



Summaries of UW ICTR Basic & Clinical Pilot Awards, Round 9, 2015 (awarded in 2015)

PI: [Rozalyn Anderson, PhD](#), UW School of Medicine & Public Health

Title: *Plasma Diacylglycerol Biomarker for Elevated Diabetes Risk in Overweight Subjects*

Collaborator: Steve Cummings, California Pacific Medical Center Research Institute

Summary

The goal of this study is to generate proof of concept data for a biochemical method to detect insulin resistance in advance of changes in fasting blood glucose and independent of BMI. This technology will allow for much earlier detection of elevated risk for metabolic syndrome, pre-diabetes, and diabetes, permitting earlier intervention and improved patient outcomes. In addition to early detection, the biomarkers may also be relevant in monitoring the course of corrective interventions in diabetic and pre-diabetic individuals, or for identifying elevated risk of diabetes associated with widely prescribed medications targeting other disorders, including statins used to lower risk for cardiovascular disease.

PI: [Amy M Fowler, MD, PhD](#), [Roberta M Strigel, MD, MS](#), UW School of Medicine & Public Health

Title: *Targeted Breast Cancer Imaging of Angiogenesis and Progesterone Receptor with MR/PET*

Collaborators: Wendy DeMartini, Alan McMillan, Scott Perlman, UW SMPH; Walter Block, UW COE

Co-Funding: UW Carbone Cancer Center, UW Department of Radiology

Summary

A noninvasive imaging method to investigate early endocrine sensitivity provides the opportunity to reveal a patient's cancer biology and sensitivity to various treatments in "real-time" and within the entire tumor that a biopsy sample alone cannot provide. The hypothesis of this pilot study is that simultaneous imaging of tumoral progesterone receptor with FFNP-PET and angiogenesis with DCE-MRI is feasible and accurate for patients with newly diagnosed ER α +PR+ invasive breast cancer. Data gained through the successful completion of the proposed pilot study will serve as the foundation for larger scale trials testing the predictive value of FFNP-PET with DCE-MRI in measuring endocrine responsiveness in patients with newly diagnosed ER α +PR+ breast cancer. Earlier identification of an endocrine-resistant cancer would support the use of an alternative adjuvant endocrine agent and/or the addition of cytotoxic chemotherapy and may improve patient survival.

PI: [Hrissanthi Ikonomidou, MD PhD](#), [Diane Puccetti, MD](#), UW School of Medicine & Public Health

Title: *Methods to Study Chemotherapy-Related Neurotoxicity in Children*

Collaborators: Jens Eickhoff, UW SMPH, Michael Kelly, Children's Hospital of Wisconsin

Summary

Clinical studies investigating the effects of Chemo and radiation on CNS in children with cancer have reported causative associations with the development of leukoencephalopathies as well as smaller regional grey and white matter volumes, and these were found to correlate with neurocognitive deficits. The goal of this project is to prospectively characterize the evolution of biochemical features of Chemo-induced CNS toxicity in children. We expect that the proposed study will identify early biochemical biomarkers of Chemo-induced CNS toxicity in children undergoing treatment for acute lymphoblastic leukemia. These biomarkers can then be used to monitor and help develop strategies to prevent CNS injury in response to Chemo.



PI: [Matthew V Jones, PhD](#), [Rama K Maganti, MD](#), UW School of Medicine & Public Health

Title: *Role of the Dentate Gyrus in Seizures and Cognitive Deficits*

Collaborator: Randall Ashton, UW COE

Summary

Our central hypothesis presumes the dentate gyrus (DG) is a common site of malfunction that leads to seizures as well as dysfunctions in memory, navigation, social interactions, and lucid perception/cognition. The DG is the first stage of hippocampal processing, and performs the function of "pattern separation". However, our current lack of understanding of the underlying mechanisms presents a major obstacle to identifying new and effective treatments for epilepsy and associated cognitive disorders. The long-term goals of this research are a) to elucidate the synaptic and network mechanisms underlying pattern separation, b) to understand how and when this function fails during the development of epilepsy, c) to understand behavioral correlates of such failure that may predict development of epilepsy and cognitive dysfunction.

PI: [James Keck, PhD](#), UW School of Medicine & Public Health

Title: *Fanconi Anemia/Bloom Dissolvasome Interaction Inhibitors as Novel Chemotherapeutics*

Collaborators: Randall Tibbetts, UW SMPH

Co-Funding: UW Carbone Cancer Center

Summary

Recently, selective genomic destabilization agents that block activity of specific DNA repair proteins have shown great promise as chemotherapeutics. This proposal seeks to extend the range of selective chemotherapeutic DNA repair targets by investigating the therapeutic potential of small-molecules that block interaction between two DNA repair complexes, the Fanconi Anemia and the Bloom dissolvasome complexes. In our proposed experiments, we test the hypothesis that our inhibitors will induce genomic instability in vivo and that they will have selective toxicity against cancer cell lines. Biochemical and structural approaches will then be used to determine the mechanisms of action of compounds that show in vivo activity and to drive future rational lead improvement.

PI: [Lingjun Li, PhD](#), UW School of Pharmacy

Title: *Novel Imaging Mass Spectrometry-based Proteomics Technology to Identify Autism Biomarkers*

Collaborator: Hrissanthi Ikonomidou, UW SMPH

Summary

Evidence supports the hypothesis that, although pathogenetically different, Autism spectrum disorders (ASD) share common dysfunctional mechanisms and pathways which, unfortunately, remain largely unknown. We hypothesize proteins and peptides that play a key role in the pathogenesis of autism demonstrate similar regional and age-dependent expression patterns in the brain in different syndromes of autism, and differ from those expressed in normal brains. Such proteins/peptides can be useful as biomarkers for early identification of individuals at risk for developing ASD, and some may even constitute novel therapeutic targets. We will explore this hypothesis by combining novel high resolution proteomics methodologies and gene expression technology with behavioral, pharmacological and neuropathological studies in established mouse models of autism.

PI: [Eneida Mendonça, MD, PhD](#), UW School Medicine & Public Health

Title: *Surveillance of Hospital Acquired Infections Using Natural Language (SHANL)*



Collaborator: Nasia Safdar, UW SMPH

Summary

Clostridium difficile is the major infectious cause of healthcare-associated diarrhea, resulting in as many as 25% of cases of nosocomial diarrhea. Whereas conventional risk factors for recurrence have been evaluated (such as comorbidities), data on other patient centered and patient reported outcomes such as quality of life, duration of diarrhea, weight loss, dehydration, appetite changes, fecal incontinence and limitation in function and mobility have not been evaluated as predictors of readmission to the healthcare system because these data usually do not exist in a structured format but are part of the narrative in the electronic health record. These data are critical to devising effective treatment and prevention strategies for CDI. We propose to develop and test a prediction model of CDI that incorporates clinical data from the electronic health records such as CDI signs and symptoms and effect of treatment including patient centered outcomes such as diarrhea, incontinence, dehydration and functional limitation.

PI: [Paul E Peppard, PhD](#), UW School of Medicine & Public Health

Title: *The Role of Duration of Sleep-Disordered Breathing in Brain Injury*

Collaborators: Sterling Johnson, Erika Hagen UW SMPH

Summary

Our hypotheses are that long-term exposure to sleep-disordered breathing (SDB) in adults results in brain injury that is quantifiable by structural and functional neuroimaging; and that intermittent hypoxia, sleep disruption and vascular pathology mediate, to varying degrees, the association between SDB and brain injury. Whereas much of the research relating SDB to organ system damage has focused on the cardiovascular system, many of the outcomes of SDB—cognitive dysfunction, depression and others—may be due to brain injury. To date, there has been no largescale longitudinal investigation of SDB and brain injury or attempts to measure the importance of potential mediating mechanisms connecting SDB with brain injury. We propose to provide pilot and baseline neuroimaging studies that assess brain volumes, ischemic lesions, white matter health, and cerebral blood flow.

PI: [Michael D Repplinger, MD, MS](#), UW School of Medicine & Public Health

Title: *Contrast-Enhanced MRI to Diagnose Appendicitis: Translating a UW Protocol to a Community-Based Program with a Different Scanner Platform*

Collaborators: Scott Reeder, UW SMPH; Marshfield Clinic

Summary

Although computed tomography (CT) is the standard imaging test used to diagnose appendicitis in the general population of the United States, it has potential risks including nephrotoxicity and allergic reactions to the intravenous contrast agent, as well as radiation-induced cancers. Despite these known harms, there has been a 40-fold increase in the number of CTs performed in the U.S. over the past 30 years. This study aims to improve patient health and quality of life by evaluating the use of safer imaging practices for a very common gastrointestinal surgical emergency, thereby mitigating the long term risk of developing various cancers.

PI: [Federico E Rey, PhD](#), UW College of Agriculture & Life Sciences; [Barbara B Bendlin, PhD](#), UW School of Medicine & Public Health

Title: *Alzheimer's Disease and the Gut Microbiome*

Summary



Given the link between gut microbiota and insulin resistance, and the strong association between metabolic disease and Alzheimer's Disease (AD), our overarching hypothesis is that gut microbial composition affects the development of AD pathology. We propose to (i) examine the microbiota profiles of subjects with and without diagnosed AD, and participants who are asymptomatic but enriched for AD risk factors; (ii) derive a germ-free mouse model genetically predisposed for AD development; and (iii) test the causal relationship between gut microbiota and AD pathology under controlled genetic, environmental and dietary conditions by transplanting fecal samples from characterized subjects into the germ-free mouse model.

PI: [Masatoshi Suzuki, DVM, PhD](#), UW School of Veterinary Medicine

Title: *Dual Modality Manganese-based Imaging for in vivo Stem Cell Tracking*

Collaborators: Mary Elizabeth Meyerand, UW COE, SMPH

Summary

In preclinical and clinical trials of stem cell therapy, it is essential to investigate engrafted cell dynamics to understand patient effects. The goal of this project is to develop and evaluate a new dual modality imaging approach for monitoring the location and survival of engrafted stem cells in the central nervous system. Our specific hypothesis is that viable DMT1-expressing stem cells will take up high levels of Mn and be selectively enhanced on images, permitting visualization of the live cells via contrast with respect to surrounding tissue. With the availability of this imaging tool, it will become increasingly possible to assess the dynamics of cells engrafted for therapy, including their proliferation, migration, and integration into the host environment.

PI: [Ei Terasawa, PhD](#), UW School of Medicine & Public Health

Title: *Generation of GnRH Neurons from Stem Cells*

Co-Funding: Wisconsin National Primate Research Center

Summary

Although the absence of reproductive function is not a life-threatening condition, it is a serious problem for Idiopathic Hypogonadotropic Hypogonadism (IHH) patients, who do not have functional gonadotropin-releasing hormone (GnRH) neurons in the hypothalamus. This study will explore methods for generating GnRH neurons from embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) derived from humans. The generation of GnRH neurons would not only help to better understand the basic physiology of human GnRH neurons, but would also provide a potential treatment tool for IHH patients.

