ABSTRACT BOOK

Selections Presented at the 2010 OCTRI Awards Dinner

OREGON CLINICAL
+ TRANSLATIONAL
RESEARCH INSTITUTE

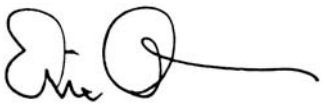
Dear Colleagues,

The Oregon Clinical & Translational Research Institute represents a unique partnership between Oregon Health & Science University and the Kaiser Permanente Center for Health Research. Established in 2006 with major funding from the National Institutes of Health through the Clinical and Translational Science Awards (CTSA), and significant institutional commitment from both OHSU and Kaiser Permanente, OCTRI pursues a mission to improve human health by enhancing clinical and translational research. With this NIH award, OCTRI is part of a national effort to promote scientific collaboration across disciplines, to facilitate more efficient translation of scientific discoveries into clinical practice, and to support community health by fortifying the connections between researchers and communities.

OCTRI directly supports translational research through the OCTRI Awards Program. The goal of this program is to stimulate new research programs that yield grants, publications, career development opportunities, new research partnerships, and positive health outcomes. This Abstract Book is a collection of the pilot project awards and strategic investments that OCTRI has supported since 2006. We have published this book in conjunction with the 2010 OCTRI Awards Dinner, an annual event that brings together the research community to celebrate innovation, collaboration, and improved human health.

This book is a showcase of the exceptional work being conducted at Oregon Health & Science University, the Kaiser Permanente Center for Health Research, and at our many partnering institutions. As we continue to build connections and share resources across institutions, the credit for our collective successes is due to an increasingly large group. With this book, we pay tribute to the outstanding efforts of research teams across Oregon who are advancing science and developing innovative approaches to the way research is conducted.

Sincerely,



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Learn more at www.octri.org.

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Learn more about OCTRI projects and funding opportunities at www.octri.org/funding.

Grazyna Adamus, PhD, MS (2010) *Immunotherapy with Recombinant T-cell Receptor Ligand (RTL) for Retinal Degeneration*

Co-Investigator: Shaomei Wang, MD, PhD

The proposed study will determine the potential of a novel immunotherapeutic approach in limiting retinal degeneration as a possible treatment for retinitis pigmentosa (RP), age-related macula degeneration (AMD), autoimmune retinopathy (AR), and other related retinal diseases. This pilot project aims to examine whether novel immunotherapy with recombinant T-cell receptor ligand (RTL) will protect photoreceptors and vasculature from degeneration in a rodent model for retinal degenerative diseases. The project represents a new avenue of research that has arisen out of recent discoveries made by the PI and her co-investigators (Dr. Shaomei Wang) as well as other groups as described below. The intent of this project is to generate the proof of principle data to support a future NIH grant application. If positive results are obtained they will be applied to developing a pre-clinical application.

Eric Adler, MD (KL2) *Primate Induced Pluripotent Stem Cells for the Treatment of Ischemic Cardiomyopathy*

Mentor: Markus Grompe, MD

The objective of our research proposal is to determine the therapeutic benefit of stem cell derived cardiomyocytes using a primate model of ischemic cardiomyopathy. We have previously developed techniques for the isolation of enriched populations of cardiac progenitor cells using the embryonic stem cell and pluripotent stem cell system. Preliminary data from the murine system suggests these cells help improve cardiac function after myocardial infarction. Our unifying hypothesis is that pluripotent stem cells will improve cardiac function more than hematopoetic stem cells. To explore this hypothesis we will create a primate model of ischemic cardiomyopathy using previously developed protocols. Stem cells will then be transplanted directly into the myocardium of primates. Engraftment of cells, angiogenesis, and cardiac function will all be determined non-invasively. Studies will be performed using syngeneic cell lines, hence obviating the need for immunosuppression. This work will help answer fundamental questions regarding the efficacy of stem cells to treat cardiovascular disease.

Joshi Alumkal, MD (KL2) *Sulforaphane destabilizes the androgen receptor in prostate cancer cells by inactivating HDAC6*

Co-Investigators: Shannon McWeeney, PhD; Motomi Mori, PhD; Christopher Corless, MD, PhD

Mentors: Tomasz Beer, MD & Grover C. Bagby, MD

Prostate cancer is the most common and second most lethal cancer in men in the United States. It is now clear that molecular events are critical for cancer development and progression, and prostate cancer is no exception. Ultimately, we believe that a better understanding of the molecular basis for prostate cancer will lead to improved outcomes for patients.

In prostate cancer, genetic mutations in tumor suppressor genes or oncogenes that are frequently mutated in other epithelial cancers are rare. Epigenetics is the heritable control of gene expression in the absence of changes to the DNA sequence, and recent work demonstrates that epigenetic changes are important in cancer. Indeed, many key epigenetic proteins that regulate gene expression have oncogenic functions. However, the mechanisms by which these key epigenetic proteins promote prostate cancer survival are largely unknown. Additionally, there is great potential for epigenetic therapy in cancer as pharmacological inhibitors of many of these key epigenetic proteins exist. However, the effectiveness and safety of these inhibitors is still largely unknown.

Our work focuses on three main areas: 1) determining the downstream genes and pathways that key epigenetic proteins modulate to promote prostate cancer development and progression, 2) determining the safety and effectiveness of epigenetic therapy in pre-clinical studies, and 3) translating this work to patients by identifying diagnostic, prognostic, or predictive biomarkers and by testing epigenetic therapies in patients with prostate cancer.

Susan Bankowski, MS, JD (2009) *Joint VA-OHSU eIRB*

Co-Investigators: Christine Nelson, PhD, RN; Sola Whitehead; Kathryn Schuff, MD; Darlene Kitterman, MBA

Problem. Investigators conducting research at both OHSU and Portland VA Medical Center (PVAMC) are currently required to complete two separate IRB applications, undergo duplicate and often conflicting IRB reviews, and comply with differing oversight requirements.

Purpose. The joint PVAMC-OHSU IRB initiative was undertaken to establish a combined IRB that utilizes a single submission and review process employing the OHSU electronic IRB management system. OCTRI supported a project manager, Dr. Christine Nelson, to facilitate this initiative.

Implementation. The joint VA-OHSU IRB is poised to launch in February 2011, followed by eIRB implementation in ensuing months. We look forward to having created a system that provides OHSU and PVAMC researchers with a streamlined IRB review process.

Nicola S. Carter, PhD (2010) *Comparative Proteomics to Define Adaptations to Purine Stress in Leishmania*

Co-Investigators: Scott Landfear, PhD; Buddy Ullman, PhD; Phillip Yates, PhD

Leishmania are protozoan parasites that cause significant morbidity and mortality in humans, afflicting approximately 12 million people worldwide. These parasites are auxotrophic for purines and have evolved a unique set of purine transporters and salvage enzymes to scavenge these essential nutrients from their host. Hence, purine salvage components provide attractive targets for drug design. An ability to adapt to changes in the purine milieu is vital for Leishmania to survive in their host. Withdrawal of extracellular purines leads to an acute increase in key purine transporters and salvage enzymes. This augmentation is not due to an increase in mRNA abundance or stability. Since regulation is post-transcriptional, it is our goal to use proteomic methods to provide insight into the cellular networks and pathways involved in this adaptation to purine stress. Two strategies are proposed. First, to quantify the temporal changes in the Leishmania donovani proteome upon purine-starvation, an accurate mass and time (AMT) tag strategy is delineated. A broad AMT database will be constructed from parasites grown under purine-free and purine-replete conditions and used to facilitate high-throughput accurate measurements on relative protein abundance between purine-starved and purine-replete parasites. Second, since it is conjectured that part of the response to purine stress involves the post-translational modification of regulatory proteins, the phosphoproteome of purine-starved and purine-replete L. donovani will be compared. It is anticipated that these studies will be of broad impact, illuminating the means by which Leishmania adapt to changes in their host purine environment and likely providing novel targets and pathways for future therapeutic exploration.

Yiyi Chen, PhD (2010) *The Use of Testing Confidence Value for Transitional Decisions of Single-Arm Phase II Oncology Trials*

Co-Investigators: Motomi Mori, PhD & Tomasz M. Beer, MD

Many phase II oncology trials are single-arm clinical trials that aim to decide whether the test treatment has sufficient therapeutic efficacy for a phase III study. Such a decision is called a transitional “Go / No Go” decision.

The high failure rate in phase III oncology trials suggests that the “Go / No Go” decisions based on traditional hypothesis testing are often incorrect, at least for the “Go” decisions. We show that the actual type I and type II error rates are typically much higher than the set targets (5% type I error and 20% type II error) for single-arm trials. This is partly due to ignoring the uncertainty associated with the specified null hypothesis.

We propose the Testing Confidence Value Decision Rule (TCVDR), a statistical decision rule for transitional “Go / No Go” decisions for single-arm phase II trials with binary endpoints. The TCVDR is based on a new statistical index, Testing Confidence Value (TCV), which evaluates confidence on the hypothesis testing result by incorporating the uncertainty associated with the specified null. We show that for single-stage phase II trials, TCVDR has a lower probability of making incorrect “Go / No Go” decisions than both the traditional frequentist hypothesis testing method and Thall and Simon’s Bayesian method (the most widely used Bayesian approach for single-arm phase II trials).

There are an increasing number of two-stage phase II oncology trials. In this pilot project, we propose to extend the development of TCVDR to two-stage single-arm phase II trials, and compare the operating characteristics of the TCVDR with the decision rule of Simon's two-stage design. We also propose to apply the new decision rule retrospectively to phase II prostate cancer trials for a comparison to the actual decisions made in these trials.

Greg Clarke, PhD (2009) *Accelerating the pace of translating evidence-based mental health treatments into practice: a pilot dissemination of brief CBT for youth depression*

Co-Investigators: Christina Gullion, PhD (KPCHR) & Mark Spofford, PhD (KPCHR)

Naturalistic outcomes study of youth depression CBT delivered by community therapists, relative to outcomes obtained in more controlled, parallel randomized clinical trial funded by a separate NIMH grant.

Major depression is the 3rd leading cause of premature death and disability out of all health conditions. However, evidence-based treatments (EBTs) for depression, such as cognitive-behavioral therapy (CBT), are incompletely disseminated in community care. Although antidepressants are widely available, their significant side effects (e.g., increased suicidality) and modest benefit reduce their usefulness and reach. CBT is a much more acceptable EBT with no known side effects; its dissemination is a key public health need. Pilot data are needed to understand whether community providers can adopt and adhere to CBT, whether such adherence is related to CBT effects, across the range of community patients We propose to conduct a naturalistic outcomes study of this CBT model delivered by community agency therapists to 25 depressed youth. This naturalistic outcomes study will be conducted in parallel to our ongoing, NIMH-funded randomized trial of this same CBT model, using identical measures of youth outcomes and therapist adherence. We will train community therapists in our CBT approach and record CBT sessions to characterize what is delivered. We will also assess outcomes of depressed youth over 6 months. We will employ benchmarking statistical methods to compare outcomes across the community cases and the RCT cases, adjusted for case differences. These results will help prepare for future dissemination efforts by answering these questions: Does poor therapist CBT adherence lead to inferior patient outcomes relative to results obtained in controlled trials? How should dissemination efforts promote adherence? Do these guidelines vary per the clinical presentation of the patients?

Aaron Cohen, MS, MD (2008) *Identifying Candidate Researchers for Collaboration in Clinical and Translational Research*

Co-Investigator: Nathan Bahr, MS

In this study, a software application was developed, which permitted investigators to browse a visual network of researchers and MeSH terms to help identify partners for future research collaboration. The intent of this was to improve the rate of multidisciplinary, or translational,

research by suggesting researchers whom the investigator would not have normally considered or find, but shared complementary interests, as indicated by publications or grants.

The system was evaluated through use cases and surveys. The use cases guided the application's development by in that user needs were identified and then incorporated into the system. The main needs were to: have filters which showed only the most prominent suggestions; provide controls to see how a researchers coauthor and MeSH term connections changed over time; and to incorporate grants into the application's database.

The surveys were used to measure the efficacy of the system versus using traditional means, prior knowledge or the Internet. Users would make a list of researchers using the Internet and then add to that list using the application. Then, experts graded the quality of those researchers on novelty, essentialness, and appropriateness. Two surveys were run and the application was able to find an additional 50% (8/15) and 110% (11/10) set of different researchers who were graded to be of similar quality to the researchers found using the Internet.

In a follow up, the users were asked to evaluate using the Internet and the application for this task. In using the Internet, they found that it had a lot of noise and presented many irrelevant results that had to be investigate manually. In using the application, users found the ability to explore on related MeSH terms helpful as it expanded their search spaced in a focused manner. The application provided a means of identifying researchers beyond using current Internet search tools, because it provides a focused database for that task and a means of expanding the user's search space in a relative manner.

Christopher Corless, MD (2008) *OHSU Biolibrary*

Co-Investigators: Alison Grossblatt-Wait, MA; Gregg Hoshovsky; Teresa Mason, CTR; Robert Schuff, MS; Kathryn Schuff, MD

Translational research is critically dependent on the availability of human tissue samples annotated with clinical, genomic, and other data. Increasing the quantity, quality and accessibility of tissue samples available to campus researchers will benefit translational research activities at OHSU.

The OCTRI Biolibrary project is a collaboration between OCTRI and the Knight Cancer Institute to develop a web portal with information about various tissue collections at OHSU and KPCHR. and a specimen search engine that OHSU researchers can use to locate specimens in preparation for their research projects.

The Biolibrary Search Engine consists of a web-accessible database with information about human tissue samples that are available on-campus for research use. Currently, searchable specimen collections include the OHSU Cancer Institute Tissue Bank and the Department of Pathology specimen archive. Specimens are enriched with clinical annotations from OCTRI's Research Data Warehouse, and from the Cancer Registry. The project includes plans to incorporate additional collections over the next several months.

Harry B. Davis, PhD (2008) *Preparation and confirmation of the bioactive characteristics of silicate-based glasses for the repair and reconstruction of damaged tooth and bone tissue*

Mentor: John Mitchell, PhD

Silicate-based bioactive glasses (BAGs) have been in use for over 30 years; they act as scaffolds upon which growth of bioorganic materials can occur, have very low rejection potential by the immune system, carry no risk of viral or bacterial infection, act as a reservoir for ions necessary for the formation of new bioinorganic materials, are easily prepared, and have long shelf-lives. These have shown a remarkable ability to effect the formation of new apatite, Ca10(PO4)6(OH)2, that is necessary for repairing damaged tooth and bone tissue. We propose to make new BAGss that, when used in dental composites, will enhance the formation of new tooth and bone tissue. We will prepare new silicate-based glasses containing Ca, P, F, and B by a metalorganic sol-gel route which involves the homogeneous combination of tetraethyl orthosilicate (TEOS), triethyl phosphate (TEP), calcium methoxyethoxide ((CMOE) and boron trifluoride diethyl etherate (BF3•OEt2). Bioactivity of the resultant BAGs will be confirmed by the observation of apatite formation and ion release profiles upon exposure to simulated body fluid (SBF). Beyond the scope of the initial project, the new BAGs will ultimately be tested in orthodontic applications to see if they help prevent decalcification around spots where brackets are bonded to the tooth, and to determine if they are better able to block dentin tubules for the purpose of preventing tooth sensitivity. These BAGs might also be useful as coatings for implant materials in order to prevent rejection and to enhance bone repair and regeneration.

Michael Deininger, MD, PhD (2009) *Pathogenesis of chronic myelomonocytic leukemia (CMML)*

Co-Investigators: Shannon McWeeney, PhD & Beth Wilmot, PhD

Chronic myelomonocytic leukemia (CMML) combines features of a myelodysplastic syndrome with those of a myeloproliferative disease (MPD). It affects mainly elderly individuals and has a poor prognosis (median survival from diagnosis approximately 20 months). Therapy consists of cytotoxic agents for reduction of elevated white blood cell counts as well as supportive care. The only curative treatment is allogeneic stem cell transplant, but most patients are not eligible due to age and concomitant medical conditions. While hypersensitivity to GM-CSF is a common feature of CMML cells, the pathogenesis is heterogeneous at the molecular level. RAS mutations occur in 30-40% of patients, and some 5-10% of patients have activating mutations in tyrosine kinases such as PDGFR and JAK2, while pathogenesis remains unclear in the remainder. Uniparental disomy (UPD), i.e. copy number neutral loss of heterozygosity (LOH) is emerging as a recurrent theme in the pathogenesis of MPD. The best example is the association of JAK2V617F with UPD of chromosome 9p in patients with polycythemia vera. To identify UPD, but also regions of genetic gain or loss and copy number changes in patients with CMML we will carry out genome-wide high density SNP array analysis using the Affymetrix 6.0 chip, comparing leukemia cell DNA with constitutional DNA (mouthwash). Downstream analysis will focus on regions with recurrent abnormalities and candidate genes involved in the GM-CSF hypersensitivity. Preliminary data generated with the pilot funding will be used to support an R01 application, which will propose studies to discover and validate new therapeutic targets in CMML.

Mary Anna Denman, MD *Skin Distensibility as a Marker of Pelvic Organ Prolapse*

Background: Clinical studies support the concept that connective tissue abnormalities may predispose women to pelvic organ prolapse (POP). Mechanical changes in vaginal skin are associated with POP, as are differences in the extra cellular matrix (ECM). Measures of skin biomechanical properties in vivo, using a DermaLab® suction device, may provide a simple, clinical measure of intrinsic connective tissue function, which in turn can be correlated with differences in biochemical ECM composition.

Objective: Our central hypothesis is that women who develop POP are more likely to have intrinsic connective tissue differences reflected in both clinical and biochemical measurements.

Design: We will use a case control study design to measure skin biomechanics using the DermaLab® device in 120 total women with and without POP. A subset of 16 women (8 cases/8 controls) planning hysterectomy will be recruited for biopsies of the lower abdominal skin and anterior vaginal wall cuff for ECM gene expression analysis in addition to skin suction testing.

Setting and Subjects: Women with and without POP will be recruited from the Divisions of Urogynecology and General Gynecology for participation in this study.

Intervention: Clinical measurements will be taken at the time of a regular office visit. Tissue biopsies will be obtained in the operating room at the time of the subject's surgery.

Measurements: The DermaLab® device will be used to quantitatively evaluate skin laxity through measurements of stiffness, recoil, and hysteresis. In the subset, skin and vaginal biopsies will also be evaluated using a targeted gene array for 96 ECM components. Reverse transcriptase polymerase chain reactions (RT-PCR) will be used to evaluate significantly up-or down – regulated genes identified in tissues from subjects with POP. Similarly, elastin synthesis will be quantified thorough the expression of the elastin monomer tropoelastin mRNA, and lysyl oxidase mRNA, a catalyst for elastin fibril formation.

Analysis: Measures of skin biomechanics will be analyzed, comparing women with POP to those without POP using standard statistical tests. ANOVA will be used to evaluate differences when stratified by covariates such as age and parity. In the subset analysis, differences in mRNA expression will be graphically analyzed and compared with standard statistical tests using the false discovery rate (FDR) approach to control for the multiple comparisons inherent to gene array analysis. Skin biomechanical properties will be correlated with the results of quantitative RT-PCR. We anticipate greater skin laxity in women with POP, reflecting an intrinsic difference in connective tissue function. Furthermore, we expect to detect genes associated with decreased synthesis, and/or increased degradation of elastin and collagen in the ECM to be associated with increased skin laxity and POP.

Jennifer DeVoe, MD, DPhil & Rachel Gold, PhD, MPH (2009) *Developing Safety-Net Clinic Electronic Practice Management Data for Use in Translational Health Services and Health Policy Research*

Co-Investigator: Susan Chauvie, RN, MPH (OCHIN)

This study aims to determine the extent to which electronic Practice Management (PM) data from Our Community Health Information Network (OCHIN) can be linked with Oregon's Medicaid claims data. After creating a successful linked database, we will assess the extent to which OCHIN's adult Medicaid recipients with diabetes access preventive care services outside of the OCHIN network.

Background. Safety net clinics provide excellent care to vulnerable populations. However, data are limited about the extent to which patients exclusively utilize the safety net system as a medical home. This relationship is important to understand as a step towards translating and disseminating clinical evidence into safety net populations. Specific Aims. In our efforts to develop the unique Practice Management (PM) data source from Our Community Health Information Network (OCHIN) as a research-ready population-based denominator, we propose: 1) To develop and evaluate methods for linking OCHIN's PM data with Oregon's Medicaid claims data, among OCHIN patients who receive Medicaid (>55% of OCHIN patients have Medicaid coverage). Hypothesis 1: Linking OCHIN PM data with Oregon's Medicaid claims data will be feasible and will create a more robust combined database then either alone would provide. 2) To test the linked OCHIN/Medicaid database, described in Aim 1, by determining the extent to which OCHIN's population of adult diabetics, with continuous Medicaid coverage, receive preventive care services outside of the OCHIN network. Hypothesis 2: OCHIN patients have limited access to healthcare services, so few individuals will have received preventive diabetes care outside of the extensive OCHIN network. Significance. We will design and demonstrate methods for utilizing the OCHIN data in future translational research projects in public clinic and public insurance settings; We will build a tool that contributes to our larger research agenda including assessing health policy reforms; and (3) we will develop methods that can be generalized and disseminated to other CTSAs.

Richard Deyo, MD, MPH (2008) *Long-term Opioid Therapy for Chronic Back Pain: Correlates and Consequences*

Co-investigators: Steven Dobscha, MD & David Smith, PhD (KPCHR)

Chronic pain is a common complaint in primary care. Over 2% of US adults report regular use of prescription opioids, and over half of these have chronic back pain. Surveys suggest that many such patients have persistent high levels of pain and poor quality of life. Despite uncertainties about long term efficacy and safety for chronic back pain, prescription opioid use is increasing rapidly, and complications related to overdoses have risen in parallel.

Chronic back pain is often associated with psychological distress. Patients with anxiety or major depression are typically excluded from clinical trials, yet are more likely than others to be prescribed opioid therapy. Unfortunately, they may have less analgesic benefit and be prone to medication misuse.

It is often difficult for physicians to distinguish inadequate pain relief from addictive behavior when

patients request increased opioid doses or early refills, and patients sometimes “doctor shop” for prescriptions. As a result, these patients are often time-consuming; clinicians may respond with frustration or resentment; and mutual distrust may undermine therapeutic dialogue.

Given these challenges, it is important to better understand which patients are started on long-term opioids, how these drugs are initiated, whether certain patient characteristics and dosing patterns are associated with long-term use, and what the benefits and risks of long-term use may be. Such data in turn may suggest interventions to improve the quality and safety of opioid prescribing in primary care. We will use the Kaiser Permanente Northwest (KPNW) Center for Health Research electronic data to examine patterns of opioid use among patients with chronic back pain, correlates of long-term opioid use, and quality of opioid management.

David Ellison, MD & Katrina Goddard, PhD (2009) *A Study of Thiazide Sensitivity: A Prognostic Risk Score to Identify Causative Mutations*

Essential hypertension is a disorder with both genetic and environmental causes that affects 50 million Americans, and is a major cardiovascular risk factor for mortality from stroke, heart and kidney disease. Treatments for hypertension are well-suited to tailoring to individuals because multiple antihypertensive drugs are available and act on a variety of blood pressure (BP)-regulating systems. However, fewer than 40% of treated patients achieve adequate BP control. Thus, targeting the right therapy to the right patients could have a significant impact on this widespread and serious health problem. In particular, we are interested in figuring out which patients should receive thiazide diuretics, since they are often recommended as initial therapy. When used as a monotherapy, however, thiazide diuretics only control BP in 50% of patients.

Our aim is to explore two different approaches to tailoring treatments for hypertensive patients. First, testing for specific genetic polymorphisms and sequencing the genotype of a patient may allow us to predict response to specific antihypertensive agents, thereby optimizing initial therapy in individual patients. This approach has the advantage that identification of involved genes may provide clues as to underlying mechanisms of disease. Second, we will explore the possibility of devising and using a prognostic risk score, based on clinical factors typically found in the medical record, to identify patients who are highly likely to respond to thiazide treatment. With the use of electronic medical records in large health care systems, prognostic risk scores can be applied to large numbers of patients with little added cost, providing a nearly instant assessment to providers making clinical decisions. In this pilot study we will 1) determine the feasibility of developing a risk score, and 2) establish a large cohort of thiazide-sensitive patients for further investigation. The proposed study brings together population scientists from the Kaiser Permanente Center for Health Research, and clinical researchers from Oregon Health & Sciences University. We used OCTRI resources to generate preliminary data for an NIH R01, thus combining the strengths of both institutions.

C. Kristian Enestvedt, MD (2007) *Examining the Application of Gene Therapy to Improve Healing in the Gastrointestinal Tract*

Co-Investigator: Shelley Winn, PhD

BACKGROUND: Proper anastomotic healing is dependent upon many factors, including adequate blood flow to healing tissue. The aim of this study was to investigate the impact of vascular endothelial growth factor (VEGF165) transfection on anastomotic healing in an ischemic gastrointestinal anastomosis model.

METHODS: Utilizing an established opossum model of esophagogastrectomy followed by esophageal-gastric anastomosis, the gastric fundus was transfected with rhVEGF165 via direct injection of a plasmid-based non-viral delivery system. Two concentrations of VEGF were employed. Outcomes included VEGF mRNA transcript levels, neovascularization, tissue blood flow, and anastomotic bursting pressure. To determine whether local injection resulted in a systemic effect, distant tissues were evaluated for VEGF transcript levels.

RESULTS: Successful gene transfection was demonstrated by qPCR analysis of anastomotic tissue with significantly higher VEGF mRNA expression in treated animals compared to controls. At the gastric side of the anastomosis, there was significantly increased neovascularization, blood flow and bursting pressure in experimental animals compared to controls. There were no differences in outcome measures between low and high dose VEGF groups; however, the high dose group demonstrated increased VEGF mRNA expression across the anastomosis. VEGF production was not increased at distant sites in treated animals.

CONCLUSION: In this animal model, VEGF gene therapy increased VEGF transcription at a healing gastrointestinal anastomosis without systemic VEGF upregulation. This treatment lead to improved healing and strength of the acutely ischemic anastomosis. These findings suggest that VEGF gene therapy has the potential to reduce anastomotic morbidity and improve surgical outcomes in a wide array of patients.

Deniz Erten-Lyons, MD (2009) *OCTRI Pilot to Create a Biolibrary for Aging Relevant Data*

Co-Investigators: Jeffrey Kaye, MD; Patricia Kramer, PhD; Joseph Quinn, MD; Randall Woltjer, MD, PhD

Background: Integrating data from diverse cohorts increases the power of studies and enables examination of cross-cohort effects. Prior to integration, data needs to be pooled and ideally harmonized. The Integrative Analysis of Longitudinal Studies on Aging (IALSA) research network is a collaborative effort of 26 longitudinal aging studies spanning eight countries to accomplish this goal. While a data dictionary which primarily describes the clinical data exists (http://lifelab.tss.oregonstate.edu/), there is no systematic description or approach to harmonizing the biomarker data that may be contained within each study.

Objective: This pilot project aims to: 1) create a database of biomarkers from the IALSA network studies, 2) develop methods to harmonize this biomarker data and, 3) examine other existing biomarker databases in the field of aging.

Methods: To accomplish the first two aims, a questionnaire was developed as a data collection tool to create an inventory of existing biomarker data in IALSA studies. This was sent to 26 studies. The

goals of the BARD project and issues related to data harmonization were discussed at the 2010 IALSA meeting in Canada. As part of the last aim, all existing databases of biomarker data from longitudinal aging studies were identified through web searches.

Findings to Date: Response rate from IALSA studies to the initial questionnaire has been 50%. Seven of the 13 studies that responded have banked DNA and APOE genotype data available. Three studies have genome-wide genotype data available. Seven studies have banked plasma and six studies have brain imaging data. One study has banked cerebrospinal fluid and brain tissue available. As part of the last aim, we identified five databases with biomarker data from longitudinal studies of brain aging, two databases with a focus specifically on Alzheimer disease and two databases with a genetic focus not limited to but including aging relevant data.

Work in Progress: We are contacting study centers to increase the response rate to the initial questionnaire. We are also currently updating the IALSA database for biomarker data and mapping the data fields to determine methods for harmonization. A paper describing the current state of databases of longitudinal studies in brain aging is in preparation.

Damien Fair, PhD, PA-C (2009) *Using resting-state functional connectivity MRI to characterize typical development and ADHD*

Co-Investigators: Bonnie Nagel, PhD & Joel Nigg, PhD

The first two decades of life represent a period of extraordinary developmental change in sensory, motor, and cognitive abilities. One of the ultimate goals of developmental cognitive neuroscience is to identify the principles that guide the maturation of functional networks that flexibly support these functions. Achieving this goal not only gives us a deeper understanding of typical development, but also provides a richer insight into the nature of developmental disorders as well. In a series of studies, we have used various resting state functional connectivity MRI approaches, including graph theory, to examine both cortico-cortical and cortico-subcortical interactions across development. Our studies have highlighted the increased consolidation of the default network over age, the existence of multiple developmental changes between cortical and subcortical structures, and the notion that large-scale networks develop from a local to distributed organization.

We now use the developmental context and approaches afforded by these studies to provide insights into ADHD. With the support of the Oregon Clinical and Translational Research Institute (OCTRI) we have identified the developmental consolidation of the default network as being atypical in youth with ADHD. We have also identified atypical circuit organization between cortical and subcortical structures such as the thalamus and basal ganglia. We are now using the information obtained from these studies to better subtype ADHD children. This work supported by OCTRI is currently guiding new investigations aimed at early recognition and therapeutic responses to targeted therapies in hopes of reducing the burden of ADHD.

David Feeny, PhD (2007) *Developing Health-Related Quality of Life Measurement Tools to Enhance Research and Treatment for Methamphetamine Substance Abuse*

Co-Investigators: Suzanne Mitchell, PhD & Bentson McFarland, MD, PhD

Methamphetamine consumption, withdrawal, abstinence, and relapse are complicated by the multiple effects of the drug on the health of its users. To cite just a few health domains, methamphetamine can influence mood, cognition, sleep, and irritability. If treatment interventions are to be successful, the services should influence those health domains considered most important by methamphetamine users. Similarly, if animal models are to be relevant for humans, the organisms should mimic those health domains that are most pertinent to methamphetamine addicts. Unfortunately, there are few if any data on the importance attached to various health-related domains by methamphetamine users. The purpose of the proposed project is to provide this information.

More specifically the aim is to develop and test a multi-dimensional patient-centric instrument to assess health-related quality of life (HRQL) in users or former users of methamphetamine. This program of research will identify the most salient set of dimensions and appropriate levels within each dimension. It is intended that the instrument span the experiences of use, treatment, and recovery from addiction. Additional aims include an assessment of the feasibility of using direct preference-elicitation techniques in respondents with substance abuse problems. A long-run aim is the development and testing of a multi-attribute measure of HRQL in methamphetamine that could be used both at the individual and group levels.

Peter Francis, MD, PhD (2007) *Preclinical Model of Cell-based Therapies for Retinal Disease*

Co-Investigators: Raymond Lund, PhD; Richard Weleber, MD; Thomas Hwang, MD; Brett Jeffrey, PhD; William Hauswirth, PhD (University of Florida)

Age-related macular degeneration (AMD) and the inherited retinal degenerations (IRD) are very significant causes of visual loss. In both diseases, vision loss occurs primarily due to death of retinal photoreceptors and the supporting retinal epithelium. We are actively involved in the development of two new types of therapy, both holding great promise for the future treatment of these blinding conditions: gene therapy in which therapeutic gene replacement can correct the molecular defect that results in disease, and cell-based therapy which encompasses cell transplantation, cell replacement and the introduction of cells that encourage host cell survival. These technologies are rapidly approaching the final translational step from the laboratory to human clinical trial. However, therapeutic techniques to be used in humans must achieve a high level of safety, and studies have not been undertaken to optimize the surgical delivery of cells and gene therapy vectors to the retina and to evaluate the potential specific local and systemic toxicity of such therapy. Thus, the acute lack in knowledge of how to best surgically deliver these therapies to the human retina to ensure safety and maximal efficacy remains the critical barrier to their application in human patients.

Extensive studies of both modalities have been undertaken almost exclusively in rodents and have repeatedly demonstrated their efficacy in treating IRDs and models of AMD. However, there are

fundamental structural and functional differences between the eyes of small mammals and those of humans, so that it is not possible to extrapolate directly to the Operating Room. In contrast, non-human primates (NHPs) have eyes almost indistinguishable from humans, and therefore provide the optimal model for preclinical studies.

We have assembled a multidisciplinary team of basic and clinician scientists, together with expertise from the ONPRC, to address the following specific aims:

1. Optimize the techniques of subretinal cell- and gene therapy delivery to the NHP eye, including (a) injection cannula design, and (b) procedures for the controlled delivery of the cells and vectors into the subretinal space; 2. Conduct initial test of the safety and biodistribution of these therapies in these non-human primates.

Peter Gillespie, PhD (2010) *Identification of Deafness-Causing Mutations Using Proteomics-Identified Candidates*

Co-Investigators: Richard J. Smith, MD (University of Iowa) & Ulrich Müller, PhD (Scripps Research Institute)

This new project couples proteomics (Gillespie), human genomics (Richard J. Smith, University of Iowa), and mouse molecular genetics (Ulrich Müller, Scripps) in an integrated program for identification and description of molecules essential for hearing and balance. The proteomics work will be done at OHSU/PNNL and is described here. When studying monogenic and complex genetic diseases, standard linkage mapping and/or association approaches to identify disease-relevant genes suffer from low throughput and lack of insight into function. Our approach provides high throughput in a contextual functional framework. We begin by noting that specific organelles are often implicated in disease. Focusing on the auditory system, we will first define the complete proteome (especially the membrane proteome) of the hair bundle, the mechanically sensitive organelle of sensory hair cells, which comprises <<1% of total protein in inner-ear epithelia. This work will be carried out at OHSU/PNNL by the Gillespie lab. Second, to link new genes to auditory disease, we will use next-generation sequencing to interrogate en masse the genes encoding bundle proteins in hundreds of affected families with uncharacterized forms of hearing loss. Sequencing will be carried out at Iowa by the Smith lab. Third, we will generate mouse lines carrying the orthologous human mutations and analyze the functional consequences of these mutations on bundle-protein networks. These mice will be generated by the Müller lab at Scripps, then mutant hair bundles will be examined using proteomic techniques by the Gillespie lab at OHSU/PNNL. This project is iterative, so novel members of disrupted networks will be screened in human families as well. This composite approach provides an understanding of a disease phenotype at the molecular level, knowledge requisite to developing novel approaches to disease treatment.

Melanie Gillingham, PhD, RD (2007) *Metabolic Consequences of CPT1A Deficiency in Alaska Native Children*

Co-Investigators: David Koeller, MD; Cary Harding, MD; William Lambert, PhD; Jonathan Purnell, MD

With the advent of enhanced screening (via tandem mass spectroscopy, MS/MS), the Northwest Regional Newborn Screening Program (NWRNSP) has identified a high incidence of carnitine palmitoyl transferase type 1A (CPT1A) deficiency in Alaska Native infants. Over the past two years, approximately 60 Alaska Native infants have been identified with this condition; previously only 30 published cases were known worldwide. All of the infants are homozygous for a c.1436C→T sequence variant in the CPT1A gene, which results in the substitution of a leucine for proline at amino acid position 479 (P479L), and an approximately 80% reduction of CPT1A activity (non-classic CPT1A deficiency, 1). The clinical implications of this very restricted level of activity are not known. However, patients with more severe reductions of CPT1A activity (as the result of other mutations) are known to be at high risk for hypoketotic hypoglycemia, liver dysfunction and, sudden unexplained death (2). Hepatomegally with micro and macro-vesicular steatosis is also common (3). Currently the treatment of Alaska Native infants and children with CPT1A deficiency is based on data from patients with severe forms of CPT1A deficiency and other fatty acid oxidation (FAO) disorders. Our ultimate goal is to establish evidence-based guidelines for treatment of the form of CPT1A deficiency prevalent in the Alaska Native population. This pilot study consists of two specific aims, which will provide the first glimpse of the physiologic effects of homozygosity for the c.1436C→T sequence variant in the CPT1A gene. These data will aid in the development of strategies for clinical management that can be evaluated in future prospective studies.

Hypothesis 1: We hypothesize that in the absence of complete FAO, excess lipids will accumulate in normal fat depots and deposited in organs such as liver, and muscle, predisposing affected patients to impaired metabolic function in those organs. Therefore, children with non-classic CPT1A deficiency will have mild, subclinical increases in hepatic and myocellular lipid deposition detected by magnetic resonance spectroscopy (MRS).

Hypothesis 2: Because the risk of fasting-induced hypoglycemia in Alaska native children with non-classic CPT1A deficiency is unknown, current treatment guidelines for parents and health care providers are based on data from other FAO disorders. We hypothesize those children homozygous for the c.1436C→T sequence variant will develop fasting hypoglycemia, and will have a blunted level of ketone production.

Jessica Gregg, MD, PhD (KL2) *Health Beliefs, Level of Acculturation, and Pap Smear Use among Latinos from Mexico*

Mentor: Thomas Becker, MD, PhD

We are using the principles and practices of community based participatory research to investigate sociocultural barriers to cervical cancer screening among Latinas in Oregon. During the first phase of our research we worked with lay health workers to develop an interview protocol concerning health and health care in general and cervical cancer screening in particular. We then used that protocol to interview 24 men and 27 women in the local Latino community. Analysis of our interview data demonstrated that while many respondents knew that the Pap smear tests for some

type of cancer, the majority also believed that the Pap smear screens for, or even prevents, sexually transmitted infections (STIs), including HIV. We also found that most respondents felt that while men play a significant role in health care decision making within the family, men generally have less access to health education and are much less well informed about health and health care than women. Based on our results, we developed a survey administered to 241 women and 228 men, all self-identifying as Mexican or Mexican American. We are currently analyzing those results.

Elizabeth Haney, MD & Kimberly Vesco, MD, MPH (2010) *Bone Turnover Among SSRI Users*

Background: Osteoporosis and depression are increasingly important health problems in the United States. Reports demonstrating lower bone mineral density and increase fracture risk in patients with depression as compared with those without depression suggest that BMD and depression are related. Whether depression is a risk factor for osteoporosis remains unclear and there are numerous hypotheses about the mechanism of such a potential association. One question involves whether depression itself or treatment for depression might be a risk factor for osteoporosis. Recently, functional serotonin transporters have been discovered in bone. Serotonin transporters play an important role in depression in that most pharmacologic anti-depressants including selective serotonin reuptake inhibitors (SSRIs) function by blocking this transporter. Thus the serotonin transporter provides a potential link between osteoporosis and depression and anti-depressant treatment. Indeed, studies have demonstrated lower BMD, higher rates of bone loss and fracture among SSRI users. Understanding the impact of serotonin on bone development and loss is important because there are a large number of people treated for depression with SSRIs.

Objective: The objectives of this proposal are to examine the impact of SSRI use on bone turnover.

Design: This is a longitudinal case-control study.

Setting and Subjects: We will recruit patients from primary care clinics at Oregon Health & Science University and Kaiser Permanente Northwest (KPNW). We will use the electronic medical record system at both institutions to obtain lists of new SSRI prescriptions and contact providers to send letters inviting patients to participate. We will enroll two groups of approximately 75 people each: 1) a sample of postmenopausal women age 50 and older (menopause defined as no menses within the past 12 months) and men age 50 and older who are initiating therapy with SSRI medications and 2) a comparison group of non-SSRI users. We will follow these groups for 1 year to compare changes in bone mass and markers of bone turnover. Exclusion criteria are listed in Table 4. In addition, any subject with a baseline BMD T score < -2.0 with risk factors (see table 4) or < -2.5 will be excluded. We expect that most of these patients will have depression, but some will have other indications for SSRIs.

Measurements: Study participants will provide urine samples for cortisol and calcium (in addition to a salivary cortisol measure) and n-telopeptide (nTx); blood samples for osteocalcin (OC), 5-HTT genotyping, 25 (OH) vitamin, and metabolic functioning. They will have height and weight measured, and will undergo two DXA scans. Participants will complete a medication questionnaire, and a questionnaire assessing health and lifestyle behaviors.

Analysis: We will compare changes in bone biomarker levels (OC and nTx), paroxetine uptake

levels (5-HTT binding assays) and BMD at 1 year between the SSRI user and non-user groups using independent two sample 2-sided t-tests. Although we expect the most dramatic change to be present at 1 year, we will utilize repeated measures ANOVA in an exploratory framework to explore possible interactions between time, SSRI use, and biomarkers of bone turnover. We will perform regression analyses in order to account for other variables that might be influencing bone turnover.

Chris Harrington, PhD (2007) *Microelectrode Array Cell Sorter for Rapid Separation of Blood Cells*

Co-Investigators: Vindhya Kunduru, MS (PSU); Shalini Prasad, PhD (PSU); David Lee, MD; Timothy Johnstone

The objective of this pilot project was to demonstrate rapid and efficient sorting of eukaryotic cell mixtures using dielectrophoresis on a microelectrode array (MEA), with preservation of cell viability and limited impact on cell physiology. The device tested in this study is based on the concept of lab-on-a-chip technology and utilizes the influence of gradient electric fields on cells with inherently different dielectric properties to sort complex cell mixtures. We have demonstrated the reduction to practice of this technology by separating white blood cells (WBCs) of interest for molecular analyses, such as quantitative PCR (Q-PCR) and whole genome expression profiling on DNA microarrays, from red blood cells (RBCs) in fresh samples of murine blood. Messenger RNA transcripts from WBCs are of interest for gene expression studies and clinical evaluations, however, the heterogeneity of blood and the abundance of RBCs complicates the process of isolating and analyzing mRNA from WBCs. Using our microelectrode cell sorter on whole blood suspensions, we were able to successfully collect white blood cells from which intact total RNA could be isolated and analyzed. Our results show that MEAs have significant potential as microfluidic separation tools for biomedical studies that require the analysis of individual cell types from complex tissues such as blood.

Ann Hill, PhD (2008) *The relationship between CMV infection, distorted CD8 T cell compartment and response to influenza vaccination in the elderly*

Co-Investigators: Allison Naleway, PhD (KPCHR) & Katrina Goddard, PhD (KPCHR)

Elderly persons are more likely to be hospitalized or die from influenza and its related complications than younger adults; however, elderly individuals frequently fail to respond to flu vaccination. The specific goal for the pilot project is (a) to identify biomarkers in the peripheral blood that predict a poor response to influenza vaccine in the elderly, and (b) to determine whether these biomarkers associated with cytomegalovirus (CMV) activity. We will recruit approximately 100 elderly (70+ years of age) health plan members seeking influenza vaccination during the annual Kaiser Permanente flu shot clinics. We will collect blood and urine samples from each participant at the baseline visit and at the follow-up visit four weeks after vaccination. Flu vaccine will be administered during the initial visit by Kaiser Permanente clinical staff as part of routine clinical care. We will measure the correlation between CMV titre and CD8+CD28-population size,

CD8+CD28- population size and response to flu vaccine, CMV serostatus and titer and response to flu vaccine, and CMV shedding on the day of vaccination and the response to flu vaccine. This pilot study will allow us to develop both our participant recruitment methods and our laboratory methods, and the preliminary data we collect will support a larger research proposal and a continued collaboration between OHSU and KPCHR.

Fay B. Horak, PhD, PT (2007) *Balance Lab*

GOAL. The goal of this Discovery Award is to facilitate the development of a Clinical Balance Disorders Laboratory for OHSU. This shared core resource allows faculty from many clinical departments to conduct clinical research that requires quantification of balance and balance disorders. This project directly translates research of basic neurophysiology underlying posture control into clinical research quantifying the effects of treatment for balance disorders.

NEED. Falls and immobility due to balance disorders is one of the largest and fastest growing health care problems today. Control of balance involves many physiological systems, including the nervous system, musculoskeletal system, vestibular and other sensory systems, and the endocrine system, so it is not surprising that clinical faculty from many departments at OHSU are interested in studying the effects of innovative treatments on balance control.

FACILITIES. The best, state-of-the-art clinical balance research equipment from Neurocom, Inc Portland was installed in the Dept of Rehabilitation Services on the 8th floor of OHSU hospital. The Neurocom Clinical Research System allows the quantification of many different aspects of balance control including: 1) sensory interactions under changing surface and visual conditions, 2) postural evoked responses to surface slips and rotations, 3) voluntary motor control such as weight bearing squats, limits of stability and weight shifting, and 4) functional limitations of stability. It is used for both research relevant for a wide range of clinical disciplines as well as rehabilitation assessment and balance training.

John Hunter, MD (2009) *Optical Fiber Spectroscopy in the Assessment of Gastrointestinal Ischemia*

Co-Investigators: Dan Gareau, PhD; Kristian Enestvedt, MD; Vincent Harrison, MD; Erin Gilbert, MD; James Dolan, MD; Steven Jacques, PhD

Anastomotic complication is a major morbidity associated with esophagectomy. Gastric ischemia after conduit creation contributes to anastomotic complications, but a reliable method to assess gastric conduit perfusion is lacking. We hypothesize that fiber optic spectroscopy can reliably assess conduit perfusion and that intraoperative gastric ischemia will correlate with the development of anastomotic complications. A simple optical fiber probe spectrometer was designed for nondestructive laparoscopic measurement of blood content and hemoglobin oxygen saturation in the stomach tissue microvasculature during human esophagectomies. In 23 patients, the probe measured the light transport in stomach tissue between two fibers spaced 3-mm apart (530-700 nm wavelength range). The stomach tissue site of measurement became the site of a gastro-esophageal

anastomosis following excision of the cancerous esophagus and surgical ligation of two of the three gastric arteries that provided blood perfusion to the anastomosis. Measurements were made at each of 5 steps in the surgery. The resting baseline saturation was 0.73 and decreased to 0.46 with ligation. Seven patients developed anastomotic complications, and a decreased saturation at either of the last two steps (completion of conduit and completion of anastomosis) was predictive of complication with a sensitivity of 0.71 when the specificity equaled 0.71.

Eric Johnson, PhD (2008) *The use of Angiotension Converting Enzyme Inhibitors (ACEIs) and Chronic Kidney Disease*

Co-Investigators: Sharon Anderson, MD; Jason Deville, DO; Amanda Petrik, MS (KPCHR); David H. Smith, RPh, PhD (KPCHR); Micah L. Thorp, DO, MPH (Kaiser Permanente Northwest)

The use of angiotensin converting enzyme inhibitors (ACEIs) is an important part of the clinical management of several chronic conditions, including coronary artery disease, congestive heart failure, and chronic kidney disease (CKD). Evidence of benefit from ACEIs in these conditions is significant, and their use has been recommended by numerous organizations (e.g., American Diabetes Association, American College of Cardiology, National Kidney Foundation). In spite of their proven benefits, ACEIs are prescribed to only a fraction of patients who might benefit from their use. Many health care providers do not use them out of concern for potential adverse effects. Many patients lose out on clinical management with these important medications; work to help translate trial findings into practice is needed. Tools that can aid clinicians in determining which patients are at highest risk of adverse outcomes are an important way to move the use of these medications from clinical trials to patient care. The points-based system we plan to produce from our analysis can be used in direct patient care to help clinicians make decisions regarding for whom they can most safely prescribe ACE inhibitors.

Eric Johnson, PhD (2010 Talk) *Translating nephrology research into clinical practice at Kaiser Permanente Northwest: Pragmatic risk scores*

Co-Investigators: Jessica R. Weiss, MD; Micah L. Thorp, DO, MPH (Kaiser Permanente Northwest); Robert W. Platt, PhD; Amanda Petrik, MS (KPCHR); Xiuhai Yang, MS; Sharon Anderson, MD; David H. Smith, PhD, RPh (KPCHR)

Pragmatic research differs from other clinical research because investigators must design for decision-makers instead of their peers. Pragmatic risk scores may offer solutions to decision-makers' questions: How can we predict clinical events under usual practice conditions based on routinely collected data? We'll discuss two pragmatic risk scores for patients with chronic kidney disease that we developed using data from Kaiser Permanente Northwest (KPNW): (1) a risk score to predict the onset of dialysis or kidney transplant; (2) a risk score to predict the onset of hyperkalemia in patients who started treatment with lisinopril. The risk score to predict dialysis or transplant has been translated into practice at KPNW; we'll discuss the challenges of its translation and how they were overcome.

Brian Johnstone, PhD (2010) *Chondrogenesis of rhesus macaque SCNT-ES and iPS cells in bioresponsive hydrogels*

Co-Investigator: Shoukhrat Mitalipov, PhD

Dr. Johnstone's laboratory has recently developed novel bioresponsive hydrogel scaffolds that can be tuned to suit the cell types encapsulated in them. These scaffolds are degraded by the differentiating cells as they produce their own extracellular matrix. The work so far has involved postnatal human cells, both chondrocytes and mesenchymal stem cells (MSC). For this pilot study, we are proposing to create a bioresponsive scaffold for somatic cell nuclear transfer-derived embryonic stem cells (SCNT-ES cells) and induced pluripotent stem cells (iPS cells) from the rhesus macaque. These cell types have been developed by Dr. Mitalipov's laboratory. For translation to in vivo implantation, these bioresponsive scaffolds will need to contain stimuli for the cells to differentiate. Our hypothesis is that engineering chondrogenic signals into the bioresponsive scaffolds we have developed will stimulate differentiation of rhesus embryonic stem cells and facilitate the production of a regenerative cartilaginous tissue. The specific aims of the pilot project are to (i) tether RGDS cell adhesion peptides and (ii) TGF-1 into hydrogels with differentially degradable tethers to stimulate macaque SCNT-ES and iPS cell chondrogenesis in the bioresponsive scaffolds. The result should be biomimetic, bioactive, bioresponsive stem cell implants for articular cartilage regeneration.

Christopher Kroenke, PhD (2008) *White matter damage in age-related cognitive decline*

Co-Investigator: Stephen Back, MD, PhD

The objective of the proposed studies is to undertake an integrated neuroimaging, cellular, and molecular approach to define mechanisms of age-related cognitive decline (ARCD). ARCD is a complex convergent phenotype that describes declining cognitive function from a variety of causes as people age, and it is a major source of disability and reduced autonomy that will challenge our health care system and tax our economy in the coming decades. Though the primary focus of dementia research has been to understand mechanisms of gray matter damage, increasingly mounting evidence supports a role of white matter damage in ARCD. In particular, neuroimaging-based studies have identified a role of vascular cognitive impairment in ARCD. We propose to examine human autopsy brains from the Adult Changes in Thought (ACT) study to characterize the biochemical and cellular-level basis of these neuroimaging-based findings. We will utilize the OHSU ultra-high field 12 Tesla MRI system to identify abnormalities in white matter in this population. We will then employ immunohistochemical markers specific to the oligodendrocyte lineage, other glia, and axons to define cellular mechanisms related to myelination disturbances in the MR-defined lesions. Both experimental approaches will be referenced to biochemical assessments of oxidative damage within adjacent brain regions characterized through the ACT study. Through this combined effort we will generate a unique and highly complementary resource of frontal lobe white matter from a human population-based study of brain aging and cognitive impairment.

Michael Kruer, MD (2010) *Gene discovery as a means of identifying novel therapeutic targets in neurodegeneration with brain iron accumulation (NBIA)*

Co-Investigators: Susan Hayflick, MD & Wei-Hong Xiong, PhD

Neurodegeneration with brain iron accumulation (NBIA) is characterized by abnormal brain iron deposition and relentless progression. Converging evidence indicates that NBIA may serve as a valuable monogenic model of sporadic neurodegenerative diseases. A substantial proportion of NBIA patients do not have mutations in any of the known NBIA genes. If novel NBIA genes can be identified in this group with 'idiopathic NBIA,' this would accelerate our understanding of the abnormalities of lipid signaling and metabolism observed in NBIA, the accumulation of iron, and ultimately, the basic mechanisms underlying neurodegeneration. To address these gaps in current understanding, we will employ homozygosity mapping to identify prominent haplotype blocks that segregate with disease in multiplex consanguineous families with idiopathic NBIA. Candidate gene sequencing will then be performed to identify mutations in novel NBIA genes. Once a mutation is confirmed, we will then determine the effect of the mutation on protein function in vitro. We will also test patients with sporadic NBIA for mutations in the newly-identified gene. Using this approach, we will thus characterize new genes that lead to NBIA, improving clinical care for patients with this rare disease while also elucidating important pathophysiologic mechanisms.

Scott Landfear, PhD (2010) *Developing a High-Throughput Screen to Identify Novel Anti-infectious Drugs*

Malaria parasites were estimated by the World Health Organization to cause approximately 243 million cases and 863,000 deaths globally in 2009, establishing malaria as one of the most important global health problems. Anti-malarials in use currently are limited in number and are subject to declining efficacy due to increasing development of resistance among parasites. Hence, development of new drugs with efficacy against this parasite is an urgent need.

Malaria parasites live inside red blood cells during the disease causing intraerythrocytic stage of the infection. The parasites are highly dependent upon uptake and metabolism of glucose, available at -5 mM concentration in human blood. Infected red blood cells utilize large amounts of glucose and are completely dependent upon this nutrient for survival. Research by the laboratory of Dr. Sanjeev Krishna has further greater is considered acceptable for an assay to enter high throughput screening, and a value of 1.0 would be a perfect assay with no experimental scatter (Assay Guidance Manual). Additional statistical criteria outlined in the Assay Guidance Manual are also applied to multiple plates read on multiple days to ensure that the assay has acceptable uniformity from plate to plate and from day to day and that there are no significant systematic positional effects on the plates. These control experiments were performed initially in our laboratory but subsequently at OTRADI using 384-well plates. robotic pipeting, and reading of plates on an automated plate reader. In summary, the results ofthe growth assays employing the PfHT-line were excellent, generating a Z'factor of 0.89. 0.91. and 0.88 in 3 separate experiments. In addition, the coefficients of variation (standard deviation divided by the average) for H, M, and L samples were well below the maximum

acceptable value of 20%, the uniformity of signals from plate to plate was high, and there were no significant position effects (e.g. systematically higher or lower values in edge rows or columns). Hence this growth assay meets all acceptability criteria with high stringency.

The subsequent step in assay validation (Assay Guidance Manual) is to perform a genuine screen using a small library of compounds and to evaluate the assay, e.g., to calculate a Z-factor for that screen. (Z-factor refers to the value calculated for a screen of a library, whereas the Z'-factor discussed above refers to the value calculated only using Hand L controls representing uninhibited and fully inhibited growth respectively (10». We have recently performed a screen using both the PfHT-and GLUT1-lines of the -2000 compound MicroSource Spectrum Collection library and are in the process of analyzing those data.

Hence, the assay is ready to employ in a true HTS to search for selective inhibitors of PfHT.

Erin LeBlanc, MD, MPH (2010) *The role of Vitamin D in menopause: Relationship to menopausal symptoms and body composition*

Co-Investigators: Teresa Hillier, MD, MS (KPCHR); Heidi Nelson, MD, MPH; Jonathan Purnell, MD; Nancy Perrin, PhD (KPCHR)

Menopause-related symptoms occur in over half of women transitioning through menopause and can negatively impact quality of life, work, and relationships. Menopausal hormone therapy, the previous mainstay, has serious long-term side effects, so a safe, well-tolerated treatment is urgently needed. The growing obesity epidemic is an escalating public health crisis, and safe, effective, and, low cost treatments are urgently needed. We present data that Vitamin D insufficiency is associated with both menopause-related symptoms and obesity and therefore calls for evaluation as an inexpensive, safe treatment for both menopause-related symptoms and menopause-related fat gain. We propose a 9 month blinded, randomized controlled trial (RCT) assessing the effects of Vitamin D on menopause-related symptoms and body composition in early menopausal women. We employ rigorous measurements of Vitamin D, menopause-related symptoms, and body composition. The preliminary data we gather will be used to develop a larger high quality RCT of Vitamin D's role in menopause-related symptoms and obesity. Specifically, we will determine Vitamin D's effect size on menopause-related symptoms and body fat and estimate how many overweight and obese middle-aged women will achieve Vitamin D sufficiency after 1 month and what characteristics predict achievement of sufficiency by 1 month. We expect Vitamin D to decrease menopause-relate symptoms and to attenuate the increase in body fat that occurs during the menopausal transition. Understanding whether Vitamin D is a modifiable risk factor for symptom development and fat accumulation during the menopause will have a large public health impact on middle aged women.

Robert Lowe, MD (2008) *Emergency Medical Services Monitoring Project*

OHSU Team: Merlin Curry, EMT-P; Richard Harper, MD, MS; William Hatt, BA, EMT; Holly Jimison, PhD; Robert Norton, MD; Ritu Sahni, MD, MPH; Edward Kim, MD; Helmi Lutsep, MD; O. John Ma, MD; Robert M. Strongin, PhD (PSU)

Intel Team: Lenitra Durham, PhD; Tim Hansen; Phil Muse; Sangita Sharma, PhD; Mary Smiley; Thomas Stroebel; Chieh-Yih Wan, PhD; Rita Wouhaybi; Mark Yarvis, PhD

The Emergency Medical Services (EMS) environment is plagued by many challenges: unpredictability; limited resources; challenges of communication between paramedics and hospital-based clinicians; pressure to act quickly with limited information; distractions; and requirements of record-keeping. This project sought to address some of these challenges – to develop and evaluate a prototype to enhance communication, information flow, and documentation in the EMS setting.

OHSU physicians and paramedics worked with Intel engineers to develop specifications for the prototype, after which Intel engineers engaged in rapid cycles of prototype development, demonstration to clinicians, and revision until the prototype performed as desired by the clinicians. The prototype was evaluated in a medical simulation laboratory using a mannequin that simulated palpable pulse, respirations, breath sounds, speech, and physiological parameters (cardiac rhythm, SPO2, ETCO2, etc.). Paramedics were recruited as study subjects and trained in the use of the prototype. Then, they treated simulated patients for acute myocardial infarction, major trauma and cardiac arrest. All cases were videotaped and the paramedics were debriefed to ascertain their perceptions of the system. Separately, emergency physicians were asked to simulate their role of providing medical direction to paramedics while interacting with a hospital-based component of the prototype that mirrored the information on the EMS unit in near-real time.

A grounded theory approach was used to develop a coding scheme and to identify emergent themes describing paramedics' and physicians' perceptions of the value and usefulness of the potential features. Domains addressed included paramedic training; paramedic data input; paramedic charting; physician interface; smart alarms; technology issues; privacy and legal issues; efficiency and quality; impact on roles, responsibility and workflow; suggested additional features; and market forces.

The evaluation demonstrated great enthusiasm by paramedics and physicians; it also suggested substantial opportunities to refine certain features. Furthermore, this investigation identified important questions about optimal strategies to integrate such a system into existing practices and technologies within a complex organizational structure.

Svetlana Lutsenko, PhD (2008) *Characterization of a copper carrier in the urine of Atp7b-/- mice and Wilson disease patients*

Co-Investigators: Dominik Huster, MD (University of Leipzig) & Martina Ralle, PhD

Copper is essential for normal human metabolism; disruption of copper homeostasis results in severe disorders, such as Wilson disease (WD). WD is caused by mutations in the copper-transporting ATPase ATP7B and is associated with toxic accumulation of copper in the liver. An

early diagnosis is essential for successful treatment of WD. However, timely diagnosis is often challenging, because the manifestations of the disease are diverse and non-specific. None of the currently available tests, alone, identifies WD with certainty. New non-invasive tests that increase the specificity of WD detection and point to the stage of the disease will be highly beneficial. Recent genetic and biochemical studies led to a better understanding of the molecular basis of copper metabolism. However, it remains unknown which molecule(s) "sense" and regulate copper status at the organism level. We have recently discovered that in Atp7b-/- mice, an animal model of WD, copper is excreted into the urine in a complex with a small copper carrier (SCC), which facilitates the removal of excess copper from the body via kidney when liver function is compromised. The major goals of the proposed research are to isolate SCC from the urine of Atp7b-/- mice, verify the presence of SCC in WD patients, and determine whether SCC can be utilized as a predictor of the stage of pathology development in WD. The proposed studies represent the first step towards the development of new diagnostic/monitoring tests for WD.

Daniel Marks, MD, PhD (2007) *Epigenetic Metabolic Programming in the Non-human Primate*

For the last four years, investigators at the ONPRC campus have been developing a model of maternal overnutrition and obesity to study fetal metabolic programming in the non-human primate (NHP). The main goal of these studies is to use a NHP model to determine if maternal diet combined with a metabolic phenotype causes abnormalities in the development of metabolic systems in the offspring, predisposing them to health problems later in life. I will focus this proposal on the analysis of liver disease in G130 (end of the 2nd trimester) fetuses.

Lynn Marshall, ScD (2007) *Amount of variability in abdominal body composition measures due to QCT scanner differences*

Co-Investigators: Kathleen F. Holton, MPH; Noal A. Clemons, BA; Jodi A. Lapidus, PhD

Background: Quantitative computed tomography (QCT) is a non-invasive imaging modality frequently used for abdominal body composition assessment. Quantifying sources of variability in body composition measures, such as from the use of different scanners, image processing, or anatomic location of the tissue, has received little attention.

Objectives: Our objectives were to 1) quantify the sources and magnitude of variability in volumes (cm3) of abdominal adipose tissue (AT) and skeletal muscle, and 2) determine if any observed variability could be reduced by adjusting the scans to a known standard.

Methods: Baseline abdominal QCT scans were obtained using the same scanning parameters among 3786 men age ≥65 yrs enrolled in the Osteoporotic Fractures in Men (MrOS) study. A calibration standard was scanned with each man. From the 7 scanners used, 5 scans were selected randomly. One reader used a standardized 4-slice processing protocol based on published Hounsfield unit (HU) ranges to estimate volumes of subcutaneous AT, visceral AT, skeletal muscle,

and intermuscular AT. Scans were processed first using native HU and second after the HU in each voxel was scaled to the water equivalent calibration standard. Proportions of variance in each tissue measure due to between-scanner, between-person, within-person and within-reader variability was estimated with random effects models.

Results: Mean (Çsd) HU in a water equivalent (0 HU) calibration standard varied significantly by scanner ($p<0.001$), ranging from 11.4 (Ç2.5) HU to -19.8 (Ç2.5) HU. The percent of between-scanner variance was ≤10% for subcutaneous and visceral AT volumes, but 20%-36% for muscle volumes. Between-person variance was ≤20% for all measures. Within-person variance was greatest for paraspinal muscle (63%) and visceral AT (11%) volumes. Within-reader variance was ≤2.5%. Variance proportions in each measure attributable to these sources were unchanged by adjustment to the calibration standard.

Conclusions: QCT-derived skeletal muscle measures were more affected than were AT measures by possible measurement error from the use of different scanners.

Cheryl Maslen, PhD (2009) *Genetic modifiers of cognitive function in Down syndrome*

Co-Investigators: Eleanor Feingold, PhD (University of Pittsburgh); George Capone, MD (Kennedy Krieger Institute); Dana Kostiner, MD (Kaiser Permanente Northwest); Lynn Nadel, PhD (University of Arizona); Joseph Pinter, MD; Roger Reeves, PhD (John Hopkins University); Jacob Reiss, MD (Kaiser Permanente Northwest); Stephanie Sherman, PhD (Emory University)

Down syndrome (DS) is a commonly occurring condition resulting from trisomy 21. One of the principle features of DS is decreased cognitive function. Nearly 1 in 700 children is born with DS, making it one of the most frequent causes of mental retardation. Individuals with DS require considerable resources for special education, long-term supervisory care, and economic support because of their limited intellectual capabilities. The presentation of trisomy 21 is highly variable between individuals. In particular, levels of cognitive function vary across a large range. Some individuals with DS have nearly normal cognitive function, while others are severely limited. This suggests that the initial genetic challenge represented by trisomy 21 is further modified by genetic background variation. The goal of this project is to gather preliminary data to support a large-scale study of genetic factors that influence cognitive variability in DS. Successful genetic analyses require well-defined phenotypes, but little is known about the specifics of cognitive deficiency in DS. It is clear that standard IQ measures do not reflect true cognitive ability in DS. The aim of this pilot study is to carefully define cognitive phenotypes in DS using a series of validated tests that measure cognitive function of different areas of the brain. These phenotypes will become the basis for identifying well-characterized cohorts for genetic analyses designed to discover genetic variation contributing to cognitive deficits. Once identified, these genetic sources of variability become targets for improving the lives of individuals with DS by optimizing functions at every opportunity.

Owen McCarty, PhD (2008) *Contrast-enhanced ultrasound imaging of thrombotic thrombocytopenic purpura*

Co-Investigators: David Jacoby, MD; Jonathan Lindner, MD; Jose Lopez, MD (University of Washington); David Motto, MD, PhD (University of Iowa); Adam Munday, PhD (University of Washington); Sandra Rugonyi, PhD

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening, multisystemic disorder resulting from the formation of platelet microthrombi, which in turn results from the incomplete processing of the adhesive protein von Willebrand factor (VWF). In TTP, VWF-induced platelet aggregates form in the microcirculation throughout the body, causing partial occlusion of vessels and leading to organ ischemia, thrombocytopenia, and erythrocyte fragmentation. Presently, the TTP mortality rate is about 95% for untreated cases. In contrast, the survival rate is 80-90% with early diagnosis and treatment with plasma infusion and plasma exchange. However, at present, the detection of TTP relies on clinical diagnosis of a pentad of signs and symptoms, as there is no pathognomonic laboratory assay for TTP. Diagnostic medical imaging has been explored recently to enable the detection of underlying pathophysiologic cellular and molecular processes of diseases. We propose to create novel, targeted contrast agents that specifically bind to TTP-related antigens. We hypothesize that non-invasive detection of VWF, the principal adhesive protein involved in initiating platelet microthrombi formation, could be used to diagnose TTP. The goal of our research is to develop a contrast-enhanced ultrasound (CEU) molecular imaging method that targets to VWF via the high-affinity platelet receptor glycoprotein (GP) Ib.

Cindy McEvoy, MD, MCR (2010) *Pregnancy Weight Gain in Obese Mothers and Bronchodilator Use in Their Children*

Co-Investigators: Victor Stevens, PhD (KPCHR); Kelvin MacDonald, MD, RRT; Kim Vesco, MD (KPCHR)

The incidence of both obesity and childhood asthma has increased alarmingly in recent years, and both epidemics substantially increase morbidity, mortality, and the public health burden. The prevalence of obesity among reproductive-aged women has tripled from 1960 until 2004. Asthma is now the most common chronic disease of childhood. The rates of asthma in children doubled between 1980 and 1996 and the Center for Disease Control recently reported that 14% of children had received the diagnosis of asthma at some point in their life. In adults, obesity is associated with increased levels of inflammatory cytokines and in animal models, exposure to these cytokines is associated with airway hypersensitivity. Thus there is a possible common etiologic pathway for both obesity and respiratory inflammatory diseases. Since the intrauterine environment exerts an important influence on the development of the fetal airways and the fetal immune system, it is important to identify the possible effects of the ongoing epidemic of maternal obesity, specifically during pregnancy, on subsequent child respiratory health. The primary aim of this study is to gather pilot data from an existing data set abstracted from the Kaiser electronic medical record on the possible association between weight gain during pregnancy in obese mothers and subsequent bronchodilator use (as a surrogate for wheezing) in their children. This study will gather unique data to investigate the confluence of two alarming epidemics: obesity and asthma, from the vantage point of weight gain during pregnancy in obese mothers and its association with subsequent child respiratory health.

Jessina McGregor, PhD (KL2) *Antimicrobial resistance surveillance to improve empiric therapy in outpatients*

Mentor: David H. Smith, PhD, MHA, RPh (KPCHR)

Surveillance of antimicrobial resistance is lacking in outpatient populations despite the increasing prevalence in this setting. In the hospital setting, microbiology data are used to create surveillance reports known as antibiograms, which are commonly distributed in hospitals as a tool for the empiric therapy decision-making process. Similar methods could be employed in outpatient clinics. However, passive methods of distributing information have typically had minimal impact on prescriber behavior. The use of electronic health record (EHR) systems provides the opportunity to integrate surveillance data into the prescriber workflow thereby facilitating a greater potential impact on prescriber behavior. The overarching objective of this application is to conduct surveillance for antimicrobial resistance in primary care clinics and utilize these data to create and evaluate clinical decision support for prescribers in those clinics. The central hypothesis is that population-specific antimicrobial resistance surveillance can be used to improve antimicrobial prescribing in outpatient settings, and that the impact is greater when distributed at the point-of-care through an EHR system interface. The specific aims of this research are to: (1) identify changes over time in the prevalence of antimicrobial-resistant infections in the primary care clinic population, (2) assess the effect of distributing antibiograms on empiric antimicrobial therapy selection, secondary antimicrobial prescriptions, and repeat visits (3) compare the effects of point-of-care distribution of antimicrobial resistance surveillance data through the EHR system to the effects of antibiogram distribution. This research has the potential to improve empiric antimicrobial therapy for outpatients thereby improving patient outcomes and decreasing associated healthcare costs.

Sahana Misra, MD (2010) *Research Consent Capacity in Individuals with and without Traumatic Brain Injury (TBI)*

Co-Investigators: Elizabeth Goy, PhD; Linda Ganzini, MD, MPH; Daniel Storzbach, PhD (OHSU-PVAMC)

Background: There is substantial support from funding bodies to improve treatments and interventions for traumatic brain injury (TBI), particularly as war veterans sustaining blast-related TBI return to civilian life. The National Bioethics Advisory Commission, however, expressed concern that individuals with cognitive impairment due to head trauma are potentially vulnerable regarding provision of informed consent to research participation. The relationship between TBI and capacity to consent to research is currently not known. Growth of research in TBI spotlights an unavoidable and ethically critical gap in knowledge: does TBI undermine individuals' ability to consent to TBI research?

Aims: The goal of this pilot study is to determine the feasibility of a larger study to examine whether individuals with mild-to-moderate TBI have deficits in research consent capacity (RCC). The specific goals are to determine the power needed for a larger study of RCC in individuals with TBI, and to refine and evaluate measures for such a study.

Design/Methods: RCC will be assessed in 20 Iraq and Afghanistan war veterans with TBI and

20 veteran controls for an imaginary, placebo-controlled, double-blind medication trial. Among a subgroup of subjects who have previously completed neuropsychological testing, we will correlate those results to their performance on the measure of RCC in order to determine the best neuropsychological measures for the planned study. The test-retest reliability of additional previously developed questions that further assess RCC, independence versus reliance on others, and influence of external factors such as monetary payment, will be determined.

Terry Morgan, MD, PhD (2007) *Improving the Reproducibility and Predictive Value of Cervical Biopsy Diagnoses by Immunostaining for P16*

Co-Investigators: Michelle Berlin, MD; Anna Dowling, MD; Emily King, MD; Robert Krum, MD; R. Lindsay-Anderson, MD; Motomi Mori, PhD; Christopher Rozelle, MD; G. Wettach, MD

Background: Cervical biopsy diagnoses show poor reproducibility between pathologists, which has become even more significant with the implementation of new clinical management guidelines. Low grade (CIN 1) and moderate (CIN 2) dysplasia have interrater kappa statistics ranging from 0.25-0.4 (poor). Severe dysplasia (CIN 3) generally has excellent reproducibility (kappa 0.7-0.8). Our objective was to determine whether immunostaining cervical biopsies for p16 improves diagnostic precision and predictive value in a large randomized cohort with 5 year clinical followup.

Design: We performed a retrospective analysis of a 5000 patient cohort at Kaiser Northwest with de novo diagnoses of cervical dysplasia (CIN 1-3). We randomly selected 450 biopsies from this cohort and tested for improved diagnostic precision by comparing the interrater kappa statistic for each diagnostic category (CIN1-3) using H&E stained sections compared to serial sections immunostained for p16 (mtm laboratories). Diffuse strong contiguous p16 staining of more than ½ of the epithelial thickness was defined as positive for CIN2+. We tested for improved predictive value of p16 staining compared to H&E-based diagnoses by comparing results to the 5 year "Clinical Consensus Diagnosis" determined by the agreement of two gynecopathologists (tkm and rk) employing p16 and Ki67 on followup LEEP/cones, or multiple negative pap smears.

Conclusions: Our data support the hypothesis that p16 immunostaining of challenging cervical biopsies significantly improves reproducibility and predictive value. Enhancing diagnostic precision and accuracy will improve patient care by detecting cases requiring therapy and reducing the number of unnecessary surgeries.

Catherine Morgans, PhD (2009) *Identification of the retinal bipolar cell antigen causing melanoma-associated retinopathy*

Co-Investigator: Shi-Xi Zheng, PhD

This grant will investigate an antigen expressed by both melanocytes and retinal ON-bipolar cells that we predict is the target of an autoimmune response causing visual deficits experienced by some melanoma patients.

Melanoma-associated retinopathy (MAR) is a condition experienced by some melanoma patients, believed to be caused by an autoimmune response to retinal antigens expressed by the tumor. The visual deficits include a "shimmering light" effect, night blindness, and a progressive loss of vision. Electroretinogram recordings from many of these patients indicate a block in visual processing at the bipolar neurons in the retina, and serum from these patients contains antibodies that label retinal bipolar cells. Furthermore, the titer of the bipolar cell antibody appears to be directly related to the stage of the melanoma, with higher antibody activity being associated with advanced stages of the disease. Identification of the bipolar cell antigen is essential to understanding the link between melanoma and vision loss. On a clinical level, identification of the bipolar cell antigen will lead to the development of ELISA assays to identify melanoma patients at risk for MAR, allowing early intervention. An assay for the bipolar cell antigen could also be used with other diagnostic procedures in assessing the stage of a patient's melanoma. Morgans and her colleagues have recently identified a TRP ion channel in retinal bipolar cells that is also expressed by melanocytes. The gene encoding this channel has previously been shown to be down-regulated in highly metastatic melanomas. This grant will test the hypothesis that this TRP channel is the bipolar cell antigen causing MAR.

Michael Neal, MS (2008) *Strategic Management in Research: Implementation of Novel Strategic Planning Methods in C/T Research*

Co-Investigators: Julie Earnest, PhD; Anne King, MBA; Jennifer Boyd, PhD, MBA; Eric Orwoll, MD

While anecdotal evidence indicates widespread strategic planning activity, there are relatively few published references to strategic planning in healthcare and in particular in academic medicine. In contrast there is a vast base of literature on strategic management in the commercial world. The Oregon Clinical and Translational Research Institute (OCTRI) set out to build a strategic management system for C/T research by adopting and adapting methods widely used in business to implement a novel strategic planning system that would work for a research organization and yield tangible results that would encourage sustained effort.

OCTRI's objectives for the process aligned well with attributes of Hoshin Planning and Strategy Mapping including translating the mission and vision into agreed objectives, focusing discretionary resources on the attainment of a few vital breakthrough objectives, maintain and improving day to day control and performance of fundamental business processes, and communicating and linking the necessary supportive plans in a participative and involving manner.

Unlike the commercial enterprise which tends to drive top down plans, the OCTRI planning system emphasized the creating of a top down strategic breakthrough plan coupled with development of business fundamental plans for individual programs. The two plans allowed the organization to capture both deliberate (top down) strategies as well as emergent (bottom up) strategies. Both plans were launched simultaneously and were synchronized and aligned through a series of catch-ball sessions among plan owners.

In its first cycle of implementation OCTRI has realized benefits in establishing goals and standards for everyday work that have provided an objective yardstick for evaluating performance. The plans have also provided an intellectual framework for aligning goals and resources for assessing the

productivity of programs. The planning process has highlighted several fundamental improvements needed resulting in a “Top 5” list of productivity investments.

Anh Nguyen-Huynh, MD (KL2) *The Role of Endolymphatic Sac in the Pathophysiology of Meniere’s Disease*

Mentor: Peter Gillespie, PhD

Meniere’s disease is thought to be a disorder of inner ear fluid homeostasis, and its histopathologic hallmark is endolymphatic hydrops. The affected cellular and molecular processes remain unknown, but several lines of evidence have suggested a role for the endolymphatic sac. Existing models for Meniere’s disease do not replicate all of its characteristics and are not amenable to genetic analysis. Recent advance in transuterine microinjection of mouse otic vesicle opens the door to the misexpression of specific genes in the inner ear. Thus a mouse model may be developed to evaluate whether a gain or loss of function can lead to hydrops, hearing loss or vestibular deficit. Plasmid and lentiviral vectors have been developed for in utero gene transfer and expression of miRNA cassettes. Lentiviral vector with CMV promoter targets predominantly the endolymphatic sac. Plasmid vector with CMV promoter tends to target the endolymphatic duct. In this system the EF1α promoter is not as effective as the CMV promoter. Proof of long-term expression of transgenes and adequate knock down by miRNA will be needed. Gain or loss of function studies will be directed against gene products in the endolymphatic duct and sac hypothesized to regulate fluid balance in the inner ear, including genes not amenable to study in transgenic mouse because of lethality.

Christina Nicolaidis, MD, MPH (2009) *Community Based Participatory Research to Improve the Health Care of Autistic Adults*

Co-Investigators: Melanie Fried-Oken, PhD; Morton Gernsbacher, PhD (University of Wisconsin); Katherine McDonald, PhD (PSU); Dora Raymaker, MS (Academic Autistic Spectrum Partnership in Research and Education)

Using a CBPR approach, we will partner with autistic adults to conduct a mixed methods study on autism-specific barriers and facilitators to quality primary care services for adults on the autistic spectrum.

There is reason to believe that, like people with other disabilities, autistic adults face significant disparities in health and healthcare. Moreover, the core features of autism – namely impairments in communication, social interaction, and focused interests – may create autism-specific barriers. However, few studies have specifically addressed these important issues. We plan to apply for NIMH R01 funding to conduct a large prospective study on healthcare access and quality for autistic adults. The goals of this proposal are to translate traditional health services methods for use with autistic adults and to collect important preliminary data that will be needed to obtain NIH funding. We will use a community-based participatory research (CBPR) approach to conduct

a mixed-methods (survey and qualitative interview) study with the following specific aims: 1) to adapt standard healthcare service instruments so they can be effectively used in an Internet-based study that will describe the healthcare characteristics of autistic adults that use the Internet; 2) to compare healthcare access and quality between three groups of Internet users: autistic adults, adults with other disabilities, and adults without disabilities; 3) to identify barriers and facilitators to care that may be unique to autistic adults, as compared to adults with other disabilities; and 4) to use qualitative data to obtain a more in-depth understanding of barriers and facilitators to quality healthcare for autistic adults. Our multi-disciplinary team includes experts in autism, disability, and health services research. Autistic community partners serve as equal partners, ensuring that methods are practical, accessible, safe, effective and ethical.

Thuan Nguyen, MD, PhD (2010) *Fence Methods in Genetic Applications*

Co-Investigators: Robert Klein, MD, PhD; John Belknap, PhD; Jiming Jiang, PhD

Gene mapping techniques play a vital role in identifying the genes that are associated with a trait. Furthermore, gene mapping elucidates how these genes function interactively in their relation to each other and to environment, and hence contribute the variation of the phenotypes. Gene search is practically a long process, and, as an important first step, the goal is usually to identify the genomic area(s) that harbor genes attributed to the trait. For many simple traits, strong correlation between the phenotype and markers have been established. However, for complex traits to which many genes are attributed, the contribution of a particular gene is quite small. This leads to the difficulty in detection of the genomic region(s) near such gene(s) due to fairly weak correlation(s) between the markers and phenotypes. Several statistical methods have arisen to take advantage of the availability of numerous informative markers, hoping to map the genes more successfully in complex traits. Model search strategies play an important role in finding such susceptible genes simultaneously. Fence method [21] was motivated by a number of limitations of traditional information criteria in selecting optimal models. The goal of this project is to bring this method to genetics applications, hoping the method is able to detect the specific genome region that is tightly linked to genes attributed to complex traits.

Melissa Nyendak, MD, MHS (KL2) *Definition of Human Immunodominant CD8 Antigens in Tuberculosis*

Mentor: David Lewinsohn, MD, PhD

Co-Mentors: Deborah Lewinsohn, MD; Shannon McWeeney, PhD

RD1-based interferon gamma release assays offer improved specificity in detecting Mycobacterium tuberculosis (Mtb) infection but do not discern active from latent disease (LTBI). $CD8^+$ T cells are found in high frequencies in individuals infected with Mtb and are capable of recognizing heavily infected cells, thus may be a surrogate of bacterial burden. The repertoire of $CD8^+$ T cell antigens is not well defined.

To define immunodominant, disease-specific $CD8^+$ T cell antigens, we have undertaken a comprehensive CD8 antigen discovery program. This approach is characterized by (1) a bioinformatic evaluation of gene families resulting in a peptide library containing 10% of the genome; (2) a local donor screen to assess preliminary recognition [LTBI (n = 15) and active TB (n=5) using a CD8 IFN-γ ELISPOT]; and (3) a statistically robust two-stage validation in Kampala, Uganda. In this regard, 50 antigens from the donor screen were selected based on commonality and strength of response, where 5 antigens eventually were studied in a cross sectional study powered to detect differences in recognition between active TB (n = 50) and LTBI (n = 50) using CD8 IFN-γ ELISPOT.

While the peptide library was enriched for the PE/PPE families (64%), 54% of the 'hits' in the local donor screen were derived from antigens from the cell wall family. Of the 5 antigens studied in the cross sectional study (PPE 50:51, PE3, CTPf, PPE:15, EsxJ), we report that 64% Ugandans with either active or LTBI infection responded to at least one novel CD8 antigen, with 19.2% responding to all 5 antigens. We did not find evidence of disease specificity for these first five antigens studied.

We conclude that newly discovered $CD8^+$ T cell antigens are broadly recognized in Uganda. Future work includes (1) the design of a new Mtb library using tools to predict clusters of epitopes across the 12 HLA supertypes and (2) the inclusion of new validation cohorts to include children and HIV co-infected subjects with the aim of elucidating immunodominant, disease-specific CD8+ T cell antigens.

Barry Oken, MD (2008) *Effects of dopamine agonists on depression and cognitive function in Parkinson's disease*

Co-Investigator: Julie Carter, RN, MS, ANP

Depression is extremely prevalent in Parkinson's Disease (PD), occurring in 20-50% of PD patients. Depression accelerates the progression of the disease by increasing the influence of motor symptoms on activities of daily living. Thus, treating depression in PD delays the onset of the need for treatment of PD symptoms, thereby saving significant costs of treatment and improving quality of life. The present project is a pilot study for a planned randomized clinical trial. The subsequent trial will test the efficacy of an 8-week meditation-based intervention for depression in PD where physiologic and behavioral markers of depression will be measured pre- and post-intervention. The present cross-sectional study will measure cognitive, behavioral, and self-report indices of depression in 15 unmedicated PD subjects, 15 PD subjects taking dopamine agonists, and matched controls. PD subjects will be recruited from the Parkinson's Center of Oregon at OHSU. This pilot will provide invaluable data for evaluating the feasibility of recruitment, the validity of cognitive outcome measures for depression, and the impact of first-line PD medications (dopamine agonists) on these measures. This will provide invaluable pilot data for both the planned randomized clinical trial and for the PI's application for career development support from the NIH. The public health implications of this research are vast, given the potential for savings by delaying the onset of pharmaceutical treatment in PD. Utilizing the sophisticated methodology of cognitive neuroscience to explore mechanisms of depression in PD is at the leading edge of translational research between cognitive neuroscience and behavioral interventions.

Susan Orloff, MD (2008) *Cohort Study of Cytomegalovirus Accelerated Transplant Vasculopathy and Chronic Rejection in Cardiac Transplant Recipients*

Co-Investigators: Daniel Streblow, PhD; Craig Kreklywich; Takeshi Andoh, PhD; Ashlee Moses, PhD; Jerome Dumortier, PhD; Patsy Smith, MS; Victor Defilippis, PhD; Klaus Fruh, PhD; Jay Nelson, PhD

Human Cytomegalovirus (HCMV) accelerates transplant vascular sclerosis (TVS), a consequence of angiogenesis (AG) and wound repair (WR). While HCMV can be localized to TVS lesions, the low number of infected cells suggests a global effect on target tissues. We used microarray analysis followed by RT-PCR in an RCMV-accelerated TVS rat cardiac transplant model to determine whether CMV activates host WR and AG factors. Dysregulated cellular genes in allografts from RCMV-infected recipients were compared to those from uninfected recipients and native hearts. We demonstrated that RCMV up-regulates genes involved in WR and AG, which was highest during the critical time of TVS acceleration (21 to 28 days). Using a standard in vitro AG assay, virus and serum-free supernatants collected at 48hrs post-infection significantly induced EC migration, branching, and tubule formation compared to supernatants from mock-infected cells. Supernatants from UV-inactivated RCMVinfected cells failed to induce AG indicating that virus replication is required. Up-regulation of WR and AG genes occurs during the critical period of CMV-accelerated TVS. Targeting these genes may prevent this process and improve allograft survival.

Tanja Pejovic, MD, PhD (2008) *The role of Fanconi Anemia proteins in ovarian cancer predisposition*

Background: Mutations in BRCA1 and BRCA2 genes account for about 60% of familial ovarian cancer cases leaving at least 40% of cases unaccounted for. Recently we tested the contribution of Fanconi DNA repair genes to ovarian cancer predisposition. Our results indicate that non-cancerous ovarian surface epithelial cells (OSE) from members of high-risk families show excessive chromosomal breakage after exposure to DNA-damaging mitomycin C (MMC) and significantly reduced levels of the protein FANCD2. Interestingly, the peripheral blood lymphocytes did not show these aberrations. We found no mutations and no evidence of epigenetic suppression of FANCD2 gene. Therefore, we suspect that an inherited defect in a gene that controls FANCD2 expression may exist. While no molecular explanation for FANCD2 suppression has been found, our work has indicated that: (1) genetic instability may be tissue specific, (2) genetic instability of the target cell population occurs early in carcinogenesis, and (3) that the screening approach we have developed may distinguish women at high risk of ovarian cancer from their relatives who are not.

Objective: This proposal is designed to test the hypotheses that: (1) inherited mutations that result in suppression of the FANCD2 gene represent a common cause of familial ovarian cancer and (2) measuring chromosomal breakage responses to MMC is a highly sensitive screening test for women who may be at high risk, genetically, for ovarian cancer. While our initial testing was done on ovarian epithelial cells, we believe that common lineage shared by ovarian epithelial and cervical cells justify application of our screening methods to cervical cells too.

Study Design: We will establish primary ovarian cell cultures using samples from a) ovarian surface epithelial cells obtained by minimally invasive laparoscopy and b) cervical cells obtained from the same patients as a cervical swab as both cells types share the common embryologic origin/lineage.

We will determine proportion of Fanconi cell phenotypes in both cell populations. If comparable results are obtained, we could predict defects in the Fanconi pathway for increased ovarian cancer risk from an noninvasive cervical smear analysis. We will also quantify mRNAs that we have observed to be at low levels in some of the high risk samples including: FANCD2, FANCJ, BRCA1, BRCA2. Retroviral mediated gene complementation analysis and gene suppression studies using siRNA will be utilized to determine the deficiency of any particular gene is the cause of the genetic instability. These methods will also permit us to evaluate whether the expression of any one of these genes influences the expression of the others.

Analysis: The proportion of women with abnormal breakage will be computed for each of the three groups for both the ovarian and cervical cell populations. T-tests of proportions will be used make initial pairwise comparisons between two groups. Logistic regression will be used to determine whether the odds of abnormal breakage differ between the three groups both before and after adjustment for additional covariates. McNemar's test will be used to assess whether there is concordance in abnormal breakage between the ovarian and cervical cells.

Mike Powers, MD (2009) *Predicting Genetic Susceptibility to Onset and Severity of Retinopathy of Prematurity (ROP) in Low Birth Weight Infants, for Pre-Pathology Diagnosis and Intervention*

Co-Investigators: Binoy Appukuttan, PhD; Timothy Stout, MD, PhD, MBA; David Wheeler, MD

To develop a gene/SNP testing diagnosis kit that will be used whenever an infant is born prematurely to predict the likelihood of this individual developing clinically significant retinopathy of prematurity (ROP), and thus allow the administration of preventative therapy tailored specifically for that individual, prior to onset of disease, to prevent blindness or visual impairment.

Retinopathy of prematurity (ROP) is a common blinding disease of premature infants in the United States. Our long term goal is to develop therapies tailored to an individual's genotype to prevent vision loss as a result of ROP in low birth weight (LBW) premature infants. Our hypothesis is that polymorphisms within genes or the promoter of these genes that promote angiogenesis or antiangiogenic processes can be used to predict whether a premature infant will develop ROP. By comparing the genotypes from a large number of premature patients with and without ROP that have been clinically well characterized according to the international ROP grading system we aim to determine whether a single polymorphism or a haplotype within a single or a combination of genes is associated with any form of ROP. We have established a ROP database and are initiating a gDNA bioresource with information on premature infants observed at Doernbecher Children's Hospital (DCH) and Casey Eye Institute (CEI). We will expand this database to include other centers within Oregon and other national CTSA centers. We have categorized premature infants into 3 main groups: A) Low Birth Weight (LBW) infant with no signs of ROP; B) LBW infant with ROP but not treated for neovascular disease and C) LBW with ROP and treated for neovascular disease. This database/gDNA resource is a crucial requirement for genetic analysis of a complex disease and will give this study a unique advantage over previous studies that have used far too few numbers to obtain a significant result and less well phenotypically characterized populations. Identifying specific genes responsible for the pathogenesis of ROP may identify those children at risk for the

development of neovascular disease. This may prompt stringent monitoring of these children and possibly earlier intervention.

Jonathan Purnell, MD (2008) *Disordered lipid and glucose metabolism in the non-human primate model of diabetes*

Co-Investigators: Kevin Grove, PhD & William Rooney, PhD

Disordered regulation of fatty acid metabolism has emerged as a key link between inflammation, insulin resistance, dyslipidemia, non-alcoholic steatoheptitis, and abnormal weight regulation leading to obesity. High-fat diets promote weight gain and excess deposition of lipids in the liver and muscle, cause dyslipidemia, and impair insulin signaling. Using a novel nonhuman primate (NHP) model of diabetes, the studies proposed here will bring together researchers from OHSU, the Advanced Imaging Research Center (AIRC), and the Oregon National Primate Research Center (ONPRC) to use in-vivo imaging and glucose clamp techniques that will provide detailed analysis of the role of disordered lipid metabolism in the expression of insulin resistance in liver and muscle in this model.

Sue Richards, PhD & Sheila Weinmann, MPH, PhD (2009) *Breast Cancer OCTRI Strategic Initiative*

Co-Investigators: Monique A. Johnson, PhD; Kathryn Richert-Boe, MD, MPH (KPCHR); Barbara Armstrong, MD, PhD (Kaiser Permanente Northwest); Katrina Goddard, PhD (KPCHR)

The aim of this pilot study is to demonstrate the capability of the OHSU Molecular and Medical Genetics laboratory to genotype for variants of the CYP2D6 gene using formalin-fixed, paraffin-embedded (FFPE) tissue specimens from a sample of Kaiser Permanente Northwest (KPNW) women diagnosed with breast cancer and treated with tamoxifen. The results will be used as the preliminary data to obtain funding for a NIH grant proposal entitled "CYP2D6 gene variants and effectiveness of adjuvant tamoxifen therapy in postmenopausal breast cancer." The impact of the full study may result in more effective treatment for breast cancer patients through clinical genotyping prior to treatment.

In this pilot study, the KPNW investigators used KPNW tumor registry and pharmacy databases to randomly select 25 deceased women who were treated for breast cancer with tamoxifen. The study pathologist (BA) reviewed H&E slides of the FFPE specimens to select normal breast tissue and normal lymph node tissue. In the research and development section of their clinical molecular genetic laboratory, the laboratory investigators (CSR and MJ) implemented and validated an assay for CYP2D6 genotyping using an Allelic Discrimination platform for point mutation detection and Pyrosequencing for copy number determination. They demonstrated proficiency of both extraction of the FFPE specimens provided from KPNW as well as CYP2D6 genotyping for both specimen types. These data are critical for obtaining support for the larger RO1 application.

Charles Roberts, PhD (2010) *Ex vivo analysis of primate islet function*

Co-Investigators: Anda Cornea, PhD; Paul Kievit, PhD; Linda Lester, MD, MS; Stephen Rayhill, MD

There is a worldwide epidemic of obesity, diabetes, and attendant serious complications, including cardiovascular disease. Type-1 diabetes mellitus (T1DM) is characterized by autoimmune-mediated ß-cell destruction, while T2DM is characterized by progressive ß-cell insufficiency. The transition from pre-diabetes to frank T2DM occurs when ß-cell function becomes inadequate to maintain insulin levels high enough to overcome peripheral insulin resistance. Thus, ß-cell failure is the critical defect in both T1 and T2DM. The successful treatment of T1DM and comprehensive therapy for T2DM will involve the propagation, maintenance, or restoration of ß-cell/islet function, which requires an understanding of the requirements for the survival, function, and potential expansion of intact islets ex vivo. We hypothesize that novel culture techniques will increase ex vivo primate islet survival and function and amenability to molecular analyses. We will address this hypothesis through the following specific aims.

1. Determine the effects of physiological O2 and microgravity/3-D culture on islet survival, integrity, and function.

2. Assess the effect of current diabetes therapies on the function of isolated primate islets.

3. Assess potential factors stimulating ß-cell replication.

4. Extrapolate non-human primate islet behavior to human islets.

This proposal will employ non-human primate islets that closely approximate human islets in order to examine both basic and translational aspects of islet function, treatment response, and potential for islet cell propagation, which will then be translated to the human situation. The proposed studies have direct relevance to diabetes therapy in humans and will additionally provide the foundation for pre-clinical transplantation studies in the diabetic macaque model developed at ONPRC. The interdisciplinary nature of the proposed work is exemplified by the contributions of co-investigators with expertise in molecular endocrinology, imaging, ß-cell/islet biology, clinical diabetes research, and pancreas pathobiology and transplantation.

William Rooney, PhD (2007) *Quantitative Molecular MRI at High Magnetic Fields; Optimizing Measurement of Iron Concentration in Human Brain*

Co-Investigators: Neil Roundy, MD; James Pollaro, MS; Jeffrey Njus, PhD; Charles Springer, PhD

Background. Iron (Fe) is an essential element for almost all living organisms. In mammals, iron is crucial for oxygen transport, electron transport reactions associated with oxidative metabolism, DNA replication and repair, and many other biochemical functions (1-3). In the human brain non-heme iron content varies regionally, with the highest concentration in the globus pallidus (21 mg Fe/100 g tissue; 5.2 mM Fe), and relatively low concentration in the cortical gray matter (3 mg Fe/100 g tissue; 0.7 mM Fe) (4). Iron concentration in the human brain parenchyma increases non-linearly with age (4). Ferritin is the primary iron storage protein in the brain, and can accommodate up to 4500 iron (Fe3+) atoms (5). Since free iron can catalyze oxidative tissue injury, elaborate iron handling and storage mechanisms exist to mitigate such effects.

Increased brain iron has been implicated in many neurodegenerative disease states including Alzheimer's disease, Parkinson's disease, multiple sclerosis and others (1-3). For some conditions, such as neurodegeneration with brain iron accumulation, a rare autosomal recessive neurodegenerative disease (1,2), massively increased brain iron deposition is thought to be a primary disease pathology.

Objective. To investigate high-field MRI relaxometry for non-invasive brain iron measurement in healthy controls and individuals with multiple sclerosis.

Martin Schreiber, MD (2009) *The Effect of Uncontrolled Hemorrhagic Shock on EETs Production in an Uncontrolled Hemorrhagic Shock Model in Swine*

Co-Investigators: Nabil Alkayed, MD, PhD; Dennis Koop, PhD; Charles Phillips, MD; William Holden, MD

Nitric oxide and the P450 eicosanoids epoxyeicosatrienoic acids (EETs) play a major role in vasoreactivity and inflammatory states following trauma. EETs are primarily produced by vascular endothelium and they serve as major components of key vasoregulatory mechanisms. EETS play an important role in regulating tissue perfusion in the heart, brain and kidney. The natural history of EETS production during hemorrhagic shock with and without resuscitation has not been studied nor have the effects of blocking and potentiating these important vascular mediators. The production of EETs in an uncontrolled hemorrhagic shock model in swine will be studied. Animals will undergo anesthesia with isoflurane and a well-described femoral vascular injury. This model is known to produce a rapid decrease in mean arterial blood pressure followed by a spontaneous increase in blood pressure (auto-resuscitation) after bleeding subsides. Nitric oxide and EETs measurements will be made at baseline, during hemorrhage, during auto-resuscitation and during the recovery period. We hypothesize that auto-resuscitation will be associated with a decrease in measurable EETs levels.

Kathryn Schuff, MD (2008) *3-Monoiodothyronamine: A novel thyroid hormone metabolite with a potential role in thyroid hormone regulation of metabolism*

Co-Investigators: Mary Samuels, MD & Thomas Scanlan, PhD

Obesity is one of the most significant public health problems and thyroid hormone is a major regulator of basal metabolism. The mechanism of this is unclear and may not be mediated via direct effects of the classic thyroid hormone, T3. Thyroid hormones are metabolized by deiodination and decarboxylation to iodothyronamines. 3-monoiodothyronamine (T1AM) is found endogenously, correlates with thyroid hormone levels, and has profound metabolic effects when administered to rodents, suggesting it may be involved in thyroid hormone regulation of energy expenditure and nutrient flux. Our objective is to evaluate the role of T1AM in mediating energy expenditure and nutrient flux. We hypothesize that thyroid hormone levels correlate with T1AM, and T1AM levels correlate with resting energy expenditure (REE) and respiratory quotient (RQ) across a range of TSH levels. To evaluate this, we propose two studies: 1) A cross-sectional baseline study of patients

with overt hyperthyroidism (TSH <0.01, elevated FT4 and/or T3), subclinical hyperthyroidism (TSH 0.01-0.28, normal FT4 and T3), euthyroid (TSH 0.28-4.5), subclinical hypothyroidism (TSH 4.5-20), and overt hypothyroidism (TSH > 20). 2) A longitudinal, parallel arm, randomized, double blind interventional study of experimentally manipulated thyroid hormone dosing to target TSH levels to induce euthyroidism, subclinical hypo- or hyperthyroidism. In both studies, predictor variables are final thyroid hormone levels; outcome variables are T1AM, REE and RQ. Demonstration of the hypothesized association will support the involvement of T1AM in thyroid hormone regulation of metabolism. Further mechanistic studies will support this pathway as a pharmacologic target for treatment of obesity.

Rosalie Sears, PhD (2007) *Software Analytic Tools to Define Discriminating Gene Signatures*

Co-Investigators: Carl R. Pelz, MA; Molly Kulesz-Martin, PhD; Grover Bagby, MD; Jan L. Christian, PhD

Global Rank-invariant Set Normalization (GRSN) to reduce systematic distortions in microarray data

We sometimes observe intensity-dependent technical variation between samples in a single microarray experiment when the array data is processed with MAS 5.0, RMA, or dChip®. We have developed a method based on using rank-invariant, endogenous transcripts as reference points for normalization (GRSN). Our method makes use of a global rank-invariant set of transcripts selected using an iterative process which results in a robust average reference that preserves the unbalanced gene expression often found in cancer and disease related datasets as well as gene knockout models. This method is implemented in the open source "R" statistical environment and works well as an overlay that can be applied to data already processed with other probe set summary methods. Recently published in BMC Bioinformatics (2008).

Jackie Shannon, PhD (2008) *From Nutrition World to Health Discoveries Program: The Evolution of a Community Education and Research Program*

The OHSU Health Discoveries Program hosts an interactive health exhibit. Originally titled "Nutrition World", the exhibit debuted for two weeks in 2007 at the Oregon Museum of Science and Industry (OMSI) in Portland, in conjunction with the museum's Body Worlds 3 exhibit. Nutrition World proved enormously popular with the public, prompting requests to reproduce the exhibit at health fairs, schools, and other venues. In addition, numerous requests to address other health issues prompted the exhibit name to change to "Let's Get Healthy!" so that the fair topics can expand beyond nutrition should the community request it. Let's Get Healthy! is a popular interactive education and research exhibit that allows community members to learn important information about their bodies while contributing to science. Attendees are invited to enroll as research participants where they learn about the research process and the quality of their own diet and body composition. They can contribute their anonymous health information to a population database that researchers can use to the study the relationship between eating habits, body composition and genetics. Schools and communities also have access to the anonymous data, which can be used

to encourage healthy living in their communities or teach scientific inquiry to their students using real data. All information collected is completely anonymous. Let's Get Healthy! health fairs are open to the public and we welcome community member volunteers of all backgrounds to help with the exhibit. We also partner with schools to help teachers meet Oregon's state standards in health education.

Stephen Smith, MD (2010) *Calcium-sensing receptor - a novel target in rare forms of epilepsy*

Extracellular calcium-sensing receptor (CaSR) is a G-protein coupled receptor that plays a central role in calcium homeostasis. In well-characterized regulatory schemes, involving the parathyroid and thyroid glands, CaSR defends blood Ca concentrations against changes and regulates bone development. However, CaSR is also localized in brain neurons where its function remains less certain. Recently, mutation of CaSR was identified as a new cause of a dominant familial form of idiopathic epilepsy. Moreover ~5% of patients with juvenile myoclonic epilepsy were found to possess novel, point mutations of CaSR. In our studies of neocortical neurons CaSR was present in most nerve terminals where it regulated a non-selective cation channel and modulated excitatory transmission. We propose that CaSR is the sensing arm of a homeostatic mechanism that sustains synaptic transmission during physiological decreases in brain extracellular [Ca]. Since seizures arise from excessive uncontrolled and abnormal electrical brain excitation, this compensatory activity could trigger epileptic activity under certain conditions. Our Research Plan builds on our expertise in CaSR, including the methodologies to evaluate its trafficking and function, and its role in synaptic transmission. Our Plan will test how idiopathic epilepsy-associated mutations alter the membrane trafficking using EGFP-tagged CaSR and a heterologous expression system. Using single cell Ca fluorimetry, we will test how the mutation affects CaSR function. If CaSR agonists reverse the action of idiopathic epilepsy-associated mutations it will indicate these drugs may be useful to prevent seizures not only for children with these rare mutations, but also for others with different seizure types.

Amala Soumyanath, PhD (2010) *Piperine and melanoma - a crucial issue for future clinical studies*

Co-Investigators: Philippe Thuillier, PhD & Steven Jacques, PhD

Our preclinical studies have identified piperine (PIP) as a potential novel treatment for the skin depigmentary disease vitiligo. PIP stimulates normal melanocyte proliferation in vitro and increases pigmentation in mouse skin. PIP accelerates the pigmentary effects of UV in mice, and may be useful in reducing current UVB doses used in vitiligo. The PI (Soumyanath) recently applied to NIH/NIAMS to fund a Phase I clinical trial of PIP and UVB in vitiligo subjects. The reviewers expressed enthusiasm for PIP as a novel treatment for vitiligo and for our trial design. However, a concern was the lack of information on PIP's effect on melanoma, particularly if used with UV radiation. This is a major hurdle to the future clinical investigation of PIP in vitiligo that must be addressed. AdPharma (a licensee of OHSU's vitiligo patents) has committed funds to study the effect of PIP on human melanoma development using an in vitro model. This pilot study proposal being submitted to OCTRI

will synergize with this in vitro study. The single, specific aim of this proposal is to investigate the effect of topically applied PIP with or without UVR in the HGF-BL6 mouse, an established model for human UV-induced melanoma. Other evidence suggests that PIP is actually likely to prevent melanoma formation. We are optimistic that this project will produce data that will strengthen the confidence of the scientific community regarding PIP's lack of melanomagenic effect, and accelerate the translation of our preclinical studies into clinical trials of PIP in human vitiligo.

Jason Taylor, MD, PhD (2009) *Genetic modification of T-cells in a simian model for HIV*

Co-Investigator: Louis Picker, MD

This study experiments with genetic modification of rhesus macaque T-cells with foamy viral vectors to develop an in vivo simian model for HIV.

Simian immunodeficiency virus (SIV) is used in primates as a large animal model for human immunodeficiency virus (HIV). With both viruses, CD4-positive T-cells are one of the critical cell types that are infected and depleted during infection. One of the untapped potentials of the SIV model is the ability to modify and track T-cells within individual animals. This would allow researchers to determine how modifications affect T-cell homing, survival and turn-over which are critical to both better understand the pathophysiology and develop therapeutic treatment for HIV. However, to date, this avenue of research has been hampered by the inability to efficiently genetically modify (transduce) large numbers of primary T-cells. In a preliminary study, we tested several vector systems and were able to effectively transduce primary rhesus macaque T-cells using a foamy virus (FV) vector.

Proposal: The purpose of this study is two-fold: 1) Optimize rhesus macaque T-cell transduction and ex vivo expansion conditions; 2) Develop foamy viral vectors expressing non-antigenic selectable surface markers.

Method: We will initially optimize the transduction and expansion of primary macaque T-cells using a marker gene (green fluorescent protein [GFP]). Simultaneously, we will engineer non-antigenic cell surface markers of transduction so that transduced cells can be followed in vivo without being immunogenic. Once the conditions have been optimized, we will transduce, expand, and purify large numbers of rhesus macaque T-cells with the non-immunogenic FV vectors as proof-of-principle for this approach.

Gary Thomas, PhD (2008) *Role of PACS-2 in colorectal cancer*

Co-Investigators: Garth Anderson, PhD (Roswell Park Cancer Institute); Christopher Corless, MD, PhD; Huihong You, PhD; Charles Lopez, MD, PhD; Motomi Mori, PhD; Doug Runckel, MD (Kaiser Permanente); Brett Sheppard, MD; Melissa Wong, PhD

The long-range goal of this research is to determine the role of the novel sorting protein PACS-2 in regulating apoptosis and colorectal cancer, a leading cause of cancer death in the United States. Colorectal cancer results from genetic instability that stimulates tumorigenesis by dysregulating

proliferative and apoptotic genes, but the molecular details of this transformation pathway remain elusive. We recently reported PACS-2 is a multifunctional protein that integrates endoplasmic reticulum (ER) trafficking with apoptotic pathways. PACS-2 function is lost in up to 40% of sporadic colorectal cancers. In healthy cells, PACS-2 regulates ER trafficking, but our preliminary data show that in response to apoptotic inducers, PACS-2 binds to proapoptotic Bcl2-family members and translocates them to mitochondria to trigger apoptosis. The goal of this proposal is to determine the extent to which the loss of PACS-2 contributes to the onset and severity of colorectal cancer. We hypothesize that the dysregulated expression of PACS-2 accelerates tumorigenesis in colorectal cancer. Studies in Aim 1 will determine when PACS-2 is lost during the adenoma-carcinoma sequence whereas studies in Aim 2 will determine the effect of targeted disruption of the mouse PACS-2 gene on the onset and severity of adenocarcinomas. Successful completion of our studies will illuminate how loss of PACS-2 contributes to colorectal cancer.

Jeff Tyner, PhD (2008) *Tyrosine Kinases as Targets for Therapy in Pediatric Acute Lymphoblastic Leukemia*

Co-Investigators: Bill Chang, MD, PhD & Brian Druker, MD

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, comprising 24% of all childhood malignancies. Although great strides have been made in the identification of biologic markers to risk stratify treatment, one-third of patients will have resistant disease and eventually succumb to their leukemia. To improve therapy, disease-causing gene targets must first be identified, and then drugs to modulate these targets can be employed. This strategy of targeted intervention may overcome treatment obstacles to our current therapies. We have employed RNAi technology to demonstrate that a functional screen can rapidly identify target genes crucial for viability of cell lines derived from cancer patients as well as primary patient samples. This technology allows for rapid target identification that can be used to tailor therapy for individual patients.

Samuel J. Wang, MD, PhD (2008) *A Regression Model Decision Aid for Determining the Benefit of Adjuvant Chemoradiotherapy for Biliary Tract Cancers*

Co-Investigators: Jong Sung Kim, PhD (PSU); Dean F. Sittig, PhD (Kaiser Permanente); Charles R. Thomas Jr., MD

Because of the rarity of biliary tract cancer, the role of adjuvant chemotherapy and/or radiotherapy remains controversial since there have been no large-scale clinical trials that have clearly defined the benefit of adjuvant therapy. The specific aim of this research project is to build a regression model for use by clinicians and patients as a decision aid to help in determining whether adjuvant chemoradiotherapy would be beneficial for patients with resected biliary tract cancer. We will use Cox proportional hazards multivariate regression analysis to construct prediction models from both the SEER-Medicare and Kaiser CHR research databases. The model will be validated for discrimination using the concordance index, and for calibration using a calibration curve. Each

model will initially be internally validated on the same derivation dataset using bootstrapping to correct for optimistic bias, and then also externally validated using the other database. Model parameters will then be incorporated into an interactive web browser-based software application so that the tool can be used to make predictions for individual patients. We will evaluate the usability of this interactive software tool in the clinic setting using standard usability metrics. We will also measure the impact of this tool on provider decision-making by conducting a survey of oncologists using case scenarios to determine whether the tool influences adjuvant treatment recommendations. Our hypothesis is that a regression model can be built that can accurately predict the benefit of adjuvant chemoradiotherapy for individual patients, and that such a model would be useful in the clinic setting.

Jessica Weiss, MD (2009) *Systolic blood pressure and mortality among older, community-dwelling adults with chronic kidney disease*

Co-Investigators: Eric Johnson, PhD (KPCHR); David Smith, PhD (KPCHR); Micah L. Thorp, DO, MPH (Kaiser Permanente Northwest)

Background: Chronic kidney disease (CKD) is an increasingly common condition, especially among older adults. CKD manifests differently in older versus younger patients, with a risk of death that far outweighs the risk of CKD progression to require dialysis. Current CKD guidelines recommend a blood pressure target of <130/80 mmHg for all CKD patients, but it is unknown how lower versus higher baseline blood pressures may affect older adults with CKD.

Study Design. Retrospective cohort study

Setting and Participants: Older patients (age 75+ years) with CKD (eGFR <60 ml/min/1.73 m2) in a community-based health maintenance organization.

Predictor: Baseline systolic blood pressure (SBP) <130, 130-160 (reference group), and >160 mm Hg.

Outcomes: Subjects followed for 5 years to examine rates of mortality (primary outcome) and cardiovascular disease hospitalizations (secondary outcome).

Results: At baseline, 3099 subjects (38.5%) had SBP <130 mm Hg, 3772 subjects (46.9%) had SBP 131-160 mm Hg, and = 1171 (14.6%) had SBP >160 mm Hg. A total of 3734 (46.4%) died and 2881 (35.8%) were hospitalized. Adjusted hazard ratios (HR) and 95% confidence intervals (CI) for mortality in SBP <130 and >160 mm Hg group were 1.22, (1.11; 1.34) and 0.99 (0.89; 1.10), respectively. Adjusted HR (CI) for cardiovascular hospitalization in these groups were 1.10 (1.09; 1.45) and 1.26 (1.09; 1.45), respectively.

Limitations: While causality should not be implied from this retrospective analysis, the results from this study can generate hypotheses for future randomized controlled trials to investigate the relationship between blood pressure and outcomes in older CKD patients.

Conclusions: Our study suggests that lower baseline SBP (≤130 mmHg) may predict poorer outcomes in terms of both mortality and cardiovascular hospitalizations among older adults with CKD. Conversely, higher baseline SBP (>160 mmHg) may predict increased risk of cardiovascular hospitalizations but does not predict mortality. Clinical trials are required to test this hypothesis.

Anna Wilson, PhD (2009) *Gender differences in pain and somatic complaints in adolescence*

Co-Investigators: Lynn DeBar, PhD, MPH (KPCHR) & Tonya Palermo, PhD

Recurrent aches and pains, such as headaches and abdominal pain, affect up to 30% of otherwise healthy adolescents and are associated with activity limitations and reduced quality of life. In middle childhood, boys and girls evidence similar rates of recurrent pains, but by early adolescence, girls begin a lifelong pattern of increased risk for chronic pain, activity limitations, and disability compared to boys. Little is known about the mechanisms that contribute to the gender disparity in pain prevalence and related disability. A potential set of mechanisms that has been largely unexplored are the physical activity patterns and beliefs about physical activity that emerge in early adolescence. Psychosocial risk factors such as depressive symptoms, cognitions about pain, and parent pain may also contribute to pain and somatic complaints in adolescent girls and boys. This study will help clarify the potential role of physical activity reductions and psychosocial risk factors in the occurrence of pain and somatic complaints in early adolescence in girls and boys. A sample of n=182 11-13 year old girls and boys were recruited through 6th and 7th grade classrooms in public schools in the greater Portland, Oregon area. Children underwent 5-7 days of actigraphy monitoring to objectively assess physical activity patterns. Children and their parents completed questionnaire measures of pain, somatic symptoms, physical activity participation, depressive symptoms, pain catastrophizing, and fear and avoidance of physical activity. Results indicate that girls engage in lower levels of physical activity than boys according to self-report and actigraphy measures. Contrary to hypotheses, pain and somatic symptoms were similar in girls and boys in this healthy community sample. However, physical activity was more strongly associated with pain and somatic symptoms for girls than for boys, supporting the hypothesis that physical activity may contribute to the development of pain for girls. Psychosocial factors including child depressive symptoms and parent history of pain were associated with pain and somatic symptoms for both girls and boys. Results will inform future longitudinal studies with this cohort and will aid in the development of preventive interventions designed to reduce pain and related disability in adolescence.

Kerri Winters-Stone, PhD (2008) *Comprehensive Fall Risk Assessment in Breast Cancer Survivors*

Co-Investigators: Stephen Chui, MD; Alvin Eisner, PhD; Ginger Hanson; Fay Horak, PhD; Shiuh Wen Luoh, MD, PhD; Lillian Nail, PhD; Nancy Perrin, PhD (KPCHR); Camella Potter; Maureen Toomey; Devon Webster, MD

Introduction: The purpose of this preliminary study was to identify treatment, symptom, neuromuscular, balance and vision factors that contribute to falls in recently treated breast cancer survivors (BCS).

Methods: BCS who finished chemotherapy within the previous two years and/or were currently treated with adjuvant endocrine therapy for the past six months participated in the study. Falls were determined retrospectively by self-report and prospectively for 6 months by monthly reports. Treatment history and current symptoms were determined by self-report, balance by computerized dynamic posturography (CDP), vision characteristics from a visual assessment battery, muscle mass by DXA, muscle function by 1-repetition maximum, chair stand and stair climb tests, gait speed by

timed walk, and physical function by self-report.

Results: 59 BCS enrolled in the study (mean age: 58 yrs; mean time since diagnosis: 21 mos). 58% of BCS had a history of falls in the past year and 53% fell during the six-month follow up period. BCS with a history of falls had significantly lower scores on CDP tests for a vestibular deficit in postural control ($p<.01$) and were also significantly more likely to take a longer time to read letters on the contrast sensitivity chart ($p<.05$). No measured variable was a significant predictor of prospectively tracked falls. Vestibular scores on CDP mediated the relationship between treatment and falls among BCS who received chemotherapy only.

Conclusions: Our preliminary data suggest that poor balance is associated with falls in BCS and that balance disturbances may be vestibular in origin. Our data also suggest that delays in detecting stimuli of sufficiently low contrast may contribute to falls in this population. Future studies that track falls and fall risk factors in BCS from diagnosis through treatment are warranted as are studies that can identify treatment-related vestibular dysfunction and altered visual processing.

Melissa Wong, PhD (2007) *Identifying a molecular signature for aggressive metastatic colorectal cancer to inform treatment*

Co-Investigators: Charles Lopez, MD, PhD & Rosalie Sears, PhD

Despite advances in screening, diagnosis and treatment, colorectal cancer (CRC) remains a leading cause of cancer-related deaths. While primary CRC can be cured if detected early, metastatic disease, commonly to the liver, is almost always fatal. Focal hepatic CRC metastases are curable in 25% of patients after surgical resection. The remaining 75% re-occur after resection with widespread metastasis. Unfortunately, these different clinical behaviors are pathologically indistinguishable and often display variable response to current chemotherapeutic regimens. The molecular basis for the diverse clinical behavior of metastatic CRC is currently unknown, highlighting the profound need for improved diagnoses to guide treatment. The ultimate goal of our project is to decrease mortality and morbidity associated with CRC.

Lisa Wood, BSN, PhD (2007) *Adjuvant BC Treatment Induces a Loss of LBM by Increasing Systemic IL-6 Production Independent of Physical Activity*

Co-Investigators: Kerri A. Winters-Stone, PhD; Stephen Chui, MD; Devon Webster, MD; Nancy A. Perrin, PhD (KPCHR)

Breast cancer (BC) patients treated with adjuvant chemotherapy, particularly with doxorubicin-(Adriamycin™) containing regimens, often experience a change in body composition including a loss of LBM, which can impact fatigue, quality of life and physical functioning during treatment and sometimes years after treatment has ended. Of the few studies that have examined changes in body composition during treatment, LBM decreased while fat mass (FM) increased. Although LBM decreased during active treatment, FM tended to increase in the months after treatment ended. The cause of these treatment-induced changes in body composition is unclear. Growing evidence

generated in experimental systems and in diverse clinical settings implicates the inflammatory cytokine, interleukin-6 (IL-6) in LBM homeostasis. Increased serum IL-6 levels have been reported in breast cancer survivors following treatment. Taken together we hypothesize that the adjuvant BC treatment induces a loss of LBM by increasing interleukin-6 (IL-6) production. Our pre-clinical data support this hypothesis. The purpose of the OCTRI funding is to support a study aimed at examining these relationships in a clinical setting. The Specific Aims of the proposed project are to: 1. Examine changes in LBM, FM, and physical activity in women undergoing adjuvant breast cancer treatment, 2. Examine the plasma IL-6 response in women undergoing adjuvant breast cancer treatment, 3. Determine the association between the IL-6 response to treatment and treatment related changes in LBM and FM, controlling for physical activity. This project has the potential to lead to new targeted treatment strategies aimed at improving physical functioning in women undergoing adjuvant BC chemotherapy. For instance, monoclonal antibodies that block the activity of IL-6 are clinically available and could be used in a future clinical trial aimed at preventing loss of LBM in women undergoing BC chemotherapy. This project arises from a unique collaboration among molecular, behavioral, and clinical investigators in a variety of disciplines and research areas and represents a major innovation in cancer symptom research.

Mark Zornow, MD (2010) *Apnea Device*

In recent years, there have been increasingly aggressive attempts to treat post-operative pain. This trend was instigated, in part, when the Joint Commission on Accreditations of Hospital Organizations (JCAHO) designated pain as the “fifth” vital sign. Unfortunately, as an unintended consequence, more and more patients are being overdosed with narcotics, either from Patient Controlled Analgesia (PCA) devices or via neuraxial narcotics (epidurals). This has resulted in more and more cases of profound respiratory depression, apnea, hypoxemia and brain injury or death. The literature would suggest that between 0.1% and 1% of patients on PCA will have one or more episodes of serious respiratory depression. The Anesthesia Patient Safety Foundation (APSF), which has been recognized as a leader in the field of patient safety by the Institute of Medicine, has identified narcotic-induced post-operative respiratory depression as a major cause of perioperative morbidity (See APSF Newsletter, Vol. 21, No. 4). Current monitoring modalities are inadequate to detect and treat the respiratory depression seen in post-operative patients. Intermittent nursing assessments, even if done on a frequent basis, are not adequate to detect the rapid onset of airway obstruction, apnea, and hypoxia that can occur in many of these patients. Continuous nursing observation, as in an ICU setting, is cost-prohibitive and simply not practical given the large number of patients at risk. What is needed is a continuous monitor of a patient’s oxygenation coupled to a device that will stimulate the patient’s respiratory drive while summoning medical assistance.

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