The Xiaotu Ma lab

Computational Biology

Cancer early detection, monitoring, and personalized therapy using genome editing

Intensive efforts in the past decade have revolutionized our understanding of the genetic basis of many human cancers using high throughput DNA sequencing. These invaluable insights opened two avenues to our ultimate goal of bring cure to cancer patients: 1) early detection or monitoring of cancers by using our knowledge learned from patient tumors; 2) to develop personalized therapy by integrating the genomic information from the patient and the state-of-art genome editing technology enabled by CRISPR-Cas9 system (via collaboration with Shondra Miller lab in St. Jude).

The student can choose either of these directions to focus their study on. To be productive, the student is expected to have a good programming skill, a habit of critical and quantitative thinking, a solid foundation in molecular biology and human genetics, and most importantly, a curious mind—if you keep asking WHY questions in your daily life like when you were before 10 years old, you are a perfect fit. We want thinkers, not just doers. The PI is a highly curious person and would love to ask and discuss all kinds of silly questions with lab members that frequently bring us to new territories.

The McKinney-Freeman lab
Hematology

The McKinney-Freeman lab is focused on better understanding the fundamental biology of hematopoietic stem cells (HSC). HSC are currently the most therapeutically exploited adult stem cell compartment, used routinely to treat leukemia and hematologic (blood) disease via HSC transplantation. However, many patients that might benefit from HSC transplantation lack access to a suitable donor.

By better understanding the intrinsic and extrinsic factors that control the ability of HSC to home to, engraft, and repopulate the hematopoietic system after transplantation, we hope to design therapies targeted at improving the efficiency with which HSC engraft patients. This would allow us to expand access to this life-saving therapy by making it possible for more patients to take advantage of valuable sources of HSC for transplantation, such as cord blood, whose application is limited by small cell numbers. We recently completed a functional screen in which we identified 20 genes as novel regulators of HSC *in vivo* hematopoietic repopulating activity. We are currently working to dissect the cellular and molecular mechanisms by which these genes regulate the function of HSC.

We are also studying how chronic disease damages HSCs and their ability to sustain blood production throughout life. Here, we focus on sickle cell disease. Sickle cell disease is an inherited hemolytic anemia that results in vascular occlusions and systemic inflammatory stress. This causes organ damage, accelerated aging and repeated pain crisis. Recent studies reveal that the pathophysiology of sickle cell disease damages the bone marrow microenvironment that supports and sustains healthy HSCs. We are investigating replicative stress and DNA damage in HSCs isolated from both experimental models and individuals with sickle cell disease. We are also studying loss of function in the ability of bone marrow stromal cells isolated from individuals with sickle cell disease to support HSC function. Finally, in partnership with our clinical collaborators, we are investigating if the bone marrow microenvironment recovers its ability to support HSCs in individuals who have been cured of sickle cell disease via allogeneic bone marrow transplantation.

A student in our laboratory, depending on the exact project, may learn: flow cytometry, how to work with mice, how to work with and culture bone marrow patient samples, cell culture, molecular biology, molecular cloning, lentivirus production and in vitro and in vivo transplantation assays for HSC activity and transplantation.

The Hatley Lab

Oncology

PI: Mark Hatley, M.D., Ph.D., Director Molecular Oncology Division, Department of 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, four graduate students, a senior lab manager, and two gap-year technicians. The lab has a current Rhodes Summer Plus student and has had four 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.

The Zhou Lab

Computational Biology

Join the Zhou lab ProteinPaint team (https://proteinpaint.stjude.org/team/) to contribute to the development of a web platform for genomic/biomedical data visualization and analysis. The ProteinPaint began as a cancer mutation visualization tool (https://pubmed.ncbi.nlm.nih.gov/26711108/), and is now an umbrella platform spanning GenomePaint (https://pubmed.ncbi.nlm.nih.gov/33434514/), Neuro-Oncology portal (https://proteinpaint.stjude.org/?mass-session-id=SJPNET), and Survivorship Portal (https://survivorship.stjude.cloud/, manuscript in preparation). A portfolio of the software features are showcased at https://proteinpaint.stjude.org/. Major ongoing initiatives include NCI GDC (Genomic Data Commons) integration, St. Jude Survivorship Portal, Neuro-Oncology portal, and American Society for Hematology data portal, as well as numerous tasks on feature improvements and codebase hardening. We're developing software features to be adaptable for multiple data modalities, interoperable for feature integration, and accountable with scientific rigor, to support molecular and clinical data integration needs in cutting edge research. Fields of application include cancer genomics, single-cell omics, oncology, pharmacogenomics, population science, and epidemiology.

The student should be highly interested in exploring a career of software development in genomics and general biomedical research. No specific background or skills will be required, but the student must commit to intensive self-learning to become productive with our technology stack, including Linux, JavaScript, Node.js, R, Rust, and SQL. While on the team, the student will be exposed to ongoing projects, and has the opportunity to work on one or multiple projects depending on interest and priority. Depending on the project, the student will work alongside staff including PhD scientists and software engineers, and generally be embedded in the team. The student will join weekly team discussions and give progress reports, and participate in discussions with external collaborators including St. Jude Cloud, departments of Oncology, Epidemiology, Biostatistics, and NCI GDC.

The Loeffler Lab

Hematology

The Loeffler lab is focused on better understanding the fundamental biology of hematopoietic stem cells (HSC). The ability of HSCs to regenerate all blood cells lifelong is therapeutically used to treat leukemia and hematologic (blood) disease via HSC transplantation. However, only a very small number of HSCs can be isolated from a single donor. Low HSCs number thus limit the more widespread application of HSC transplantations because patients that could benefit from transplants lack access to a suitable donor.

By better understanding how intrinsic and extrinsic factors regulate HSCs differentiation and self-renewal, we hope to develop novel therapies that improve HSC transplantations. Knowing how to expand HSCs would allow us to overcome the critical bottleneck of low HSCs numbers in biomedicine and provide access to this life-saving therapy to tens of thousands of patients each year. We recently discovered that HSCs use Asymmetric Cell Division (ACD) to regulate HSC daughter cell fates. During ACD, cell fate determinants such as proteins and/or organelles are preferentially segregated into one daughter cell to instruct later cell behavior. We are currently working to dissect the cellular and molecular mechanisms by which HSCs regulate the segregation of these proteins to regulate HSC function.

We are also interested in better understanding the development and progression of hematopoietic diseases, such as leukemias. This work is crucial to treat the many thousands of cancer patients that are diagnosed each year and to prevent disease progression and relapse after therapy. Leukemia development starts with the acquisition of mutations in HSCs. These cells are called Leukemic Stem Cells (LSCs) and can remain undetected for decades in the body. LSC drive disease progression and often survive therapy because of their stem cell properties. Better ways to treat patients thus depends on the efficient detection and eradication of LSCs by identifying novel molecular marker and properties that can be targeted pharmacologically.

We recently developed for this purpose novel quantitative single-cell bioimaging that allows us to continuously monitor and quantify HSC and LSC marker expression and behavior for several weeks and cell generations. This system allows us to observe precise cellular dynamics with single-cell resolution that cannot be measured with cell and molecular biology techniques used by other labs. This includes, for instance, 1) the inheritance of factors during cell division; 2) changes in signaling pathway activity over time; 3) metabolic activity over time; 4) transcription factor dynamics; 5) cell cycle dynamics, and 6) chromatin modification dynamics.

This unique system allows us to measure precisely how events that happen today, affect HSC behavior tomorrow, a week, or a month from now. This system allows us for the first time to directly observe how LSCs survive and escape therapy. And these long-term observations allow us to study how epigenetic memory is created, inherited, and lost over many cell generations. Our work and our approach are unique in the USA. We leverage time and single-cell dynamics as novel features to better understand stem cell behavior in health and disease to develop novel therapies.

A student in our laboratory, depending on the exact project, may learn: flow cytometry, how to work with mice, bone marrow collection and dissection, cell culture, molecular biology, molecular cloning, lentivirus, bioinformatics, production and cutting-edge advanced microscopy of fixed and living stem cell populations.

The Heitzer Lab

Psychology

Andrew Heitzer, PhD
Pediatric Neuropsychologist
Instructor
St. Jude Children's Research Hospital

Dr. Heitzer is a neuropsychologist trained to examine brain-behavior relationships in various neurological conditions. His research focuses on 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 brain complications, including stroke and silent infarctions. He 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. Additional projects examine school readiness and the role of neurocognitive functioning in the transition from pediatric to adult care in sickle cell disease. Students will assist with literature review, data collection, and manuscript/presentation preparation. The student will attend weekly psychology, neuropsychology, and hematology didactics. Opportunities to learn and administer neuropsychological measures are available.

Completion of introductory courses in psychology, neuroscience, research methods, and statistics is preferred. Candidates with prior research experience are desired. The research experience is likely best suited for an individual interested in pursuing graduate school in clinical psychology or medical school.

The Selukar Lab

Department of Bone Marrow Transplantation & Cellular Therapy

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

Subodh Selukar, PhD

The Department of Bone Marrow Transplantation & Cellular Therapy (BMTCT) at St. Jude Children's Research Hospital is an internationally recognized center that works to fulfill St. Jude's mission to advance cures for pediatric catastrophic diseases through research and treatment focused on bone marrow transplant, gene therapy and immunotherapy. The center has pioneered a special type of transplant called "haploidentical" donation and also studies novel treatments using CAR-T cell therapy. By working with BMTCT's affiliated faculty statistician, Dr. Subodh 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 projects showcase the wide array of research under study: kidney toxicity outcomes for patients treated with CAR-T cell therapies, malignant disease outcomes for patients who received multiple transplants, and responses to vaccinations following transplant. These projects help inform future care of St. Jude patients and motivate 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.

The Krenciute Lab
Bone Marrow Transplantation & Cellular Therapy

2023 St. Jude-Rhodes Summer Plus Fellowship Program

Krenciute Laboratory

My laboratory is focused on developing effective immunotherapy approaches for pediatric brain tumors using engineered T cells. By modifying T cells with a chimeric antigen receptor (CAR) molecule, we can make them tumor-specific and train T cells to specifically recognize and kill tumor cells. This approach showed unprecedented success for hematological malignancies and now my team is working on establishing such an approach for brain tumors.

Projects include:

- Generating and optimizing CAR T cells to target brain tumor associated antigens
- Enhancing CAR T cell effector function by different genetic manipulations to render them resistant to tumor microenvironment
- Understanding the tumor microenvironment and CAR T cell biology in order to design superior immunotherapy-based treatments

Motivated, bright and ambitious students are welcome to join my team and work on exciting projects that involve designing, engineering, and testing CAR T cells to target brain tumor antigens. Through this process students will be engaged in critical thinking and will learn how to design, plan and perform experiments as well as analyze and present data.

Experience in the following techniques is preferred but not required:

- Cloning (PCR, Restriction enzyme cutting, In-Fusion cloning, Cut/Paste cloning)
- DNA propagation in bacteria and isolation
- Tissue culture
- Flow cytometry
- WB
- Transfection, transduction and transformation.
- Plasmid design using SnapGene

The Guenther Lab
Division of Molecular Oncology
Department of Oncology

St. Jude Children's Research Hospital

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.

The Ates Lab

Radiation Oncology

Adaptive Proton Therapy in Radiation Oncology

I am an assistant professor at the radiation oncology department of St Jude Children's Research Hospital. My training and research background involve radiation treatments of young children with cancer. At St Jude, we use an advanced technique called proton therapy, where we accelerate sub-atomic particles to the ranges that we could see the therapeutic effects of protons in tumor.

Radiation therapy is an interdisciplinary field of biology and physics. We have several projects for undergraduate science majors who are interested in learning more about radiation therapy, proton physics and radiobiology. Currently, we are working on a deep-learning based auto-segmentation of organs from Computed Tomography (CT) images. When the project is finished, it would substantially reduce the time we spend on manual contouring of organs for treatment planning. To make sure that the algorithm works as expected, we would need to compare automated organ segmentation against ground truth contours manually drawn by the dosimetrists or the physicians. Therefore, we plan to use several quantitative metrics to determine the performance and accuracy of the deep-learning based auto-segmentation.

We expect that the prospective student would run the finished algorithm on large amount of CT images from our patients, and help us design the testing tools, and aggregate the data in a scientific manner to present the algorithm's performance results to the broader audience. The required skillset would be the basic understanding of human anatomy, advanced algebra, basic level of radiation physics and programming skills in Microsoft Excel and/or MATLAB.

==========

Ozgur Ates, PhD, DABR
Assistant Member
St Jude Children's Research Hospital
Department of Radiation Oncology,
262 Danny Thomas Place
Mail Stop 210
Memphis, TN 38105
Phone: 901-595-2404
Email: ozgur.ates@stjude.org

==========

The Kodani Lab

Division of Center for Pediatric Neurological Disease
Department Cell & Molecular Biology Department

Rhodes College Summer Plus Program

Brain development involves the timely and coordinated expansion and differentiation of neuronal progenitors (stem cells) to form the highly organized layers of the mammalian brain. Many brain abnormalities, including microcephaly (small head and brain) are caused by the premature differentiation of neuronal progenitor cells, limiting the expansive potential of the growing brain. Microcephaly is a neurodevelopmental disorder defined by a head circumference (occipital frontal circumference) that is 4-5 standard deviations below the expected age-sex matched child. Individuals with microcephaly suffer from intellectual disability, intractable seizures and impaired motor movement that diminishes their quality of life. There are currently no measurable treatments for microcephaly individuals. My lab uses human genetics, mice to model the disease, omics-approaches, high resolution images, and biochemistry to uncover the etiological causes of microcephaly.

Through our collaborations with clinicians from around the world we've identified upwards of 200 individuals with brain malformations associated with inherited and *de novo* genetic mutations. Many of the mutated genes encode for proteins of unknown function. We hope to recruit motivated undergraduates from Rhodes College to work alongside talented senior researchers, postdocs and graduate students in my lab to uncover the underlying mechanism of human disease. Research projects will include microscopy, biochemistry, quantitative PCR, help with mouse brain analysis, cell culture of established cell lines and patient-derived cells, and openness to learn machine learning quantitative approaches (not required). We promote equal opportunities in the lab and welcome all scientists with and without laboratory training.

Andrew Kodani, Ph.D.

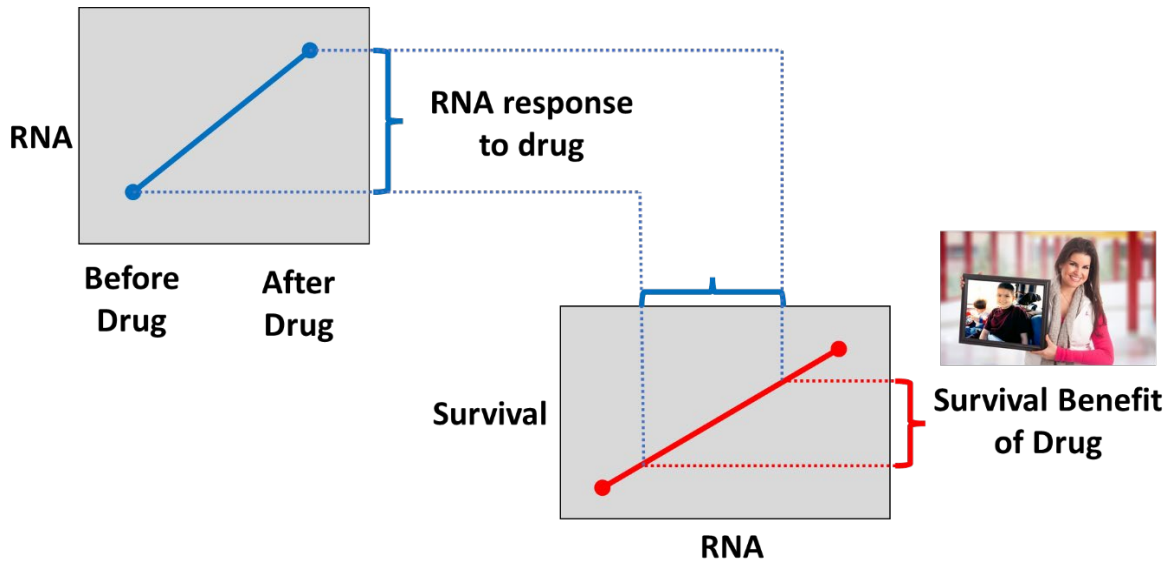
St. Jude Children's Research Hospital
Department of Cell & Molecular Biology
Center for Pediatric Neurological Disease Research

The Pounds Lab

Biostatistics

In Silico Drug Screening by Integrating Molecular Drug Response and Prognostic Association Data

In this project, the intern(s) will work under the guidance of Dr. Stan Pounds in Biostatistics to develop a data warehouse and software infrastructure to predict the cure rates of incorporating a new agent into chemotherapy combinations that have been previously evaluated in clinical trials for the treatment of various cancers. The completion of the project will provide a system to prioritize preclinical and clinical research evaluations of potential new chemotherapy combinations based on a direct computational extrapolation of patient benefit. The project will involve three major phases: (1) assembling a knowledgebase of the molecular (methylation, RNA expression) response of various cancer cells to a series of drugs from existing public data resources (such as St. Jude Cloud, Gene Expression Omnibus, Cancer Cell Line Encyclopedia, NCI60 cell line data, etc); (2) assembling a knowledgebase of the statistical associations of molecular characteristics with patient survival in clinical trials; and (3) substituting the molecular response profiles into the patient survival association models to empirically predict the patient survival that can theoretically be achieved by adding those drugs to the clinical trial chemotherapy combinations. The results of the final substitution calculation will be computational estimates of the survival probabilities of patients theoretically achievable by incorporating a new drug into a previously evaluated chemotherapy combination. Chemotherapy combinations with greatest estimates of patient benefit can then be prioritized for preclinical and/or clinical testing. The intern must have strong computer coding skills and knowledge of calculus and matrix algebra.

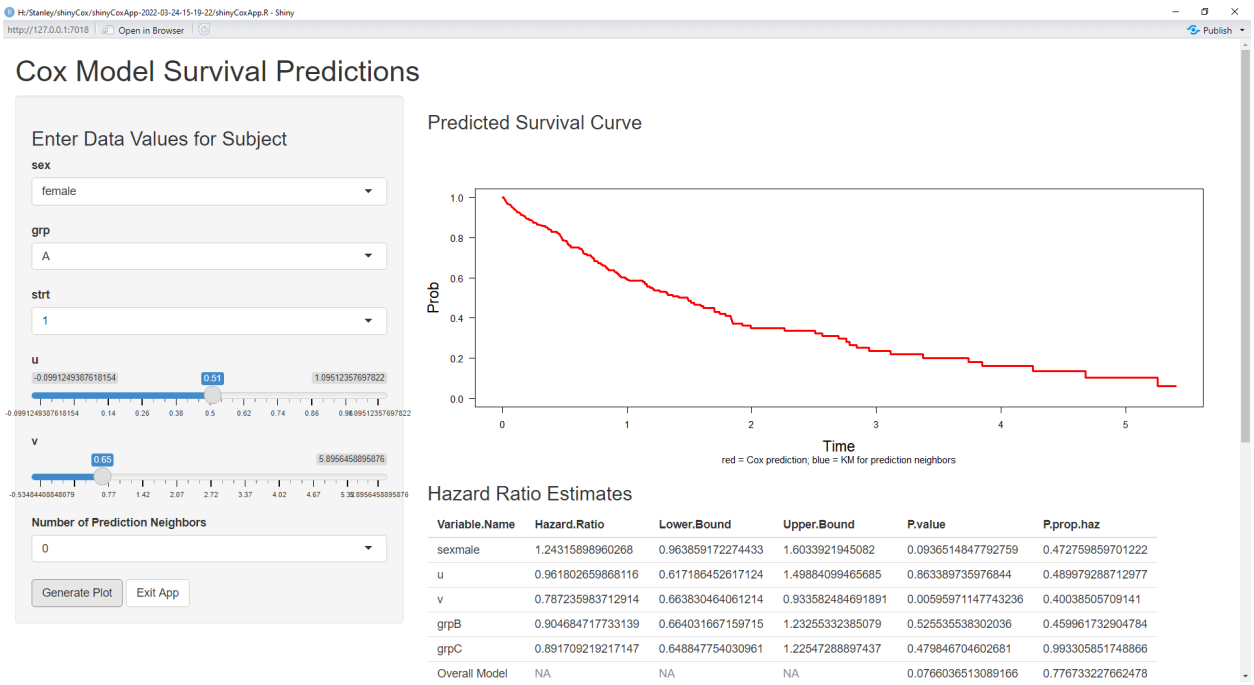


Graphical Schematic of Project: The student will assemble data sets that characterize the molecular response (such as RNA) to drugs and data sets that characterize the association of molecules (such as RNA) with patient survival in clinical trials. The molecular response estimates from the first collection of data sets will be substituted into the survival association models from the second collection of data sets

to extrapolate the theoretical survival benefit of adding a drug to the chemotherapy given in those clinical trials. This system will provide critical guidance to preclinical and clinical researchers for prioritizing drugs to evaluate in their research and is likely to be cited in future research articles.

Automated Development of Prognostic Score Calculators with Graphical User Interfaces

The intern(s) will work under the guidance of Drs. Stan Pounds, Yimei Li, and Subodh Selukar in Biostatistics to develop functions that automatically generate graphical user interfaces for prognostic score calculators based on proportional hazards and/or logistic regression models. These prognostic score calculators will have broad utility in oncology research by empowering biostatisticians to quickly represent statistical models of patient outcome in a modern dynamic media that is more accessible to clinicians and biologists than the traditional tables and graphs. The intern(s) will further develop our prototype function that accepts a fitted statistical model object as input and represents it as a prognosis calculator with a dynamic graphical user interface. The intern(s) must have knowledge and experience in coding and developing graphical user interfaces.



The purpose of the project is to empower biostatisticians to easily produce an outcome calculator like this for the models they fit to survival outcome data. This will be published as an R software package and research article.

The Mefford Lab

Center for Pediatric Neurological Disease Research

St. Jude Children's Research Hospital

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 uses cutting edge technologies including whole genome sequencing and genome-wide methylation arrays to identify disease-causing mutations. We then use genome-engineered cells and cells from patients to study the effects of mutations on gene expression, signaling pathways, and other relevant cellular processes. The cell models we develop, including stem cells and brain organoids, can be used to test potential therapies for specific genetic epilepsies. Project opportunities for an undergraduate student range from gene and mutation discovery to functional analysis in a cellular model of genetic epilepsy. Students will be paired with a senior lab member, so previous lab experience is not required. Upon completion of their studies, the student will have learned a set of cell biological and genetic techniques commonly used in biomedical research.

The Peng Lab

Structural Biology and Developmental Neurobiology

PI:
Peng, Junmin, Member (Professor)
Department of Structural Biology and Developmental Neurobiology
Director, Center for Proteomics and Metabolomics
(https://www.stjude.org/directory/p/junmin-peng.html)

Publication (>200 papers)
https://scholar.google.com/citations?user=vFzS-awAAAAJ&hl=en

Title
Omics-based Systems Biology to Human Disease

Description
The ultimate goal in biomedical research is to understand the molecular mechanism of life and disease and to develop rational therapeutic strategies for a cure. For decades, the main approaches are reductionism methods such as studying one or a few genes. Although those methods have contributed to our understanding of many basic principles, a comprehensive picture will not be captured until more integrative approaches are utilized. Recently, efforts in genomics, proteomics, metabolomics, and bioinformatics have made it possible to study all molecules in biological systems.

Our mission is to develop novel mass spectrometry-based proteomics and metabolomics technologies, systems biology approaches, and to apply these tools to biomedical challenges (e.g. Alzheimer's disease and cancer). We seek to obtain the full spectra of temporal omics data including protein modifications (e.g. phosphoproteome and ubiquitinome) from cellular and animal models as well as human clinical specimens. Network analysis and integration of such large-scale omics data with genome, transcriptome, interactome and phenotypic information offer a systems or holistic view, for unbiased identification of central disease gene/protein networks, functional modules and master regulators. Beyond big data analysis, we perform a series of functional experiments to validate the derived hypotheses. These studies provide novel insights into the pathogenesis for therapeutic intervention, and may discover disease biomarkers for precision medicine.

We also trained several previous students in the St. Jude-Rhodes Summer Plus Fellowship Program, who are now continuing to pursue advanced degrees. For example, Ariana Mancieri becomes a student in the Royal (Dick) School of Veterinary Studies (the Dick Vet) at the University of Edinburgh. David Vanderwall has recently accepted as an MD-PhD trainee at Harvard Medical School!

Requirement
Course of Chemistry, Biochemistry, Biology or Neurobiology

Lab of Agulnik
Global Pediatric Medicine

PI: Asya Agulnik, MD, MPH
Department: Global Pediatric Medicine

Cause of Death in Clinical Deterioration Events Among Children with Cancer Hospitalized in Resource-Limited Settings

Children with cancer frequently develop critical illness, particularly in resource-limited hospitals where material and human resources to manage critical illness are limited. Unfortunately, mortality among pediatric oncology patients with deterioration remains high, ranging from 10-30% depending on setting. In 2017, the Global Critical Care Program at St. Jude Global worked with regional stakeholders in Latin America to start Proyecto EVAT, a multidisciplinary quality improvement collaborative to improve the care of children with cancer who develop clinical deterioration. Over the past 5 years, Proyecto EVAT has supported the implementation of a Pediatric Early Warning System (PEWS) to improve early identification of clinical deterioration in over 80 collaborating hospitals in the region[1] (see https://global.stjude.org/en-us/pews-evat-report.html for mor information on PEWS). As part of participation in this collaborative, hospitals start a prospective quality improvement registry of clinical deterioration events occurring among children with cancer in their hospitals, which currently includes over 2500 events from over 80 hospitals. While prior work has shown a high mortality among these patients,[2] no dedicated work has been done to explore the cause of event mortality among these patients.

Project aims:

1) Describe the cause of death among hospitalized children with cancer who develop clinical deterioration.
2) Identify risk factors for cancer-related vs toxicity-related mortality

Student Perquisite Skills:

- Interest in global health research
- Detail-oriented
- Comfort working in Microsoft excel
- The student will work with our biostatistician on data analysis, so no coding or analytic experience is necessary, however basic understanding of statistics is helpful
- The data is originally collected in Spanish. While it will be translated to English, a basic knowledge of Spanish would be helpful, though not required.

References

1. Agulnik A, Gonzalez Ruiz A, Muniz-Talavera H, et al. Model for regional collaboration: Successful strategy to implement a pediatric early warning system in 36 pediatric oncology centers in Latin America. *Cancer.* 2022.
2. Agulnik A, Cárdenas A, Carrillo AK, et al. Clinical and organizational risk factors for mortality during deterioration events among pediatric oncology patients in Latin America: A multicenter prospective cohort. *Cancer.* 2021;127(10):1668-1678.

Labs of Baker and McNeil

Global Palliative Care and Division of Quality of Life and Palliative Care

Interested students will have the opportunity to work in two vibrant areas of St Jude Children's Research Hospital – the St Jude Global Palliative Care program and the Division of Quality of Life and Palliative Care.

The mission of the St. Jude Global Palliative Care Program is to attend to the suffering of children with cancer and their families regardless of prognosis or location through high-quality evidence-based medicine and the art of healing through compassionate and empathetic care. Our focus is on quality of life by addressing the physical, psychological, social, and spiritual suffering of patients, and family members. We do this by defining the current state of palliative care in underserved communities worldwide and driving interventions in collaboration with our global partners to relieve suffering of patients and families facing the challenges of pediatric cancer through culturally sensitive projects. These efforts inform the creation and implementation of standard operating procedures and policies at the regional/national level to optimize the provision of palliative care.

The Division of Quality of Life and Palliative Care is home to a comprehensive clinical palliative care program, a Memphis-wide home-based care program, a field-leading grief and bereavement program, a robust education program and an innovative research division. Students will have a variety of project-based and clinical experiences while working closely with thought leaders in the field of pediatric palliative care.

Interested students will learn mixed methods research including quantitative survey development and qualitative methodologies. Additionally, these students will be able to gain skills in improvement science in quality improvement and capacity building endeavors on a global scale and implementation science to understand critical features of these projects to understand key features required for sustainability and scalability. This research includes collaboration with our global partners and bereaved parents.

Knowledge of a second language is a helpful skill but not required to participate. Having a background in psychology, epidemiology, statistics, or principles of public health is recommended, but not required.

Justin Baker, MD, FAAP, FAAHPM
Department: St. Jude Global PalliativeCare Program
Division: Quality of Life and Palliative Care

Michael McNeil, MD, MPH
Department: Global Pediatric Medicine
Division: Quality of Life and Palliative Care

The Zhongbo Hu Lab

Oncology

Screening small molecular inhibitors of integrin VLA-5 to block the interaction between Ph+ ALL and their microenvironment

Acute lymphoblastic leukemia (ALL) is the most common type of cancer in childhood. Although the treatment result has been significantly improved during last several decades, ALL with certain genetic features is still hard to treat. One type of these high-risk type o leukemia is Philadelphia positive (Ph+) ALL. The incidence of Ph+ ALL increases with the patient's age. About 10-20% ALL in the adolescent and young adult (AYA) group is Ph+ ALL, which makes the relapsed and resistant leukemia population higher in this age group.

After tyrosine kinase inhibitors (TKI) have been used together with regular chemotherapy, the survival rate of Ph+ ALL patients also improved. The current thing challenging the oncologists is that up to 55% of Ph+ ALL and chromic myeloid leukemia which is also Ph+ develops TKI resistance sooner or later. One of the mechanisms of resistance is the bone marrow (BM) microenvironment makes the leukemia stem cell quiescent through integrin adhesion between the leukemia stem cells and BM endothelial cells. Integrin VLA-5 (α5β1, CD49e/CD29) plays an important role in hematopoietic cells functioning through adhesion as well as in promoting tumor angiogenesis and tumor metastasis. Molecules targeting VLA-5 can be rapidly developed into anti-inflammatory and anti-tumor pharmaceuticals.
Our preliminary research showed that blocking VLA-5 signaling or combining FAK inhibitors with TKI targeting BCL/ABL are good strategies to improve treatments in patients with Ph+ ALL. By altering Ph+ leukemia cell interactions with the microenvironment, we may increase their susceptibility to therapy targeting BCR/ABL (*Hu, Z & Slayton WB. Frontiers in Oncology, 2014; 4:112*). Since the X-ray crystal structure of VLA-5 ectodomain is published (*Nagae M, et al. J Cell Biol, 2012; 197: 131*), we will generate an atomic model of VLA-5 based primarily on the crystal structure of the extracellular segment of integrin VLA-5 using the SWISS-MODEL web server. The P1D6 epitope will be selected as the target for in virtual high throughput small molecule screening. The top scoring compounds will be screened in a solid phase assay (protein binding assay) for their ability to inhibit the binding of VLA-5 to fibronectin and in a cell adhesion assay inhibiting the binding of Ph+ ALL cells to fibronectin. Surface plasmon resonance (SPR) will be used to characterize the top hits. The lead compounds will be modified by the St Jude Chemistry Biology Therapeutics (CBT) program and tested in the leukemia xenograft animal model combining with TKI to show the preclinical effect. If successful, we will develop clinical trial to test the effect to efficacy in shortening the TKI treatment duration and decrease the chance of relapse in Ph+ ALL patients.

Zhongbo Hu, MD & PhD

Assistant Member, faculty, Department of Oncology Hospitalist Medicine Program

The Kriwacki Lab

Structural Biology

Project Title: Discovering how fusion oncoproteins form phase separated condensates and recruit other biomolecules into them

Background: Fusion oncoproteins (FOs) that arise from gene translocations (*e.g.,* gene A fuses with gene B) are drivers of poor-prognosis cancers, often in children. FOs often incorporate an intrinsically disordered region (IDR) from an endogenous transcription factor (parent protein A) and a DNA or chromatin binding domain from a second protein (parent protein B). IDRs derived from transcription factors have been shown to promote liquid-liquid phase separation (LLPS) in the nucleus with the transcription machinery, forming centers of high-level gene expression. We and others discovered that these so-called transcriptional condensates formed by FOs promote aberrant gene expression and drive oncogenesis. IDRs promote condensate formation via multivalent interactions, acting as scaffolds for the recruitment of other biomolecules. *We seek to understand how FO-derived IDRs promote condensate formation and how they mediate the recruitment of other biomolecules into condensates.*

We first identified IDRs in LLPS-prone FOs that promote phase separation by testing ~200 of them using the following *in vitro E. coli* screening platform. Individual IDRs were fused to eGFP and expressed in *E. coli*, followed by cell lysis and testing of the soluble fraction for condensate formation using confocal fluorescence microscopy. We scored IDRs that form round condensates in the lysate as LLPS-positive [LLPS(+)]. We recently extended our studies to test GFP-tagged IDRs for condensate formation in human HEK293T cells. In addition, we have begun purifying individual, LLPS(+) IDRs and characterizing their biophysical properties using turbidity assays, fluorescence microscopy, and circular dichroism (CD). We hypothesize that different LLPS(+) IDRs have distinct structural characteristics and will form condensates with distinct material, or fluid, properties (*e.g.,* viscosity and surface tension). In addition to studying individual LLPS(+) IDRs, we hypothesize that some will interact heterotypically with each other (*e.g.,* self with non-self). We seek to discover LLPS(+) IDR pairs that interact favorably (with each other) within condensates and to understand the “molecular grammar” underlying such interactions. A Rhodes SummerPlus Fellowship student will contribute to these studies, as follows.

1) **Express and purify differentially labelled IDRs for *in vitro* screening.** FO-derived IDRs will be either eGFP- or mCherry-labelled at the C-terminus for fluorescence detection and expressed in *E. coli*. We will start with 8 IDRs, and all possible binary combinations of these IDRs will be mixed and screened for co-partitioning. The student will use well-established column chromatography methods to purify the 8 different eGFP- or mCherry-tagged IDRs. Purity will be assessed using gel electrophoresis (*e.g.,* SDS-PAGE).
   The student will learn: How to express proteins in *E. coli* and purify them and analyze purity using SDS-PAGE.
2) **Evaluate co-partitioning of pairs of IDRs *in vitro*.** Pairs of purified IDRs, one tagged with eGFP and the other with mCherry, will be mixed in all possible combinations under conditions that prevent condensate formation. After mixing the two IDRs, condensate formation will be triggered by changing the solution conditions. Condensate formation will be monitored using turbidity assays and co-partitioning of IDRs will be quantified using confocal fluorescence microscopy.
   The student will learn: How to perform phase separation assay with pairs of purified IDRs using turbidity measurements and confocal fluorescence microscopy.
3) **Co-transfection of pairs of differentially labelled LLPS-prone IDRs in HEK293T cells.** Two LLPS-prone IDRs in CL20 expression plasmids, one tagged with eGFP and the other with mCherry, will be co-transfected into HEK293T cells. Co-partitioning of IDRs will be evaluated based on co-localization of the two proteins within condensates using confocal fluorescence microscopy.
   The student will learn: Basic cell culture techniques, cell transient transfection with plasmids, and live cell imaging using confocal fluorescence microscopy.

Impacts/Future Directions: Aberrant transcriptional condensates formed by FOs are known to contain many other proteins that contribute to promoting aberrant gene expression. However, how proteins and other biomolecules are recruited into FO-driven condensates is poorly understood. The studies described above will reveal fundamental principles explaining how pairs the FO-derived IDRs become co-localized within condensates both *in vitro* and in cells. The student will learn commonly used lab techniques and take their first

steps to being an independent member of the Kriwacki lab. Finally, these experiments will provide a foundation for more detailed biophysical characterization of FO-derived IDRs using NMR spectroscopy and small-angle x-ray scattering (SAXS) that will be performed by others in the lab.

The Wilson Lab

Radiation Oncology

Revealing associations between radiation therapy exposures and long-term side effects in survivors of childhood cancer

Advancements in cancer care in recent decades enable more children than ever to reach long-term survival. Unfortunately, these survivors are also at a high risk for wide-ranging chronic health conditions as they age, many of which are associated with the very treatments that saved their lives. Radiation therapy is one of the most commonly used tools in the treatment of cancer, largely thanks to its many benefits including that it is safe, effective, and one of the least invasive of the cancer treatment options. At the same time, radiation exposures are known to be associated with many side effects experienced by long-term survivors. As a result, radiation therapy treatments are always a balancing act where we try to deliver the maximum therapeutic benefit, or chances of tumor cure, for the lowest risk of side effects.

Radiation therapy is a local treatment, as opposed to a systemic treatment like chemotherapy, and modern technologies empower us to precisely target carefully designed volumes of tissue in each patient while specifically sparing others. To fully benefit from this capability, however, we now need to improve our knowledge of which organs and tissues are most sensitive to radiation damage. My research uses modern computational tools, like data mining, to interpret radiation therapy treatment and follow-up data and identify associations between radiation exposures and long-term health effects. With deeper knowledge of the link between radiation exposures and biologic effects, we will be able to effectively prioritize our treatment designs to improve healthy function while maintaining tumor kill.

During the Rhodes Summer Plus Program, you will learn and gain experience in:

- Radiation therapy treatment workflow and practices
- Radiation therapy treatment planning data types and formats
- Organizing and interpreting long-term follow-up data
- Using commercial and in-house computational tools (e.g., MATLAB, coding in lua and python)
- Performing voxel-based statistical analyses
- Verbal and written science communication

Lydia J Wilson, PhD
Department of Radiation Oncology, St. Jude Children's Research Hospital

Lab of Cai Li

Biostatistics

Precision medicine for pediatric oncology based on statistical and machine learning methods

Pediatric cancer survival rates have been continuously improved over the past decades. However, different treatment options, health disparities, and even genetic predisposition may lead to distinct late effects greatly impacting patients' quality of life, such as neurodevelopment of medulloblastoma (brain tumor) survivors, general intelligence of acute lymphocytic leukemia survivors, and graft vs host disease after hematopoietic stem cell transplantation. To this end, it is imperative to study the interaction between treatment regimens and patient's heterogeneous profile that is crucial for developing personalized treatment strategies and prognostic models to inform early intervention. Dr. Li and his group have been working on developing innovative computational tools and analyzing longitudinal neuroimaging and high-dimensional longitudinal biomarkers to further our understanding of catastrophic pediatric diseases.

In this project for Summer Plus students, machine learning techniques, such as tree- and random-forest-based methods, deep learning, regularized and nonparametric regression, will be promising analytical tools to decipher complex and high-dimensional imaging and longitudinal biomedical data, with the goal of building up machine learning-based personalized risk prediction models. We will exploit the PI and his collaborators' extensive expertise on nonparametric statistical/machine learning, statistical computing, bioinformatics, and rich data source of pediatric cancer survivorship at St. Jude. 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.

Cai Li, Ph.D., Assistant Member
Department: Biostatistics

The Derecka Lab

Hematology

The major focus of Derecka laboratory is to dissect the "seed and soil" hypothesis, which explains how blood cells communicate with their environment in the bone marrow. We have identified several genes that are important for this process. To further study the crosstalk of the blood stem cells with their surrounding microenvironment, we are targeting these identified genes in the bone marrow microenvironment of model organisms. We will then be able to determine how the blood stem cells function and gene expression changes when their microenvironment has been compromised. Furthermore, the function of the cells that form and maintain the bone marrow microenvironment is often altered in disease conditions such as blood cancers. A prime example of such a functional alteration is observed in myelofibrosis, a rare and debilitating bone marrow cancer. In myelofibrosis, the communication between the environment and blood cells is perturbed and the microenvironment cells produce an excessive amount of scar tissue (fibrous) in the bone marrow. Due to the bone marrow scarring, normal production of blood cells is disrupted, leading to anemia and fatigue. Ultimately, more than twenty percent of myelofibrosis patents will develop an aggressive secondary leukemia. Therefore, a better understanding of the interaction between blood stem cells and the bone marrow microenvironment is critical for innovative and curative approaches to many bone marrow failure diseases. Research into the communication between the blood cells and their environment will allow us to interrupt scar tissue formation in the bone marrow, preventing the destruction of new blood cell development and alleviating the symptoms seen in myelofibrosis patients. Our work will contribute to the understanding of blood formation and provide insights into mechanisms that lead to blood diseases such as myelofibrosis and leukemia.

Current projects ongoing in our laboratory involve mouse models, tissue culture and variety of molecular biology techniques including CRISPR-based genome editing, siRNA-mediated knock downs of genes, and retroviral expression of genes. A student in our laboratory will have an opportunity to learn how to isolate blood stem cells and mesenchymal stromal cell from the bone marrow of mice; how to differentiate mesenchymal stromal cells to fat, bone, and cartilage; how to perform co-culture experiments of blood stem cells with mesenchymal stromal cells. Moreover, a student will be able to perform DNA and RNA isolation, PCRs, genotyping of mouse tissues, western blot analysis to estimate protein levels in cultured cells and assist with flow cytometry experiments. Additionally, a student will have a chance to present and discuss their data with a group of scientists during lab meetings.

Lab of Gibson
Cell & Molecular Biology

Mapping Chromatin Interaction Networks in Human Cells

To fit into cells, our genome must become compact, but remain amenable to DNA-templated processes and differential regulation. Errors in this packaging can affect how genes are transcribed, leading to developmental abnormalities and cancer, and suggesting an improved understanding of this process can impact the treatment of human disease. In my lab, we want to understand how different chromatin assemblies form to package and regulate genome functions.

We are mapping the network of protein, RNA, and DNA interactions unique to each of these chromatin assemblies, which is essential to understand their construction. This project will provide training in cutting-edge chemical biology techniques (click chemistry) as well as practical instruction in next generation sequencing analysis, all while making advances in our understanding of genome structure. Students will collaborate with senior scientists to generate and analyze proteomic and genomic datasets from cultured human cells, providing new insights into how our genome is packaged and improving outcomes in human disease.

Requirements: Completion of a course in either Biochemistry or Cell Biology or Molecular Biology is strongly recommended, but not required.

Bryan Gibson, PhD
Department: Cell & Molecular Biology

Lab of VanGilder

Diagnostic Imaging

Rhodes College's students are invited to gain acknowledge and experience in the Multimodal Functional Brain Imaging and Neurorehabilitation Hub at St. Jude Children's Research Hospital. In our group, we focus on understanding the neural basis for cognitive problems that arise due to cancer, cancer treatment, or other catastrophic diseases.

We employ multiple non-invasive neuroimaging modalities to evaluate brain activity in order to better understand neural processes underlying normal and abnormal functioning. In addition to the well-known magnetic resonance imaging (MRI) for viewing brain structures and anatomy, functional MRI (fMRI) is used to measure the activation and connectivity of brain regions during rest or cognitive tasks. We can record the activity of specific neurotransmitters with the use of functional magnetic resonance spectroscopy (fMRS). Both of these techniques utilize magnetic resonance scanners located at the St. Jude campus. Additionally, we utilize more portable imaging modalities such as functional near-infrared spectroscopy (fNIRS) to measure the hemodynamic activity of the cerebral cortex using infrared light shined through the scalp. Our high-density electroencephalography (HD-EEG) system uses 128 electrodes placed on the surface of the head to measure electrical activity in the brain. In addition to neuroimaging, our group is also interested in neuromodulation to improve brain function. This is a process whereby we non-invasively modulate neural activity using low-intensity focused ultrasound.

We are using these tools in a number of projects investigating how brain activity is affected by childhood diseases:

In one project, we are interested in sleep quality in pediatric oncology populations. We analyze the HD-EEG signals to identifying different signatures of sleep electrophysiology through signal processing, and utilizing machine learning/artificial intelligence approaches for detection or classification of sleep stages. Rhodes college students interested will learn how to record brain signals, process, analyze, and interpret the results in the context of sleep related neuroscience. Skills needed would be an understanding of MATLAB/python programming, some basic understanding of time-series signals, and an interest in electrophysiological brain signals.

On another project, we are interested in the functional connectivity of brain regions involved in cognitive processing. We have collected fMRI data from patients who have undergone treatment for acute lymphoblastic leukemia (ALL) and would welcome students who want to participate in the analysis and interpretation of the data. We recorded neural activity while patients performed tasks in the MR scanner that tested cognitive domains such as working memory and attention. We are interested in how treatment for ALL has impacted the brain networks involved in the cognitive processes. Students from Rhodes will learn how to process, analyze, and interpret fMRI data. They will learn how fMRI studies are designed and how imaging data can be used to better

understand brain function. Students should have a working knowledge of MATLAB programming, competency in file/data management, math skills, and interest in data analysis. Students interested in fMRI studies, neuroanatomy and physiology, cognitive processing, and computational image analysis are encouraged to apply.

In other project, we use real-time fMRI and fMRS in a closed-loop system enabling participants to modulate their brain activity using neurofeedback with the purpose of improving cognitive processes that may be impaired in the pediatric oncology population. Rhodes students interested will learn how to acquire MR brain images, how to process and analyze them computationally, and how to interpret them. They will gain experience in real-time neuroimaging setups, important for neurofeedback approaches to brain neuromodulation. Interested students should have some experience with MATLAB programming and some exposure to signal analysis.

Additionally, our group is interested in exploring focused ultrasound stimulation to modulate neural activity in specific brain regions with the goal of improving functioning on cognitive tasks. This work is still in the preliminary development stage, and Rhodes students could help us develop computer models of the spatial extent, precision, and intensity of ultrasound stimulation using CT scans of rodent brains. We are in the early stages of developing an experiment wherein we deliver focused ultrasound stimulation to rodents' frontal cortex and assess the effects using fMRI and fMRS. This work would require students to be capable in MATLAB programming, interested in computer modelling, some very basic understanding of energy transfer, and interested in neuroanatomy.

Paul VanGilder, PhD
Department: Diagnostic Imaging

Lab of Margolis

Infectious Diseases

Research project:

Antibiotic resistant organisms continue to be a problem despite stewardship efforts to limit to how much antibiotics we are all exposed. All of us are coated in and colonized with trillions of microbes (bacteria, viruses, etc.). The collections of these different kinds of microbes that form complex communities are called the "human microbiome." The microbes that live in the gut are especially important as they perform vital functions such as utilize undigested food components and produce essential metabolites, train immune cells, and stimulate intestinal maturation. One of the most important roles they play is in excluding 'bad' bacteria, including multi-drug resistant organisms. The Margolis lab studies how these collections of bacteria that live within the human gut can interact with multi-drug resistant organisms- some help them to survive and others competitively edge these enemies out.

The project will focus on the role of the microbiome in stopping colonization Vancomycin Resistant Enterococcus (VRE). It will have two components: one characterizing VRE plasmids and determining the role of these plasmids with VRE strains in competing in a diverse community. This will involve culturing anerobic communities, isolating plasmids, learning how to handle sequences (bioinformatics in microbiome, plasmid sequencing, etc), antibiotic resistance testing and genetic manipulation of VRE isolates.

Ellie Margolis MD, PhD
Department: Infectious Diseases

The Jun Yang Lab
Surgery

Dissecting and targeting cancer metastasis

Lung metastasis is one of the leading reasons causing death in patients with high-risk liver cancers and other solid tumors. However, what drives primary cancer cells to spread to distant organs remains elusive. How to target metastasis is enormously challenging due to our incomplete understanding of the mechanism. Jun Yang laboratory in the Surgery Department is tackling these important and clinically relevant questions, thereby developing novel therapies for high-risk patients who run out therapeutic options, in addition to his other focuses in epigenetics (Science Translational Medicine 2022; Journal of Medicinal Chemistry 2022; Cell Reports 2022; Science Immunology 2022; Science Advances 2021; Nature Communications 2021; iScience 2021, Genome Biology 2021). By using cutting-edge technologies including single-cell RNA-sequencing, spatiotranscriptomics, proteomics and metabolomics, as well as epigenic and functional genomics approaches, Jun Yang laboratory will ask the following questions using their newly developed liver cancer and rhabdomyosarcoma models. (1) *What are the drivers of lung metastasis?* This specific aim will be investigated by genome-wide CRISPR screening in combination with validation by gain-of-function and loss-of-function studies. (2) *What are the molecular mechanisms of lung metastasis drivers?* This specific aim will be investigated by using a variety of sophisticated techniques and molecular tools in combination with disease models. (3) *How to block lung metastasis?* This specific aim will be investigated by using genetic and pharmacologic approaches, and test new targeted therapies and combination therapies in disease models. The students in The Summer Plus Program who are interested in Jun Yang's laboratory have to meet the minimum requirements as follows. (1) Highly motivated, (2) Dedicated team member, (3) Excellent communication skills, (4) Knowledge in biochemistry and cell biology, (5) Some previous benchwork experience and basic techniques such as cell culture and pipetting.

Lab of Orr

Pathology

Accurate pathologic diagnosis and risk stratification are essential for making the best therapy decisions for children with cancer. Tumor diagnosis and risk assessment has historically relied on evaluation of the tumor by a pathologist under light microscopy. Refinement of this process has occurred through recognition of additional histologic patterns and by integrating results from testing modalities such as cytogenetics, immunohistochemistry, and nucleic acid sequencing. More recently, Genome-wide DNA methylation signatures have been established as reliable biomarkers, which can refine the classification of tumors and aid in the clinical diagnosis. The goal of our research in the Orr lab is to uncover molecular tumor subgroups in pediatric tumors. We accomplish this goal by creating and applying computational tools and machine learning models to genomic data for patient samples. The specific summer project will involve processing and analyzing tumor DNA methylation profiles obtained from Illumina Infinium 850K arrays to establish molecular classes within pediatric brain and solid tumor types. These molecular classes will be used to improve supervised machine learning models for clinical diagnosis. These studies contribute to the ultimate goal of identifying novel molecular biomarkers and developing models for prognostic and therapeutic risk assessment of pediatric cancer patients.

As a mentee of the Orr lab, students are required to have prior programing knowledge in either R or Python. Although it is not required, students are encouraged to acquire some background in molecular biology. Students will be mentored by experienced scientists in pathology, bioinformatics, and machine learning. After completion of the mentorship program, students are expected to gain greater understanding of epigenetic regulation in tumors, bioinformatics skills to analyze DNA methylation data obtained from high throughput technologies such as microarrays and/or sequencing, and how informatic modeling techniques can be used to improve clinical diagnostics.

Brent Orr, MD, PhD
Department: Pathology

Lab of Hai Dao

Chemical Biology & Therapeutic

The Dao lab at St. Jude Children's Research Hospital

Research Description:

Despite having the same genetic makeup, 37 trillion cells in the human body can be divided into 200 different cell types that perform a wide variety of functions. The organization of genomic DNA into chromatin is the catalyst for this diverse cell identity and function, and abnormal chromatin processes can cause numerous diseases, including cancer. Chromatin regulation involves multi-step chemical reactions that often result in the dynamic reorganization of a chromatin's structure, which impacts the regulation of gene expression. The Dao lab uses chemical probes, engineered enzymes, and synthetic chromatins to dissect and manipulate these processes and understand their roles in normal and disease states.

Students in the lab will have hands-on training in organic synthesis, bioconjugation, macromolecule assembly, molecular cloning, protein expression, mammalian cell culture, proteomics, and genomics. Students are expected to have general knowledge of chemistry, biochemistry, or molecular biology.

Hai Dao, PhD
Department: Chemical Biology & Therapeutic

Lab of Jiyang Yu
Computational Bioloby

Yu Lab Research Overview (https://www.stjude.org/research/labs/yu-lab.html)
Our lab leverages expertise in computational and experimental biology, utilizes multi-omics technologies including single-cell and spatial omics, and collaborates with biologists, immunologists, and clinicians to explore the intracellular and intercellular networks within and between cells in complex systems and diseases (e.g., tumor and tumor microenvironment) and develop therapeutic strategies targeting the underlying hidden drivers to improve patient outcomes. Below are a few example proposals that might be interesting for students at Rhodes college.

Project 1: Single-cell and spatial omics integrative analysis for novel therapeutic discovery of ATRT
Atypical teratoid/rhabdoid tumors (ATRTs) are among the most common aggressive brain tumors in infants. Approximately 70% of all cases arise in children younger than 1 year of age and over 90% of cases occur before 3 years of age. Overall survival of ATRT patients is poor with median survival around 17 months despite intensive therapies including surgery, radiation, and chemotherapy. Thus, a more robust understanding of the mechanisms driving this set of cancers is vital to improving patient treatment and outcomes. The genetic hallmark of ATRTs are mutations in SMARCB1 and rarely SMARCA4, two components of the SWI/SNF chromatin remodeling complex. However, genome-wide methylation profiling and RNA sequencing studies have revealed the existence of heterogeneity of ATRTs, which indicated the complexity of tumorigenesis, and microenvironmental features in ATRTs. In our lab, we used a combination of single-cell gene expression, chromatin accessibility, and spatially resolved transcriptomics to study the cell-type-specific changes in gene regulation, providing an integrated spatial architecture and tumor-TME interactions in ATRTs, which potentially improve the understanding of ATRT and to identify more effective targets for molecularly based therapies.

Project 2: Spatial multi-omics technology development and analysis
Spatially resolved transcriptomics, as the method of 2020 nominated by Nature, has been booming in recent years. Multiple technologies and algorithms have been developed to measure and analyze expression levels of all or certain genes across tissue space with different angles. In general, current spatial transcriptomics technologies can be categorized into two major types. One is based on the next-generation sequencing (NGS) method, where unique barcodes are used to label spatial positions across tissue space, to obtain the entire transcriptome as final outputs (e.g., 10X Visium, DBiT-Seq). The other uses imaging-based technology to obtain single-cell level resolution image of entire tissue space, where interested gene/protein sets are labeled using fluorescence tagged antibodies/probes for spatial locations demonstration (e.g., CODEX, CosMx, 10X Xenium). Alzheimer's disease (AD) is the most common type of dementia. To better study the pathogenesis of AD, we propose to profile the AD mouse model using both spatial transcriptomic technologies (10X Visium, CODEX, CosMx, and 10X Xenium) and use in-house computational algorithms to analyze the results. Analysis and integration of data from these two types of technologies could precisely restore spatial location of interested cells within tissue space and generate accurate spatial cell-cell communication networks. Students will participate in bench experiments to learn how to prepare and profile mouse samples and study basic computational analysis pipelines. Basic understanding of biology is required.

Project 3: Single-cell analysis of lentil-viral gene therapy

Recent advancements of single-cell profiling provide an opportunity to dissect the interactions between various cell types in bone marrow, a complex microenvironment that coordinates hematopoiesis, i.e., the formation of blood cellular components. Tremendous research efforts have been spent on understand the complex developmental process in the light of health and disease. X-linked severe combined immunodeficiency (X-SCID) is in immunodeficiency disorder in which the body produces very few T cells and NK cells. An on-going clinical trial at St Jude has shown that gene therapy can safely correct the immune systems of infants with X-SCID. To better characterize the therapy at a molecular and cellular level, we profiled the bone marrow of two patients using scRNA-seq and scATAC-seq. Following the data, we propose a computational project that study the patients' bone marrow from various perspective, including cell-type composition, developmental trajectories, and cell-cell communications in hematopoietic niche, etc. The student is expected to learn the standard computational tools and in-house algorithms in single cell analysis and apply them to perform data analysis. Basic understanding of biology is required, and the student should be proficient in at least one programming language, preferably R.

Project 4: Design and develop visualization tools to effectively transform the analysis results of system biology related algorithms

Current research often involves the large-scale of omics data. Meanwhile, lots of system biology related algorithms have been developed for deep data mining and investigation. However, the analysis results of those algorithms are often hard to explain to researchers with pure biology background. Based on the NetBID (Du et al Nature 2018, an existing algorithm for hidden driver analysis), develop a shiny app that could load in analysis results for different projects, and display detailed information for all hidden drivers. The app will include:

- Display for the detailed information for each hidden driver
- Visualization plots for the targets of each hidden driver
- Visualization plots for the selected list of hidden drivers, e.g., bubble plot, functional enrichment plot, heatmap plot
- Search engine to find the driver or the targeted genes
- Automatic report generation for the selected list of hidden drivers
- Documentation for the usage

Project 5: Combination therapies for high-risk medulloblastoma

Medulloblastoma (MB) is the most common type of pediatric brain tumor. For high-risk MB patients, standard multimodal treatment failure and relapse occur in up to one-third of patients with 90% of patients eventually dying in 5 years post relapse. Group 3 (G3) MB is the deadliest form of the disease with the worst prognosis and highest metastatic rate, for which novel treatment is urgently needed. G3 displays complex genetic, epigenetic and gnomic abnormalities, making this subtype less susceptible to targeted therapies. We hypothesize that applying network-based systems biology analyses to identify hidden drivers in G3 and guide drug combination screens will minimize drug resistance and improve outcomes for high-risk G3 MB. We will integrate systems biology, high-throughput drug screening, and multi-omics approaches to accelerate the process of tailored combination therapy for G3 MB. The student will apply cutting-edge bioinformatics techniques to analyze large data sets from in vitro drug screening, PDX models, and MB patients. Primary tasks will include in vitro cell viability assay, analyzing both in-house and public drug screening data, bulk RNA-seq and single-cell RNA-seq data, and creating creative visual summaries of the data. Additional responsibilities will include exploring public databases (i.e. Depmap, Drugbank, TCGA), keeping up to date with scientific literature, and presenting in meetings.

Lab of Mullighan and Iacobucci

Pathology

Single cell genotypic and phenotypic analysis of measurable residual disease in acute lymphoblastic leukemia

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 acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), and develop experimental models to gain mechanistic insight into the pathogenetic basis and 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 genome libraries, and preclinical modeling in genetically engineered mice and patient derived xenografts. Although cure rates now exceed 90% in children with ALL thanks to risk-adapted therapy and improved supportive care, relapses still occur in 20% and are associated with a poor outcome. Detection of early measurable residual disease (MRD) is crucial to monitor disease burden, predict relapse, assess initial treatment response and define MRD-based risk groups. Current approaches to define MRD include cytogenetics, flow cytometry, PCR-based tools, and next generation sequencing methods, which held higher sensitivity. However, they fail in assessing the order of acquisition of mutations and dissecting clonal heterogeneity at the single cell level under therapeutic pressure. In this study, we aim to use single cell genotypic and phenotypic analysis by a custom ALL target panel for over 300 genes and Tapestri instrument (Mission Bio) of measurable residual disease of ALL samples at diagnosis and during therapy (Day 15 of therapy and end of induction) to study mutation acquisition, ALL clonality and detection of early clones responsible for high MRD levels and/or relapse. Correlation of single-cell sequencing data with clinical features and results from conventional molecular assays will provide insights for systematic genomic analysis of the MRD samples in clinical setting. Our lab has already demonstrated the feasibility of this single-cell approach and showed that in B-ALL lineage-related mutations (e.g. *ETV6, IKZF1*, and *PAX5*) occur early during disease evolution, while kinase-related mutations (e.g. *FLT3, PTPN11, NRAS, KRAS*) are secondary and, most frequently, mutually exclusive events.

Skills

In this role, the student will have the opportunity to pursue research of the biology of genetic alterations in acute leukemia by using cutting-edge approaches. To succeed in this position, the student should have demonstrated proficiency in molecular biology, molecular cloning, mammalian cell culture, functional genomic screens, single cell approaches, immunoblotting, in vitro and in vivo drug screening and in vivo modeling of cancer/leukemia. Additional required skills must 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.

Lab of 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 levels of their specific substrates and can result in disease processes. The speckle-type POZ protein (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., how SPOP recognizes specific substrates. 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.

Lab of Blair

Chemical Biology and Therapeutic

Reprogramming biology using chemical reactivity.

What we do: Synthetic organic chemistry has long been an expert driven process; however, change is on the horizon. Many advances in autonomous programmable chemical synthesis suggest that those previously excluded from innovating on the molecular scale will now be empowered to use their scientific curiosity in the pursuit new molecular functions. In the Blair laboratory we are at the forefront of this industrial revolution for molecule making. We recently created an automated synthesis machine and are now scaling this technology to provide broad on-demand access to small organic molecules. Building on this success we are creating a unified pipeline for making molecules and finding biological functions. We are specifically interested in leveraging chemically reactive small molecules to activate or deactivate biological machinery. The study of this type of reactivity involves aspects of organic chemistry, physical organic chemistry, and chemical biology.

What you should expect: The intersection of our personal histories creates the melting pot of ideas and experiences which lead to the best science. So, expect a flat structure for scientific discourse where you will have a voice in lab meetings and scientific discussions. We take mentorship of the next generation of scientists seriously; you will be paired with a senior lab member (post-doctoral or above) and receive regular input from the lab head. We will match you with a research project which fits your developing personal narrative, so when you apply to graduate school you can present a complete story to the outside world. Previous students have published research articles and are now graduate students at Stanford, Caltech, UCSB, and Scripps (FL). Please reach out to Dr Blair if you want to know more about the lab.

What skills could I learn: The science of covalent protein inhibition, synthetic organic chemistry, automated chemical synthesis, LC-MS, NMR.

What we expect from you: You are enthusiastic about doing rigorous science. Consistency is key to productive research; we expect you will be predictable in lab attendance.

Recent publications featuring **Undergraduate Mentees**:

Chen PJ, **Kelly AM**, Blair DJ, Burke MD*
Preparation of MIDA anhydride and reaction with boronic acids
Org. Synth. **2022**, *99*, 92 doi: 10.15227/orgsyn.099.0092

Blair DJ*, **Chitti S**, Trobe M, **Kostyra DM**, Haley HMS, Hansen RL, Ballmer SG, Woods TJ, Wang W, **Mubayi V**, Schmidt MJ, Pipal RW, Morehouse GF, Palazzolo Ray AME, Gray DL, Gill AL, Burke MD*
Automated iterative Csp^3-C bond formation.
Nature **2022** *604*, 92 doi:10.1038/s41586-022-04491-w

Kelly AM, **Chen PJ**, Klubnick J, Blair DJ,* Burke MD*
A mild method for making MIDA boronates,
Org. Lett. **2020**, 22, 9408. doi: 10.1021/acs.orglett.0c02449.

Contact: Daniel.Blair@stjude.org https://www.stjude.org/blair

Lab of Bagga

Diagnostic Imaging

Metabolic Imaging Research Lab (Puneet Bagga, PhD)

Non-invasive metabolic imaging can provide critical insights into cellular and tissue function in health and disease. At the Metabolic imaging research lab, we develop clinically feasible magnetic resonance imaging methods for evaluate cellular and tissue metabolism for biomarker discovery and therapy design. Metabolic reprogramming is a hallmark of cancer. The reprogrammed pathways contribute to cancer progression by excessive cell proliferation, cell survival and immune evasion. The importance of studying cancer metabolism is emphasized by the fact that non-invasive imaging tools and therapeutic strategies in cancer exploit the altered metabolic states in tumors. The metabolic imaging lab uses metabolomics, metabolic flux analysis, cell biology and patient derived xenograft models of cancer to study how tumor cells metabolize small molecules including glucose, acetate, and glutamine, build macromolecules and proliferate, and maintain cell survival and cellular energetics in severe microenvironment. We develop clinically translatable metabolic imaging techniques using multiparametric MRI, proton magnetic resonance spectroscopy (^{1}H MRS), multinuclear MRS (^{13}C/^{2}H/^{31}P MRS), and molecular MRI to identify predictive biomarkers correlating with altered metabolism. Additionally, we perform stable isotope tracer analysis *in vitro* and *in vivo* in patient derived xenograft (PDX) models to potentially drug targetable metabolic pathways for enhancing therapeutic efficacy.

The ideal candidate should be a motivated to work in a highly collaborative environment. As a part of the metabolic imaging hub, we are proud to have a very diverse collaborative efforts on the fields of pediatric cancers and neuronal disorders. During the Rhodes Summer Plus Program, the candidate will be mentored and trained in:

1. Acquiring, processing, and analyzing MRI/MRS data in preclinical and clinical settings.
2. Performing in vitro and in vivo stable isotope tracing experiments for metabolic flux analysis.
3. Writing abstracts, manuscripts, and scientific reports.
4. Presenting scientific findings at group/departmental meetings and Journal club.
5. Perform research in biomarker discovery in pediatric cancers, survivorship, and neuromuscular disorders.