2023-2024 St. Jude Summer Plus Projects

St. Jude Faculty Member	Department
Dr. Adam Durbin	Oncology
Dr. Anand Patel	Oncology
Dr. Andrew Heitzer	Psychology and Biobehavioral Sciences
Dr. Aseem Ansari	Chemical Biology & Therapeutics
Dr. Cai Li	Biostatistics
Dr. Charles Mullighan & Dr. Nicole Michmerhuizen	Pathology
Dr. Chi-Lun Chang	Cell & Molecular Biology
Dr. Chunliang Li	Tumor Cell Biology
Dr. Ellie Margolis	Host Microbe Interactions
Dr. Erica Kaye	Oncology
Dr. Hai Dao	Chemical Biology & Therapeutics
Dr. Heather Conklin	Psychology and Biobehavioral Sciences
Dr. Heather Mefford	Center for Pediatric Neurological Diseases Research
Dr. Jamy Peng	Developmental Neurobiology
Dr. Jane Hankins, Mr. Ombeni Idassi, Mr. Nick Faris	Global Pediatric Medicine
Dr. Jasmine Plummer	Developmental Neurobiology
Dr. Jason Vevea	Developmental Neurobiology
Dr. Jay Bikoff	Developmental Neurobiology

St. Jude Faculty Member	Department
Dr. Jun Yang	Surgery
Dr. Katianne Sharp	Psychology and Biobehavioral Sciences
Dr. Kim Nichols	Oncology
Dr. Lily Guenther	Oncology
Dr. M. Madan Babu	Structural Biology
Dr. Marcus Fischer	Chemical Biology & Therapeutics
Dr. Mark Hatley	Oncology
Dr. Min Ni	Oncology
Dr. Mondira Kundu	Cell & Molecular Biology
Dr. Myriam Labelle	Oncology
Dr. Ozgur Ates	Radiation Oncology
Dr. Paul Northcott	Developmental Neurobiology
Dr. Stacey Ogden	Cell & Molecular Biology
Dr. Subodh Selukar	Biostatistics
Dr. Tanja Mittag	Structural Biology
Dr. Tommaso Cupido	Chemical Biology & Therapeutics
Dr. Young-Goo Han	Developmental Neurobiology

Dr. Adam Durbin

Oncology

The Durbin Lab in the Division of Molecular Oncology at St. Jude Children's Research studies the fundamental mechanisms that drive children's cancer. While pediatric cancer outcomes have improved in some diseases, children with solid tumors continue to do poorly with little improvements over the past decades. **In many of these diseases, no targeted therapies are available.** Our laboratory uses a variety of cutting-edge genome-scale technologies to identify and target the fundamental mechanisms controlling high risk pediatric solid tumors. Our lab bridges chemical biology, animal modeling of human cancer and genome editing to identify and develop new methods to target key cancer drivers

We have identified several key cancer drivers and compounds in high risk pediatric solid tumors in which there are limited options for therapy, such as neuroblastoma. We focus on two main areas:

1. Chemical Epigenetics: We have developed strategies targeting novel epigenetic regulators that control the transcriptome of neuroblastoma (*Molecular Cell* 2020; *Science Advances* 2021; *Cancer Discovery* 2022), as well as other methods to specifically target proteins involved in driving neuroblastoma pathogenesis. We are studying these targeted compounds, both alone and in combination, for their potent and wide-ranging effects on tumor cell identity and fate.

2. Transcription Factor complexes and control of transcription: We have identified a group of transcription factors that function to establish the malignant identity of neuroblastoma (*Nature* 2015; *Nature Genetics* 2018; *Nature Communications* 2019; *Cell Reports Medicine* 2022). We dissect these and other transcription factor complexes using a variety of technologies, including mass spectrometry-based proteomics, chemical biology, advanced genome editing and imaging-based approaches, to identify key targets for therapeutic inhibition.

Students working in the Durbin laboratory will learn and use a variety of cell culture and molecular biology techniques to work on either of these projects. Students will work directly under the supervision of a post-doctoral fellow focused on the above

concepts. Students will be expected to read the primary literature, present in laboratory meetings, and develop technical and intellectual skills in a mentored environment in cell culture, molecular cloning, compound treatment, western blotting, immunofluorescence, RT-qPCR, mouse modeling of cancer and more advanced technologies including ChIP-seq, CUT&RUN sequencing, RNAseq and proteomics technologies, depending on the demands of the project.

Dr. Anand Patel

Oncology

2024 Rhodes College Summer Plus Program Project

For many of our cancer patients, treatment causes a tumor to shrink; but after months or years, tumors inevitably return. I am a pediatric oncologist and physician-scientist whose lab focuses on the process of tumor recurrence. Our lab seeks to understand the rare cells that survive therapy, and to develop treatments to overcome this effect. We use a variety of tools, including cell culture, mouse models of pediatric cancer, and molecular biology technologies to investigate the variety of cells within tumors. A student in our lab would work directly with Dr. Patel and have an opportunity to develop skills in cell culture, nucleic acid isolation, protein purification, and flow cytometry. There are no prerequisites, save for an interest in science and a willingness to learn new things.

Dr. Andrew Heitzer

Psychology and Biobehavioral Sciences

Dr. Heitzer is a neuropsychologist trained to examine brain-behavior relationships. His research focuses on assessing and improving neurocognitive functioning in sickle cell disease, an inherited red blood cell disorder with multisystemic effects. Patients with sickle cell disease are at increased risk for numerous neurological complications, including stroke and silent infarctions. Dr. Heitzer has several ongoing projects exploring risk and resiliency factors associated with neurocognitive outcomes in sickle cell disease utilizing biological (e.g., lab values, genetic modifiers) and environmental (e.g., socioeconomic status) predictors. Dr. Heitzer's lab utilizes various neuroimaging techniques (e.g., fNIRS, fMRI, DTI, MRS) to examine structural and functional correlates of neurocognition in sickle cell disease. Additional projects are focused on the development and implementation of behavioral interventions to remediate cognitive and academic deficits.

Students will assist with data collection, literature review, and manuscript/abstract preparation on research projects of interest. The student will attend weekly lab meetings as well as psychology and neuropsychology didactics. Opportunities to learn and administer neuropsychological measures are available. Completion of introductory courses in psychology and neuroscience may be beneficial but are not required.

Dr. Aseem Z. Ansari
Chemical Biology & Therapeutics

Designing Synthetic Genome Regulators (SynGRs)

Our recent breakthrough in rationally designing *synthetic gene regulators* (SynGRs) that overcome epigenetic silencing to restore expression of targeted genes, fuels our efforts to develop this class of molecules as precision-tailored therapeutics.

Synthetic gene regulators as precision-tailored therapeutics to remedy various diseases

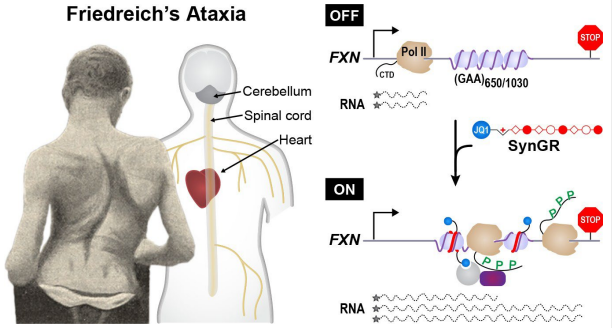

Figure 1. **Friedreich's ataxia targeted SynGR**. Friedreich's ataxia, is a progressive neurodegenerative disorder which has no therapy. The disease causes cardiac hypertrophy, ataxia and diabetes. Silencing of frataxin (*FXN*) by GAA trinucleotide repeat expansions underlies the etiology of the disease in more than 96% of the patients. SynTEF1 is a first-in-class SynGR that targets GAA repeats via a polyamide composed of imidazoles (filled red balls) and pyrroles (open circles). The bi-functional molecule delivers JQ1 (blue ball) to the GAA repeats in *FXN*. The repurposed JQ1 functions as an "epigenetic mimic" of the acetyl-lysine on histone tails and recruits the transcription elongation machinery to *FXN*. The targeted cellular machinery modifies the stalled RNA polymerase II (Pol II) and enables it to transcribe across the repressive GAA microsatellite repeats and restores *FXN* expression in vivo (Erwin et al. *Science* 2017).

To target desired genomic loci in vivo, we use the *polyamide* class of small molecule DNA binders. These imidazole/pyrrole based molecules can be rationally designed to target desired sequences in the genome. To the polyamide scaffold, we conjugate specific ligands that engage specific cellular machines to modify local epigenetic/chromatin states and regulate the expression of targeted genes. We recently created a SynGR (SynTEF1) to enable transcription across the repressive GAA repeats that cause Friedreich's ataxia, a lethal neurodegenerative disease (Fig. 1) (Erwin et al. *Science* 2017).

SynTEF1 is a powerful tool to explore the mechanisms by which GAA repeats silence *FXN* expression in patient cells. In parallel, using cutting-edge approaches, we are defining the sequence of mechanistic events by which SynTEF1 overcomes multiple layers of *FXN* silencing in vivo.

Internship Project: Our design principles, now enable the creation of precision-tailored SynGRs that act at different stages of transcriptional dysfunction that occur in a wide array of diseases.

The summer interns will work with talented team of scientists to create novel SynGRs as gene-targeted therapeutics for personalized medicine

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Aseem Ansari's laboratory studies the mechanisms of gene regulation in human development and disease. A major focus of the laboratory is to design and fabricate synthetic transcription factors that target specific loci in the genome and regulate gene and cell-fate defining networks. The research integrates concepts and tools from multiple disciplines, including Genomics, Chemistry, Biology and Computation.

We seek talented, creative and passionate young scientists to join a team of students, postdocs and technicians who have unique strengths and expertise in engineering, organic chemistry, computer science, genomics/proteomics, molecular biology and stem cell biology.

Dr. Cai Li
Biostatistics

Leveraging Machine Learning to Analyze Complex Data in Pediatric Neuroscience Research

Neuroscience is on the cusp of a data-driven metamorphosis, propelled by advancements in neuroimaging technology that provides higher resolution and bigger data. Unraveling the complexities of human brain is essential for understanding and battling brain disorders, ranging from neurodevelopmental issues like schizophrenia to the neurodegeneration seen in pediatric cancer survivors. In our lab, we harness cutting-edge machine learning tools that go beyond merely examining the brain's components. Instead, we aim to unveil the grand principles orchestrating this intricate system. Moreover, our methods adeptly weave together genetic information, painting a holistic picture of the neuropathological cascade. This paves the way for the transition towards precision medicine and enhance life quality for cancer survivors. This internship presents a unique avenue for individuals with a clinical/scientific foundation keen to apply machine learning or for those deeply rooted in data science eager to channel their skills into impactful scientific inquiries.

Development of statistical tools, computational software, as well as discovery of novel scientific findings are expected. The student will be paired with a senior group member, and mentorship would take place through group meetings and 1:1 discussion with the PI. To succeed in this position, the student should have demonstrated proficiency in programming language (R/Python/C) and solid statistical/mathematical skills. Good time management, the ability to work independently, work ethic, excellent written and verbal communication skills are required.

Dr. Charles Mullighan and Dr. Nicole Michmerhuizen
Pathology

Identification of key NUP98 fusion interacting proteins for effective therapeutic targeting

Description

This is an exciting career opportunity to join the laboratory of Dr. Charles G. Mullighan at St. Jude Children's Research Hospital. Our laboratory is at the forefront of landmark studies that define the genetic basis of acute leukemia, particularly pediatric acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). An additional focus of our lab is developing experimental models to gain mechanistic insight into the pathogenetic basis of these leukemias and to identify drug targets for effective therapeutic intervention. The laboratory uses a broad range of approaches including genome, transcriptome, epigenome and single cell sequencing approaches, mammalian cell culture, mouse model generation using viral transduction and genome editing, functional genomic screening in vitro and in vivo using CRISPR/Cas9 technologies, and preclinical modeling in genetically engineered mice and patient derived xenografts. Rearrangements of the nucleoporin 98 gene (*NUP98*) define a high-risk subset of childhood AML that is of especial interest in the Mullighan lab. *NUP98* rearrangements result in fusion oncoproteins (FOs) involving the N-terminal, intrinsically disordered region of NUP98 and the C-terminal portion of one of more than thirty identified fusion partners. We have developed mouse models of multiple NUP98 FOs to better understand the biology and therapeutic targeting of *NUP98*-rearranged leukemia. In particular, we described NUP98 FO interacting proteins using rapid immunoprecipitation mass spectrometry of endogenous proteins (RIME) as well as performed integrated functional genomic and chemical screens to identify key mediators of NUP98 FO-mediated transformation. These studies showed that inhibition of NUP98 FO interacting proteins, including histone acetyltransferase MOZ as well as transcriptional coactivators CBP and/or p300, can induce cell differentiation and/or death. We are currently using treatment with small molecule inhibitors of MOZ, CBP and/or p300, and other NUP98 FO interactors to better understand the molecular mechanisms contributing to NUP98 FO AML. Furthermore, we are performing in vivo preclinical studies using these therapeutic agents in patient derived xenografts to provide rationale for

clinical advancement with the ultimate goal of improving outcomes in *NUP98* fusion-driven AML.

Skills

In this role, the student will have the opportunity to pursue research on the biology and therapeutic targeting of *NUP98*-rearranged AML using cutting-edge approaches. To succeed in this position, the student should ideally have previous experience in molecular biology, molecular cloning, mammalian cell culture, and/or immunoblotting. Throughout the course of his/her experience in the Mullighan lab, s/he will be exposed to and/or have the opportunity to perform colony forming unit assays, immunofluorescence, functional genomic screens, qPCR/RNA sequencing, epigenetic profiling using Cleavage Under Targets and Release Using Nuclease (CUT&RUN) and other approaches, in vitro and in vivo drug screening, and in vivo leukemia modeling. Additional required skills include strong determination and organizational skills, time management, the ability to work both independently and in a team setting, ability in troubleshooting and confidence in new approaches, work ethic and outstanding communication, writing, and presentation skills.

Dr. Chi-Lun Chang
Cell and Molecular Biology

Research Summary:

Nutrients and metabolites need to be distributed carefully between organelles within cells to integrate cellular function and meet metabolic demands in a human body. Our laboratory investigates the formation, organization, regulation, and function of a complex inter-organelle logistic network. We address these questions via cutting edge light and electron microscopy tools in conjunction with a multidisciplinary approach, including molecular and cell biology, biochemistry, *in vitro* reconstitution, real-time metabolic analyses, and genome-editing technology. Our goal is to gain mechanistic insights into this logistic network in normal cells so we can translate this knowledge into the understanding of pathogenesis of diseases.

We are looking for talented students to join us. Motivation to understand how organelles communicate is a must. Prerequisites are creativity, passion, dedication, competitiveness, and the ability to work collaboratively in a small group. The accepted students will be working closely with senior scientists in the lab. Specific projects are,

1. Interrogating lipid droplet-organelle contact sites during metabolic switch
Fatty acids are indispensable materials for lipid synthesis and energy production. Lipid droplets play important roles in fatty acid metabolism via functional alliances with many other organelles at contact sites. However, the molecular basis of lipid droplet-organelle contact sites formation and regulation are largely unknown. Our team has developed synthetic tools that selectively label lipid droplet-organelle contact sites with minimal perturbation to cells. These tools enable us to quantitatively describe the dynamics of contact sites in conditions of energy surplus or starvation. Students involved in this project will perform experiments to interrogate the molecular basis behind the dynamic regulation of contact sites.

2. Investigating protein trafficking between the ER and Golgi
The endoplasmic reticulum (ER) and Golgi apparatus are the center hubs for protein trafficking. Although we have a comprehensive understanding of these

organelles, many aspects of the mechanistic and physical nature of trafficking pathways between them remain unclear. We hypothesized that dynamic assembly-disassembly of coat proteins drives the formation of these membrane structures. We recently developed an in vitro reconstitution system and gene-edited synthetic degron cell lines to test this hypothesis. Students participating in this project will also have the opportunity to work on questions related to Golgi-to-ER protein recycling pathway.

References:

1. Chang, C.-L., *et al*. (2019). Spastin tethers lipid droplets to peroxisomes and directs fatty acid trafficking through ESCRT-III. *Journal of Cell Biology*. 218(8): 2583-2599. PMC6683741.
2. Weigel, A. V.*, Chang, C.-L.*, *et al*. (2021). ER to Golgi protein delivery through an interwoven, tubular network extending from ER. *Cell.* 184: 1-18. (*equal contribution).

Dr. Chunliang Li
Tumor Cell Biology

Functional interrogation of RNA-binding protein function in MLL-rearranged leukemia

Research Summary

Aberrant expression of development-associated HOX genes, particularly HOXA9, is a hallmark of most aggressive acute leukemias. These include a large majority of human acute myeloid leukemia (AML) and subtypes of acute lymphoblastic leukemia (ALL), such as refractory MLL-rearranged (MLL-r) ALL and NPM1c^{+} AMLs. Overexpression of HOXA9 predicts not only poor patient survival but also plays a critical role in leukemia development and maintenance. HOXA9 is a homeodomain-containing transcription factor that has been shown to bind genomic regions directly. Oncogenic translocation such as NUP98-HOXA9 retained the DNA-binding domain of HOXA9, again suggesting DNA binding affinity to specific target genes is essential for HOXA9's function in leukemogenesis and tumor maintenance. A growing body of evidence indicates that HOXA9 dysregulation is both sufficient and necessary for leukemic transformation. However, HOXA9 protein itself is a poor therapeutic target as it lacks targetable binding domains.

RNA binding proteins (RBPs) control transcriptional regulation, RNA subcellular localization, translational efficiency, and metabolism, by binding to target messenger RNAs (mRNAs), thereby controlling the expression of the encoded proteins[1]. Multiple lines of evidence indicated many RBPs (e.g., RBM39 and RBM17) are essential for leukemia survival and differentiation, which were also targetable therapeutically[2-4]. For instance, the Carbonic Anhydrase inhibitor, Indisulam, induces a ternary protein complex between RBM39 and the E3 ubiquitin complex resulting in rapid proteasomal degradation of RBM39, aberrant RNA splicing, and cell death of AML[5]. Besides these progresses, the functional role of most RBPs and its regulation of HOXA9 in AML and its therapeutical innovation is still limited by a lack of systematic evaluation for RBPs and their connection with specific oncogenic targets in cancer. Here, our goal was to use functional HOXA9-reproter based CRISPR screens to dissect the roles of RBPs and the molecular mechanism in AML.

This project is designed to prioritize and validate the screen candidates. It will consist of conducting CRISPR editing-mediated validation, epigenetic characterization of transcriptional regulation (RNA-CLIPS-seq, CUT&RUN, ChIP-seq, and ATAC-seq), and leukemia cell biology (*in vitro* leukemia culture, proliferation, and apoptosis) to dissect the molecular regulation network driven by the RBP and HOXA9 in leukemia. The student will be under one-to-one direct supervision by the PI with technical assistance from other laboratory members. We anticipate these studies will increase our understanding of the mechanisms driving HOXA9-driven leukemia and identify potential therapeutic targets. Welcome to join us! For more information, feel free to reach me at chunliang.li@stjude.org or our homepage at https://www.stjude.org/directory/l/chunliang-li.html

Relevant References

1 He, S., Valkov, E., Cheloufi, S. & Murn, J. The nexus between RNA-binding proteins and their effectors. *Nat Rev Genet* (2022). https://doi.org:10.1038/s41576-022-00550-0

2 Hodson, D. J. *et al.* Deletion of the RNA-binding proteins ZFP36L1 and ZFP36L2 leads to perturbed thymic development and T lymphoblastic leukemia. *Nat Immunol* **11**, 717-724 (2010). https://doi.org:10.1038/ni.1901

3 Elcheva, I. A. & Spiegelman, V. S. Targeting RNA-binding proteins in acute and chronic leukemia. *Leukemia* **35**, 360-376 (2021). https://doi.org:10.1038/s41375-020-01066-4

4 Tran, T. M. & Rao, D. S. RNA binding proteins in MLL-rearranged leukemia. *Exp Hematol Oncol* **11**, 80 (2022). https://doi.org:10.1186/s40164-022-00343-5

5 Wang, E. *et al.* Targeting an RNA-Binding Protein Network in Acute Myeloid Leukemia. *Cancer Cell* **35**, 369-384 e367 (2019). https://doi.org:10.1016/j.ccell.2019.01.010

Dr. Ellie Margolis

Host-Microbe Interactions

Research project:

Despite efforts to reduce antibiotic use, antibiotic-resistant bacteria remain a problem. The human microbiome comprises various complex microbe communities that colonize us. The microbes that live in the gut are crucial for tasks like digesting food, producing vitamins, training the immune system, and preventing harmful bacteria, including drug-resistant ones. The Margolis lab studies how these human gut bacteria can aid or out-compete multi-drug resistant organisms.

The project aims to understand how the order of antibiotic doses influences recurrence of multi-drug resistant bacteria. The recovery time and ability to exclude multidrug resistant bacteria vary for different antibiotics and may depend on which components of the microbiome they alter. We will identify the antibiotic-community interactions that make certain patients more susceptible to challenging-to-treat infections.

Requirements include willingness to perform mouse experiments and familiarity with molecular biology (like pipetting, working with plasmids, and growing bacteria).

Dr. Erica Kaye

Quality of Life and Palliative Care

Dr. Erica Kaye and the Quality of Life and Palliative Care (QOLA) Research Program seek Rhodes Summer Plus applicants who are interested in gaining skills and expertise in the conduct of clinical research focused on patient-centered care, humanism, equity, and dignity. Within the Department of Oncology, the QOLA Division comprises a robust research program with more than thirty active clinical research studies and a strong track record of successful student internship opportunities. Dr. Erica Kaye, Director of the QOLA Research Program, has mentored more than twenty undergraduate and graduate students, including two recent Rhodes Summer Plus scholars, in her QOLA Communication Laboratory.

The selected Rhodes Summer Plus student will participate in the RIGHTime trial (Revealing Information Genuinely and Honestly over Time), a 5-year mixed methods study funded by the National Cancer Institute to improve how clinicians communicate difficult information about prognosis with children with advanced cancer and their families. The student will learn how to analyze and synthesize data from interviews with patients and parents about best practices for prognostic communication, to inform collaborative stakeholder-driven design of a clinical tool to improve timely, patient-centered communication about prognosis in the setting of advanced childhood cancer.

The ideal student will be thoughtful, dedicated, organized, empathic, self-reflective, and interested in learning new analytic approaches in communication-based research. A student who enjoys reading, writing, and critical thinking is preferred. No prior experience with mixed methods or qualitative analysis is required. All QOLA research interns are encouraged to write and present abstracts at national conferences and serve as authors on all manuscripts published related to their project. The student also will be invited to join structured clinical shadowing experiences to learn about integration of palliative care in the management of children with advanced cancer. Students who apply should have an interest in learning about compassionate holistic care with a focus on mitigating suffering and improving quality of life for children with serious illness and their families.

Dr. Hai Dao

Chemical Biology & Therapeutics

Research Description: In-silico Evolution of Chromatin Binding Peptides

DNA in eukaryotic organisms is packaged into a nucleoprotein complex called chromatin. The repeating unit of chromatin is the nucleosome, which consists of approximately 147 base pairs of DNA wrapped around an octameric protein complex assembled from two copies of each of core histones H2A, H2B, H3, and H4. Under physiological conditions, chromatin is associated with many chromatin effector proteins (e.g., remodeling proteins, transcription factors), which act as a means for shaping the chromatin landscape to bring about downstream biological events. Aberrant chromatin regulation can serve as an underlying cause of genetic disorders and cancers. To better understand chromatin regulation, our lab is developing chemical probes by combining computational design with high-throughput experimental screening. This project exploits AlphaFold and biochemical assays to discover peptide-based binders of chromatin regulators. AlphaFold is a recent deep-learning protein structure prediction algorithm from Google's subsidiary, DeepMind, which has reached experimental accuracy in predicting protein structures. An extension of AlphaFold, AlphaFold- Multimer, is trained on multimeric protein structures and can be used to predict the structures of protein complexes. In our recent study, we developed a platform to evolve nucleosome-specific peptides by emulating the process of natural selection. This project extends this pipeline to the ATP-dependent chromatin remodeling complexes, key regulators in gene regulation.

Students in the lab will have hands-on training in bioconjugation, macromolecule assembly, molecular cloning, protein expression, mammalian cell culture, and computational design. Students are expected to have general knowledge of chemistry, biochemistry, or molecular biology. Students can select a computation- or experiment- focused project.

Dr. Heather Conklin

Psychology

Dr. Conklin is a pediatric neuropsychologist who dedicates her time to clinical investigation, provision of clinical care and training/supervision. Her research program is focused on improving cognitive outcomes following treatment for childhood cancer. Primary research aims include using cognitive outcomes to inform modifications in cancer-directed treatment, improving specification of cognitive deficits following treatment, and developing empirically valid interventions that mitigate cognitive late effects. Current research projects include investigation of: computerized cognitive training to off-set working memory problems among brain tumor survivors, the potential neuroprotective benefits of medications taken during radiation therapy, cognitive benefits of aerobic exercise, impact of hearing loss associated with cancer treatment on cognitive development, cognitive sparing offered by proton beam radiation therapy, and harnessing aspects of socioeconomic status that may be protective with respect to cognitive outcomes for childhood cancer survivors. Her work is multidisciplinary with frequent collaboration with neuro-oncologists, radiation oncologists, neurologists, neuroimagers, geneticists and rehabilitation therapists.

The student chosen to work with Dr. Conklin would assist with literature reviews, study design, data collection, data analysis and dissemination of findings (manuscripts and presentations). Students would be encouraged to participate in weekly psychology and neuropsychology didactics, as well as lab meetings and multidisciplinary rounds. Opportunities to learn administration of neuropsychological tests would be provided. The ideal candidate will have completed coursework in psychology, neuroscience and statistics; prior research experience is desired but not required.

Dr. Heather Mefford

Center for Pediatric Neurological Disease Research

The Mefford laboratory is dedicated to identifying and understanding genetic, genomic, and epigenetic causes of pediatric neurological disorders, with a focus on childhood-onset epilepsy disorders called developmental and epileptic encephalopathies (DEE). These are severe conditions characterized by developmental delays and seizures that are difficult to treat. More precise and effective treatments are desperately needed to improve quality of life for individuals with DEE. We believe that identifying the genetic causes helps us understand the pathways that are affected and highlights potential targets for new, gene-targeting therapies.

The lab applies clinical, experimental, and computational approaches to address various aspects of identifying, characterizing, and treating genetic epilepsies. Students interested in computational projects will learn how to perform analysis of gene expression, genomic, or methylation data from patient-derived or engineered cells and organoids. Clinical projects involve studying the natural history of specific genetic DEEs using data collected from electronic medical records and family surveys. The student will perform summary statistics as well as trend analysis to understand disease progressions and aid in better treatment outcomes. Students will be paired with a senior lab member, so previous lab experience is not required. Experimental projects will be considered for students with some lab experience. Upon completion of their studies, the student will have learned a set of computational, biological and genetic techniques commonly used in biomedical research.

Dr. Jamy Peng

Developmental Neurobiology

The Jamy Peng lab investigates epigenetic mechanisms that regulate stem cell functions. Stem cells are responsible for originating and maintaining tissues in the human body. Over proliferation of stem cells can cause cancer, and under proliferation of stem cells can cause tissue dystrophy, immuno-deficiency, and even death. We are most interested in how stem cells make decisions to live, differentiate, or die. We study a specific pathway, named H3K27 modifications, which is causally implicated in the progression of many adult and pediatric cancers. The Rhodes Summer Plus student will work closely with Dr. Peng to evaluate how mutations in regulators of the H3K27 modifications alter stem cell survival, proliferation, and differentiation to brain organoids. If the student is more interested in mouse work, then we will work on an alternative project of examining the effect of newly discovered pathway players on the progression of a pediatric high-grade glioma. The student will join a highly enthusiastic and collaborative team and learn techniques that include culturing stem cells, mouse embryo analyses, nucleic acid and protein purification, cell sorting, gene expression profiling, immunoprecipitation, and immunofluorescence microscopy. While learning experimental techniques, past students have opted to participate in data presentations to the lab and regional conference(s).

Dr. Jane Hankins, Mr. Ombeni Idassi, Mr. Nick Faris

Global Pediatric Medicine

The vision of the Global Hematology program at St. Jude Children's Research Hospital is to create a world where every young person with non-malignant catastrophic blood disorders receives specialized, compassionate care leading to prolonged life and a meaningful existence. We pursue this vision by leveraging research, technology, and organizational skills to advance knowledge of non-malignant catastrophic blood disorders across the globe.

Our goal is to aid partners in low- and middle-income countries (LMICs) in caring for children with catastrophic hematologic disorders. We are in the process of creating clinical and research tools that will enhance the LMICs' ability to diagnose and care for children with hematologic conditions such as sickle cell disease, hemophilia, thalassemia, and bone marrow failure. These tools include a global registry for hematologic diseases (REGHEM), a clinical platform that adapts evidence-based guidelines to low-income contexts (ARIA-HEM), and a situational analysis evaluation survey that quantifies gaps in care delivery at health institutions and in health systems (PrOHFILE). As a Summer Plus student, you will work under the mentorship of the St. Jude Global Hematology faculty and their team to help develop these tools and participate in regular Global Hematology program meetings. You will learn research skills in Global Health, including how to critically appraise literature in global health, conduct systematic reviews, structure data for statistical analysis, and measure quality indicators for health delivery. Additionally, you will learn how to synthesize and communicate research results to LMIC partners and publish the results of your work.

Dr. Jasmine Plummer

Developmental Neurobiology

Unraveling genetic pathways to prevent ovarian cancer development in patients with BRCA1 mutations

Ovarian cancer, with its low survival rate, stands as one of the most formidable challenges in women's health. Over the past four decades, advancements in its prevention and treatment have remained elusive. Central to this problem is our limited understanding of the early mutations that trigger ovarian cancer. Our lab is dedicated to unraveling the genetic processes underlying the earliest stages of high-grade serous ovarian cancer (HGSOC), with the goal of finding effective solutions. A pivotal genetic factor associated with HGSOC is the BRCA1 gene mutation, significantly increasing the lifetime risk of ovarian cancer. However, not every BRCA1 carrier develops ovarian cancer, indicating the involvement of additional genetic events. One such event is the mutation in the P53 gene, prevalent in high-grade serous ovarian tumors and pre-cancerous lesions in the fallopian tube.

This project's primary focus is identifying genes responsible for the early development of HGSOC and their role in BRCA1 mutation carriers with p53 lesions. Employing cutting-edge technological tools such as CRISPR-Cas9 and chemoprotective drug screens with spatial omics methods, we systematically analyze human genes to determine their potential to either stimulate or inhibit the growth of fallopian tube cells carrying mutations in both P53 and BRCA1. Our research aims to pinpoint genes capable of restoring normal P53 signaling and subsequently employ drug screening to target these mutations for reversal. In our preliminary screening, we have already identified promising target genes like KEAP1, a regulator of BRCA1 known to influence HGSOC. The ability to halt the transformation of healthy cells into cancerous ones by targeting these mutations offers hope for treating precancerous cells in women before they progress to untreatable stages.

Exchange scholars joining our lab will have the unique opportunity to interact and collaborate with leading experts in the field. This will be an excellent opportunity to learn and become familiar with state-of-the-art tools such as CRISPR editing, genomics, multiomics cutting-edge spatial omics methods and various computational approaches we use in the lab to solve complex problems. The Plummer lab are leaders in the development and implementation of single cell and spatial genomic

laboratory techniques and computational methods. This group leads funded efforts within the human cell atlas and other global consortia. Moreover, scholars will actively contribute to the development of innovative strategies for the prevention of ovarian cancer.

Dr. Jason Vevea

Developmental Neurobiology

Each human cell is composed of small sub-structures called organelles which conduct specialized biochemical tasks to support cellular health and function. As their name suggests, organelles are to the cell, as organs are to the body. Maintaining organelle homeostasis in time and space is a major objective of cells, but how the cell accomplishes this feat is largely unknown. This process is generally termed organelle quality control (QC) and must be exerted with special intensity on organelles like the synaptic vesicle (SV) that undergo countless rounds of destruction and reformation, far from sites of protein translation and lipid synthesis in the neuron. Our lab has developed two novel SV isolation techniques that allow us to study this organelle with unprecedented detail. The first method is a rapid immunoprecipitation (IP) technique based on a newly validated, high functioning antibody to an SV protein, enabling scientists to study pure populations of SVs from mice to man, of any age or disease context. The other is a new technique to pulse-chase label SVs with an affinity tag, allowing researchers to begin to study the temporal heterogeneity of these small organelles.

We have begun these studies and are seeking a motivated student to learn and develop a targeted lipidomics pipeline in our lab for absolute quantification of lipid species from neuronal organelles. This student will work closely with the St. Jude Center for Proteomics and Metabolomics core facility. The student will learn many lab techniques like rapid IPs, immunoblotting, thin layer chromatography (TLC), and of course analytical chemistry via lipidomics analysis.

Dr. Jay Bikoff

Developmental Neurobiology

St. Jude-Rhodes Summer Plus Fellowship Project Description

Understanding how neural circuits implement behavior is one of the fundamental challenges in modern neuroscience. At a basic level, an animal's behavior is expressed through movement. Work in our lab seeks to understand the organization and function of neural circuits that enable animals to move, with a focus on circuits in the spinal cord that are directly responsible for controlling muscle contraction. Toward this end, we use a combination of mouse genetics, microscopy, single-cell transcriptomics, viral tracing, and behavior to better understand how neurons in the spinal cord and brain interact to control limb movement.

Under guidance of Bikoff lab members, students will be directly involved in experiments exploring the molecular and cellular diversity of spinal neurons, and how they connect with descending motor pathways from the brain to influence motor output. These projects involve both wet-lab components (i.e. molecular biology, microscopy, stereotaxic surgery), as well as the opportunity to develop computational skill sets in image analysis and bioinformatics that are broadly useful in science. While a background in introductory neuroscience and some familiarity with programming is ideal, all interested students regardless of background are encouraged to apply.

Dr. Jun Yang
Surgery

New mechanisms by which cells generate oncogenic mutants

The majority of protein-coding genes in human genome are regulated by multiple promoters. Context-specific alternative promoter usage (APU) initiates gene transcription from distinct promoters of the same gene, thus mainly affecting the 5' untranslated regions and first exons of transcripts. However, we recently applied an epigenomic algorithm (MethylationToActivity, M2A), a machine learning program to define promoter activity, and identified a subpopulation of genes undergoing cryptic APU, resulting in remarkable alterations in protein sequences. These cryptic APU genes function as novel oncogenes promoting tumorigenesis. The goal of this project is to fill the knowledge gap by understanding how cryptic APU is regulated, and why cryptic APU enhances tumor growth.

Through this project, the student will gain important knowledge in genetics, epigenetics, molecular and cellular biology, as well as cancer biology. The student will also master lab skills including western blotting, real-time PCR, plasmids packaging, and cutting-edge technologies including genetic manipulation of APU genes by using CRISPR-based genomic editing approach. Importantly, the PI laboratory is sitting in Department of Surgery. The student will be further nurtured in a unique environment by interacting with surgical oncologists and clinical fellows in Department of Surgery.

Dr. Katianne Sharp
Psychology and Biobehavioral Sciences

Genomic sequencing is increasingly being integrated into children's cancer care, resulting in increasing disclosure of cancer predisposition (i.e., genetic cancer risk) and uncertain germline findings during childhood. However, very little is known about children and their parents' coping, adjustment, and communication in the context of learning their child's genetic risk. The studies in my lab broadly seek to understand such topics as (1) child and parent emotional, behavioral, identity, and parenting outcomes following genetic testing results; (2) parent-child communication about genetic test results and genetic cancer risk; (3) children's involvement in genetics consults and return of results. Students in my lab learn such skills as electronic medical record chart review, data management and analyses in SPSS, qualitative coding, manuscript writing, and presentation preparation. Additional lab opportunities include psychology department didactics and seminars, exposure to interdisciplinary research and clinical teams through collaboration with the Division of Cancer Predisposition, and clinical shadowing. Specific projects for students are decided on through a combination of student interest and availability of data.

Dr. Kim Nichols
Oncology
Cancer Predisposition Division

In a healthy individual, exposure to an external trigger, such as an infection, leads to activation of the immune system and elimination of the trigger. Once the trigger has been eliminated, the immune system returns to its normal quiescent state. In patients with a disease called hemophagocytic lymphohistiocytosis (HLH), the immune system becomes activated in response to a trigger but cannot effectively eliminate the trigger. As a result, the immune system stays activated, leading to increased recruitment and stimulation of immune cells and release of pro-inflammatory signals called cytokines. Together, this feed forward process results in a state of hyperinflammation that causes organ damage and ultimately death if not recognized and appropriately treated. HLH can be subdivided into familial (also known as primary) HLH, in which patients carry mutations in one of several genes required for immune cell activity, and secondary HLH, in which patients have no apparent genetic predisposition but instead acquire immune dysfunction after exposure to a strong immunologic trigger.

My lab primarily focuses on understanding the mechanisms that drive inflammation in primary HLH. These patients often require treatment with a bone marrow transplant (BMT) to replace their defective immune system with a healthy immune system. However, many patients die before being able to receive a BMT due to uncontrolled inflammation. By understanding HLH pathogenesis, we identify pathways that can be targeted to better treat the disease. Any successful treatments can then be taken forward in the form of a clinical trial.

We are also examining the underlying causes of primary HLH, which is a genetically heterogeneous disease, with genetic testing often reporting variants of unknown significance (VUS), for which not enough data exist to know whether the variant is pathogenic, and therefore associated with the disease, or if it represents benign variation within the population. As a result, the challenge arises in identifying patients with true primary HLH who will need a stem cell transplant. To address this problem, we have developed a computational tool that synthesizes information about a VUS, such as its location within the protein, conservation throughout evolution, and the type of resulting amino acid change, to predict whether that VUS is likely to be pathogenic or benign. Our initial analysis suggests that this tool is highly accurate for identifying pathogenic variants within HLH genes, and ongoing experimental studies are needed to further validate this tool.

A student in my lab would have the opportunity to develop and execute the *in vitro* experiments needed for this validation as well as other studies examining disease mechanism and treatment. Through this work, they will learn skills including cell culture, CRISPR-mediated gene editing, molecular cloning, viral transduction, and flow cytometry. The project examining

VUS is a collaborative effort between my laboratory and investigators at other institutions across the country, who will also be involved in mentoring a student researcher. There is a high likelihood of publication within the next 1-2 years, and a student researcher would be included as a co-author. This is an ideal project for a student interested in biomedical research of significant medical impact with potential for translation to the clinical realm.

Dr. Lily Guenther

Oncology

Division of Molecular Oncology

The Guenther Lab is focused on understanding the molecular drivers of osteosarcoma, the most common malignant bone tumor in children and a major cause of childhood cancer morbidity and mortality. Osteosarcoma, unique amongst pediatric solid tumors, is a genomically complex disease characterized by heterogeneous point mutations, copy number changes, and chromosomal rearrangements. Unlike adult tumors that have recurrent targetable alterations, osteosarcomas have a diverse spectrum of molecular changes that make this a challenging disease for which to design targeted interventions. Our lab utilizes a variety of modalities, including CRISPR-Cas9 gene editing and other screening approaches as well 'omics' classification in diverse disease models to identify and investigate genes which are selective dependencies (survival factors) in osteosarcoma. Based on preliminary analyses, we are currently interested in targets involved in DNA damage repair, which are likely to be biologically important in this disease. Along with this, we are interested in designing more efficacious combination drug strategies by using screening approaches to classify response in a variety of osteosarcoma models. The overarching goal of all our work is to bring unique and highly effective treatment strategies forward in osteosarcoma that can be translated into patients with this devastating malignancy.

Several basic molecular biology and genomics-based projects as well as translational projects in the lab are conducive to involvement by a motivated undergraduate student. Students will be closely mentored by a post-doctoral fellow and/or senior PhD scientist in the lab, as well as by PI Dr. Guenther. Projects will be designed appropriate to student interest and length of time to be spent in the lab, as well as student past laboratory experience, if applicable. Students in the lab will be expected to read and interpret primary literature as well as to learn to employ the following molecular biology techniques in a mentored environment: mammalian cell culture, cellular drug treatment, lentiviral infection, DNA/RNA/protein extraction, PCR/RT-qPCR, molecular cloning, western immunoblotting, ELISA, as well as other molecular biology methods that apply to the specific project.

Dr. M. Madan Babu
Structural Biology

Babu Group Rhodes College Summer Plus Program Proposal

The Babu group aims to investigate and bridge knowledge across scales of complexity (atomic, cellular, and population) to understand human biology and diseases. The sequence-function relationship of proteins governs all biological processes. My group investigates how a protein sequence achieves its function. The structure-function paradigm states that proteins must adopt a defined structure to perform their function. The disorder-function paradigm says that the very lack of a precise structure gives them an ability to adopt different conformations and perform diverse functions. Our group uses data-driven approaches to ask and answer biological questions by mining biological data to develop hypotheses that can be tested in our lab. We focus on medically relevant protein families such as G protein-coupled receptors (GPCRs), intrinsically disordered proteins or protein regions (IDPs/IDRs), and kinases.

For this internship opportunity, we propose two project options. Two are computational, and one is experimental.

Project 1: Uncovering flexible protein-protein interactions in cell receptor signaling (Mr. Balint Meszaros will lead the project)

Cells respond to environmental changes via specialized receptor proteins on their surface. These receptors serve as sensors for various cues, including nutrients, changes in the physicochemical environment, various stressors, or the presence of pathogens. Humans have roughly 5,000 receptors, yet the mechanism of signaling is unknown for the majority of them. However, recent advances in computational structural biology revealed the structure of these receptors, showing that a vast number of them have long flexible regions pointing inside the cell. Similar flexible proteins are known to form protein-protein interactions (PPIs), serving critical cellular processes. This project builds on our previous experience with a special class of receptors. It aims to generalize it to identify new PPIs that can provide an understanding of how these receptors function and can offer starting points to modulate them via drug-like compounds.

- Experience or interest in coding is needed. However, a good basic understanding of a common programming language is sufficient to produce results.

Project 2: Synthetic biology design of cAMP genetic reporter / Synthetic biology platform for optimization of cAMP sensor for GPCR signalling
(Mrs. Katarina Nemec and Mr. Vikas Trivedi will lead the project

As part of the GPCR Collaborative, we are designing a screening approach to enable real-time read-out of the cAMP signaling cascade activity. To optimize the reporter design with the best signal-to-noise ratio and reproducibility, we aim to optimize it with a synthetic biology approach. The required modular building parts will be cloned using Golden Gate cloning methodology and built into a genetic circuit. Different barcoded circuit designs will be probed with fluorescence-activated cell sorting (FACS) and plate readers, followed by next-generation sequencing. The data obtained will be analyzed to determine the optimal design for cAMP genetic reporter. This project will provide ample opportunities to deepen the knowledge of molecular and cell biology and analyze big data.

- Experience with standard cloning techniques and molecular and cell biology is preferred.
  Knowledge about G-protein coupled receptor signaling is desired.

Dr. Marcus Fischer
Chemical Biology & Therapeutics and Structural Biology

Revealing invisible differences in near identical proteins

Protein isoforms are sets of highly similar proteins. They often share very high sequence similarity, are structurally indistinguishable and conduct similar function. Their near identical nature makes it challenging to find small molecules that target individual isoforms specifically. The motivation for this project is threefold: Isoform-selective small molecules would help us better understand subtle differences in their biological role, they would help us target disease-driving isoforms, and they would reduce off-target side effects of current promiscuous binders.

To achieve this, we use a spin on common X-ray crystallography that provides key information about structural dynamics at the molecular level. While 95% of all structures in the Protein Data Bank are collected at cryogenic temperatures (100K), we will solve structures at physiologically relevant temperatures. We have shown that this can unmask biologically meaningful conformations and reveal minor differences that can help us distinguish isoforms. The goal of the project is to leverage these insights towards finding isoform-selective small molecules to probe biology and treat disease.

The Rhodes Summer Plus fellow involved with this project will learn state-of-the-art molecular biology and structural biology techniques along the gene-to-protein-to-structure pipeline that are relevant for academic research and industry. No prerequisite skills required, but prior hands-on experience in molecular biology techniques and programming skills for data analysis (Python, R, Matlab) would send you off to a flying start.

References:
• Stachowski et al. (2022). Water Networks Repopulate Protein–Ligand Interfaces with Temperature. *Angew Chem* 61, e202112919.
• Fischer (2021). Macromolecular room temperature crystallography. *Q Rev Biophys 54, e1.*
• Darby et al. (2019). Water Networks Can Determine the Affinity of Ligand Binding to Proteins. *JACS* 141, 15818-26.

Dr. Mark Hatley

Oncology

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma of childhood. Despite three decades of rigorous and intensive clinical trials the overall survival of RMS has not increased from 70%. Fusion oncoproteins of PAX3-FOXO1 and PAX7-FOXO1 drive rhabdomyosarcomagenesis in approximately 30% of RMS patients (fusion-positive RMS, FP-RMS). FP-RMS tumors are defined by positive-fusion status with few other deleterious mutations. The remaining RMS patients have a more heavily mutated genotyped and do not express these fusion oncoproteins; these patients are termed fusion-negative (FN-RMS) and account for approximately 70% of all RMS. Large-scale genomic analyses from several consortia, including St. Jude, have indicated many putative driver mutations and genomic alterations responsible for FN-RMS tumorigenesis. However, there is a paucity in understanding the causal events that lead to FN-RMS. Our laboratory studies these causal events by using a variety of scientific tools to definitively determine these events, including genetically engineered mouse models, gene editing, and *in vitro* tissue culture systems including induced pluripotent stem cells. Ultimately, we hypothesize that data obtained from our laboratory will rigorously define the molecular mechanisms underlying FN-RMS and FP-RMS tumorigenesis and will lead to better treatment modalities and regimens to thwart this devastating disease. Techniques actively performed in the laboratory include, but are not limited to: laboratory animal husbandry, CRISPR-Cas9 gene editing systems, mammalian tissue culture, molecular cloning, viral expression systems, RNA and protein isolation, immunoblotting, quantitative real-time PCR, and cell growth and death assays. No technical prerequisites are required – just an eagerness and excitement to learn. Student(s) will participate in weekly lab meetings and periodically present their findings at these meetings to hone their scientific presentation skills. The laboratory has three postdoctoral fellows, three graduate students, a senior lab manager, and two gap-year technicians. The lab has a current Rhodes Summer Plus student and has had five students in the Rhodes Summer Plus program. All former summer plus students have matriculated into graduate programs including medical school and graduate school. All members of the lab will facilitate a nurturing

educational environment to further the student's growth into a young scientist.

Dr. Min Ni

Oncology

Metabolomics-based screening for targeting metabolic vulnerabilities in high-risk neuroblastoma

Our research focuses on understanding the genetic and metabolic mechanisms that control tumorigenesis and therapeutic resistance in childhood cancer, including neuroblastoma and leukemia. During cancer progression, tumor cells undergo metabolic reprogramming to support the acquisition of new biological functions, enabling them to adapt to changing microenvironments, such as new metastatic sites or responses to drug treatments. Nutrient availability and utilization are critical to tumor cell survival and growth. Our previous studies, through integrating metabolomics and genomics analyses, have revealed new metabolic features associated with high-risk neuroblastoma. In our ongoing efforts to identify clinically actionable targets for the treatment of high-risk neuroblastoma, the Ni lab has developed an innovative platform using advanced mass spectrometry technologies. This project is designed to evaluate the effect of targeting candidate metabolic enzymes or pathways in combination with frontline chemotherapy drugs on neuroblastoma. We will employ a metabolomics-based screening approach, utilizing both genetic targeting techniques like CRISPR/Cas9 and pharmacological inhibitors. Throughout the project, the student involved will benefit from mentorship by two experts in mass spectrometry, gaining hands-on experience in conducting metabolomics assays. Additionally, Dr. Ni will provide direct training in data analysis, experimental design, and techniques, ensuring a comprehensive learning experience for the student. We welcome those interested in applying their knowledge of biology and chemistry to pediatric cancer research.

Dr. Mondira Kundu
Department of Cell & Molecular Biology

One of the goals of my lab is to gain insight into the physiological functions of autophagy-related genes. Autophagy is a process by which cellular contents are sequestered and targeted to lysosomes for degradation and recycling. Ulk1 and ULK2 are kinases that exert higher order regulation of the process by phosphorylating multiple components of autophagy machinery. Although these kinases are best characterized for their roles in autophagy, using animal models to guide our research, my lab has identified additional non-canonical functions of ULK1/2 (i.e. not related to their roles in autophagy). We recently observed that deficiency of ULK1/2 results in activation of certain interferon (INF)-stimulated genes. Aberrant activation of the INF response contributes to a wide variety of conditions, including hematological disorders, autoimmune diseases, and neurodegenerative diseases. The purpose of the project is to dissect the mechanism(s) by which ULK1/2 suppress innate immunity responses. Working closely with an experienced member of the lab, the student will learn about good laboratory practices, animal research, and experimental design and gain experience applying these skills to their project. The student will learn and apply techniques in molecular biology and cell biology, including the following - cell culture, immunostaining, microscopy, RNA isolation and real-time quantitative PCR. The student will also receive training on statistical packages and other software that are instrumental in the analysis and presentation of their research findings.

Dr. Myriam Labelle
Oncology

Impact of host-tumor cell interactions on cancer metastasis

Metastasis is responsible for ~90% of cancer-associated deaths, yet the mechanisms governing this clinically important process remain poorly understood. To metastasize, tumor cells must break away from the primary tumor and transit through the blood circulation, before seeding and growing into distant organs.

Our laboratory studies how interactions between tumor cells and the normal cells of the body (the host) contribute to metastasis. For example, our previous work has revealed that blood platelets and neutrophils interact with tumor cells during the process of metastasis. These interactions alter the gene expression profile of cancer cells and this, in turn, increases their ability to invade, to survive at the metastatic site, and to give rise to lethal metastases.

Our ongoing projects investigate how metastasis and the crosstalk between tumor cells and normal cells are modulated by factors such as primary tumor progression, anti-cancer treatments, and aging. With this work, we hope to identify novel pharmacological targets to prevent cancer metastasis and improve the survival of cancer patients.

We are looking for a highly motivated and organized student to join our team and contribute to the above-mentioned projects. The student will have the opportunity to learn a broad array of techniques including mouse models of metastatic cancer, tissue culture assays, co-culture systems, molecular cloning, and advanced microscopy.

Dr. Ozgur Ates
Radiation Oncology

Adaptive Proton Therapy for Pediatric Radiation Oncology

I am writing to propose an undergraduate research project in the field of adaptive proton therapy, specifically focusing on the assessment of changes in patient anatomy, particularly weight gain or loss. This assessment will be conducted by comparing Cone Beam Computed Tomography (CBCT) images of the abdominal and pelvic regions with the initial CT and MR images. Our project's central aim is to address the need for accurate monitoring in Image-Guided Radiation Therapy (IGRT), thus enhancing treatment effectiveness.

The proposed research project will encompass several key phases. We will commence by acquiring the initial CT and MR images of the patient's abdominal and pelvic areas to establish a reliable baseline for comparison. Subsequently, periodic CBCT scans will be conducted during the proton therapy course, providing real-time imaging to monitor anatomical changes and assess the impact of weight gain or loss.

For image processing, we intend to utilize MATLAB as the primary tool. Leveraging its capabilities, we will preprocess and enhance CBCT images, correct artifacts, and extract relevant anatomical information. The project will also entail the development of sophisticated algorithms for change detection, quantifying alterations in organ shape, position, and volume. This phase will necessitate a deep understanding of image analysis techniques to ensure the accuracy and reliability of the assessments. A pivotal outcome of this research will be the development of a user-friendly assessment tool or software that can take processed images and provide precise measurements of weight gain or loss. To validate the accuracy of this tool, we plan to conduct validation exercises against documented cases of weight changes, potentially utilizing a dataset of patients with known weight fluctuations.

In conclusion, this research project in adaptive proton therapy, supported by daily CBCT imaging in IGRT, aims to provide a robust and reliable tool for monitoring patient anatomy changes. By doing so, it seeks to enhance treatment planning and delivery, ultimately benefiting cancer patients. The project's results will allow us to

ascertain the extent of anatomical changes and their impact on plan quality, thereby contributing significantly to the advancement of adaptive proton therapy and IGRT.

We anticipate that the aspiring student will acquire a strong understanding of CT and MR imaging, gain insights into human anatomy and physiology, develop proficiency in image processing through MATLAB, and harness programming skills to contribute to the development and evaluation of assessment and testing tools. The necessary skillset for this research project includes basic knowledge of human anatomy, advanced level of algebra and physics, and familiarity in MATLAB.

Dr. Paul Northcott
Developmental Neurobiology

Molecular Basis of Medulloblastoma

Mentor Areas
Dr. Paul A. Northcott is a Member (equivalent to Professor) in the Department of Developmental Neurobiology and Neurobiology and Brain Tumor Program at St. Jude Children's Research Hospital. He is also an active Member of the Children's Oncology Group, the American Association of Cancer Research, and the Society for Neuro-Oncology. He is the recipient of numerous prestigious awards including The Sontag Foundation Distinguished Scientist Award, Pew-Stewart Scholar for Cancer Research, St. Baldrick's Foundation Robert J. Arceci Innovation Award, and was an inaugural recipient of the AACR NextGen Grant for Transformative Cancer Research.

Research Summary
Medulloblastoma is one of the most common and lethal childhood brain tumors. Current therapeutic approaches are successful in only a portion of cases, and survivors often face severe long-term side effects. To improve the effectiveness and safety of clinical intervention, a deeper understanding of the biological and clinical heterogeneity of medulloblastoma is required.

To explore the clinical heterogeneity, lineage-specific origins, and potential vulnerabilities of medulloblastoma, the Northcott Lab uses a multi-faceted approach that includes translational genomics, discovery-driven bioinformatics, functional validation analyses, and fundamental neurodevelopmental studies. The current focus is to dissect molecular landscapes in the context of tumor subgroups and functionally validate candidate driver genes and potential dependencies using innovative modalities and preclinical models. The overall goal is to translate discoveries into improved diagnosis, stratification, and treatment options for affected children and their families.

His lab research has disclosed the molecular mechanisms underlying medulloblastoma pathogenesis and established the importance of contextualizing clinical trial outcomes with biology, leading to many

high-impact publications in *Nature*, *Nature Genetics*, *Cancer Cell*, *Lancet Oncology*, and the *Journal of Clinical Oncology*, as well as NIH R01, P01 and R21 grant funding.

Selected Publications:

(1) Northcott et al, The whole-genome landscape of medulloblastoma subtypes. Nature. 2017 Jul 19;547(7663):311-317. doi: 10.1038/nature22973.

(2) Hovestadt et al, Resolving medulloblastoma cellular architecture by single-cell genomics. Nature. 2019 Aug;572(7767):74-79. doi: 10.1038/s41586-019-1434-6.

(3) Waszak et al, Germline Elongator mutations in Sonic Hedgehog medulloblastoma. Nature. 2020 Apr;580 (7803):396-401. doi: 10.1038/s41586-020-2164-5.

(4) Kumar et al, Clinical Outcomes and Patient-Matched Molecular Composition of Relapsed Medulloblastoma. J Clin Oncol. 2021 Mar 1;39(7):807-821. doi: 10.1200/JCO.20.01359.

(5) Smith et al, Unified rhombic lip origins of group 3 and group 4 medulloblastoma. Nature 2022 Sep; 609(7929):1 012-1020. doi: 10.1038/s41586-022-05208-9.

Dr. Stacey Ogden

Cell & Molecular Biology

The Ogden laboratory studies the Sonic Hedgehog (SHH) signal transduction pathway, which plays an evolutionarily conserved role in patterning fields of cells during embryonic development. SHH signals guide cell fate decisions that result in proper formation of left and right brain hemispheres, faces with one nose and two eyes, and hands with one thumb and four fingers. Disruption of SHH pathway regulation is causative in neurodevelopmental disorders and pediatric cancers including medulloblastoma and rhabdomyosarcoma. We research SHH signaling during formation of healthy tissue to better understand how its activity can be corrupted to cause disease. We hope this this knowledge will lead to novel prevention and/or treatment options for developmental disorders and cancer.

The laboratory utilizes a combination of biochemical, cell biological and genetic mouse models. There is a project available for a Summer Plus student to research how SHH signal-producing cells use specialized filopodia called cytonemes to transport SHH pathway components across developing tissues to instruct organ formation. Research in the Ogden Lab is highly collaborative, so students will be paired with a senior lab member. Previous lab experience is not required. During their Summer Plus studies, students will learn how to perform cell culture-based experiments, be introduced to confocal and electron microscopy techniques, and gain experience in standard molecular biology techniques. They will learn how to interpret results and present conclusions. Upon completion of their studies, the student will have learned a set of biochemical, cell biological, and genetic techniques commonly used in biomedical research.

Dr. Subodh Selukar

Bone Marrow Transplantation & Cellular Therapy

Investigating clinical outcomes for patients treated by the Department of Bone Marrow Transplantation & Cellular Therapy at St. Jude

Dr. Subodh Selukar is a Biostatistics faculty member at St. Jude Children's Research Hospital who primarily collaborates with St. Jude's Department of Bone Marrow Transplantation & Cellular Therapy (BMTCT). By working with Dr. Selukar, a selected student will have the opportunity to collaborate on cutting-edge clinical research projects arising from St. Jude BMTCT. Dr. Selukar's current research includes identifying risk factors for complications after CAR-T cell therapies and evaluating outcomes following novel bone marrow transplantation regimens. The student can learn advanced statistical methodologies suitable for analyzing these data and contribute to research that informs future care of St. Jude patients and motivates future studies to continually advance toward cure for all children with catastrophic diseases.

This opportunity is ideal both for students interested in a career in statistics and data science with a focus on clinical research and students interested in careers as clinicians who want to expand their research background. Candidates are expected to have familiarity with the fundamentals of programming (e.g., have completed COMP 141) and introductory statistics (e.g., MATH 111). Students will learn how to manage and analyze data using R statistical software, and they will learn how to interpret results and communicate conclusions to clinicians. This opportunity will be tailored to the selected student: future statisticians and data scientists may extend the clinical research to develop specialized tools (e.g., R Shiny application) and future clinicians can extend the biomedical aspects to better understand the mechanisms of therapy and disease and to possibly motivate future research.

Dr. Tanja Mittag
Structural Biology

Molecular basis of cancer through structural analysis of SPOP complexes

Ubiquitin ligases play critical roles in the maintenance of cellular proteostasis. In the modular Cullin-RING ubiquitin ligases (CRLs), substrate receptors recruit specific proteins, which are then marked by ubiquitination for proteasomal degradation. Hence, mutations in substrate receptors result in altered cellular levels of their substrates and can result in disease processes. *SPOP* is an important tumor suppressor and the most frequently mutated gene in prostate cancer and frequently mutated in other solid tumors. The **S**peckle-type **PO**Z **P**rotein, short SPOP, is a substrate receptor of the Cullin3-RING ubiquitin ligase (CRL3). SPOP substrates include proto-oncogenes such as androgen, estrogen, and progesterone receptor, MYC, the Hedgehog pathway transcriptional regulators Gli2 and Gli3, the BET family of proteins BRD2, BRD3 and BRD4, the apoptosis regulator DAXX, and the DNA-damage response protein 53BP1. Dysregulation of SPOP activity alters the levels of those proteins and can result in oncogenesis in susceptible cell types. Indeed, *SPOP* is the most frequently mutated gene in prostate cancer and is also often mutated in endometrial, breast, colon, and other solid tumors. SPOP is thus regarded as an important tumor suppressor across cancers) and it is important to understand how it functions at a molecular level.

In this project, we will build on recent breakthroughs in SPOP structure determination achieved in the Mittag lab. Single-particle cryo-EM analysis has allowed us to solve the structure of linear SPOP oligomers. The structure reveals the interfaces through which SPOP self-assembles. Interestingly, many of the residues in these interfaces are mutated in cancer patients. While it was not previously understood why mutation of these residues leads to dysregulation, our structures have revealed the underlying molecular mechanisms. We will leverage our recent advances to address open questions, e.g., why certain disease-associated mutants change the quaternary assembly drastically, while disease mutants often just destabilize proteins. The altered structures suggest the possibility of developing disease-specific therapeutics, which would have much reduced side effects. The student will work closely with an experienced staff scientist in the lab, learn how to prepare samples for cryo-EM, take advantage of reagents and assays we have built over the last 10 years, and contribute to an

exciting research project that aims to understand the molecular basis of certain cancers by solving structures using cutting-edge technology.

Dr. Tommaso Cupido

Chemical Biology and Therapeutics

Several lines of evidence suggest a connection between the molecular mechanisms governing normal organism development and the processes underlying cancer diseases. These mechanisms involve the reorganization of the cell nucleus and, consequently, alterations in chromatin structure and function, which in turn affect gene expression. Understanding these processes at the molecular level, in both normal and disease states, is crucial for developing more effective cancer therapeutics and controlling cell fate. Some of these mechanisms are mediated by RNA molecules and ancient RNA-protein complexes that regulate gene expression programs. In our laboratory, we use a combination of chemical and genetic approaches to investigate the role of enzymes that remodel RNA-protein complex structures in gene regulation, with a specific focus on those involved in maintaining abnormal chromatin states in pediatric cancers. To address these fundamental questions in biology and cancer drug discovery, we utilize small molecules that we either discover or design through high-throughput screening and structure-based optimization. Our goal is to gain a better understanding of how cells use RNA molecules not only as carriers of genetic information but also for regulatory purposes.

We seek strongly motivated, early-stage scientists who are passionate for understanding basic biochemical mechanisms of gene regulation and/or interested in translational chemistry sciences. Specific projects employ methods from science fields ranging from cell biology to synthetic chemistry. Rhodes College applicants will receive extensive training in biochemistry of gene regulation, cancer genetics, drug discovery, and effective scientific communication. While our primary focus isn't structural biology, we use structural methods to support drug discovery and enhance our understanding of biochemical processes, providing training in these techniques as well.

Dr. Young-Goo Han

Developmental Neurobiology

My lab studies molecular, cellular, and evolutionary mechanisms of brain development and tumorigenesis. The neocortex is a unique mammalian brain structure that computes high-order sensory, motor, and cognitive processes. Humans have the largest neocortex relative to brain size, and its folded surface is thought to be the root of our superior cognitive abilities. What are the underlying mechanisms for the development and evolution of this remarkable structure? How do alterations in these mechanisms lead to neurodevelopmental disorders and brain tumors? My lab aims to answer these questions through the lens of the neural progenitor cells that construct the brain during development.

At early development stages, the brains of humans and mice (the prime animal model for biomedical research) are similar. However, a robust expansion of neural progenitor cells, especially outer radial glial (oRG) cells, in humans during development gives rise to the large, folded human cortex. However, little is known about the mechanism by which those neural progenitors expand. To fill this important gap in knowledge, my lab developed the first stable and robust genetic mouse model, where oRGs greatly expand to transform the small and smooth mouse cortex into an expanded and folded one. Using this unique mouse model and cerebral organoids ("minibrain" grown from human pluripotent stem cells), we showed that SHH signaling is necessary and sufficient for the expansion of oRGs. Importantly, our organoids and unique mouse models also enable us to reveal the mechanisms of human brain development and neurodevelopmental disorders that have been difficult to illuminate by using conventional mouse and *in vitro* models. An intern student will participate in our current investigations on the molecular and cellular mechanisms that expand human neural progenitors and how such mechanisms are disrupted in neurodevelopmental disorders and brain tumors.

The experimental techniques used for these studies may include *in vivo* handling of rodents, *in vitro* cell culture, immunostaining, microscopy, molecular biology, cell biology, and protein biochemistry.