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.
Pre-MSTP Summer Research Program
Life Sciences Summer Undergraduate Research Programs (LSSURP)
University of Minnesota
Summer 2016 Research Opportunities

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.
Jeffrey S. Miller, MD
Professor of Medicine
Division of Hematology, Oncology and Transplantation
Deputy Director, University of Minnesota Cancer Center
Roger L. and Lynn C. Headrick Chair in Cancer Therapeutics
Director, Stem Cell Institute
Professor, Pediatric Blood and Marrow Transplantation

Jeffrey S. Miller, MD, received a Bachelor of Science degree from Northwestern University in Evanston, Illinois and received his MD from Northwestern University School of Medicine. He completed an internship and residency in Internal Medicine at the University of Iowa in Iowa City. After completing a post-doctoral fellowship in Hematology, Oncology and Transplantation at the University of Minnesota, he joined the faculty in 1991. Dr. Miller is currently a Professor of Medicine at the University of Minnesota. He is the Deputy Director of the University of Minnesota Masonic Comprehensive Cancer Center. He has more than 20 years of experience studying the biology of NK cells and other immune effector cells and their use in clinical immunotherapy with over 170 peer-reviewed publications. He is a member of numerous societies such as the American Society of Hematology, the American Association of Immunologists, a member of the American Society of Clinical Investigation since 1999. He serves on the editorial board for Blood and is a reviewer for a number of journals and NIH grants. He was the recent recipient of the National Cancer Institute Outstanding Investigator Award for 2015.
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 (O2 Km = 22 uM) 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.
Improve Systemic Mesenchymal Stromal Cell Therapy for Dystrophic Epidermolysis Bullosa by Ex Vivo Cell Surface Modification

Cell-cell communication and migration of cells from one organ to another in development, health and disease or injury is accomplished by series of long distance and short distance mediators and their receptors on target cells. Gradients of molecules, typically peptides, can provide directionality to cell movement. In the setting of acute injury cells from close and afar are mobilized in a stereotypical manner that mediates tissue repair tissue stem cells. Mesenchymal stromal cells (MSCs) are reparative cells that aid in healing, however, their numbers maybe inadequate after large tissue destruction. Therefore, their adoptive transfer, both as autologous and allogeneic cells, has been investigated in preclinical injury models and in clinical trials of heart, lung, and kidney tissue repair. The goal of this proposal is to extend this concept, along with the latest advances in cellular graft engineering, to skin repair. Building upon our expertise in stem cell biology, in experimental and clinical transplantation of hematopoietic and non-hematopoietic cells in animal models and in clinical trials, we have initiated MSC therapy in people with in severe genodermatosis, recessive dystrophic epidermolysis bullosa (RDEB). Preliminary data are positive, but clearly show that the migration of MSCs to skin wounds has to be improved to translate this approach into full clinical benefit. To achieve this goal and ultimately provide a generalizable strategy for RDEB therapy, we aim to improve the homing of MSCs to skin and their persistence after intravenous infusion by fucosylation of donor MSCs and by systemic inhibition of a cell surface serine dipeptidylpeptidase IV (CD26)-mediated processing of growth factors needed for MSC survival and biodistribution.
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 cytolysis. 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 vasooclusion 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. The project now is focusing on clearance of hemoglobin, the source of free heme, from the circulation by the scavenging molecule haptoglobin and hemopexin. Sickle cell patients and mice have low haptoglobin and hemopexin levels and we will be making gene constructs of haptoglobin and hemopexin to overexpress this protein in sickle animals using a non viral vector, Sleeping Beauty transposase. Our hypothesis will test whether sickle mice that overexpress haptoglobin or hemopexin will have less vaso-occlusion since clearance of hemoglobin will decrease the amount of free heme the vasculature sees.
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.