Summaries of UW ICTR Voucher Pilot Awards, 2013

1. **PI: Ian Bird, PhD, UW School of Medicine & Public Health**
   Affiliated Laboratory: Small Molecule Screening & Synthesis Facility
   Title: *High Throughput Screening of CLA Isoforms as a Novel Therapy for Preeclampsia*

   Summary
   The main objective of this project is to develop an endothelial cell-targeted therapy for preeclampsia. We propose herein to now use the human umbilical vein endothelial cell (HUVEC) model to screen the ability of conjugated linoleic acid (CLA) isomers to protect endothelial cells against damage by a wide variety of growth factors and cytokines, as a basis for possible therapeutic effects of CLA in preeclamptic human pregnancy, in conjunction with the SMSSF. Success in these studies would lead to the first clinical trial of dietary intervention to minimize the onset and or severity of preeclampsia.

2. **PI: Wei Xu, PhD, UW School of Medicine & Public Health**
   Affiliated Laboratory: Small Molecule Screening & Synthesis Facility
   Title: *Cell-Based HTS for Chemical Modulators of the CARM1 Arginine Methyltransferase*

   Summary
   CARM1, coactivator associated arginine methyltransferase 1, activates a number of transcriptional factors with documented roles in cancer including NF-kB, p53, E2F1, and estrogen receptor alpha (ERα). Identification of small molecule modulators of CARM1 through HTS assays would enable more facile and rigorous approaches to understanding the roles of CARM1 activity in cancer cells in vitro and in vivo, as well as provide leads for anticancer drugs with a novel mechanism of action. We propose to implement an in-house screen of the ~50,000 compounds available at the UW Small Molecule Screening & Synthesis Facility. Successful completion of this screen at SMSSF will identify candidate compounds with the drug-like properties amenable for lead optimization by medicinal chemistry.

3. **PI: David M Lynn, PhD, UW College of Engineering**
   Affiliated Laboratory: Cardiovascular Physiology Core Facility
   Title: *Transfer of DNA to Arteries using Film-Coated Catheter Balloons*

   Summary
   The proposed work will provide insight into fundamental processes underlying the development of intimal hyperplasia and provide new tools to study vascular disease and promote surface-mediated gene transfer in other clinically important contexts. The Physiology Facility will perform additional balloon catheter experiments in pigs to determine whether shorter inflation times will promote contact-transfer of genes to injured vascular tissue. The specific experiments proposed are designed to address concerns related to clinical translation that were raised during the recent review of a grant proposal, and will provide preliminary data that considerably strengthen the revised proposal and increase the likelihood of funding upon resubmission.

4. **PI: Albee Messing, VMD, PhD, UW School of Veterinary Medicine**
   Affiliated Laboratory: UW CCC 3P Laboratory
   Title: *Pharmacological Suppressors of GFAP Expression for Alexander Disease*

   Summary
   Current standard of care for Alexander Disease, a rare and generally fatal neurogenetic disorder, is simply symptomatic, and no treatments directly target the underlying mechanisms. We have proposed that a rationale strategy for therapy is pharmacological suppression; we identified a short list of candidate compounds that meet our hit criteria, exhibit oral bioavailability, and are known to cross the blood brain barrier. The critical missing piece of information that is needed before beginning any in vivo testing is the Maximum Tolerated Dose (MTD) for each hit. Even though these are approved drugs for which considerable information already exists, the dose necessary to affect the target (GFAP expression) is completely unknown. The 3P Lab will define in mice an MTD for each of the three compounds selected for study, in the particular age groups that we believe to be the best for assessing efficacy in vivo.

5. **PI: Mark E Burkard, MD, PhD, UW School Medicine & Public Health**
   Affiliated Laboratory: Small Molecule Screening & Synthesis Facility
   Title: *Modification of Polyploid-Specific Chemicals for Target Identification*

   Summary
   The ultimate goal of this project is to develop a drug that specifically targets polyploid breast cancers. Using screens, the group identified a lead small molecule that selectively interrupts proliferation of polyploid cells. However, they have been unable to identify the specific mechanism of action of the lead compound. To determine a potential mechanism, they propose to identify specific intracellular interactors by creating a functional 'handle' on the lead molecule. SMSSF will make the necessary chemical modifications that will allow for interrogation of cellular extracts (DNA, RNA, micelles, and protein fractions) by using assays for binding affinities. Such information will support ongoing development activities and provide data for an ACS grant application.