Summaries of UW ICTR Basic & Clinical Pilot Awards, Round 9, 2015 (Awarded in 2016)

PI: Erin Costanzo, PhD, UW School of Medicine & Public Health
Title: *A Biobehavioral Intervention to Enhance Stem Cell Transplant Recovery*
Collaborators: Meredith Rumble, Mark Juckett, Paul Rathouz UW SMPH; Lisa Cadmus-Bertram, UW SOE; Kristine Kwekkeboom, UW SON.
Co-Funding: UW Carbone Cancer Center
Summary
Hematologic cancer patients undergoing hematopoietic stem cell transplantation (HSCT) frequently experience physical and psychological sequelae that impair their quality of life and undermine recovery. Insomnia, fatigue, and depression are among the most persistent, distressing, and debilitating quality-of-life concerns after HSCT. Modifying sleep and circadian rest-activity patterns has been suggested to be a particularly promising intervention strategy for alleviating this symptom cluster. The proposed project will refine and evaluate the feasibility of a biobehavioral intervention to alleviate insomnia, fatigue, and depression by optimizing sleep and rest-activity patterns during the first 3 months following HSCT. The overarching goal is to optimize recovery following HSCT with a brief, non-invasive intervention that can be implemented as a part of routine clinical care.

PI: John Denu, PhD, UW School of Medicine & Public Health; Weiping Tang, PhD, UW School of Pharmacy
Title: *Developing therapeutics to restore metabolic flexibility*
Collaborators: Manish Patankar, UW SMPH
Summary
This proposal seeks to develop small-molecules to bind and activate an enzyme (SIRT6) that represses carbohydrate and fat catabolism, and restores metabolic flexibility in disease states that are 'stuck' in one metabolic mode. SIRT6 acts as a repressor of genes involved in glycolysis and lipid synthesis, processes that can lead to the well-known Warburg effect of cancer cells, the manipulation of metabolism by viruses, and the metabolic inflexibility associated with the metabolic syndrome. In this ICTR pilot, the team will focus on: i.) synthesizing rationally-designed SIRT6 activator compounds (Co-PI: Weiping Tang); ii.) biochemical and cell-based validation of compound efficacy (PI: John Denu);, and iii.) effectiveness as anti-ovarian cancer agents (Collaborator: Manish Patankar) and broad spectrum antivirals (FORGE Life Science).

PI: Corinne Henak, PhD, UW College of Engineering; Richard Kijowski, MD, UW School of Medicine & Public Health
Title: *mcDESPOT and qMT Parameters for Estimating Micro- and Nano-Scale Cartilage Mechanics*
Collaborators: Melih Eriten, Darryl Thelen, UW COE
Summary
The process of cartilage degeneration that culminates in osteoarthritis (OA) is long and may therefore be amenable to pharmacological or surgical intervention. We propose to address the opportunity to improve treatment efficacy by leveraging novel quantitative magnetic resonance (MR) techniques for the prediction of micro- and nano-scale mechanical behavior of cartilage. The long-term aim of this research is to develop novel MR methods that can be performed on clinical 3T scanners to estimate nano- and micro-scale properties of cartilage. Successful completion of the proposal will provide the first link between clinical

resolution MR imaging and higher-resolution cartilage properties, ultimately improving the efficacy of intervention for cartilage damage.

PI: Yao Liu, MD, UW School of Medicine & Public Health
Title: *Macular Pigment as a Modifiable Glaucoma Risk Factor in Older Women*
Collaborators: Julie Mares, Ronald Gagnon, UW SMPH; Thasarat Vajaranant, U Illinois-Chicago
Summary
There is growing literature that macular pigment levels—modifiable through dietary carotenoid intake—may be a risk factor for glaucoma. If low macular pigment levels predict glaucoma development, then early detection would permit the targeting of high-risk individuals for prevention, such as through dietary supplementation and/or lifestyle modifications that enhance carotenoid accumulation in the eye. This project will add measures of glaucoma to the second Carotenoids in Age-Related Eye Disease Study (CAREDS2), for which study visits will occur in 2016. The immediate outcome will be the first longitudinal evidence as to whether low macular pigment levels are associated with an increased risk of glaucoma. This new line of innovative research could ultimately lead to clinical trials of low-cost dietary carotenoid supplements or lifestyle modifications to prevent vision loss from glaucoma worldwide.

PI: Peter Nichol, PhD, UW School of Medicine & Public Health; Chad Vezina, PhD, UW School of Veterinary Medicine
Title: *Generating autologous intestinal organoids to treat intestinal diseases*
Summary
The vast majority of intestinal diseases irreversibly damage the intestinal epithelium. Intestinal transplantation is the only therapy available to replace intestinal epithelium. For the majority of patients with chronic disease arising from loss of region intestinal epithelium we have no therapies. The biggest obstacle in developing therapies for these patients is that we currently no means to redirect existing epithelial cells to assume the fate and functions of unique epithelial cell populations lost to disease. Our goal is to generate autologous, transplantable intestinal organoids within the next ten years that can overcome this obstacle. This will enable us to treat the large number of patients suffering from chronic, non-life threatening disease states while avoiding the risks, complications and costs associated with intestinal transplantation.

PI: Ari Rosenberg, PhD, UW School of Medicine & Public Health; Brittany Travers, PhD, UW School of Education
Title: *Computational Predictors of Learning and Neurobiology in Autism*
Co-Funding: Waisman Center
Summary
The complexity of the physiological and environmental factors that give rise to autism are reflected in the broad diversity of behavioral phenotypes associated with the disorder. This heterogeneity poses significant barriers to the development of effective treatments. The pilot will combine behavioral testing of children with autism spectrum disorder (ASD), computational modeling, and magnetic resonance imaging to examine if alterations in neural circuits supporting learning can be identified in ASD. Exploratory neuroimaging will be used to correlate performance and ASD symptomatology with differences in white matter connectivity, both within and across brain regions contributing to learning and visual search. If successful, these results will show that computationally-guided approaches can be used to identify

functional/anatomical changes in a mental health disorder. The team would then collaborate with clinicians to identify effective treatments for ASD.

PI: Lixin Rui, MD, PhD, David T Yang, MD, UW School Medicine & Public Health
Title: *Oncogenic Cooperation of BCL2 and BTK Signaling in Mantle Cell Lymphoma*
Summary

The B cell antigen receptor (BCR) signaling pathway is known to play an important role in the pathogenesis of mantle cell lymphoma (MCL), an incurable non-Hodgkin lymphoma. The ultimate goal of the study is to identify co-targeting of Bruton tyrosine kinase (BTK) and BCL2 by their specific inhibitors as a potential novel strategy to improve targeted therapy in MCL. The proposal will extend preliminary data demonstrating oncogenesis of the BCL2 anti-apoptotic and BCR/BTK signaling pathways in MCL cell lines and xenograft mouse models to primary patient samples, and has the potential to lead to a new treatment protocol for MCL. Specifically, the study will be expected to support new clinical trials of Ibrutinib in combination with ABT-199 in relapsed or refractory MCL.

PI: Jeffery VanWormer, PhD, Marshfield Clinic Research Foundation; Dale Schoeller, PhD, UW College of Agriculture & Life Science
Title: *Surveillance of Pediatric Obesity Patterns in Wisconsin: Identifying Optimal Points of Intervention*
Collaborators: Burney Kieke, MCRF; Larry Hanrahan, UW SMPH
Summary

Nearly one in every five U.S. kids is now clinically obese. In response to this epidemic, medical entities have initiated multiple obesity prevention efforts, but population level success has been limited to children under age 6. This will be the first EHR-based, month-by-month epidemiologic study of seasonal weight gain patterns in pediatric patients. From a methodological perspective, this project will entail a novel secondary use of EHR data to gain a much more precise understanding of when kids gain the most body weight over a given year and how these differ by age, gender, race, economics, and geography. Thus the ultimate goal of this research is to inform and evaluate population-level interventions that prevent more children from becoming obese, thereby reducing incident diabetes and cardiovascular disease in adulthood.

UW ICTR Partners
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