

Pre-MSTP Summer Research Program
Life Sciences Summer Undergraduate Research Programs (LSSURP)
University of Minnesota
Summer 2019 Research Opportunities



[Joan Beckman, MD/PhD](#)

Assistant Professor of Medicine

Division of Hematology, Oncology, and Transplantation

Thrombosis is the leading cause of mortality among patients with myeloproliferative neoplasms (MPNs). MPNs are characterized by excessive production of blood cellular components (red blood cells, platelets, and/or leukocytes) due to dysregulated Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling. Disrupted JAK-STAT signaling in MPN patients is the result of a somatic *JAK2* V617F mutation or somatic mutations in exon 9 of the Ca²⁺-binding chaperone protein calreticulin (*CALR*⁺). Compared to healthy controls, both *JAK2* V617F and *CALR*⁺ MPN patients are at increased risk of thrombosis. Thrombosis may result from abnormal interaction of the vascular endothelium with coagulation factors, activated platelets, and adhesion between blood cellular components. My lab's central hypothesis is that in response to *JAK2* V617F and *CALR*⁺ mutations the vascular endothelium increases procoagulant and pro-inflammatory expression profiles leading to increased thrombotic risk. Recently, the development of endothelialized microvascular models has allowed for a more controlled and systematic investigation of hemodynamic forces and cellular interactions involved in thrombosis. Therefore, endothelialized microfluidics devices provide a new and powerful method to evaluate how flow impacts coagulation-related gene profiles in *JAK2* V617F endothelial cells. The student who selects my lab will learn how to culture endothelial cells in microfluidics devices. Upon achievement of this skill they will use molecular techniques to survey expression of coagulation genes under flow using mRNA. Lastly, they will determine if kinase inhibition changes expression of genes. Finally, the student will have the opportunity to shadow me in either my Masonic Cancer Center clinic (general benign hematology) or my Center for Bleeding Disorders Clinic weekly.

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[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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[Kathryn Cullen, MD](#)

Associate Professor of Psychiatry
Division Chief, Child & Adolescent Psychiatry
Center for Neurobehavioral Development

Dr. Cullen's research primarily focuses on depression and related problems in adolescents. Her research approaches include the use of brain imaging to examine the biology underlying these problems in teenagers, and to elucidate the mechanisms of existing treatments for depression. Dr. Cullen is currently leading two research projects that are testing novel treatments for severe depression in teenagers whose depression has not improved despite treatment with antidepressant medications. Additional topics of interest in her research in adolescents include non-suicidal self-injury, bipolar disorder, borderline personality disorder, and (in collaboration with Dr. Gail Bernstein) obsessive-compulsive disorder.

Dr. Cullen's summer project is a treatment study of depression in young people (age 16-24) that involves a combination of mindful breathing training and neuromodulation. Outcomes include depression symptoms and neural network changes as measured by MRI and EEG

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[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 (\pm)-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 (\pm)-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.

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[Kurt Prins, MD/PhD](#)

Assistant Professor of Medicine
Cardiovascular Division

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.

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[Zohar Sachs, MD/PhD](#)

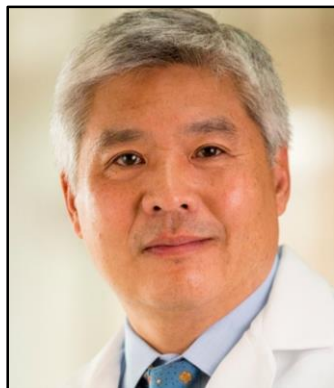
Assistant Professor of Medicine
Division of Hematology, Oncology, and Transplantation

I am a physician-scientist with a clinical subspecialty in adult hematological malignancies. My lab's goal is to identify molecular mechanisms of leukemia stem cell self-renewal in primary murine and human acute myeloid leukemia (AML). Self-renewal is a feature of leukemia stem cells that allow them to recapitulate leukemia and cause relapse. Since AML cells are highly heterogenous, 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 use these approaches to study mouse models of AML and primary patient AML samples. 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. What are the features of patient AML samples that correlate with response to therapy (using primary patient samples from patients enrolled on our clinical trials)?
3. How does the mTOR-activation of the immunoproteasome facilitate self-renewal in AML?
4. What are the molecular pathways that allow leukemia stem cells to persist through chemotherapy and cause relapse?
5. How does alternative splicing alter the proteome in leukemia stem cells?

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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.