Research in Dr. Beckman’s lab in the University of Minnesota’s Vascular Biology Center focuses on development of thrombosis in myeloproliferative neoplasms and patients with genetic mutations. We are modeling the vascular endothelium to determine how molecular mutations drive thrombosis development with the goal of identifying safer antithrombotic targets. Techniques a trainee would learn while doing research in Dr. Beckman’s lab include flow cytometry, PCR, ELISA, standard histology, immunohistochemistry and immunofluorescence microscopy. Dr. Beckman is an adult hematologist. Students and residents interested in pursuing a career in this field or who are interested in small clinical projects (case reports, case series) related to hematology are also encouraged to contact Dr. Beckman for advice/guidance.
Allogeneic hematopoietic cell transplantation (HCT) can cure high risk leukemia, lymphoma, and marrow failure syndromes. However, graft-versus-host disease (GVHD) remains a life threatening side effect of this procedure. The Betts lab is interested in developing selective pharmacologic and cellular immunotherapy strategies to separate GVHD from beneficial graft-versus-leukemia (GVL) effects of the allograft. This includes small molecules targeting T cell costimulation and cytokine activation, dendritic cell ER stress response, and various pathways directing donor T cell differentiation. The lab also uses xenotransplantation models to test engineered human immune cells for GVHD and solid organ rejection prophylaxis; including Tregs, innate lymphoid cells, and chimeric antigen T cells (see work presented at ASH 2019 https://ash.confex.com/ash/2019/webprogram/Paper124031.html). Importantly, the lab is focused on translation and our work has directly led to innovative GVHD prevention trials.

Lab PI, Brian C. Betts MD, was chief resident at the University of Minnesota (internal medicine) and chief fellow at Memorial Sloan Kettering Cancer Center (medical oncology and hematology). He enjoys teaching and has mentored successful pre-med students, graduate students, and junior faculty. Under Dr. Betts’ mentorship, it is expected that you will gain practical experience in human immune cell functional assays, multi-parameter flow cytometry and immunohistochemistry, and novel xenogeneic transplant models. You will also gain experience in selecting patients for allogeneic and autologous HCT, cell therapy including chimeric antigen T cells, managing transplant and cell therapy complications, using post-transplant maintenance strategies to prevent relapse, as well as how to identify and treat GVHD.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1DESb01Xvb6QI/bibliography/40972017/public/?sort=date&direction=ascending
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.
Tyler Bold, MD/PhD
Assistant Professor of Medicine
Division of Infectious Diseases and International Medicine

Using Salmonella to deliver TB antigens to CD4 T cells
An effective new vaccine is direly needed for tuberculosis (TB), the world's leading infectious cause of death. However, it remains unclear which of the >4,000 antigenic proteins potentially produced by the bacterial pathogen Mycobacterium tuberculosis (Mtbc) can elicit the most effective CD4 T cell responses, and why. To answer these questions, we will establish a system to test Mtbc genes of interest, in a way that provides a link between the efficacy of a T cell response and its antigenic target. We are developing a method to use Salmonella, a more tractable phagosomal pathogen, to deliver various TB antigens to CD4 T cells. The goals of this undergraduate research project would be to 1. construct a Salmonella phagosomal expression vector, 2. demonstrate expression of a test antigen of interest, 3. and determine whether this recombinant strain can trigger functional, antigen-specific CD4 T cell responses in vitro and in vivo.
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.
David Potter, MD, PhD
Associate Professor, Department of Medicine

Our research focus is to identify the mechanisms by which CYP3A4 arachidonic acid (AA) epoxygenase enzymes promote the growth of ER+ breast tumors and to inhibit these enzymes using novel, potent biguanide compounds that function as informative chemical probes. My laboratory has contributed new knowledge regarding the roles of arachidonic acid (AA) epoxygenase enzymes in breast cancer progression. We have discovered that conversion of AA to epoxyeicosatrienoic acids (EETs) by breast cancer cytochrome P450 enzymes promotes autocrine/paracrine-mediated breast cancer cell growth by driving STAT3 phosphorylation and translocation to the nucleus. When CYP3A4 is knocked down, breast cancer cells fail to form tumors in nude mice, indicating that cancer cell intrinsic CYP3A4 activity is essential for tumor establishment. Furthermore, we have discovered that EET biosynthesis not only promotes STAT3 signaling, but also stabilizes the electron transport chain (ETC) and promotes oxygen consumption rates (OCR). These data suggest two sites of activity of CYP3A4, at the plasma membrane and mitochondria. We have discovered that the biguanide diabetes drug metformin specifically inhibits the biosynthesis of EETs in breast cancer cells and in CYP3A4-expressing microsomes, while (+)-14,15-EET rescues clonogenicity of breast cancer cells treated with metformin. These findings indicate that metformin inhibits breast cancer, in part, by inhibition of CYP3A4 AA epoxygenase activity. Metformin co-crystallized in the active site of CYP3A4 (in collaboration with Dr. Thomas Poulos and Irina Sevrioukova; University of California, Irvine) and using this co-crystal structure we have used in silico modeling to develop more potent biguanide inhibitors of CYP3A4 AA epoxygenase activity. From these studies we propose that CYP3A4 promotes breast progression, in part, through biosynthesis of cancer cell intrinsic (+)-14,15-EET and that metformin and more potent biguanides inhibit breast cancer, in part, by inhibition of CYP3A4 AA epoxygenase activity. We have identified a lead neo-biguanide compound, N1-hexyl-N5-benzyl-biguanide (HBB) that is 500-fold more potent than metformin as an inhibitor of AA epoxygenase activity and ~100-fold more potent than metformin in the MCF-7 xenograft model of ER+ breast cancer. We now propose to use HBB as an inhibitor of OCR in ER+HER2- breast cancer models, thereby reversing hypoxia and glucose consumption and promoting cytotoxic T cell function. Furthermore, lymphocytes appear to lack CYP3A4, potentially conferring tumor selectivity of HBB. We also have preliminary data supporting the hypothesis that mitochondrial CYP3A4 may promote nuclear transit of the RagC component of the mTOR complex, thereby licensing mTOR to promote biomass synthesis in ER+ breast cancer cells. We will investigate these dual mechanisms of biguanide inhibition of ER+ breast cancer, providing a new avenue for cancer drug development.
A pre-MSTP student working with Dr. Prins will investigate the link between interleukin-6 and right ventricular dysfunction in pulmonary arterial hypertension. In this project, the summer student would work to isolate right ventricular cardiomyocytes from rats. Then isolated cardiomyocytes would be treated as a sham, interleukin-6, and interleukin-6 with Stattic, a STAT3 inhibitor. Cardiomyocyte contractility and calcium handling will be examined. Furthermore, the relationship between STAT3 and the microtubule network will be examined under the same conditions.
Despite more than 100 years of sickle cell disease (SCD) research, patients still suffer significant morbidity and early mortality due to the consequences of hemolysis and vaso-occlusion (VO). Sickle crises frequently occur with bacterial infections and enhanced hemolysis challenging the innate immune system. These insights point to the central role of hemolysis in the pathophysiology of SCD. However, in the absence of robust therapies to arrest hemoglobin S (HbS) polymerization, the clinician must deal with the consequences of hemolysis, including NO depletion, oxidative stress, inflammation, coagulation, complement activation, VO, ischemia-reperfusion, vascular dysfunction, and ultimately organ damage. To understand mechanisms that would lead us to effective therapies, we showed that heme derived from sickle red blood cells (SS-RBCs) acts as a damage-associated molecular pattern (DAMP) that can activate toll-like receptor 4 (TLR4) of the innate immune system, independently of its cognate ligand lipopolysaccharide (LPS), leading to oxidant production, inflammation, VO, ischemia, and tissue injury. We believe that hemolysis and the intravascular release of HbS and heme are central to the pathophysiology of SCD. We hypothesize that the innate immune system, including TLR4 and complement, is fundamental to understanding hemolysis-driven inflammation, coagulation, VO, and vasculopathy in SCD. We will define the role of innate complement activation in hemolysis, inflammation, and VO and its link to TLR4 in SCD. Present studies are focusing on development of gene therapy for sickle cell disease and are measuring biomarkers of endothelial activation/vasculopathy that could be used to monitor its success including circulating endothelial cells and endothelial microvesicles in sickle patients.
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.