Translational Basic & Clinical Pilot Awards ($50,000 for one year)

**Role of ERα Following Brain Injury: Ligand Dependent or Independent?**

**PI:** Pelin Cengiz, MD PhD, School of Medicine & Public Health  
**Collaborator:** Jon Levine, SMPH  
**Co-Funding:** Waisman Center

**Summary:** Clinical and experimental studies have shown that male newborns are two times more susceptible to the effects of global brain injury, a phenomenon that is poorly understood. We have recently established a previously unrecognized role of estrogen receptor alpha (ERα) in sex specific responses to neonatal hypoxia and ischemia injury in the developing brain, enabling a new line of research that can lead to developing sex-specific neuroprotective therapies. In this proposal, we hypothesize that ERα is activated via brain-derived estradiol following aromatization of the testosterone resulting in TrkB phosphorylation and neuronal survival. Understanding the different mechanisms that lead to neuroprotection in female neonate brains that is insufficient or lacking in male neonate brains will fill a critical gap in our understanding of neuroprotective mechanisms in this vulnerable population.

**Pharmacological Modulation of ErbB Signaling to Prevent Type1 Diabetes**

**PI:** Feyza Engin, PhD, School of Medicine & Public Health  
**Collaborator:** Deric Wheeler, SMPH

**Summary:** To date, due to the autoimmune nature of T1D the majority of the pre-clinical studies and therapeutic approaches focused mainly on immunotherapy, including antigen specific, anti-inflammatory specific, and T and B cell specific targeting. However, despite the success in preclinical studies, translation of these therapies to humans has failed. We previously showed that adaptive stress responses were severely impaired in β-cells of two different mouse models of T1D and in human T1D patients and restoration of this stress response in mice via a chemical chaperone, TUDCA, could prevent diabetes in these pre-clinical models. We recently generated a unique genetic model that allows us to delete the most conserved adaptive stress gene, IRE1α, specifically in β-cells in a T1D pre-clinical model (NOD mice). First, by using this mouse model, as well as the existing tools in our laboratory, we will have the opportunity for the first time to assess fully the function of a key adaptive stress response mediator in β-cells in T1D. Second, by identifying the molecular mechanisms and targets of this pathway, we will have the opportunity to develop novel therapeutic approaches against this disease.

**Improving Right Ventricular Function in Young Adults Born Preterm**

**PI:** Kara Goss, MD, School of Medicine & Public Health  
**Collaborators:** Chris Francois, Oliver Wieben, SMPH  
**Co-Funding:** Department of Radiology

**Summary:** While lung disease is the most frequently recognized complication of prematurity, adults born moderately to extremely preterm have a 3-fold increased risk for the development of pulmonary
hypertension and a 17-fold increased risk for heart failure. Young adults born premature have biventricular hypertrophy, though the right ventricle (RV) is disproportionately affected. The University of Wisconsin has recruited a rare cohort of approximately 265 young adults born premature between 1988-1991. Our recent work in this cohort demonstrates that young adults born premature have lower exercise tolerance, early pulmonary vascular disease, and impaired cardiac reserve. Novel 4D cardiac flow imaging demonstrates a higher kinetic work for a given stroke volume in young adults born premature, representing a decreased cardiac energetic efficiency that may predispose to heart failure. We hypothesize that RV energetic inefficiency in young adults born preterm can be improved through therapeutic intervention, including afterload reduction with sildenafil and heart rate reduction with metoprolol. Completion of the proposed aims will establish a potential therapeutic role for afterload reduction and beta blockade in modulating acute RV function and energetic efficiency in young adults born premature.

General Anesthetics and Outcome from Blunt Trauma in Aged Animals
PIs: Michael Perouansky, MD; David Wassarman, PhD, School of Medicine & Public Health

Summary: Trauma in the aged remains a leading cause of death, prolonged disability, and poor functional outcome. Nonetheless, trauma models in aged animals are rare and models analyzing genetic contributions are virtually nonexistent. Moreover, victims of severe trauma will almost invariably undergo (frequently multiple and long-lasting) exposure(s) to general anesthetics (GAs). The degree to which GAs affect outcome from trauma in aged individuals is unknown. To address these gaps, we developed a fruit fly (Drosophila melanogaster) model of severe blunt trauma with brain injury (bTBI). The goal of this proposal is to investigate this phenomenon in aged animals. Modulation of trauma outcome by GAs in geriatric patients would be important for health care given that this underserved population accounts for an increasing fraction of health care resource utilization.

Validation of Mass Spectrometry and Micronucleus Assays for a Molecular Epidemiologic Study of Shared Bladder Carcinogen Exposures in Humans and Dogs
PI: Lauren Trepanier, PhD, School of Veterinary Medicine
Collaborators: Daniel Kurtycz, Kristen Malecki, SMPH; State Laboratory of Hygiene; James Schauer, COE

Summary: Bladder cancer is the sixth most common cancer affecting Americans, the majority of which are transitional cell carcinomas (TCC). Human TCCs harbor a wide variety of acquired somatic mutations, which have been attributed to environmental carcinogen exposures. The long latency period for bladder cancer in humans make it difficult, however, to tease out the importance of specific household chemical exposures in risk assessment. However, the pet dog may shed light on human bladder cancer risk. In addition to comparable clinical and mechanistic features, canine TCC has been associated with similar environmental risk factors as human TCC, although studies have been limited. We propose to study both humans and dogs in the same households to improve understanding of important exposure pathways and potential mechanisms underlying bladder cancer risk in the setting of common household environmental exposures. The goal of this ICTR pilot grant is to validate key assays and instruments.
Identifying Novel Mechanisms for Sudden Infant Death Syndrome
PI: Ravi Vaidyanathan, PhD, School of Medicine & Public Health

Summary: Sudden infant death syndrome (SIDS) is an unexplained death of a seemingly healthy baby between 1 month and a year old that is unexpected by history and in which a thorough post-mortem examination fails to demonstrate the cause of death. Autopsy and molecular pathology have identified that at least 14-20% of SIDS cases stem from cardiac arrhythmias due to mutations in ion channels or regulatory/structural proteins that modulate their function. I propose to use adeno-associated virus (AAV) technology to create mouse models of SIDS. I will study whole animal phenotype and cellular electrophysiology within weeks after injection of virus. The significance of these studies is in identifying if the SIDS mutations are malignant or benign, and if understanding the molecular basis of disease will lead to novel target identification. Such information will aid in contributing towards precision diagnosis and personalized medicine contributing towards the identification of at-risk individuals.

Toward an Understanding of the Molecular Mechanism Underlying Success of the Ketogenic Diet and its Application to Fragile X Syndrome
PIs: Cara Westmark, PhD; Jerry Yin, PhD, School of Medicine & Public Health
Collaborator: Rama Maganti, SMPH

Summary: The best studied dietary intervention to date for any neurological disorder is use of the ketogenic diet (KD) to control seizures in refractory epilepsy. Numerous biochemical changes occur in the brain in response to the KD, but how the diet stops seizures at a cellular and molecular level remains an enigma. This project is a new collaboration between the investigators to study cAMP/beta-amyloid homeostats as a potential underlying mechanism of a successful KD as well as the potential utility of this diet in treating the spectrum of fragile X syndrome (FXS) phenotypes. This project will have impact far beyond a potential dietary intervention for a rare disorder as the KD is the new fad diet for weight loss and is also under study for the prevention of Alzheimer’s disease (AD) and the treatment of autism, cancer, obesity and pain.

Overcoming Resistance to AXL Based Therapies in Head and Neck Cancer
PIs: Deric Wheeler, PhD; Randall Kimple, MD PhD, School Medicine & Public Health
*Co-Funding: UW Carbone Cancer Center

Summary: Head and neck squamous cell carcinoma (HNSCC) represents the eighth most common malignancy worldwide. Standard of care treatments for HNSCC patients include surgery, radiation and chemotherapy. Despite clinical success with these therapeutics, HNSCC remains a difficult to treat malignancy. Thus, identification of new molecular targets to treat this disease is critical. The receptor tyrosine kinase AXL is a member of the TAM family of receptors (Tyro, AXL, MERTK) and has been implicated in the development and progression of many malignancies, including lung, breast, and ovarian cancer. Despite the identification of AXL as a novel target in HNSCC, we found that resistance to AXL inhibition inevitably occurs. We hypothesize that MERTK plays an important role in resistance to AXL
guided therapeutics in HNSCC and that co-targeting MERTK will circumvent AXL resistance. To test this hypothesis, we will use HNSCC patient derived xenografts to simultaneously target AXL and MERTK and measure several parameters of tumor growth, metastasis and tumor mediate immunological responses. Although we focus on HNSCC in this application, lessons learned from this research may be applied to other tumor sites where AXL targeting is advancing, mainly lung and breast cancer and thus broadening the overall impact of this investigation.

**Developing Novel Kynurenine Derivatives for Mitigating Inflammatory Human Diseases**

**PIs: Yongna Xing, PhD; Dinesh Shah, MD, School Medicine & Public Health**

**Summary:** Kynurenine is a tryptophan metabolite and its cellular levels and downstream metabolites play crucial roles in regulating the immune system, vascular biology and neurological function. Altered kynurenine function is associated with a variety of human health issues including cancer, hypertension, chronic inflammation, and neurodegenerative disorders. The physiological effects of kynurenine are mediated by the aryl hydrocarbon receptor (AHR), a PAS family transcriptional factor that is essential for development and normal function of vascular and immune systems. Understanding underlying mechanisms of kynurenine in AHR activation holds novel promises for mitigating broad inflammatory diseases and pregnancy complications. We recently made a striking discovery that kynurenine activates AHR by formation of trace extended aromatic condensation products, abbreviated as TEACOPs. The goal of this study is to obtain preclinical data on novel AHR targeting compounds that best mimic endogenous kynurenine for mitigating inflammatory diseases and pregnancy complications.

**A New Approach for Treatment of Endocrine Resistant Breast Cancer**

**PI: Wei Xu, PhD, School Medicine & Public Health**

**Collaborator:** Weiping Tang, SOP; Shunqiang Li, Washington University at St. Louis

**Co-Funding:** UW Carbone Cancer Center

**Summary:** Estrogen receptor alpha (ERα) is expressed in over 70% of human breast cancers, and these cancers rely upon estrogen for growth. Consequently, ERα is the major therapeutic target for endocrine therapies. Nonetheless, approximately 50% of responsive tumors eventually relapse due to development of resistance. One emerging mechanism of resistance is drug-induced mutations on ERα, which reduce the binding of ERα to anti-estrogens. Strategies that can lead to complete degradation of wild type and mutant ERα will comprise a novel approach to combat endocrine resistance. In a small molecule library screen, we identified a natural plant product diptoindonesin G (Dip G) that significantly decreases ERα protein stability and activity in breast cancer cells via a novel mechanism. This study will compare the anti-cancer effect of Dip G with the existing clinically investigated agents in various endocrine-resistant animal models. We expect Dip G may be developed as a safe and effective drug to reduce the mortality associated with metastatic, ERα-positive breast cancer.