Summaries of UW ICTR Basic & Clinical Pilot Awards, Round 8, 2014

PI: Douglas G McNeel, MD, PhD, UW School of Medicine & Public Health
Title: *Molecular Imaging to Identify Response to Tumor Immunotherapy Using Anti-PD-1*
Collaborator: Weibo Cai, UW SMPH
Co-Funding: UW Carbone Cancer Center
Summary
We have been interested in anti-tumor vaccines, and DNA vaccines encoding tumor antigens in particular, as treatments for human cancer. We hypothesize that systemic evaluation of PD-L1 expression on tumors will predict the likelihood of anti-tumor response using anti-PD-1 treatment, when delivered alone or as a combination approach with an anti-tumor vaccine. To test this hypothesis, in this proposal we will label an antibody specific for murine PD-L1 with 64Cu suitable for in vivo imaging using positron emission tomography (PET). We will then explore whether this agent might be used as a molecular imaging biomarker of response to treatments using anti-PD1.

PI: Anjon Audhya, MD, UW School of Medicine & Public Health
Title: *Motoneuron and Optic Axonopathy in Hereditary Spastic Paraplegia*
Collaborator: David Gamm, Su-Chun Zhang, UW SMPH
Co-Funding: UW Stem Cell and Regenerative Medicine Center
Summary
Hereditary spastic paraplegias (HSPs) are a clinically and genetically heterogeneous group of gait disorders characterized by progressive weakness (paraplegia) and stiffness (spasticity) of the legs, which often result in paralysis. Treatment consists of physical therapy, but no intervention is currently available to slow or alter the progression of the disease. Our goal is to develop an induced pluripotent stem cell (iPSC)-based model to study neurodegeneration observed in patients with HSP, which can ultimately be used as a platform to identify new therapeutics to combat the disease.

PI: Ruth M Benca, MD, PhD, UW School of Medicine & Public Health
Title: *Sleep Apnea and Dense EEG: Early Biomarkers and Risk Factors for AD*
Collaborator: Barbara B Bendlin, UW SMPH
Summary
Converging evidence suggests a promising role for sleep in early detection and intervention in Alzheimer's Disease; nonetheless, sleeping brain activity has not been examined in the early, preclinical stage of AD. The objective of this proposal is to determine whether obstructive sleep apnea exacerbates amyloid pathology in an asymptomatic population at risk for AD and whether markers of brain change in pre-clinical AD are evident in sleep EEG.

PI: Diego Hernando, PhD, UW School of Medicine & Public Health
Title: *MRI-based Susceptibility Mapping As an Imaging Biomarker of Liver Iron Overload*
Collaborator: Scott Reeder, Ryan Mattison, Samir Sharma, UW SMPH
Summary
Excess iron accumulation in the body, due to excess intestinal absorption (hemochromatosis) or multiple blood transfusions (hemosiderosis), is toxic and requires treatment to reduce iron levels. The goal of this proposal is to develop and validate a novel method for magnetic resonance imaging (MRI) based quantitative susceptibility mapping (QSM), as an imaging biomarker of liver iron overload. We will provide the necessary pilot data to seek extramural funding for a definitive clinical validation of QSM as an imaging biomarker of liver iron overload.

PI: Gordon S. Mitchell, PhD, UW School of Veterinary Medicine
Title: *Phrenic Motor Neuron Derivation and Transplantation*
Collaborator: Randall Ashton, UW COE
Co-Funding: UW Stem Cell & Regenerative Medicine Center
Summary
There are no therapies to permanently restore respiratory function once phrenic motor neurons (pMNs), which project from the spinal cord to the diaphragm, have been lost due to injury or neurodegenerative disease. Transplantation of pMNs derived from human pluripotent stem cells (hPSCs) could be part of a curative, regenerative therapy; however, there are currently no protocols for deriving pMNs from hPSCs or methods to ensure their engraftment upon implantation. Thus, this proposal aims to develop the first ever pMN derivation protocol, and examine whether their engraftment upon transplantation can be enhanced using intermittent hypoxia treatments.

PI: Michael S. Pulia, MD, UW School Medicine & Public Health; Nasia Safdar, MD, PhD, UW School Medicine & Public Health
Title: *Methicillin-Resistant Staphylococcus aureus (MRSA) Colonization Detection as a Potential Strategy to Reduce Unnecessary Vancomycin Usage in the Emergency Department*
Collaborator: Kurt Reed, UW SMPH; Sanjay Shukla, MCRF
Summary
Emergency physicians often treat critically ill patients with infections due to unknown pathogens and guidelines recommend early administration of broad-spectrum antibiotics. This approach provides comprehensive bacterial coverage, but compared to more targeted therapy, it has numerous negative implications such as promoting antimicrobial resistance, adverse medication reactions, and increased cost. The primary aim of this proposal is to determine whether or not comprehensive MRSA colonization screening (multiple anatomic sites) has sufficient sensitivity to be used in screening for invasive MRSA infections.

PI: Christian M. Capitini, MD, UW School of Medicine & Public Health
Title: *Infusing MEMs as Protection from Radiation Injury and GVHD*
Collaborator: Peiman Hematti, UW SMPH
Co-Funding: UW Carbone Cancer Center
Summary
There is considerable interest in developing therapies that can protect patients that have been exposed to high doses of radiation for either medical purposes, such as in preparation for bone marrow transplant (BMT), or accidental trauma. Preliminary data in my laboratory has suggested that macrophages educated from mesenchymal stem cells (MEMs) have potent immunosuppressive properties that can minimize tissue damage from radiation, decreasing GVHD and aplastic anemia and improving overall survival. Results from this proposal may lead to a novel cellular therapy, as being the first clinical indication for human macrophages, that could be applied to medical and nonmedical setting involving radiation, and could be rapidly translatable to the clinic.

PI: Pelin Cengiz, MD, UW School of Medicine & Public Health
Title: *Role of Estrogen Receptor Alpha in Sex-Specific Neuroprotection by a TrkB Agonist*
Collaborator: Jon Levine, UW SMPH
Co-Funding: UW Waisman Center
Summary
Male neonates are more susceptible to hypoxia ischemia (HI) related brain injury, respond less to existing treatments, and develop cerebral palsy and learning disabilities at higher rates. A better understanding of the

mechanisms underlying sex-based susceptibility to HI will facilitate development of sex-specific treatments and identify novel targets for neuroprotection in this vulnerable population. Our preliminary data support a model in which estrogen receptor alpha (ERα), selectively expressed in females following HI, is coupled via Src family kinases (SFK) to tyrosine kinase B (TrkB) phosphorylation and enhanced neuroprotection in female neonates.