OREGON CLINICAL & TRANSLATIONAL RESEARCH INSTITUTE

Catalyst Awardees

The Catalyst Award supports the development of major new clinical and translational research directions at OHSU, and the funding is specifically intended to enable the development of compelling new grant applications that will sustain the proposed research activity.

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2017 - CATALYST AWARDEES

Craig Dorrell, Ph.D., Oregon Stem Cell Center, Department of Pediatrics

Assessment of Anti-Cancer Drugs Against Patient-Specific Pancreatic Cancer Organoid Cultures

There is an urgent need for new therapies to treat pancreatic cancer. Among cancers, it recently became second only to lung cancer as a killer of Americans. Unfortunately, the models currently used for pancreatic cancer drug development are either difficult to work with or cannot represent individual patient tumor characteristics. In this proposal, these issues are addressed with a collection of tumor-derived 3D organoid cultures. Cancer organoids are highly proliferative 3D structures initiated by stem cells recovered from patient tumors during surgery. Organoid cultures retain the specific genetic characteristics of the tumor from which they were initiated and can be adapted to medium-throughput drug screening. Since they represent the stem cell component of the tumor thought to be critical for its resilience, drugs, which kill these cells may be especially useful. Ten different OHSU patient tumor-specific organoid lines will be cultured and treated with panels of known and proposed anti-cancer drugs. The first goal will be to optimize culture conditions for handling by automated instruments for medium-throughput testing. Drugs already approved for the treatment of pancreatic cancer patients will be evaluated first, followed by novel compounds. These experiments will determine the most efficient ways to evaluate human cancer organoid drug responsiveness, assess the suitability of current drugs for killing cancer stem cells, and will evaluate novel drugs for efficacy against this important cell type. These results will be applicable to future testing of other cancer organoids such as those from lung or colon, and to additional compounds and targeted inhibitors.

Peter Jacobs, Ph.D., Assistant Professor, Biomedical Engineering

iPancreas: Internet Based On-Demand Artificial Pancreas App-Generator to Accelerate Clinical Trials Research

The objective of this project is to translate the OHSU artificial pancreas (AP) technology for use by other research groups through the creation of iPancreas, an Internet-based on-demand AP app generator. The OHSU AP is comprised of (1) a continuous glucose sensor, (2) two pumps to deliver insulin and glucagon, and (3) a smart phone running custom software that includes a control algorithm to automate delivery of insulin and glucagon in response to the continuous glucose sensor data. We have shown that the OHSU AP is effective at improving glycemic control in type 1 diabetes. More research groups are doing research on the AP, yet many are hindered because they lack the time, resources and technical expertise required to develop an AP. We will make iPancreas available to the research community, enabling them to rapidly develop their own custom AP that will run on an Android smart phone. Researchers will procure their own glucose sensors and insulin/glucagon pumps from commercial partners, and use iPancreas to integrate their own control algorithm, user interface, and patient alarms. Using the iPancreas API and Cloud Server, researchers will load their design files onto our server, perform a remote compilation, and then receive a file via email that can run an AP on a smart phone. iPancreas reduces time required to develop an AP from years to weeks and reduces cost to near zero. iPancreas will be designed by our engineering team, evaluated in a clinical study, and then released to the research community.

Alison Hill, Ph.D., Associate Professor, Computer Science and Electrical Engineering

An Automated, Multi-modal Tool for Quantifying the Autism Phenotype

To advance knowledge about the causes of autism as well as how best to treat symptoms of autism, it is critical to have objective, quantitative measures of the behavioral phenotype alongside a better understanding of the genetic and biologic underpinnings of these diseases. The goal of this proposal is to develop a sensitive, automated tool that captures developmentally trackable behaviors relevant to ASD and provides quantitative measures of the autism phenotype. Toward this end, we propose to develop and validate a novel measurement tool, the Multi-modal Autism Phenotype Snapshot (MAPS). If successful, we will have developed a novel measure that has demonstrated validity for measuring ASD-specific impairments that co-vary with severity of ASD symptoms. The MAPS stimuli and algorithms we develop in this project will lay the foundation for important future steps such as creating multiple parallel versions for repeated assessments, expanding the age range and evaluating developmental change, and ultimately enabling in-home assessment. The current proposal is also part of a larger vision, whose goal is to obtain a large center or program project (U54/P50) aimed at understanding the associations between atypical brain development and genetic risk with core deficits in autism by identifying mechanisms that relate genes to brain functioning and brain functioning to behavior. This proposal, therefore, represents the "missing link" by advancing our ability to link the observable and objectively measured autism phenotype to underlying biological and neurological mechanisms.

Sandra Rungonyi, Ph.D., Associate Professor, Biomedical Engineering, School of Medicine

Predicting Treatment Outcomes of Infants with Cyanotic Heart Disease Using Computational Modeling

The objective of this project is to develop computational models of babies with cyanotic congenital heart disease, with the ultimate goal of using model simulations as a tool in surgical intervention planning. Cyanotic heart defects, which cause “blue-baby syndrome”, occur when the blue (deoxygenated) blood returning from the body bypasses the lungs and is then pumped back into the body. In such cases, a BlalockTaussig-Thomas (BTT) shunt, essentially a tube, is placed in the baby to redirect blood flow from the systemic (body) circulation to the pulmonary circulation to increase blood oxygenation. The procedure has dramatically increased survival rates of infants with cyanotic heart disease, but still carries about 10% mortality.

In addition, there is a lack of consensus on how to proceed in cases of small premature babies or babies with rare defects. Computational models, which could be used to perform virtual surgeries and determine babies’ outcomes under different scenarios prior to surgery, have great potential to become a tool to guide physicians in intervention planning. The proposed computational models will be infant-specific. Because the models will be infant-specific, they will account for the individual cardiac defect and characteristics of the specific baby under consideration, and therefore will provide a personalized surgery approach for intervention planning.

Takahiro Tsujikawa, M.D., Ph.D., Adjunct Assistant Professor, Department of Cell, Developmental and Cancer Biology

Practical and Cost-effective Multiplexed Immunohistochemistry for Comprehensive Immune Complexity Analysis of Solid Tumors

Immunohistochemical (IHC) evaluations of solid tumors are a mainstay for cancer diagnosis, as well as for determining biomolecular characteristics of tumors that correlate with therapeutic response. These applications require molecular profiling of tissues at the single cell level with high resolution, and typically utilize one tissue section per biomarker evaluated, thus requiring use of multiple sections when evaluating panels of biomarkers for molecular correlates. To get around this limitation, and to enable simultaneous evaluation of up to 11 biomarkers in one formalin-fixed paraffin-embedded (FFPE) tissue section, we developed high-throughput multiplexed, quantitative IHC imaging. The objectives of this proposal are: 1) to develop an automated and high-throughput workflow for staining, image processing, and analysis; 2) to establish a molecular profiling panel for quantitatively auditing immune complexity of tumors; 3) validate our methodology to quantitatively evaluate molecular correlates in the tumor microenvironment across a diversity of human and murine tumors tissues. Successful completion of this endeavor will significantly impact clinical studies wherein molecular correlates are used for risk stratification, tumor subtyping, and evaluating response to therapy.

Nicole Weiskopf, Ph.D., Assistant Professor, Medical Informatics and Clinical Epidemiology, School of Medicine

Development and Evaluation of an EHR Data Quality Assessment Tool

We propose the development and evaluation of a novel methodology for assessing the quality and suitability of clinical data for secondary use in research. The broad purpose of this project is to enable the goals of a learning healthcare system, in which patient care generates new medical knowledge through the translation of clinical data into research findings. Specifically, this research aims to ensure the validity of retrospective observational research conducted with electronic health record data through the development, evaluation, and dissemination of a partially-automated guideline to allow clinical researchers to determine the quality and suitability of an EHR-derived dataset for use in a research study. This project will include 1) the creation and partial automation of a web-based platform to inform and assist users of 3x3 DQA, a guideline for EHR data quality assessment, and 2) a formal, scenario-based evaluation of the usefulness and usability of the tool as well as its impact on user confidence in data quality assessment.

2015 - CATALYST AWARDEES

Joshi Alumkal, MD, Associate Professor, Knight Cancer Institute

Bromodomain Inhibition for the Treatment of Lethal Prostate Cancer

Prostate cancer is the second leading cause of cancer-related death among American men. Nearly all of these deaths are due to metastatic, advanced prostate cancers that are progressing despite male hormone-lowering therapies – the principal treatment for this disease. This underscores the urgent need to develop more effective treatments for men with advanced prostate cancer. Recently, we demonstrated that the bromodomain inhibitor JQ1 shuts down many genes that are critical for survival of cells from advanced prostate cancer patients. This drug also causes these advanced prostate cancer cells to die. However, several important questions must be addressed before developing optimal clinical trials with bromodomain inhibitors in men with advanced prostate cancer. In this proposal, we will: 1) Test JQ1 in vitro and in vivo using advanced prostate cancer models and quantify the cellular changes that contribute to the tumor-suppressive effect and 2) Identify a gene signature of response using RNA-sequencing of advanced prostate cancer models after JQ1 treatment. We will then apply these results to a large cohort of patients with advanced prostate cancer under our care whose tumors have already undergone RNA-sequencing. Completion of the proposed work will: 1) Identify specific subsets of patients with advanced prostate cancer that may be ideal candidates for treatment with bromodomain inhibitors like JQ1and 2) Identify markers indicating that JQ1 has hit its target. In the future, we will apply these results to a phase I clinical trial testing bromodomain inhibition in men with advanced prostate cancer in the near-term.

Willi Horner-Johnson, Ph.D., Associate Professor, OHSU-PSU School of Public Health

Reproductive Health of Women with Disabilities Initiative

People with disabilities represent a substantial portion of the U.S. population, yet little is known about prevalence, course, and outcomes of pregnancy in women with disabilities, or about factors influencing these women's reproductive decisions. This research void leaves clinicians with a limited knowledge base for anticipating and responding to the reproductive healthcare needs of female patients with disabilities.

The Reproductive Health of Women with Disabilities Initiative (RHOWDI) will develop a research cohort that will enhance OHSU's capacity to conduct future research and clinical interventions in the understudied area of family planning, pregnancy, and childbirth among women with disabilities. We will leverage existing OHSU expertise in pregnancy and disability research, as well as strengths in electronic health record use and patient surveying techniques. Women with potential physical, vision, or hearing disabilities will be identified through a search of OHSU patient records. Women thus identified will be electronically surveyed to determine cohort eligibility and gather initial data on family planning, pregnancy, and related healthcare experiences. Women with confirmed disabilities will be enrolled in an ongoing cohort for subsequent research. Pilot data collected from the cohort will provide initial information about contraceptive use, pregnancy desires, and pregnancy history that will inform our future studies.

R. Stephen Lloyd, Ph.D., Professor, Oregon Institute of Occupational Health Sciences, Department of Molecular and Medical Genetics

DNA Glycosylases: Novel Targets for Small Molecule-induced Synthetic Lethality

Many nonsurgical cancer treatments utilize combinations of chemotherapeutic agents and targeted ionizing radiation that can produce severe toxic side effects for patients. This proposal focuses on the development of a novel treatment strategy that has the potential to increase therapeutic effectiveness, while potentially reducing adverse side effects. The underlying principle is the recent

discovery of a previously unidentified therapeutic target, the DNA base excision repair (BER) DNA glycosylase NEIL1 and the potential therapeutic benefit of the inhibition of this enzyme. NEIL1 functions in the BER pathway to catalyze the excision of DNA bases that have been damaged by ionizing radiation or other sources of reactive oxygen. The potential to exploit NEIL1 as a potential therapeutic target has been recently demonstrated in studies showing that synergistic cytotoxicity was achieved by the depletion of NEIL1 and treatment with drugs that function to limit DNA replication through dNTP pool depletion, such as 5-fluorouracil (5-FU) and methotrexate (MTX). These drugs are routinely used in combination with ionizing radiation for the treatment of patients with a variety of solid tumors. We hypothesize that effective inhibition of this glycosylase has the potential to be used in a variety of therapeutic settings thereby increasing the therapeutic index of the combined treatments. The investigative team that has been assembled for this application brings diverse complementary expertise, including structural biology, biochemistry, cell biology, radiation biology, animal model systems, immunology, and human clinical perspectives.

William Messer, MD, Ph.D., Assistant Professor of Medicine, Department of Molecular Microbiology and Immunology

Long-term DENV Immunity in a Human Cohort

Dengue virus (DENV) is the most important words). insect-borne viral pathogen of humans worldwide and a significant threat to global public health, with ~1/3 of the world's population at risk of DENV infection. There are four serotypes, DENV-1 through DENV-4. First infection with one induces short-term cross-protective immunity that wanes to a long-term serotype-specific immunity. Subsequent second infection with a different serotype confers broader immunity but also carries an increased risk of severe dengue disease - dengue hemorrhagic fever. Neither DENV vaccine nor antivirals are available to protect against DENV infection. To design effective dengue vaccines, the determinants of long-term serotype-specific protection, which are as yet unknown, must be defined. Despite this knowledge deficit, there have been no comprehensive studies of long-term DENV immunity in human cohorts, nor is there a central DENV immune sera or cell repository required to identify the critical determinants of long-term DENV immunity. To address this deficit, over the next year (July 1/2014-June 30/2015) we propose to: 1) recruit a cohort of local DENV immune individuals with the intent to 2) use cohort sera and immune cells to characterize the determinants and correlates of natural long-term DENV immunity in humans. This cohort will enable us to prospectively study DENV immunity over time, including developing a human dengue challenge model, and will serve as a reference repository for samples and data to be utilized by OHSU researchers and the larger DENV research community, providing high value correlates of DENV immunity, leading to more effective development of DENV vaccines.

2014 - CATALYST AWARDEES

Penelope Hogarth, M.D., Associate Professor, Molecular & Medical Genetics

Neurodegeneration with Brain Iron Accumulation: Research Cohort Development

This project focuses on cohort development in a group of rare disorders which share the feature of abnormal brain iron. "Neurodegeneration with Brain Iron Accumulation" (NBIA) comprises many different disorders, six of which have been genetically defined. While the OHSU research registry and biorepository has been in existence for many years, its scope and productivity have grown enormously in the last 3-4 years as international collaborations have been forged, the pace of gene discovery has picked up, basic science interest in the disorders has increased, and patient advocacy groups have found strength in numbers. Along with this success and growth have come challenges and opportunities. The OCTRI catalyst funding will allow us to 1) develop and begin testing a clinical outcome test battery, and 2) investigate a tantalizing connection between a newly-discovered form of NBIA and Rett syndrome.

Cynthia McEvoy, M.D., M.C.R., Professor of Pediatrics, Division of Neonatology, School of Medicine

From Mother to Baby: Blocking Lung Disease and the Epigenetic Changes in Childhood Caused by Maternal Smoking During Pregnancy

We are requesting Catalyst funding to assemble, maintain and characterize a unique cohort of offspring of mothers who smoked and were randomized to supplemental vitamin C or placebo during pregnancy, and to profile their DNA methylation patterns from birth to childhood in relation to the vitamin C intervention and asthma development. Smoking during pregnancy remains a major problem with at least 12% of women smoking during pregnancy. Children whose mothers smoked during pregnancy show lifetime decreases in pulmonary function and increased asthma risk. Our data in animal and human studies strongly supports that the lifelong

consequences of this in utero exposure can be lessened by maternal vitamin C supplementation. The objectives of this proposal are: 1) to create, maintain, and follow the clinical cohort assembled from a completed K23-trial which randomized 159 pregnant smokers to vitamin C (500 mg/day) versus placebo (and studied 70 non-smokers), and from an ongoing R01 randomizing pregnant smokers to vitamin C versus placebo; 2) to investigate altered epigenetic profiles of DNA methylation that may predict disease susceptibility using biospecimens collected at delivery, 3 months, 12 months, and ages 2-7 years to measure global and gene specific DNA methylation. During the Catalyst (9/1/13 - 8/31/14) we will collect cross-sectional samples on 188 patients from the K23 (age range of 2-7 years old) and delivery samples on 120 patients and 3-month samples on 80 patients from the ongoing R01. This data will support a planned application to NIH PAR-13-109 "Mechanistic Insights from Birth Cohorts" planned for October 2014.

Garet Lahvis, Ph.D., Associate Professor of Behavioral Neuroscience, School of Medicine

Oregon Animation Test for Social Reciprocity

Autism Spectrum Disorders (ASD) feature deficits in social interaction, communication and repetitive interests. Drug and behavioral treatments for ASD are undergoing rapid development, yet our diagnostic tools are not suitable for efficacy assessment. The Autism-Diagnosis Observational Schedule (ADOS) is a clinical interview with the child and the gold standard for diagnosis. However, this test is subjective, course grained and costly, precluding repeated tests of the same child to assess treatment efficacy and large-scale control assessments of typically developing (TD) children. For these reasons, the ADOS can impede imaging and genetic research. In light of these concerns, the Oregon Animation Test for Social Reciprocity (OATS) will be developed to evaluate distinct autistic behavioral phenotypes, including joint attention, empathy, imitation, and lack of narrative coherence. The main idea of OATS is that animated characters and social scenarios are presented on a computer screen while the responses of the child are recorded by video camera, microphone, and eye-tracking equipment. Animations are used to test each behavioral phenotype of autism. The long-term vision for OATS is to evaluate behavioral and physiological responses of autistic children, including heart rate variability, pupil dilation, and EEG. Our first objective is to use existing animations to build an OATS "Prototype" that discriminates autistic from normal children (Aim 1). From these results, and use of a defined library of still frame posed images, we will design our own animation platform to assess differences between autistic and normal children (Aim 2).

2013 - CATALYST AWARDEES

David Huang, M.D., Ph.D., Professor of Ophthalmology

Functional Optical Coherence Tomography Resource Center

Optical coherence tomography (OCT) is a micron-resolution 3D imaging modality commonly used in ophthalmology. Our research group has developed novel functional OCT technologies to image and measure ocular blood flow. In pilot studies of glaucoma, total retinal blood flow measured by Doppler OCT and ONH perfusion measured by OCT angiography were both found to be highly repeatable and diagnostic, and well correlated with visual field loss. The goal of the proposed project is to demonstrate a wider range of applications for functional OCT and develop preliminary results for an NIH P41 center grant. The specific aims are: 1. Develop functional OCT technology. Algorithms will be developed to quantify perfusion and detect retinal and choroidal neovascularization. 2. Use functional OCT to map perfusion loss. Pilot clinical studies will be performed to detect parafoveal retinal ischemia in diabetic retinopathy (DR) and choriocapillaris flow defect in agerelated macular degeneration (AMD). 3. Use functional OCT to detect neovascularization. OCT angiography will be used to map retinal neovascularization in proliferative DR and choroidal neovascularization in wet AMD. 4. Use functional OCT to evaluate the role of vascular dysfunction in neurodegenerative diseases. Functional OCT will be performed in multiple sclerosis patients to evaluate loss of ONH and macular perfusion in the neurodegenerative process. 5. Use functional OCT to evaluate tumor vascularity. OCT angiography will be used to differentiate benign choroidal tumors from malignant melanomas based on their vascular patterns. Functional OCT will be used to evaluate the tumor, ONH, and retinal response to radiation treatment.

Scott Landfear, Ph.D., Professor, Molecular Microbiology and Immunology

Endochin-like Quinolones (ELQs) as Broad Spectrum Anti-Parasitic Drug

This pilot project represents an emergent interdisciplinary collaboration among three established OHSU investigators, Dr. Scott Landfear (MMI), Buddy Ullman (BMB), and Michael Riscoe (VAMC), that will explore the therapeutic potential of the Endochin-like quinolones (ELQs) as broad-spectrum anti-parasitic agents. Several ELQs have already shown remarkable curative properties against two important parasitic infections, malaria and toxoplasmosis, and are currently being readied for clinical trials. The overall objective

of this proposal is to examine whether efficacy of these ELQs can be extended to other parasites of medical importance, specifically Leishmania mexicana, Leishmania donovani, and Trypanosoma cruzi, the etiologic agents of cutaneous leishmaniasis, visceral leishmaniasis, and Chagas' disease, respectively. Preliminary data obtained in the Landfear and Ullman laboratories demonstrate that many of the >100 currently available ELQs, synthesized in the Riscoe laboratory, are toxic toward the insect forms of both L. mexicana and L. donovani, and some ELQs are also remarkably effective against the mammalian form of L. mexicana. The three Specific Aims of this proposal will extend the initial observations of ELQ efficacy to the murine model of cutaneous leishmaniasis (Specific Aim 1), improve upon the potency of the current ELQ armamentarium (Specific Aim 2), and extend our drug discovery stratagem to L. donovani and T. cruzi (Specific Aim 3). The methodology required to accomplish the 3 Specific Aims amalgamates state-of-the-art techniques in molecular parasitology, pharmacology, and medicinal chemistry and will identify 'lead' compounds for treating the 3 diseases. The research in this proposal will be initiated 02/01/2013 and completed by 01/31/2014.

Owen McCarty, Ph.D., Professor, Biomedical Engineering, School of Medicine

Development of Contact Pathway Inhibitors for the Treatment of Thrombotic Diseases

Thrombotic diseases remain the leading cause of morbidity and mortality in the US. While conventional anticoagulants are effective at both preventing and treating thrombosis, the potential for bleeding side effects limits their use or requires sub-optimal therapeutic dosing when bleeding risks are high. Consequently, a critical unmet medical need remains for a safe antithrombotic drug. Our goal is to develop contact pathway inhibitors that specifically target pathological thrombus formation while preserving hemostatic mechanisms. Our team has demonstrated that pathological activation of the FXII/FXI axis contributes to occlusive thrombus formation, inflammation, and circulatory changes in rodent and primate models of thrombosis, stroke and sepsis. We hypothesize that the FXII/FXI axis represents a promising antithrombotic drug target. We have generated a set of unique neutralizing monoclonal antibodies against the FXII/FXI axis. Our promising preliminary data provide a rationale for the development of a novel class of safe anticoagulants targeting contact activation. Our program is designed to develop these inhibitors for the prevention of thrombus formation in medical devices and prevention of pathological thrombus formation in the macro- and micro-circulation.

Kevin Winthrop, M.D., MPH, Associate Professor of Infectious Diseases

The Oregon Non-tuberculous Mycobacteria (NTM) Cohort; Immune Correlates of Pulmonary NTM Disease Progression

This application seeks to develop a biorepository for a cohort of patients with pulmonary nontuberculous mycobacterial (NTM) infection, and leverages an existing NIH-funded project evaluating the natural history of this chronic and debilitating disease. NTM are ubiquitous within municipal water systems and soil, and our epidemiologic work has documented NTM disease rates to be rapidly increasing, particularly among older adults without recognized immune deficits. While our work has elucidated certain risk factors for disease, there has been little evaluation of the host response to exposure and infection, and currently, the pathogenesis of pulmonary NTM disease is unexplained. Our NIH-funded project supports the longitudinal follow-up of a population-based cohort of patients with pulmonary NTM infection (n=371) identified in 2005-6, and the ongoing expansion of this cohort with newly infected individuals (n=180/year). From our 2005-6 cohort, we know that some have progressed to active disease (cases) while others have not (non-cases), allowing us to evaluate various host factors that potentially serve as biomarkers for disease progression. Our epidemiologic and clinical observations to date suggest the possibility that adipokines (e.g. adiponectin) and/or differential T lymphocyte responses are important to disease pathogenesis. OCTRI support (anticipated start date 2/2013) will allow us to collect/store blood from these patients, and to evaluate these hypotheses from a subset (n=100) of our cohort. With this preliminary data, and the biorepository which will store samples from newly infected individuals, we will submit an R01 application (anticipated 2/2014) that seeks to prospectively identify predictors of disease development and progression.

2012 - CATALYST AWARDEES

Joel Nigg, Ph.D., Director, Division of Psychology, Professor of Psychiatry, Pediatrics, and Behavioral Neuroscience

Catalyzing ADHD and Autism Spectrum Disorder Centers via Advancing Brain Imaging Development in Rodent Models

Brain imaging has transformed modern medicine. In the clinical neurosciences, MRI has been particularly important for localizing structural brain abnormalities underlying several neurologic conditions. Yet, in most instances the clinical management of brain disorders that do not cause structural lesions has not moved forward alongside the introduction of clinical neuroimaging. Metabolic disorders, chronic pain syndromes, movement disorders, and, in particular, neuropsychiatric disorders, such as ADHD and Autism,

typically do not correspond to a focal structural abnormality that can be identified with standard clinical MRI protocols. To improve clinical management of disorders such as ADHD and Autism it is critical that objective biological measures (i.e. biomarkers) be created alongside a better understanding of the genetic and biologic underpinnings of these diseases.

Developing a program capable of informing these disease types in this way would significantly advance modern medicine - both in terms of clinical management and understanding underlying neurobiological mechanisms - a critical goal to many OHSU investigators. Toward this end, the current proposal is part of a larger vision, which aims at obtaining a large center or program project aimed at clarifying heterogeneity, understanding etiology, and developing markers of ADHD and/or Autism. Developing the means by which to obtain such an award has been ongoing over the last 1-2 years. This proposal represents the "final piece of the puzzle," by conducting experiments to advancing the potential to use resting-state functional connectivity MRI (rs-fcMRI) as a biomarker, to clarify heterogeneity, and to understand etiology for ADHD and Autism.

Janne Boone-Heinonen, Ph.D., MPH, Associate Professor, Epidemiology & Traci Rieckmann, Ph.D.

Astoria Women's Heart Health Initiative: Cohort Development Pilot

The proposed project responds to the high priority, yet largely unexplored need to develop and test community prevention strategies in rural areas. We will construct the Astoria Women's Heart Health Initiative (AWHHI) cohort composed of women in Astoria, a semi-rural town with elevated heart disease mortality. In the long term, the AWHHI cohort will support development of community interventions that target women and incorporate an unprecedented range of community sectors to reduce CVD morbidity and mortality. We leverage existing relationships between OHSU and the Astoria community – a critical prerequisite for successful participant recruitment and retention and multi-component intervention in community-based, translational research. We will (1) recruit women residing in the City of Astoria (35-69 years; participation goal n=1,378) and collect baseline clinical and survey measures; (2) identify key correlates of CVD risk factors and preventive practices in women using baseline data, and (3) develop community profiles of heart disease burden and risk factors using existing administrative and surveillance data. We build on preceding qualitative research findings and apply a mixed method, community participatory approach throughout the study. We will conduct the proposed research from 6/30/2012 through 6/29/2013 and submit an R01 proposal to develop a community-wide intervention to improve behavioral CVD risk factors in women in October 2013. The proposed study will provide baseline measures and preliminary data and demonstrating relationships with the community to support our R01 application, as well as numerous other grant applications to develop and test a wide range of translational therapies and behavioral interventions.

Peter Steyger, Ph.D., Professor, Otolaryngology

Genetic Association in Aminoglycoside-induced Ototoxicity

Patients with cystic fibrosis (CF) experience frequent respiratory infections that are controlled by obligatory aminoglycoside treatment that induces sensorineural hearing loss in a sub-group of patients, while the remainder with equally extensive aminoglycoside exposure retains normal auditory function. This bimodal distribution is highly suggestive of genetic susceptibility to aminoglycoside ototoxicity. Aminoglycosides are trafficked into the cochlea and sensory hair cells via drug-permeant cation channels that also mediate pain sensitivity and systemic water balance functions. We hypothesize that single nucleotide polymorphisms (SNPs) in three aminoglycosidepermeant channels enhance cochlear and sensory cell uptake of aminoglycosides and predispose individuals to aminoglycoside ototoxicity. We have a cohort of CF patients with chronic exposure to aminoglycosides and monitor their hearing status. We will genotype 34 SNPs with a minor allele frequency >10% in 3 genes for aminoglycosidepermeant channels expressed in the cochlea. Prospective identification of individuals with genetic susceptibility to aminoglycoside ototoxicity will permit individually-tailored antibiotic therapy to prevent or ameliorate ototoxicity, and permit optimal (and early) allocation of otoprotective or rehabilitation resources when aminoglycoside exposure is obligatory and there is a greater risk of ototoxicity. Preventing hearing loss is especially crucial for children developing listening skills essential for speech and language acquisition that leads to optimal educational attainment. The significance of this research-driven cohort development study is that it will allow, for the first time, the ability to screen individuals for genetic susceptibility (in genomic DNA) to aminoglycoside-induced ototoxicity prior to treatment.

Peter Steyger, Ph.D., Professor, Otolaryngology

Preventing Acquired Hearing Loss in the Neonatal Intensive Care Unit

This is a prospective study examining the roles of noise exposure and aminoglycoside exposure on hearing outcomes in the neonatal intensive care unit (NICU). Noise and aminoglycosides can both independently, and synergistically, induce permanent hearing loss in rodent models. Hearing loss rates in NICU patients run at 2-15% of admissions, compared to the 0.2-0.3% prevalence of congenital hearing loss present in full-term births. Although the management of NICU admissions is medically more challenging than full-term births, the precise etiology behind this increased prevalence (10-50x greater) hearing loss remains unknown. While some NICU admissions may have congenital hearing loss, these cases represent an insignificant fraction of the total rate of hearing loss in NICUs. Substantial noise is generated by medical equipment in the vicinity of the patient, and no studies measuring the effects of these sound levels on individual patients have been reported. This pilot investigation will establish a human cohort to examine the synergistic effect of sustained noise and aminoglycoside exposures on hearing loss. We will test the hypothesis that aminoglycoside-related ototoxicity and noise exposure synergistically enhance the rate and onset of acquired hearing loss in humans. The innovation in this study resides in measuring sound levels within the occupied isolette. If the above hypothesis is not disproven, these data will lead to improved standard of care policies to prevent or ameliorate life-long auditory dysfunction induced by noise and/or aminoglycoside exposure for those infants who graduate from the NICU.

Tom Scanlan, Ph.D., Professor, Physiology and Pharmacology, School of Medicine

A Pharmacologic Strategy for Genetic Complementation in X-linked ALD: Novel Use of the Thyromimetic Compound Sobetirome

Our long-range goal is to test the potential of sobetirome, an experimental selective thyromimetic drug, as a treatment for X-linked adrenoleukodystrophy (X-ALD), an inherited neurodegenerative disorder with no effective therapy. X-ALD is caused by mutations in the ABCD1 gene, which encodes a peroxisomal membrane transporter (ABCD1) required for very long chain fatty acid (VLCFA) metabolism. The defect in VLCFA metabolism in X-ALD can be corrected by the closely related protein ABCD2, suggesting that manipulation of ABCD2 expression may have therapeutic potential. Both ABCD1 and ABCD2 are transcriptionally regulated by thyroid hormone, leading to the hypothesis that sobetirome may have efficacy as a treatment for X-ALD. Selective thyromimetics such as sobetirome that lack the adverse thyrotoxic effects of thyroid hormone have been shown to be safe and efficacious as lipid-lowering agents. The FDA viewed our hypothesis favorably as evidenced by granting an Orphan Drug Designation for use of sobetirome in X-ALD. We propose a pilot study in which we will administer sobetirome for up to 30 days in a small number of X-ALD patients. The primary outcome measure will be VLCFA levels, which are elevated in X-ALD patients. This study will be the first step in a long-term development program, and if successful, we envision a future grant from the Orphan Products Division of the FDA and the subsequent recruitment of industry partners to fund the continued development and commercialization of sobetirome for X-ALD, based on the novel mechanism of genetic complementation via transcriptional activation of ABCD2.