

# FRED HUTCHINSON/UNIVERSITY OF WASHINGTON CANCER CONSORTIUM PROGRESS REPORT FOR 2007

December 2007

Below are key highlights of scientific progress and accomplishments in 2007 for the Hutchinson/University of Washington Cancer Consortium.

## **Scientific Focus**

The Fred Hutchinson/University of Washington Cancer Consortium's (Consortium's) strategic goals include the following:

1. Build greater strength in clinical solid tumor research
2. Strengthen molecular approaches to population based sciences
3. Strengthen information technology and quantitative sciences
4. Encourage interdisciplinary and inter-institutional communication
5. Develop greater capability in biomarker discovery to enhance early disease detection and evaluate new therapeutics.
6. Develop a Phase I drug development program with capabilities that will complement the Consortium's focus on molecular biomarkers and strength in imaging

The Consortium continues to maintain its considerable strengths in fundamental sciences, clinical transplantation, hematologic diseases, prevention, and immunotherapy.

## **Major Scientific Accomplishments**

During this past year the Consortium's major scientific accomplishments included:

### **MRI screening detects additional cancers missed by mammography in women with recently diagnosed breast cancer**

Even after careful clinical and mammographic evaluation, cancer is found in the opposite (contralateral) breast in up to 10% of women who have received treatment for breast cancer in a single breast. **Dr. Constance Lehman** and colleagues conducted a study to determine whether magnetic resonance imaging (MRI) could improve on clinical breast examination and mammography in detecting breast cancers in the opposite breast soon after the initial diagnosis breast cancer. They performed MRI on 969 women with a recent diagnosis of breast cancer and no abnormalities on mammographic and clinical examination of the other breast. The diagnosis of MRI-detected cancer was confirmed by biopsy within 12 months after study entry. MRI detected breast cancer in the contralateral breast in 30 of 969 women who were enrolled in the study (3.1%). Thus, MRI can detect cancer in the contralateral breast that is missed by mammography and clinical examination at the time of the initial breast-cancer diagnosis. The findings helped to inform new guidelines for women at high risk of developing breast cancer. (Lehman CD et al. N Engl J Med. 2007 Mar 29;356(13):1295-303.)

### **“Tumor paint” to improve surgical removal of tumors**

A tumor paint developed by **Drs. Jim Olson, Robert Hackman, Norman Greenberg, William Grady** and colleagues will help surgeons see where a tumor begins and ends more precisely by illuminating the cancerous cells. The paint is a scorpion-derived peptide called chlorotoxin that is linked to the molecular beacon Cy5.5. Until now, there has been no way to allow surgeons to see tumors "live" during surgery. Chlorotoxin: Cy5.5 is a fluorescent molecular beacon that emits photons in the near infrared spectrum. This illumination gives surgeons a better chance of removing all of the cancerous cells during surgery without injuring surrounding healthy tissue. This is particularly significant in the brain, where approximately 80 percent of malignant cancers recur at the edges of the surgical site. Current technology, such as magnetic-resonance imaging (MRI) can distinguish tumors from healthy tissue only if more than 1 million cancer cells are present. But Cy5.5 can identify tumors with as few as 200 cancer cells, making it 500 times more sensitive than MRI. (Veisoh, M et al. Cancer Research 67(14):6882-88, 2007.)

### **Potential preventive interventions for esophageal cancer**

**Drs. Brian Reid, Patricia Blount, Tom Vaughan, Peter Rabinovitch** and colleagues found that people with the most-aggressive form of Barrett's esophagus, a precancerous condition that can lead to esophageal cancer, may benefit the most from preventive therapy with aspirin, ibuprofen and other nonsteroidal anti-inflammatory drugs, or NSAIDs. The researchers also identified a cluster of four known cancer biomarkers, or genetic abnormalities, in people with Barrett's that significantly increases their risk of developing esophageal cancer. The researchers found that those with three or more of the cancer biomarkers upon enrollment in the study who also used aspirin or other NSAIDs had a 30 percent risk of esophageal cancer after 10 years, while those with the same biomarkers who did not use NSAIDs had a 79 percent risk of developing cancer within a decade of joining the study. The biomarkers hold promise for use in a clinical setting to identify which Barrett's patients are most likely to develop esophageal cancer and therefore benefit from aggressive cancer surveillance via endoscopy and chemoprevention with aspirin and other NSAIDs. (Galipeau PC et al., PLoS Med 4:e67.)

### **Vaccine against human papillomavirus prevents precursors to cervical cancer**

Infection with certain subtypes of human papillomavirus (HPV) can cause cervical cancer. **Dr. Laura Koutsky** and colleagues have been instrumental in the development of a vaccine to prevent infection with these HPV strains. In a trial sponsored by Merck to test the vaccine, known as Gardasil, the researchers evaluated an HPV vaccine that targets cancer-causing subtypes of the virus for the ability to prevent precursor conditions to cervical cancer (for example, genital warts) or cancer associated with these viral strains in more than 12,000 women aged 15 to 26. The women were followed for an average of 3 years after administration of the first dose. The HPV vaccine was nearly 100% effective in preventing the cancer precursor conditions and cancer in women who were not previously infected with these viral strains. (FUTURE II Study Group, N Engl J Med. 2007 May 10;356(19):1915-27.)

### **Significant Published Scientific Accomplishments**

The following brief paragraphs describe over 30 of the most significant publications from the Consortium over the last year.

The reprogramming of DNA-binding specificity is an important challenge for computational protein design and has considerable practical relevance for biotechnology and medicine. **Drs.**

**David Baker, Barry Stoddard and Ray Monnat** demonstrated the computational redesign of the cleavage specificity of the intron-encoded homing endonuclease I-MsoI using a physically realistic atomic-level forcefield. A redesigned enzyme that was predicted to display altered target site specificity, while maintaining wild-type binding affinity, was experimentally characterized. The redesigned enzyme binds and cleaves the redesigned recognition site approximately 10,000 times more effectively than does the wild-type enzyme, with a level of target discrimination comparable to the original endonuclease. These results suggest that computational protein design methods can have an important role in the creation of novel highly specific endonucleases for gene therapy and other applications. (Ashworth J et al. *Nature*. 2006 441(7093):656-9.; Comment in: *Nat Biotechnol*. 2006 Aug;24(8):954-5.)

Current criteria for the selection of unrelated donors for hematopoietic cell transplantation (HCT) include matching for the alleles of each human leukocyte antigen (HLA) locus within the major histocompatibility complex (MHC). Graft-versus-host disease (GVHD), however, remains a significant and potentially life-threatening complication even after HLA-identical unrelated HCT. The total number of transplantation antigens is unknown. Genes that influence transplantation outcome could be identified by using linkage disequilibrium (LD)-mapping approaches, if the extended MHC haplotypes of the unrelated donor and recipient could be defined. **Drs. Effie Petersdorf, Ted Gooley and Paul Martin** isolated DNA strands extending across 2 million base pairs of the MHC to determine the physical linkage of HLA-A, -B, and -DRB1 alleles in 246 HCT recipients and their HLA-A, -B, -C, -DRB1, -DQB1 allele-matched unrelated donors. MHC haplotype mismatching was associated with a statistically significantly increased risk of severe acute GVHD (odds ratio 4.51; 95% confidence interval [CI], 2.34-8.70,  $p < 0.0001$ ) and with lower risk of disease recurrence (hazard ratio 0.45; 95% CI, 0.22-0.92,  $p = 0.03$ ). They conclude the MHC harbors genes that encode unidentified transplantation antigens. The phasing method provides an approach for mapping novel MHC-linked transplantation determinants and a means to decrease GVHD-related morbidity after HCT from unrelated donors. (Petersdorf EW, Malkki M, Gooley TA, Martin PJ, Guo Z. *PLoS Med*. 2007 Jan;4(1):e8.)

Terminal differentiation is often coupled with permanent exit from the cell cycle, yet it is unclear how cell proliferation is blocked in differentiated tissues. **Dr. Bruce Edgar** examined the process of cell cycle exit in *Drosophila* wings and eyes and discovered that cell cycle exit can be prevented or even reversed in terminally differentiating cells by the simultaneous activation of E2F1 and either Cyclin E/Cdk2 or Cyclin D/Cdk4. Enforcing both E2F and Cyclin/Cdk activities is required to bypass exit because feedback between E2F and Cyclin E/Cdk2 is inhibited after cells differentiate, ensuring that cell cycle exit is robust. In some differentiating cell types (e.g., neurons), known inhibitors including the retinoblastoma homolog Rbf and the p27 homolog Dacapo contribute to parallel repression of E2F and Cyclin E/Cdk2. In other cell types, however (e.g., wing epithelial cells), unknown mechanisms inhibit E2F and Cyclin/Cdk activity in parallel to enforce permanent cell cycle exit upon terminal differentiation. (Buttitta LA et al. *Dev Cell*. 2007 12(4):631-43.)

CD8-positive T lymphocytes recognize peptides that are usually derived from the degradation of cellular proteins and are presented by class I molecules of the major histocompatibility complex. **Dr. Edus Warren** and colleagues described a human minor histocompatibility antigen created by a polymorphism in the SP110 nuclear phosphoprotein gene. The antigenic peptide comprises two noncontiguous SP110 peptide segments spliced together in reverse order to that in which they occur in the predicted SP110 protein. The antigenic peptide could be produced *in vitro* by incubation of precursor peptides with highly purified 20S proteasomes. Cutting and splicing probably occur within the proteasome by transpeptidation. (Warren, E.H. et al. *Science* (2006) 313:1444-1447.)

Primate genomes contain a large number of endogenous retroviruses and encode evolutionarily dynamic proteins that provide intrinsic immunity to retroviral infections. **Drs. Harmit Malik and Michael Emerman** reported the resurrection of the core protein of a 4-million-year-old endogenous virus from the chimpanzee genome and show that the human variant of the intrinsic immune protein TRIM5alpha can actively prevent infection by this virus. However, we suggest that selective changes that have occurred in the human lineage during the acquisition of resistance to this virus, and perhaps similar viruses, may have left our species more susceptible to infection by human immunodeficiency virus type 1 (HIV-1). (Kaiser SM, Malik HS, Emerman M. *Science*. 2007 Jun 22;316(5832):1756-8.)

The glmS ribozyme is the only natural catalytic RNA known to require a small-molecule activator for catalysis. This catalytic RNA functions as a riboswitch, with activator-dependent RNA cleavage regulating glmS messenger RNA expression. **Dr. Adrian Ferré-D'Amaré** reported the crystal structures of the glmS ribozyme in precleavage states that are unliganded or bound to the competitive inhibitor glucose-6-phosphate and in the postcleavage state. All structures superimpose closely, revealing a remarkably rigid RNA that contains a preformed active and coenzyme-binding site. Unlike other riboswitches, the glmS ribozyme binds its activator in an open, solvent-accessible pocket. The structures suggest that the amine group of the glmS ribozyme-bound coenzyme performs general acid-base and electrostatic catalysis. (Klein DJ, Ferré-D'Amaré AR. *Science*. 2006 Sep 22;313(5794):1752-6.; Comment in: *Science*. 2006 Sep 22;313(5794):1745-7.)

Cancer cells contain numerous clonal mutations, i.e., mutations that are present in most or all malignant cells of a tumor and have presumably been selected because they confer a proliferative advantage. An important question is whether cancer cells also contain a large number of random mutations. Such random mutations could contribute to the morphologic and functional heterogeneity of cancers and include mutations that confer resistance to therapy. **Drs. Keith Loeb, Larry Loeb and Larry True** have postulated that malignant cells exhibit a mutator phenotype resulting in the generation of random mutations throughout the genome. They have recently developed an assay to quantify random mutations in human tissue with unprecedented sensitivity. Here, we report measurements of random single-nucleotide substitutions in normal and neoplastic human tissues. In normal tissues, the frequency of spontaneous random mutations is exceedingly low, less than  $1 \times 10^{-8}$  per base pair. In contrast, tumors from the same individuals exhibited an average frequency of  $210 \times 10^{-8}$  per base pair, an elevation of at least two orders of magnitude. The data document tumor heterogeneity at the single-nucleotide level, indicate that accelerated mutagenesis prevails late into tumor progression, and suggest that elevation of random mutation frequency in tumors might serve as a novel prognostic indicator. (Bielas JH et al. *Proc Natl Acad Sci U S A*. 2006 Nov 28;103(48):18238-42.)

Cellular memory is maintained at homeotic genes by cis-regulatory elements whose mechanism of action is unknown. **Dr. Steven Henikoff** examined chromatin at *Drosophila* homeotic gene clusters by measuring, at high resolution, levels of histone replacement and nucleosome occupancy. Homeotic gene clusters display conspicuous peaks of histone replacement at boundaries of cis-regulatory domains superimposed over broad regions of low replacement. Peaks of histone replacement closely correspond to nuclease-hypersensitive sites, binding sites for Polycomb and trithorax group proteins, and sites of nucleosome depletion. The results suggest the existence of a continuous process that disrupts nucleosomes and maintains accessibility of cis-regulatory elements. Mito Y, Henikoff JG, Henikoff S. *Science*. 2007 315(5817):1408-11.)

The cell cycle inhibitor p27Kip1 also has cyclin-cyclin-dependent kinase (CDK)-independent functions. To investigate the significance of these functions in vivo, **Drs. Jim Roberts, Bruce Clurman** and colleagues generated a knock-in mouse in which four amino acid substitutions in the *cdkn1b* gene product prevent its interaction with cyclins and CDKs (p27CK<sup>-</sup>). In striking contrast to complete deletion of the *cdkn1b* gene, which causes spontaneous tumorigenesis only in the pituitary, the p27CK<sup>-</sup> protein dominantly caused hyperplastic lesions and tumors in multiple organs, including the lung, retina, pituitary, ovary, adrenals, spleen, and lymphomas. Moreover, the high incidence of spontaneous tumors in the lung and retina was associated with amplification of stem/progenitor cell populations. Thus, the p27CK<sup>-</sup> mouse unveils a dual role for p27 during tumorigenesis: It is a tumor suppressor by virtue of its cyclin-CDK regulatory function, and also an oncogene through a cyclin-CDK-independent function. This may explain why the *cdkn1b* gene is rarely inactivated in human tumors, and the p27CK<sup>-</sup> mouse in which the tumor suppressor function is lost but the cyclin-CDK-independent-oncogenic-function is maintained may represent a more faithful model for the widespread role of p27 misregulation in human cancers than the p27 null. (Besson A et al. *Genes Dev.* 2007 Jul 15;21(14):1731-46. Epub 2007 Jul 12.; Comment in: *Genes Dev.* 2007 21(14):1703-6.)

T cells causing autoimmunity must escape tolerance. **Dr. Mike Bevan** observed that CD8(+) T cells with high avidity for an antigen expressed in the pancreas, kidney, and thymic medulla were efficiently removed from a polyclonal repertoire by central and peripheral tolerance mechanisms. However, both mechanisms spared low-avidity T cells from elimination. Neither the introduction of activated, self-antigen-specific CD4(+) helper T cells nor a global inflammatory stimulus were sufficient to activate the low-avidity CD8(+) T cells and did not break tolerance. In contrast, challenge with a recombinant bacterium expressing the self antigen primed the low-avidity T cells, and the animals rapidly developed autoimmune diabetes. The findings suggest that whereas thymic and peripheral tolerance mechanisms remove cells that can be primed by endogenous amounts of self antigen, they do not guard against tissue destruction by low-avidity effector T cells, which have been primed by higher amounts of self antigen or by crossreactive antigens. (Zehn, D. and M.J. Bevan. *Immunity* (2006) 25:261-270.)

Activated CD8(+) T cells discriminate infected and tumor cells from normal self by recognizing MHC class I-bound peptides on the surface of antigen-presenting cells. The mechanism by which MHC class I molecules select optimal peptides against a background of prevailing suboptimal peptides and in a considerably proteolytic ER environment remained unknown. **Dr. Stan Riddell** and colleagues identified protein disulfide isomerase (PDI), an enzyme critical to the formation of correct disulfide bonds in proteins, as a component of the peptide-loading complex. They show that PDI stabilizes a peptide-receptive site by regulating the oxidation state of the disulfide bond in the MHC peptide-binding groove, a function that is essential for selecting optimal peptides. Furthermore, they demonstrate that human cytomegalovirus US3 protein inhibits CD8(+) T cell recognition by mediating PDI degradation, verifying the functional relevance of PDI-catalyzed peptide editing in controlling intracellular pathogens. These results establish a link between thiol-based redox regulation and antigen processing. (Park B, Lee S, Kim E, Cho K, Riddell SR, Cho S, Ahn K. *Cell.* (2006) 127:369-82.)

It is important to integrate the computations and code used in data analyses, methodological descriptions and simulations with the documents that describe and rely on them. This integration allows readers to both verify and adapt the claims in the documents, and allows authors to easily reproduce the results in the future and present the document's contents in a different medium. **Dr. Robert Gentleman** described a software framework for both authoring and distributing these integrated, dynamic documents that contain text, code, data, and any

auxiliary content needed to recreate the computations. The documents are dynamic in that the contents can be recalculated each time a view of the document is generated. His model treats a dynamic document as a master or "source" document from which one can generate different views in the form of traditional, derived documents for different audiences, and introduces the concept of a *compendium* as a container for one or more dynamic documents and the different elements needed when processing them. (Gentleman R, Lang DT., Journal of Computational and Graphical Statistics 2007;16:1-24.)

Recent human deaths due to infection by highly pathogenic (H5N1) avian influenza A virus have raised the specter of a devastating pandemic like that of 1917–1918, should this avian virus evolve to become readily transmissible among humans. **Dr. Ira Longini** used a large-scale stochastic simulation model to investigate the spread of a pandemic strain of influenza virus through the U.S. population of 281 million individuals for  $R_0$  (the basic reproductive number) from 1.6 to 2.4. The simulations demonstrate that, in a highly mobile population, restricting travel after an outbreak is detected is likely to delay slightly the time course of the outbreak without impacting the eventual number ill. The model suggests that the rapid production and distribution of vaccines, even if poorly matched to circulating strains, could significantly slow disease spread and limit the number ill to <10% of the population, particularly if children are preferentially vaccinated. Alternatively, the aggressive deployment of several million courses of influenza antiviral agents in a targeted prophylaxis strategy may contain a nascent outbreak with low  $R_0$ . For higher  $R_0$ , they predict that multiple strategies in combination (involving both social and medical interventions) will be required to achieve similar limits on illness rates. (Germann et al. Proceedings of the National Academy of Sciences 2006;103:5935-5940.)

The breast cancer suppressor protein, BRCA1, is a ubiquitin ligase expressed in a wide range of tissues. However, inheritance of a single BRCA1 mutation significantly increases a woman's lifetime chance of developing tissue-specific cancers in the breast and ovaries. Recently, studies have suggested this tissue specificity may be linked to inhibition of estrogen receptor alpha (ERalpha) transcriptional activation by BRCA1. **Dr. Rachel Kleivit** showed that ERalpha is a putative substrate for the BRCA1/BARD1 ubiquitin ligase, suggesting a possible mechanism for regulation of ERalpha activity by BRCA1. The results show ERalpha is predominantly monoubiquitinated in a reaction that involves interactions with both BRCA1 and BARD1. The identification of ERalpha as a putative BRCA1/BARD1 ubiquitination substrate reveals a potential link between the loss of BRCA1/BARD1 ligase activity and tissue-specific carcinoma. (Eakin, C. M. et al. Proc Natl Acad Sci U S A. 2007 104(14):5794-9.)

Despite their potential to impact diagnosis and treatment of cancer, biomarker discovery is plagued with difficulties ranging from technological to biological. To minimize biological variation and facilitate testing of proteomic approaches, **Drs. Amanda Paulovich, Martin McIntosh, Christopher Kemp** and colleagues performed LC-MS/MS of tumor and normal mammary tissue from a conditional HER2/Neu-driven mouse model of breast cancer, identifying 6758 peptides representing >700 proteins. They developed a novel statistical approach (SASPECT) for prioritizing differentially represented proteins in LC-MS/MS datasets and identified proteins over- or under-represented in tumors. They confirmed the overproduction of multiple proteins at the tissue level, identified fibulin-2 as a plasma biomarker, and extensively characterized osteopontin as a plasma biomarker capable of early disease detection in the mouse. The results show that a staged pipeline employing shotgun-based comparative proteomics for biomarker discovery and multiple reaction monitoring for confirmation of biomarker candidates is capable of finding novel tissue and plasma biomarkers in a mouse model of breast cancer. Furthermore, the approach can be extended to find biomarkers relevant to human disease. (Whiteaker JR et al. Journal of Proteome Research 2007; In Press.)

Fine particulate air pollution has been linked to cardiovascular disease, but previous studies have assessed only mortality and differences in exposure between cities. **Drs. Lianne Sheppard, Garnet Anderson** and colleagues examined the association of long-term exposure to particulate matter of less than 2.5  $\mu\text{m}$  in aerodynamic diameter (PM<sub>2.5</sub>) with cardiovascular events in 65,893 postmenopausal women without previous cardiovascular disease. A total of 1816 women had one or more fatal or nonfatal cardiovascular events, as confirmed by a review of medical records, including death from coronary heart disease or cerebrovascular disease, coronary revascularization, myocardial infarction, and stroke. In 2000, levels of PM<sub>2.5</sub> exposure varied from 3.4 to 28.3  $\mu\text{g}$  per cubic meter (mean, 13.5). Each increase of 10  $\mu\text{g}$  per cubic meter was associated with a 24% increase in the risk of a cardiovascular event and a 76% increase in the risk of death from cardiovascular disease. They concluded that long-term exposure to fine particulate air pollution is associated with the incidence of cardiovascular disease and death among postmenopausal women. Exposure differences within cities are associated with the risk of cardiovascular disease. (Kristin A. Miller et al. *N Engl J Med* 2007;356:447-458.)

Adult tissues need to solve the same problems as embryonic tissue: maintaining form even as constituent cells proliferate, move, differentiate and die. The maintenance of epithelial tissues requires, like morphogenesis, a method of relating cell position to function. **Dr. John Potter** discussed that by analogy with morphogens, morphostats maintain normal tissue microarchitecture in the adult. In addition to established molecular abnormalities, the most prominent feature of cancer is the disruption of tissue microarchitecture. Cancer arises more readily in tissues where morphostatic fields fail, in tissues removed from their normal morphostatic fields, and in areas situated at the junction of two tissues where morphostatic fields compete or conflict. Known morphogens are agents that are capable of creating morphostatic fields; disruption of morphogen signalling is increasingly implicated in the aetiology of various cancers. Morphostats most plausibly originate in stem cells and in stromal cells that are adjacent to epithelia. Various testable hypotheses follow on from this, most notably, that some cancers will arise as the result of a different two-hit model (either mutation or hypermethylation of genes) — one in a stromal cell and one in the epithelium. (John D. Potter *Nature* 2007;7:464-474.)

High grade prostatic intraepithelial neoplasia is likely a premalignant lesion of the prostate. Decreasing the frequency of high grade PIN may decrease the risk of prostate cancer. The Prostate Cancer Prevention Trial is a randomized, placebo controlled clinical trial that enrolled 18,882 men without evidence of prostate cancer and randomized them to 5 mg finasteride daily or placebo. **Dr. Mary Redman** and colleagues evaluated the impact of finasteride on the risk of a needle biopsy diagnosis of high grade prostatic intraepithelial neoplasia. The number of men evaluable for high grade prostatic intraepithelial neoplasia was 4,568 in the finasteride group and 4,886 in the placebo group. High grade prostatic intraepithelial neoplasia alone was diagnosed in 276 men (6.0%) in the finasteride group vs 347 (7.1%) in the placebo group. High grade prostatic intraepithelial neoplasia accompanied by prostate cancer was diagnosed in 144 men (3.2%) in the finasteride group vs 223 (4.6%) in the placebo group. Finasteride significantly decreased the overall risk of high grade prostatic intraepithelial neoplasia (alone and with cancer) from 570 cases (11.7%) in the placebo group to 420 (9.2%) in the finasteride group. Finasteride significantly decreased the risk of high grade PIN, which may explain how finasteride decreased prostate cancer in the Prostate Cancer Prevention Trial, supporting the notion that high grade prostatic intraepithelial neoplasia is a premalignant lesion of the prostate. The findings provide new information relevant to the consideration of finasteride for prostate cancer prevention. (Ian M. Thompson et al. *J of Urology* 2007;178:107-9.)

Treating breast cancer under the constraints of significantly limited health care resources poses unique challenges that are not well addressed by existing guidelines. **Dr. Ben Anderson** and colleagues present evidence-based guidelines for systematically prioritizing cancer therapies across the entire spectrum of resource levels. Compared with the treatment of early breast cancer, the treatment of advanced breast cancer is more resource intensive and generally has poorer outcomes, highlighting the potential benefit of earlier detection and diagnosis, both in terms of conserving scarce resources and in terms of reducing morbidity and mortality. Use of the scheme outlined here should help ministers of health, policymakers, administrators, and institutions in limited-resource settings plan, establish, and gradually expand breast cancer treatment services for their populations. (Eniu A, Carlson RW, Aziz Z, Bines J, Hortobágyi GN, Bese NS, Love RR, Vikram B, Kurkure A, **Anderson BO**. *Breast J*. 2006 Jan-Feb;12 Suppl 1:S38-53.)

Aside from chronic reflux, the etiology of Barrett's esophagus (BE) remains largely unknown. **Dr. Tom Vaughan** led a case-control study that investigated body mass index (BMI), central adiposity, and cigarette smoking and risk of BE in 193 Washington residents newly diagnosed with specialized intestinal metaplasia on at least 1 of 4 esophageal biopsy specimens taken at community gastroenterology clinics. All measures of central adiposity were strongly related to BE risk. For the high category of waist-to-hip ratio (WHR), the adjusted odds ratios were 2.4 for all cases, 2.8 for visible BE, and 4.3 for LSBE. In contrast, the associations with BMI were weaker. Cigarette smoking moderately increased risk but with no evidence of a dose-dependent response or increasing strength by case group. These observations indicate the importance of identifying the mechanisms underlying obesity's role in BE and esophageal adenocarcinoma, and suggest that weight loss might be a fruitful approach to the prevention of these diseases. (Edelstein ZR et al. *Gastroenterology*. 2007 Aug;133(2):403-11.)

**Dr. Ray Monnat** developed a novel system to create DNA double-strand breaks (DSBs) at defined endogenous sites in the human genome, and used this system to detect protein recruitment and loss at and around these breaks by chromatin immunoprecipitation (ChIP). The detection of human ATM protein at site-specific DSBs required functional NBS1 protein, ATM kinase activity and ATM autophosphorylation on Ser 1981. DSB formation led to the localized disruption of nucleosomes, a process that depended on both functional NBS1 and ATM. These two proteins were also required for efficient recruitment of the repair cofactor XRCC4 to DSBs, and for efficient DSB repair. These results demonstrate the functional importance of ATM kinase activity and phosphorylation in the response to DSBs, and support a model in which ordered chromatin structure changes that occur after DNA breakage depend on functional NBS1 and ATM, and facilitate DNA DSB repair. (Berkovich E, Monnat RJ Jr, Kastan MB. *Nat Cell Biol*. 2007 Jun;9(6):683-90.)

Currently, screening for ovarian cancer is not recommended for the general population. **Drs. Barbara Goff, Robyn Andersen and Charles Drescher** conducted a case-control study of 149 women with ovarian cancer, 255 women who were in a screening program and 233 women who were referred for pelvic/abdominal ultrasound by inviting women to complete a survey of symptoms. Symptom types, frequency, severity, and duration were compared between cases and controls and a symptom index was developed, which was tested for sensitivity and specificity. Symptoms that were associated significantly with ovarian cancer were pelvic/abdominal pain, urinary urgency/frequency, increased abdominal size/bloating, and difficulty eating/feeling full when they were present for <1 year and occurred >12 days per month. In a logistic regression analysis, symptoms that were associated independently with cancer were pelvic/abdominal pain ( $P < .001$ ), increased abdominal size/bloating ( $P < .001$ ), and difficulty eating/feeling full ( $P = .010$ ). The index had a sensitivity of 56.7 for early-stage disease

and 79.5% for advanced-stage disease. Specificity was 90% for women age >50 years and 86.7% for women age <50 years. Specific symptoms in conjunction with their frequency and duration were useful in identifying women with ovarian cancer. (Goff BA et al. Cancer. 2007 Jan 15;109(2):221-7.)

Accumulating data indicate that tumor-infiltrating regulatory T cells (Treg) are present in human tumors and locally suppress antitumor immune cells. In this study, **Drs. Nancy Kiviat and Andre Lieber** found an increased Treg/CD8 ratio in human breast and cervical cancers. A similar intratumoral lymphocyte pattern was observed in a mouse model for cervical cancer (TC-1 cells). In this model, systemic Treg depletion was inefficient in controlling tumor growth. Furthermore, systemic CTL-associated antigen-4 (CTLA-4) blockade, an approach that can induce tumor immunity in other tumor models, did not result in TC-1 tumor regression but led to spontaneous development of autoimmune hepatitis. They hypothesized that continuous expression of an anti-CTLA-4 antibody localized to the tumor site could overcome Treg-mediated immunosuppression and locally activate tumor-reactive CD8+ cells, without induction of autoimmunity. They created TC-1 cells that secrete a functional anti-CTLA-4 antibody. When injected into immunocompetent mice, the growth of TC-1/alphaCTLA-4-gamma1 tumors was delayed compared with control TC-1 cells and accompanied by a reversion of the intratumoral Treg/CD8 ratio due to an increase in tumor-infiltrating IFN-gamma-producing CD8+ cells. When local anti-CTLA-4 antibody production was combined with Treg inhibition, permanent TC-1 tumor regression and immunity was induced. Importantly, no signs of autoimmunity were detected in mice that received local CTLA-4 blockade alone or in combination with Treg depletion. (Tuve S et al. Cancer Res. 2007 67(12):5929-39.)

There is increasing evidence that genome-wide association (GWA) studies represent a powerful approach to the identification of genes involved in common human diseases. The Wellcome Trust Case Control Consortium, including **Dr. Lon Cardon**, described a joint GWA study of ~2,000 individuals for each of 7 major diseases and a shared set of ~3,000 controls in the British population. Case-control comparisons identified 24 independent association signals at  $P < 5 \times 10^{-7}$ : 1 in bipolar disorder, 1 in coronary artery disease, 9 in Crohn's disease, 3 in rheumatoid arthritis, 7 in type 1 diabetes and 3 in type 2 diabetes. This study thus represents a thorough validation of the GWA approach; has generated a genome-wide genotype database for future studies of common diseases in the British population; and shown that, provided individuals with non-European ancestry are excluded, the extent of population stratification in the British population is generally modest. The findings offer new avenues for exploring the pathophysiology of these important disorders. (Wellcome Trust Case Control Consortium 2007 Nature 447: 661-678.)

Haplotypes are a powerful tool for identifying the genetic basis of common complex diseases. Disease-association mapping requires molecular methods for haplotyping biallelic SNP variation and highly complex polymorphisms. **Dr. Effie Petersdorf** and colleagues developed a method for phasing HLA-A, HLA-B, and HLA-DRB1 alleles on chromosome 6 in unrelated individuals. This method uses the highly polymorphic HLA-B locus to discriminate the two HLA haplotypes in heterozygous individuals and its ideal location 1.4 Mbp telomeric to HLA-DRB1 and 1.2 Mbp centromeric to HLA-A to capture 2-Mbp-long genomic DNA. Genomic DNA representing a single HLA-B-captured haplotype is genotyped for HLA-A and HLA-DRB1 alleles and linkage to HLA-B is established. Proof of principle was established in a large blinded study of phase-known samples. Availability of an efficient method for MHC haplotype phase determination will facilitate the mapping of causative MHC-resident genes in many human diseases and has the potential to be broadened to other polymorphic gene complexes. (Guo Z et al. Proc Natl Acad Sci 103: 6964, 2006.)

A physiologic role for Notch signaling in hematopoiesis has been clearly defined in lymphoid differentiation, with evidence suggesting a critical role in T-cell versus B-cell fate decisions. Previously, **Drs. Irwin Bernstein and Paul Martin** demonstrated that activation of endogenous Notch receptors by culture of murine lin(-)Sca-1(+)-kit(+) (LSK) hematopoietic progenitors with exogenously presented Delta1(ext-IgG) promoted early T-cell differentiation and increased the number of progenitors capable of short-term lymphoid and myeloid reconstitution. Now they show that culture of LSK precursors with Delta1(ext-IgG) increases the number of progenitors that are able to rapidly repopulate the thymus and accelerate early T-cell reconstitution with a diversified T-cell receptor repertoire. Most of the early T-cell reconstitution originated from cells that expressed lymphoid-associated antigens, whereas the most efficient thymic repopulation on a per cell basis originated from the smaller number of cultured cells that did not express lymphoid-associated antigens. These findings demonstrate the potential of Delta1(ext-IgG)-cultured cells for accelerating early immune reconstitution after hematopoietic cell transplantation. (Dallas MH et al. *Blood*. 2007 Apr 15;109(8):3579-87.)

The Wnt and Notch signaling pathways have been independently shown to play a critical role in regulating hematopoietic cell fate decisions. Previously results have shown that induction of Notch signaling in human CD34(+)-CD38(-) cord blood cells by culture with the Notch ligand Delta1 resulted in an increased number of cells with T or NK lymphoid precursor phenotype. Here **Drs. Colleen Delaney, Randall Moon and Irwin Bernstein** show that addition of Wnt3a to Delta1 further increased the percentage of CD34(-) CD7(+) and CD34(-)CD7(+)cyCD3(+) cells with increased expression of CD3epsilon and preTalpha. In contrast, culture with Wnt3a alone did not increase generation of CD34(-)CD7(+) precursors or expression of CD3epsilon or preTalpha gene. Furthermore, Wnt3a increased the amount of activated Notch1, suggesting that Wnt modulates Notch signaling by affecting Notch protein levels. In contrast, addition of a Wnt signaling inhibitor to Delta1 increased the percentage of CD56(+) NK cells. These results demonstrate regulation of Notch signaling by the Wnt pathway plays a critical role in differentiation of precursors along the early T or NK differentiation pathway. (Aoyama K et al. 2007 *Stem Cells* Jul 19; In press.)

Current research is inconclusive regarding the effect of obesity on outcomes after a prostate cancer diagnosis. **Drs. Janet Stanford and Alan Kristal** examined associations between obesity and the risks of developing metastasis or prostate cancer-specific mortality in a population-based cohort of 752 men with prostate cancer. Obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) was associated with a significant increase in prostate cancer mortality. Among men who were diagnosed with local- or regional-stage disease, obesity also was associated with an increased risk of developing metastasis (HR, 3.61; 95% CI, 1.73-7.51). Associations generally were consistent across strata defined by Gleason score (2-6 or 7 [3 + 4] vs 7 [4 + 3] or 8-10), stage (local vs regional/distant for mortality), and primary treatment (androgen-deprivation therapy use: yes vs no). They conclude that obesity at the time of diagnosis was associated with increased risks of prostate cancer metastasis and death. The increased risk of prostate cancer death or metastasis associated with obesity largely was independent of key clinical prognostic factors at diagnosis. (Gong Z et al. *Cancer*. Mar 15 2007;109(6):1192-1202.)

Human embryonic stem cells (hESCs) are important tools for the study of stem cell biology and may ultimately be used in cellular therapies and regenerative medicine. For hESCs to achieve their potential, stable genetic modification of the hESC genome will be required. **Drs. Carol Ware and David Russell** have studied the transduction of hESCs by vectors based on foamy virus (FV), an integrating retrovirus with no known pathogenicity. We find that hESCs and also ESCs derived from rhesus monkeys can be efficiently transduced by FV vectors at frequencies

of 14-48%. Integration of FV vector DNA was demonstrated by Southern blot analysis, and stable expression was observed from a single integrated provirus in several clones. Transduced hESCs expressed markers characteristic of undifferentiated cells, differentiated and expressed markers from all three germ layers after serum exposure, and formed teratomas with persistent transgene expression in differentiated cells. Thus, FV vectors are promising tools for the genetic modification of hESCs. (Gharwan H et al. Mol Ther. 2007 In press).

In 87 patients with aplastic anemia who failed to respond to immunosuppressive treatment, **Drs. Joachim Deeg, Ann Woolfrey, Barry Storer and colleagues** determined the minimal dose of total body irradiation (TBI) required when added to antithymocyte globulin (ATG) plus cyclophosphamide to achieve engraftment of unrelated donor marrow. TBI was started at 3 x 200 cGy, to be escalated or deescalated in steps of 200 cGy depending on graft failure or toxicity. Patients were aged 1.3 to 53.5 years (median, 18.6 years). The interval from diagnosis to transplantation was 3 to 328 months (median, 14.6 months). Donors were HLA-A, -B, -C, -DR, and -DQ identical for 62 patients, and nonidentical for 1 to 3 HLA loci at the antigen or allele level for 25. The optimum TBI dose was 1 x 200 cGy. Nine patients did not tolerate ATG and were prepared with CY + TBI. Graft failure occurred in 5% of patients. With a median follow-up of 7 years, 38 (61%) of 62 HLA-identical, and 10 (40%) of 25 HLA-nonidentical transplant recipients are surviving. The highest survival rate with HLA-identical transplants was observed at 200 cGy TBI. Thus, low-dose TBI + CY + ATG conditioning resulted in excellent outcome of unrelated transplants in patients with aplastic anemia who had received multiple transfusions. (Deeg HJ et al. Blood 108: 1485-1491, 2006.)

More effective therapeutic strategies are required for patients with poor-prognosis systemic sclerosis (SSc). **Drs. Richard Nash, Ted Gookey, Leona Holmber, Lee Nelson, Howard Shulman, Rainer Storb** and colleagues conducted a phase 2 single-arm study of high-dose immunosuppressive therapy (HDIT) and autologous CD34-selected hematopoietic cell transplantation (HCT) in 34 patients with diffuse cutaneous SSc. Seventeen of 27 (63%) evaluable patients who survived at least 1 year after HDIT had sustained responses at a median follow-up of 4 (range, 1 to 8) years. There was a major improvement in skin (modified Rodnan skin score, -22.08;  $P < .001$ ) and overall function (modified Health Assessment Questionnaire Disability Index, -1.03;  $P < .001$ ) at final evaluation. Importantly, for the first time, biopsies confirmed a statistically significant decrease of dermal fibrosis compared with baseline ( $P < .001$ ). The estimated progression-free survival was 64% at 5 years. Sustained responses including a decrease in dermal fibrosis were observed exceeding those previously reported with other therapies. HDIT and autologous HCT for SSc should be evaluated in a randomized clinical trial. (Nash RA et al. Blood 110: 1388-1396, 2007.)

HIV-1-infected persons with HLA-B27 and -B57 alleles commonly remain healthy for decades without antiretroviral therapy. Properties of CD8+ T cells restricted by these alleles considered to confer disease protection in these individuals are elusive but important to understand and potentially elicit by vaccination. To address this, **Dr. Julie McElrath** and colleagues compared CD8+ T cell function induced by HIV-1 immunogens and natural infection using polychromatic flow cytometry. HIV-1-specific CD8+ T cells from all four uninfected immunized and 21 infected subjects secreted IFN-gamma and TNF-alpha. However, CD8+ T cells induced by vaccination and primary infection, but not chronic infection, proliferated to their cognate epitopes. Notably, B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles. Hence, CD8+ T cells restricted by certain protective alleles can resist replicative defects, which permits expansion and antiviral effector activities. The findings suggest that the capacity to maintain CD8+ T cell proliferation, regardless of MHC-restriction,

may serve as an important correlate of disease protection in the event of infection following vaccination. (Horton et al., J Immunol. 2006 177(10):7406-15.)

## **Other Accomplishments and Progress**

This past year we have made noteworthy progress in the areas of faculty recruitments, Shared Resources, and inter-institutional collaborations.

### **New Recruitments**

We recruited 10 new faculty members Consortium-wide during the past year who were not previously reported. All of these recruitments directly support one or more of our key strategic goals.

#### **Basic Sciences**

**Wenyng Shou, PhD** is an Assistant Member who has designed a model system to study biological cooperation using an artificial network of two mutually dependent microorganisms. In this model two yeast cells are co-dependent on each other for an essential metabolite. She has successfully described the dynamics of this co-operative system by generalizable mathematic equations. In the future, Dr. Wenyng plans to analyze the evolutionary trajectories that the system adopts to achieve increasingly stable cooperative states. Also, she has begun to investigate the origin and persistence of 'cheater' cells that subvert the co-operation of other cells for their own benefit.

#### **Clinical Sciences**

##### *Physician/Scientists*

**Jason Chien, MD** is Joint Assistant Member with expertise in clinical, molecular, and genetic epidemiology. Dr. Chien's laboratory focuses on conducting translational research that spans the characterization of clinical phenotypes using standard epidemiologic methods to the identification of genetic variants that predispose to the development of these phenotypes - then translating these findings into potential biomarkers that can be used to identify individuals at risk for developing these phenotypes. His research has also recently expanded to include tobacco related respiratory diseases, identifying genetic and molecular markers that will identify individuals who are at risk for developing chronic obstructive pulmonary disease and lung cancer. Dr. Chien conducts a weekly Long Term Follow-Up Pulmonary clinic for transplant recipients who develop chronic pulmonary problems, and has expertise in the management of noninfectious pulmonary complications. He also serves as the Medical Director of the Pulmonary Function Laboratory at the SCCA.

##### *Clinician/Scholars*

**Marc Chamberlain, MD** is a nationally recognized leader in clinical neuro-oncology with strong clinical research and therapeutic trial expertise, who was recruited from the H. Lee Moffitt Cancer Center and Research Institute. His research is mainly focused on clinical trials related to the management of primary brain tumors. Dr. Chamberlain's clinical interests include management of metastatic brain tumors and neoplastic meningitis.

**Vijayakrishna K. (V.K.) Gadi, MD, PhD** is a medical oncologist who sees breast cancer patients at the SCCA. His research interests include clinic practice in breast and hematologic malignancy and hematopoietic transplantation, immunogenetics of/immunotherapy for solid tumors (breast), cell-based therapy for immunologic tolerance in hematopoietic and solid organ transplantation, and non-invasive surrogate biomarkers for transplant rejection and cancer detection.

**Keith Loeb, MD, PhD** joined the Hutchinson Center's Pathology Lab as an Assistant Member. Prior to his appointment, Loeb was a hematopathology research fellow in the UW's Department of Laboratory Medicine. Dr. Loeb's research focuses on the processes that lead to genetic instability and cancer. His major work showed that misregulation of cyclin E, a key factor in promoting DNA synthesis, can promote chromosomal abnormalities and cancer. His future studies will focus on the role of cyclin E in promoting myeloproliferative and myelodysplastic disorders in humans.

**Lupe Salazar, MD** is a medical oncologist whose clinical expertise focuses on immunotherapy, endogenous tumor immunity, and breast cancer treatment and prevention. She sees breast cancer patients at the SCCA and currently leads four clinical research studies.

### **Public Health Sciences**

**Phil Bradley, PhD** is an Assistant Member who joined the Computational Biology group after a postdoctoral fellowship in the laboratory of **David Baker** at the UW. Dr. Bradley's research is focused on the general problem of molecular recognition, in particular the question of how proteins recognize specific sequences in their peptide, DNA, and RNA ligands. He is one of the primary developers of the Rosetta molecular modeling package, which he uses to develop predictive models of molecular interactions based on high-resolution all-atom modeling.

**Yu (James) Dai, MD, PhD** is an Assistant Member recruited from UW to work in the Hutchinson Center's Vaccine and Infectious Disease Institute (VIDI). He is an expert in the area of statistical methods for the analysis and interpretation of complex, high-dimensional biological data. He has a specific focus on analytic approaches to human genomics data.

**Holly Janes, PhD** is an Assistant Member who was recruited following her post-doctoral fellowship at Johns Hopkins to work in VIDI's vaccine group. Dr. Janes is an expert in the area of statistical methods for the evaluation and application of medical diagnostics, and also has expertise in the analysis of environmental studies.

**Mario Kratz, PhD** is an Assistant Member who is a nutritional interventionist. He was recruited following his senior research fellowship in the Department of Medicine at UW.

### **Progress in Shared Resources**

The Consortium's shared resources continue to provide services for a wide spectrum of research activities, many of which are also focal points for technology dissemination and collaborative endeavors. These state-of-the-art resources provide key support required for programs within the Consortium.

During the past year, contributions from outside donors and funding from the Hutchinson Center provided support for continued investment in shared resources, and ensured their ability to provide quality service to the research community. This included purchase and installation of the high throughput Illumina Genome Analyser System for the Genomics Resource, continued upgrade of the instrumentation platform within the Flow Cytometry resource with the purchase of a Becton Dickinson FACSAria, and acquisition of cryo equipment, including a high pressure freezing apparatus and other support equipment for the Electron Microscopy Shared Resource.

Phase 2 of a significant remodeling project at the Center was completed, resulting in the expansion of the Hutchinson Center's Small Animal Facility. Phase 3 is underway with planned relocation of the Research Pathology resource to the E level of the Hutchinson Center's Thomas Building, and development of new laboratory space for the Immune Monitoring Resource.

Resource usage across the group has been consistent with historical experience, with continued expanded usage in either units of activity and/numbers of investigators for whom service has been provided. Significant areas of growth have been experienced within several resources, including GeneScan Analysis services within the Genomics Resource, histology services provided by the Research Pathology Resource, data management and programming services provided by Collaborative Data Services, and deliverables provided by the Prevention Center.

The shared resources continue to play a critical role in support of research activities across the consortium as demonstrated by the following:

- Support of solid organ transplantation surgery and tissue tolerance investigations in canine mixed hematopoietic chimeras (Animal Health Resources)
- Mesenchymal stem cell imaging in a canine model (Molecular Imaging)
- Expansion of customized histology services, including offering additional immunohistochemistry stains with antibodies against phosphorylated proteins (Research Pathology)
- Building of new partnerships between institutional resources as the Hutchinson Prevention Center has teamed with the UW Clinical Nutrition Research Unit to expand offerings for human intervention studies; and increased collaboration between the therapeutic manufacturing facilities based at both the Hutchinson Center and UW to facilitate early Phase I clinical trials (Prevention Center)
- Development and use of touch screens, self reported 24 – hour dietary recalls via the web as a means to upgrade collection tools (Nutrition Assessment Shared Resource)
- Continued development of informatics tools and infrastructure in support of Proteomics and Genomics shared resources

The development of animal imaging capabilities continues as a collaborative effort between the Hutchinson Center and the UW Department of Radiology. This partnership brings together the biological expertise to formulate and pursue the physiological questions to be investigated, with a team whose expertise can provide basic support of imaging systems, image analysis techniques, and chemistry. Key projects include a multidisciplinary project to synthesize novel nanoparticle probes for magnetic resonance imaging detection, treatment and response monitoring of medulloblastoma, and investigation of novel treatments for hematologic malignancies. Anatomic Imaging is also playing a critical role in understanding the transition of

normal epithelium to prostate cancer and in breast cancer using MRI. A recent project includes the first mesenchymal stem cell imaging at the Hutchinson Center and UW in a canine model.

In preparation for the Consortium's CCSG competitive renewal process, there have been continued efforts to assess shared resource performance, and also to develop financial models for their continued support. Consistent with our policy on shared resources, Center and Core support is utilized to both facilitate development of new resources and to provide a stable source of support for ongoing operations. A number of resources have seen a consistent growth in usage levels and are attaining a sustainable level of activity. Resources providing high volume services at sustainable levels may be in the position to become self supporting or decrease their levels of support. In addition, we are currently evaluating possible reorganization of several resources to gain enhanced efficiencies and expand support to a broader research community within the Consortium.

### Other Institutional Accomplishments

#### Inter-Institutional Research Collaborations

The Consortium institutions continued to collaborate in a number of areas this year, with key highlights including:

- **Clinical and Translational Science Award (CTSA):** the University of Washington Institute of Translational Health Sciences was among 12 additional academic medical organizations nationwide to receive funding through the NIH CTSA's. The UW Institute will receive approximately \$62 million over five years. The Institute of Translational Health Sciences is a consortium of six UW health science professional schools and multiple partner institutions covering 12 sites, involving 67 key scientific personnel, and connecting researchers to more than 150 centers. This CTSA site includes the UW, Children's Hospital and Regional Medical Center, the Hutchinson Center, Seattle Cancer Care Alliance, Group Health Cooperative Center for Health Studies, Benaroya Research Institute at Virginia Mason, and the Northwest Association for Biomedical Research. The institute is led by **Nora Disis**.
- **Phase I Program Leadership: John Thompson** was appointed director of the Consortium's new phase I clinical trials program for solid-tumor cancers. In this role, he will be involved in developing new early phase clinical trials; helping to coordinate the infrastructure needed for such studies, working with medical oncology and other faculty to assure patient accrual to studies; and directing care of a portion of the study patients. Dr. Thompson has served as medical director of the Seattle Cancer Care Alliance's general oncology service since 2001 and co-directs the Melanoma Clinic.
- **NIH Grant to Study Gene Repair:** Children's Hospital received the largest research award in its 100-year history for a new five-year NIH grant to study gene repair. The \$23.7 million grant supports the Northwest Genome Engineering Consortium (NGEC), led by **Andrew Scharenberg** of Seattle Children's Hospital Research Institute, in partnership with the UW School of Medicine and the Hutchinson Center. Approximately \$13.2 million was awarded to Children's, \$5.3 million to UWSOM, and \$5.2 million to the Hutchinson Center. The project was funded by the NIH Roadmap for Medical Research. The NGEC research project features 11 different inter-related components, bringing together staff and resources from Children's, UWSOM and the Hutchinson Center. Other Consortium members joining

Scharenberg on the grant include **David Baker, Nancy Maizels, Raymond Monnat, Hans-Peter Kiem, and Barry Stoddard.**

- **Genome coordination center:** a four-year, \$4.8 million contract to coordinate activities for several whole-genome studies of human disease was awarded to the UW and the Hutchinson Center by the National Human Genome Research Institute. The new coordinating center will provide statistical and data-management advice and services to a number of specific disease studies across the United States. The studies will compare the genetic profiles of individuals with a certain disease to the profiles of healthy people to determine the location of the genes that contribute to the disease. Two of the three principle investigators who will be leading the new coordinating center include Consortium members **Bruce Weir and Lon Cardon.**
- **UW to lead local center in landmark national study of children's health:** the UW was selected as one of 22 new study centers in the National Children's Study to assess the effects of environmental and genetic factors on child and human health in the United States. The NIH grant to the UW study center totals approximately \$26 million over five years. Collaborating partners include the Hutchinson Center, which will contribute valuable lessons learned from the Women's Health Initiative, and Public Health -- Seattle & King County. Both will work with the UW to recruit participants for the research project beginning in 2009. Consortium member Shirley Beresford is a co-director of the Pacific Northwest Center for the National Children's Study.

#### Inter-Institutional Educational and Training Events

The Hutchinson Center and UW jointly sponsored and participated in a number of interinstitutional educational and training events, with examples including:

- The Hutchinson Center and SCCA co-sponsored a continuing medical education course in partnership with UW School of Medicine, "Challenges and Controversies in Breast Cancer" in October 2007. **Julie Galow** and **Connie Lehman** co-chaired the course.
- The Hutchinson Center, in collaboration with the UW, hosted a 2007 Biomedical Research Integrity series during the summer of 2007. The series included three lectures and nine faculty-led discussion groups.
- Consortium members were well represented among the speakers at the June 2007 10th annual American Society of Gene Therapy (ASGT) meeting, held in Seattle. The society is a non-profit medical and professional organization that represents researchers and scientists devoted to the discovery of gene therapies. Conference speakers included consortium members **David Emery, Philip Greenberg, Hans-Peter Kiem, Andre Lieber, Charles Murry, Rainer Storb, and Christopher Wilson.** **David Russell** serves on the board of directors for ASGT.

## Institutional Accomplishments

Other accomplishments at the individual Consortium institutions this year included:

### *Fred Hutchinson Cancer Research Center*

- **Formation of Vaccine and Infectious Disease Institute (VIDI):** the Hutchinson Center established the VIDI as its newest administrative unit. It was formed to bring together scientists from different disciplines to work on global infectious diseases such as AIDS, malaria, hepatitis C and tuberculosis. The members encompass a variety of scientific disciplines and they will work closely with industry to bring new preventive and therapeutic discoveries to the market. While the institute is not restricted to cancer, it is anticipated that the industry collaborations that will develop will be valuable in aiding the development of cancer vaccines.
- **Phase Two of Women's Health Initiative (WHI):** the Hutchinson received more than \$4.6 million for three new WHI research contracts funded by the National Heart, Lung and Blood Institute. The contracts are part of a second phase of WHI research to study genetic and biological markers of common diseases in postmenopausal women. The new two-year projects will apply innovative technologies to study factors that affect the major diseases in postmenopausal women. Researchers will conduct their research using blood, DNA and other biological samples and clinical data from the 161,808 postmenopausal women who participated in one or more of the three WHI clinical trials or in the observational study. The Hutchinson Center serves as the Clinical Coordinating Center of the WHI, which was a major 15-year research program designed to address the most frequent causes of death, disability and poor quality of life in postmenopausal women: cardiovascular disease, cancer and osteoporosis.
- **Group Health Affiliation Agreement:** the Hutchinson Center and Group Health Center of Health Studies signed an affiliation agreement December 2006, formalizing a long-standing partnership in cancer research. For more than 20 years, the two institutions have collaborated through affiliate and joint faculty appointments and joint research projects in areas such as cancer of the breast, lung, colon and pancreas. The new affiliation agreement is intended to support further collaboration, including joint faculty recruitments, use of shared resources, and the establishment of an affiliation committee to evaluate the progress of the relationship.
- **Pacific Health Summit:** the Hutchinson Center, National Bureau of Asian Research, and the Bill & Melinda Gates Foundation hosted the third Pacific Health Summit in June 2007. The summit focused on how Pacific Rim countries can prepare for and handle an avian-flu pandemic. Highlights included attendance by World Health Organization Director General Margaret Chan and an announcement by drug maker Eli Lilly of a new Seattle-based public-private partnership to conduct early phase discovery of new medicines to treat tuberculosis.

### *University of Washington*

- **Research milestone** - The UW achieved the \$1 billion research milestone in 2007, receiving over \$1 billion in grant and contract research funding for the most recent fiscal year, marking the first time it has reached this level. Virtually all of the funding results from peer-reviewed research proposals by individual faculty members. The UW has been the top public university in federal research funding every year since 1974 and among the top five

universities, public and private, in federal funding since 1969. Federal grants comprise nearly 80 percent of the UW research funding.

- **NIGMS award to UW for human embryonic stem cell research** - The National Institute of General Medical Sciences funded a new research program at the UW focused on the study of the basic biology of human embryonic stem cells, one of only two such programs in the nation. The research funded through this grant is restricted to the 21 human embryonic stem cell lines approved by President Bush in August 2001. The UW research program is comprised of four projects and a human embryonic stem cell core laboratory, with leadership by consortium members **Carol Ware** and **Tony Blau**. This team will receive about \$10 million over five years, and will study the pathways human embryonic stem cells use to self-renew and how they differentiate into heart muscle cells and retinal nerve cells.
- **SCCA/UW participation in national prostate-cancer consortium:** the Department of Defense awarded **Celestia (Tia) Higano** a two-year \$0.9 million grant to enable participation in a national clinical research group. The DOD began the group, the Prostate Cancer Clinical Trials Consortium, in 2005 with the objective of streamlining the implementation and conduct of multi-institutional phase I and phase II trials. The grant aims to reward collaboration among the nation's top cancer centers by hastening the development of prostate-cancer clinical studies.
- **U.S. News & World Report** and medical experts ranked UW Medical Center the 11th best hospital in the country this year. The cancer program was rated 6th, ranking as the best cancer program west of the Mississippi River (following 1) University of Texas, MD Anderson, 2) Memorial Sloan-Kettering Cancer Center, 3) Johns Hopkins Hospital, 4) Mayo Clinic, and 5) Dana-Farber Cancer Institute).

#### *Children's Hospital and Regional Medical Center*

- **100 Year Anniversary:** Children's celebrates its 100 year anniversary this year since its founding in 1907.
- **Research Institute and Campus:** In October 2006, Children's announced the creation of the Seattle Children's Hospital Research Institute to provide state-of-the-art laboratory facilities for pediatric physician-researchers. During the past year, Children's acquired nearly four acres and 1.5 million developable-square feet of research property in downtown Seattle's prime biotech corridor. Well ahead of schedule, Children's surpassed its goal to acquire all the research space outlined in its strategic plan.

Children's chose the downtown locations next to the South Lake Union neighborhood to be near Seattle's growing research community, including its partners, the UW and the Hutchinson Center. Physicians and scientists who staff Children's Research Institute are faculty members at the UW. Plans for the facilities are to have an initial staff of approximately 250, and ultimately, interdisciplinary teams totaling approximately 500 collaborating researchers conducting bench research and clinical trials.

- **Oversight of UW Research at Children's:** Consortium senior leader, **Bruder Stapleton**, who also serves as the chief academic officer for Children's, was appointed associate dean of the UW School of Medicine. In his capacity as associate dean, he will coordinate student and graduate medical education between Children's and the UW School of Medicine, and research programs for faculty based at Children's.

### Awards to Consortium Members

- **Wylie Burke** was elected to the Institute of Medicine.
- **Mary-Claire King** received the American Cancer Society's highest honor, the Medal of Honor in recognition for her pioneering work in the genetics of breast cancer.
- **Mark Roth** was a recipient of a \$500,000 MacArthur Fellowship, a "genius" award given annually by the John D. and Catherine T. MacArthur Foundation. Dr. Roth also received a Defense Advanced Research Projects Agency Award for Excellence.
- **Linda Buck** received a 2007 Medal of Merit, Washington state's highest honor for civilians.
- The American Society of Clinical Oncology selected **Fred Appelbaum** to receive a Statesman Award.
- **Colleen Delaney** won a prestigious, three-year Damon Runyon research award, and will receive \$450,000 to support the development of her cancer-research program.
- **Peter Eby** was named the 2007 American Roentgen Ray Society (ARRS)/Philips Medical Systems Scholar.
- **Barbara Goff** and **Connie Lehman** received the Ladies Home Journal's Health Breakthrough Award for early breast, ovarian-cancer detection work.
- **Maynard Olson** received the 2007 Gruber Prize for Genetics. Olson, one of the main architects of the Human Genome Project, created a method to break the yeast genome into manageable pieces for analysis. His pioneering work paved the way for analysis of the entire human genome.
- **Carlos Pellegrini** received the highest honor of the Society for Surgery of the Alimentary Tract, being presented Pellegrini with the Founders Medal, which recognizes members who have served with distinction.
- **Rainer Storb** was honored for pioneering mini-transplant research, receiving a \$150,000 award from the prestigious Jacqueline Seroussi Memorial Foundation for Cancer Research in Israel.

### Changes in Consortium Key Personnel

**John Potter** stepped down as Division Director of the Hutchinson Center's Public Health Sciences division and Associate Director of the Consortium on July 1, after serving in that capacity for over four years. A search process has been initiated and **Ross Prentice**, who formerly held this position before Dr. Potter, is serving as interim Associate Director for the Consortium until the position is filled.

### Membership Status

Consortium membership levels reported to NCI in the 2007 CCSG progress report totaled 393 faculty. There was a net increase of approximately 10 new faculty members in 2007 over 2006 levels.

### **Funding to Consortium Members**

As of June 2007, funding to Consortium members totaled \$300.9 million (direct costs), with the following breakdown:

- NCI: \$74.4 M
- Other NIH: \$157.3 M
- Industry: \$2.4 M
- Other funding agencies: \$66.9 M

85% of total funding was received from sponsors that meet NCI's criteria for peer-review. 48 awards were \$1 million and above (direct costs).

### **Patients and Protocol Accruals**

Patient volume and accrual data reported to NCI in the CCSG 2007 progress report reflected an increase in new patient levels compared to 2006. A total of 4,338 new patients were seen at the consortium institutions, representing a 7% increase over the prior year. Patient accruals to therapeutic clinical trials, however, remained flat in fiscal year 2007 over the prior year at an overall 16% accrual rate. Various efforts are underway with Consortium work groups to identify opportunities to enhance clinical trial processes and increase patient accruals across disease areas.