

Pre-MSTP Summer Research Program
Life Sciences Summer Undergraduate Research Programs (LSSURP)
University of Minnesota
Summer 2017 Research Opportunities



[Bryce Binstadt, MD, PhD](#)

Associate Professor, Department of Pediatrics
MSTP Associate Director

The Binstadt lab studies the pathogenesis of autoimmune diseases in animal models. Current projects focus on 1) the contribution of macrophages to cardiovascular inflammation in a model of rheumatoid arthritis and 2) the contribution of specific T cell populations to the development of type 1 diabetes. The student would also spend one half-day per week shadowing Dr. Binstadt in the outpatient pediatric rheumatology clinic at the University of Minnesota Masonic Children's Hospital

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[Michael Georgieff, MD](#)

Professor, Department of Pediatrics and the Institute of Child Development
Executive Vice Chair, Department of Pediatrics
Head, Division of Neonatology
Director, Center for Neurobehavioral Development

My laboratory studies the effect of fetal and neonatal iron deficiency on the developing brain, and specifically the hippocampus, which underlies recognition memory processing. We investigate hippocampal development and memory function in humans and rodent models. We utilize genetic models of fetal /neonatal brain iron deficiency in order to elucidate the specific requirement of iron for brain development and to understand the lifelong consequences of early life iron deficiency. My expertise in basic laboratory science includes conditional knock-out technology, neurometabolism, neuronal structural analysis, electrophysiology, gene expression and animal and human behavior. My clinical research expertise is in Neonatal Follow-up. Current studies focus on defining the critical period for iron during hippocampal development, the role of iron in mitochondrial health and disease, and the role of iron in epigenetic programming of synaptic plasticity genes. Students in my laboratory would work in either wet lab (bench) research using animal models of early life nutritional deficiencies and their effect on hippocampal development or in clinical research studying populations of babies with perinatal risk factors to hippocampal development.

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[David Potter, MD, PhD](#)

Associate Professor, Department of Medicine

My laboratory works on the roles of cytochrome P450 epoxygenases in breast cancer progression. While EETs are important in health for regulation of blood pressure and the survival of hematopoietic stem cells, they are exploited by cancer cells to promote tumor growth. We have discovered that the cytochrome P450 enzyme CYP3A4, which metabolizes more than half of prescription drugs in the liver, also synthesizes epoxyeicosatrienoic acids (EETs) in breast cancer and thereby promotes breast cancer progression. CYP3A4 activity is induced by hypoxia in

breast cancer cells and is required for mammary tumor engraftment and angiogenesis in a xenograft model of human breast cancer. Furthermore, CYP3A4 is active as epoxygenase under conditions of hypoxia (O_2 Km = 22 μ M) and under hypoxic cell culture conditions EET biosynthesis is induced. CYP3A4 knock down significantly diminishes hypoxia-induced EET biosynthesis. These results implicate CYP3A4 as an epoxygenase enzyme that promotes breast tumor growth and angiogenesis. We hypothesize that CYP3A4 promotes the Warburg effect in breast cancer cells, which is the dependence of cancer cells on glycolysis even in the presence of adequate oxygen for respiration. The advantage of the Warburg effect to cancer cells is that it supports the anabolic biosynthesis of cellular components. We've discovered that there's a feedback loop between mitochondrial respiration and glycolysis that's regulated, in part, by EETs. We've also discovered that the muscle isozyme of pyruvate kinase, PKM2, an important regulatory glycolytic enzyme, is increased in activity when EET biosynthesis is inhibited, thereby temporarily abolishing the Warburg effect. This project will test the hypothesis that CYP enzymes and their EET products determine, in part, the phosphorylation state and activity of PKM2, thereby regulating the Warburg effect. The project will involve the use of genetic methods and chemical probes to determine the mechanisms of this feedback loop in models of human and mouse mammary carcinoma. The assays involved will include western blotting, quantitative PCR and mass spectroscopy. Impact of CYP gene knock down and CYP inhibitors will be compared. This project, when completed, will define a novel mechanism by which cancer cells evade restraints on growth regulation by exploiting endogenous signaling molecules that promote cell proliferation and survival.

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[Zohar Sachs, MD/PhD](#)

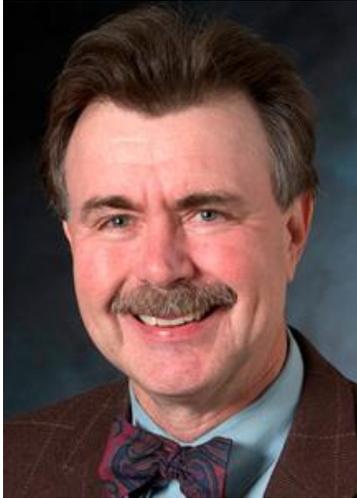
Assistant Professor of Medicine
Division of Hematology, Oncology, and Transplantation

My lab's goal is to identify molecular mechanisms of leukemia stem cell self-renewal in primary murine and human acute myeloid leukemia (AML) because we believe this will lead to therapies that cure this disease. Self-renewal is a feature of leukemia stem cells that allow them to recapitulate leukemia and cause relapse. Since AML cells are highly heterogeneous, and only a small minority of them can self-renew, we specialize in the application of single-cell, high throughput technologies (including mass cytometry/CyTOF and single-cell RNA sequencing) to address these research questions. We believe that this approach will identify effective therapeutic targets to prevent relapse in this deadly disease.

We have well, defined projects for summer students with in these research questions:

1. What are the molecular mechanisms of NRAS-mediated self-renewal in AML?
2. How does the mTOR-activation of the immunoproteasome facilitate self-renewal in AML?
3. What are the molecular pathways that allow leukemia stem cells to persist through chemotherapy and cause relapse?
4. How does alternative splicing alter the proteome in leukemia stem cells?

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[Gregory Vercellotti, MD](#)

Professor, Department of Medicine

For 30+ years at the University of Minnesota I have been involved in research, teaching and patient care. I have focused on understanding the interactions of inflammation, oxidative stress and vascular biology which underpin a variety of disease states from atherosclerosis to sickle cell disease (SCD). Our lab demonstrated that the abundant physiological iron contained in heme, is a powerful catalyst for LDL oxidation which could activate and damage endothelial cells. Heme readily enters cell membranes and the endothelium becomes hyper-susceptible to oxidant-mediated cytotoxicity. We demonstrated how the vasculature defends itself against heme mediated injury by the induction of the cellular cytoprotectants, heme oxygenase-1 (HO-1) and ferritin, leading to resistance to oxidant-mediated injury. We showed in vivo relevance of this cytoprotection in a variety of models from rhabdomyolysis to sickle cell disease (SCD). Our lab provided significant evidence for the important role of inflammation in vaso-occlusion in SCD. We demonstrated that decreasing inflammation or decreasing reactive oxygen species, inhibiting adhesion molecules, all decrease vaso-occlusion in murine models of sickle cell disease using a unique physiological model. Due to hemolysis, both human SCD and murine SCD model have increased HO-1. We demonstrated that HO-1, when overexpressed in sickle animals, prevents hypoxia induced vaso-occlusion. Furthermore, the products of HO-1, biliverdin and CO could also modulate vaso-occlusion. Recently the laboratory has examined how dimethyl fumarate can activate NRF2, which serves as a transcription factor for cytoprotective genes including HO-1. We have shown that free heme interacts with endothelial cells through TLR4, ultimately activating Weibel Palade body exocytosis with surface expression of P-selectin and von Willebrand factor. We are now attempting to identify the binding site of heme on the TLR4, MD-2, CD14 complex using site directed mutagenesis of these proteins and transfection in HEK cells. The project now is focusing on clearance of hemoglobin, the source of free heme, from the circulation by the scavenging molecule haptoglobin and hemopexin. We are testing whether supplementation of hemopexin and/or haptoglobin would prevent vaso-occlusive crises in sickle mice.

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[Doug Yee, MD](#)

Professor of Medicine and Pharmacology
John H. Kersey Chair in Cancer Research
Director, Masonic Cancer Center

The Yee laboratory focuses on growth regulatory pathways in breast cancer. Our aim is to develop new cancer therapeutic strategies based on a detailed understanding of the signaling pathways that regulate breast cancer survival, proliferation, motility, and metastasis. The work has focused on the function of the insulin-like growth factor (IGF) signaling system and the highly related insulin signaling pathway. We have shown that inhibitors of the IGF receptor are not effective in breast cancer because of their inability to block insulin signaling. Current projects in the lab focus on strategies to improve the targeting of this pathway. Laboratory projects include genetic and pharmacologic methods to block activation of a key adaptor protein (insulin receptor substrate-1) downstream of the receptors, defining regulatory pathways activated by IGF/insulin signaling to co-target the pathway, validation of an IGF gene expression signature in cell line models and human tumors, and development of insulin receptor targeting agents using monoclonal antibodies and insulin receptor isoform specific binding proteins identified from a yeast expression system. The student would also have the opportunity to participate in several clinically focused activities including the weekly breast cancer multi-disciplinary conference, the monthly breast cancer translational working group meeting, and shadowing Dr. Yee in his weekly medical oncology clinic. Trainees in the Yee laboratory will have exposure to laboratory, translational, and clinical research venues.