pre-MSTP (Medical Scientist Training Program)  
Summer Research Opportunity  
Life Sciences Summer Undergraduate Research Program (LSSURP) at the University of Minnesota

Sponsored by the Medical School and College of Biological Sciences  
Celebrating our 25th anniversary in 2014

Dates: May 28 – August 8, 2015

Application Deadline: Monday, February 16, 2015 at 8 A.M. CST

The pre-MSTP program is an NIH-funded summer research experience for rising seniors interested in pursuing the MD/PhD degree. Those admitted to the pre-MSTP program are placed in labs with Physician-Scientists for their research project. They will also have weekly clinical shadowing with their mentor and will participate in all the summer activities of the University of Minnesota MSTP.

Successful applicants will have prior research experience and should have a personal statement and letters of recommendation (2) that convey the applicant's intention to pursue the dual MD/PhD degree.

Submissions are evaluated as they are received. Submissions before the Feb. 16 deadline will have a greater chance of acceptance.

Admitted students receive a stipend, room and board and travel support (up to $500).
All students participate in:
• Orientation Weekend at the Itasca Biological Station
• Weekly research project seminars with cohort members
• Multiple career development activities including GRE and MCAT test preparation.
• All-campus poster symposium presentations

Visit our website:  http://cbs.umn.edu/lssurp
Bryce Binstadt, MD, PhD
Assistant Professor, Department of Pediatrics

The Binstadt lab studies the pathogenesis of autoimmune diseases. The summer research project would focus on the role of the interleukin (IL)-17 family of cytokines in a mouse model of co-existing inflammatory arthritis (similar to rheumatoid arthritis) and cardiovascular inflammation. The student would become familiar with PCR-based genotyping of mice, assessment of arthritis, standard histology, immunohistochemistry, ELISAs, and flow cytometry. 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.

Peter Bitterman, MD
Professor, Department of Medicine

Idiopathic Pulmonary Fibrosis (IPF) is a lethal fibrotic lung disorder that kills 40,000 Americans each year and over 1 million persons worldwide. We have discovered a cell-of-origin for IPF. Systems-level OMICs studies are underway to characterize the molecular underpinnings of this pathological cell and to discover targets for new therapeutics.

Dan Kaufman, MD, PhD
Associate Professor, Department of Medicine

Research in the Kaufman lab uses human stem cells to both better understand basic mechanisms of human development, as well as to derive potentially novel therapeutic cell populations. Our work uses human pluripotent stem cells as the starting point for most of these studies. We use both human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs) to study development of blood cells and related cell populations. While a specific project will be determined with the student, these studies include derivation of early hematopoietic cells, human lymphocytes, vascular cells, and mesenchymal cells. New work is focused on use of CRISPR/Cas9 system with iPSCs to do specific genetic gain and loss of function studies to better understand specific regulatory pathways. We are also deriving new human iPSC lines from both normal and genetically abnormal individuals.

David Potter, MD, PhD
Associate Professor, Department of Medicine

My laboratory works on the roles of cytochrome P450 epoxygenases in breast cancer progression. 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, thereby promoting 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 a new epoxygenase in breast cancer angiogenesis-CYP3A4. We hypothesize that hypoxia-induced HIF1-alpha and/or HIF2-alpha transcription factors activate CYP3A4 gene expression in breast cancer cells and that knock down of HIF1-alpha and/or HIF2-alpha will inhibit hypoxia mediated induction of CYP3A4 gene expression and EET biosynthesis. The project will involve testing the effects of stable knock down of HIF genes on CYP3A4 expression and EET biosynthesis in ER+ and triple negative breast cancer cells. Assays involved will include Western blotting, quantitative PCR and mass spectroscopy. Impact of HIF1a and HIF2a gene knock down will be compared. This project, when completed, will define a novel mechanism by which hypoxia induces breast cancer angiogenesis.

Lisa Schimmenti, MD
Associate Professor, Department of Pediatrics

The Schimmenti laboratory studies hearing and vision disorders using zebrafish as a model organism. For our hearing studies, we are using zebrafish to model three common forms of human hearing loss caused by mutations in MYO7A (Usher Syndrome), GJB2, and SLC26A4 (Pendred Syndrome). We are conducting a gene specific trial of pharmacologic agents to modulate the behavioral response to sound in zebrafish harboring mutations of MYO7A. We are using genomic engineering techniques (TALENs) to generate zebrafish lines for GJB2 and SLC26A4, and upon characterization of the lines, will begin specific pharmacologic trials. For our vision studies, we have been characterizing a human condition that causes eye and kidney abnormalities, Renal Coloboma Syndrome. We are working to identify genes downstream of PAX2 that are important for eye development with the aim of identifying the mechanism by which mutations in this transcription factor cause human disease.

Jakub Tolar, MD, PhD
Director, Stem Cell Institute
Professor, Pediatric Blood and Marrow Transplantation

Improving 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 may 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.
Pre-MSTP Summer Research Program  
Summer 2015 Research Mentors

**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 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 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. 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.

**Bryan Williams, MD, PhD**  
Assistant Professor, Department of Medicine

All patients with cystic fibrosis eventually develop a chronic infection of their lungs due to poor mucous clearance from their airways. The types of bacteria that infect their lungs are unusually hardy, and able to adapt quickly to the lung environment, avoiding clearance by the immune system. These bacteria also become tolerant of many antibiotics simply by the way they are growing in the lung. To make matters more challenging, they also develop significant resistance to the antibiotics we use to treat them in time. It is expected that by the time most patients die with CF, it is usually due to their lung infection, and that infection is usually due to strains of bacteria that are resistant to all known therapies. Finding new therapies to interrupt this cycle of persistent infection would allow us to spare antibiotics, the only real way to prevent resistance formation. The development of these therapies requires us to better understand how it is these bacteria are able to do what they do in the lung. When does the infection actually start? What are the cues in the lung that tell the bacteria to adapt? What changes do the bacteria make to adapt, and can we undo these? Ongoing projects in the Williams lab include: 1) development of a new animal model of chronic lung infections; 2) investigation of the adaptation of P. aeruginosa to the CF lung 3) screening patients that harbor metabolic mutants of P. aeruginosa.