s Information Technology (IT) department. The infrastructure is made up of a central computer server connected to a hierarchical data management system, a high performance computer cluster, and a Microsoft SEQUEL relational database.

Two general workflows are available for processing proteomics data. The first workflow is built around the TransProteomic Pipeline (TPP) built at the Institute for Systems Biology and it is used for large-scale data analysis, such as a data collected from highly fractionated serum samples for biomarker discovery. Here, data collected on the mass spectrometer are directed to the central computer server and hierarchical data management system for storage and archival. Next, data are moved to the computer cluster to perform protein identification using the algorithm X!TANDEM. Then, quantification is performed using XPRESS or Q3 along with statistical analysis of the protein identification results using PEPTIDE PROPHET and PROTEIN PROPHET. Finally, qualitative, quantitative, and statistical results are uploaded into a relational database called CPAS, which has a web-based viewer associated with it allowing users of the resource to view their data as well as analyze the results with built in tools that filter, sort, and compare datasets. The pipeline and CPAS system require continuous development and maintenance to meet the needs of facility users. Resource staff work closely with the Computational Biology Shared Resource and IT Department to maintain CPAS and the pipeline, as well as develop and implement new software tools for analyzing proteomics datasets. The second workflow for analyzing proteomics data uses ThermoScientific’s Proteome Discoverer v1.4 (PD1.4) data analysis package and is used for small-scale data analyses such as protein identification and peptide mapping for protein modification analysis. The software allows for the construction of highly customizable qualitative and quantitative analysis pipelines and is operated on a standard desktop PC with a quad core processor. A read-only viewer can be downloaded from ThermoScientific’s website that allows results to be viewed and exported for further processing by the resource user.

For metabolomics, different platforms provide their own software packages for data processing, metabolite identification, statistical analysis and pathway mapping. Agilent provides a data workflow that consists of two main software programs, Mass Hunter and Mass Profiler Professional. Mass Hunter works with LC-MS data, and extracts metabolite features and their intensities, thereby reducing data complexity including adduct peaks and interferences. Mass Profiler Professional (MPP) provides a chemometrics platform which can be used with any MS dataset. MPP provides metabolite identification using its own library of authentic compound spectra for both aqueous and lipid metabolites, and connects with online databases (METLIN, HMDB, and others) to provide additional capabilities for identification. MPP also incorporates a number of statistical methods to analyze the data, including commonly used multivariate methods. MPP works with Mass Hunter as well as ChemStation software (used on our GC-MS) and even will import integrated NMR peaks. For ThermoScientific instruments, the resource utilizes SIEVE v2.0 for automated differential expression analysis
of LCMS-generated metabolomics data. The resource also uses a number of web-based analysis tools such as Lipid Data Analyzer (genome.tugraz.at/lda/lda_download.shtml) for monitoring quantitative changes in high-throughput lipidomics experiments and XCMS (xcmsonline.scripss.edu) for the determination of metabolomics profile differences and metabolite identification. MetaboAnalyst (www.metaboanalyst.ca/MetaboAnalyst/faces/Docs/Overview.jsp) is also used for both NMR and LCMS data allowing for data processing, statistical analysis, functional enrichment analysis, and metabolomic pathway analysis. NMR metabolomics analysis software used is provided by the versatile Bruker AMIX software package, which incorporates a number of methods for peak integration, identification and multispectral processing capabilities.

**Importance to Scientific Programs**

One of the great promises for the detection and treatment of cancer lies in the understanding of molecular basis for disease initiation, progression and treatment based on the discovery of unique biomarkers. Although progress in cancer genomics has been rapid during the past few years, it only provides us with a glimpse of what may occur as dictated by the genetic code. In reality, we still need to measure what is happening in a patient in real time, which means finding tell-tale proteins that provide insight into the biological processes of cancer development. This is because genes are only the "recipes" of the cell, while the proteins encoded by the genes are ultimately the functional players that drive both normal and disease physiology.

The objective of the Proteomics and Metabolomics resource is to provide cost-effective, state-of-the-art services and research support in a timely manner to the Cancer Consortium. Research in a variety of Consortium programs is supported by the resource. Proteomics research supported by the resource includes characterizing modifications on proteins like acetylation, methylation, and ubiquitylation to determine how they control the function and fate of cells, and supporting the development of a new class of peptide-based drugs. While biomarker discovery in plasma and serum has been a major effort of the resource for many years, over the last granting period biomarker validation and targeted proteomics have evolved from the discovery work. The resource is highly skilled in developing targeted quantitative multiplexed peptide assays as well as providing high quality data for these assays. Overall, the resource takes great pride in being able to support proteomics research that ranges from simple identification of a single protein to in-depth identification and quantification of proteins in complex mixtures.

While metabolomics services offered by the resource are relatively new, these services are already making an impact in cancer consortium research. Metabolomics research supported by the resource includes biomarker discovery in a number of cancers, detailed studies of altered metabolism in cancer cells and mitochondria, quantitation of global DNA methylation to better understand the probable link between shiftwork and cancer, and lipid profiling in model organisms to understand the role of altered lipid metabolism in cancer development. Currently the resource supports over 20 different metabolomics assays. Moving forward, continuing effort will be to expand the number of metabolomic assays offered by the resource in order to meet the growing metabolomics research needs of the consortium members.

Examples of research supported by the resource are described below for proteomics and metabolomics.

**Ru Chen, PhD, Sheng Pan, PhD, and Teresa Brentnall, MD, GI Cancer**

**Marty McIntosh, PhD, Biostatistics and Computational Biology**

**Biomarker Discovery and Validation in Serum**

Drs. Ru Chen, Sheng Pan, and Teresa Brentnall of the GI Program have had a long-standing collaboration with Dr. Martin McIntosh of the Biostat-Computational Biology Program to identify protein biomarkers in pancreatic cancer. The collaboration has used the Proteomics and Metabolomics resource for a number of biomarker discovery studies that led to candidate biomarkers to be used in subsequent biomarker validation studies. The resource recently developed a targeted proteomics assay based on selective reaction monitoring (SRM) with the resource’s triple quadrupole mass spectrometer to evaluate the utility of the candidate biomarkers to detect pancreatic cancer in the plasma of patients with pancreatic cancer, chronic pancreatitis, and healthy age-matched controls. Three of the proteins in the assay, gelsolin, lumican, and tissue inhibitor of metalloproteinase 1, demonstrated an AUC value greater than 0.75 in distinguishing pancreatic cancer from controls (Pan et al., J. Proteome Res, 2012). Based on these results, additional protein biomarkers have been
added to the SRM assay in hopes of further increasing the classification power of the assay. These data are currently being collected in the resource.


**Jim Olson, MD, PhD, Julian Simon, PhD and Patrick Paddison, PhD, Cancer Basic Biology**

**Roland Strong, PhD, Immunology and Vaccine Development**

**Eduardo Mendez, MD, Cancer Epidemiology, Prevention and Control**

**Development of Peptide Toxins as Therapeutic and Diagnostic Agents**

The Proteomics and Metabolomics resource has worked for over eight years with Dr. Jim Olson’s lab (Cancer Basic Biology Program) providing HPLC purification and mass spectrometry services to help develop tumor paint reagents. These reagents are based on the chlorotoxin peptide, from the venom of the deathstalker scorpion, covalently attached to near infrared dyes. The chlorotoxin:dye conjugates have high binding affinity to various cancer cell types (glioma, medulloblastoma, prostate cancer, intestinal cancer and sarcoma) and allow delineation of malignant tumor from adjacent non-neoplastic tissue in mouse models. Based on the successful use of chlorotoxin as a diagnostic reagent, Dr. Olson is now teaming with Drs. Roland Strong, Julian Simon, Patrick Paddison, and Eduardo Mendez to use other naturally occurring peptide toxins as drug scaffolds. The scaffolds can be optimized and produced as large libraries, called optides, using biotechnology techniques developed by the team. The high resolution mass spectrometers in the Proteomics and Metabolomics resource are critical to deciphering which molecules are properly expressed, which have good pharmacokinetics, and which home to the targets of interest. It is hoped these new anti-cancer compounds will target cancer cells without harming the healthy cells around them, and thus, improve treatments for cancer. This research has not yet been published.

**David Hockenbery, PhD and Toshio Tsukiyama, DVM, PhD, Cancer Basic Biology**

**Quantification of Histone Modifications**

In 2003, the Proteomics and Metabolomics resource reported a method with Dr. Gottschling’s lab on using chemical derivatization and mass spectrometry to quantify acetylation on histones (Smith et al., Anal Chem, 2003). Since this initial report the resource has used the method on a number of chromatin biology studies, including two studies over the last funding period. In the first study, Dr. David Hockenbery (Cancer Basic Biology) followed the fate of [13C]glucose carbons in myc+/- and myc-/- cells to demonstrate that Myc activates mitochondrial metabolism to increase the supply of mitochondrial acetyl-CoA as a substrate for histone acetylation (Morrish et al., J Biol Chem, 2010). The resource performed the acetylation quantification assay and then worked with the Computational Biology Shared Resource to derive a formula to subtract 13C isotopes in “naturally occurring” acetyl groups from the [13C]-glucose fed acetyl groups to accurately quantify the acetylation from glucose derived carbons. In the second study, Dr. Tsukiyama’s Lab isolated histone proteins from minichromosomes in yeast at distinct stages of the cells cycle and mass spectrometry was used to identify and quantify modifications on the histones. Through the use of the developed acetylation assay, results showed that acetylation of histone H3 and H4 is regulated around an origin of replication, with the involvement of multiply acetylated histones, and that acetylation is required for efficient origin activation during S-phase.


**Thomas Vaughn, MD, MPH, and Chris Li, MC, MPH, Cancer Epidemiology, Prevention and Control**

**Validation of Serum Cancer Biomarkers for Early Detection**

Dr. Raftery’s group has made significant progress in utilizing metabolite profiling methods to identify potential biomarkers for a number of cancers, including esophageal, liver and breast (Zhang et al., PloS ONE, 2012; Banaisadi et al., Electrophoresis, 2013; Asiago et al., Cancer Res, 2010; Wei et al., Mol Oncol, 2013). Since moving to UW and the FHCRC, Dr. Raftery has been working with Dr. Vaughan to validate biomarkers of esophageal adenocarcinoma and to discover new biomarkers for identifying patients with Barrett’s esophagus who are at elevated risk of developing esophageal cancer using his large sample bank. Dr. Vaughan chairs BEACON, the International Barrett’s and Esophageal Adenocarcinoma Consortium. The resource has modified its large targeted assay to include many of the putative biomarkers discovered earlier for a validation study with Dr. Vaughan. Dr. Raftery is also working with Dr. Li to validate early detection metabolite biomarkers for breast cancer. Previously, Dr. Raftery identified a number of potential biomarkers of breast cancer recurrence. With Dr. Li, the resource is performing targeted metabolite profiling of these metabolite biomarker candidates as well as global profiling to identify additional metabolites of interest for early detection. Dr. Li is also pursuing early detection biomarkers using proteomics approaches, which will ultimately be combined with the findings from this metabolomics study to improve diagnostic performance and provide improved information on the changes in cancer biology that affect both the proteome and metabolome.


**Parveen Bhatti, PhD, Cancer Epidemiology, Prevention and Control**

**Global Quantification of DNA Methylation Status**

The Proteomics and Metabolomics resource has implemented an assay to quantify 2′-deoxy-5-methylcytidine following enzymatic digestion of DNA isolated from blood leukocytes. The LC-MS assay is built on measuring the ratio of 2′-deoxy-5-methylcytidine to 2′-deoxyguanosine using selective reaction monitoring. A major use of this assay has been to measure the global DNA methylation of shift workers in a project called the Biological Effects of Shift Work Study (BESS) being run by Dr. Bhatti. The International Agency for Research on Cancer (IARC) has labeled shiftwork that involves circadian disruption as a probable carcinogen, thus motivating Dr. Bhatti and colleagues to better understand the biological pathways that underlie the association between shift work and cancer. One arm of the BESS study is to measure the global DNA methylation in healthcare workers (primarily nurses) who either predominantly work the day shift or predominantly work the night shift to determine if methylation levels are significantly different between the two groups. The Proteomics and Metabolomics resource recently performed replicated measurements on 60 day shift and 60 night shift workers and the results are currently being analyzed.

**David Hockenbery, MD, Cancer Basic Biology**

**Isotope flux measurements**

1H NMR based metabolomics studies of mouse hepatocytes, (TAMH) cells, a model for human hepatocellular carcinoma studies, were made in collaboration with Dr. Hockenbery (FHCRC). TAMH cells (2S) express Bcl-X<sub>L</sub>, an antiapoptotic protein that has been implicated in cancer cell resistance to treatment and the overexpression of the Bcl-X<sub>L</sub> oncogene in TAMH cells mimics the intrinsic resistance of cancer cells to chemotherapeutic drugs. The isogenic (NEO) cells were used as controls. Both, Bcl-X<sub>L</sub> overexpressing cells and control cells were treated with methoxy antimycin A and its metabolic effects were followed using NMR...
spectroscopy. Further, focused on tracing metabolic pathways associated with glucose metabolism and measuring fluxes, cells were also incubated with U-13C-labeled glucose for different time periods and 13C labeled metabolite products were analyzed using NMR. Metabolic differences between these two cell lines were observed through isotope labeled products including lactate, whose production rate was higher in the TAMH cells compared to controls. Continued work is focused on further developing these methodologies for following the incorporation of other substrates such as labeled glutamine and for understanding the changes in metabolism and flux under different cell conditions and drug treatments.


Cost Effectiveness
The PMSR provides the highest quality proteomics and metabolomics service to Consortium investigators. Price comparisons between core facilities at other institutions and commercial entities revealed that the resource is one of the most cost effective options in Washington State. Furthermore, the resource offers custom services that are not available from other sources. Outsourced services are available however, the turnaround time from sample submission to receiving results can take weeks to months and communication of the results can be challenging. The resource aims to provide fast turnaround (2-3 weeks) for most analyses when possible.

Use of Services

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<th>Peer Reviewed</th>
<th>Non-Peer Reviewed</th>
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<tr>
<td>Metabolomics</td>
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<td>8 (100%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Management Structure, Policies and Operations

Administration
For the PMSR, leadership is provided jointly by Phil Gafken, Ph.D. (Proteomics) and Dan Raftery, Ph.D. (Metabolomics). The resource directors supervise their technical staff, and ensure they fulfill their responsibilities and for the overall operations of the laboratories including hiring staff, managing workflow, verifying billing, and management of projects. The PMSR works in consultation with Paul Woloshin, MBA, Ph.D., Consortium Director of Shared Resources. Resource directors and staff receive assistance from the Shared Resources administrative team for administrative tasks such as billing and purchasing.

Faculty oversight of the resource is provided by an advisory committee responsible for reviewing Shared Resource operations on annual basis, providing review of user fee changes, evaluating capital budget requests and providing guidance on future goals and objectives. The directors of PMSR meet annually with the resource’s Faculty Advisory Committee. Current members include Dan Gottschling and Julian Simon (Cancer Basic Biology), Paul Lampe (Cancer Prevention and Epidemiology), Sheng Pan (Gastrointestinal Oncology), and Amanda Paulovich (Women’s Cancer). The committee provides useful feedback concerning the type of services they require, the overall quality of specimens, input on capital equipment for shared instrumentation, and help the director focus resources to new technologies. The Consortium’s Scientific Steering Committee ensures that this and other Consortium resources are aligned with the Consortiums strategic goals and its continued value to the Cancer Center.

Access and Usage Policy
Services are available to all members of the Consortium, on a first-come, first served basis. Support is provided to external users as time permits. Costs are charged directly to applicable awards based on actual usage. Rates are based on projected operating costs net of CCSG and institutional support. Rate schedules are evaluated and revised as required on an annual basis. External user fees reflect the full cost (both direct
and indirect) of rendering service according to the most recent rate revision. No benefit of institutional or federal funding received by the resource is considered in the establishment of outside rates.

**Billing**

Standardized service request forms provide authorization of service and requested information for each respective transaction. Services are billed upon completion and information is entered into a Shared Resource billing system which provides the ability to track resource use at the project level by activity. Ongoing review is conducted to monitor activity levels and observe usage trends to ensure appropriate adjustments are made in operations to adapt to changing demand. Usage is assessed and summary reports are develop by institution, by investigator, and by program for each service provided by the resource. Ongoing evaluation of resource operations is conducted through implementation of appropriate analyses, benchmarking studies, surveys and other tools.

**Education and Outreach**

Users are kept up to date on changing technologies and services offered by the facility through the FHCRC and Consortium websites, Share Resources Newsletter, and special memo distributions. Outreach to the broader Consortium community, particularly those within the UW and Children’s Hospital and Regional Medical Center (Children’s), will be enhanced through the activities of the Institute of Translational Health Sciences (ITHS). As an ITHS approved facility, it is anticipated that the Resource will play an ongoing and expanded role in support of translational research activities.

The resource offers a week-long course entitled Mass Spectrometry-based Proteomics twice a year (offered since 2005) that is taught by Drs. Gafken and Ogata. Topics include components of mass spectrometers, protein identification, protein quantification, characterizing protein modifications, sample preparation, computational algorithms for identifying proteins, and analyzing proteomics results. During the last funding period, approximately 122 people took the course and 249 people have taken the course since its inception. Since metabolomics is a new service offered by the resource, it is expected that a metabolomics course will be started in the upcoming year. It is important to note that Dr. Raftery has started a 2-day metabolomics course followed by 1-day symposium at the University of Washington that is offered yearly. The course teaches the basics of mass spectrometry and NMR, sample preparation, and data analysis and uses lectures, hands-on experiments, and computer exercises to teach the fundamentals of metabolomics research. The UW Metabolomics Course will serve as the foundation for developing a more in-depth metabolomics course for the Cancer Consortium to educate consortium members on conducting metabolomics experiments.

**Priorities and New Initiatives**

A primary focus of the resource is to implement new services that would be most useful to a wide breadth of resource users. The following areas of interest are a few that will be investigated over the next grant period with the goal of developing them into new services.

**Proteomics Analysis of Laser Capture Microdissection (LCM) samples**

Collection of tumor tissue at the time of biopsy or surgical resection is central to diagnosing cancer. Biopsy and resected tumor are available through the NW Biotrust Shared Resource are valuable resources for retrospective studies on cancer; possibly to support studies to find early detection biomarkers or predictive biomarkers. Isolating homogenous populations of tumor cells is critical for the proteomic analysis of a pure population of cancer cells, and methods employing LCM are typically used to achieve this. The Proteomics and Metabolomics resource recently provided mass spectrometry analysis service on LCM samples prepared at the College of Medicine at the Ohio State University. Based on encouraging protein identification results from fewer than 8,000 cells in frozen tissue, the resource is planning to test the LCM methods. With the help of the Experimental Histopathology Resource, the initial plan is to test LCM methods on fresh, frozen, and formalin-fixed paraffin-embedded (FFPE) frozen animal tissue (i.e. mouse liver) and move towards clinically relevant samples. As the combined LCM and mass spectrometry methods become optimized, the methods will be advertised as a service for use by the consortium.

**Utility of ultra-High Performance Liquid Chromatography (uHPLC)**

The resource has recently acquired two uHPLCs, one compatible with proteomics analyses and one compatible with metabolomics analyses. uHPLC works at higher pressures (>5000 psi) than conventional
HPLC and has the potential to offer superior chromatographic resolution and faster assay times than conventional HPLC. The resource will be testing uHPLC for both proteomic and metabolomic applications to determine if uHPLC should be utilized in methods and assays offered by the facility.

Optimizing Metabolite Assays

The Proteomics and Metabolomics resource site at UW currently has developed a large targeted metabolite assay of about 170 metabolite and several smaller targeted assays. Based on guidance from the UW site, the FHCRC site has acquired about 115 of the standards and is in the process of optimizing those standards (collision energy and chromatography). As the metabolites become optimized, they will be used to construct multianalyte targeted assays appropriate for consortium member’s needs.

Current development activities at the UW facility are focused on measuring the absolute concentrations of the ~170 targeted metabolites, instead of just relative concentrations. A combination of internal isotope labeled standards and external standards are being used to accomplish this goal. Once completed, studies from different time periods can be compared and even combined. Currently, quality control samples run multiple times during each batch allow adjustments and normalization, but absolute quantitation will take this assay to a new level, especially for the analysis of blood analytes. Additional work will then be focused on developing absolute quantitation for our global aqueous and lipidomics platforms. For NMR, we are continuing to develop isotope tagging methods (Tayyari et al., Anal Chem, 2013) for increased resolution and for improving the detection of metabolites by both NMR and MS. Finally, we are continuing to develop isotope tracer methods to measure the flux of specific substrates such as glucose, glutamine and others as a function of different cancer cell states.

iLab online scheduling/management system

Implementation of iLab Solutions Software for core facility management has been will be launched for the Proteomics laboratory. This system allows Consortium researchers and Shared Resource staff to manage service requests, equipment reservations, usage tracking and billing online.

Personnel

Key Staff Qualifications

Philip Gafken, PhD, Staff Scientist and Proteomics Director was hired in August 2000 to develop proteomics-based mass spectrometry operations within the FHCRC’s Shared Resources. Dr. Gafken has served as director of the facility since its inception and he has built the facility from one mass spectrometer and a staffing of one to its current state of six mass spectrometers and a staffing of four. Dr. Gafken oversees the general operations of the resource, the implementation of new technology, and the supervision of resource staff. His leadership responsibilities also include consultation and providing assistance with data analysis to users, writing material for grants that require proteomics or metabolomics research, and summarizing data for publications. Prior to joining FHCRC, Dr. Gafken obtained his PhD in biochemistry and biophysics from Oregon State University in the lab of Douglas Barofsky. Dr. Gafken has also served on a number of technical and scientific evaluation panels for reviewing grant applications submitted to the National Cancer Institute in the areas of proteomic biomarker development and proteomics technology development.

Daniel Raftery, PhD, Professor, Metabolomics Director, University of Washington School of Medicine and Member Fred Hutchinson Cancer Research Center (Cancer Basic Biology Program), is a highly recognized expert in the field of metabolomics. His research has focused on developing methods for using NMR and mass spectrometry for metabolomics studies as well as applying metabolomics to cancer research, most notably breast cancer and Barrett’s esophagus. Dr. Raftery was recruited to the UW and FHCRC in 2012 to extend his metabolomics research and foster metabolomics studies at both institutions. Dr. Raftery advises Dr. Gafken in the implementation of metabolomics assays that can be provided as services through the FHCRC Proteomics and Metabolomics resource. Additionally, through his research lab at UW he assists consortium members with those assays or research projects that are too complex to offer as services, including NMR-based projects. As assays are refined and developed in his research lab, it is the goal to then transfer them to the resource to make them widely available as a service. Prior to moving to Seattle in 2012, he was a Professor of Chemistry at Purdue University for 17 years. He received a PhD in chemistry from the University of California, Berkeley and completed postdoctoral training at the University of Pennsylvania.
Yuko Ogata, PhD, Staff Scientist oversees operation and maintenance of the resource’s OrbiTrap XL and OrbiTrap Elite mass spectrometers, develops and implements new methods for characterizing proteins and protein modifications, most importantly phosphoproteomics methods, and provides assistance with data analysis to resource users. Dr. Ogata received a Bachelor’s of Science degree in environmental toxicology form the University of California, Davis, a PhD in analytical chemistry from the University of Washington (Dr. Frank Turecek’s group) and completed post-doctoral fellowships at the University of Washington (Dr. Erkang Fan’s group) and the Mayo Clinic (David Muddiman’s group).

Nagana Gowda PhD, is an Assistant Research Professor at UW, and focuses on NMR-based metabolomics and the development of advanced NMR analyses methods. Dr. Gowda is an expert in a range of NMR based methods, including 1D and 2D methods, quantitative methods, isotope tracer analysis, the structural identification of unknown metabolites, and novel methods to derivatize metabolites with isotope tags for improved resolution and quantitation. Dr. Gowda has over 25 years of experience in NMR, more than 120 peer-reviewed publications, and has worked with Dr. Raftery for 8 years, first at Purdue as a Research Scientist and since 2012 at UW. He received his PhD from the Indian Institute of Science, Bangalore University, India.

Danijel Djukovic, PhD is an Instructor under the supervision of Professor Raftery. His main duties involve developing and managing the mass spectrometry (MS)-based metabolic profiling capabilities at UW South Lake Union, with an emphasis on developing and providing quantitative and qualitative targeted and global metabolic profiling analysis for clinical and basic-research investigators. Prior to joining UW, Dr. Djukovic worked as a research scientist for Matrix-Bio, Inc., West Lafayette, IN, where he successfully led the development of the first metabolic LC-MS-based test for breast cancer recurrence monitoring (BCR). Previously, he received his PhD in chemistry from Purdue University working with Dr. Raftery.

Haiwei Gu, PhD is an Acting Assistant Professor at UW under the supervision of Dr. Raftery. He is an expert in both MS and NMR based metabolomics, with significant experience in chromatography including LC, GC, and GCxGC-MS. Dr. Gu has developed the lipidomics platform on the Agilent QTOF MS instrument, along with several targeted assays. Dr. Gu has extensive experience with advanced multivariate statistical analysis methods in metabolomics, including PCA, PLS-DA, SVM, etc., and is proficient in Matlab and R programming for the purpose of chemometrics analysis using MS and NMR data, both individually and in combination. Prior to joining UW, Dr. Gu was a postdoctoral scientist with Peter Carr at the University of Minnesota. Previously, he worked as a Senior Analytical Chemistry for Validation Resources, LLC and for Matrix-Bio, Inc. Dr. Gu received his PhD in physics from Purdue University working with Dr. Raftery.
Basic Sciences/Translational Research

RESEARCH PATHOLOGY SHARED RESOURCE

Introduction
The Research Pathology Shared Resource (RPSR) provides state of the art, cost-effective, readily accessible services and instrumentation that allow for the microscopic analysis of tissue and cells. The resource includes two service-based laboratories, the Experimental Histopathology Laboratory (EHL) and the Specialized Pathology Laboratory (SPL). The EHL provides tissue harvesting at necropsy, expert consultation on fixation and processing specific for staining and subsequent immunohistochemistry, laser capture microdissection, and digital pathology slide scanning and/or unbiased expert interpretation. The SPL provides tissue microarray consultation, construction, imaging and interpretation, and expert pathology review for solid tumor specimens from large research studies. These services make it possible for individual investigators to apply methods that otherwise would not be available to them due either to the lack of expertise and/or lack of funds to introduce the expertise to their lab. The RPSR received an outstanding to excellent merit assessment in the 2008 competitive renewal.

Major Services
Experimental Histopathology Laboratory

Facilities and Equipment
The EHL is located on the on the Fred Hutchinson Cancer Research Center (FHCRC) Campus. Total facility space is approximately 1,900 square feet. The space is located in proximity to other shared resources including Comparative Medicine, Antibody Development, Proteomics, Genomics, and the Cellular Imaging Facility. Equipment includes a Mopec tissue grossing station, biosafety cabinet, 2 automated Sakura tissue processors, 1 Sakura and 1 Leica paraffin embedding center, 4 automated Leica microtomes, Leica CM1800 cryostat, and Sakura robotic histology stainer. Immunohistochemistry and immunofluorescence is performed utilizing 3 Leica Bond Rx immunohistochemistry stainers. The resource also has 3 microscopes including a Nikon 5 headed scope and 2 Nikon duel headed scopes, all outfitted with a digital camera system. Laser capture microdissection is performed on the Arcturus Veritas LCM system which incorporates an inverted microscope, video monitor and an image archiving workstation for analyzing and documenting all microdissections performed. In addition, the resource has an Aperio AT and an Aperio FL for brightfield and fluorescent slide scanning, respectively, and 3 computers designated for image analysis utilizing Aperio IA Toolbox and Definiens Tissue Studio software.

Technologies and Expertise
The EHL provides support for the preparation, analysis, and interpretation of tissue and cell specimens using histological, immunohistochemical, and molecular methods. The EHL team has extensive experience in working with human tissue as well as many experimental model systems including murine, canine, fish, non-human primate, xenografts, and insect samples. The resource focuses on protocols that accommodate the specialized needs of each research project. This often requires the adaptation of techniques in unique ways to accommodate novel model systems not seen in a clinical histology environment.

The resource provides research quality histology and uses paraffin processing, embedding, sectioning and staining with standard histological methods as well as special orientation of tissues, serial and/or step sections and sectioning for molecular analyses. The lab also routinely processes and sections frozen tissues as well as prepares cytology specimens. In addition to hematoxylin and eosin (H&E) staining, the resource performs a wide variety of special stains including silver, iron, PAS, Movat’s pentachrome, trichrome, Alcian blue, Congo red, oil red O, GMS fungus stain, and beta-galactosidase. The resource also provides special stain development services to meet the needs of individual research projects.

A wide range of immunochemistry and immunofluorescence services are available including utilizing polyclonal or monoclonal antibodies and a variety of detection methods, to demonstrate markers for apoptosis, cell proliferation, tumors, and differentiation. A full list of available antibodies is on the shared resource web site: http://sharedresources.fhcrc.org/documents/list-antibodies-experimental-histopathology. A great deal of the immunochemistry focus is on novel applications for antibody staining and characterization. To support murine
and xenograft models of disease, the laboratory has developed flexible methods to use mouse monoclonal antibodies on mouse tissue without detecting endogenous immunoglobulin. In addition the laboratory has extensive experience in performing multiple antibody staining on the same tissue section to localize antigens. Laser Capture Microdissection (LCM) is available and the resource provides training and instrument time to investigators throughout the Consortium. The resource also offers specimen preparation, sectioning, and RNase-free staining to support LCM research.

Digital pathology services include brightfield slide scanning, access to fluorescent slide scanning, and access to image analysis software. The resource provides both instrument and image analysis software training.

The EHL provides consultations in the following areas: study design, the best methods for thorough analysis and interpretation of histopathological results, perspectives on species-specific differences and the comparative value of animal models. Pathologists can assist with interpretation of histochemical and immunochemical stains. Necropsy training and consultation are coordinated with the comparative pathologist (Comparative Medicine Shared Resource) and includes sample preparation for mouse phenotyping. Consultation is also available to modify and build image analysis solutions, select regions of interest, and analyze digital pathology images.

Semi-annual classes on the fundamentals of immunohistochemistry are also offered. Basic histology and special techniques, including tissue cryopreservation and bone decalcification, are taught as needed. Protocols and reference materials are made available through the resources website.

Specialized Pathology Laboratory
Facilities and Equipment
The Specialized Pathology Laboratory occupies 700 square feet in the Hutchinson Building, FHCRC Campus. The lab is fully equipped for tissue microarray (TMA), image acquisition and molecular biology. Additional shared space for cold rooms, large equipment, dark rooms, microscopy and tissue culture is located on the same floor. Available equipment includes a Beecher manual tissue microarrayer and a Beecher automated tissue microarrayer (ATA 27). Digital imaging is performed with a Hamamatsu Nanozoomer RS high-resolution digital slide scanner. This digital imaging system consists of a Windows workstation, image acquisition software and a fully automated 3 chip TDI camera. Images can be securely shared via the internet or a local area network as well as accessed via an internet portal that allows for the capture and storage of pathology review data. There is access to a triple viewing Olympus BH-2 microscope in addition to two Olympus microscopes, and an Optronics MicroFire digital color camera.

Technologies and Expertise
The SPL provides tissue microarray (TMA) and standardized pathology review services for investigators within the Consortium involved with large, long-term population-based studies that often require pathology services and testing of hundreds to thousands of tissue samples. The services are customized on an individual basis to meet the specific needs of each research project.

The resource has established a complete TMA service that includes design consultation, automated construction, microtome sectioning, imaging, pathology interpretation and resulting image and data acquisition/management. The staff has worked closely with programmers to develop a web-based interface for facilitating the interpretation, data entry and data management of TMA studies and this completed system is now available to Consortium members. The Specialized Pathology Image Data Exchange (SPIDE) interface links the TMA images to a database so that collaborators can access, interpret and capture data for TMA studies through a web browser portal. The resource provides the highest quality imaging and data collection tools for investigators through this access protected, web-based platform for image viewing and data recording. This system allows for on-screen data entry of results, incorporates data from multiple assessments to allow intra-and inter-observer evaluations, and allows definition and monitoring of data quality. These state-of-the-art TMA assessment tools are efficient, easily accessed, securely linked to established statistical analysis groups, and shared by investigators nationwide.

Specialized Pathology also provides expert pathology review. Of great value to many studies that include biomarker testing of large numbers of samples, a staff pathologist, Dr. Minggang Lin, is available to review
The SPL is a central pathology resource that supports investigators in a variety of scientific programs, including Cancer Basic Biology, Cancer Prevention and Epidemiology, Gastroenterology, Global Oncology, Hematologic Malignancies, Immunology and Vaccine Development, Prostate Cancer, and Women’s Cancer scientific programs. Services have been expanded to support investigators using animal models of cancer including patient derived xenografts and genetically engineered mice. These services include specialize histology techniques, multi-color immunofluorescence on formalin-fixed, paraffin-embedded samples, and high resolution slides scanning with image analysis. The SPL is particularly important for support of large prevention and epidemiology studies that include biomarker assays. Non-laboratory based investigators often need pathology review and assessment of tissue samples and tissue processing prior to assay testing. The pathology expertise provided by Dr. Porter and staff pathologist Dr. Lin, allows the SPL to support the pathology needs of large studies with a cost-effective and highly efficient system. For example, SPL will assist in a new project (NCI-UM1CA173642) led by Dr. Garnet Anderson (CPEC) to build core infrastructure and specimen resources for the Women’s Health Initiative (WHI) Cancer Survivor Cohort.

RPSR collaborates with over 65 Consortium laboratories as well as laboratories from other cancer centers and academic institutions. In addition to the highest quality of routine histology and immunohistochemistry, the resource excels at utilizing the core staff’s extensive expertise to develop specialized protocols for pathology review and sample testing.

**James Olson, MD, PhD, Cancer Basic Biology**


The Olson lab has been using genetically engineered mouse models of medulloblastoma to study the natural history of the disease and also as a platform to test anti-cancer therapies. In addition, the lab has been developing less invasive imaging techniques to track cancer progression or regression. In order to accomplish this, H&E stained histology sections needed to be developed to correlate MRI images. Experimental Histopathology developed a completely novel method to fix, decalcify, paraffin-process, embed and section whole mouse heads to produce horizontal sections that maintained the necessary morphology to evaluate important pathology such as tumor induced hydrocephalus. The work was published and the lab contributed to figures 1 and 3 in the following paper cited above.

**Paul Nghiem, MD, PhD, Cancer Basic Biology**


Merkel cell carcinoma is a very aggressive skin cancer that has been shown to be associated with a polyomavirus. RPSR has optimized several immunohistochemistry protocols to detect the polyomavirus in patient samples as well as characterize immune response to the tumors. The lab has performed immunohistochemistry and immunofluorescence on tissue microarray samples that were constructed by the Specialized Pathology Lab, as well as larger tissue samples. In addition, dual immunofluorescence protocols were developed for formalin-fixed paraffin embedded samples to evaluate CLA/CD8 co-expression on samples. Digitized images were generated with the laboratory’s Aperio system followed by developing image analysis solutions utilizing Definiens Tissue Studio software to distinguish expression of these antigens in tumor or surrounding stroma and normal tissue. RPSR contributed to figures 1 and 4 of the paper cited above.
Pancreatic ductal adenocarcinomas (PDA) have a very robust stroma that appears to form a barrier that excludes chemotherapy agents from penetrating into the tumor. Specifically, the Hingorani lab had identified hyaluronan, or hyaluronic acid (HA), as a major component of this stromal barrier. Experimental Histopathology utilized a combination of special stains, immunohistochemistry and binding proteins to characterize the stroma and the matrix elements. Masson’s Trichrome and alpha smooth muscle actin immunohistochemistry were used to evaluate collagen deposition and myofibroblastic reaction to the tumor. A Movat’s pentachrome special stain proved a valuable tool to track the evolution of collagenous components of the stroma as the collagen stains yellow and HA stains blue. Early in collagen formation, HA is deposited into the collagen and the resulting mixture of yellow and blue dyes gives the collagen an aqua to greenish color. As the collagen matures over the course of a few months, the amount of HA diminishes leaving the collagenous deposits increasingly yellow. Finally, a biotinylated HA-binding protein, in conjunction with hyuanidase treated controls, were used to confirm the HA present in the stroma. By using HA degrading enzymes systemically, more chemotherapy agents could be delivered to the tumor, leading to an increase in survival in GEM models of PDA. The laboratory’s contribution can be seen in Figures 1, 5 and 6 in the paper cited above.

Janet Stanford, PhD, and Peter Nelson, MD, Prostate Cancer

The Stanford group has identified novel markers for prostate cancer progression based on a whole-exome sequencing project of prostate carcinoma (PCa) families. Experimental Histopathology optimized immunohistochemistry protocols to characterize the expression of these proteins in tissue micro arrays (TMA) of patients with PCa. Furthermore, RPSR optimized Aperio software to segment the digital images of the TMA’s, utilized pathology pattern recognition software to automatically mark regions of interest including normal and abnormal glands, and then analyzed the relative expression and number of cells expressing these markers in each region. The streamlining of this process has greatly improved the turnaround time and efficiency of these large TMA projects. We also plan to utilize this technology for Peter Nelson’s laboratory (Prostate Cancer). These projects have not yet been submitted for publication.

Jon Grim, MD, PhD, and Bruce Clurman, MD, PhD, Cancer Basic Biology

GEM models of colorectal cancer (CRC) have proven to be valuable in gaining insight into the pathogenesis of this disease. However, most models fail to recapitulate what happens as the disease progresses, specifically metastasis and chromosomal instability. The Grim/Clurman laboratory developed new models involving the inactivation of two tumor suppressors that are mutated in human CRCs, the Fbw7 ubiquitin ligase and p53. In order to accurately phenotype these new models, Experimental Histopathology collaborated with the investigators and a comparative pathologist, Dr. Sue Knoblaugh (Comparative Medicine). We were able to coordinate sample procurement, ensure proper fixation techniques, and then identify the necessary H&E, special stains, and immunohistochemistry protocols required to describe this model that yielded highly penetrant, aggressive, and metastatic adenocarcinomas. Furthermore, subsequent studies have utilized Experimental Histopathology’s laser capture microdissection to separate tumor from normal tissue in order to perform DNA methylation studies. Experimental Histopathology contributed to figures 1 and 3 in the cited paper.

William Grady, MD, GI Cancer

The Grady laboratory uses human tissue and mouse models to study colon and liver cancer. Experimental Histopathology has collaborated with the lab for several years to provide routine histology support. For
example, Experimental Histopathology contributed to figures 2 and 6 in Morris et al., Hepatology 2012. Recently, we have worked with this group to characterize new mouse models of liver cancer that exhibit a unique phenotype. For this project, we developed triple immunofluorescence staining for immature cells expressing cKit, cytokeratin positive epithelial cells, and hepatocytes. The results of this study have been submitted for publication. Finally, the lab is now working with the Grady lab to characterize the expression of markers that may predict to therapeutic responses in the treatment of human colon cancers. This work involved optimizing immunohistochemistry protocols for tissue microarrays and then analyzing the data utilizing the Aperio Digital Pathology technology.

**Eduardo Mendez, MD, Cancer Epidemiology, Prevention and Control**

Squamous cell carcinomas of the oral cavity and oropharynx (OSCCs) include different types of cancers, some of which are associated with human papillomavirus (HPV). RPSR is staining mouse xenograft models of human OSCCs with specific tumor markers (annexin A2, MMP2, EGFR, CK19, S100). Many of these antibodies are mouse monoclonals so special care must be taken so that the IHC detection systems do not also detect endogenous mouse immunoglobulin. The laboratory has developed and in house mouse-on-mouse system that is cost effective and flexible to address this issue. This work has been submitted for publication (Tracy Goodpaster and Julie Randolph-Habecker, A Flexible Mouse-on-Mouse Immunohistochemical Staining Technique Adaptable to Biotin-Free Reagents, Immunofluorescence, and Multiple Antibody Staining, Journal of Histochemistry & Cytochemistry). In addition, these mice have been injected with chlorotoxin or “tumor paint,” that target the tumor cells and emit a near-infrared fluorescent signal using ICG dye. Experimental Histopathology has worked with Jim Olson’s lab for several years in the development of chlorotoxin so the lab is utilizing our experience to develop new tools to track the tumor paint. Specifically, we are testing antibodies generated in Antibody Development against chlorotoxin and ICG so we can colocalize the tumor paint to tumors in histological sections. We are using immunofluorescence technology in conjunction with the Aperio FL for imaging. This project is at the initial stages and has not been published.

**Polly Newcomb PhD, MPH, Cancer Epidemiology, Prevention and Control**


In a population-based prospective cohort study for cancer survival, Dr. Newcomb and her collaborators have focused on the identification of risk factors for the incidence of common cancers, and characteristics associated with survival. Since many of these risk factors appear to have only modest magnitudes of effect, more precisely identifying susceptible individuals defined by genes, epigenetic changes, or personal characteristics such as exogenous body size are being investigated in the population, laboratory and clinic. Dr Newcomb’s work in colorectal cancer is primarily focused on the heterogeneity of disease, Specialized Pathology has provided extensive pathology review of tumor and normal colon samples, and selection and cutting of samples for testing for the study. The detailed pathology review includes histologic diagnosis, assessment of amount of tumor in the tissue block, marking of tumor area for microdissection and a quantitative assessment of tumor infiltrating lymphocytes (TIL). This work has supported numerous publications including both Seattle Colon Cancer Family Registry and CCFR wide.
This study is a prospective cohort study of colorectal cancer patients recruited as part of the ColoCare Consortium at the Fred Hutchinson Cancer Research Center and at the National Center for Tumor Diseases (NCT)/German Cancer Research Center (DKFZ). The ColoCare Study in Seattle is an ongoing prognostic study started in 2007 in which patients are followed at regular intervals for outcomes of cancer recurrence, survival, health-related quality of life and treatment toxicities. Biospecimens are collected from participants and Specialized Pathology has assisted in developing and implementing systematic and consistent study-specific pathology review criteria for collected colorectal tumor samples across multiple ColoCare sites including a pilot project to assess tumor infiltrating lymphocytes (TIL) in colon cancer. Several publications identifying methylation-associated silencing of tumor suppressor genes in colon cancer and tumor infiltrating lymphocytes in colon cancer have been supported by the SPL.

Garnet Anderson, Cancer Epidemiology, Prevention and Control

A new project will use SPL services to assist in expanding the biorepository for the Women’s Health Initiative (WHI) by collecting and assessing paraffin embedded tumor tissue from selected cancers sites (NCI-UM1CA173642; P.I. Garnet Anderson). This infrastructure grant will enhance opportunities for molecular epidemiological and cancer survivorship studies in WHI and facilitate research on the etiology and risk factors for cancer incidence, cancer recurrences and survival, with a particular emphasis on the contribution of co-morbidities lifestyle factors, molecular and genetic factors, and treatment-related factors (ie type of treatment and adherence) that decrease the risk of second and recurrent cancers. By creating a repository that will use up-to-date phenotyping methods for a large number of tumors from many sites, WHI will contribute to the advancement of our understanding of the molecular basis of several cancer types and treatment of those cancers. The SPL will do tissue block triage, H&E sections and pathology review and assessment of tumor content for nearly 30,000 tissue blocks over a five-year period. They will work closely with WHI staff to maintain a repository of samples and data that can be accessed for studies by investigators throughout the country.

Cost Effectiveness

RPSR provides the highest quality histology, special stains, and immunohistochemistry samples for the Consortium investigators. Price comparisons between core facilities at other institutions and commercial entities revealed that the resource is the most cost effective option in Washington State. Furthermore, the resource offers custom services that are not available from other sources. It would also be very expensive for individual investigators to employ staff with the same level of histology and immunohistochemistry experience and purchase and maintain the equipment necessary to produce high quality samples.

Use of Services Data

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<th>Peer Reviewed</th>
<th>Non-Peer Reviewed</th>
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<td>7 (9%)</td>
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<tr>
<td>TMA consultation, construction, imaging, interpretation, data capture/management</td>
<td>3</td>
<td>3 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>Pathology Review</td>
<td>7</td>
<td>7 (100%)</td>
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Management Structure, Policies and Operations

Administration

The Research Pathology Shared Resource operates in accordance with Consortium and institutional policies for Shared Resources.

The Experimental Histopathology Lab is under the direction of Julie Randolph-Habecker, Ph.D. She is responsible for the overall operations of the laboratory including hiring staff, managing workflow, verifying billing, and management of large projects and operates in consultation with Paul Woloshin, MBA, Ph.D., Consortium Shared Resources Director. Dr. Randolph-Habecker also provides consultation for research projects, reviews histology and immunohistochemistry slides, and performs image and data analysis. Lead Histotechnologist, Tracy Goodpaster, assists the director in the day-to-day operations of the lab. Resource managers and staff receive assistance from the Shared Resources administrative team and other FHCRC administrative departments for tasks such as billing and purchasing.

The Specialized Pathology Laboratory is under the direction of Peggy Porter, MD, Member, FHCRC. Dr. Porter is co-head of the Women’s Cancer Program and Professor of Pathology at the University of Washington (UW). She is board certified in anatomic pathology with added certification in cytology. Specialized Pathology is staffed by project manager, Elizabeth Donato, MT; staff pathologist, Minggang Lin, MD; histotechnologist, Kelly Wirtala, and programmer/database manager, Stephanie Stafford. Ms. Donato has 27 years of pathology and immunohistochemistry laboratory experience gained both at the UW and the FHCRC and has managed the resource for 10 years. Dr. Lin worked as a pathologist in China for 8 years before coming to the U.S. in 1997 to work with Dr. Porter. Ms. Wirtala has over 20 years of experience as a histotechnologist and is a master at sectioning TMA blocks. Ms. Stafford has over 20 years experience in designing and implementing shared databases and manages the databases for multiple large population-based studies in addition to her data management and programming for the resource.

Faculty oversight of the RPSR is provided by an advisory committee responsible for reviewing Shared Resource operations on annual basis, providing review of user fee changes, evaluating capital budget requests and providing guidance on future goals and objectives. Drs. Randolph-Habecker and Porter meet annually with Faculty Advisory Committee including Beverly Torok-Storb (Hematologic Malignancies), Maria Lemos (Immunology and Vaccine Development), Jim Olson and Paul Nghiem (Cancer Basic Biology), and Bill Grady (Gastroenterology). The committee provides useful feedback concerning the type of services they require, the overall quality of specimens, input on capital equipment for shared instrumentation, and help the directors focus resources to new technologies. The Consortium’s Scientific Steering Committee ensures that this and other Consortium resources are aligned with the Consortiums strategic goals and its continued value to the Cancer Center.

Access and Usage Policy

Services are available to all members of the Consortium, on a first-come, first served basis. Support is provided to external users as time permits. Costs are charged directly to applicable awards based on actual usage and rates are based on projected operating costs net of CCSG and institutional support. Rate schedules are reevaluated and revised as required on an annual basis. External user fees reflect the full cost (both direct and indirect) of rendering service according to the most recent rate revision. No benefit of institutional or federal funding received by the resource is considered in the establishment of outside rates.

Billing

Standardized service request forms provide authorization of service and requested information for each respective transaction. Services are billed upon completion and information is entered into a Shared Resource billing system which provides the ability to track resource use at the project level by activity. Ongoing review is conducted to monitor activity levels and observe usage trends to ensure appropriate adjustments are made in operations to adapt to changing demand. Usage is assessed and summary reports are develop by institution, by investigator, and by program for each service provided by the resource. Ongoing evaluation of resource operations is conducted through implementation of appropriate analyses, benchmarking studies, surveys and other tools.
**Education and Outreach**

Users are kept up to date on changing technologies and services offered by the facility through the FHCRC and Consortium websites, Shared Resource Newsletter, and special memo distributions. Outreach to the broader Consortium community, particularly those within the UW and Children’s Hospital, will be enhanced through the activities of the UW Institute of Translational Health Sciences (ITHS). As an ITHS approved facility, it is anticipated that the Resource will play an ongoing and expanded role in support of translational research activities. Also, Consortium Shared Resources can be found through eagle-I, a web-based, searchable nationwide network of scientific services. Resource employees keep current in their field through scientific publications, seminars and national conferences.

**Priorities and New initiatives**

**Experimental Histopathology**

*New IHC staining platform*

Experimental Histopathology is changing our staining platform from the Dako Autostainer to the Leica Bond Rx. This new equipment will further streamline our staining process to include onboard deparaffinization and antigen retrieval and allow for greater control over protocols and reagents. In addition, these new stainers will allow us to be more productive, cut reagent volumes, and improve turnaround time. The system also has a powerful database that will allow us to more easily track usage, numbers of slides stained with different antibodies, and workflow.

*In Situ Hybridization*

The Leica Bond Rx will also give the resource the opportunity to offer automated in situ hybridization. We will focus on both probes to DNA and RNA and target protocol development for formalin-fixed, paraffin-embedded tissue. We are initiating a collaboration with Affymetrix to test the QuantiGene View RNA in situ system that utilizes a novel probe construction with amplification to visualize low copy numbers of target nucleotide. We plan to develop protocols to detect human and mouse DNA to support investigators using xenograft models. We have also had request from laboratories studying infectious diseases such as HIV, HSV, HHV6, and helicobactor and from investigators who want to study immune modulating proteins such as PDL1.

*New LCM platform*

The resources existing Veritas LCM system is over 10 years old. We have demoed instrumentation from different vendors to establish what platform will work for the various labs that use this technology.

**Pathology Image Analysis**

As the laboratory gains experience with the Aperio scanning platform, we are adding more support for the image analysis capabilities of the technology. As we work with more investigators, we are collaborating to establish new solutions to their image analysis needs for both bright field and fluorescent images. Staff from Experimental Histopathology and “super users” from various labs will attend advanced training for both Aperio IA Toolbox and Definiens Tissue Studio software systems. By optimizing a variety of approaches, we hope to offer a wide range of customized analysis support that is integrated with our histology and immunohistochemistry/fluorescence services. We also coordinate with Specialized Pathology in the evaluation and optimization of imaging solutions for specific projects.

*iLab online scheduling/management system*

Implementation of iLab Solutions Software for core facility management will be launched for eleven resources, anticipated January 2014. This system will allow Consortium researchers and Shared Resource staff to manage service requests, equipment reservations, usage tracking and billing online.

**Specialized Pathology**

*Updated TMA Imaging platform*

The SPL has updated its outdated, 10 year old TMA imaging system with the Hamamatsu Nanozoomer RS high-resolution digital slide scanner. This system was selected for it’s excellent image quality, fast scan speed, user-friendly scanning software interface and comparatively inexpensive hardware costs which have allowed the SPL to continue to offer very competitive TMA imaging pricing. This state of the art technology has been integrated seamlessly into the existing TMA imaging workflow and has been particularly useful in supporting
projects requiring the generation of large numbers of high-resolution TMA images that need to be accessed through the web.

Integration of DigitalScope image server software for distribution of TMA images via the web
In order to continue to serve TMA images over the web in a cost effective manner we replaced outdated and unsupported Bliss WebSlide server technology with DigitalScope post image processing server software developed by Aptia Software. This image processing technology allows the SPL to serve very large, high-resolution TMA images over the web with no annual recurring costs and is essential in supporting world-wide TMA collaboration efforts.

Development of cutting edge DigitalScope TMA Griding Software
The SPL is working closely with Serenus Group to complete development of a TMA module that allows for the efficient image annotation of TMA XY coordinates. The basic mapping functionality has been implemented and is robust. The mapped TMA images provide researchers with a method for maintaining data integrity between research data and associated de-identified clinical data and are an invaluable tool in supporting TMA research projects. Increased functionality of this TMA module is under development and will be implemented within the next few months which will result in an advanced TMA mapping method that rivals existing technologies at a fraction of the cost.

Personnel
Key Staff Qualifications
Julie Randolph-Habecker, PhD, Staff Scientist and Director of the Experimental Histopathology Lab, was hired in 2003. Dr. Randolph-Habecker oversees the general operations of the laboratory, keeps abreast of the latest relevant technology advancements, and ensures that the resource continues to meet the needs of investigators in a timely manner. She received her Master’s in Clinical Chemistry and a Doctoral degree in Pathology from The Ohio State University. She did a postdoctoral fellowship with Beverly Torok-Storb, PhD, (Hematologic Malignancies). She is a member of the American Society of Investigative Pathology and the National Society for Histotechnology.

Experimental Histopathology is staffed by 7 technicians, many certified by the American Society for Clinical Pathology (ASCP) as HT or HTL technicians, and represent over 100 years’ experience. Tracy Goodpaster, BA, HTL and QIHC, has 20 years’ experience in histology and research immunohistochemistry and is the lead histotechnologist in the lab. Her experience includes work in the laboratory of Allen Gown, MD, where she specialized in hybridoma production and antibody work-ups. Sharon McLaughlin, HT, has 43 years’ experience in both clinical and research histology laboratories and specializes in special stains. Kim Melton, BS, HTL and QIHC, has 33 years’ experience in clinical and research immunohistochemistry and is certified in immunohistochemistry techniques by the ASCP. Ms. Melton is also experienced in image analysis. Sunni Farley, BS and HTL, has 10 years’ histology experience in research, clinical, and industry settings and specializes in immunohistochemistry and image analysis. Lizzy Benetiz, BS, has 4 years’ experience and specializes in histology and tissue grossing. Jones Son, AAT and HT, has 2 years of experience and specializes in histology and special stains. Marcia Beers, AAT, has 2 years’ experience and specializes in histology, frozen tissue sectioning, and routine immunohistochemistry. Both Mr. Son and Ms. Beers completed histology training at Clover Park Technical College in Washington.

Peggy Porter, MD, Director of the Specialized Pathology Lab, is a board-certified Anatomic Pathologist and a member of the FHCRC Divisions of Human Biology Division and Public Health Sciences, Co-Leader of the Women’s Cancer Program, Principal Investigator of an NCI Specialized Program of Research Excellence in breast cancer, director of the Breast Specimen Repository, and Professor in the UW Department of Pathology. She has directed SPL for 8 years and has been in the field of cancer research for nearly 20 years. Her laboratory at the FHCRC is primarily focused on identifying and understanding the molecular events associated with the initiation and progression of breast cancer, particularly through collaborative research in large clinical and population-based studies. This research has required optimization of histology and molecular assays done on archival tissue samples and she has designed and led laboratory investigations in population-based studies that together have involved over 8000 subjects. She has collaborated on and led multiple projects involving tissue microarray (TMA) construction and IHC-determined protein expression and
molecular alterations in population-based and clinical studies and regularly provides pathology consultation to Consortium investigators.

Specialized Pathology is staffed by project manager, Elizabeth Donato, MT; staff pathologist, Minggang Lin, MD; histotechnologist, Kelly Wirtala, and programmer/database manager, Stephanie Stafford. Ms. Donato has 27 years of pathology and immunohistochemistry laboratory experience gained both at the UW under the direction of Dr. Allen Gown and the FHCRC. She has managed the resource for 10 years. Dr. Lin worked as a pathologist in China for 8 years before coming to the U.S. in 1997 to work with Dr. Porter. Ms. Wirtala has over 20 years of experience as a histotechnologist and has excellent technical sectioning skills, which are particularly important for conservative sectioning of TMA blocks. Ms. Stafford has over 20 years experience in designing and implementing shared databases and manages the databases for multiple large population-based studies in addition to her data management and programming for the resource.
Clinical/Translational

THERAPEUTIC MANUFACTURING SHARED RESOURCE

Introduction
The Therapeutic Manufacturing Shared Resource (TMSR) offers a broad range of facilities and qualified trained personnel to support the development and manufacturing of novel biological molecules and innovative cell-based therapies for Phase I/II clinical testing. These facilities are an integral part of the Consortium’s world-renowned translational research efforts. To enhance these endeavors, we have consolidated two Good Manufacturing Practice (GMP) facilities into one jointly co-administered and operated Therapeutic Manufacturing Shared Resource. Combining the Biologics Production and Cell Processing Facilities (previously supported by this grant) has allowed the Consortium to further build on their leadership role in the application of immunotherapy for the treatment of hematological malignancies, and to extend this innovative work to other clinical settings such as autoimmune disorders, melanoma, sarcoma, breast, ovary, and prostate cancers.

Formation of this combined unit greatly enhances efficiencies of operation, thus providing more Consortium investigators with greater access to a wider range of therapeutic products. GMP manufacturing capabilities include specialized equipment and trained staffing necessary for supporting clinical studies that incorporate specific cell selection, genetic modification and/or ex vivo manipulation of patient stem cells, dendritic cells and T-cells, as well as the production of research and clinical grade monoclonal antibodies, antibody-streptavidin fusion proteins, vaccines, lentivirus vectors and other therapeutic molecules. The facilities assist investigators at the University of Washington (UW), Fred Hutchinson Cancer Research Center (FHCRC), Seattle Cancer Care Alliance (SCCA), and Seattle Children’s Hospital (Children’s) in their pre-clinical research efforts, pilot production requirements, clinical trial design, and other support activities needed for filing of both Investigational New Drug (IND) Applications and Drug Master Files (DMF), and finally for clinical manufacturing activities once IND approval has been received, all while providing appropriate levels of quality control, quality assurance, and regulatory oversight to ensure compliance with strict FDA requirements. The TMSR received an Outstanding assessment in the 2008 competitive renewal with no major criticisms. To consolidate resources and maximize personnel utilization, CCSG funding support for the UW facility is no longer being requested.

Major Services
Facilities and Equipment
A total of 5300 square feet of cleanroom space is provided for current Good Manufacturing Practices (cGMP) manufacturing activities. Facilities include 4000 square feet of space for cellular processing and 1300 square feet for the production of biological therapeutics. In addition, 2000 square feet of non-classified space is provided for pre-clinical production, quality control testing, storage of qualified materials and reagents, product development/process transfer, and other support activities. Both cGMP facilities were constructed according to specifications set by Code of Federal Regulations Title 21, Sections 210 and 211. Validation of clean rooms and utilities were conducted in accordance with established standards and each facility has been qualified and utilized for therapeutic manufacturing.

Each of the facilities is designed to satisfy cGMP requirements, which exceed those found in standard research laboratories. Individual manufacturing suites are supplied with single-pass, class 10,000 HEPA filtered air, and all critical operations are carried out within class 100 vertical-flow biosafety or clean bench laminar flow hoods located in each area. Directional work-flow has been established so that personnel, products under manufacture, as well as equipment, components and waste follow a specific path through the suites. Qualified automation systems continuously monitor, control and alarm various aspects within the facilities, including: energy management, lab data acquisition, lighting control, access control, the status of air flow and pressurization of individual spaces within the suites, as well as the correct operation of critical equipment such as the incubators.

The facilities contain a broad range of specialized instrumentation to accommodate specific manufacturing activities. Equipment that is available for manufacturing antibodies, drug conjugates, fusion proteins, lentiviral vectors and other DNA-based products allows production at scales that readily exceed the capabilities of most Consortium research laboratories, and provides the added benefit of clinical cGMP compliance that would not otherwise be available to investigators. Production is typically started as bulk cell culture in either static or...
Manufacturing suites supporting the production of cellular therapeutics are equipped with biological safety cabinets and numerous double stack incubators. Other major equipment includes floor and table top centrifuges, sterile connecting devices and large scale cell enrichment devices from Miltenyi Biotec. In conjunction with these core equipment capabilities, the TMSR maintains separate quality control (QC) laboratory space to provide product characterization capabilities, such as automated cell counts and flow cytometry, required by the FDA for clinical studies. Every processed component is quality control tested using standardized and validated assays, with a subsequent independent quality assurance review before release for therapeutic use.

All manufacturing activities are conducted using approved written procedures performed by trained, qualified personnel in accordance with cGMP and current Good Tissue Practices (cGTP) guidelines. Production in individual suites is limited to single patient preparations and/or products as much as possible to facilitate process control and minimize the potential for errors or cross-contamination. At times when overlapping concurrent productions are required, segregation by types of manipulations and/or stages in the manufacturing cycle is implemented. Each facility is designed to provide adequate space for manufacturing activities and appropriate separation of materials. Quality assurance is further insured by strict process control, including spatial and temporal separation of individual manipulations. Regularly scheduled cleaning of facilities and appropriate gowning of personnel ensure product safety, and contamination concerns are further minimized by the frequent use of closed production systems.

Procedures are in place for validation of production and assay methods, development of specifications for in-process and final product release, and qualification of outside suppliers and vendors. Calibration programs, along with a comprehensive preventative maintenance plan, have been implemented for all utilities, equipment and instrumentation used for production activities. Qualified supervisory staff and/or contracted vendors provide operational instruction. As applicable, staff members enroll in programs conducted by outside training institutions, with a focus on attending seminars providing specialized skills/information specific to an individual's job responsibilities. Periodic cGMP training is scheduled, focusing on review of applicable FDA guidelines and associated Standard Operating Procedures.

**Expertise Provided**

The TMSR provides translational investigators within the Consortium with the infrastructure and technical expertise necessary to develop biologic and cellular products under the strict FDA regulations required for clinical evaluation. Senior personnel within the TMSR start at the very earliest phases of a project to collaborate with and assist investigators throughout the process development lifecycle, from initial research and pilot process stages to final manufacture and release of therapeutic products.

Process development services are far ranging and include pre-clinical development of scaled-up optimized production methodologies to satisfy parameters of product yield and functionality, compliance with requisite safety and release specifications and other regulatory requirements, development of standard operating procedures and batch records, and performing pilot studies and validation of key systems prior to process transfer and initiation of full clinical manufacture. The development lifecycle for both biological and cell therapeutic projects can be complex. Typically, these require initial assessment of existing research laboratory-based procedures, conversion to cGMP compliant materials and clinical-grade reagents, process optimization to address culture conditions and scale-up issues, development of standard operating procedures and appropriate batch records for documentation, followed by completion of an appropriate number of pilot or full-scale validation studies prior to IND submission and initiation of therapeutic manufacturing. For example, clinical projects utilizing production capabilities encompassing both biological reagents and cellular...
components typically require a concerted development effort of up to two years prior to delivery of an approved product. This timeframe is not unusual for those projects intended for clinical manufacture.

The TMSR produces a broad spectrum of unique reagents not readily available from commercial sources. While our focus is on the development and manufacture of materials for clinical studies, as time permits, facility services are utilized to support pre-clinical research activities. Specific biologics production services include: adaptation of cell lines to serum free medium, characterization of cell lines, cell banking, production of purified biologics (e.g. antibodies), expressed proteins and DNA from various mammalian and prokaryotic cells, modification of proteins with biotin or fluorochromes, custom formulation and chemical modification of therapeutic peptides. Production of pre-clinical material can vary from as little as one month to a half year depending upon cell line productivity, purity requirements and expected final yield. Output usually ranges from mg to gram quantities. Clinical campaigns typically run 4 months, with output ranging from 5 to 10 grams of vialled product appropriately prepared, tested, and qualified for clinical use.

Pre-clinical cell production services include enrichment or depletion of specific cell subsets, provision of normal donor feeder cells, maintenance of transformed feeder cell lines, cloning, ex-vivo antigen priming, cytokine and antibody-based activation, genetic modification, expansion, cryopreservation and/or preparation for infusion of many different types of extensively manipulated cell populations. Production runs can vary from as short as one day to several months depending upon the specific project requirements for the type of cell manipulations and the final yield. Output usually ranges from \(10^7\) to over \(10^{11}\) cells.

Quality control testing using validated test methods is a critical function of the TMSR, with staff providing key support for all facets of pre-clinical and clinical manufacture. Primary responsibilities focus on compliance with cGMP and cGTP mandated FDA regulations and safety guidelines. Various analytical methods are utilized to insure that all components and materials in contact with the product stream, and the final therapeutic products, meet defined release specifications and acceptance criteria. Monitoring is also performed to safeguard that the production process is operating in a state of control. Testing includes Bioburden (sterility, microbial identification, mycoplasma, and endotoxin), Biochemical Analysis (SDS PAGE, IEF, ELISA, total protein, osmolality), and/or Cell Product Characterization (cell counts, flow cytometry phenotyping for purity, cell surface expression of specified markers, viability, colony-forming activity, and production of cytokines in culture supernatant as a demonstration of potency and functionality). TMSR staff also support further assay optimization, preparation of standard operating procedures and supporting documentation, validation of procedures, environmental monitoring of the production suites to assure compliance with classification specifications, calibration and maintenance of equipment, and other administrative tasks.

Quality Assurance personnel provide independent oversight of manufacturing and QC testing across the various facilities, thus assuring consistency, reliability, and regulatory compliance. Activities include deviation investigations, corrective and preventative action plans, complaint resolutions, and on-going validation studies, encompassing all phases of manufacturing, testing methods and associated documentation. As specified by Federal guidelines, yearly review and update of these methods are performed. To meet cGMP and cGTP specifications, facility staff provide tracking of controlled inventory (e.g. raw materials, production intermediates, final product) in addition to an extensive program for environmental monitoring. Annual audits are performed to ensure facility compliance with FDA and other regulatory agencies as appropriate for each clinical product. The resource also provides regulatory support through liaison with the appropriate accrediting bodies, federal and state agencies. In conjunction with manufacturing, quality assurance provides assistance with the preparation and filing of both IND Applications and DMFs with the FDA. To date, TMSR has filed nine DMFs and contributed to the filing of twenty-eight INDs.

**Importance to Scientific Programs**

The TMSR addresses a wide range of investigator needs, including basic reagents for *in vitro* research, qualified pre-clinical material for intravenous use in animals, and rigorously qualified and tested clinical products intended for FDA-regulated investigational trials. The Consortium hematopoietic cell transplantation program is internationally recognized and these facilities have been in the forefront of supporting the development of new procedures for cell enrichment or depletion, activation, genetic modification, and generation of antigen-specific immunotherapy-focused cell populations. Selected descriptions of projects being conducted within the facilities are outlined below, emphasizing the importance of the resource to peer...
reviewed research and clinical translational efforts of Consortium investigators. Selected publications resulting from support provided by the resource are cited in this narrative.

**Ollie Press, MD, PhD, Hematologic Malignancies**

Pretargeted radioimmunotherapy

Dr. Press has conducted animal studies and pilot clinical trials in a variety of malignancies (e.g. lymphoma, leukemia, myeloma, and solid tumors), demonstrating convincingly that multistep pre-targeting methods for delivering radioimmunotherapy (RIT) are superior to conventional RIT. The TMSR has produced and purified a variety of monoclonal antibodies (1F5, anti-CD20; BC8, anti-CD45; etc.) for murine and monkey studies and has optimized and adapted for clinical use anti-CD45-streptavidin (SA) and anti-CD20-SA constructs for use in pretargeted RIT clinical trials. The facility has produced and characterized BC8-SA conjugates that have been administered to nine patients so far in a Phase I clinical trial of pretargeted RIT for patients with acute myeloid leukemia and myelodysplasia IND Application 104683 and associated Drug Master File BB-MF-12366). The facility not only provides the cGMP environment required for this clinical project, it also provides the necessary scale of production that could not be readily achieved by other means. Selected publications;


**Study to Evaluate the Safety of Cellular Immunotherapy using Genetically Modified Autologous CD20 Specific CD8+ T cell Clones for Patients with Relapsed CD20+ Indolent Lymphomas.**

Follicular non-Hodgkin’s lymphoma (FL) is one of the most common sub-types of NHL, accounting for 20-30% of all cases, and nearly 85% of FL patients have widespread (stage III-IV) disease at the time of diagnosis. No curative treatment is available for advanced FL, with the possible exception of high dose chemoradiotherapy with stem cell transplantation. However, most patients who develop FL are elderly and are not suitable candidates for aggressive stem cell transplantation protocols. Innovative new treatments are therefore needed. This protocol examines the safety of administering a novel new treatment for patients with relapsed FL, using cloned T-cells genetically engineered to recognize CD20, a marker found on a majority of FL. The Lentiviral Core Facility has produced an anti-CD20 chimeric antigen receptor vector that incorporates an inducible Caspase 9 suicide gene and a truncated CD19 selection marker for a Phase I clinical trial that is anticipated to be submitted to FDA within a few months and open for clinical trial accrual next year. The TMSR will be responsible for the transduction, expansion, characterization and quality control testing of patient derived gene-modified T cells for the trial which will be conducted in patients with relapsed/refractory indolent and mantle cell lymphomas.

**Colleen Delaney, MD, and Irwin Bernstein, MD, Hematologic Malignancies**
Cord blood has been widely used as a source of hematopoietic stem cells (HSC) for transplantation, particularly because it is a readily available source of histo-compatible cells from an unrelated donor. However, outcomes have suffered due to inadequate stem cell numbers and the resultant delayed engraftment, often associated with development of lethal infectious complications. Drs. Delaney and Bernstein have developed novel methods for enhancing the repopulating ability of hematopoietic precursor cells. In studies with human cord blood cells, culture with engineered Notch ligand dramatically increased the number of CD34+ precursors and enhanced their repopulating ability in immunodeficient mice. In the past 5 years of CCSG support, the TMSR has provided critical equipment and expertise at several levels for this project: 1) production of cGMP compliant engineered Notch ligand (6,455 vialed units from five production campaigns) and maintained the corresponding DMF (BB-MF-12366); 2) continued to make process improvements in the clinically relevant ex vivo culture system used for expanding the cord blood using the cGMP Notch ligand; this included processing of fresh cells followed by cryopreservation and banking as well as the conversion from static T-flask cultures to the use of roller-bottle technology; 3) performed numerous full-scale validation runs to verify performance of the banked cryopreserved final products and the roller-bottle culture system; 4) helped in the submission of amendments to existing IND application (BB-IND-12657) and two new INDs with expanded cord blood clinical applications; and 5) produced fresh expanded cord blood cells for over 20 patients treated to date on the original IND and over 100 expansion products banked for treatment under the new INDs. Selected publications;


Ayaj Gopal, MD, and John Pagel, MD, PhD, Hematologic Malignancies
The TSMR has produced the entire clinical grade BC8 (anti-CD45) antibody used in Drs. Pagel and Gopal clinical trials since 1995. The current studies involve the use of radiolabeled antibodies to deliver targeted hematopoietic irradiation, with the goal of increasing anti-tumor efficacy without excessive toxicity in leukemia and lymphoma patients undergoing hematopoietic stem cell transplantation. This approach has been taken from the first pre-clinical experiments examining the biodistribution of trace Iodine-131 and In-111/Y-90-labeled anti-murine-CD45 antibody in mice, to ongoing Phase I and Phase II clinical trials using I-131-BC8 and In-111/Y-90-BC8, antibodies combined with conventional or non-myeloablative transplantation preparative regimens. In addition, Dr. Pagel is the principal investigator on the Phase I trial of pre-targeted RIT for patients with leukemia and myelodysplasia mentioned above and the sponsor of the associated IND 104683. Selected publications;


**Phil Greenberg, MD, Immunology and Vaccine Development**

A study was previously completed which involved the infusion of donor-derived WT1-specific T-cell clones targeting the over-expressed tumor-associated antigen Wilms Tumor Antigen 1 (WT1). Eleven patients received escalating doses of cells and the results are published. Although WT1-specific cells demonstrated anti-tumor activity, the cells had variable avidities and many persisted for <14 days in vivo. To address these issues, a high-affinity TCR targeting the same epitope was isolated from a normal donor and is now being used in the clinics. The current project involves the ex-vivo generation of virus (EBV or CMV) specific T cells transduced to express a characterized high affinity T cell receptor targeting a HLA A*0201-restricted epitope of WT1. An extensive program of process development, followed by several sets of full-scale validation runs were completed. To date 14 patients have enrolled on the study, 5 patients are currently having their cells generated for future infusions, 1 product was generated for a patient who was removed from the study for clinical reasons, and 3 patients have received escalating doses of transduced cells for a maximum dose of 1 x 10E10 cells/m2.


**Kim Margolin, MD, Unaligned (Phase I program)**

Adoptive cell therapy using tumor-infiltrating lymphocytes (TIL) has been shown to be more effective than any FDA-approved treatment for metastatic melanoma, with both higher overall response rates and more durable responses than standard of care treatments of high-dose IL-2, ipilimumab, and vemurafenib. However, the generation of TIL is technically challenging and has been available only at 3 other academic institutions in the country. When FHCRC protocol 2643 opened in July 2013, TM was the only institution on the West Coast to offer TIL therapy. We have enrolled 3 patients so far to this protocol for TIL harvest and generation. While providing a meaningful therapeutic treatment for these patients, we will be studying which TIL populations and T cell subsets are more likely to achieve a clinical response, the persistence of antigen-specific T cells after treatment, the influence of T cell exhaustion markers on the TIL generation process as well as the clinical efficacy of the TIL product. With this initial TIL protocol, we hope to establish a streamlined, well-running clinical and laboratory infrastructure that will serve as a platform for the development of a larger investigative TIL program at FHCRC for melanoma and other cancers.


**Nora Disis, MD, Immunology and Vaccine Development, Women’s Cancer**

Cancer vaccine clinical trials performed over the last few years have demonstrated that patients can be immunized against specific tumor antigens. Studies performed by Dr. Disis’ Tumor Vaccine Group, targeting the HER-2/neu (HER2) and IGFBP-2 antigens, have demonstrated that T-cell precursor frequencies can be boosted with active immunization. Cancer, however, is not caused by a single genetic alteration but rather by multiple genetic alterations and the function of multiple aberrant proteins. DNA based immunization offers a technology that is easily adapted to the delivery of multiple antigens driving the malignant process. Her group has demonstrated that it is possible to improve the efficacy of in vivo antigen presenting cell transfection with...
DNA vaccines by the use of local soluble cytokines such as GM-CSF. In a rodent model, a plasmid based DNA vaccine: (1) encoding the HER2 intercellular domain, administered intradermally concurrently with GM-CSF, could stimulate both HER2 specific T cell immunity as well as an anti-tumor response and (2) immunization with IGFBP-2 peptides as well as adoptive transfer of IGFBP-2–competent T cells mediated an antitumor effect.

A phase I dose escalation study of the DNA vaccine has been manufactured by the TMSR. The study met its accrual goal of 66 subjects in the first quarter of 2008. Another phase I study of a DNA Plasmid Based Vaccine Encoding the Amino Acids 1-163 of IGFBP-2 in Patients with Advanced Ovarian Cancer has been initiated under IND P50 CA083636. The TMSR was critical in the clinical translation of a HER2 specific DNA vaccine. Staff worked with investigators in the Tumor Vaccine Group to “scale up” production of the vaccine; developing a master cell bank and lot release criteria. The staff submitted a DMF with the FDA, produced, vialed, and stored the vaccine and participated in the writing of an IND. The trial was completely enrolled within 18 months. Preliminary data support an excellent safety profile for IGFBP-2 DNA vaccination. Early data also shows augmentation of IGFBP-2 specific humoral and cellular immunity in response to vaccination. The Tumor Vaccine Group are planning phase II studies using this vaccine and the TMSR will be involved with stability testing and production of additional vaccine if needed.

**Stanley Riddell, MD, and Cameron Turtle MBBS, PhD, Immunology and Vaccine Development**

A promising advance in cancer immunotherapy involves the adoptive transfer of T cells engineered to have tumor specificity by gene transfer, which has shown significant therapeutic activity in patients with incurable CD19+ B-cell malignancies. This approach employs T cells that are modified to express a chimeric antigen receptor (CAR) consisting of an extracellular single chain variable fragment (scFv) of a CD19 specific monoclonal antibody fused to transmembrane and intracellular domains from one or more T cell signaling molecules. We are conducting two clinical trials to deliver CAR T cell therapy to patients with incurable B cell malignancies. Cameron Turtle’s IND 015017 is a phase I/II clinical trial of therapy of B cell malignancies with CD8+ central memory (TCM)-enriched T cells that are obtained from healthy hematopoietic stem cell transplant (HCT) donors, engineered to express a CD19 CAR and infused into HCT recipients at least 30 days after HCT. Stan Riddell’s IND 015453 is a phase I/II clinical trial of therapy of patients with B cell malignancies with autologous CD4+ and CD8+ TCM-enriched T cells that are genetically modified to express a CD19 CAR. TMSR participated in pre-clinical development activities, full-scale validation run submitted as part of the IND submissions, and now production of final therapeutic products. Selected publications:


**Cost Effectiveness**

The production of novel biological molecules or cells for therapeutic testing is costly by virtue of the rigorous processes and time required, as well as the scale and cost for use of clinically compliant equipment, reagents and materials. The FDA mandates that such agents must be manufactured and tested in accordance with cGMP and cGTP regulations, processes that require dedicated and sophisticated facilities, specialized equipment, along with uniquely trained and qualified personnel. Commercial vendors for these processes might be available, however the innovative approaches developed by Consortium investigators are frequently too preliminary for routine contract manufacturing, costs are usually extremely prohibitive (greater than 50% more than the TMSR for similar reagents), and there is an inability to obtain service in a timely manner. The TMSR facilities are integral to Consortium efforts in translational medicine, and are essential to sustain some of our novel and promising avenues of clinical research. In addition the unique availability of on-site therapeutic manufacturing capabilities and cGMP experienced personnel translates directly into enhanced project translation timelines, improved efficiencies for our faculty and consortium members, and a considerable reduction in overall project costs.

**Use of Services**
<table>
<thead>
<tr>
<th>Service</th>
<th>Total Users</th>
<th>Peer Reviewed</th>
<th>Non-Peer Reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Manufacturing</td>
<td>12</td>
<td>10 (83%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Non-clinical Manufacturing</td>
<td>5</td>
<td>5 (100%)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Management Structure, Policies and Operations**

**Administration**
The management of the TMSR is under the direction of Ronald Manger, Ph.D. for biological materials and David Shank for cellular processing. Operations are facilitated by contributions from the General Counsel's Office (FHCRC), Quality Council (FHCRC and SCCA), regulatory support from the Research Trials Office, and project associated oversight by the faculty clinical sponsors (IND holders). The resource directors supervise their technical staff, and ensure they fulfill their responsibilities. Staff performance is evaluated at least once a year. Staff development is ensured through in-house training sessions and discussions, hands-on experience, seminars, and technical workshops. Resource managers and staff receive assistance from the Shared Resources administrative team and other FHCRC administrative departments for tasks such as billing and purchasing.

The Therapeutic Manufacturing Facilities operate in accordance with Consortium and institutional policies for Shared Resources and in consultation with Paul Woloshin MBA, Ph.D., Consortium Director of Shared Resources. Faculty advisory committees are responsible for reviewing shared resource operation on an annual basis, providing review of user fee changes, evaluating annual capital budget requests and providing guidance on future goals and objectives. Committee members for 2013 include Stan Riddell, MD, (Immunology and Vaccine Development), Phil Greenberg, MD, (Immunology and Vaccine Development), Colleen Delaney, MD, MSc and Shelly Heimfeld, PhD (Hematologic Malignancies), and Oliver Press, PhD (Global Oncology and Hematologic Malignancies). The Consortium’s Scientific Steering Committee ensures that this and other Consortium resources are aligned with the Consortiums strategic goals and its continued value to the Center.

**Access and Usage Policy**
Services are available to all members of the Consortium. The goal is to provide services to any member with conflicts and prioritization determined by the scientific steering committee. Support is provided to external users as time and resources permit. Costs are charged directly to applicable awards based on actual usage. Rates are based on projected operating costs net of CCSG and institutional support. Rate schedules are revaluated and revised as required on an annual basis. External user fees reflect the full cost (both direct and indirect) of rendering service according to the most recent rate revision. No benefit of institutional or federal funding receive by the resource is considered in the establishment of outside rates.

**Billing**
Standardized service request forms provide authorization of service and requested information for each respective transaction. Services are billed upon completion and information is entered into a Shared Resource billing system which provides the ability to track resource use at the project level by activity. Ongoing review is conducted to monitor activity levels and observe usage trends to ensure appropriate adjustments are made in operations to adapt to changing demand. Usage is assessed and summary reports are develop by institution, by investigator, and by program for each service provided by the resource. Ongoing evaluation of resource operations is conducted through implementation of appropriate analyses, benchmarking studies, surveys and other tools.

**Education and Outreach**
Users are kept up to date on changing technologies and services offered by the facility through the FHCRC and Consortium websites, Share Resource Newsletter, and special memo distributions. Outreach to the broader Consortium community, particularly those within the UW and Children’s, will be enhanced through the activities of the Institute of Translational Health Sciences (ITHS). As an ITHS approved facility, it is anticipated that the Resource will play an ongoing and expanded role in support of translational research activities.

**Priorities and New Initiatives**
The priority of the facility is to provide translational services to bring potential therapeutics from the basic research laboratory to a suitable level for early clinical studies of both safety and efficacy (Phase I and II). The
service provides therapeutic products that address the clinical investigators’ pe-clinical, IND submission, and final therapeutic manufacturing needs and address the stringent regulatory requirements of the FDA. A secondary priority is to provide material for non-clinical studies that may eventually lead to promising new therapeutics.

The Therapeutic Manufacturing Facilities and staff are uniquely positioned to provide clinical production services in support of the evolving research programs in the Consortium. The demand for new clinical biological products and cell based therapies continues to grow rapidly. The resource recently produced its first clinical grade lentiviral vector and has submitted an associated Drug Master File, “Manufacture and Quality Control of Lentivirus Vectors”, with CBER FDA (MF 15464). The intended purpose of this clinical vector will be as a tumor specific therapy using chimeric antigen receptor CAR produced by lentiviral transduction. The vector was produced from a plasmid that contains both a CAR component as well as a selection component. The clinical sponsors are Drs. M. Jensen and S. Riddell. In addition the facility is in the early stages of process development focused on adeno-associated viral vectors for potential clinical studies. The facility has completed initial process development and preliminary production of a new therapeutic protein, JO-1, for Dr. Andre Lieber, Women’s Cancer Program. JO-1 increases the intratumoral penetration and efficacy of monoclonal antibodies and chemotherapeutic drugs in a broad range of human xenograft models as well as in human desmoglein 2 (DSG2) transgenic mice with syngeneic epithelial tumors. The facility has produced non-clinical JO-1 and is staging for manufacture of cGMP material in support of the sponsor’s future filing of an IND. For cell-based therapeutic manufacturing, new studies on the immediate horizon include additional CAR T-cell therapies targeted unique antigens, genetic modification of CD34+ cells for fanconi anemia patients, expansion of NK cells, , and generation of regulatory T-cells for treatment of GvHD and autoimmune diseases. Fortunately, the facilities were designed to accommodate flexibility in both project scope and scale while addressing compliance with FDA requirements, thus facilitating multi-product production of therapeutic agents. Therapeutic Manufacturing has played and will continue to play a critical role in what has been a highly productive and very successful Consortium translational program.

**Personnel**

**Key Staff Qualifications**

*Ronald L. Manger, PhD, serves as the Director of biological products within the Therapeutic Manufacturing Unit. He has been Director of the Biologics Production Facility since 1996. Dr. Manger has a PhD in biomedical science, and has 20 years of experience in related areas including industry positions of manufacture, testing, and quality control of therapeutic products, and as a research scientist with the FDA. Dr. Manger serves on the board of a local college biotechnology training program and has served as a regional science advisor to the FDA while in his current position at the Center.*

*David Shank, serves as the Director* for cellular products within the Therapeutic Manufacturing Unit. He has been director of the Cell Processing Facility since August 2011. Mr. Shank has 25 years of related industry experience in bioprocessing development and FDA regulated human therapeutic production.

*Shelly Heimfeld, PhD, serves as Scientific Director*, a position he has held for the last 13 years. Dr. Heimfeld received his PhD in Developmental Biology, post-doctoral training at Stanford with Irving Weissman, then industry positions at SyStemix and CellPro, Inc before coming to the Center with a focused research effort on Immunology and Hematopoiesis. In his role as Scientific Director he has developed a very strong appreciation for quality control, quality assurance, and compliance with federal regulations. His previous biotech experiences, along with current research and clinical responsibilities, have emphasized the need for teamwork, collaboration, and cooperation to help advance scientific understanding, consistent with the Shared Resources model. Under his leadership as Scientific Director, the TMSR has experienced tremendous growth, supported numerous investigators at the Center, and contributed to a very extensive number of publications.

*Michael Linenberger, MD, serves as Medical Director* for the Therapeutic Manufacturing Unit, as well as the Apheresis unit at the Seattle Cancer Care Alliance (SCCA). He also serves as Medical Director for the National Marrow Donor Program (NDMP) Collection Center activities of the SCCA. Dr. Linenberger has been a clinician and researcher in the Division of Hematology at the UW since 1989. He has extensive experience in hematopoiesis research in both animal and human models. His laboratory work has involved the isolation, expansion, and cryopreservation of hematopoietic and lymphoid cells.
**Clinical/Translational Resources**

**TRANSLATIONAL BIOIMAGING CORE NARRATIVE**

**Introduction**
The Translaional BioImaging Core (TBIC) provides state of the art imaging capabilities, including magnetic resonance imaging (MRI), positron emission tomography (PET), computed tomography (CT), ultrasound, and optical imaging, to support preclinical and clinical research projects conducted by Consortium members. Operations are coordinated between the University of Washington (UW) Department of Radiology and the Fred Hutchinson Cancer Research Center (FHCRC).

During the current project period, the TBIC (formerly the Animal Bio-imaging Core) focused on further development of preclinical imaging capabilities. New instruments such as 14T MRI, research PET-CT, high-intensity focused ultrasound, a large research data server, and an animal angiographic device have been implemented through NIH/NSF Shared Instrumentation grants, institutional support, and industrial collaborations. A MicroPET scanner has been obtained through an NIH Shared Instrumentation grant and has been used already for multiple Consortium projects. A new tabletop MRI unit and a two-photon microscope for in vivo tumor imaging are currently being installed at FHCRC. In addition, the existing high-frequency ultrasound platform for preclinical studies has been upgarded. A proposal for a MicroCT scanner that can be docked with the MicroPET scanner is currently under NIH Shared Instrumentation review. A new Molecular Tracer Laboratory has been established in downtown Seattle. This facility provides radiotracers for PET imaging at multiple sites across institutions, a capability that was not available during the last funding period. In collaboration with the Radiochemistry Laboratory that provides outstanding expertise in radiotracer developments, investigators employed new tracers such as [C-11]clorgyline and [C-11]rosuvastatin. New immunology imaging studies have been initiated in collaboration with UW and FHCRC experts, radiochemistry, and local industries. The technology can be applied widely to new projects that involve biologics in their therapeutic or diagnostic research. Such planning priorities are determined by the TBIC, Steering Committee, and advisory committees as described below ("Administration"). The addition of the MicroPET scanner and the strong relationship with the Molecular Tracer Laboratory directly answer two of the critiques from the 2008 renewal.

To support a large number of clinical translational imaging studies conducted by Consortium members, we have developed an inter-institutional process to review and implement clinical cancer imaging research protocols in collaboration with the Department of Radiology and medical centers (see “New Initiatives”). These activities will be further developed during the new project period.

The TBIC consolidates inter-institutional efforts to support Consortium preclinical and clinical imaging research. The goal of these efforts is to facilitate more translational imaging research among Consortium members and to better support cancer imaging research. Imaging instrumentation and its maintenance are costly, and the Consortium or a single institution cannot acquire or support all imaging resources. The shared resource is not only effective in bringing imaging experts and scientists together, but is also a cost-effective and sustainable way to support cancer imaging research across programs, institutions, and sites.

**Major Services**
The TBIC supports and facilitates imaging research for members of the Cancer Consortium using resources at UW and FHCRC, in collaboration with interdisciplinary imaging research groups specializing in specific imaging technologies. In addition to the specific imaging services described below, TBIC general services include: consultation for research use of imaging resources to achieve specific research goals; feasibility review of imaging protocols proposed by Consortium investigators; help establishing budgets for research imaging protocols; implementation of imaging protocols; support for the execution of imaging experiments; support for image data analysis; and training and education for the use of imaging resources.

**Facilities and Equipment**
The TBIC operates collaboratively with facilities and programs at FHCRC and UW that house major imaging instruments. The imaging resources are housed in four research facilities - FHCRC, UW Health Sciences Building (HSB), UW School of Medicine South Lake Union (SLU), and UW Radiology Tracer Lab (downtown...
Seattle). These facilities are located within 5-15 minutes driving distance from each other. Animal transportation through UW and FHCRC Comparative Medicine is regularly available and used. FHCRC has completed renovation of the imaging area of the vivarium, creating an imaging suite that increases the size of imaging area and allows use of multiple instruments in a large shared area.

Preclinical Research Imaging Equipment, Facility Locations, and current Usage / Capacity

<table>
<thead>
<tr>
<th>Equipment</th>
<th>Facility</th>
<th>Usage / Capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 14T MRI (mouse / rat)</td>
<td>South Lake Union</td>
<td>65%</td>
</tr>
<tr>
<td>- 4.7T MRI (small to medium animal)</td>
<td>Health Sciences Building</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>- 3T MRI (small to large animal)</td>
<td>South Lake Union</td>
<td>60%</td>
</tr>
<tr>
<td>- 3T MRI (small to large animal)</td>
<td>Health Sciences Building</td>
<td>65%</td>
</tr>
<tr>
<td>- Desktop MRI (mouse / rat, low resolution)</td>
<td>FHCRC (operational in 2014)</td>
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</tr>
<tr>
<td>- MicroPET (mouse / rat)</td>
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<td>40%</td>
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<tr>
<td>- Primate PET (medium to large animal)</td>
<td>Health Sciences Building</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>- PET-CT (small to large animal)</td>
<td>Harborview Medical Center</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>- IVIS optical Imager (small animal)</td>
<td>FHCRC</td>
<td>30%</td>
</tr>
<tr>
<td>- Multi Photon microscope (small animal)</td>
<td>FHCRC (operational in 2014)</td>
<td>n/a</td>
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<tr>
<td>- High-intensity focused ultrasound (small to large)</td>
<td>South Lake Union</td>
<td>15%</td>
</tr>
<tr>
<td>- High-frequency ultrasound (small to large animal)</td>
<td>FHCRC</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>- 64-slice CT (small to large animal)</td>
<td>Harborview Medical Center</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>- MicroCT (small animal)</td>
<td>Health Sciences Building (under NIH S10 review)</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Clinical Research Imaging Equipment and Facility Locations (please see 'New Initiatives')

- 3T&1.5T MRI, PET-CT, CT, Nuclear Medicine, ultrasound, radiographs | UW Medical Center (UWMC)
- 3T MRI, PET-CT, CT, Nuclear Medicine, ultrasound, radiographs | Seattle Cancer Care Alliance (SCCA)
- PET-CT, CT, 3T&1.5T MRI, Nuclear Medicine, radiographs | Harborview Medical Center (HMC)

Technologies and Expertise

The TBIC provides various levels of expertise for conducting cancer imaging research. TBIC core members, as well as leaders in collaborating imaging laboratories, have many years of imaging experience. They provide guidance for tasks from day-to-day operations to development of new imaging technologies and grant submissions. Such expertise is provided in the form of consultation, on a project-by-project basis, or through coordinated outreach seminars. Research scientists who are well trained in imaging modalities are available to provide assistance in animal use and human subject applications, protocol implementation, and execution of imaging protocols. Imaging technologists at medical centers who support clinical research imaging are well trained and certified and dedicate their efforts to perform high-quality imaging studies.

Preclinical Research Imaging Resources

Magnetic Resonance Imaging (MRI): The TBIC supports preclinical imaging protocols that use MRI technology at UW South Lake Union, UW Health Sciences Building, and FHCRC (operational in 2014). MRI technology has been used for delineation of tumors, evaluation of tumor biochemistry (such as oxygenation), development of new diagnostic and therapeutic agents, and development of new quantitative imaging protocols. Different types of scanners, owned by UW Department of Radiology and FHCRC, are available for Consortium research. These are 1) 14T MRI; 2) 4.7T MRI; 3) 3T MRI; and 4) desktop MRI (operational in 2014). The service provides standard structural imaging as well as opportunities to develop specific imaging protocols (such as BOLD sequence for tumor hypoxia, diffusion sequence for cancer detection). Animals are transported between facilities that house the scanners, and short-term and long-term animal housing is available at each site.

Positron Emission Tomography (PET) and Radiotracers: Preclinical imaging protocols that use PET and radiotracer technology are available at UW Health Sciences Building and UW Harborview Medical Center. PET technology has been used to assess tumor biochemistry (such as receptor expression, hypoxia, cell proliferation), new molecular probe development for translational cancer research (such as Zr-89 antibody imaging), and new PET imaging technology development (such as high-resolution detectors). Three types of scanners are available for preclinical imaging studies: 1) MicroPET for small animal imaging; 2) Primate PET for medium to large animal imaging; and 3) PET-CT for medium to large animal imaging. To support PET imaging research, two radiotracer production programs are capable of supplying radiotracers for preclinical
research: 1) Radiochemistry laboratory at UW Health Sciences Building and 2) new Molecular Tracer Laboratory in downtown Seattle. The first facility can produce radiotracers labeled with F-18, C-11, and N-13 for use in the Health Sciences Building. The second facility can produce radiotracers labeled with F-18, C-11, Zr-89, and long half-life radioisotopes and can transport these tracers to the UW Health Sciences Building, Harborview Medical Center and other facilities in the greater Seattle area (such as FHCRC and South Lake Union). PET service along with radiochemistry support provides standard imaging services (such as glucose metabolic imaging, cell proliferation imaging, hypoxia imaging) as well as specialized imaging developments (such as tumor receptor imaging, tumor antibody imaging). Currently, [F-18]fluorodeoxyglucose (FDG); [F-18]fluoromisonidazole (FMISO); [F-18] Fluorothymidine (FLT); F-18]fluoroestradiol (FES); [Zr-89] labeled antibodies are available regularly. Animals are transported between facilities, and short-term and long-term animal housing is available for PET imaging.

**IVIS Optical imaging:** Fluorescent and bioluminescent imaging in mice using the IVIS Spectrum instrument is available at the FHCRC Comparative Medicine facility. There are two IVIS devices and one backup device available. Optical imaging links in vitro cell imaging and in vivo tumor model imaging. The devices have been used routinely for the brain cancer imaging program and for material science development of diagnostic and therapeutic probes. The devices are supported through Comparative Medicine.

**Ultrasound Imaging and Intervention:** The TBIC makes available a high-frequency high-resolution ultrasound scanner (VEVO 2100) at FHCRC and high-intensity focused ultrasound (HIFU, Philips) device at South Lake Union. VEVO 2100 has linear array technology and color Doppler mode. VEVO 2100 is currently used to look at early tumor development in pancreatic tumor models, evaluate large tumors in xenograft mouse models, as well as image guided targeted injections and therapies. The HIFU scanner is attached to the 3T MRI that provides structural guidance and temperature measurement for interventional studies. Short-term and long-term animal housing is available at both facilities.

**Computed Tomography:** Computed tomography (CT) for preclinical animal imaging is available. CT is used to visualize tumors and other organs and also to provide structural information to localize functional signals measured by PET. The research PET-CT scanner has a 64-slice CT scanner that is available for dedicated CT imaging at Harborview Medical Center. This scanner has been used for imaging of lungs in dogs following radiation. Animals are transported between facilities. A proposal for acquisition of a MicroCT scanner that is dockable to the MicroPET scanner is currently under NIH Shared Instrumentation Grant review. This scanner will be installed in the MicroPET scanner facility in the Health Sciences Building.

**Multi Photon In Vivo Microscopy:** A Zeiss LSM 7 MP, two-photon laser microscope is currently being installed at the FHCRC facility. This equipment allows real time high resolution optical imaging of tissues in live animals. The device is supported by Comparative Medicine.

**Other Modalities:** A preclinical animal angiography laboratory has been established to provide a service for interventional research. A digital angiographic device is installed in the surgical suite. This has been used for gene therapy development for hepatobiliary cancer and stem cell delivery under fluoroscopy through interventional techniques. This service is operated jointly by UW Radiology and Comparative Medicine at the South Lake Union facility.

**Image Analysis, IT Support, and QA/QC**
In imaging research, imaging is one part of the experiment, but image data analysis often requires a greater amount of time and expertise. When Consortium members propose research projects, TBIC core members and resource core directors discuss with investigators possible image analysis pipelines for individual projects. Three levels of support for image analysis are provided: Level 1: The TBIC provides standard tools and education for users to perform simple region-of-interest analysis, image realignment, statistical analyses, visualization, and other routine image analyses. These are performed in users' laboratories or on workstations within the core facilities. Level 2: For more complex analyses such as tracer kinetic analyses, quantitative image-based mapping, multi-dimensional image registration, parametric image analyses, the TBIC core members establish pipelines in their laboratories and perform image analyses for projects. Level 3: For projects that require development of new techniques, such as unique pulse sequences, new image analysis techniques, and new tracers, the TBIC core members collaborate with Consortium members to investigate
such technologies via collaboration with auxiliary laboratories (below). TBIC core members operate individual laboratories equipped with workstations, general and customized software, and data access capabilities. Numerous in-house software programs are available for specific imaging devices. To support imaging data management, we were successful in obtaining an NIH shared instrumentation grant to purchase a large imaging data server (50TB) which serves as a backbone for preclinical imaging data management. We are in the process of expanding the use of this system to accommodate all imaging research data.

Routine QA/QC and maintenance of preclinical imaging resources are performed by specific resource core directors as required. Members in the Imaging Research Laboratory (below) and medical physicists in the Department of Radiology perform QA/QC of clinical imaging resources in accordance with American College of Radiology (ACR) guideline. Members in the Imaging Research Laboratory also provide specific QA/QC protocols (i.e., phantom imaging and test-retest evaluation) that are required by specific imaging trials. We are currently collaborating with an outside consultant to explore GLP environment for preclinical imaging operations. The extensive level of data and QA/QC support directly addresses one of the 2008 critiques.

Collaborating and Auxiliary Laboratories
The TBIC operations are supported through collaborations with multi-disciplinary research groups and auxiliary laboratories. These laboratories help support imaging research for the Consortium and help develop new imaging technologies. These laboratories reside in the Departments of Radiology, Bioengineering, and Materials Sciences at the University of Washington, and are led by respective leaders in each of the fields.

Radiochemistry / Cyclotron Facility, UW HSB: Radiochemistry facilities contain laboratories devoted to radiochemistry, including a hot lab for radionuclide syntheses, organic chemistry space for precursor production and compound development, and a radiopharmacy. Radionuclide production uses a dedicated cyclotron in the Department of Radiology. The group provides support for radiochemistry work and provides beam time for the production of radiochemicals required for PET imaging studies. The group is led by international leaders in radiochemistry, Kenneth Krohn, PhD and Jeanne Link, PhD. The collaborative relationship between TBIC and the UW Radiochemistry group increases the resources available to support cancer member research.

Imaging Research Laboratory, UW HSB: The Imaging Research Laboratory in the Department of Radiology provides physics expertise in PET, CT, and molecular imaging and image analyses for cancer research across institutions. This group is actively developing high-resolution small animal PET detectors and assisting small animal PET imaging for the Cancer Consortium. This laboratory, which has expertise in image analyses, QA/QC, and provides IT support at both UW and FHCRC, is led by Thomas Lewellen, PhD, Paul Kinahan, PhD, Robert Miyaoka, PhD, Adam Alessio, PhD, and Lawrence MacDonald, PhD.

Diagnostic Imaging Sciences Laboratory and MR Physics Laboratory, UW HSB: This laboratory provides expertise for 3T MR imaging at UW HSB and custom coil production for animal imaging. The laboratory has extensive experience in both animal and human imaging and has helped a large and diverse collection of investigators from UW and FHCRC. This group is led by Kenneth Maravilla, MD. Several animal imaging coils have been developed by Cecil Hayes, PhD, internationally known investigator in MRI coil development, and these coils are available at the following two laboratories as well.

Systems Biology Laboratory, UW SLU and HSB: This laboratory provides expertise for high-resolution MR imaging and MR spectroscopy and has assisted with molecular MR imaging for FHCRC investigators. This group provides animal imaging expertise for both 4.7T and 7T MRI scanners using custom-made coils and pulse sequences in collaboration with the above MR Physics Laboratory. This group is led by Donghoon Lee, PhD, David Marcenik, PhD, and Kevin Conley, PhD.

Vascular Imaging Laboratory, UW SLU: This laboratory provides expertise for 3T MR imaging at UW SLU and assistance with animal imaging research for cancer and stem cell imaging. This laboratory is equipped with extensive image analysis software and provides IT support for imaging data. The group is led by Chun Yuan, PhD, Anna Naumova, PhD, and Vasily Yarnykh, PhD.
Neuroimaging and Biotechnology Laboratory, UW HSB: This laboratory provides animal imaging expertise for both rodents and primates and has an extensive experience in MR and PET imaging, tracer-kinetic modeling, and technology developments including probes and image analysis software. The group is led by Donna Cross, PhD, Satoshi Minoshima, MD, PhD, and John Grierson, PhD.

Optical Imaging Laboratory, UW Bioengineering: This laboratory develops the state-of-the-art optical imaging devices such as optical coherent tomography (OCT) for animal research and provides assistance with optical imaging in conjunction with optical imaging probe development. This group is led by Ricky Wang, PhD.

Material Sciences Laboratory, UW College of Engineering: This laboratory develops imaging probes based on nano-materials and optical dyes. This group has been assisting FHCRC investigators for MRI and optical imaging research and provides expertise in tracer development. This group is led by Miquin Zhang, PhD.

Consultation Service
Since research imaging experiments not only use standard imaging protocols, but also often require customization or development of technology and protocols, the TBIC provides consultation services as needed. The consultation is also critical for investigators who would like to know what imaging modalities address their research questions best. The TBIC provides a web page with contact information as a starting point. General inquires as well as multimodal imaging proposals are reviewed and triaged by the TBIC Director. The consultation requests are reviewed in the TBIC monthly meetings for feasibility, cross-modality capabilities, and proposed resource use. The TBIC core members also act as a liaison to other laboratories and experts within UW and FHCRC. When needed, the TBIC core members refer investigators to UW and FHCRC experts specific to the proposed research protocol (such as a protocol involving new radiotracer development for PET, new pulse sequence development for MRI), and the TBIC core members work with the investigators and experts to implement such new technologies as described above.

Importance to Scientific Programs
In vivo imaging biomarkers have become indispensable biomarkers in cancer research. Imaging can provide pathophysiological findings of cancers, evaluate potential therapeutic targets and its alterations, monitor disease progressions, help cancer drug and therapeutic developments through preclinical studies, proof-of-concept studies and translational studies in human subjects, and eventually diagnostic information in human subjects. As seen in the following examples, the TBIC supports Consortium members at various levels of their research developments from initial proof of concept in animals to clinical trials in humans. During the next project period, we will build on our successful support of preclinical research imaging support (Animal Bioimaging Core) to incorporate clinical research imaging support, which will further facilitate translational imaging research in the Consortium.

In response to one of the 2008 critiques, we initiated new collaborative projects with immunology specialists (Drs. Park and Baird) in Surgery and Laboratory Medicine and have advanced immunoPET technology that can potentially benefit a great number of CCSG investigators. This is in addition to FHCRC immunology experts' projects (Drs. Pagel/Press). We have completed the first Zr-89 labeled antibody imaging in mice which outcome is already in press for journal publication this year.

Examples of Supported Projects
JAMES OLSON, MD, PhD, CANCER BASIC BIOLOGY
*bHLH factors in medulloblastoma genesis and maintenance*

The project is to develop genetically precise mouse models to ‘Avatar’ (patient derived tumor xenograft - PDX) models of medulloblastoma to provide insight into disease pathogenesis and molecular pathways appropriate for therapeutic targeting. Dr. Olson uses 4.7T MRI and 14T MRI to assess therapeutic responses of brain tumors using a longitudinal protocol with and without contrast, to evaluate blood brain barrier permeability, and to monitor treatment responses for a mouse model.


Sunil Hingorani, MD, PhD, Gastrointestinal Cancer
Therapeutic development for pancreatic cancer
Dr. Hingorani studies the molecular and cellular origins of pancreas cancer through the use of genetically engineered mouse models for preclinical studies of disease-specific detection and treatment strategies in the Center for Accelerated Translation in Pancreas Cancer (CATPAC). Optical imaging and ultrasound is mainly used for early detection as well as to track progression. The 14T MRI was mainly used to monitor treatment responses of pancreatic tumors in a transgenic mouse model (KPC model). Dr. Hingorani also uses medical center resources for his human imaging trials.


John Pagel, MD, PhD, Hematologic Malignancies
Therapeutic development for leukemia and lymphoma
Dr. Pagel develops more effective and less toxic curative treatments for leukemia and lymphoma using monoclonal antibodies (such as anti-human (h)CD45 antibody) either alone or in conjugation with drugs, toxins and radioisotopes. Optical imaging using IVIS Spectrum is used to monitor biodistribution over time of injected agents and cell lines in various mouse models. Therapeutic antibodies were labeled with radioisotopes, and in vivo imaging of the biodistribution in animals was performed using molecular imaging techniques. Dr. Pagel also uses medical center resources for his human imaging trials.


Pete Nelson, MD, Bob Vessella, PhD, Prostate Cancer, Jeanne Link, PhD, Women's Cancer MAOA PET imaging of prostate cancer
Targeting the monoamine oxidase A gene (MAOA) for prostate cancer is a novel concept that originated with Dr. Nelson. Their research group has used bioluminescence / biofluorescence imaging as well as high-frequency ultrasound. The investigators developed [C-11]clorgyline and performed MicroPET imaging of LuCap78 xenografts implanted in mice.


Raymond Yeung, MD, Gastrointestinal Cancer
Effects of mTORC1 on glucose metabolism
The goal of this work is to study the effects of mTORC1 on glucose uptake in vivo. The investigators developed two mouse models of liver-specific ablation involving Tsc1 and Pten, whose primary difference lies with the Akt activities. MicroPET imaging was conducted in mice to investigate liver glucose uptake. Dr. Yeung also uses medical center resources for his human imaging trials.


Miqin Zhang, PhD, Hematologic Malignancies
Brain tumor diagnosis and treatment
The project is to develop multi-functional nanoparticles for imaging and therapy for pediatric brain tumors. Chlorotoxin, fluorophore, and radioisotopes were attached to a nanoparticle with an iron oxide core to form a
multifunctional nanoparticle for both imaging and therapy. Biodistribution studies were conducted in tumor bearing mice using MicroPET, MRI, and optical imaging to investigate the targeting and stability of the multifunctional nanoparticle.


Joo Ha Hwang, MD, PhD, Gastrointestinal Cancer
Pancreatic cancer treatment using high intensity focused ultrasound (HIFU)
This project is to develop an effective treatment approach with HIFU. KPC mouse model was used to develop MR methods to identify tumors and monitor treatment response. The investigators performed high resolution MRI at 14T for a transgenic mouse model (KPC model) of pancreatic tumor to identify pancreatic tumor and to treat the tumor with HIFU at 3T.


James Park, MD, Gastrointestinal Cancer, Satoshi Minoshima, MD, PhD, unaligned
ImmunoPET for hepatocellular carcinoma
This study was to use newly developed Zr-89 labeled antibodies targeting glypican-3 (GPC3), a proteoglycan implicated in promotion of cell growth that is overexpressed in most hepatocellular carcinoma, to detect tumors in xenograft rodent models using MicroPET. Antibodies were developed by the Consortium member, Dr. Park in the Department of Surgery, and a radiolabeling method in Dr. Minoshima’s laboratory. In vitro binding and competition assays of radiolabeled antibodies have confirmed affinity of radiolabeled antibodies to the target. In vivo imaging confirmed displaceable ligand binding to the implanted tumor. This is the first Zr-89 labeled antibody imaging studies conducted at UW and FHCRC, and the technique can be applied to other types of antibodies. Dr. Minoshima is currently developing Zr-89 labeled antibody targeting prostate-specific membrane antigen (PSMA) and Zr-89 labeled aptamer for epidermal growth factor receptor (EGFR).


Savannah Partridge, PhD, Women’s Cancer, Satoshi Minoshima, MD, PhD, Radiology, Alanna Ruddell, PhD, Cancer Basic Biology
MRI of lymphatic system and Breast Cancer
This study is to assess the utility of a novel lipophilic nanoparticle gadolinium contrast for characterization of tumor-induced alterations in lymph drainage through lymph nodes that could help to accurately identify tumor-drainage lymph nodes and also assess metastatic potential. Comparison of conventional low molecular weight and nanoparticle gadolinium contrast for 3T MRI lymphography in mice developing melanoma demonstrated that both contrasts are useful for these purposes. The nanoparticle contrast was found to be most useful for analysis of tumor-induced alterations of lymph node architecture, while the low molecular weight contrast was more useful for analysis of tumor-induced lymph flow. The mouse experiments use the 14T and 3T MRI suites at SLU, while the human studies will use the 3T MRI suites at SLU and at the SCCA.

Cost Effectiveness
One major challenge for imaging research is the cost to purchase, install, and maintain expensive imaging instruments for cancer research projects. Although the Consortium research is conducted at multiple sites and institutions, it is not possible to duplicate all imaging devices and operations redundantly at each site. Therefore, major instruments in the TBIC are sited relative to the demands, and subjects are transported between sites for specific imaging procedures. Also, these instruments are shared for multiple research purposes to mitigate excessive cost for the Consortium and to sustain financial stability. This shared resource model across programs, sites, and institutions in the TBIC is a cost effective way to provide the broadest array of imaging resources to the Consortium investigators, while not inflating the budget for Consortium research.

UW and FHCRC collectively own a large number of imaging resources, however, it was difficult for individual Consortium members to know about all imaging resources available within the system and to employ appropriate imaging technology for their research projects. There were also imaging devices that would be difficult to be implemented by a single institution due to cost (i.e., purchase price and service contracts) and a limited user base. In vivo imaging in particular using high-end instrumentation is expensive, and often investigators use such technologies in a limited number of subjects for the investigational and proof-of-concept studies. Although such imaging studies provide precious and indispensable information for their research, the volume of cancer imaging research from a single program cannot fill the capacity of the imaging device. Therefore, it is not financially possible for the Consortium or a single institution to own and support a wide array of imaging devices. A shared use model of imaging resources (and collaborative expertise) as established in the TBIC is a cost-effective way to make imaging resources available to the Consortium members regardless of the volume of use. The TBIC has been a catalyst to create interdisciplinary support for imaging research and advance imaging research and necessary resources for the Consortium. A new initiative of clinical research imaging support will permit the same Consortium members to tap into both animal and human imaging resources, and the TBIC will be able to coordinate such support with a goal to facilitate translational imaging research in the Consortium.

Use of Services

<table>
<thead>
<tr>
<th>Service</th>
<th>Total Users</th>
<th>Peer Reviewed (%)</th>
<th>Non-Peer Reviewed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging</td>
<td>49</td>
<td>29 (59.2%)</td>
<td>20 (40.8%)</td>
</tr>
</tbody>
</table>

Management Structure, Policies and Operations

Administration
Satoshi Minoshima, MD, PhD, the TBIC Director and Vice Chair for Research, UW Radiology oversees the UW based TBIC operations in collaboration with modality leaders (preclinical) and medical center imaging services (clinical) and in consultation with Paul Woloshin, PhD MBA, Consortium Director for Shared Resources. Rajesh Uthamanthil, DMV, Ph.D. manages the FHCRC-based imaging instruments and works jointly with Dr. Minoshima in coordinating inter-institutional imaging programs and animal transport. Drs. Minoshima and Uthamanthil meet at least quarterly to discuss operational and strategic issues, including potential joint grant applications, anticipated changes in resource usage and incorporation of new technologies.

Each TBIC imaging resource is managed financially by the respective collaborating institution (FHCRC and UW Radiology), and the TBIC operations for the Consortium cancer imaging research are implemented through operations by modality leaders (preclinical studies) and medical center service directors (clinical studies) through the established administrative processes and standing operational meetings.

Oversight of the shared resources is provided by a faculty advisory committee. Advisory committees are responsible for reviewing shared resource operation on an annual basis, providing review of user fee changes, evaluating annual capital budget requests and providing guidance on future goals and objectives. Committee members include Sunil Hingorani, MD, PhD and Raymond Yeung, MD (Gastrointestinal Cancer), John Pagel, MD, PhD (Hematologic Malignancies), Laura Chow, MD (Unaligned), Mary Nora Disis, MD (Immunology and Vaccine Development, Women’s Cancer), and Edus Houston Warren, MD, PhD (Immunology and Vaccine
The Comparative Medicine shared resource advisory committee also incorporates imaging issues into their recommendations, and Drs. Minoshima and Uthamanthil stay informed about the discussions at each meeting through their regular meetings. The Consortium’s Scientific Steering Committee ensures that this and other Consortium resources are aligned with the Consortium’s strategic goals and its continued value to the Cancer Center.

The TBIC Director organizes monthly meetings at medical centers with imaging service directors to review clinical research studies.

**Access and Usage Policy**
Services are available to all members of the Consortium, on a first-come, first-served basis. When conflicts arise, priorities are voted in the TBIC monthly meeting.

**Protocol Review**
Proposed protocols are received by the imaging service staff and reviewed by the imaging service director for each modality. As described in the usage policy, it is based on the first-come-first-served scheduling. However, when scheduling conflicts occur, federally funded projects have priority. Currently, we do not support non-funded projects. Research staff members who operate high-end instruments (MRI and PET) in the imaging services are all specialized in their modalities and have a minimum 5 years of experiences. For low-end instruments (such as ultrasound), the TBIC staff provide education to research staff prior to their usage of the instrument if it is required by the user. This process directly answers one of the 2008 critiques. Support is provided to external users as time permits.

**Usage Policies and Billing**
Standardized service request forms provide authorization of service and requested information for each respective transaction. Services are billed upon completion and information is entered into a Shared Resource billing system for FHCRC resources, Cost Center system for UW Radiology owned resources, and CRBB billing for clinical resources, which provides the ability to track resource use at the project level by activity. Ongoing review is conducted to monitor activity levels and observe usage trends to ensure appropriate adjustments are made in operations to adapt to changing demand. Usage is assessed and summary reports are develop by institution, by investigator, and by program for each service provided by the resource. Ongoing evaluation of resource operations is conducted through implementation of appropriate analyses, benchmarking studies, surveys and other tools.

Costs are charged directly to applicable awards based on actual usage. Rates are based on projected operating costs net of CCSG and institutional support for FHCRC resources, operational costs net for UW Radiology owned resources, and research pricing established by medical centers for clinical resources. Rate schedules are re-evaluated and revised as required on an annual basis. External user fees reflect the full cost (both direct and indirect) of rendering service according to the most recent rate revision. No benefit of institutional or federal funding received by the resource is considered in the establishment of outside rates.

**Education and Outreach**
Users are kept up to date on changing technologies and services offered by the facility through the Consortium website, Shared Resource Newsletter, and special memo distributions. The TBIC has organized several educational imaging resource seminars during the past funding cycle. The TBIC members also participated in individual Consortium Program meetings to discuss potential use of imaging in their specific projects. The TBIC will continue similar educational activities and will also partner with the local CTSA (the Institute of Translational Health Science – “ITHS”) to extend the reach of these activities. As many instruments in the TBIC operated by the Department of Radiology have been used for ITHS projects, it is anticipated that the Resource will play an ongoing and expanded role in support of translational research activities. Staff development is ensured through in-house training sessions and discussions, hands-on experience, seminars, and technical workshops.

**Priorities and New Initiatives**

**Priorities**
The priorities of the TBIC operations are as follows:
- Meet needs and requests for imaging services for Consortium members and NCI- and other peer reviewed research projects
- Facilitate translational cancer research through preclinical and clinical imaging services
- Support new imaging resources, such as new desktop MRI that can benefit Consortium research
- Develop new preclinical and clinical imaging technologies that are critical for specific projects
- Monitor service efficiencies and continue to improve processes and workflow across institutions
- Maintain financial and operational sustainability through the shared model and collaborations.

**New Initiatives**

**Support for Solid Tumor Translational Research Program (STTR).** A multi-institutional, collaborative STTR initiative is currently being established by Dr. Eric Holland, a neurosurgeon and laboratory brain cancer researcher recruited to our center in 2013. This effort will facilitate multidisciplinary collaborations among genome scientists, computational biologists, researchers developing novel therapy platforms, imagers and clinicians. This initiative is expected to increase use of imaging resources for both preclinical and clinical studies. New preclinical imaging resources (desktop MRI, multi Photon microscope) have been purchased to support this initiative at FHCRC, and the TBIC will provide technical support and educational efforts to help operate these devices. To support clinical translational imaging research, ‘Clinical Translation Imaging Research’ (below) will be supported by the TBIC in collaboration with the Department of Radiology.

**Support for Clinical Translational Imaging Research**
The Department of Radiology has established a collaborative process to consolidate the clinical imaging resources available at the UW and FHCRC to conduct both investigational research and clinical trials involving human subjects. In collaboration with Radiology, the TBIC will advance clinical imaging support for Consortium members to facilitate translational research. A new departmental agreement now permits up to 10% of each scanner’s service for funded research projects (up to 30% for PET-CT at UWMC and 80% at HMC). During the last academic year, 33 Consortium members applied for research use of the medical center resources. We will support the following processes in collaboration with Radiology for Consortium members who wish to access clinical imaging resources for their funded projects.

**Feasibility Review:** The TBIC through the Department of Radiology provides feasibility review of all cancer imaging protocols that propose to use imaging resources at the three medical centers: UW Medical Center, Seattle Cancer Care Alliance, and Harborview Medical Center. The TBIC collaborates with UW School of Medicine Clinical Research Budget and Billing to establish a detailed billing grid for each project. If special imaging protocols are proposed, we discuss with the director of imaging services feasibility of implementing such protocols in the medical center and develop an appropriate billing code. **Implementation and Execution:** Research using standard imaging protocols (such as some clinical trials) requires only protocol registration. Unique protocols are implemented in collaboration with the service director and technologists. Research imaging studies are conducted by trained and qualified technologists in each imaging service. The TBIC Director and collaborating Radiology staff members assist regulatory applications, communicate with respective imaging modality services, and assist implementation of specialized imaging protocols, whenever necessary, for Consortium members. **Translational Research Implementation Group (TRIG):** Some unique research imaging protocols require additional resources, compliance and regulatory review, and appropriate billing setup. The TRIG was created in 2013 to systematically address these issues in Radiology and facilitate implementation of translational imaging research protocols in the medical centers. The TBIC will collaborate with the group for clinical cancer imaging research. An on-line application process for the translational imaging research protocols in medical centers is currently being developed.

**Personnel**

**Key Staff Qualifications**

**Satoshi Minoshima MD PhD,** the **TBIC Director,** oversees the general operations of the resource. Dr. Minoshima is Professor and Vice Chair for Research, Department of Radiology, Adjunct Professor of Bioengineering, University of Washington, and affiliated investigator at the Washington National Primate Research Center. Dr. Minoshima has been facilitating multi-disciplinary imaging research on the UW and FHCRC campuses over 6 years as the director of the Consortium ABIC and the director of imaging research overseeing research administration in the department and at medical centers. Dr. Minoshima has 25 years of hands-on experience in imaging research concerning neurodegenerative disorders, cancer, and imaging
physics, including PET and MR imaging in animals and humans, computer image analysis, Alzheimer's disease, stem cell imaging, development of MR contrast agents, imaging of lymphatics, and labeled antibody PET imaging for cancer as well as research administration in the Department of Radiology. His current research projects include new PET imaging for an apoptosis inhibitor suppressant in lung cancer in humans, preclinical PET antibody imaging for prostate cancer, and preclinical PET aptamer imaging for EGFR-expressing tumors. He acts as a liaison to many core research laboratories within UW and FHCRC taking full advantage of local expertise to assist Consortium research. Dr. Minoshima has also established a collaborative model to support clinical cancer imaging research at medical centers through his initiatives of review and implementation of translational cancer imaging research. Dr. Minoshima serves as the Chair of the Molecular Imaging Committee for the Radiological Society of North America (RSNA) and the Chair of the Scientific Program Committee for the Society of Nuclear Medicine and Molecular Imaging (SNMMI).

**Rajesh Uthamanthil DVM, Ph.D.** is the Director of Comparative Medicine at FHCRC and Attending Veterinarian. Dr. Uthamanthil is a veterinarian with a post graduate degree (MVSc) in veterinary surgery and radiology. Dr. Uthamanthil was an Associate Professor in the Department of Veterinary Medicine and Surgery at MD Anderson Cancer Center. He has a doctoral degree in comparative biosciences from the University of Wisconsin-Madison and a postdoctoral fellowship in bioengineering at Rice University. Dr. Uthamanthil has lengthy experience using animal models of cancer and is interested in small animal imaging. He supports translational studies as a collaborator, researcher and animal care program administrator.

**Robert Miyaoka PhD, Research Professor, Department of Radiology, University of Washington.** Dr. Miyaoka is an imaging physicist whose research focus is development and implementation of PET and CT devices. Dr. Miyaoka leads support for applications of PET and micro PET in cancer research projects. Dr. Miyaoka is internationally recognized in the field and successively funded by federal and non-federal grants for his work of PET imaging. He has played a critical role for several new projects in the Consortium research including the most recent Zr-89 labeled antibody PET imaging of hepatocellular carcinoma and implementation of clinical PET imaging protocols for cancer projects. He also acts as a liaison to the Imaging Research Laboratory and Radiochemistry Program to facilitate image analysis and radiochemistry support.

**Donghoon Lee PhD, Research Associate Professor, Department of Radiology, University of Washington.** Dr. Lee is an MRI and MRS expert whose research focus is development of MRI protocols and applications of molecular MRI technology in cancer and other medical conditions. Dr. Lee is also an expert in computational image analysis. Dr. Lee is leading the high-tesla MRI for cancer detection and quantitative MR imaging and contributed significantly for the Consortium research including pancreatic cancer and brain tumor projects.

**Ruikang Wang, PhD, Professor of Bioengineering and Ophthalmology, University of Washington.** He was a chair professor in Biomedical Optics with Cranfield University, England, where he created and directed the Biophotonics and Imaging Laboratory. In 2005, he joined Oregon Health and Science University, Oregon, where he was the Director of Biophotonics and Imaging Laboratory. He is known internationally as a leader in optical imaging, biophotonics, optical coherence tomography, and optical microangiography. He actively supports applications of optical imaging in neurology, ophthalmology, and cancer.

**Charles Frevert, DVM, ScD, Associate Professor of Comparative Medicine, University of Washington,** has been using in vitro imaging and in vivo imaging to elucidate early response of the immune system to viral and bacterial infections. He has developed expertise in imaging and helped establish cell imaging program at the South Lake Union campus and animal angiography laboratory for the Consortium research through the TBIC. He is currently helping the arrangement of animal transport for the TBIC and working with UW Comparative Medicine to secure additional imaging laboratory space at the UW Health Sciences Building that will be highly valuable for the Consortium TBIC operations.
Part I: Clinical Protocol and Data Management: Clinical Research Support (CRS)

Glossary: Consortium Clinical Research Support (CRS); Data Safety and Monitoring Plans (DSMP); Data Safety and Monitoring Committee (DSMC); Protocol Review and Monitoring System (PRMS); Investigational New Drug (IND); Clinical Trials Reporting Program (CTRP); Clinical Research Oversight Committee (CROC).

Overview. The Consortium Clinical Research Support (CRS) Office serves as the Clinical Protocol and Data Management core. CRS facilitates the efficient review, approval, and implementation of cancer clinical research throughout the cancer center. Its role is to assure high quality, regulatory compliant clinical research through day-to-day management of clinical research support activities, coordination of clinical research committees for protocol review and monitoring, coordination of training programs, delivery of centralized services for clinical trial implementation, development of standard operating procedures and templates, management of quality control and assurance activities, and coordination of data collection and reporting.

To strengthen operational efficiency, Consortium Senior Leadership reorganized and consolidated the former clinical research core resources (Research Trials Office Administration, Clinical Informatics, and the Clinical Trials Support Office) under one senior administrator during the project period. All functions of the previous Clinical Trials Support Office, including education, research monitoring and auditing, and protocol submission support have been consolidated into CRS. CRS services do not duplicate the work of research study teams, which focus on direct daily conduct of trials. Instead, CRS services are complementary and highly specialized, enabling the conduct of clinical research in a more timely, effective and efficient manner.

CRS functions that support Consortium PIs include the following:

1. Assistance with protocol development and preparation of packet submissions;
2. Review of protocol-specific Data Safety and Monitoring Plans (DSMP) before submission;
3. Management of the protocol review process, and the Consortium and study-specific Data Safety and Monitoring Committees (DSMC).
4. Assistance in preparing responses to the Protocol Review and Monitoring System (PRMS) and Institutional Review Board (IRB);
5. Centralized protocol activation and support throughout the protocol life cycle;
6. Training and education for clinical research;
7. Monitoring and auditing to ensure the safety of study participants;
8. Coordination with institutional budgeting and contracting offices;
9. Maintenance of a central repository of Consortium protocols, consent forms, and other documents;
10. Management of the database containing protocol status, accruals and other data;
11. Dissemination of changes in clinical research regulations;
12. Assistance in addressing compliance vulnerabilities;
13. Support for Investigational New Drug (IND) submissions, FDA reporting, and external audit preparation;
14. Incremental clinical research staffing on a fee for service basis; and
15. Oversight of Clinical Trials Reporting Program (CTRP) and clinicaltrials.gov submissions.

Details are provided below in the Services section.

Response to 2008 review.

1. The reviewers expressed concern that CRS (formerly the Research Trials Office/RTO) did not service all oncology specialties and that solid tumor researchers were underserved. CRS now oversees all cancer-related clinical trials in the Consortium.

2. Reviewers encouraged broader usage of the Clinical Trials Support Office and implementation of a Clinical Trials Management System. All functions of this office are now in CRS. During the project period, Senior Leaders assessed the previous Clinical Trials Support Office and found that providing centralized clinical trials support staff was not cost effective or efficient for researchers. Improved service is now provided through a distributed system of coordinators with centralized training, monitoring, auditing, and enforcement of Consortium policies and procedures. CRS has conducted an initial analysis of Clinical Trials Management Systems (CTMS) and contract negotiations are ongoing.

3. Increased physician and administrative leadership were strongly recommended. A strong leadership team has been established for clinical research. Paul Martin, MD, was appointed Medical Director and commits 40% to both CPDM and PRMS, in contrast to the previous Medical Director, who contributed 10% effort. Dr. Martin
is also a leader in the UW-based Clinical and Translational Science Award (CTSA) program, linking these clinical research efforts to better leverage the support and training activities of both programs. Dr. Ulrich Mueller PhD, the FHCRC Vice President for Technology Transfer and Clinical Research Support, was appointed Consortium Director of Clinical Research Support. As such, he provides administrative and operational oversight for CRS and ensures constant communication and collaboration among executive leadership at Consortium institutions. Drs. Mueller and Martin recruited a seasoned administrator to serve as Associate Director for Clinical Research Support, Ms. Kristi Stiffler, who has the requisite program development, organizational and technical skills and knowledge to provide day-to-day management of the service. Fred Appelbaum, MD, is the senior leader for Clinical Research for the Consortium and was recently promoted to Deputy Director. The Clinical Research Oversight Committee (described below) provides additional physician input and leadership.

4. Leadership to improve recruitment to solid tumor clinical trials was recommended. To strengthen clinical research in solid tumors, Dr. Eric Holland, Consortium Associate Director for Solid Tumor Translational Research, was recruited to our center in 2013 and is actively building Consortium-wide, adult solid tumor multidisciplinary clinical research teams. In addition to his Consortium role, Dr. Holland has senior leadership positions at FHCRC and UW.

**Organization.** The faculty leader for CRS is Medical Director Paul Martin, MD (Figure 1). Dr. Martin is an experienced clinical investigator in hematopoietic cell transplantation. The Associate Director of CRS, Kristi Stiffler, has 10+ years of experience in oncology clinical research administration. Most recently, she served as Associate Administrator of the Clinical Research Division at FHCRC. Ms. Stiffler reports to Ulrich Mueller, PhD, Director of Clinical Research Support, who provides operational and administrative supervision and direct communication with Consortium Leadership. CRS staff members are organized into four interactive divisions:

1) Study Implementation Support (9 FTEs), 2) Quality and Compliance (7 FTEs plus contractors), 3) Study Support Services (5 FTEs), and 4) Data Management and Reporting (6 FTEs). An organizational chart of these functions is provided in Appendix 1.

Deputy Director Appelbaum meets at least weekly with Director Corey, which provides ample opportunity to discuss CPDM and PRMS, and Drs. Mueller and Martin meet with Drs. Appelbaum and Corey monthly.

Each partner institution is responsible for directing the day-to-day activities of staff that support faculty in conduct of clinical trials in accordance with Consortium policies and practice standards. The clinical research staff based at the FHCRC is organized into research groups collectively overseen by a research manager who has a direct reporting line to Ms. Stiffler. Clinical research staff employed at UW is organized into disease-specific groups collectively overseen by a clinical research manager who meets weekly with Ms. Stiffler to discuss issues and review staffing. Ms. Stiffler attends the UW monthly clinical research manager meeting, where issues and changes in Consortium clinical research policy are reviewed. A coordinator and nurse with a joint Consortium/Children’s reporting structure support Consortium trials involving pediatric subjects conducted at Seattle Children’s. Ms. Stiffler meets regularly with the Children’s pediatric cancer research manager.

**Figure 1: Clinical Research Support Organization**

![Clinical Research Support Organization](image-url)
Clinical Research Oversight Committee (CROC). CROC oversees all aspects of clinical research, ensures compliance with all regulations, and approves and enforces Consortium policies and procedures. Both CRS and the DSMC can escalate safety and compliance issues to this committee. Dr. Appelbaum chairs the committee, which includes FHCRC Sr. VP for Clinical Research, UW Head of the Division of Medical Oncology, Consortium Associate Director for Solid Tumor Research, Children’s Associate Division Chief for Hematology/Oncology, Medical Director, and 1-2 Consortium members with clinical research programs. The Current committee roster is included in Appendix 2. CROC has a standing quarterly meeting and the committee may also be called upon for ad hoc meetings if needed.

CRS Operational Advisory Committee. The CRS director has formed a team of lead clinical research faculty and staff to provide strategic guidance, feedback and support to CRS. Members identify areas for improvement, provide input on process improvement efforts and initiatives to decrease activation time as well as provide feedback on existing and proposed CRS operations. The group facilitates communication, sharing of ideas, and changes that benefit the clinical research community.

Location. The CRS office is located in the Minor Building and has 8,500 nsf of space. This is an easily accessible, convenient location with ample space for growth. The office is just a few-minute walk to the SCCA, where most clinical research is performed. A shuttle between the FHCRC/SCCA, UW Medical Center, UW South Lake Union, and Children’s Hospital operates throughout the workday.

Volume metrics. In FY 2013, 411 therapeutic trials and 75 non-therapeutic interventional trials were open, as compared with 347 and 62 in 2008 (20% increase in therapeutic trials, Table 1). Of the interventional trials, 37% were investigator-initiated, 24% were National Cooperative Group, and 38% were Industry. Distribution of trials by phase is shown in Table 1. Between 10/1/12 and 9/30/13, the Consortium reported 4181 newly treated patients and had 961 (23%) local enrollments in therapeutic trials (Figure 2). The CRS manages approximately 10-15 new IND applications per year. Nearly 50 INDs held by 12 FHCRC and 14 UW-based investigators are currently active. Internal monitoring and auditing conducted 168 monitoring and auditing visits and provided oversight for 40-45 for investigator-initiated protocols per year during the project period. During the same timeframe, CRS has sponsored 40-50 training programs or classes per year.

Impact. Since CRS directly manages Consortium training, protocol submission through activation, protocol and consent form control, and provides other critical support for clinical trials, its impact to the Consortium’s research base is exceptionally strong, and all clinical investigators and study teams utilize its services on an everyday basis through the life of a study. This impact has increased over the project period (Table 2).

<table>
<thead>
<tr>
<th>Phase</th>
<th>FY08</th>
<th>FY13</th>
<th>Increase (%)</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>49</td>
<td>80</td>
<td>63</td>
</tr>
<tr>
<td>I/II</td>
<td>32</td>
<td>43</td>
<td>34</td>
</tr>
<tr>
<td>II</td>
<td>160</td>
<td>162</td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>96</td>
<td>112</td>
<td>17</td>
</tr>
<tr>
<td>Total*</td>
<td>347</td>
<td>411</td>
<td>18</td>
</tr>
</tbody>
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*pilot and other phases included in total

Figure 2: Therapeutic Enrollments

![Figure 2: Therapeutic Enrollments](image-url)
communication to study teams as part of ongoing efforts to further reduce turnaround time.

As a result of the improvements made to date, a protocol submission packet that is deemed complete will be assigned an SRC review date within approximately 5 business days (one meeting every week).

The time for sending an SRC response letter to the PI ranges from 2 to 5 business days. Should a PI need to respond to criticisms from the SRC, reviewers are given a maximum of 5 business days to complete their review of the PI’s response. Once reviewers approve the PI’s changes, the PI is notified on the same day. The CRS facilitates IRB submission using the same protocol packet application. Time from SRC submission to first Consortium IRB meeting is an average of 32 days, result letters are sent to the PI in 24hrs, and details of required modifications are sent within 5 days.

Since Dr. Martin and Ms. Stiffler’s appointments, a number of strategies have been employed to reduce PRMS turnaround time and streamline processes. These include changes in the SRC meeting structure that allow for one meeting per week, regardless of the scientific nature of the protocol (see PRMS section), development of a pre-review prioritization process to enhance the quality of submitted protocols and eliminate protocols of low scientific merit, appointment of highly qualified scientific and administrative leaders to manage the SRC more effectively, and the development of forms, policies and document management systems to ease reviewer and PI burden and to facilitate timely communication and access to documents. A protocol facilitator position has been added within the CRS to assist faculty in the preparation and submission of protocols and to assist in responding to SRC and IRB critiques. Many of these activities are further described in the PRMS section.

**Additional Improvements.** In 2010, an independent consultant engaged to review CRS made several recommendations. Consortium Leadership responded, making the following improvements:

1) As described above, a seasoned Medical Director has been appointed who devotes 40% effort to the role, improving physician leadership. Dr. Paul Martin has taken an active role in developing and improving CRS and the PRMS.

2) Research and modality groups have been developed to conduct pre-reviews and prioritize protocols.

3) The clinical IT group was moved within CRS, which now sets priorities (Figure 1). The group has introduced several IT tools, as described below. One example is eReview, which enables SRC reviewers to access protocol documents and complete their evaluations online. While a commercial CTMS was to be implemented during the project period, we delayed deployment until the new team was in place.

4) The CRS Operations Advisory Committee was charged with increasing services to PIs and reducing turnaround time. Analysis by an external consultant led to the creation of several new positions within the office. These positions include a medical writer, protocol submission specialist, study activation manager, communications coordinator, and clinical trials budget specialist.

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**Table 2: CRS volume**

<table>
<thead>
<tr>
<th></th>
<th>FY2011</th>
<th>FY2013</th>
<th>% Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Studies Managed</td>
<td>830</td>
<td>1168</td>
<td>40</td>
</tr>
<tr>
<td>Total Investigators</td>
<td>228</td>
<td>236</td>
<td>8</td>
</tr>
<tr>
<td>New Applications</td>
<td>133</td>
<td>206</td>
<td>54</td>
</tr>
<tr>
<td>Modifications</td>
<td>676</td>
<td>842</td>
<td>20</td>
</tr>
<tr>
<td>Renewals</td>
<td>562</td>
<td>764</td>
<td>36</td>
</tr>
</tbody>
</table>

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**Table 3: Protocol turn around metrics (80% of trials)**

<table>
<thead>
<tr>
<th></th>
<th>Submission to SRC approval</th>
<th>Time to WIRB approval</th>
<th>Time to CC IRB approval</th>
<th>Time to activation</th>
</tr>
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<tbody>
<tr>
<td>Average</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FY10</td>
<td>32</td>
<td>93</td>
<td>106</td>
<td>154</td>
</tr>
<tr>
<td>FY11</td>
<td>29</td>
<td>126</td>
<td>133</td>
<td>135</td>
</tr>
<tr>
<td>FY12</td>
<td>31</td>
<td>120</td>
<td>136</td>
<td>145</td>
</tr>
<tr>
<td>FY13</td>
<td>26</td>
<td>106</td>
<td>102</td>
<td>110</td>
</tr>
</tbody>
</table>
5) Director Corey placed contracting services for FHCRC under the CRS, better integrating this component into the study activation process and improving time to completion. The UW and Children’s provide contract services for studies based at those institutions.

6) To enhance staff skill levels and minimize risk, a full-time trainer position has been approved, with recruitment underway. This individual will implement a strategic plan that was developed with the support of a training consultant who evaluated our program during the past year.

7) The IND service has been expanded to include a review of all investigator-initiated protocols before submission. INDs continue to be managed centrally with the use of a CRS database. CRS staff are available to assist PIs in fulfilling their regulatory requirements. The need for this service expansion is evident from the increasing number of new INDs, from 1 in 2008 to 16 in 2011, 13 in 2012 and 11 in 2013 as of October.

8) Consortium Leaders at Seattle Children’s have improved pediatric budgeting, billing compliance, staff on-boarding and IRB coordination. A Seattle Children’s-based research coordinator and nurse are responsible for helping Consortium teams access the latest protocols, coordinating specimen acquisition and distribution, and addressing other barriers in real time. The ultimate goal of this program is to increase pediatric accrual to Consortium studies.

9) Processes have been streamlined to reduce faculty burden and study team administrative burden. Consortium standards, forms, and tools have been created. A consultant was engaged to help identify additional strategies for improving clinical trials operations.

10) The PDMC function and name has been changed to reflect its function as the institutional DSMC, and a Compliance Sub-committee of the DSMC has been formed to specifically review monitoring and audit reports for compliance issues.

11) The requirement for a Data and Safety Monitoring Plan for investigator-initiated protocols has been clarified and incorporated into relevant policies and procedures. The CRS now performs a detailed review of the DSMP before approving the investigator-initiated protocol for PRMS review.

**Services.** The services provided by the CRS are described below, in order of the protocol life cycle.

**Study Activation**

**Protocol development.** With the support of the study team, the PI is accountable for preparing the protocol and submission packet. As noted above, a CRS medical writer, protocol submission specialist, and regulatory affairs associate are available to assist in writing or editing protocols, application materials, and consent forms. CRS provides templates, tools, including eligibility checklists, and best practice guidance to ensure that protocols are correctly prepared in an efficient manner.

**Pre-review.** All protocols undergo a pre-review by Research Groups prior to submission. The PI submits the protocol to the appropriate disease research group directly. The research group determines whether the protocol may be submitted to CRS, based on established criteria. The group’s written review and approval must accompany the packet when it is submitted.

**Packet review.** The CRS (protocol review coordinator) assesses the protocol packet for quality and completion. This includes a review of the DSM plan and regulatory components by CRS Quality and Compliance. Once any outstanding issues are resolved, the packet is deemed complete and is formally submitted to the SRC via the PRMS committee coordinator.

**PRMS review.** The PRMS coordinator confirms that the packet is ready for PRMS review, including receipt of the Research Group review and approval, and logs the protocol into the PRMS database (PIRO). The committee coordinator works with the SRC chair to select reviewers. The coordinator prepares the SRC agenda, coordinates the meeting, records minutes, and prepares and distributes the result letter describing the decision of the SRC to the PI.

**IRB review.** All cancer protocols are reviewed by the Consortium’s IRB (CC IRB), with the exception of UW industry trials, which may be reviewed by Western IRB, and trials with enrollment limited to children, which are reviewed by the Seattle Children’s IRB. Phase III NCI cooperative group studies are reviewed by the NCI IRB. Approval is contingent on funding source verification, including a final signed contract for industry-sponsored trials. After the protocol is approved by the IRB, CRS provides PIs the approved packet and version-controlled documents and regulatory support throughout the life of the study.
Regulatory review. For investigator initiated trials, the CRS Quality and Compliance team assures that FDA requirements are fulfilled and that the DSMP is appropriate and consistent with the Consortium DSMP. The team also provides guidance on regulatory matters at any time.

Financial review. The disease groups perform an initial financial feasibility review. The CRS clinical trial budget specialist may assist study teams during the initial financial review and budgeting process. A Clinical Trial Activity Summary (CTAS) is developed for every Consortium clinical trial; this document is reviewed by each of the clinical sites of practice and is used to provide study-specific pricing. The CTAS is maintained with the protocol throughout the life of the study and document controlled by CRS. This tool helps to standardize the budgeting process across the institutions.

Contracting. CRS performs contracting functions for FH protocols. The activation manager oversees contract services to ensure that these activities synchronize with SRC and IRB reviews. The UW Office of Sponsored Projects and Children’s Office of Sponsored Research provide contracting services studies for based at their institutions. Studies are not approved and CRS does not release documents until a final contract is in place.

Activation oversight. The study activation manager oversees the protocol submission and review processes including the packet review, PRMS review, budget support and FH contracting as well as the receipt and release of final documents when a study is IRB approved and activated. Dedicated oversight of the activation process ensures that studies move through the activation process efficiently and helps to continuously identify areas of improvement in the system. While the SRC and IRB are reviewing the protocol, the CRS study activation manager seeks to facilitate prompt action in order to reduce time to activation, acknowledging that the investigator team is accountable for many delays. For example, she may provide guidance in preparing documents or responses to SRC/IRB and helping to resolve issues that could delay activation, as identified in operational reviews.

Activation/enrollment. CRS activates enrollment after IRB approval is confirmed, and after a budget and contract are executed and operational reviews have been resolved. Activation is achieved when the CRS posts protocol documents on the online database, FYI, where the PI, study teams and clinic staff can access the current documents, including consent forms.

Trial registration. CRS registers newly activated clinical trials with NCI CTRP. This registration includes all Data Table 4-defined interventional clinical trials, including externally peer-reviewed, institutional, and industry trials that were open to accrual as of January 1, 2009 or later. CRS also submits trial amendments and updates within the guidelines specified. CRS communicates with NCI CTRP, provides feedback on training and documentation, responds to queries and participates in teleconferences with NCI.

Study Management

ClinicalTrials.gov result reporting. CRS reviews and identifies all clinical trials for ClinicalTrials.gov results reporting, and informs investigators of results reporting guidelines as new applicable studies are approved. For applicable studies, CRS tracks study status changes and as the study enters the results reporting stage, provides informational sessions or one-on-one guidance for investigators to ensure that reporting occurs within the required time frame.

Interim staffing. When a trial is activated, the PI may hire CRS clinical research coordinators and data coordinators on an interim basis to ensure appropriate staffing levels. These services, which are available to all PIs, provide a cost-effective staffing solution during periods of growth or personnel changes.

Cooperative group management. FHCRC will serve as a National Clinical Trials Network – Lead Academic Participating Site (LAPS) with Dr. Fred Appelbaum, Consortium Deputy Director for Clinical Research, serving as PI (1U01 CA180828). Dr. Appelbaum will continue to develop CRS services for Cooperative group studies and expand the current dedicated regulatory and data-management team in the CRS. The CRS team conducts a feasibility assessment for all studies that PIs wish to open. The assessment includes Research Group review and meetings with the PI study team to review specific trial requirements and the availability of sufficient staffing. For activated trials, the CRS team works in close collaboration with the study team to manage the study. CRS is responsible for data management, including data submission and query resolution and communications with cooperative groups. The CRS team registers patients after ensuring that eligibility requirements are met. CRS notifies the PI and applicable staff that the subject has been registered and assigned to a treatment arm. The CRS team also works closely with the PI and study staff to ensure timely expedited adverse event reporting via AdEERs. The CRS team maintains ongoing communications with the
study team regarding patient visit dates, routine and expedited adverse event reporting requirements, protocol updates and data reviews. CRS provides study management tools such as subject calendars and visit reminders to assist with study management.

**Regulatory affairs guidance and support.** The CRS Quality and Compliance Team manage regulatory affairs for Consortium human subjects research. This function includes interpreting current federal, state and local regulations, policies and trends that affect clinical research activities and informing the clinical research community through training, e-newsletters and website. As described above, this team provides the initial review of a study for regulatory issues before protocols are submitted to SRC. CRS works closely with study teams to ensure that PIs and staff are familiar with FDA requirements and guidance for INDs, IDEs and GCP. The regulatory affairs team assists in preparation of IND and IDI applications, annual reports, audits and other FDA correspondence. This team is available for ongoing guidance as needed.

**Training and Education.** All investigators and staff involved in the design, conduct, or reporting of human subjects research in the Consortium and affiliates must complete human subjects training, which is available via web-based on-line modules or through in-person lectures. GCP training is available through web-based courses, and a Consortium policy requires it for all sponsor/investigators, investigators and research staff in the Consortium, and for affiliates engaged in the design, conduct or reporting of therapeutic clinical studies or prevention studies that involve drugs, biologics or devices.

CRS provides training in protocol development, review and compliance. It offers training on scientific and human subjects review, federal reporting requirements, including clinicaltrials.gov, and protocol data and monitoring oversight. CRS works with the CTSA Education Core on clinical research training resources and promotes CTSA programs to members. CTSA resources range from full degree and certification programs to a library of clinical trial template documents and RedCAP training and support. The training manager will implement a strategic plan that was developed with the support of a training consultant who evaluated our program during the past year. This plan includes enhanced new hire training, continued development of role specific training, and increased access to training through use of different platforms.

Training for research nurses, clinical research coordinators and other staff involved in the conduct of clinical research is available on an ongoing basis and in a multitude of platforms including ad hoc in person trainings, broadcast webinars, role-specific forums and all-clinical research staff meetings. A comprehensive 3-day training course is offered by CRS biannually. This program focuses on clinical trial design, ethical conduct, FDA regulations, Consortium policies and site-specific operations. During 2013, 55 clinical research staff attended the training program with representation from each Consortium site. This program complements monthly CRS Consortium study coordinator meetings, topical educational seminars, monthly brown bag lunches that include CRS and IRB staff as well as CTSA seminars. Findings from monitoring visits and audits are used by the CRS Quality and Compliance team to refine training content. A full list of training opportunities will be available at the site visit.

During the project period, CRS instituted a monthly regulatory affairs forum and an online regulatory affairs education series focused on education and discussion of federal regulations and the conduct of clinical trials in human subjects. Specific topics include FDA regulations and Good Clinical Practice (GCP), best practices for consistent study management, and regulatory aspects of clinical trials, INDs, and IDEs. This forum helps CRS identify opportunities for Consortium guidance, policies, and tools.

**Communication.** CRS recognizes that in a multi-institutional consortium structure, robust central communications are essential. The CRS manages multiple role-specific list servs and uses a combination of tools, including e-newsletters, emails, and a website, to support compliant conduct of clinical research throughout the Consortium. These vehicles provide the latest information about regulations, changes in Consortium policies and practices, announcement of new or revised tools, ways to streamline effort, and other relevant information.

**Quality control and assurance.** The Quality and Compliance team manages the Consortium’s monitoring and audit programs as described in the DSMP. Both programs are based on risk level and focus primarily on those studies that are not monitored or audited via another approved entity. High-risk trials include sponsor-investigator INDs, Phase I, and trials in gene therapy or other areas designated by NIH as high-risk. Such trials are monitored for data safety and audited twice yearly, as long as subjects are enrolling and receiving study intervention. Medium risk trials are all other therapeutic intervention studies and are monitored for data safety and audited at least once every 12 months while subjects are enrolling and receiving study intervention. Low
risk trials are non-therapeutic interventions and are monitored for data safety and audited once within the first year of enrollment and thereafter based on the decision of the CRS Quality and Compliance Manager, Medical Director, and DSMC.

**CRS oversight of quality control and assurance.** CRS identifies studies requiring data safety monitoring or auditing and schedules visits accordingly. Visit scheduling includes the date and location, appointments with Investigational Drug Services pharmacies and laboratories, including cell therapy and nuclear medicine, and wrap-up meetings, if needed. The goal of the program is to confirm that studies are being conducted in a manner consistent with Consortium standards and relevant requirements, such as GCP guidelines and CFR Title 21. CRS completed 168 monitoring and auditing visits in 2013, up from 136 in 2008.

**Monitoring.** The Consortium uses CRS-trained contract monitors, in addition to the continuous monitoring by the study team. CRS Quality and Compliance manages the monitoring activities including monitoring SOPs and reports. The monitoring team verifies data, assesses protocol compliance, assures timely and complete safety data reporting, and confirms that processes are in place to protect human subjects. The monitoring team reviews consent forms for all enrolled subjects and performs a full review of randomly selected subjects from the most recent cohort of enrolled subjects. Activities include reviewing regulatory documents, subject source documents, and CRFs, accounting for the investigational product or device, determining that SAE/AE, IND, safety reports, noncompliance and unanticipated events are complete and reported as applicable, and determining the adequacy of PI oversight. All monitoring reports are submitted to the CRS Quality Manager for review and action as necessary.

**Auditing.** CRS Quality and Compliance ensures compliance with the requirements of the IRB approved protocol, appropriate protections of the clinical trial participants, accuracy and completeness of clinical trial data, safety reporting requirements, and clinical trial drug management. Routine and focused audits are conducted. Routine audits involve the selection of a clinical trial from the list of all ongoing Consortium clinical trials. Focused audits are conducted on a clinical trial with a known or suspected deficiency. Audit reports are submitted to the CRS Quality Manager for review and issues are escalated as described below and in the Consortium DSMP.

**Response to quality control and assurance visits.** The CRS Quality Manager reviews all monitoring and audit reports and creates corrective and preventative action (CAPA) plans as necessary. The CRS Quality Manager informs study personnel of discrepancies noted, summarizes significant findings with the study team, identifies additional documentation needed, suggests useful tools or systems, and identifies any required noncompliance or unanticipated event reporting. A list of needed changes and additions for review and verification at the next visit is provided in the final report to the PI no later than four weeks from the time of the visit. It also provides tools for the management of a trial. The Quality and Compliance Manager oversees the review of all audit and monitoring reports and escalates reports for review by the Compliance sub-committee as necessary. In addition to the Quality and Compliance Manager, this group includes the Medical Director and Associate Director of CRS. The sub-committee refers urgent or persistent problems involving a specific performance site or Principal Investigator to the Consortium DSMC or Clinical Research Oversight Committee (CROC) for further action.

**Data and Safety Monitoring Committee.** CRS assures data and safety management through its review of monitoring and auditing reports and administration of the DSMC and compliance sub-committee. CRS prepares agendas and ensures that all study-related material and data are available for review. CRS prepares and distributes minutes and facilitates follow-up as needed.

**Continuing review, including accrual monitoring.** CRS manages continuing review by SRC, including accrual monitoring. The office notifies the study team and provides documents needed for submission of continuing review applications. The office supports a new accrual monitoring policy (see PRMS). CRS gathers data, performs accrual analyses, and submits recommended actions to the appropriate committee. It also manages closures, e-mails to PIs requesting information and plans, and executes decisions to close trials, along with informing the appropriate groups.

**Centralized Technology, Data Management and Reporting.** All data and reporting related to clinical research is centrally managed by CRS. Quality controls are assured through dedicated staff, policies and practices, and the use of technology. Reflecting leadership’s commitment to technological improvements that enhance transparency, efficiency and adherence, the Consortium has funded a dedicated Regulatory Information Systems (RIS) group within CRS. RIS is responsible for system administration and database
development activities. To help CRS maintain quality control points, RIS has developed, expanded and integrated IT tools critical to the clinical research community. Centralized protocol tracking is achieved through PIRO, a protocol database that manages activation milestone tracking, study monitoring visit tracking, institutional committee activities, medical safety reports, FDA IND/IDE tracking information, study team memberships, funding sources, and linkages to protocols and study-related documents. Integrated patient registration, billing compliance, and accrual reporting has been achieved by using EPIC for registration and enrollment reporting activities. EPIC is now integrated with the Protocol Database and the Patient Accrual Tracking System (PATS), which generates Data Table 3 and 4 and creates a comprehensive reporting platform for enrollment metrics and tracking by study, disease program and Consortium institution.

Electronic PRMS and DSMC committee management and review is accomplished through eReview, a system initially introduced to facilitate IRB reviews. SRC members now use this electronic tool to review and evaluate protocols before meetings. eReview is accessible online and is integrated with the Central Protocol Database to ensure that committee decisions are tracked and reportable via a central location. The current version of online study documents is available through Clinical FYI (FYI), an electronic system that provides version-controlled access to approved study protocols, consent forms, and related documentation. In 2010, access was expanded to network and affiliate sites. FYI's integration with the Protocol Database provides the ability to publish, withdraw, and track document versions from a central location.

Consortium policies, procedures and practices. The Clinical Research Oversight Committee approves and enforces Consortium-wide policies, and as defined by the CCSG, all cancer-related protocols must adhere to Consortium, NCI, and national standards, policies and practices. It is the role of the CRS to ensure that individuals and groups consistently adhere to these standards and expectations and to bring issues to leadership through an established escalation system.

Consortium policies guide all aspects of clinical research within the Consortium. Examples of Consortium-wide policies include the following. 1) GCP training is required for all investigators and staff involved in the design, conduct or reporting of clinical research within the Consortium. 2) Distribution of consents is controlled through a central database (FYI); all Consortium investigators are required to use consents printed from this source within three days of a consent signature. 3) Consortium investigators are required to provide all internal and external monitoring and audit reports to CRS for review. 4) Consortium PI's are required to document delegation of authority as described in the procedures maintained by CRS. 5) SRC has the authority to close clinical trials that do not make scientific progress according to the Consortium accrual criteria.

Part II: Data and Safety Monitoring

Overall purpose and focus. Data and safety monitoring encompasses all aspects of data monitoring, verifying data validity and integrity, and ensuring the safety of study participants in clinical trials. Clinical trials are monitored based on degree of risk, size and complexity. The Cancer Center Director has ultimate responsibility for the data safety and monitoring processes. The Data and Safety Monitoring Plan (DSMP) embodies Consortium values and is consistent with the NIH/NCI guidelines. The Plan relates to all clinical trials conducted by the Consortium, and is particularly focused on quality control and assurance of institutionally sponsored, investigator-initiated research, and those trials without external oversight. This DSM plan was last reviewed and approved by the NCI October 12, 2012, and will be reviewed prior to the site visit.

Management of plan. The CRS supports and manages the DSM Plan. The DSM Plan provides a road map for monitoring trials, informing PRMS and IRB of critical issues, ensuring subject safety, and maintaining research integrity. It also identifies rules for suspension, closure and notification. CRS works with PIs and study teams to ensure that data and safety monitoring concerns are addressed in compliance with the Plan.

DSMC responsibility. The CRS provides administrative support and database management to the DSMC, which meets every 2 weeks, when it reviews summary reports of patient data and safety. The Compliance sub-committee of the DSMC meets monthly to review monitoring reports and audit findings. Together, the DSMC and its compliance sub-committee ensure that all trials are properly managed and reported in order to protect the rights and welfare of human subjects. In 2013, the DSMC reviewed 129 studies, including 65 investigator initiated and 62 externally funded studies. As described above, internal monitoring and auditing conducted 168 monitoring and auditing visits and provided oversight 40-45 for investigator-initiated protocols per year during the project period. Monitoring and auditing are completed according to risk, as described above.
The DSMC and the Compliance sub-committee may request new or ongoing corrective actions and require changes to improve study safety and quality. They may also request follow-up information on AEs/SAEs or provide recommendations regarding the status of the study or consent form modifications to address concerns about safety or quality. The DSMC has defined authority for suspending or closing a protocol or suspending and investigator or program because of safety concerns or major audit deficiencies. In the event of a suspension or termination, the DSMC notifies the IRB or asks to the IRB to make a final determination. The SRC will be notified if matters relate to scientific merit. The IRB assists in ensuring that all protocol activities cease until issues are resolved to the DSMC’s satisfaction, and the IRB office notifies NCI of suspensions or closures.

**DSMC relationship to SRC.** The DSMC is independent of the SRC, but together they ensure a comprehensive data and safety monitoring system. All new studies undergo initial scientific review by the SRC. During this review, the SRC confirms the adequacy of the DSMP, taking into account the CRS assessment of DSMPs in investigator-initiated studies. Upon SRC approval, the CRS Quality and Compliance team notifies the DSMC and the PI regarding the reporting and monitoring requirements based on the assigned risk level.

**DSMPs.** All investigator-initiated interventional studies must include a DSMP embedded in the protocol. The SRC may require that investigator-initiated interventional non-treatment studies have a DSMP. CRS reviews the DSMP and works with PIs on revisions. If a DSMP is needed but not provided, the packet is returned. If an external DSMC is not utilized, PIs may assign the DSMC as the DSMP of record.

**Future plans.** Immediate priorities include the following: 1) Enhance faculty and PI training in coordination with the CTSA; 2) Continue to define study team roles in clinical research and define standard core competencies; 3) Continue to expand Consortium-wide standard policies and guidelines; 4) Develop necessary infrastructure to implement new cooperative group requirements in support of Dr. Appelbaum’s newly awarded LAPS grant.

**Part III: Inclusion of Women and Minorities in Clinical Trials**

Dr. Corey and the senior leadership team are universally committed to increasing the participation of minorities in clinical research. Consortium leaders and members believe strongly in their responsibility to build trust and engagement with special populations in the catchment area and broader service area; to minimize barriers to using the health care services of the Consortium partner institutions; to remove eligibility, recruitment or participation barriers; and to find ways to encourage participation and retention for populations of all types. We have instituted several new activities to further strengthen our commitment to achieving these goals. Activities underway, and plans proposed for the new project period, are summarized below.

**Response to 2008 Critique.** At our last renewal, reviewers expressed concerns regarding the accuracy of patient demographic data reported and the lack of consistent tracking for race and ethnicity throughout the Consortium. Senior Leaders and Consortium Administration recognized the importance of changing processes within the clinical setting to address these concerns.

The SCCA was the focus of the effort to correct the high percentage of unknown race and ethnicity data since it is the primary clinical research site for the Consortium. SCCA Administration was made accountable to change the process for requesting race and ethnicity data from patients. Changes included transitioning from a paper-based process at check-in to a computerized process, which prompts clinic staff to complete data entry. Improvements were also made to the electronic medical record to align ethnicity and race options with NIH reporting fields. As a result, we have reduced the average number of unknown new patients during the project period from 35% to 14% (Attachment 2). We have placed responsibility for the accuracy of the tables with the Associate Director for Administration and CRS Associate Director and these data will be continuously monitored.

**Catchment Area Defined.** The Consortium’s catchment area is defined as the 13 contiguous counties of western Washington. This is the area from which more than 70 percent of SCCA patients are drawn.

**Accrual of Women and Minorities on Consortium Trials.** The data for the racial, ethnic and gender breakdown of patients accrued to therapeutic and non-therapeutic trials at the Consortium during the period of 6/2013 and 12/2013 is presented in Attachment 2. Female participants were accrued to non-therapeutic trials in significantly higher numbers (Attachment 2, 85% female participants); this discrepancy is largely due to accruals to five large breast and cervical cancer studies that together account for 75% of female accruals.
In support of the inclusion of minorities and women in clinical trials, the Consortium sponsors a number of studies that focus on research questions unique to specific populations. Some examples of Consortium studies conducted during the grant period to encourage trial participation by minorities and women are: _Understanding and Preventing Breast Cancer Disparities in Latinas: Screening Mammography and Latinas_ (PI: Shirley Beresford, 5 P50 CA148143); _Center for Hispanic Health Promotion: Cervical Cancer Screening and Adherence to Follow-Up Among Hispanics_ (PI: Beti Thompson, U54 CA153502); and _Center for Native Health Disparities_ (PI: Dedra Buchwald, 3P50CA148110).

**Efforts to Enhance Accrual of Minority Populations.** During the project period, several strategies have been implemented to enhance the accrual of minorities to clinical trials. These include:

- **Review of Protocol Design by PRMS to Assure Inclusivity.** Inclusivity of women, minorities and children has been formally included as a criterion in review of protocols in the Protocol Review and Monitoring System. Scientific Review Committee members must specifically evaluate each protocol for potential for enrollment of special populations to ensure that barriers are minimized and sufficient recruitment outreach is conducted where appropriate.

- **Creation of a new Associate Director of Minority Health and Health Disparities Research Position.** One of Dr. Corey’s priorities has been to assure that his Senior Leadership team include an individual with expertise in health disparities and potential barriers to inclusion women and minorities in research. He has created a new Associate Director position and appointed Beti Thompson to fill the role. She leads three NCI grants on health disparities research, training and education (see Administration Core/Senior Leadership section).

- **Recruitment of Minority Faculty and Faculty with Research Interest in Disparities.** Dr. Thompson was instrumental in recruitment of four health disparities investigators during the project period (two supported by CCSG new investigator funds), including Rachel Ceballos, who leads an assessment of gaps and successes in the provision of information or services to African-American breast cancer survivors in the Seattle area.

- **Establishment of Health Disparities Research Center (HDRC).** With Dr. Corey’s encouragement, Dr. Thompson (FHCRC) has established a Consortium Health Disparities Research Center using institutional funds. Drs. Hannah Linden (UW) and Jason Mendoza (Children’s) are co-directors; funds have been requested in this application for their support as Staff Investigators for Special Populations. The HDRC’s strategic plan, which will be available at the site visit, includes the following aims:
  - Establish a minorities in clinical trials committee, chaired by Dr. Thompson, dedicated to developing and monitoring strategies to enhance the inclusion of minorities to Consortium clinical trials;
  - Provide outreach to diverse community organizations for Consortium members who seek participation by under-represented populations for their studies;
  - Sponsor a seminar series that bring national experts on health disparities to the Consortium to provide strategic guidance on best practices for enhancing minority participation in research;
  - Build relationships with diverse community organizations through participation in activities that are oriented toward under-represented individuals;
  - Facilitate participation by investigators in events hosted at diverse community organizations;
  - Organize educational presentations to audiences at diverse community organizations, including: curricula on the importance of participating in clinical prevention trials; curricula on participating in biospecimen collection and biobanking activities; “Cancer 101” – basic overview of cancer; and information on Consortium research and clinical trials.

**Dedicated Pilot Projects.** During the current project period, Senior Leaders targeted an RFA for CCSG Developmental Pilot Funds to support a project focused on increasing participation of minorities in Consortium research (Developing and Validating a Dietary Instrument for Hispanics, PI Beti Thompson). Another recent CCSG pilot supported a project led by Linda Ko, Cancer Communication within Social Networks, focused on improving colorectal cancer (CRC) screening uptake in Hispanics, a group with lowest CRC screening rate of any major ethnic group. Developmental funds are requested to continue this special pilot program annually.

**Improved Access to Catchment Area Data.** Consortium Administration has revised the Consortium Web site to include demographic data on the catchment area, including data on the prevalence of cancers in racial and
ethnic minorities, to improve access to this data by Research Program heads and members as they design research studies. This site will now be supported by Administration with oversight from Dr. Thompson.

**Part IV: Inclusion Of Children In Clinical Trials**

The Consortium is committed to including children in human subjects research in order to improve survival and quality of life for children with cancer and survivors of childhood cancer.

Consortium pediatric oncologists are members of the Heme Malignancies and Cancer Basic Biology Programs, and have made significant scientific contributions to improving outcomes for children with cancer during the grant period. These include maturation of prior pre-clinical studies on the use of retinoids as a treatment for medulloblastoma into a national Phase III clinical trial (Children’s Oncology Group clinical trial ACNS0332) led by Jim Olson, and studies led by Soheil Meshinchi and colleagues to develop accurate molecular assays to predict prognosis and monitor therapeutic response in pediatric acute myeloid leukemia. While pediatric oncology is not presented as a formal CCSG program, Dr. Corey has appointed Michael Jensen as Associate Director of Childhood Cancers, reflecting the growth of pediatric cancer research with the establishment of the Seattle Children’s Ben Towne Center for Childhood Cancer Research, which is directed by Dr. Jensen.

The majority of the Consortium’s pediatric hematologic transplant patients, who receive outpatient care at the SCCA and inpatient care at Children’s, are enrolled in clinical trials. All other children referred to Children’s with a malignancy are considered for participation in clinical trials, and when suitable, offered the opportunity to do so based on protocol selection criteria.

Approximately 240 new cases of children with cancer are treated at Children’s and the SCCA each year. During the 12 month period of 1/1/12-12/31/12, 91 interventional clinical trials were open to accrual for pediatric patients. The Consortium enrolled a total of 34 pediatric patients in therapeutic clinical trials. In addition, 182 patients were enrolled on biology studies collecting specimens, 164 former patients enrolled on late effects studies, 31 on cancer control studies, and 260 on local non-therapeutic studies. 51 patients also underwent hematopoietic stem cell transplants, all on FHCRC research protocols.

All protocols with issues related to children are reviewed by SRC and the Children’s Institutional Review Board (IRB), which specializes in issues related to children, or the Consortium IRB, which includes members with pediatric oncology expertise. The IRBs at Children’s and FHCRC have reciprocity with each other. As discussed above, pediatric budgeting, billing compliance, staff on-boarding and IRB coordination have been improved and two CRS staff members are now located at Children’s and are responsible for helping teams access the latest protocols, coordinate specimen acquisition and distribution, and address other needs.

Pediatrics faculty serve on numerous cooperative group committees and chair 6 nationwide protocols. Research activities at Children’s, including cooperative clinical chemotherapy trials, occur via the Children’s Oncology Group (COG), the Pediatric Brain Tumor Consortium, the New Approaches to Neuroblastoma Therapy Consortium, and the Therapeutic Advances in Childhood Leukemia Consortium. Children’s is also one of 21 institutions selected to participate in the COG Phase I Consortium. Multiple investigator-initiated studies are also conducted at the institution. Clinical trials in the treatment, biology, epidemiology, and long-term effects of cancer are currently underway.

The CTSA-supported Pediatric Clinical Research Center at Children’s provides an environment and resources for multidisciplinary clinical research on patients less than 21 years of age. Patients participating in research studies also receive outpatient treatment in the Children’s hematology/oncology clinic and infusion center. Subspecialty oncology clinics include hematology, bone tumor, neuro-oncology and Long-Term Follow-Up.
PROTOCOL REVIEW AND MONITORING SYSTEM

Overview. The activities of the Protocol Review and Monitoring System (PRMS) are essential to the Consortium’s conduct of clinical research that advances our knowledge of cancer and our development of effective new approaches to prevent, diagnose and treat the disease. PRMS activities ensure that 1) investigator efforts focus on protocols of the highest quality and most innovative character and 2) cancer patients served by the Consortium and throughout the catchment area have opportunities to enroll in clinical trials matching the types and stages of diseases that occur in this population. This approach maximizes the potential impact of the cancer center’s investment in clinical research activities. Between 10/1/12 and 9/30/13, the Consortium enrolled 961 local patients on clinical trials, representing 23% of newly treated patients.

The PRMS, through the action of the Scientific Review Committee (SRC), reviews, approves and monitors the scientific merit, feasibility and prioritization of all cancer clinical protocols conducted at the partner institutions that make up our center. In accordance with CCSG guidelines, SRC review complements, but does not overlap with the Institutional Review Board (IRB), which focuses on human subjects protection. Each protocol must be approved by the SRC before it may be considered by the IRB (which for our center includes the Consortium IRB, Western IRB, or Seattle Children’s IRB). The responsibilities, functions and authority of the SRC are separate and distinct from those of the Data Safety and Monitoring Committee (DSMC).

Response to 2008 review.

Senior leadership has devoted considerable attention to clinical research support during the project period in order to address comments raised by reviewers at our last (2008) CCSG competing renewal and to further strengthen these activities. All policies, procedures and relevant forms will be available at the site visit.

1. Reviewers commented on the practicality of having three scientific review committees that each specialized in a different area of clinical research (Solid tumor, Hematological Malignancies, and Pediatric Cancer). While effective, this structure embedded delays in time from submission to first SRC meeting due to the frequency with which each committee met. In Fall 2013, Director Corey assigned Medical Director for Clinical Research Support, Paul Martin, MD, the responsibility for reorganization of the SRCs. As a result, the committees presented in this application have co-chairs and members with sufficient breadth and depth of expertise to review protocols of any type. As such, there is now only one week between each review date, compared to up to 3 weeks previously.

2. Increase expertise on the SRC committees, including pharmacy and nursing and PhD level statisticians, and ensure that the biostatistician is not in conflict. Both committees have PhD level statisticians, a pharmacist, and research nurses. The SRC biostatistician may not review studies that they have helped to design.

3. Eliminate overlap between DSMC and SRC biostatistics: Dr. Barry Storer, who previously served as the chair of the DSMC and as a member of the SRC, now serves only as the chair of the DSMC and no longer serves on the SRC.

4. Reviewers suggested, “Solid tumor programs may want to formally emulate” the Transplant Program's Clinical Investigators meeting and establish a protocol pre-review process. Using the transplant program’s well-established clinical investigator meeting as a model, senior leaders worked with Dr. Martin to establish 14 disease-specific and modality focused Research Group committees (described in Table 2 below). Now fully established, the Research Groups are formally responsible for protocol portfolio management, including the initial evaluation of all relevant protocols before submission to the PRMS.

Dr. Martin developed an evaluation form to aid and document Research Group assessments. The form ensures comprehensive, objective and consistent evaluation across reviewers and groups and assessment of required CCSG criteria. As a result, protocols are carefully scrutinized for scientific merit, overlap with existing or planned trials, ability to accrue subjects given open protocols and the Consortium’s patient base, as well as member interest in participating in the protocol. Only those protocols that successfully pass this stringent evaluation process are submitted for further review by the SRC.

5. Increase the number of SRC reviewers: As of November 2013, primary and secondary reviewers are assigned for all protocols reviewed by the SRC.

6. Reviewers commented on prioritization of clinical research protocols within the Consortium, which were not conducted uniformly across all disease groups. As noted above, the transplant group has a well-established,
effective process for prioritizing protocols within the program, resulting in 60% of new patients with hematologic malignancies participating in a clinical trial. Similarly, the Phase I group, developed during the project period (see Early Phase Clinical Research Support), also tightly controls the protocols offered, based on patient population, scientific interest, and space within the Phase I unit at the SCCA; the Phase I unit has generally been running at capacity since it opened in 2010. Following these two models, Research Groups are establishing prioritization systems that are most compatible with their research interests and patient population. Consortium Leadership also recognized the need to increase leadership in solid tumor translational research and recruited Eric Holland, MD, PhD, a prominent neurosurgeon and brain cancer researcher previously at Memorial Sloan Kettering Cancer Center, to lead solid tumor translational research across the Consortium. Dr. Holland’s team has completed an extensive evaluation of Consortium solid tumor research, developed a pilot grant program to support novel solid tumor clinical trials, and identified eight established and emerging disease groups that will be targeted for further development (prostate, breast, pancreas, colon, brain, ovary, lung, and head/neck cancers) over the next several years. Consortium and institutional funds will support these priority areas and these priorities have been communicated to the SRCs. In general, the SRC sets priorities for clinical trials based on scientific merit, clinical significance, currently accruing trials, and available patient population.

7. Increase oversight of financial regulatory issues: In fall of 2013, CRS led an evaluation of CTMS vendors and negotiations are ongoing. While conceptually endorsed several years ago, leadership elected to delay the actual purchase of the CTMS until a new Medical Director and Director of Clinical Research Support were appointed and could make foundational improvements. In late 2013, senior leadership felt that sufficient progress had been made to move forward on this critical acquisition that will increase Consortium oversight and financial regulatory control of clinical research. Conflict of interest is managed by the investigator’s home institution; CRS ensures investigator conflict of interest has been reviewed and approved by the investigator’s institution as part of the submission process and prior to IRB review.

8. Reviewers raised “the question of whether the reviews are as rigorous” as other Cancer Centers. Dr. Martin now regularly attends SRC meetings and provides immediate feedback to reviewers or the chairs when inconsistencies are identified. He also provides one-on-one guidance after meetings as needed. Members who are not able to provide excellent reviews and contribute to the PRMS process may be excused before the end of their terms, with the approval of the Consortium Director. In December 2013, an SRC review form was instituted to further ensure consistency and high quality review.

9. Increase oversight of protocol accrual: Oversight of accrual has moved from the DSMC (formerly Protocol Data Safety and Monitoring Committee) to the SRC and a new process has been developed. The PI is notified if their study meets the low accrual criteria (described below) and is invited to provide a response. The SRCs review the PI response and votes. In November, 2013, 18 low accrual notices were sent and responses received; 6 studies were closed. This process will continue, with protocols reviewed for accrual every 6 months.

10. Data Safety and Monitoring Plan: The review committee recommended that all Phase I trials with dose escalation be reviewed in “real time.” Investigators leading Phase I trials conduct continuous review of data and patient safety. Within the Phase I unit, bi-weekly review meetings for Phase I trials are required and include the Principal Investigators, data manager and study coordinator and other members per the Principal Investigator’s discretion. Discussion includes number of subjects, significant toxicities as described in the protocol, dose adjustments, and response observed. In the case of a dose limiting toxicity event, a meeting occurs within 2-7 days of the event for discussion of toxicity and evaluation.

11. Timely review and initiation of investigator initiated protocols was encouraged: Between 10/1/2012 and 9/30/2013, the SRC reviewed 44 investigator initiated studies. Of these, 41 studies have been approved, and 37 of the 41 studies have been activated.

Organizational Structure.

Consortium Director Corey is ultimately responsible for the proper functioning of the PRMS (Figure 1). Dr. Appelbaum, Deputy Director for Clinical Research, supports him in this role as does the Clinical Research Oversight Committee (CROC), which Dr. Appelbaum chairs. The CROC ensures that clinical research is conducted according to Consortium policies and procedures. Members of the CROC include: the FHCRC Sr. VP and Director of the Clinical Research; the UW Division Head of Medical Oncology; the Consortium
Associate Director for Solid Tumor Research; Children’s Associate Division Chief for Pediatric Hematology/Oncology, Medical Director; and 1-2 Consortium members with active clinical research programs. Dr. Martin, Medical Director for Clinical Research Support, leads the PRMS. Ulrich Mueller, PhD, Director of Clinical Research Support and the Institutional Review Office, provides administrative and operational support and oversees Kristi Stiffler, MPH, Associate Director of Clinical Research Support (the Consortium’s CPDM office), which supports the PRMS. Together, Drs. Mueller and Martin and Ms. Stiffler have successfully planned and implemented changes in PRMS and CPDM functions to enhance the quality of protocol review, streamline processes, ease PI burden, and improve turnaround time. The PRMS coordinator is Ms. Johanna Salmonson. She has performed this role for 7 years and reports administratively to Ms. Stiffler.

**PRMS structure and organization.** The PRMS has two SRCs (Figure 1). The SRCs meet bi-weekly, resulting in one meeting per week to review new protocols. With support of the Institutional Planning Committee (IPC), Drs. Martin and Appelbaum reorganized the SRC from a previous structure with committees specialized by the type of protocols reviewed (i.e., Solid Tumor, Hematologic Malignancies, Pediatric Cancer) to one in which both committees have sufficient expertise to review all protocols, thereby eliminating needless delays. Each SRC has an experienced chair and co-chair. The scientific breadth of membership has been expanded and now includes expertise needed to review the full scope of protocols submitted.

Consistency of reviews and activities across committees is assured through several mechanisms. 1) Dr. Martin attends meetings frequently to identify and address in real time potential inconsistencies; 2) Dr. Martin provides ongoing education and feedback to reviewers, as issues arise; 3) Reviewers use a new evaluation form to complete their reviews and, as such, are guided to apply the same criteria for each protocol. A recently established semi-annual meeting of SRC Chairs and Co-chairs and IRB Chairs further ensures consistency.

**Role and responsibilities of PRMS.** The PRMS assures that cancer-relevant human research is 1) scientifically important, 2) biostatistically sound, 3) designed appropriately without excluding special populations for non-scientific reasons, 4) feasible, with reasonably attainable accrual targets given the available patient population, and 5) supportive of the research mission of the Consortium. The PRMS further ensures that during the course of accrual, the scientific rationale for the protocol has remained relevant and that accrual is progressing at a reasonable pace. All protocols approved by PRMS have access to CCSG-supported centralized resources, including CPDM and biostatistics. As described below, Consortium protocols must go through rigorous prioritization prior to and during the PRMS.

The central feature of the PRMS is the Scientific Review Committee (SRC), which focuses its energies on the scientific merit, feasibility, prioritization, and progress of protocol research at the Consortium. The PRMS committee structure is responsible for ensuring that cancer clinical trial protocols conducted throughout the Consortium are of high scientific merit and feasible in light of trial design, subject accrual targets, and concurrently open trials. Protocols must meet internal research priorities and standards and serve the overarching mission of the Cancer Consortium. The PRMS is sensitive to addressing the special research needs of the catchment area and to ensuring (through the protocol review form) that eligibility criteria do not restrict participation by women, minorities, children and other special populations unless scientifically justified. PRMS has the responsibility and authority to approve protocols that meet its stringent, well-defined criteria and to suspend or close further accrual to protocols when they no longer demonstrate scientific progress.
Benefits of the PRMS.

- Centralized administrative pre-review and support for all cancer center members.
- Uniform review of protocols by Research Groups using defined criteria.
- Uniform protocol submission packet, forms, and consistent administrative support of initial and ongoing PRMS reviews.
- Universal forms used by PRMS reviewers so that evaluations address all required elements and are consistent across reviewers and committees.
- Centralized coordination of submissions to IRB, after receiving PRMS approval.
- Centralized activation of approved protocols by CRS.
- Universal management of PRMS and IRB review documents.
- Centralized management of PRMS policies, procedures, and processes.
- Dedicated medical and administrative leaders responsible for improving workflow, quality of reviews, process, and turnaround.
- Centralized management of clinical trials data, metrics, protocol and consent form versions, and protocol amendments.

Progress during the project period.

1. Dr. Corey appointed a highly respected clinical investigator, Dr. Paul Martin, as Medical Director of Clinical Research Support. In this capacity, Dr. Martin, a senior hematopoietic cell transplant investigator who has been at FHCRC for 36 years, is directly responsible to Drs. Appelbaum and Corey for enhancing and overseeing the PRMS process.

2. After spending his inaugural year assessing current processes, seeking input from investigators, and holding discussions with Dr. Appelbaum other senior leaders, Dr. Martin developed a vision and long-term plan for process improvement. His first priority was to champion a reorganization of the Consortium’s CPDM into the Clinical Research Support Office, which is responsible for managing the PRMS and all stages of the protocol lifecycle and is described in detail in the CPDM section. The CRS office was pivotal to Dr. Martin’s plan since it manages, coordinates and supports the PRMS. Kristi Stiffler became the CPDM Associate Director in 2012 after a successful tenure managing the FHCRC Clinical Research Division. Dr. Martin then proceeded with a re-organization of the SRCs, as described above.

3. In consultation with Dr. Appelbaum and the Clinical Research Oversight Committee (CROC), Dr. Martin has revised or developed a number of SRC policies, guidance documents and reviewer forms to help ensure that reviews are high quality, comprehensive, and consistent across committees. In addition, the forms help assure that reviews address all of the criteria set forth in CCSG guidelines and those adopted by the Cancer Consortium.

4. The CROC, in collaboration with Dr. Martin, has instituted a policy with objective criteria for determining ‘low accrual,’ and defining actions to be taken should accrual not reach targets. This policy excludes rare diseases and narrowly targeted therapies and accounts for potentially slow accrual during the initial start-up of the trial. The accrual monitoring policy and the Research Group pre-review process are expected to minimize the percentage of low accruing protocols in the Consortium’s portfolio.

5. Responsibility for continuing scientific review, including accrual monitoring, has shifted from the Data Safety and Monitoring Committee (DSMC, formerly PDMC) to the SRC.

6. The Consortium has built and enhanced new IT tools, such as a PRMS document management system (eReview) that enables SRC reviewers to submit their reviews online.

7. A CRS position for facilitation of protocol review has been created and a highly qualified individual hired. This individual will provide guidance and services to help PIs navigate their protocols through the review process.
8. The CRS has expanded training and the distribution of information to PIs and study teams.

While much has been accomplished since the appointment of the Consortium Director and Medical Director for CRS, further improvements are planned, as highlighted in the Future Plans section, below.

**Criteria for selection, term and renewal of committee members.** SRC committee members are formally appointed by the Consortium Director on the recommendation of the Medical Director for CRS, who confers with the SRC chairs and the Clinical Research Oversight Committee. SRC committees must have sufficient diversity and depth of faculty membership with respect to disease focus (solid tumors, hematologic malignancies, adult/pediatrics), research discipline (basic, translational, clinical, population sciences), and institutional representation. The PMRS is particularly sensitive to the need to avoid overburdening young faculty, while at the same time balancing professorial rank and developing future clinical research leaders. Ultimately, each committee is organized to have the range of skills and experience required to conduct a critical and fair scientific evaluation. Should additional expertise be required, the Consortium Director may appoint additional reviewers, although this has not been necessary. There is no overlap between SRC and DSMC membership.

<p>| <strong>Table 1:</strong> Current members of SRC-A, SRC-B, and <em>ad hoc</em> members |
|------------------|------------------|------------------|------------------|
| <strong>Sub-Committee A</strong> | <strong>Title</strong> | <strong>Program</strong> | <strong>Expertise</strong> |
| Ben Greer (Co-Chair) | Professor | Women’s Cancer | Gynecologic Oncology |
| Joachim Deeg (Co-Chair) | Member | Heme Malig | Myelodysplastic syndrome, leukemia, and myelofibrosis and Laboratory research |
| Bill Bensinger | Member | Heme Malig | Autologous transplant program, multiple myeloma, amyloidosis, and plasmacytoma |
| Ed Libby | Assoc. Professor | Heme Malig | Multiple myeloma |
| Veena Shankaran | Assoc. Professor | GI Oncology | Esophageal and stomach cancers, other GI malignancies |
| Scott Tykodi | Assist. Member | Immunology &amp; Vaccine Dev. | Kidney cancer, melanoma |
| Keith Loeb | Assist. Member | Heme Malig | Pathology |
| Ann Woolfrey | Member | Heme Malig | Bone marrow transplant, Pediatrics |
| Edward Kim | Assist. Professor | GI Oncology | Radiation Oncology |
| Sarah Holte | Principal Staff Scientist | Biostatistical Modeling &amp; Methods | Biostatistics |
| Seth Eisenberg | RN | SCCA | Nursing |
| Nissa Abbasi-Shaffer | IDS Pharmacy | Dept. of Pharmacy | Pharmacy |
| <strong>Sub-Committee B</strong> | <strong>Title</strong> | <strong>Program</strong> | <strong>Expertise</strong> |
| Ajay Gopal (Co-Chair) | Professor | Hematologic Malignancies | Lymphoma, chronic lymphocytic leukemia, and novel low toxicity therapies |
| Gabi Chiorean (Co-Chair) | Assoc. Professor | GI Oncology | Colorectal, gastrointestinal, hepatobiliary, and pancreatic cancers. |
| Mary Redman | Assoc. Member | CEPC | Biostatistics, Public Health Sciences |
| Evan Yu | Assoc. Professor | Prostate Cancer | Prostate, bladder, testicular cancer |</p>
<table>
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<th>Expertise</th>
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<td>Jen Specht</td>
<td>Assoc. Professor</td>
<td>Women’s Cancer</td>
<td>Breast Oncology</td>
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<tr>
<td>Roland Walter</td>
<td>Assist. Member</td>
<td>Heme Malig</td>
<td>Acute Myeloid Leukemia &amp; Laboratory research</td>
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<td>Member</td>
<td>Heme Malig</td>
<td>Hematopoietic stem cell transplantation, graft-versus-host disease, gene therapy research</td>
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<td>Assoc. Member</td>
<td>Heme Malig</td>
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</tr>
<tr>
<td>Jim Smith</td>
<td>Assoc. Professor</td>
<td>GI Oncology</td>
<td>Radiation Oncology</td>
</tr>
<tr>
<td>Hans-Peter Kiem</td>
<td>Member</td>
<td>Heme Malig</td>
<td>Acute Myeloid Leukemia &amp; Laboratory research</td>
</tr>
<tr>
<td>Dave Myerson</td>
<td>Assoc. Member</td>
<td>Heme Malig</td>
<td>Pathology</td>
</tr>
<tr>
<td>Paul Carpenter</td>
<td>Member</td>
<td>Heme Malig</td>
<td>Leukemia, lymphoma, Pediatrics</td>
</tr>
<tr>
<td>Jim Smith</td>
<td>Assoc. Professor</td>
<td>GI Oncology</td>
<td>Radiation Oncology</td>
</tr>
<tr>
<td>Lois Williams</td>
<td>RN</td>
<td>SCCA</td>
<td>Nursing</td>
</tr>
<tr>
<td>Suni Elgar</td>
<td>RN</td>
<td>SCCA</td>
<td>Nursing</td>
</tr>
<tr>
<td>Ann Schwemm</td>
<td>IDS Pharmacy</td>
<td>Dept. of Pharmacy</td>
<td>Pharmacy</td>
</tr>
</tbody>
</table>

**ad hoc**

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Primary Appointment</th>
<th>Expertise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venu Pillarasety</td>
<td>Assoc. Professor</td>
<td>GI Oncology</td>
<td>Surgical Oncology</td>
</tr>
<tr>
<td>Eduardo Mendez</td>
<td>Assoc. Professor</td>
<td>CEPC</td>
<td>Head and Neck Surgery</td>
</tr>
<tr>
<td>Heidi Gray</td>
<td>Assoc. Professor</td>
<td>Women’s Cancer</td>
<td>Gynecological Oncology</td>
</tr>
<tr>
<td>Hisham Tamimi</td>
<td>Professor</td>
<td>Women’s Cancer</td>
<td>Gynecological Oncology</td>
</tr>
<tr>
<td>Carolyn Wang</td>
<td>Assoc. Professor</td>
<td>Dept. of Radiology</td>
<td>Radiology</td>
</tr>
<tr>
<td>Hubert Vesselle</td>
<td>Professor</td>
<td>GI Oncology</td>
<td>Radiology, Nuclear Medicine</td>
</tr>
<tr>
<td>Julie Park</td>
<td>Professor</td>
<td>Heme Malig</td>
<td>Pediatrics</td>
</tr>
<tr>
<td>Blythe Thompson</td>
<td>Assoc. Professor</td>
<td>Heme Malig</td>
<td>Pediatrics</td>
</tr>
<tr>
<td>Phuong Tran</td>
<td>RN</td>
<td>SCCA</td>
<td>Nursing</td>
</tr>
</tbody>
</table>

Members are appointed for three-year terms, and the Director approves renewals. SRC meetings may be held only if a majority of core SRC members and a biostatistician are present (quorum). *Ad hoc* members provide specialty knowledge that is needed less frequently and may serve on either committee. When present, *ad hoc* members may vote but do not contribute to the calculation of quorum. Dr. Martin attends meetings on a regular basis to ensure consistency in the review process. The CROC and other senior leaders are contacted as needed to identify a sufficient pool of future appointees and to avoid overburdening individual members.

**Pre-SRC review.** To eliminate protocols of lesser quality or interest by Cancer Consortium members, all proposed cancer protocols must be evaluated and approved by the relevant Research Group(s) (Table 2) before consideration by a Scientific Review Committee. Group leaders are free to develop a process most appropriate for their group; however a completed and signed Research Group Information Summary form (available on the Consortium website) is required for SRC submission and creates consistency across the different groups. The reviewing group is requested to provide meeting minutes or a written summary of discussion, especially in cases where prioritization of trials is a question. For local investigator initiated trials, additional documentation is requested, including a formal written evaluation of the protocol by at least one non-conflicted member of the group.
If a protocol does not match any research group, the PI may submit the required evaluation form to the SRC. If a protocol involves both disease and modality groups, both groups should review the protocol. Evaluation by the Modality Group should be provided to the Disease Group for its consideration. The Disease Group will provide final evaluation for submission to SRC. Based upon the group’s evaluation, the protocol may be approved for submission to SRC, recommended for revision and re-evaluation by the Research Group again before submission to SRC, or withdrawn from further consideration. Dr. Martin chairs quarterly meetings of the Research Group leaders to discuss further development of policies and procedures governing Research Group review.

Criteria that are used by Research Groups include the value of the protocol for patients, scientific merit, potential clinical significance, study design and biostatistical considerations, fit of eligibility criteria with the profile of consortium patients, value added by participation of consortium members, fit of the trial within the context of other open trials, feasibility, anticipated accrual and expertise needed to conduct the trial. Consideration is given to staffing and financial resources, since these factors affect the overall capability of the team to conduct protocols, achieve accrual goals, and publish results in a timely manner.

The primary responsibility of the Research Groups is to prioritize protocols within their group. Groups determine the merit of a protocol based on the criteria described above. Highest priority is given to protocols of high merit that meet the following criteria, in descending order of importance:

- Local (institutional) investigator-initiated trials
- Trials with external peer-reviewed funding
- Cooperative group trials and industry-sponsored trials

Priority will also be given to multi-site trials when a Consortium member serves as the Principal Investigator or a named investigator. The groups also assess ongoing clinical research activities, including progress of the clinical trials portfolio in meeting the target accrual goals.

**Types of protocols reviewed by PRMS and criteria applied.** PRMS is responsible for reviewing all cancer clinical protocols. Full SRC review is conducted for:

1) Institutional, investigator-initiated, interventional clinical trials involving human subjects that are designed to measure the effects or impact of a particular biomedical intervention;

2) Institutional interventional behavioral or psychosocial clinical trials developed by a member and designed to answer questions about the effect or impact of a particular behavioral intervention in order to improve coping and quality of life by reducing the impact of treatment or to change behavior in subjects other than healthy individuals;

3) Institutional prospective molecular or imaging diagnostic clinical trials that affect medical decision making for the subject;
4) Non-NCI cooperative group consortium studies that meet criteria for investigator-initiated studies; and

5) Industry-sponsored clinical trials designed to answer questions about the effect or impact of a particular biomedical intervention.

Review criteria include scientific merit and interest, potential clinical significance, study design and biostatistical considerations, fit of eligibility criteria with the profile of Consortium patients, value added by participation of Consortium investigators, fit of the trial within the context of other open trials, feasibility, and anticipated accrual. Protocols that have been approved but later require substantive changes must be amended and approved by the full SRC.

An administrative review is conducted for institutional or industry-sponsored molecular or genetic epidemiology studies that evaluate some aspect of cancer patient care but do not answer specific questions about the impact of the intervention and do not use the information from the diagnostic test in a way that affects decision making for the subject. The administrative review will either exempt these studies from the review, or forward them to the SRC chair for an expedited or full review, at the Chair’s discretion. An expedited review may be provided for qualified protocols. Protocols qualified for expedited review include cooperative group protocols and other external studies that were specifically peer-reviewed by NIH mechanisms (e.g., NCI CTEP, RO1s, P50s). If significant problems or questions are noted, the protocol is referred for full review by the SRC. Prioritization, conflicts with open protocols, and feasibility of subject accrual targets are considered in expedited reviews.

Studies exempt from review include institutional retrospective chart reviews; studies based on institutional registries, databases, and serum or tissue banks created by members, if information about patients is collected by members and information about patient identity is maintained within the Consortium; molecular or genetic epidemiology studies or other research studies that evaluate aspects of cancer patient care but do not involve the patients, do not ask specific questions about the impact of interventions, and do not use information or testing to affect medical decision making for the subject; diagnostic and correlative studies that do not impose risk and do not use test results for decision making about the subject; and institutional observational studies or others, such as questionnaires, that do not test interventions.

Procedures and criteria for full scientific review. The overarching goal of PRMS is to provide independent scientific review of protocols and to ensure timely scientific progress. The objectives are to promote interdisciplinary, inter-institutional development of trials that meet the mission of the Consortium, reflect the priorities and skills of members, and address the needs of patients and the catchment area. Each SRC is led by senior faculty with considerable experience in leading clinical trials and proven leadership skills.

The procedures for initial scientific review are:

1. Once a protocol is endorsed by the relevant Research Group(s), it may be submitted to SRC. The submission packet includes the protocol (including the DSM plan, if applicable), Research Group’s completed documentation, and the Cancer Consortium Submission Checklist, which captures information that supports Consortium metrics. Before submitting any new or continuing application for funding to support cancer clinical trials, the PI must submit forms declaring any financial conflict of interest. These forms are reviewed by the Conflict of Interest officer at the PI’s primary institution before the protocol is submitted for SRC review.

2. When CRS receives the protocol packet, the protocol is assigned a number and entered into eReview, a document management system used to facilitate access to documents by reviewers and to maintain documentation of reviews. As both SRC committees have the expertise to review all protocols, assignment is based only on agenda deadlines. There is one SRC committee meeting per week, with each committee meeting in alternate weeks.

3. The PRMS coordinator evaluates the protocol to determine whether the protocol qualifies for expedited review or requires full review. Primary and secondary reviewers with appropriate expertise are assigned to full protocol review, in addition to a biostatistician. They access the protocol online and complete their evaluation using the SRC reviewer forms. Representatives of specialty operational groups, including Research Pharmacy and Nursing, review each protocol in order to assess feasibility. Agenda deadlines are set one week in advance of each meeting. All protocols submitted before the agenda deadlines are reviewed at the next meeting.
4. SRC meetings may be held only if a majority of core SRC members and a biostatistician are present, constituting a quorum. Ad hoc members present may vote, but do not contribute to the calculation of quorum. Members with perceived or real conflicts of interest must recuse themselves from reviewing a protocol and must leave the meeting before SRC discussion of the protocol. The primary reviewer presents a summary of findings and recommendations, with further comments from the secondary reviewer and biostatistician. At the conclusion of discussion, each faculty member submits a ballot, which is counted by the PRMS coordinator. The voting categories are full approval (no further action required) and non-approval, which includes conditional approval with changes required, and disapproval. Resubmissions after non-approval because minor changes or responses are required may be reviewed and approved by chair or one of the original reviewers. Resubmissions after non-approval because of major changes or responses are required must be re-reviewed by full committee. No protocol may be approved without biostatistician approval.

5. Written minutes and reports of the SRC meeting include attendees, identified conflicts, a summary of each protocol discussion, outcome of each protocol vote, and any recommended or required conditions for protocol approval. The reports are prepared and distributed within 2 to 5 business days by the SRC coordinator.

The criteria used for full review include value for patients (i.e., benefits and risks), scientific merit and interest, potential clinical significance, study design, quality of the data and safety monitoring plan, fit of eligibility criteria with the profile of Consortium patients, value added by participation of Consortium investigators, fit of the trial within the context of other open trials, feasibility, anticipated accrual, and potential for enrollment of underserved or special populations.

**PRMS review of new protocols.** During the most recent year, 10/1/12 – 9/30/13, the SRC performed 129 reviews. Of these, 44 (34%) were fully approved at the time of first SRC review. Another 85 were not approved. 76 required revision and reviewer approval, 9 were disapproved, requiring new submission. Results of SRC reviews are shown in Table 3. Historically, the SRCs have approved only 15-25% of protocols without requiring changes. The increase in approvals to 34% reflects increased focus on expedited review of National Cooperative Group trials.

<table>
<thead>
<tr>
<th>Year</th>
<th>SRC reviews</th>
<th>Approved</th>
<th>Non-Approval</th>
<th>Disapproved</th>
</tr>
</thead>
<tbody>
<tr>
<td>FY9</td>
<td>84</td>
<td>11</td>
<td>68</td>
<td>5</td>
</tr>
<tr>
<td>FY10</td>
<td>99</td>
<td>16</td>
<td>75</td>
<td>8</td>
</tr>
<tr>
<td>FY11</td>
<td>95</td>
<td>23</td>
<td>65</td>
<td>7</td>
</tr>
<tr>
<td>FY12</td>
<td>98</td>
<td>17</td>
<td>76</td>
<td>5</td>
</tr>
<tr>
<td>10/1/12 - 9/30/13</td>
<td>129</td>
<td>44</td>
<td>76</td>
<td>9</td>
</tr>
</tbody>
</table>

Committee metrics to assess efficiency of activities. A complete discussion of metrics, efforts improve efficiency, and protocol turnaround data is included in the Clinical and Protocol Data Management (CPDM) section. The SRC chairs receive regular updates on the volume of submitted protocols and protocol turnaround metrics. SRC chairs discuss these metrics with the full committee; such discussions have led to the changes in SRC structure described above (the conversion of formerly specialized committees to committees capable of reviewing all protocols.)

**Process and criteria for prioritization.** When protocols are submitted for review to Research Groups and the SRC, PIs are required to include a list of active trials that already target the same subject population. Research Groups prioritize proposed protocols in light of the active trial portfolio and discuss any concerns regarding accrual through the evaluation process, as described in the Pre-review section above. The SRC receives the Research Group’s assessment and then independently considers the potential overlap of the protocol with the accrual progress of enrolling studies and the Consortium’s patient population, as well as the scientific merit, clinical significance and novelty of the proposed protocol. The goal is to avoid interfering with the ability of open trials to achieve their targeted accruals when multiple trials are available for the same patient population.

**Procedures for scientific progress monitoring, including accrual monitoring.** While research committees are responsible for ensuring adequate accrual to clinical trials, the SRC has independent responsibility for scientific review. More specifically, SRC has the authority to request corrective action. If an acceptable scientific rationale is not provided or if accrual challenges cannot be mitigated, then the SRC has the authority
to suspend or close the protocol to accrual of new subjects. The SRC has authority to suspend or close study at any time for scientific reasons or for low accrual. The SRC must notify the IRB of its actions.

Before this year, low accruing studies were defined as those with less than 25% of total accrual by midpoint of the target period. Accrual for each protocol was reviewed using this metric once a year. With this approach, during FY 2013 (7/1/12 to 6/30/13), 12 of the 128 active investigator-initiated research protocols were reviewed for slow accrual. Of these, one was closed before SRC review, and two were closed by the PI. Seven industry trials were reviewed, and none was closed.

Following an in-depth review, leadership determined that the accrual monitoring process needed revision in order to assure that low accruing trials are terminated in a timelier manner and the metrics used to identify low accruing trials were redefined (Figure 2). The SRC monitors accrual to each protocol at 6-month intervals after initial activation, which is defined as the date of final IRB approval to begin enrolling subjects. Notice is sent to the PI for any trial that has enrolled no subjects during the first 6-months after initial activation.

Starting 6 months after initial activation, trials projected to accrue four or more subjects each year across the duration of enrollment are expected to enroll at least 25% of projected annual accrual in each successive 6-month interval (Figure 2). The PI is notified if this goal is not met during any 6-month interval. Trials that fail to meet this goal in any two consecutive intervals are closed to further accrual. Trials that have been closed to accrual may be reopened for enrollment if the PI is able to provide a compelling scientific rationale and credible plan for improving the enrollment rate. The SRC reviews the factors involved in poor accrual, such as delayed funding, inability to identify patients who meet eligibility criteria, competing protocols and insurance denials. The SRC also considers scientific merit and priority of the trial together with the likelihood that accrual will improve in the future after a corrective action plan has been implemented by the Principal Investigator.

Separate consideration and case-by-case review is given to trials projected to accrue less than four subjects per year. In particular, enrollment may be continued in trials that focus on a rare disease or condition, those assessing narrowly targeted therapies, in trials with outstanding scientific merit, and in multi-site trials that are making overall adequate progress.

Accrual performance has been monitored closely after the changes were implemented in October 2013, and 18 closure notices were sent. The SRC reviewed responses from investigators and 6 trials were closed, in addition to 1 trial closed earlier in the year. All currently accruing trials will be reviewed at 6-month intervals beginning in 2014. SRC decisions will be based on a solid scientific rationale for continuation. Metrics reflecting the new program for monitoring accrual will be available at the site visit.

**Figure 2:** Process for SRC monitoring of Accrual

<table>
<thead>
<tr>
<th>CRS Accrual Monitoring</th>
<th>SRC Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months (from activation)</td>
<td></td>
</tr>
<tr>
<td>Has the study enrolled 25% of Annual Projected Accrual?</td>
<td>PI may respond, explaining:</td>
</tr>
<tr>
<td>No</td>
<td>• scientific rationale</td>
</tr>
<tr>
<td>Notice to PI</td>
<td>• plans to increase enrollment</td>
</tr>
<tr>
<td>6 months (consecutive)</td>
<td></td>
</tr>
<tr>
<td>Has the study enrolled 25% of Annual Projected Accrual?</td>
<td>PI may respond, as above</td>
</tr>
<tr>
<td>No</td>
<td>SRC will vote:</td>
</tr>
<tr>
<td>Closure Notice to PI</td>
<td>• Keep study open</td>
</tr>
<tr>
<td></td>
<td>• Close</td>
</tr>
</tbody>
</table>

and is focused on human subjects protection. By agreement, full approval by SRC is required for the IRB to accept a protocol for consideration. This process is assured through the efforts of the Clinical Research Support Office, which is responsible for managing the SRC process and for submitting protocols to the

**PRMS operation relative to the IRB.**

The PRMS complements, but does not overlap with the functions or role of the IRB, which functions independently.
Consortium IRB. Study teams submit protocols directly to WIRB after SRC approval. The IRB has the authority to suspend or close a trial whenever necessary in order to protect the safety, welfare or rights of human subjects.

**Future Plans**

Immediate plans include:

1. Refine the set of metrics used to monitor the PRMS and provide these expanded metrics to the Research Groups and SRC.
2. Review the impact of Research Groups, including overall protocol portfolio performance, and continue work to enhance consistency of practice.
3. Monitor the performance of the revamped SRC committees, making adjustments in composition or process and providing additional training or guidance, as needed.
4. Assess the impact of the new accrual review process and make adjustments to achieve desired outcomes.
5. Implement the clinical trials management system.

Subsequent actions will be determined based on internal assessments, EAB guidance and feedback, and expert advisory reviews.
EARLY PHASE CLINICAL RESEARCH SUPPORT

Specific Aims

The Consortium’s Early Phase Clinical Research Support program provides funding for dedicated research nurse and data manager support, and other costs associated with generation of preliminary data, for the coordination and implementation of early phase cancer clinical trials initiated by Consortium members. Studies selected for EPCRS funding are high priority trials with the potential to improve diagnosis, prevention or treatment of cancer. This program will accomplish the following objectives:

1. Continue to expand the Consortium’s phase I clinical trials portfolio through support of innovative, proof-of-principle cancer studies to evaluate new agents, medical procedures and devices in order to provide the data necessary to apply for funding of later phase studies.

2. Strengthen the clinical research portfolio of established CCSG programs as well as solid tumor programs with sufficient “readiness” to be evaluated for CCSG program development during the new project period.

3. Stimulate new novel and collaborative early phase trials across the Consortium that incorporate imaging and radiation science, areas in which Consortium members have significant strength.

Overview

The Early Phase Clinical Research Support (EPCRS) program provides funding for dedicated research nurse and data manager support, and other clinical activities, for the coordination and implementation of innovative, proof-of-principle clinical trials initiated by Consortium members. A major objective of the current project period was to develop a robust Phase I Clinical Trials Initiative, an effort that has been enormously successful. The initiative has increased access to novel therapeutics for patients in the catchment area; serves as a forum for members from established CCSG disease programs and nascent programs to plan, prioritize and implement innovative and consequential phase I protocols; and has strengthened the clinical trials portfolio of several disease groups, including lung cancer, such that they are now positioned to be evaluated for formal CCSG program development during the next project period. EPCRS (formerly Protocol Specific Research Support) funds have been instrumental to these activities.

During the next project period, EPCRS funds will be invested in the most innovative early phase trials, with continued emphasis on solid tumor early phase clinical trials, in order to further strengthen established CCSG disease programs and to build the clinical trials portfolio of nascent solid tumor programs. Another area of focus will be trials that incorporate imaging and radiation science in order to stimulate new collaborations among experts in these disciplines and disease-focused investigators.

During the past grant period, EPCRS supported 11 early phase studies, resulting in two published papers, three meeting abstracts, two follow-on grants, and two studies that have since progressed to phase II trials. Additional detail on outcomes is provided in a table later in this section. In this application, EPCRS funds are requested to support three to four projects a year. Strategic priorities for use of these funds, and the process for their allocation, are described below.

Response to Comments in the 2008 Review

Protocol Specific Research Support was rated Very Good to Excellent at the 2008 review. With our Senior Leaders and the EAB, we have responded to the comments of the last site visit team and markedly strengthened this program. Review comments and responses include:

1) **A number of the previous studies were conducted in patients with hematologic malignancies. In the next grant period, it will be important to focus this support on innovative early phase clinical trials preferably linked to other scientific programs in the Center.** Of a total of 11 awards (an increase from seven studies supported during the prior period), four were for heme malignancy trials and seven were for trials in solid tumor cancers, including breast, head and neck, lung, and Merkel cell carcinoma. As described later in this section, EPCRS proposals for solid tumor studies will continue to be strongly encouraged.

2) **There is some concern with the robustness of investigator initiated early phase therapeutic clinical trials…Dr. Appelbaum provided a clear recruitment plan to expand the effort in early phase trials. Meeting this expectation represents an important milestone.** During the current project period, a Phase I Clinical Trials Initiative was established. While not a formal CCSG program, the phase I program has evolved into a highly...
successful structure led by an experienced medical oncologist director, Dr. John Thompson. The initiative has engaged members from all CCSG disease programs as well as a solid tumor groups not presented as formal CCSG programs. The Phase I group maintains an experienced team of research and data coordinators specializing in early phase trials that provide study support, and Dr. Thompson leads twice-monthly meetings at which new trials are proposed and progress of active trials is discussed. Clear success milestones have been achieved during the project period:

- The total number of Consortium phase I trials has increased from 50 to 83.
- The number of investigator-initiated phase I trials has increased from 2 to 22.
- Patient enrollment onto phase I therapeutic studies has nearly tripled, from 96 to 264.
- We have recruited six new faculty members during the project period whose research focuses on early phase clinical trials, including four who were recipients of CCSG new investigator funds.

**Use of EPCRS Funds During the Current Project Period and Allocation Process**

Eleven early phase trials were supported during the current project period. The table below summarizes each award and outcomes. Each project was awarded $25,000 to $40,000 direct costs, with approximately three awards made each year. Mac Cheever, the former Associate Director for Solid Tumor Research, was appointed by Director Corey to oversee allocation of these funds, which occurs annually.

The process includes an RFP issued to all Consortium members; Program Leaders are expected to encourage their members to submit proposals. Applications were reviewed by a committee consisting of Dr. Cheever, Deputy Director Appelbaum, and John Thompson, Phase I Initiative director. Proposals in the project period were reviewed for overall scientific merit, innovation, likelihood of providing preliminary data for subsequent studies and funding, and consideration was also given to assure funded proposals represented a diverse range of malignancies. The process is managed by Consortium Administration, which reviews proposals to ensure that budget requests are consistent with NCI and EPCRS guidelines, and disburses funds to awardees. All funded protocols are required to use the Consortium’s Protocol Review and Monitoring System, and all recipients are required to report their progress and outcomes to Consortium Administration on an annual basis. The table below summarizes the awards made in the current project period. One additional RFA will take place in 2014, which will fund ~3 new awards.

<table>
<thead>
<tr>
<th>Investigator/Program</th>
<th>Project Title</th>
<th>Phase</th>
<th>Anatomic Site (if applicable)</th>
<th>Duration</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pagel, John/Hematologic Malignancies</td>
<td>A Study of Oral Clofarabine Plus low-dose Cytarabine in Previously Treated AML Patients at Least 60 Years of Age</td>
<td>I</td>
<td>Hematologic Malignancies</td>
<td>12/1/09 – 11/30/10</td>
<td>This study is currently in the Phase II portion of the trial, treating at the MTD of 20 mg of oral clofarabine. A manuscript is in preparation.</td>
</tr>
<tr>
<td>Rodler, Eve/Women's Cancer</td>
<td>Phase I Study of ABT-888 in Combination with Cisplatin and Vinorelbine for Patients with Advanced Triple Negative Breast Cancer</td>
<td>I</td>
<td>Breast</td>
<td>4/1/10 – 3/31/11</td>
<td>This trial shows that in patients with metastatic triple negative breast cancer and/or BRCA mutation positive breast cancer, chemotherapy with cisplatin and vinorelbine is tolerable in combination with the PARP inhibitor, veliparib at a maximum tolerated dose (MTD) of 300mg orally twice daily. This is an active regimen offering a high response rate for this group of patients with a poor prognosis. The combination of cisplatin, vinorelbine and veliparib should be considered for further study to determine if the addition of the PARP inhibitor improves outcome compared to chemotherapy alone. Publication: Rodler, ET, Specht JM, Gadi VK, et al. Poster Session: Phase I Study of PARP Inhibitor ABT-888 (Veliparib) in Combination with Cisplatin and Vinorelbine for Patients with Advanced Triple Negative Breast Cancer and/or BRCA-Mutation</td>
</tr>
</tbody>
</table>
| Chow, Laura/  
Unaligned (Phase I Group) | Phase I Clinical Trial of VTX-2337, a small molecule Toll-Like Receptor 8 (TLR8) agonist in combination with cetuximab in patients with recurrent or metastatic squamous cell carcinomas of the head and neck (SCCHN) | I | Head and Neck | 11/1/10 – 10/31/11 | This research has led to a phase II randomized trial with the toll-like receptor agent and 5FU, cetuximab and platinum that we will be opening in 2014 at multiple institutions.  
An abstract has been submitted for presentation at the Multidisciplinary ASCO/ASTRO Head and Neck Symposium in Arizona February 20-22, 2014.  
A manuscript is in preparation. |
|---|---|---|---|---|---|
| Walter, Roland/  
Hematologic Malignancies | Addition of Cyclosporine and Pravastatin to Mitoxantrone/ Etoposide based Chemotherapy to Overcome Drug Resistance in Adults with Relapsed/ Refractory Acute Myeloid Leukemia | I | Hematologic Malignancies | 3/1/11 – 2/28/12 | In a group of very heavily pretreated patients with AML, we observed no efficacy (i.e. no patient achieved CR or CRi) but 3 patients experienced toxicities that qualified as dose-limiting toxicities as per protocol (1 patient at level 1, 2 patients at level 2).  
Based on the statistical approach we used for this study, the trial had reached a premature stop because of the presence of toxicity but lack of efficacy, and we requested closure to accrual in June 2012.  
| Patel, Shilpen/  
Immunology and Vaccine Dev. | A Phase I dose-intensification study using radiation therapy and concurrent cisplatin and etoposide for patients with inoperable small cell lung cancer | I | Lung | 3/1/11 – 2/28/12 | Patients are continuing to be accrued. |
| Walter, Roland/  
Hematologic Malignancies | Liposomal Cytarabine and Daunorubicin (CPX-351) for Adults with Untreated High-Risk MDS and Non-APL AML at High Risk of Treatment-Related Mortality | 0 | Hematologic Malignancies | 9/15/12 – 9/14/13 | Protracted contracting process with the manufacturer of CPX-351 delayed final IRB approval until April 2013. Accrual opened May 2013. Nine patients have enrolled and 3 additional patients being currently screened for trial participation. |
| Walter, Roland;  
Rajendra, Rajeev/  
Hematologic Malignancies | A Phase I Trial Examining the Safety and Tolerability of Mitoxantrone, Etoposide and Cytarabine (MEC) Chemotherapy Following Epigenetic Priming with Decitabine in Adults with Relapsed/ Refractory AML | I | Hematologic Malignancies | 9/5/12 – 9/14/13 | A total of 12 patients have enrolled on this study (6 patients at dose level 1, 6 patients at dose level 2). |
| Bhatia, Shailender / Immunology and Vaccine Dev. | A pharmacodynamic study of intratumoral injection of Glucopyranosyl Lipid A (GLA), a Toll-like receptor 4 (TLR4) agonist, in patients with Merkel Cell Carcinoma | 0 | Skin | 12/1/12 – 11/30/13 | This award was critical to the procurement of external funding in the amount of $161,351 from OncoSec Inc. and resulted in successful opening of the first investigator-initiated study in Merkel cell carcinoma at our center. It is also directly responsible for opening of a similar trial using IL-12 EP in melanoma, which is accruing currently. Preliminary trial results were presented at the 2012 Annual meeting of the Society of Immunotherapy of Cancer (SITC). Publication: Bhatia S., Blom A., Iyer J., et al. Intratumoral delivery of Interleukin-12 DNA with in vivo electroporation can lead to regression of injected and non-injected tumors in Merkel cell carcinoma: Results of a phase 2 study. Journal of Immunotherapy. 35(9): pg. 783, November-December 2012. |
| Mendez, Eduardo / Cancer Epi. Prevention & Control | A phase I clinical trial of MK-1775 in combination with neoadjuvant weekly docetaxel and cisplatin prior to surgery in p53 mutated squamous cell carcinoma of the head and neck(SCCHN) | 1 | Head and Neck | 9/1/12 – 12/31/14 | Trial pending due to issues obtaining MK-1775. |
| Zeng, Jing / unaligned | Pulmonary Functional Imaging for Radiation Treatment Planning for Lung Cancer | 0 | Lung | 9/1/13 – 8/31/14 | Too early to report results or impact. |
| Bhatia, Shailender / Immunology and Vaccine Dev. | A pharmacodynamic study of immunologic effects of single fraction, high-dose radiation therapy in patients with Merkel Cell Carcinoma | 0 | Skin | 11/1/13 – 10/31/14 | This award was critical to the procurement of peer-reviewed external funding of $250,000 from the prestigious WA state Life Sciences Development Foundation. This pilot study is slated to open to enrollment in December, 2013. |

### Planned Uses of EPCRS Funds

Dr. Corey has appointed Eric Holland, CCSG Associate Director of Solid Tumor and Translational Research (STTR), to oversee the process for allocating EPCRS funds in the new project period. $120,000 (direct costs) are requested to support 3 to 4 trials each year. Dr. Holland, a renowned neurosurgeon and laboratory brain cancer researcher, was recently recruited from Memorial Sloan Kettering Cancer Center by FHCRC and UW to direct Solid Tumor Translational Research across the Consortium; he also holds the institutional roles of of Senior Vice President and Director of the Human Biology Division at FHCRC and Director of the Alvord Brain Tumor Center at UW.

Dr. Holland will oversee an EPCRS process that will use a combination of open and targeted RFAs to ensure that CCSG funds support the best science overall as well as that funds are invested in areas designated as strategic priorities by senior leadership, including solid tumor research, imaging and radiation research to facilitate more multi-disciplinary solid tumor research, and immunotherapy.

During the past six months, with the support of Senior Leaders and Program Heads, Dr. Holland has conducted an assessment of all Consortium solid tumor groups to identify strengths and gaps and to develop metrics (i.e. grants, publications, collaborations, clinical trials) to monitor program development, and to identify disease groups in which investment of CCSG EPCRS and other funds would be particularly catalytic. While his goal will be to strengthen all solid tumor areas, from his assessment he has selected an initial subset of eight
disease groups that will be of particular focus for strategic investment of CCSG and institutional funds, with the goal of achieving national leadership in each of these areas. These groups include established CCSG disease programs with strong clinical research track records (GI – colon and pancreas, Prostate, and Women’s Cancers - breast and ovary) and groups with sufficient “readiness” to be considered for CCSG program development during the next project period (lung, brain, and head and neck). In another area of strategic focus, as described in the Planning and Evaluation section, Dr. Holland will work with CCSG program leaders to stimulate new collaborations among imaging and radiation investigators and solid tumor investigators during the project period. EPCRS funds will play a critical role in all of these activities.

Dr. Holland will work closely with the Phase I program under Dr. Thompson to promote and help support laboratory-based phase I trials in the specific disease sites such as brain, colon, lung, prostate, pancreas, breast, ovary, and head and neck, as well as the most innovative trials in immunotherapy and hematologic malignancies.

During the next project period, with input from Consortium senior leaders, priorities for EPCRS funds will be established each year by an EPCRS review committee chaired by Dr. Holland, which will include representatives with solid tumor, imaging, radiation, immunotherapy and heme malignancy expertise. Proposals will be solicited through the RFA process and managed by Consortium Administration as described above for the current project period. To demonstrate its commitment to continuing to support and expand the Consortium’s phase I trials portfolio, CCSG EPCRS funds will be augmented with institional funds.

While the allocation of funds each year will be determined by the committee, several examples of phase I studies in priority areas are listed below.

- A study of radiation for brain tumors avoiding the use of dexamethasone based on pre-clinical findings.
- Trials to vary the timing of radiation doses in brain tumors based on pre-clinical findings.
- Supporting the phase 0-1 portion of co-clinical (concurrent preclinical and clinical) trials testing the efficacy of small molecule inhibitors in lung, GI and other solid tumor cancers.
- Evaluating the utility of immunotherapy such as anti-PD1 antibodies in lung and brain tumor patients based on both human and preclinical trial data.