St. Jude Children's Research Hospital®
Finding cures. Saving children.

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Scientific Report 2019

Translating Science into Survival

St. Jude Children's Research Hospital®
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Scientific Report 2019

St. Jude Childrens Research Hospital

Behind the Cover

The cover depicts the 3-dimensional structures of proteins and drug molecules inside a cell. During a catastrophic disease, the functions of proteins and other biomolecules change. Structural biologists use various sophisticated techniques to study the structural basis of those deleterious changes and determine the best therapeutic strategy. The Department of Structural Biology is expanding to become the world's premier center for structural analyses and imaging of biomolecules in health and disease. Department Chair Charalampos Babis Kalodimos, PhD, is recruiting leaders in the field to join our faculty and bringing innovative technologies to the St. Jude campus.

ST. JUDE FREELY SHARES
THE DISCOVERIES WE MAKE.
EVERY CHILD SAVED AT ST. JUDE
PROVIDES DOCTORS AND SCIENTISTS
WORLDWIDE WITH THE KNOWLEDGE
TO HELP SAVE THOUSANDS
MORE CHILDREN.

Mario Halic, PhD

James R. Downing, MD
President and Chief Executive Officer

> "**IMAGINE WHAT GREAT FEATS WE CAN ACHIEVE TOGETHER**, WORKING ACROSS DISCIPLINES, ACROSS BORDERS, AND AROUND THE WORLD."

In science and medicine, collaboration is the spark that ignites progress. At St. Jude Children's Research Hospital, talented faculty and staff work together—and with colleagues worldwide—to advance the research and treatment of pediatric cancer and other catastrophic diseases. In this *Scientific Report*, we showcase how the power of team science enhances the discovery process. Collaborative efforts in the laboratory, the clinic, and with partners around the globe are fueling discoveries and giving new hope to families everywhere.

In the first feature, we highlight how the St. Jude Comprehensive Cancer Center brings together scientists from various fields to focus on a shared problem and accelerate progress. In 2018, the Center received its second consecutive "Exceptional" rating after its 5-year review by the National Cancer Institute. This is the highest-possible ranking, placing St. Jude among the nation's elite Cancer Centers.

The second story outlines how the Structural Biology department is recruiting and expanding to transform into one of the world's most comprehensive structural biology research centers that houses imaging and analytical modalities that examine dynamic cellular processes at the atomic level. Under the leadership of Charalampos Babis Kalodimos, PhD, the department has established 6 centers to facilitate cutting-edge structural biology research and transdisciplinary collaborations with St. Jude investigators in other departments.

In the third feature, we describe how developmental neurobiologists at St. Jude are using technologic innovations to propel neuroscience and gain new insights into the nervous system during health and disease. Michael A. Dyer, PhD, David Solecki, PhD, and Daniel Stabley, PhD, are part of an elite group of 4 laboratories working with Nobel Laureate Eric Betzig (University of California, Berkeley) to co-build the next-generation lattice light-sheet microscope. This new instrument will enable scientists to visualize changes as they occur in living cells deep within the brain or other nervous system tissues.

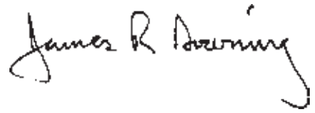
The fourth story details a new St. Jude effort to close the global gap in childhood cancer survival. Today, one of the strongest predictors of whether a child is cured of cancer is where that child lives. More than 80% of all children live in low- or middle-income countries (LMICs) that often struggle to meet the healthcare needs of local populations. In 2018, St. Jude Global was launched, with the mission to improve the survival of children with cancer or blood disorders worldwide, through the sharing of knowledge, technology, and organizational skills. Also, the World Health Organization (WHO) designated St. Jude as the first WHO Collaborating Center for Childhood Cancer. Representatives from WHO and St. Jude announced this new effort—the WHO Global Initiative for Childhood Cancer—at the United Nations General Assembly in New York City in September 2018. The goal of this initiative is to increase the survival of children with the most common pediatric cancers to 60% by 2030.

Beyond the stories in this *Report*, St. Jude saw continued growth and progress last year. We broke ground on a $412 million advanced research center that will open in 2021 and launched 2 new online data-sharing portals for the global research community: St. Jude Cloud, which offers next-generation sequencing data and analysis tools for pediatric cancer and other life-threatening diseases, and PROPEL, which freely shares patient-derived xenograft samples of leukemias with researchers around the world to accelerate leukemia biology research.

In 2018, St. Jude committed resources to tackling several faculty-proposed blue sky initiatives—ideas with the potential to have a game-changing impact on health. Several projects are underway, including expanding our cloud-based genomic data-sharing resources, initiating a gene therapy trial for hemophilia B in LMICs, and establishing a program to explore the molecular pathology of pediatric neurological diseases.

St. Jude also gained recognition from several top workplace resources, including *Fortune*'s "100 Best Companies to Work For" list, Glassdoor's "Best Places to Work" ranking, and "No. 1" on the National Society of High School Scholars' Annual Career Survey of places where high school and college students wish to work.

The past year has been a time of great productivity for our clinical, scientific, and administrative operations. By building on this foundation, working in transdisciplinary teams, and collaborating with colleagues around the world, St. Jude will advance cures for pediatric cancer and other catastrophic childhood diseases worldwide.



In Memoriam

The St. Jude family mourns the passing of Brian P. Sorrentino, MD, Wall Street Committee Endowed Chair in Bone Marrow Transplant Research, Director of the Division of Experimental Hematology, Member of the Department of Hematology, and a tremendous scientist who was also a fierce Corvette-racing, target-shooting, blues guitar–playing lover of life.

Dr. Sorrentino was born and raised in Schenectady, NY. As a teenager, he battled Hodgkin lymphoma. Late effects of the high doses of radiation therapy and chemotherapy that cured him of that childhood disease caused health complications throughout his adult life and, ultimately, the lung cancer that took him from us too soon.

Dedicating himself to becoming a physician–scientist, Dr. Sorrentino attended medical school at The State University of New York Upstate Medical Center (Syracuse, NY) and completed an internship in internal medicine at the University of North Carolina (Chapel Hill, NC). In 1988, he accepted a position as a hematology-oncology fellow at the National Heart, Lung, and Blood Institute and National Cancer Institute and joined the laboratory of Dr. Arthur Nienhuis to conduct gene therapy and hematology research, a decision that would set the course for the rest of his career.

In 1993, Dr. Sorrentino followed Dr. Nienhuis to St. Jude and spent the next 25 years leading his own research laboratory, which pioneered new approaches to hematopoietic stem cell (HSC) gene therapy for various diseases. He became renowned in his field and served on the Advisory Council of the American Society of Cell and Gene Therapy and various committees for the American Society of Hematology. He also chaired numerous National Institutes of Health study sections to award grant funding. Dr. Sorrentino was elected to the American Society of Clinical Investigation, and in 2005, he received the McCulloch and Till Lectureship Award from the International Society of Experimental Hematology. He served on the editorial boards of major scientific journals and held several patents on his work.

During his career at St. Jude, Dr. Sorrentino developed an interest in congenital immune disorders. In a 1998 article in *Nature Medicine*, his group was the first to report curing an animal model of human immunodeficiency by using HSC gene therapy. When early clinical trials of gene therapy were halted because the treatment vectors caused leukemia, Dr. Sorrentino refocused his laboratory to work on ensuring the safety of gene therapeutic approaches for monogenic disorders, while also increasing their efficacy and potency. His most recent project was gene therapy for X chromosome–linked severe combined immunodeficiency (X-SCID). He and his colleagues engineered a lentiviral vector that inserts a healthy copy of the *IL2RG* gene into the defective HSCs obtained from patients with X-SCID. The modified cells were produced in the Children's GMP, LLC, on the St. Jude campus and then transplanted back into the patients. Nine infants born with X-SCID received this therapy and are now producing fully functional immune cells for the first time. It is uncertain whether this reconstitution of their immune systems will endure for their lifetime; however, as of now, all the patients appear to have been cured without any immediate adverse side effects. In addition, this therapy has the potential to help children with other disorders, such as Wiskott-Aldrich syndrome and sickle cell disease.

This groundbreaking work was reported in the April 18, 2019, issue of *The New England Journal of Medicine*. Although the reward of Dr. Sorrentino's labor is a posthumous one, it is a remarkable stamp on the life of the man who was a colleague, mentor, and friend to so many at St. Jude and around the world.

Brian P. Sorrentino, MD
1958–2018

UNITING RESEARCHERS TO IMPROVE CURES AND SURVIVAL FOR CHILDREN WITH CANCER: THE ST. JUDE COMPREHENSIVE CANCER CENTER RECEIVES AN "EXCEPTIONAL" RATING FROM THE NATIONAL CANCER INSTITUTE

As the only National Cancer Institute (NCI)–designated Comprehensive Cancer Center focused exclusively on children, St. Jude plays a crucial role in the nation's portfolio of Cancer Centers. During the 2 most recent NCI 5-year reviews, St. Jude received a score of "Exceptional," the highest-possible ranking, placing our Center among the nation's elite Cancer Centers.

Children with cancer are a distinct population. The biological anomalies that cause oncogenesis in children are often different than those in adults, and the resulting diseases are distinct from their adult counterparts. Thus, most pediatric cancers cannot be treated in the same manner as adult cancers and warrant independent research that specifically addresses the features of those diseases. Under the direction of Charles W. M. Roberts, MD, PhD, the St. Jude Comprehensive Cancer Center is leading the nation in these efforts.

Throughout its history, St. Jude has directly contributed to seminal advances in pediatric oncology. Work from the Center has helped increase the overall survival of children with cancer to more than 80% and for children with the most common childhood cancer, acute lymphoblastic leukemia (ALL), to more than 90%. Despite these achievements, much work remains to be done in all areas of pediatric oncology.

Cancer is still the leading cause of disease-related death in children aged 1 to 14 years in the U.S., and the probability of cure for many pediatric cancers continues to be dismal. Moreover, the growing population of adult survivors of childhood cancer is at risk of severe long-term sequelae associated with their disease, its treatment, or both. Therefore, childhood cancer survivors need lifelong medical surveillance and new interventions to improve their quality of life.

To advance research, treatment, and cures of childhood cancer, the Center provides an overarching strategic vision and scientific direction, a robust collaborative framework, state-of-the-art shared resources, and an administrative hub that supports its members in making scientific breakthroughs. The Center is designed to bring together investigators with diverse expertise—oncologists, pathologists, molecular biologists, cancer geneticists, surgeons, population scientists, and many others—to identify the most promising ways to pursue new treatments and cures for solid tumors, hematological malignancies, and brain tumors and to minimize the long-term effects of cancer and its treatments.

The Center also leads the pursuit of institutional strategic plan goals that guide work in precision medicine; immunotherapy; proton therapy; preclinical and clinical research infrastructure; and basic, translational, and clinical research collaborations. Finally, Center leaders and members collaborate with St. Jude Global investigators and international partners to expand the reach of the Center and ensure that our discoveries benefit countless patients and survivors of childhood cancer worldwide.

What is a Cancer Center?

The NCI is the primary federal funding agency for cancer research in the U.S. Its Cancer Center Support Grant is awarded to institutions to recognize and support their scientific leadership, resources, and cancer-focused research in basic, clinical, and/or population science. Comprehensive Cancer Centers demonstrate an added depth and breadth of research, as well as substantial transdisciplinary research that bridges these scientific areas. Cancer Centers must also provide cancer-related professional training and community outreach activities.

St. Jude plays a crucial role in the nation's portfolio of 70 Cancer Centers, which includes 49 Comprehensive Cancer Centers, by advancing research and cures designed specifically for pediatric patients. St. Jude was designated an NCI Cancer Center in 1977 and was named a Comprehensive Cancer Center in 2008. Today, the Center includes laboratory-based and clinical faculty members working in 5 interactive research programs headed by program co-leaders; a dedicated administrative team; and directors, staff scientists, and technologists working in 9 NCI-funded shared resources that support research activities. (See p. 90 for details.) The Center also oversees strategic initiatives and the clinical trials enterprise for St. Jude.

Dr. Roberts is assisted in leading the overarching direction of the Cancer Center by Deputy Director Charles G. Mullighan, MBBS, MD, and a senior leadership team of 8 Associate Directors who oversee Administration (Dana Wallace), Shared Resources (James I. Morgan, PhD), Basic Science (Suzanne J. Baker, PhD), Clinical Research (Victor M. Santana, MD), Population Sciences (Leslie L. Robison, PhD), Outreach (Carlos Rodriguez-Galindo, MD), and Education & Training (Gerard P. Zambetti, PhD).

Charles G. Mullighan, MBBS, MD; Charles W. M. Roberts, MD, PhD

Dana Wallace, Charles W. M. Roberts, MD, PhD

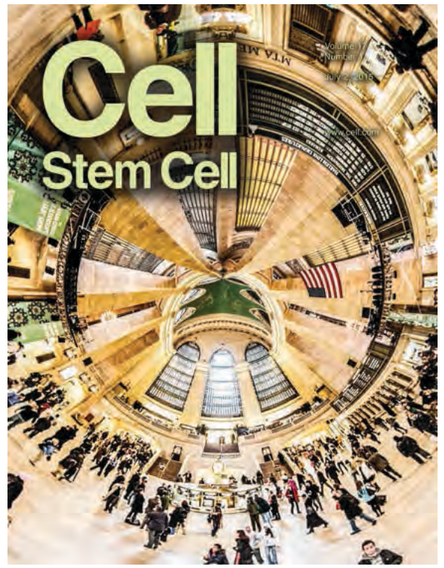
Driving Transdisciplinary Collaborations

Scientific leadership, extensive resources, and accomplished research in basic, clinical, and/or population science distinguish the 70 NCI-designated Cancer Centers from other research institutions in the U.S. The primary function of the Center is to drive transdisciplinary collaboration by bringing together diverse clinicians and scientists from across the institution, the country, and the globe. The Center also oversees the St. Jude clinical research enterprise, which treats patients in clinical trials both at St. Jude and through the St. Jude Affiliate Program comprising 8 clinics. (See p. 88 for details.) The Center additionally provides educational opportunities about cancer and healthy living to the community and educates and trains the next generation of pediatric cancer researchers.

The Center supports 5 multi-disciplinary research programs. The Cancer Biology Program is engaged primarily in laboratory-based research. Three disease-focused programs, Developmental Biology & Solid Tumor, Hematological Malignancies, and Neurobiology & Brain Tumor, translate fundamental discoveries into curative therapies. The Cancer Control & Survivorship Program assesses adverse effects of childhood cancer and treatment to improve the quality of life of long-term survivors of childhood cancer. Brief descriptions of the 5 Center programs and examples of their recent achievements are described in the following pages.

INCREASED PUBLICATIONS IN JOURNALS WITH THE HIGHEST IMPACT FACTORS

In the recent *vs.* previous 5-Year Review Period



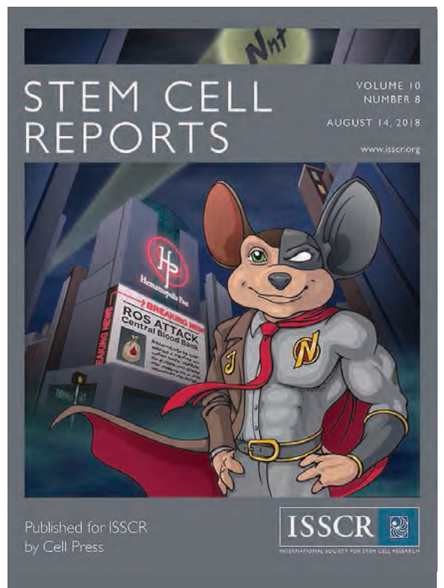
CELL +360%

NATURE +23%

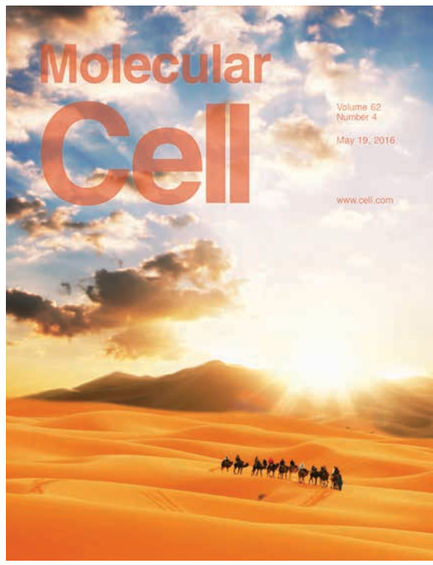
SCIENCE +40%

THE NEW ENGLAND JOURNAL OF MEDICINE +700%

NATURE GENETICS +163%



NATURE MEDICINE +200%



CANCER CELL +55%

TOTAL PUBLICATIONS 2290

Douglas R. Green, PhD; Martine F. Roussel, PhD

Cancer Biology Program

The primary goal of the Cancer Biology Program is to explore and understand the biology of cancer cells. The diverse nature of pediatric cancers and the complex molecular, genetic, and developmental contexts in which they form necessitate a broad spectrum of basic research to build a strong foundation. Basic science discoveries have driven numerous key advances in our understanding and treatment of pediatric cancers.

The Program leads integrated, multidisciplinary efforts to define pathways related to cancer and its control, identify genetic mutations and anomalies as new therapeutic targets for translation into clinical trials, and advance our understanding of the cancer microenvironment. To address unmet needs and maximize opportunities for translation, research in this Program spans 4 areas: signaling networks and therapeutics; cell stress, repair, metabolism, and death; tumor microenvironment and immunology; and genome structure and function. Here, we describe advances made in 2 of these key areas.

Establishing the Genomic and Epigenomic Landscape of Pediatric Cancer

Cancer arises from DNA mutations, epigenetic alterations, or a combination thereof. To understand the fundamental driving mechanisms of pediatric cancers, Jinghui Zhang, PhD (Computational Biology), led a team of cancer biologists and computational biologists in pioneering next-generation approaches to detailed analyses of pediatric cancer genomes and epigenomes. This work was initiated in 2010 through the St. Jude Children's Research Hospital–Washington University Pediatric Cancer Genome Project.

More recently, members of 3 programs (Cancer Biology, Hematological Malignancies, and Neurobiology & Brain Tumor) identified germline mutations in cancer-predisposition genes in 8.5% of children and adolescents with pediatric cancers. Published in *The New England Journal of Medicine*, this work demonstrates the importance of genetic counseling in this population and has shaped the development of the St. Jude Cancer Predisposition Program, which is led by Kim E. Nichols, MD (Oncology).

In 2018, Dr. Zhang's team led a pan-cancer study of pediatric cancers. The term "pan-cancer" indicates that multiple types of cancer, regardless of the cell of origin or tissue in which they initiated, were included in the analysis. The team integrated whole-genome, -exome, and -transcriptome sequencing to identify somatic alterations in 1699 pediatric leukemias and solid tumors. The findings, published in *Nature*, demonstrated that most alterations were unique to pediatric cancer and underscore the need to develop precision therapies designed specifically for pediatric cancers. (See p. 97 for details.)

Genomic discoveries and their integration into clinical care continue at a rapid pace; every eligible St. Jude patient with cancer is now offered clinical whole-genome sequencing. An innovative data-sharing platform, St. Jude Cloud (*www.stjude.cloud*), was launched in April 2018 to provide genomic datasets, analysis tools, and visualizations to the global research community. The platform, a collaboration with Microsoft and DNAnexus, currently offers more than 10,000 whole-genome sequences from pediatric patients with cancer and childhood cancer survivors. To date, it has 800 registered users from 400 institutions around the world.

Kim E. Nichols, MD; James R. Downing, MD; Jinghui Zhang, PhD

R. K. Subbarao Malireddi, PhD; Thirumala-Devi Kanneganti, PhD

Tumor Immunology and Immunotherapy

Although cancer cells evolve mechanisms to escape immune surveillance, experimental manipulation of the immune system has the potential to deliver substantial tumor-killing benefits. Efforts in the Program have provided fundamental insights into the immune system's ability to regulate cancer and effective approaches to exploit metabolic events to generate an antitumor response. These studies represent ongoing collaborative efforts among the laboratories of Hongbo Chi, PhD (Immunology), Thirumala-Devi Kanneganti, PhD (Immunology), Joseph T. Opferman, PhD (Cell & Molecular Biology), and Program Co-Leaders Douglas R. Green, PhD (Immunology), and Martine F. Roussel, PhD (Tumor Cell Biology).

In *Science Immunology*, Dr. Chi and colleagues recently reported that the integration of metabolic and signaling pathways dictates lineage choices for T cells. They found that metabolic processes guide the fate of immune cells. Signaling pathways affecting metabolism are essential to the developmental fate of not only T lymphocytes but also dendritic cells, which are crucial for stimulating T cells and guiding their differentiation, as Dr. Chi's team reported in *Nature*. (See p. 103 for details.)

Collaborative studies on macrophage activity in the tumor microenvironment have revealed an important role for a noncanonical autophagy pathway, LC3-associated phagocytosis (LAP), in the myeloid response to dying cells. A recent collaborative study led by Drs. Green and Opferman and Charles Gawad, MD, PhD (Oncology, Computational Biology), in *Cell*, showed that LAP influences anticancer T-cell responses and inhibits anticancer immunity. Targeting LAP-specific proteins may, therefore, be a promising therapeutic strategy that will not interfere with the canonical autophagy processes that are important for tumor suppression.

The Program has also made strides toward understanding the molecular basis of inflammation, a key process in tumorigenesis. Dr. Kanneganti has led multiple studies on the inflammasome, a protein complex involved in restricting the immune response to microbial challenges and tumorigenesis. In *Gastroenterology*, her team reported that the sensor protein pyrin, which initiates the assembly of the inflammasome complex, protects against colon inflammation and tumorigenesis in mice. Furthermore, work published in *The Journal of Clinical Investigation* identified tumor necrosis factor as a critical modulator of pyrin expression and inflammasome activation. These studies point to pyrin and its regulators as potential targets for therapeutic intervention. Collectively, these and other key mechanistic insights have contributed to the foundation for our rapidly expanding translational efforts in immunotherapy.

Joseph T. Opferman, PhD; Douglas R. Green, PhD; Charles Gawad, MD, PhD

Alberto S. Pappo, MD; Michael A. Dyer, PhD

Developmental Biology & Solid Tumor Program

Some of the most devastating, poorly understood cancers that affect children arise in the peripheral nervous system, muscles, or bones. Despite recent advances in genomics that have enabled us to better understand the etiology of pediatric solid tumors, the overall survival of children and adolescents with high-risk or recurrent disease has not improved in more than 20 years. This lag in improved cure rates reflects the heterogeneity and relative rarity of pediatric solid tumors.

The Developmental Biology & Solid Tumor Program aims to improve the survival and quality of life of children with solid tumors by integrating basic, translational, and clinical research. The Program has 4 working groups focused on recurrent disease, immunotherapy, rare tumors, and precision medicine. Here, we present recent advances in elucidating the developmental origins of pediatric solid tumors, developing unique preclinical resources and research pipelines, and identifying promising new therapeutic approaches.

Developmental Origins and Therapeutic Approaches to Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is the most common soft-tissue cancer in children. Histologically, these tumors resemble embryonic skeletal muscle and have been thought to arise from that tissue, but they can also arise in sites devoid of skeletal muscle. Mark E. Hatley, MD, PhD (Oncology), recently found that cellular reprogramming of nonmyogenic cells can also lead to RMS, demonstrating the disease's diverse origins. (See p. 105 for details.)

A major barrier to developing new therapies for solid tumors has been the lack of preclinical models that accurately recapitulate human disease and predict clinical responses to novel therapeutics. The Program launched a large-scale effort to develop better preclinical models, with a focus on orthotopic patient-derived xenografts (O-PDXs). This led to the development of the Childhood Solid Tumor Network (*CSTN; www.stjude.org/CSTN*). Since the CSTN was established, 498 patients have donated surplus tumor tissue, resulting in the successful generation of 201 independent xenografts that represent 27 tumor types. All models have undergone comprehensive genomic and epigenomic analyses, including whole-genome and whole-exome sequencing, RNA-sequencing, and whole-genome bisulfite sequencing; approximately half of the models have undergone chromatin immunoprecipitation sequencing analysis.

To hasten progress in pediatric solid tumor research, all O-PDXs and their associated data are freely shared with researchers around the world through the CSTN, with no obligation to collaborate. To date, 507 requests for O-PDXs have been received from 200 investigators working at 99 institutions in 16 countries.

The O-PDXs have enabled crucial insights that are driving innovative clinical studies in RMS and other solid tumors. For example, work in these models identified an inhibitor of the signaling kinase WEE1 as a promising therapeutic agent. In *Cancer Cell*, Elizabeth A. Stewart, MD, Sara M. Federico, MD (both of Oncology), and their colleagues reported the most comprehensive analysis to date of RMS that integrated transcriptomic, epigenomic, and proteomic/phosphoproteomic data to elucidate the cellular origins and therapeutic vulnerabilities of the disease. RMS has 2 major histologic subtypes: alveolar RMS and embryonic RMS. Dr. Stewart's team found that alveolar RMS, which is the more aggressive subtype, arises at a later stage in the developmental program than does embryonal RMS. Their comprehensive preclinical testing also revealed that targeting WEE1 is the most effective approach to treating high-risk RMS in vivo. These results prompted the Children's Oncology Group to expand their multicenter Phase I/II clinical trial of the WEE1 inhibitor AZD1775 and the chemotherapy agent irinotecan to include pediatric patients with high-risk RMS.

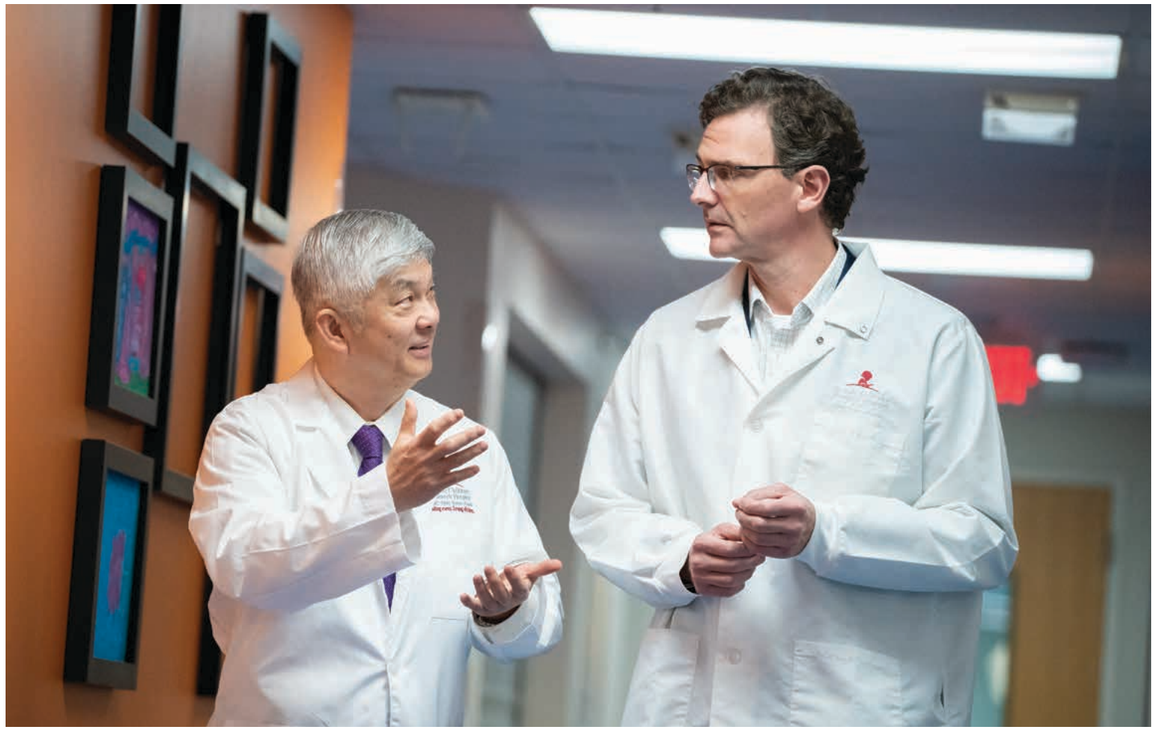
Sara M. Federico, MD; Elizabeth A. Stewart, MD

Precision Therapy for Tumors Bearing a TRK Fusion Oncogene

Gene fusions involving *NTRK1*, *NTRK2*, or *NTRK3* (TRK fusions) are found in several childhood and adult tumors. In 2018, a large multicenter trial testing the TRK inhibitor larotrectinib as a new precision therapy for TRK-bearing tumors was completed. Collaborating with Theodore Laestch (University of Texas Southwestern Medical Center) and David Hyman (Memorial Sloan Kettering), Program Co-Leader Alberto S. Pappo, MD (Oncology), served as the St. Jude investigator on the landmark Phase I/II trial of larotrectinib.

In *The Lancet Oncology*, the investigators demonstrated that larotrectinib was well tolerated by pediatric patients and showed impressive antitumor activity in all patients with TRK fusion–positive tumors. Results from this study were combined with those from a Phase I study on adults and a Phase II study on adolescents and adults and published in *The New England Journal of Medicine*. The cohort included 55 patients (aged 4 months–76 years) with 17 unique TRK fusion–positive tumors, and 75% of the tumors responded to the drug. Larotrectinib was well tolerated, and 30 (55%) patients remained progression-free after 1 year. As a result of these studies, the U.S. Food and Drug Administration approved larotrectinib as the first targeted, oral, tumor-agnostic therapy. Tumor-agnostic therapy is defined as immunotherapy that attacks any type of cancer that arises in any location, as long as the tumor cells have a specific molecular anomaly (e.g., TRK fusion) that is targeted by the drug.

Alberto S. Pappo, MD; Armita Bahrami, MD



Ching-Hon Pui, MD; Charles G. Mullighan, MBBS, MD

Hematological Malignancies Program

Hematological malignancies remain a leading cause of cancer-related death in children, despite therapeutic advances that have improved outcomes. The Hematological Malignancies Program aims to improve the cure of childhood leukemias and lymphomas, while minimizing treatment-related adverse effects.

This highly interactive, transdisciplinary Program has a long record of major discoveries in cancer biology and treatment. The translation of fundamental discoveries on the genetic basis of leukemogenesis and treatment-related toxicities into new diagnostic and treatment approaches has changed the standard of care for children with hematological malignancies and sparked innovative precision medicine studies and therapeutic strategies. Program accomplishments have had a global impact on the diagnosis, classification, and treatment of various hematological malignancies.

Research in the Program encompasses common and rare childhood leukemias and lymphomas and ranges from defining molecular taxonomy to experimental modeling, preclinical studies, pharmacogenomics, and clinical trial development. Here, we focus on recent advances in our understanding of the molecular basis of ALL, the most common childhood malignancy.

A Genomic Portrait of Acute Lymphoblastic Leukemia

ALL includes a spectrum of disease subtypes with distinct mutations. Program Co-Leader Charles G. Mullighan, MBBS, MD (Pathology), and colleagues have conducted multiple in-depth genomic investigations of ALL and defined numerous novel disease subtypes and mechanisms of pathogenesis. Recently, this work has contributed to the molecular reclassification of ALL in the revised World Health Organization guidelines. It has also provided the basis for using targeted agents in precision medicine trials, including the ongoing St. Jude Total Therapy 17 clinical trial for newly diagnosed ALL, which is led by Hiroto Inaba, MD, PhD (Oncology).

Genomic discovery studies continue to accelerate. Earlier this year in *Nature Genetics*, Dr. Mullighan's team reported their integrated genomic analysis of 1988 pediatric and adult cases of B-progenitor ALL, thereby revising the classification of ALL to comprise at least 23 genetically distinct subtypes. This comprehensive sequencing approach enabled the researchers to not only identify new subtypes but also demonstrate the power of transcriptome sequencing for guiding classification, risk stratification, and tailored therapy.

Mixed-phenotype acute leukemia (MPAL) is a rare, difficult-to-treat subtype that includes features of both ALL and acute myeloid leukemia. By integrating genome sequencing, experimental modeling, and tumor xenografting, Dr. Mullighan and colleagues identified the genetic alterations that define the most prevalent subtypes of MPAL. (See p. 101 for details.) Their findings, published in *Nature*, are now being tested in clinical trials of MPAL that are determining whether disease subtype and treatment response can be correlated with the genetic features of leukemic cells.

To promote research on leukemia biology and help develop more effective cures, the Program launched the Public Resource of Patient-derived and Expanded Leukemias (PROPEL; *www.stjude.org/PROPEL*) in 2018. PROPEL is a St. Jude–hosted resource for sharing unique patient-derived xenografts (PDXs) from patients with B- or T-lineage ALL, acute myeloid leukemia, or relapsed leukemia. In addition, PROPEL provides a tool with which to explore genomic data from both the PDXs and matched primary patient samples. This information is freely shared with researchers around the world, with no obligation to collaborate. Currently, PROPEL contains approximately 250 samples of adult and pediatric leukemias and continues to grow with the addition of other subtypes of leukemia.

Hiroto Inaba, MD, PhD

Jun J. Yang, PhD

Predisposition to Acute Lymphoblastic Leukemia

Growing evidence indicates that germline genetics influence the development of ALL, which was once regarded as a nonhereditary disease. For example, the *IKZF1* gene, a known somatic driver of high-risk ALL, is mutated in families in which multiple members have ALL and in patients with ALL with no known family history. This work was published in *Cancer Cell*. After identifying 2 members of the same family with B-progenitor ALL and an *IKZF1*-truncating mutation, the team conducted targeted sequencing of 4963 childhood ALL samples. They found 28 unique predisposing germline variants in 45 children, thereby establishing *IKZF1* as an ALL-predisposition gene and further emphasizing the importance of heredity in ALL development.

In another targeted sequencing study, Jun J. Yang, PhD (Pharmaceutical Sciences), and his team followed up prior work from St. Jude that showed *TP53* germline variants are common in childhood hypodiploid ALL. By conducting targeted germline sequencing of *TP53*-coding regions in DNA samples from 3801 children with ALL, the researchers identified 49 unique, nonsilent *TP53*-coding variants, 22 of which were predicted to be pathogenic. Children carrying *TP53* pathogenic variants had poorer survival and a substantially higher risk of subsequent cancers. This study confirms the importance of *TP53* in ALL development and treatment response. Germline mutations in *TP53* also have implications for family members, who are now being screened for this cancer-susceptibility gene through the St. Jude Cancer Predisposition Program to enable early diagnosis of cancer among siblings and parents. This work was published in the *Journal of Clinical Oncology*.

Taking a more agnostic approach, Dr. Yang and colleagues conducted genome-wide association studies to seek novel ALL-susceptibility loci in Hispanic individuals who have a high proportion of Native American ancestry and an elevated risk of ALL and poorer outcome. In the journal *Blood*, the team reported that the *ERG* gene is a novel ALL risk locus that correlates with Native American ancestry and is enriched in certain ALL subtypes. Thus, *ERG* has been added to the growing list of genetic factors that contribute to racial/ethnic disparities in ALL.

WITHIN 30 DAYS OF A CANCER DIAGNOSIS,
90% OF PATIENTS ENROLL IN A CLINICAL TRIAL;
60% ENROLL IN A THERAPEUTIC TRIAL.

In the recent *vs.* previous 5-Year Review Period

NEW PATIENTS WITH CANCER	INTERNATIONAL PATIENTS WITH CANCER	PATIENTS ENROLLED ON THERAPEUTIC TRIALS
+9%	+30%	+40%

Suzanne J. Baker, PhD; Amar J. Gajjar, MD

Neurobiology & Brain Tumor Program

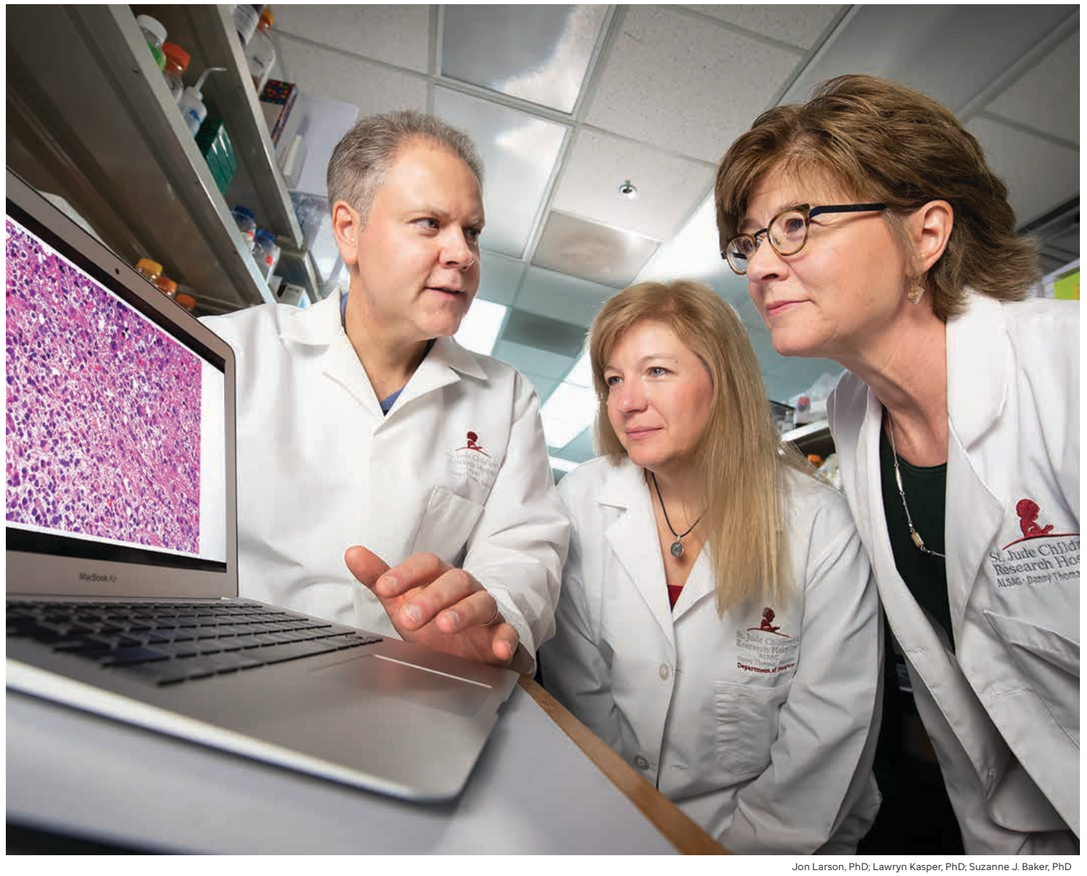
Despite rapid advances in our understanding of the biology of brain tumors, these diseases remain the leading cause of cancer-related death in children. Current treatment approaches are lacking for some patients and lead to long-term debilitating side effects for others. The Neurobiology & Brain Tumor Program aims to improve survival and morbidity of children with brain tumors by developing effective, relatively nontoxic therapies through a better understanding of disease pathogenesis. By integrating the latest genomic and genetic technologies with studies of the developing nervous system, members of this Program are translating laboratory findings into opportunities for new treatments.

Pediatric brain tumors arise during development; thus, the Program addresses regulatory mechanisms that affect normal growth and tumorigenic growth in the developing brain. Program members continue to investigate neural development, tumor cells of origin, key pathways that drive tumorigenesis, and the epigenetic landscape of brain tumors. Genome-wide studies of the major pediatric brain tumor types have identified novel mutations, defined molecular subgroups, and opened new avenues of basic, translational, and clinical investigation. Furthermore, advances in the fields of molecular pathology, imaging, and radiation oncology hold promise for advancing the treatment of these formidable diseases. Here we present recent advances made in 3 types of pediatric brain tumors.

Modeling an Incurable Tumor: Diffuse Intrinsic Pontine Glioma

In 2012, Program Co-Leader Suzanne J. Baker, PhD (Developmental Neurobiology), and Cancer Biology Program member Dr. Zhang discovered recurrent histone H3 mutations in diffuse intrinsic pontine glioma (DIPG), an incurable tumor of the brainstem, and in pediatric high-grade gliomas. As a result, the histone H3 K27M mutation was defined as a molecular hallmark of DIPG, and an essential connection between histone regulation and DIPG was revealed.

To determine how the H3 K27M mutation drives oncogenesis and why mutations in this histone selectively drive gliomas in the developing brainstem, Dr. Baker and colleagues genetically engineered mice carrying an inducible H3 K27M mutation. In *Cancer Cell*, they reported that the K27M-dependent, genome-wide decrease in H3K27me3 causes a selective increase in neurodevelopmental gene expression by releasing the epigenetic regulation of poised promoters. The K27M mutation enhances the self-renewal of neural stem cells, which could expand the pool of cells susceptible to malignant transformation. Expression of the K27M mutation throughout the central nervous system (CNS), combined with DIPG-associated mutations in the *Trp53* and *PDGFRα*α genes, selectively accelerated tumorigenesis in the brainstem. Thus, these murine models revealed novel epigenetic contributions to DIPG pathogenesis and will enable detailed studies of therapeutic response.



Jon Larson, PhD; Lawryn Kasper, PhD; Suzanne J. Baker, PhD

Molecular Characterization of Brain Tumors Guides Treatment

Medulloblastoma is the most common CNS tumor of childhood. It includes 4 molecular subtypes (SHH, WNT, Group 3, and Group 4), and each subtype has a distinct biology and treatment outcome. Work by the Program has been instrumental in further characterizing medulloblastoma subtypes and identifying the contribution of germline predisposition to the disease.

Children younger than 3 years at the time of diagnosis of medulloblastoma often have poorer overall survival, because radiation therapy must be delayed or the dose reduced to avoid debilitating side effects on the developing brain. A multicenter Phase II clinical trial (SJYC07) led by Giles W. Robinson, MD (Oncology), Program Co-Leader Amar J. Gajjar, MD (Pediatric Medicine, Oncology), and Paul A. Northcott, PhD (Developmental Neurobiology), used a risk-stratified treatment strategy that omitted or minimized radiation exposure in 81 patients younger than 3 years with medulloblastoma. The findings, published in *The Lancet Oncology*, support the pursuit of a molecularly driven, risk-adapted approach for treating young children with medulloblastoma. (See p. 96 for details.)

Historically, most medulloblastomas were thought to arise sporadically. A team led by Drs. Gajjar, Northcott, and Robinson challenged this long-held belief in collaboration with investigators at the Hopp Children's Cancer Center (Heidelberg, Germany) and The Hospital for Sick Children (Toronto, Canada). Using whole-genome and whole-exome sequencing, the teams assessed the prevalence of rare variants in 110 cancer-predisposition genes in 1022 patients with medulloblastoma. This study, which also appeared in *The Lancet Oncology*, is the largest to date on genetic predisposition to a single pediatric brain tumor entity. The team discovered that genetic predisposition plays a major role in causing medulloblastoma, particularly in patients with the WNT or SHH subtype. They also identified *APC*, *BRCA2*, *TP53*, *PALB2*, *PTCH1*, and *SUFU* as key medulloblastoma-predisposition genes. These results indicate an urgent need to provide genetic counseling and testing for patients with WNT or SHH medulloblastoma.

Ependymomas are neuroepithelial tumors of the CNS. They represent nearly 10% of all pediatric CNS tumors and about 30% of CNS tumors in children younger than 3 years. Comprehensive DNA-methylation profiling led by the Program has demonstrated distinct molecular groups of ependymoma and refined approaches to disease classification, but these developments have yet to be incorporated into standard clinical practice. In *Acta Neuropathologica*, David W. Ellison, MD, PhD (Pathology), and colleagues characterized the molecular heterogeneity in posterior fossa type A ependymomas, revealing a role for a previously uncharacterized gene, *CXorf67*. (See p. 112 for details.)

INCREASED FUNDING OF CANCER CENTER RESEARCH

In the recent *vs.* previous 5-Year Review Period

PEER-REVIEWED FUNDING	NCI FUNDING
+13%	+9%

Giles W. Robinson, MD

Melissa M. Hudson, MD; Leslie L. Robison, PhD

Cancer Control & Survivorship Program

As treatments for childhood cancers improve, the number of long-term survivors in the U.S. is expected to surpass 500,000 by the end of 2019. The Cancer Control & Survivorship Program conducts research to reduce treatment-related complications and improve the long-term outcomes and quality of life of individuals surviving childhood cancer. Two unique survivor cohorts, the Childhood Cancer Survivor Study (CCSS) and the St. Jude Lifetime Cohort Study (SJLIFE), include more than 40,000 participants who have survived childhood cancer for at least 5 years after completion of therapy.

This Program, which spans the breadth of epidemiological, clinical, and interventional research, has defined the landscape of childhood cancer survivorship, influenced the design of contemporary pediatric cancer treatment strategies, and provided crucial data to guide surveillance and health-preserving interventions for survivors. Efforts to characterize the challenges faced by childhood cancer survivors and design effective interventions are a major ongoing focus.

Identifying Genetic Risk Factors for Late Effects of Treatment

Some childhood cancer survivors fare better than others, even among those who had similar diagnoses and completed comparable therapeutic regimens. However, the way in which survivors' genetic makeup influences their long-term health outcomes has been poorly understood. In 2018, Dr. Zhang and Program Co-Leader Leslie L. Robison, PhD (Epidemiology & Cancer Control), led a study of whole-genome sequencing of germline DNA from more than 3000 pediatric cancer survivors participating in the SJLIFE study. This first-in-kind initiative was designed to enable integrated analyses of genomic data and comprehensive clinical data to identify new genetic risk factors for late effects of treatment, such as second neoplasms. This work was published in the *Journal of Clinical Oncology*. (See p. 110 for details.)

Understanding Financial Toxicity in Childhood Cancer Survivors

Minimizing the toxicity of anticancer therapy is generally considered only in terms of toxicity to cells and tissues. However, St. Jude is helping to pioneer a relatively nascent area of investigation—financial toxicity faced by childhood cancer survivors. The term "financial toxicity" is used to describe problems experienced by cancer survivors resulting from the financial implications of receiving a diagnosis and subsequent medical care for cancer. A team led by I-Chan Huang, PhD (Epidemiology & Cancer Control), assessed 3 domains of financial hardship (i.e., material, psychological, and coping/behavioral) in 2811 long-term survivors in the SJLIFE cohort. The majority (65%) of survivors reported hardship in at least 1 domain, with higher risks found in middle-aged survivors (40 years or older) versus younger survivors (18–39 years). Depressive symptoms and suicidal ideation were associated with all 3 hardship domains. This work was published in the *Journal of the National Cancer Institute*. The discovery that financial hardship is widespread among childhood cancer survivors emphasizes the importance of systematically addressing the impact of health policies on survivors and developing strategies for early detection and intervention.

I-Chan Huang, PhD

Measures of Success of an Exceptional Center

Every 5 years, the Center must reapply for funding and formal designation as a Comprehensive Cancer Center. For the recent renewal, Center administrative staff, shared resources directors, and leadership spent more than 18 months writing the 2300-page application. In May 2018, a panel of 20 reviewers representing the NCI conducted a site visit of the Center. Dozens of examples of scientific achievements across the Center were presented. These included an increase in the number of peer-reviewed publications, including a 27% increase in the number of articles published in scientific journals with an impact factor greater than 10 since the last NCI review. The Center also saw substantially more patients with new diagnoses; accruals to therapeutic clinical trials increased by 9%. Within 30 days of diagnosis, 90% of new patients with cancer enrolled in a clinical trial; 60% enrolled in a therapeutic trial. Finally, since the last NCI review, the Center's total peer-reviewed funding (i.e., federal and private foundation awards) to support cancer research increased by 13%.

The NCI awarded the Center its second consecutive highest-possible "Exceptional" ranking and the best numerical score in the Center's history. NCI reviewers referred to St. Jude as a "national treasure," invoking our remarkable success in translating science into advances for the benefit of pediatric patients with cancer everywhere. Exceptional marks were also awarded to all 6 of the essential characteristics of a Cancer Center: physical space, organizational capabilities, transdisciplinary collaboration and coordination, cancer focus, institutional commitment, and the Center Director. The outcome of the 2018 NCI review further reinforces the position of St. Jude, the only NCI-designated Cancer Center dedicated solely to children, as one of the nation's elite Cancer Centers.

Looking Ahead

With the arrival of Dr. Roberts in 2015, the Center developed a new vision to bring about a new era of precision therapies and cures for children with pediatric cancer via pursuit of discoveries in epigenetics, genomics, and immunotherapy. To realize this vision, the Center is tapping into the remarkable intellectual and philanthropic resources of St. Jude to engage leading experts within the Center and beyond in the fight against childhood cancer.

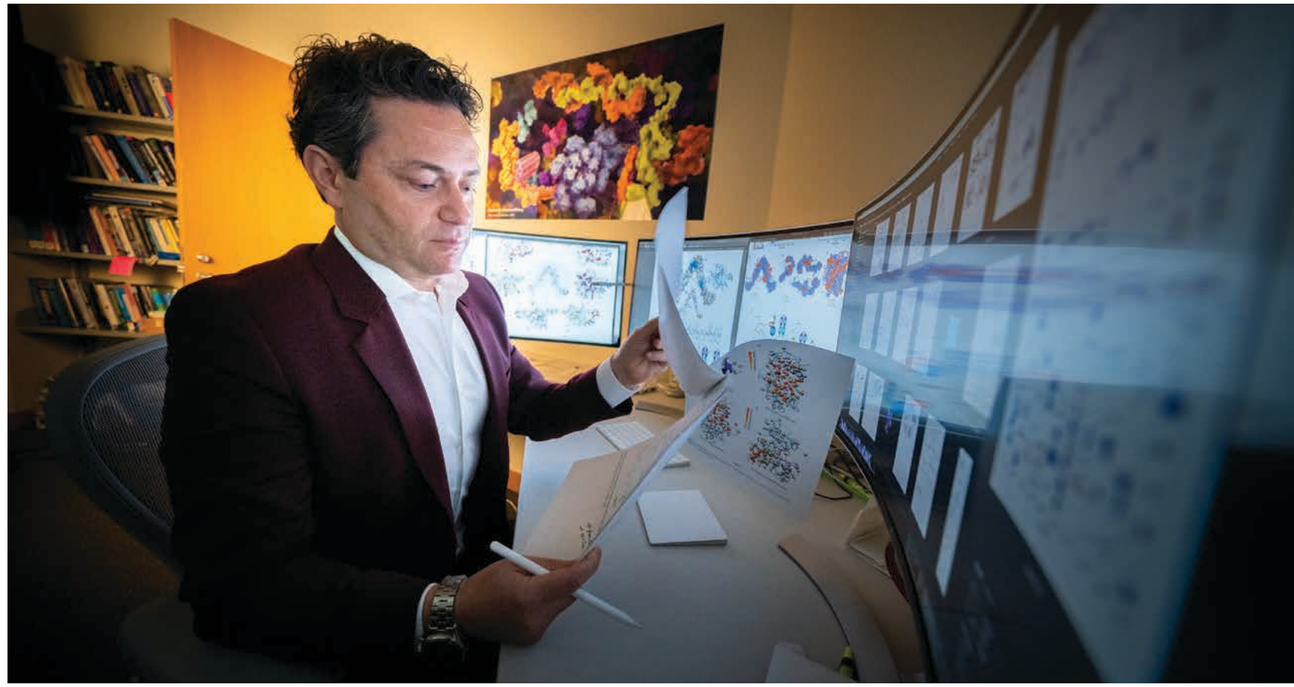
Looking ahead, the Center will advance this vision through large-scale strategic initiatives, build on its strong foundation of transdisciplinary collaboration, and serve as a model for pediatric cancer research and treatment across the globe.

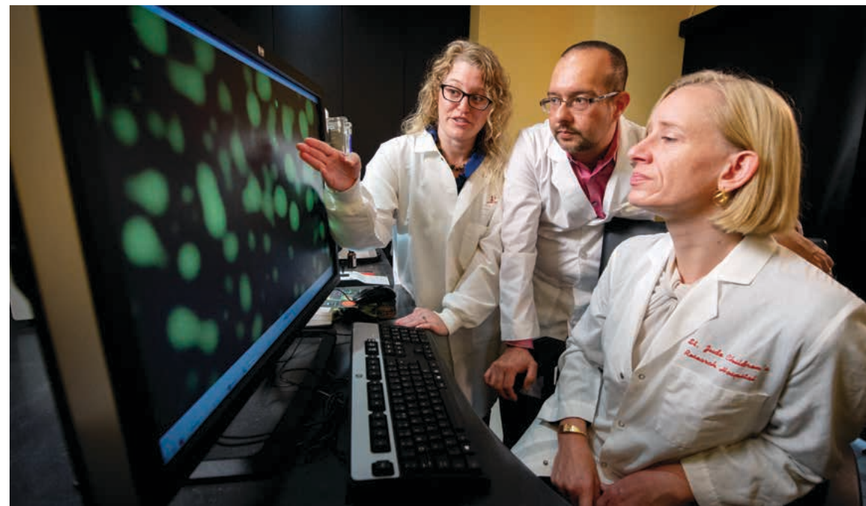
THE STRUCTURAL BIOLOGY DEPARTMENT EXPANDS TO BECOME THE WORLD'S PREMIER CENTER FOR STRUCTURAL ANALYSES AND IMAGING OF BIOMOLECULES

Biomolecules are dynamic; changes in their 3-dimensional (3D) shape endow them with an array of activities. Proteins are the main class of biomolecules in our bodies; they perform functions that make life possible. Proteins come in a range of shapes and sizes and possess distinct capabilities. Understanding how structural changes in proteins impart function is, therefore, fundamental to all biology, whether in health or disease. Providing this understanding is the task of structural biologists.

Structural biologists use sophisticated instruments to elucidate protein structures at the highest (atomic) resolution to study their functions and understand how abnormal proteins give rise to diseases. Three frontline techniques are used to examine biomolecular structures: cryogenic electron microscopy and tomography (cryo-EM/TM), nuclear magnetic resonance (NMR) spectroscopy, and X-ray crystallography. Each of these techniques has unique strengths and limitations, and structural biologists often must integrate the results from different techniques to fully visualize and understand the structures of complex biomolecular systems (e.g., multicomponent assemblies and macromolecular machines). In addition, complementary techniques are used to probe specific details of biomolecular mechanisms. These include mass spectrometry, which reveals changes in the composition and stoichiometry of protein complexes; single-molecule imaging techniques, which monitor the structure and movement of specific parts of biomolecules; and computational simulations, which use powerful computers to study the motions that occur when biomolecules function.

In catastrophic diseases, the functions of biomolecules are altered. Structural biologists examine the structural basis for such functional alterations to gain insights into new therapeutic strategies. This can occur, for instance, through the generation of new drugs that are able to counteract disease by targeting deleterious alterations in the activities of proteins and other biomolecules. The Department of Structural Biology has built an infrastructure to not only elucidate biomolecular structures fundamental to health and disease but also enable the drug-discovery process at every step. For instance, NMR-based binding screens can be used to identify the ligands of any macromolecule assembly, irrespective of shape and size, to spearhead drug-discovery campaigns. Crystallographic structure determination of targets in complex with ligands is the gold standard in drug discovery, facilitating rational design and iterative chemical synthesis and testing. Cryo-EM/TM has great potential for enabling drug discovery for difficult targets, such as membrane proteins that are difficult to visualize with other techniques. Some drug targets of interest to St. Jude investigators in structural biology include kinases, E3 ligases, protein–protein interactions, proteins involved in programmed cell death, essential bacterial enzymes, ribosomes, and various membrane proteins.



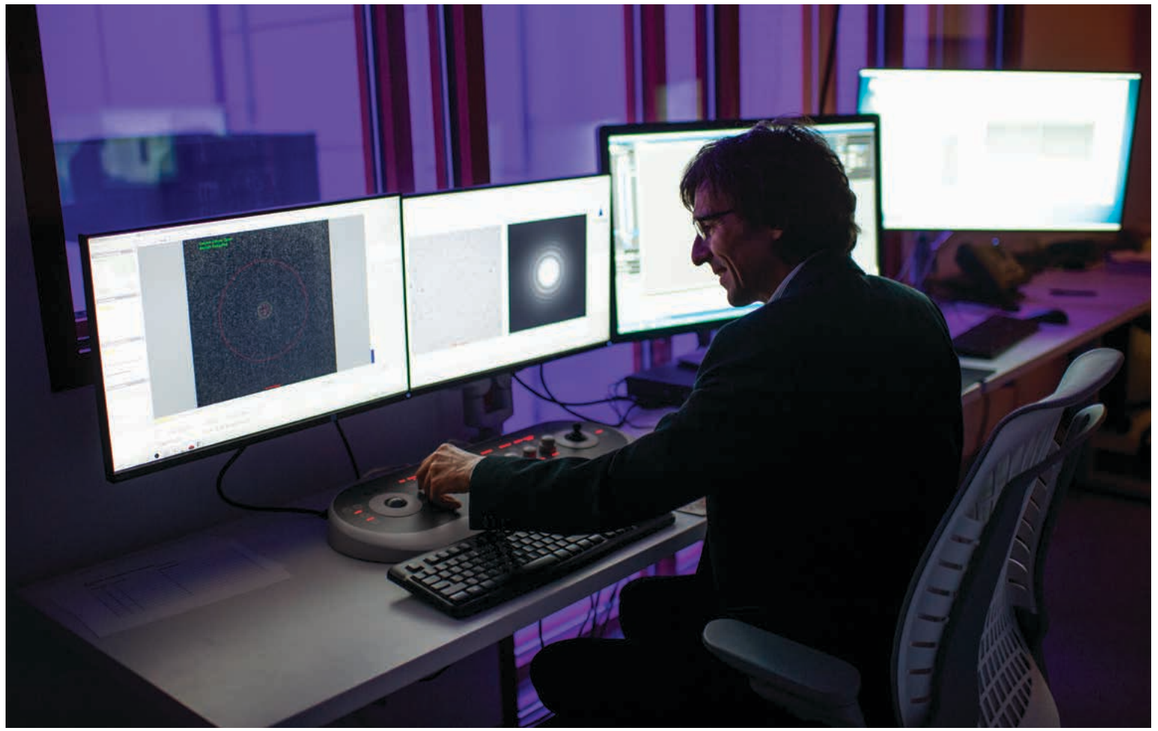


Structures are blueprints for developing hypotheses about biomolecular functions that can be tested using genetic, biochemical, and cell biological approaches. However, to fully understand function in detail, structural biologists need to examine the movement of biomolecules, which is termed protein dynamics. Proteins are not static objects; they are rapidly changing molecules that move, bend, expand, and contract. Without such motions, many proteins and nucleic acids cannot function properly. The overarching goal of structural biology is to elucidate all conformations needed for a biomolecule to function and determine how those conformations interconvert and how this interconversion between structural conformations leads to biological functions. Structural changes in proteins and other biomolecules span orders of magnitude in time and space. For example, methyl sidechain rotations take picoseconds and lead to changes measured in angstroms; different conformations of intrinsically disordered proteins occur in nanoseconds to microseconds and are measured in nanometers; and large-scale domain motions can take milliseconds to seconds and are measured in tens of nanometers. The techniques used to study these processes depend on the time scale and extent of the structural change. Cryo-EM/TM and X-ray crystallography can distinguish biomolecular conformations but typically not the movement that gives rise to them. NMR spectroscopy is particularly adept at determining the time scale and amplitude of molecular movements. Single-molecule fluorescence imaging captures individual molecules in different states, thereby enabling us to understand how an interconversion occurs.

No individual technique provides all the information needed to understand structure and activity, which is why structural biologists must integrate results from comprehensive analyses of protein structure and dynamics acquired using multiple methods. By deploying and actively developing the wide range of sophisticated techniques available, St. Jude has positioned itself at the forefront of the emergent field of integrative structural biology.

Building Cutting-Edge Structural Biology Technologies at St. Jude

The Department of Structural Biology has expanded to join premier research centers and aspires to become the top center for imaging and biophysical modalities, enabling St. Jude researchers to examine intricate cellular processes at the atomic level. Department Chair Charalampos Babis Kalodimos, PhD, a world-renowned structural biologist, is directing this effort by recruiting world leaders in structural biology to join the St. Jude faculty and bringing innovative technologies to the St. Jude campus. The department has created 6 centers: Cryo–EM/TM, NMR Spectroscopy, X-ray Crystallography, Single-Molecule Imaging, Mass Spectroscopy, and Protein Technologies. Researchers working in these centers will engage in cutting-edge structural biology research, and the Protein Technologies Center will facilitate collaborations between the department and St. Jude investigators working in other fields. Here we describe the technologic capabilities of those centers and introduce the scientists working in them.



Mario Halic, PhD

Cryo-Electron Microscopy and Tomography Center

In cryo-EM, biological samples are rapidly frozen to the solid state in a manner that prevents dehydration and ice crystallization. Biomolecules in aqueous solutions are blotted to a thin layer and plunged into liquid ethane (−182 °C) cooled by liquid nitrogen. Rapid cooling traps the biomolecules in their native hydrated state, embedded in glass-like vitreous (or amorphous) ice. The samples are then transferred to an electron microscope and imaged by electrons near the temperature of liquid nitrogen (−196 °C). The recorded images represent 2D projections of the sample and are used to reconstruct the 3D architecture of the biomolecule through intensive computational analyses. Single-particle cryo-EM technology has made remarkable progress in recent years due to the development of direct electron detector device cameras. These detectors have superior signal-to-noise performance, making it possible to generate images with unprecedented clarity and extract structural information of the finest detail. These advances have led to a "resolution revolution" in cryo-EM, which is now routinely used to generate 3D structures of biomolecules. This development was recognized with the Nobel Prize in Chemistry in 2017.

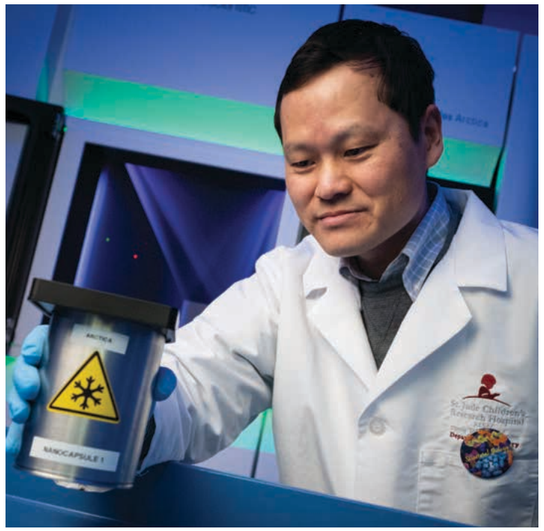
Cryo-EM is particularly powerful for studying large macromolecular complexes. Recently, it was used to solve the structures of several fundamental biomolecules, including ribosomes and ion channels, and human pathogens, such as Zika virus, influenza virus, and Ebola virus. These discoveries have greatly influenced medicine and public health. A related technique, electron cryogenic tomography (cryo-TM), also uses cryogenic methods for sample preparation and electron microscopy methods for image acquisition, but cryo-TM includes added tomographic-reconstruction methods to reveal 3D structures of cells and tissues. This makes it possible to visualize structures of biological molecules in their native cellular environment. Thus, recent advances in cryo-EM/TM are transforming many life science and biomedical disciplines.

Last year, St. Jude recruited Mario Halic, PhD, a prominent leader in the field, to establish a preeminent research program in cryo-EM. Dr. Halic's research combines cryo-EM, biochemistry, and genetics to determine how enzymes and structural proteins modify nucleosome and chromatin structure. In so doing, he is defining the molecular mechanisms that recognize specific genetic elements and target them for epigenetic silencing by heterochromatin, a specialized silent chromatin structure. Furthermore, Dr. Halic's laboratory uses structural methods to understand how heterochromatic proteins recognize and modify chromatin to establish this silent state. His long-term goals are to understand the regulation of genome expression by chromatin and discover why mutations in chromatin proteins lead to the formation of cancer cells.

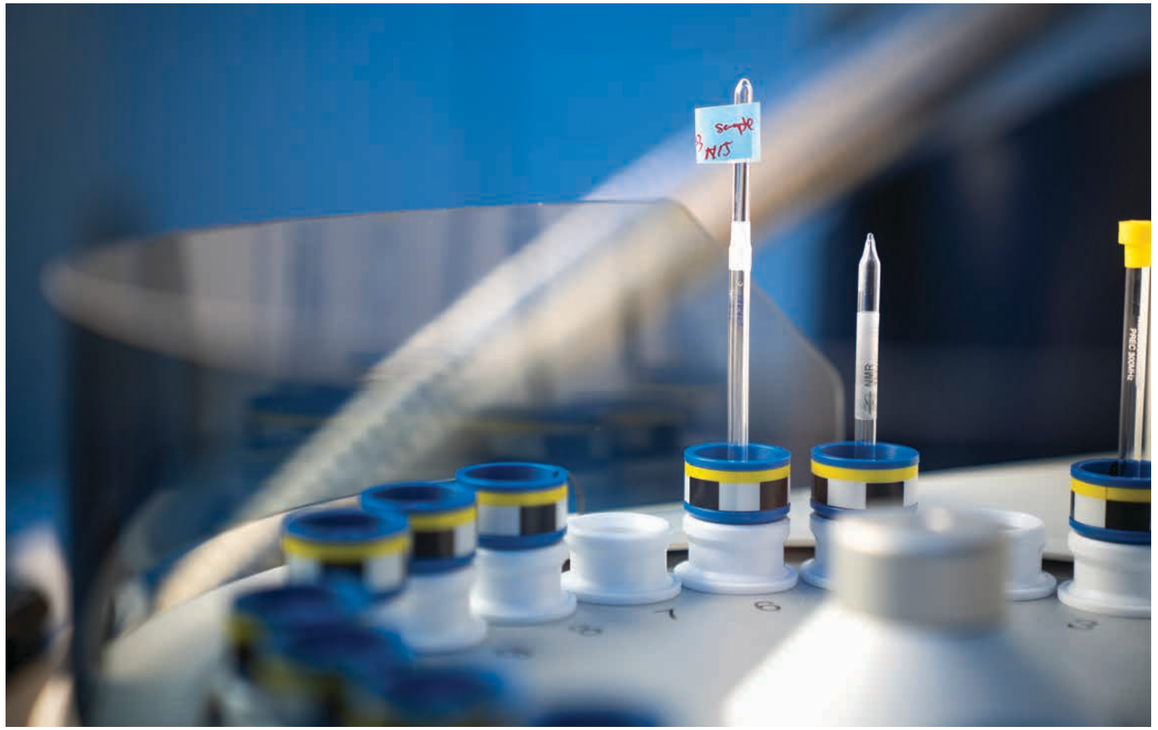
The Cryo-EM/TM Center at St. Jude has capabilities to perform single-particle cryo-EM and cryo-TM. Under the direction of Liang Tang, PhD, the Center houses a 300-keV Titan Krios transmission electron microscope that features a brilliant, highly coherent X-FEG electron source, a cryo-autoloader for automated and contamination-free sample loading, the latest K3 direct electron detector, and a BioQuantum energy filter, all of which are built onto an ultra-stable platform, ensuring maximal performance, throughput, and resolution. The Krios is equipped with a Volta phase plate, which extends its ability to image smaller proteins and perform high-resolution cryo-TM. The Center also has a 200-keV Talos Arctica transmission electron microscope equipped with a K3 direct electron detector and a BioQuantum energy filter and a 120-keV Talos transmission electron microscope for sample screening and optimization. In addition, the Center houses all essential auxiliary equipment for sample preparation, including a Vitrobot Mark IV, a Solarus II plasma cleaner, and a carbon coater. The Center plans to expand into cryo-correlative light and electron microscopy for high-resolution imaging of cells and tissues.

Cryo-EM experiments generate several terabytes of imaging data per day per instrument. The images need to be processed to generate a 3D map of the biomolecule being studied, which requires high-performance computing. The Center is supported by state-of-the-art computational resources, including a dedicated cluster with hundreds of computing central-processing units and a range of high-performance computing facilities available at the St. Jude Data Center.

The Center is committed to delivering the latest technology to the broader research community at St. Jude. Its goal is to enable researchers to visualize intricate biological structures at atomic or near-atomic resolution and cellular structures in their native context with unprecedented detail and clarity. The Center is opening avenues to various applications in basic and translational research and is expected to have an immediate, substantial impact on drug-discovery and biomedical research at St. Jude.



Liang Tang, PhD



Nuclear Magnetic Resonance Spectroscopy Center

NMR spectroscopy uses very strong superconducting magnets and high-power radio-frequency pulses to study the chemical structure of molecules, ranging from small chemicals (e.g., drugs) to biological macromolecules (e.g., RNA, DNA, proteins). When molecules are placed in a strong magnetic field, the nuclei of certain atoms (e.g., hydrogen, carbon, and nitrogen) resonate. This is detected through powerful radio-frequency pulses. NMR signals can reveal the 3D structure and motions of biomolecules, and NMR spectroscopy is used to study the motions of biomolecules in solution at ambient temperatures or in solid form, conditions that reflect their environment within living cells. By combining information about 3D structure with insight into how atoms move, we can comprehensively understand how biomolecules function in cells and how those functions are altered in diseases. Furthermore, NMR spectroscopy is a powerful tool in the development of new therapeutics; the Center has 2 spectrometers dedicated to drug-discovery research in the Department of Chemical Biology & Therapeutics.

The superconducting magnets in the Center weigh as much as 10 tons and are cooled with liquid helium (–452 °F) to remain superconducting. The magnetic field strengths range from 94,000 to 258,500 Gauss—more than 200,000 times stronger than the Earth's magnetic field. The Center houses 9 NMR spectrometers located in temperature-, humidity-, and vibration-controlled laboratories. These instruments operate at frequencies ranging from 400 to 850 MHz and represent one of the largest collections of NMR spectrometers in the world. In late 2019, the Center will receive the first of the world's most powerful NMR spectrometer, operating at 1.1 GHz. This device will enable more detailed studies of biomolecular structure, motion, and function and permit the study of more complex biomolecular systems than is currently possible.

Although a specialized technique, NMR spectroscopy is accessible to the entire St. Jude research community through the expert services of the NMR Center Director Youlin Xia, PhD, and staff scientists. Several laboratories in the Department of Structural Biology specialize in NMR studies of biomolecules, and scientists within and outside the department collaborate with the Center's staff. The staff are available to design and perform NMR experiments or train scientists working in other fields to perform their own NMR experiments. This enables the Center to influence research and discovery in many departments at St. Jude, including Cell & Molecular Biology, Chemical Biology & Therapeutics, Developmental Neurobiology, Immunology, Infectious Diseases, Pathology, and Pharmaceutical Sciences. The recent expansion of the Center and the acquisition of the 1.1-GHz NMR spectrometer will enhance our contributions to understanding the molecular basis of pediatric catastrophic diseases and our ability to devise new cures.

Youlin Xia, PhD

Darcie Miller, PhD

X-Ray Crystallography Center

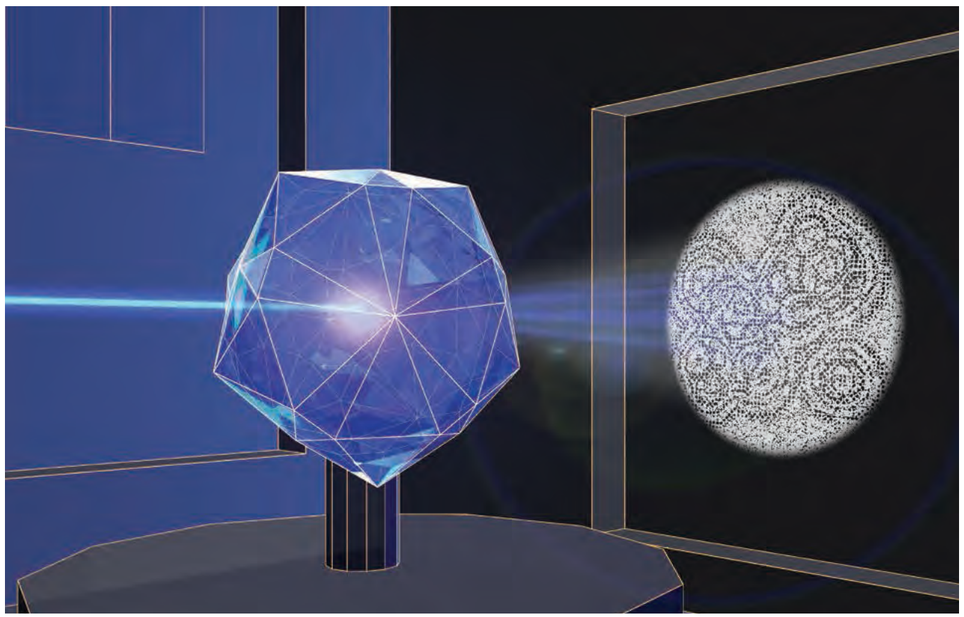
X-ray crystallography is a powerful tool that has served as a mainstay of drug-discovery programs. It is the most efficient method for obtaining high-resolution structures of targets, ranging from tiny proteins to protein assemblies. In as little as 2 weeks, crystallographic techniques can reveal the overall architecture of biomolecules, down to their atomic details. Snapshots of enzymatic reactions and ligand interactions can also be elucidated. Such exquisitely detailed structural information provides the framework for follow-up structure-to-function studies, therapeutic interventions, and understanding the molecular basis of cancer-causing mutations.

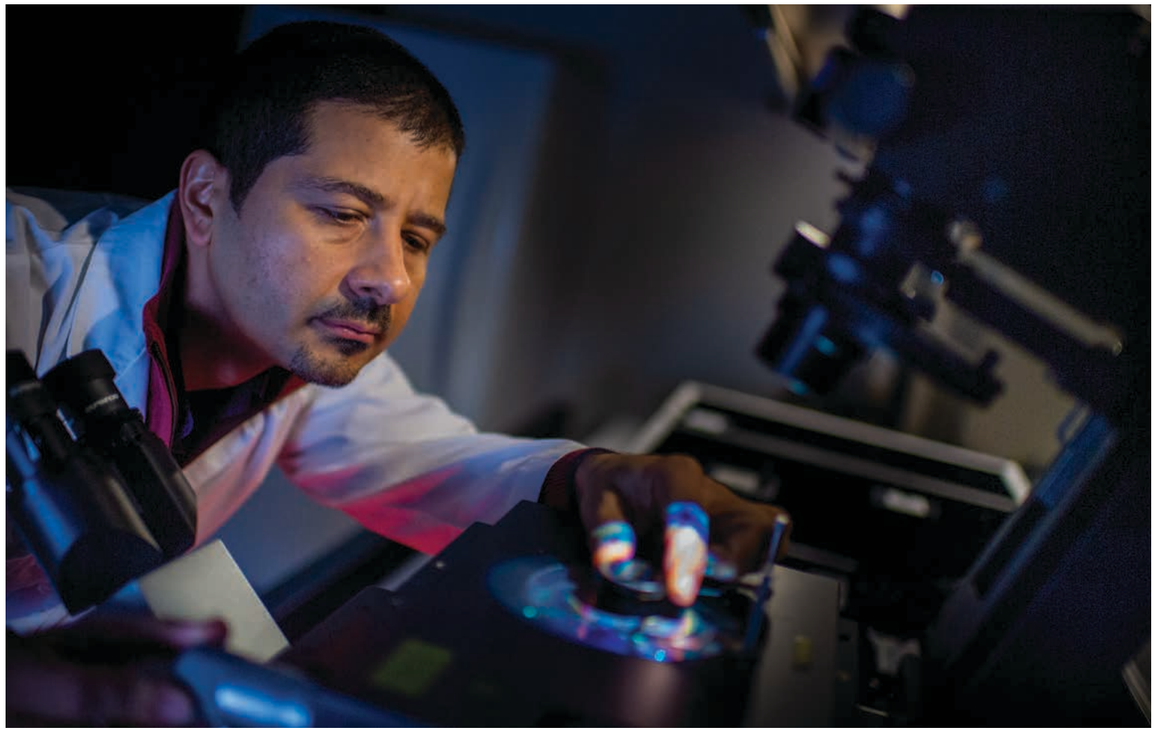
X-ray crystallography is used to determine the arrangement of atoms within a crystal. Essentially, protein crystals are grown and subjected to X-rays to produce distinctive patterns of diffraction intensities. These diffraction patterns are determined by the underlying atomic arrangement of the molecules that form the crystal and can be used to back-calculate the atomic structures of the molecules within the crystal. X-rays allow for the resolution of interatomic distances, because the wavelengths of X-rays are comparable to the distances between atoms in molecules. The purpose of the crystals is to increase the signal-to-noise ratio. Molecules in solution do not scatter X-rays to high resolution; however, in crystals, many identical molecules are arranged in a pattern that sharpens and reinforces the X-ray signal.

Under the direction of Darcie Miller, PhD, the X-ray Crystallography Center facilitates crystal structure determination efforts by St. Jude researchers at all levels of crystallographic expertise. Like other techniques, crystallography relies heavily on the purity and quality of the protein sample. Crystallographic analysis begins with obtaining a highly pure, monodispersed protein or protein complex. Next, robotic instruments are deployed for efficient screening of large numbers of crystallization conditions by using nanoliter dispensing and monitoring to identify conditions producing high-quality crystals. The latter task is greatly aided by a “plate hotel” that automatically captures high-resolution images of individual crystallization drops on a customizable, user-defined schedule.

The highest-resolution X-ray structures are afforded by synchrotron light sources that produce brilliant, tunable X-rays. St. Jude researchers working with the Center benefit from regular access to the Advanced Photon Source at Argonne National Laboratory (Lemont, IL), where remote data collection from a Center workstation is routine. A chosen crystal is mounted by a robotic arm and then rotated within the X-ray beam, while St. Jude researchers measure the directions and intensities of the resulting diffracted X-rays. The next steps are data processing and semiautomated structure determination. If this process is successful, the result is an electron-density map ready for interpretation and use in model building by the crystallographer. Finally, during refinement, the atomic model is iteratively extended and revised to better fit the original diffraction data.

X-ray crystallography continues to break new technologic ground. Recent advances in X-ray source brilliance, beam focus, detector frame rate, and sample delivery have been combined in a new method, serial synchrotron crystallography, that enables X-ray scientists to collect data and solve structures from smaller crystals than ever before possible. Several national beamlines are pioneering this method, which will enable us to determine structures from micron-sized crystals. The structural information gleaned will help us better understand and develop therapeutic approaches targeting cancer and other catastrophic pediatric diseases.





Alessandro Borgia, PhD

Single-Molecule Imaging Center

Like ordinary machines, molecular assemblies require dynamic processes to achieve their purpose and rapidly change their shape and composition. Single-molecule imaging technologies directly monitor and image time-dependent changes in molecular systems. Such efforts are equivalent to videos of biological molecules at resolutions that enable visualization of their molecular movements. By recording the performances of tens of thousands of individual molecules simultaneously, we can identify the full diversity of behaviors that are normally masked when molecules are measured as a group. In so doing, single-molecule measurements advance scientific understanding by establishing how individual members of a potentially diverse group function and respond to a stimulus. Measurements of this kind are expected to facilitate the development of precision medicines for patient care.

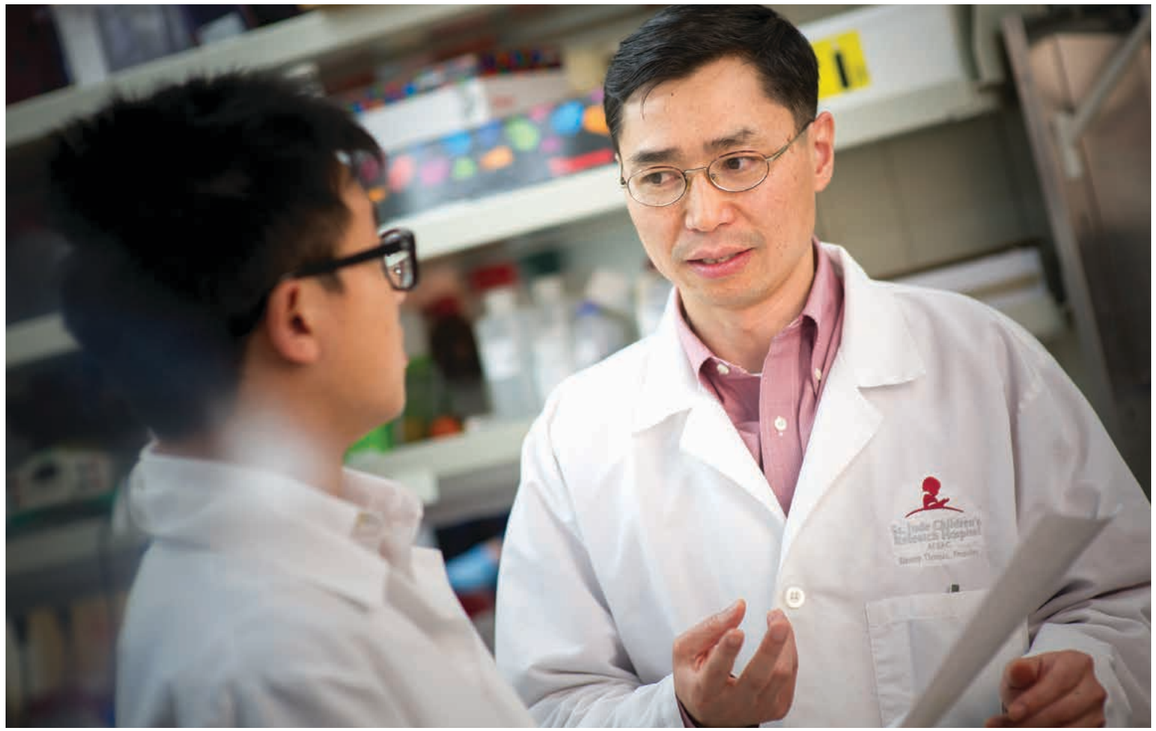
St. Jude is in the process of building a world-class Single-Molecule Imaging Center and has recruited Scott Blanchard, PhD, a preeminent scientist in this field, to lead this effort. Dr. Blanchard's research interests are focused on understanding the molecular basis of gene expression, signal transduction, solute transport across cellular membranes, host–virus interactions, and the mechanism of protein synthesis during cancer. His laboratory seeks to determine how the protein synthesis machinery in metastatic cancer cells can be most effectively targeted to treat the disease.

Under the direction of Alessandro Borgia, PhD, the Center aims to develop and implement spectroscopic techniques that will enable us to visualize proteins and their complexes in real time. To make these efforts possible, the Center is developing and using an array of cutting-edge technologies, including state-of-the-art fluorescent probes, molecular-engineering tools, super high-speed cameras, and complex data-analysis pipelines. Broadly speaking, the Center uses 2 imaging approaches: total internal reflection fluorescence (TIRF) microscopy and time-correlated single-photon counting.

In TIRF microscopy, fluorescently labeled molecules of interest are sparsely tethered to the surface of microfluidic chambers made of quartz glass. This tethering procedure enables individual molecules to be visualized for seconds to minutes. Molecules are illuminated by a focused laser that generates a thin, evanescent (shimmering) field that is hundreds of nanometers thick. This approach enhances the signal needed to see a single molecule. Despite the power of this approach to image tens of thousands of molecules simultaneously, it is limited by the fact that the plane of illumination is fixed with respect to the quartz-solution interface. To overcome this, the Center also uses time-correlated single-photon counting, which focuses the laser illumination to an extremely small volume (about 1 μm^3) at any point of interest—or an array of points of interest—in solution. This method leverages the combination of a small illumination volume and a very low concentration to ensure that individual molecules are detected. It also takes advantage of flexible control of the confocal illumination volume to visualize distal points in space in which molecules are freely diffusing. Although a more time-intensive approach, ultrafast diodes with single-photon sensitivity enable measurements at picosecond to nanosecond time scales.

The integration of single-molecule imaging studies into more conventional studies has already increased our understanding of the regulation of protein synthesis for the treatment of infectious diseases and cancer, the prevention of HIV infection, the modulation of neurotransmission in psychiatric disorders and by drugs of abuse, and the regulation of chromatin dynamics and gene expression through protein–protein and protein–DNA interactions. Staff in the Center will assist and train St. Jude researchers from other departments to plan and run single-molecule imaging experiments and initiate transdisciplinary collaborations to better understand wide-ranging aspects of biology. The overarching goal of the Center is to bring the power of single-molecule spectroscopy techniques to biomedical research at St. Jude for the betterment of human health.

Scott Blanchard, PhD



Hong Wang, PhD; Junmin Peng, PhD

Mass Spectrometry–Based Protein and Proteome Studies

Every cell within an organism has the same genome, which is the blueprint for making proteins. However, cells differ in terms of which genes are activated and which proteins are made. The proteome is defined as the full set of proteins made by a single cell type. Diseased cells often produce proteins that either are not produced by healthy cells or have altered structures and/or functions. Mass spectrometry (MS) is a fundamental approach to studying proteins and proteomes. MS employs magnets or electrical fields to resolve and measure biomolecules according to the masses of their constituent atoms. Specialized techniques provide the flexibility to profile a single protein, small protein complexes, or tens of thousands of proteins and protein modifications simultaneously in a single experiment. Our state-of-the-art MS platform can analyze samples with extremely high sensitivity, down to the level of attomoles (10^{-18} moles), and high mass accuracy (less than 1 ppm).

Staff working in the laboratory of Junmin Peng, PhD, and the Center for Proteomics and Metabolomics focus on using MS to explore protein functions and structures. They deploy several methods and instruments to identify, characterize, and quantify proteins in a way that gives insight to help discover the cause of disease, elucidate protein drivers as potential drug targets, and validate proteins recognized by drugs. Moreover, these methods facilitate the identification of clinical biomarkers that can be used to help diagnose disease or inform treatment.

MS and its use in proteomics can be thought of in terms of 3 levels of increasing complexity: (1) the identification and characterization of a single protein, (2) the study of protein complexes, and (3) whole-proteome profiling. For single-protein analysis, we use MS to identify the protein by measuring its molecular mass. This approach also identifies posttranslational modifications of the protein, which are crucial regulators of biological function, play a substantial role in cell and tissue function, and have been linked to disease causation and progression. Abnormal posttranslational modifications can serve as potential drug targets. This technique of analyzing an intact protein without digesting it with specific enzymes is often referred to as top-down MS. Bottom-up MS is also done to probe protein modifications that are present at low levels.

Identifying the interplay between proteins and protein complexes, which are key cellular components, is central to understanding how cells function. These complexes are interrogated using various approaches. Affinity purification and mass spectrometry (AP-MS) is used to determine the components of a complex. The system can then be perturbed to see how the protein complex is affected. Isotopic-labeling methods (e.g., tandem mass tags and stable isotope labeling with amino acids in cell culture) and AP-MS can also be used to measure complex protein dynamics within a cell. Cross-linking MS is used to gain insight into the structure of protein complexes and determine what proteins or regions of proteins interact and how those interactions change within a biological system.

The third level of protein complexity is whole-proteome profiling, which involves identifying and quantifying all protein components within a cell type or tissue. We have made great strides to improve this technique via many technical advances. Cutting-edge technologies allow the quantification of nearly all expressed proteins in a cell. This again involves the use of tandem mass tags coupled with 2D liquid chromatography and tandem MS. It is now feasible to identify and quantify more than 12,000 proteins from mammalian samples. By using these methods, combined with the enrichment for posttranslational modifications, it is also possible to identify and quantify protein modifications (i.e., phosphorylation, ubiquitination, acetylation, and methylation). The Center has the capacity to perform such large-scale experiments with a range of biomedical samples, from cancer cells in culture to preclinical models and clinical specimens. Proteomic data are integrated with genomic data and phenotypic information to offer a systems or holistic view. Together, these results provide an unbiased determination of disease networks and provide insights into novel therapeutic strategies.

Ravi Kalathur, PhD

Protein Technologies Center

Structural biology studies begin with producing purified samples of a biomolecule of interest. Molecular cloning and protein-engineering strategies and state-of-the-art, high-throughput instrumentation are used to optimize biomolecule production and purification. Proteins are often difficult to express outside their host or overexpress within their host; even if expressed in necessary quantities, they are sometimes not stable enough to withstand the rigors of experimentation. Furthermore, determining the best sample conditions for protein production using traditional techniques can be a slow and arduous process. The Protein Technologies Center (PTC) was established to focus on advanced technologies needed for optimized protein production and expertise troubleshooting the most challenging problems in a single center, thereby enabling investigators to make discoveries faster and tackle biological systems that have remained recalcitrant to structural studies.

Under the direction of Ravi Kalathur, PhD, a team of scientists uses semiautomated, multipronged approaches at each stage of the pipeline: from construct design, cloning, expression, and purification to characterization of all protein targets, including membrane proteins, multiprotein complexes, and assemblies. The PTC can synthesize as many as 32 different 2000-nucleotide DNA tiles in an overnight run by using the BioXp 3200 DNA printer. Synthesized DNA tiles can be inserted into expression vectors by using precise, sequence-independent, scarless cloning methods. Once the plasmid is generated, it is introduced into several hosts (e.g., bacteria, insect, and mammalian cells) to make the protein. The PTC can process various cell culture volumes (1 mL-50 L) by using a parallel bubbling system and temperature- and humidity-controlled shakers. After the protein is made, the cells are opened via a specially designed robotic sonicator, which is programmed for processing small volumes. For large volumes, the CF1 cell disruptor is used; this instrument processes as much as 6 L of cells per hour. After the cells are lysed, the samples are fractionated by high-speed ultracentrifuges to separate organelles and macromolecules.

Every protein is different, and each one needs different conditions to be stable and amenable to structural studies. For example, membrane proteins are embedded in a lipid bilayer on the cell membrane; thus, they must be handled using a mixture of detergents and lipids. Once the protein of interest is isolated from its constituents of cells, it is enriched, purified, and separated from the other proteins in the sample via chromatographic systems. These systems in the PTC are equipped for parallel processing and have a temperature-controlled autosampler and ultraviolet and fluorescence detectors, which are capable of screening and purifying 96 samples concurrently. The purified homogeneous protein sample can be tested for stability using Tycho, a modified differential-scanning fluorimetry instrument.

The PTC can also perform functional assays by using Cytation 5, a microscope with a microplate reader. After the protein sample is characterized, the labeled protein is used to solve its structure by NMR, crystallized for X-ray crystallography, and/or flash-frozen to trap the protein particles in vitreous ice for single-particle cryo-EM analysis. The PTC will accelerate projects of investigators who are keen to understand the structure of protein targets, and it is the “glue” that binds research teams in departments across the institution.

Structural Biology Contributes to Discovery and Cures

Structural biology studies provide in-depth characterization of key biomolecules and mutations or other disease-associated alterations that disrupt cell function by causing protein misfolding, aggregation, and/or altered protein dynamics. For example, NMR spectroscopic analysis revealed how mutations in the BCR–ABL fusion protein associated with chronic myelogenous leukemia (CML) cause treatment resistance. The mutation changes the equilibrium between the ground state of tyrosine kinase and a high-energy conformation that enables kinase inhibitor binding, thereby diminishing the efficacy of tyrosine kinase inhibitors, a standard chemotherapy agent used to treat CML. This information on protein dynamics can be used to develop improved, next-generation BCR–ABL inhibitors to treat drug-resistant leukemias.

Structural information has enabled rational engineering of more effective therapeutic antibodies, which have revolutionized immunotherapies against cancer. It has also enhanced CRISPR/Cas9 genome-editing enzymes to improve their performance and diminish nonspecific genome targeting. Structural information has improved fusion tags within technically challenging membrane proteins, such as G-protein–coupled receptors, to determine the structures of their various functional forms and enable visualization of how these proteins are altered by ligands that trigger cellular-signaling functions.

Atomic-resolution structures can also be used to evaluate the suitability of biomolecules for therapeutic targeting. For example, if X-ray crystallography, cryo-EM, or NMR data show that a disease-associated protein has a deep pocket within its 3D structure, new drug molecules can be synthesized to fit in that pocket and inhibit the protein. Structural biology techniques can be used to screen chemical compounds that bind in the pocket, quantify the binding affinity of those compounds, guide their optimization, and determine the 3D structure of the protein–compound complexes, thereby allowing structure-based design of further-improved compounds. Structural biology can further reveal generalizable principles of drug design. For example, the characterization of numerous structures of enzyme–inhibitor complexes revealed that inhibitors typically stabilize the transition state of enzymes, thereby inhibiting their activity. This concept now guides the development of novel enzyme inhibitors. Structural biology thus plays a fundamental role in any effort to design and characterize new therapeutics that target relevant biomolecules specifically and potently.

Although facilitating the discovery of new therapeutics is an important role of structural biology research, its contributions to elucidating fundamental mechanisms of biomolecular function underpin our understanding of molecular and cell biology. Detailed insights into the structure, dynamics, and function of specific biomolecules have revealed new information about how biomolecules function. One example relates to how the interior of cells is organized. Structural biology investigations have recently shown that transient interactions between intrinsically disordered proteins drive liquid–liquid phase separation within cells. This causes proteins and other biomolecules to co-associate and condense, forming membraneless organelles. This process goes awry in certain diseases, and the molecular insights gained from structural biology studies are providing new directions for developing therapeutics to target those diseases. The Structural Biology department has a strong research program in this area spearheaded by Richard W. Kriwacki, PhD, and Tanja Mittag, PhD. These are just a few examples of how structural biology research forms a foundation for our molecular understanding of biology and disease and promotes the rational development of novel therapeutics.

Charalampos Babis Kalodimos, PhD

In the Future

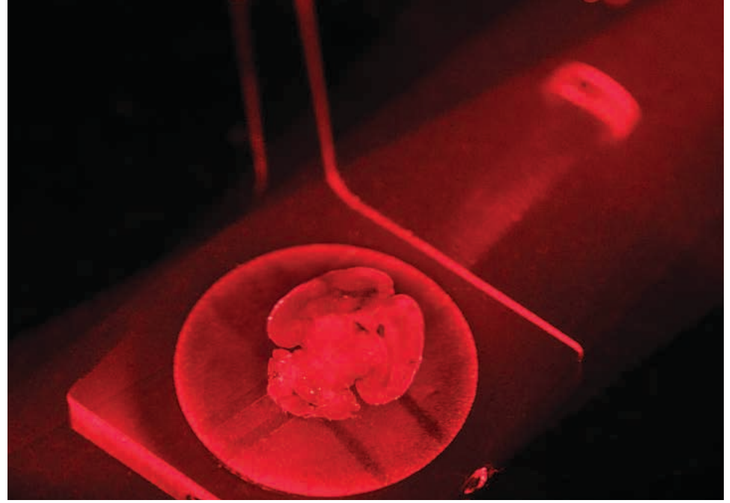
Most structural biology analyses are currently performed outside living cells. The next challenge in the field is to develop and implement technologies that allow the study of the structure, dynamics, and function of biomolecules in living cells. Cryo-TM uses electron microscopy to examine frozen cell specimens at near-atomic resolution, thereby simultaneously revealing the organization of all biomolecules in the cell. NMR spectroscopy has been used to study the structure and dynamics of individual proteins within living cells, and single-molecule fluorescence methods are used to monitor dynamic biomolecular processes inside cells. These and other methods yet to be developed will redirect the field from studies of isolated biomolecules to those of biomolecular behavior in complex biological systems in living cells. This future holds the promise of revolutionizing our molecular understanding of biology and disease.

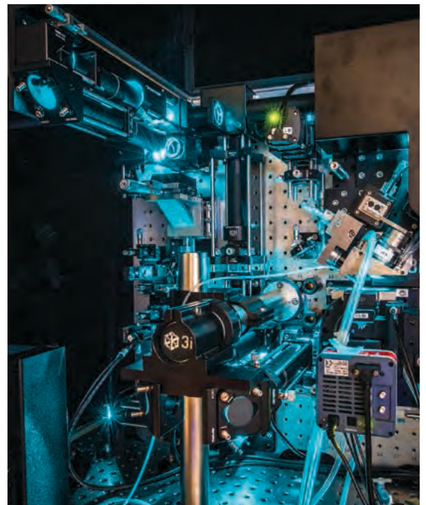
BUILDING A NEXT-GENERATION LATTICE LIGHT-SHEET MICROSCOPE TO VISUALIZE GENOMIC ACTIVITY IN LIVING NEURONS

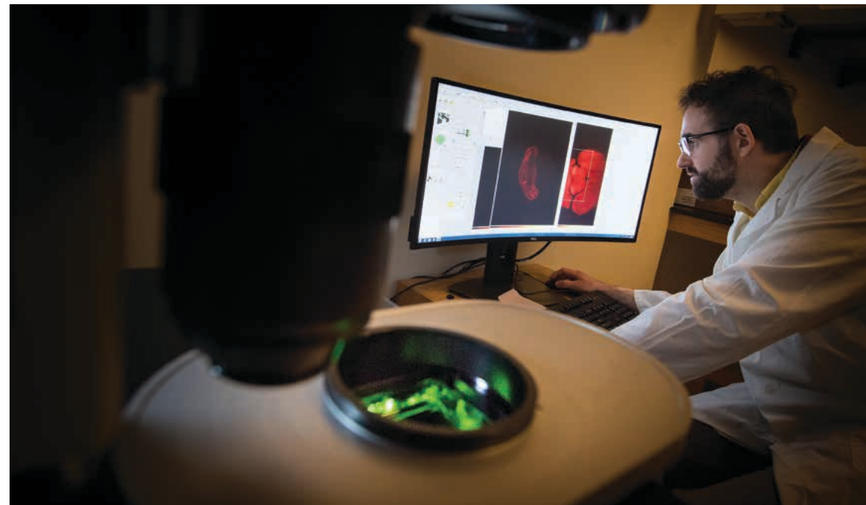
The pursuit of mechanistic insights into biological processes can drive technologic innovation. Likewise, advances in technology enable biomedical researchers to answer questions that were previously intractable. Nowhere has this been more evident than in the application of microscopy to neuroscience. Camillo Golgi published his classic silver staining method that allowed for unprecedented definition of nervous tissue by light microscopy in 1873. Ramón y Cajal then used Golgi's stain to show the remarkable diversity of neurons in the brain. In 1906, they shared the Nobel Prize in Physiology or Medicine. In 2014, the Nobel Prize in Chemistry was awarded to Eric Betzig [University of California, Berkeley; Howard Hughes Medical Institute (HHMI)], Stefan Hell (Max Planck Institute), and William E. Moerner (Stanford University) for the development of super-resolution fluorescence microscopy. Conventional light microscopy is limited by diffraction. Super-resolution fluorescence microscopy enhances resolution beyond these limits, making it possible for researchers to visualize single molecules within cells.

The Department of Developmental Neurobiology at St. Jude uses the most advanced modern microscopy platforms available to gain a deeper understanding of the development, function, and diseases of the nervous system. Stanislav S. Zakharenko, MD, PhD, uses in vivo 2-photon laser-scanning microscopy to understand the changes in neuronal function associated with schizophrenia. James I. Morgan, PhD, uses 3-dimensional (3D) electron microscopy to study synapse formation in the cerebellum, and Lindsay A. Schwarz, PhD, uses light-sheet microscopy to understand the neuronal circuits that control the autonomic nervous system's fight-or-flight response.

Two St. Jude researchers, Michael A. Dyer, PhD, and David J. Solecki, PhD, are engaged in the study of different areas of developmental neurobiology. They recently joined forces to tackle the development of new methods of light and electron microscopy. Here we retell the story of their entry into an elite group of 4 laboratories working with Nobel Laureate Eric Betzig to help build his latest instrument, the next-generation lattice light-sheet microscope. Thus, Drs. Dyer and Solecki are taking their place in helping create technologic innovations and neuroscience discoveries that will propel neuroscience in the future and continue the legacy that began with Golgi and Cajal.







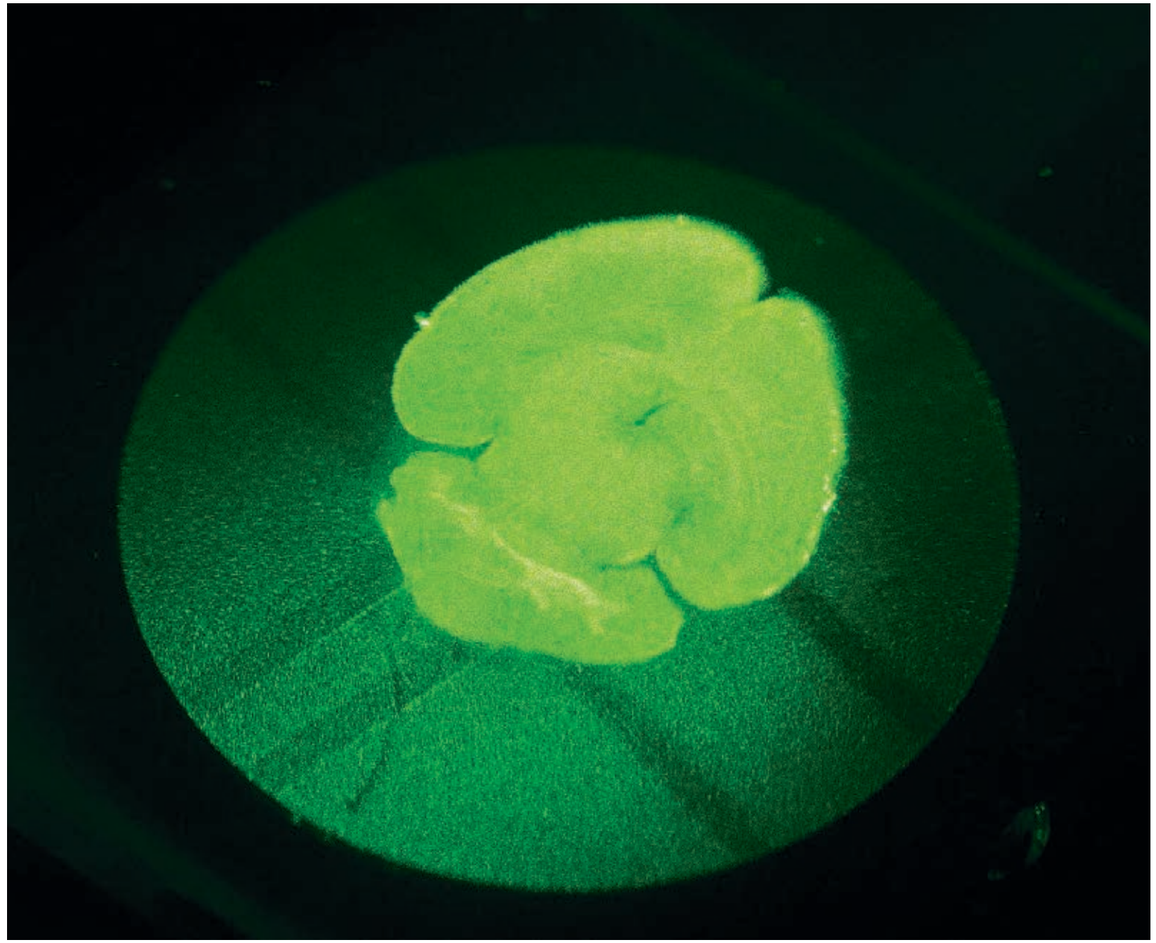
Michael A. Dyer, PhD

Epigenetic Reprogramming Mediates Retinoblastoma Formation

Retinoblastoma is a childhood cancer of the developing retina that begins in utero and is diagnosed within the first few years of life. It is initiated when the *RB1* gene is inactivated in retinal progenitor cells. Dr. Dyer's laboratory has been studying retinoblastoma for the past 15 years to elucidate its cellular origins and develop more effective, targeted therapy. Through the St. Jude Children's Research Hospital–Washington University Pediatric Cancer Genome Project, Dr. Dyer and colleagues discovered that inactivation of the *RB1* gene leads to epigenetic reprogramming and activation of potent oncogenes that are not normally expressed in the developing retina. Their discovery provided the first evidence suggesting that retinal cells are vulnerable to malignant transformation at a particular stage of development.

The epigenome comprises the dynamic and heritable modifications in the structure and organization of DNA as it is wrapped around histones, partitioned, and condensed in the nucleus. Epigenetic changes can profoundly influence gene expression. The epigenome undergoes dramatic changes during brain development, and it is often disrupted in cancer. To gain a deeper understanding of the dynamic changes that occur in the epigenome during retinal development and retinoblastoma formation, Dr. Dyer initiated a 5-year effort to profile the covalent modifications of the DNA and histones, short- and long-range DNA-looping interactions required for packing of chromatin into discrete nuclear domains and gene regulation.

The researchers discovered that the epigenetic signature of retinoblastoma cells is the same as that of retinal progenitors during the developmental stage when they produce the most retinal neurons. In addition, the team identified dozens of genes linked to retinal diseases that are epigenetically silenced in a cell type–specific manner in the mature retina. The most unexpected result from this study, which was published in *Neuron* in 2017, was that those epigenetically silenced genes are sequestered in discrete domains within the nucleus called facultative heterochromatin. This finding contradicted a long-held dogma in the field at that time—that the facultative heterochromatin region of the nucleus does not contain genes. The evidence for differential subnuclear localization of inactive genes came from fluorescence in situ hybridization studies combined with immunofluorescence studies by Marcus Valentine, the director of the St. Jude Cytogenetic Shared Resource. Those studies were performed on fixed tissue. To prove that facultative heterochromatin does contain silenced genes, Dr. Dyer and colleagues knew they had to visualize individual genomic loci moving across nuclear domains within living tissue. To do this, they needed to image developing viable retina at higher levels of magnification than were possible at the time and directly correlate those images with 3D electron microscopy images.

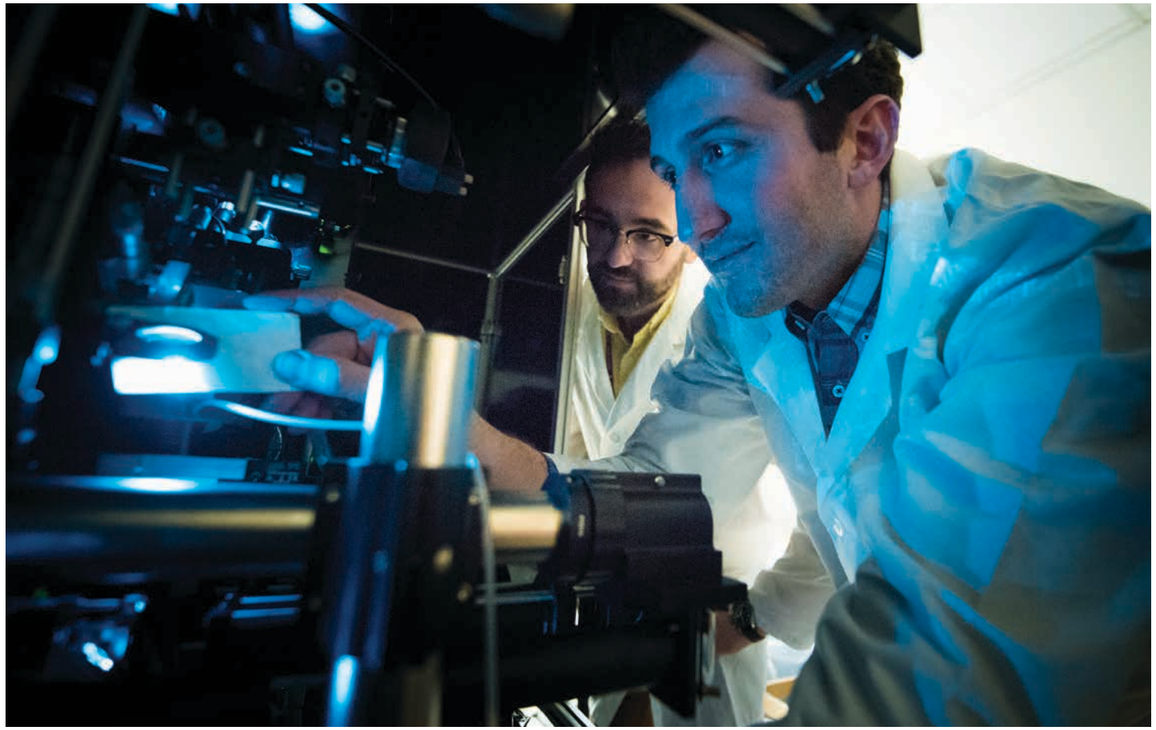


David J. Solecki, PhD

Neuronal Migration During Development of the Cerebellum

Most neurobiologists generate static snapshots of the brain regions they study; Dr. Solecki uses video microscopy to capture young, living neurons in the act of building neuronal circuits in the developing cerebellum of the mouse. The movies created by this powerful microscopy approach have revealed previously unattainable insights into how a neuron matures, migrates, and interacts with the environment as it moves from its germinal niche to a final functional position in a developing brain. These studies are crucial to understanding how brain development goes awry in children with cognitive deficits or epilepsy, in whom neurons are either misplaced in a circuit or the earliest stages of neuronal maturation are delayed.

Dr. Solecki's team has made several fundamental advances in the field of neuronal migration during brain development by using video microscopy. For example, their imaging of the cellular machinery that drives neuronal motility revealed for the first time that microtubules, the organelles that support cell migration, are located far from where, for decades, investigators presumed them to be. While studying cell migration during the development of the cerebellum, Dr. Solecki and colleagues, including Eric Betzig and Harald Hess (Janelia Research Campus, HHMI), also discovered a dramatic change in the size and organization of the nuclei of granule neuron precursors as they migrate to their final location. Like Dr. Dyer, Dr. Solecki realized that his laboratory needed even better imaging capabilities to study these changes in nuclear size and structure during cerebellar development.



Daniel Stabley, PhD; Kirby Campbell, PhD

Convergence of Neurobiology Discoveries and New Technologies

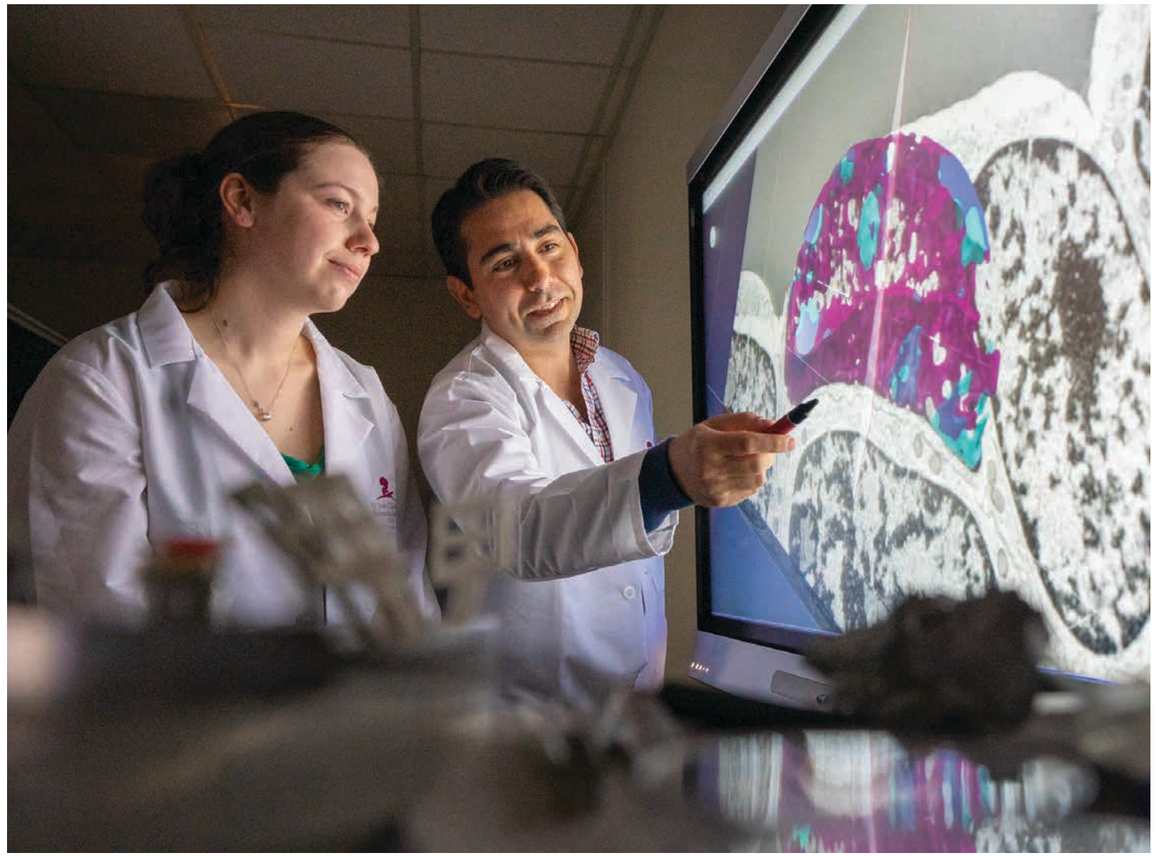
Although light microscopes are an essential tool for neurobiologists, 2 shortcomings limit their use in addressing many crucial questions. First, the limited resolution of light microscopy prevents the visualization of the smallest, unexplored subcellular structures. Second, the high-energy laser light used by more modern microscopes, such as 2-photon laser-scanning microscopes, to produce images is toxic to delicate cells, such as developing neurons.

The Department of Developmental Neurobiology has a long-standing initiative to continuously evaluate technologic advances in microscopy, so that St. Jude research programs are continuously driving forward the leading edge of their field. As part of this initiative, Dr. Solecki, Daniel Stabley, PhD, and colleagues spearheaded the acquisition and implementation of a lattice light-sheet microscope (LLSM), an experimental instrument developed by Eric Betzig to overcome limitations in current microscopy.

The LLSM produces ultrathin sheets of light that surpass the resolution limit of conventional light microscopes and substantially reduce the amount of laser light needed for imaging live neurons. Operating an LLSM is technically challenging. The next-generation optics of the instrument necessitate a high degree of refined alignment to function properly. This first-generation advanced microscope was designed with only the barest-minimum forms of environmental control. Finally, the LLSM produces nearly 2 GB of imaging data per second of operation. This rate of image acquisition creates a high demand for computational support to not only rapidly store but also analyze data captured on the instrument. Drs. Dyer, Solecki, Stabley, and Kirby Campbell, PhD, a postdoctoral fellow working in Dr. Solecki's laboratory, overcame the many challenges in developing culture conditions to keep neuronal samples alive throughout imaging experiments and to acquire optimized images with this sophisticated and sensitive instrument.

After developing the necessary expertise and formalizing processes for operating the LLSM, the department incorporated the instrument into the advanced Neuroimaging Laboratory (NIML). This departmental core facility brings together a team with expertise in advanced optics and computational data science. Dr. Stabley, the manager of the NIML, is a specialist in microscopy and advanced optics, and Abbas Shirinifard Pilehroud, PhD, a senior bioinformatics research scientist, is an expert in image and data analysis. The NIML not only oversees the LLSM but also provides training for other scientists in using its advanced optics and developing the computational image-analysis pipelines required to interpret its data.

Together, Drs. Dyer and Solecki and their teams have now developed new probes that enable developmental neurobiology researchers to track the location of individual genes within euchromatin and heterochromatin domains during retinal and cerebellar development. Their studies bridge the molecular and cellular underpinnings of how cells of the nervous system reorganize their nuclei to meet the dynamic control required for cellular gene expression during normal developmental maturation, stress responses, or malignant transformation into pediatric cancers.



Marybeth Lupo, PhD; Abbas Shirinifard Pilehroud, PhD

David J. Solecki, PhD; Michael A. Dyer, PhD

From Janelia to St. Jude and Beyond

The efforts of the Department of Developmental Neurobiology to procure and refine ground-breaking imaging technologies have recently attracted the attention of the imaging field and provided opportunities for new collaborations that have positioned St. Jude at the forefront of advanced microscopy. Luke Lavis (Janelia Research Campus, HHMI) has provided St. Jude researchers with next-generation fluorescent dyes to broaden the palette of image probes available to St. Jude investigators. Furthermore, St. Jude's LLSM expertise has fostered a collaboration among 3 external laboratories (Betzig, Hess, and Lavis) and the laboratories of Drs. Solecki and Dyer. For this collaboration, a 10K super-resolution cryostat that correlates super-resolution light microscopy images with ultra-high–resolution electron microscopy data was used to create the first correlated super-resolution/FIB-SEM CLEM (focused ion-beam combined with scanning electron microscopy correlative light and electron microscopy) analysis pipelines. Unexpected discoveries are already being made through this collaboration and as a result of this technology. For instance, these scientists have recently determined that differentiating cerebellar neurons condense their nuclear volume and compact heterochromatin 2 fold in as little as 2 hours. Drs. Dyer and Solecki are working with Cam Robinson, PhD, the director of the Electron Microscopy division of the St. Jude Cell and Tissue Imaging Center, to develop an efficient LLSM/FIB-SEM CLEM pipeline that will enable St. Jude researchers to routinely perform correlative studies on live neurons.

Eric Betzig selected the NIML as one of only 4 laboratories worldwide to co-build his next-generation microscope. This new instrument will enable neurobiologists to significantly extend LLSM-like imaging deep within brain or other nervous system tissues. Through these efforts and collaborations, St. Jude developmental neurobiologists are perpetuating the centuries-old legacy in neuroscience, whereby technologic innovations and neuroscience discoveries continuously propel one another, providing new insights into the nervous system during health and disease.

ST. JUDE GLOBAL IS IMPROVING QUALITY AND ACCESS TO CARE FOR CHILDREN WITH CATASTROPHIC DISEASES WORLDWIDE

An estimated 400,000 children (aged 0–14 years) experience cancer each year. More than 90% of them live in low- or middle-income countries (LMICs), and nearly half of those diseases are never diagnosed. Medical institutions in LMICs often struggle to meet the needs of their local population. The probability of survival of children with cancer in LMICs is 20% or less, contrasting with an overall survival of cancer in high-income countries that now surpasses 80%. Where a child lives, therefore, plays a critical role in determining the likelihood that he or she will survive.

St. Jude has worked with health care facilities in LMICs for more thean 25 years to improve the care and survival of children with catastrophic illnesses. Recently, those efforts have been boosted by the establishment of a new academic department, the Department of Global Pediatric Medicine, and the expansion and reimagining of St. Jude's international activities to create St. Jude Global, a program that supports education and training, innovation, and information sharing with international partners. These efforts have been coupled with the creation of new collaborative partnerships through the St. Jude Global Alliance, linking facilities around the world to advance clinical care delivery, education, and research on how to optimize the implementation of best-care practices everywhere.

The Department of Global Pediatric Medicine seeks to advance care and improve outcomes for children with cancer or catastrophic hematological disorders worldwide through global health research and innovation. The department's research efforts are focused in 3 broad areas: (1) Quality and Implementation Sciences, which provides the core methods for program building and impact assessment; (2) Population Sciences, which focuses on the epidemiology and estimation of burden of catastrophic childhood diseases, cost-effective and simulation analyses, and health disparities and health systems research; and (3) Resource-Adapted Clinical Trials, which consolidates the implementation of the department's interventional studies to advance care and improve outcomes. The department also works with the St. Jude Graduate School of Biomedical Sciences to develop and deliver educational programs and with the St. Jude Comprehensive Cancer Center to develop a clinical and translational research infrastructure that facilitates and supports international research programs and collaborations initiated by St. Jude researchers.

Catherine G. Lam, MD, MPH

Launching St. Jude Global

In 2018, St. Jude Global was launched, with the goal of improving the survival of children with cancer or other catastrophic diseases worldwide through the sharing of knowledge, technology, and organizational skills. The program extends beyond the Department of Global Pediatric Medicine, integrating expertise from multiple departments and programs to realize its vision through capacity building, educational initiatives, and the development of a global clinical research infrastructure. St. Jude Global has 3 key goals: (1) to train the clinical workforce needed to meet the treatment needs of children around the world; (2) to develop and strengthen health systems and patient-centered initiatives that encompass the continuum of care required for children with cancer or nonmalignant hematological diseases; and (3) to advance knowledge in pediatric oncology-hematology through research on how to improve the quality of care around the globe.

Capacity-Building Initiatives of St. Jude Global

Ensuring that all children have access to high-quality care requires a strengthening of the continuum of care necessary to carry a child from diagnosis through completion of therapy. This includes engaging all aspects of care, from disease surveillance to patient-centered care to health systems and national policies. Capacity-building initiatives are integrated at the global, regional, and hospital levels and include tools to assess, implement, and monitor programs. Administrative and organizational support is provided to help form regional networks of centers that may learn from one another, assist organizations in seeking the funding needed for care delivery and improvement efforts, strengthen existing health systems, and implement quality-control and safety programs. St. Jude support also helps regional networks develop evidence-based, resource-adjusted treatment guidelines; nursing-care standards and associated staffing models; infection control and supportive care programs; and regional centers for training and delivery of complex medical procedures, advanced diagnostics, and specialized treatment.

Educational Initiatives of the St. Jude Global Academy

Caring for children with cancer requires a multidisciplinary team, and building those teams is a major challenge to providing quality care in LMICs. In response to this need, St. Jude Global has established the St. Jude Global Academy, a comprehensive training program administered at St. Jude and at regional international sites. The educational opportunities provided by the Academy include a dedicated global health track in the Pediatric Hematology-Oncology Fellowship Program at St. Jude, fellowship programs in pediatric hematology-oncology at international locations to build regional capacity, a Masters of Science (MSc) in Global Child Health degree program through the St. Jude Graduate School of Biomedical Sciences, specialized certificate-based training for healthcare providers, and advanced distance-learning curricula to support and complement the educational initiatives described here.

Research Network Model—St. Jude Global Alliance

Advances in patient care are made by step-wise improvements and occur within the context of the local healthcare and financial environments. By carefully integrating implementation science principles, St. Jude Global will advance the knowledge needed for continuous, sustained growth. The goal is to facilitate research on a worldwide scale that enables institutions across the globe to better implement innovative and context-adapted therapeutic protocols. These efforts will be managed through the St. Jude Global Alliance, the functional structure that unites partner institutions with the shared goal of improving healthcare delivery and increasing survival of children with cancer or nonmalignant hematological disorders worldwide. The Alliance will foster the growth of regional and global networks to adopt consortium-like functions that support research optimizing resource-adapted care models.

Led by St. Jude faculty members, the Alliance integrates regional programs that form an operational framework fostering collaborative activities across institutions and transversal programs that guide uniform interventions and discipline-specific standards across all regions. Together, the regional and transversal programs form a cohesive structure that facilitates advances in local care delivery through research, sharing of knowledge and experience, quality improvement, and education and training. Alliance members will have the opportunity to develop global projects and studies, connect with committees and working groups at the regional and global level, and engage with St. Jude faculty and staff for training and development.

The Department of Global Pediatric Medicine serves as the organizational core of the Alliance, providing vision, infrastructure, and governance structure. ALSAC (the fundraising arm of St. Jude) will support the development of independent foundations in Alliance members' countries that will provide the financial support essential for sustained growth. In December 2018, the First Annual Meeting of the St. Jude Global Alliance was held on campus. In attendance were 167 participants from 52 countries, representing 123 medical institutions and foundations.

REGIONAL PROGRAMS

St. Jude Global has established 7 regional programs in LMICs: Asia Pacific, Central and South America, China, Eastern Mediterranean, Eurasia, Mexico, and Sub-Saharan Africa. These programs facilitate collaboration, research, and transfer of knowledge, and their structure defines the framework for operations and implementation. Here we present the progress made by the Mexico, Asia Pacific, and China regional programs.

Mexico

In 2016, eight Mexican institutions, the Casa de la Amistad (a local foundation), representatives from the Mexican Ministry of Health, and those from St. Jude joined forces to create Mexico in Alliance with St. Jude (MAS |α+). The group's mission is to improve the quality of care and survival for children with cancer in Mexico through multicenter collaboration and innovation in patient care delivery, education, and research. MAS |α+ membership now includes 23 institutions, various stakeholders, and a multidisciplinary team needed to achieve its mission.

From a research standpoint, the group's leadership applies a health-disparities perspective and relies on quality and implementation science methods. In Spanish, "mas" means "more"; to improve quality of care and survival for children with cancer, MAS |α+ has 4 strategies: more collaboration, more evidence, more modernization, and more quality.

Project-based research efforts of the MAS |α+ alliance include the acute lymphoblastic leukemia (ALL) trials MAS-ALL18 and Retro MAS-ALL. MAS-ALL18 studies the feasibility of implementing a multicenter prospective diagnostic and therapeutic strategy in centers with no prior experience in cooperative trials. Retro MAS-ALL is determining the outcomes of cases of ALL diagnosed at MAS |α+ centers during 2011–2015. These data serve as the historic controls for the MAS-ALL18 protocol.

Educational efforts in Mexico include the Guadalajara Pediatric Hematology/Oncology Fellowship Program and the Guadalajara Pediatric Hematology/Oncology Scholars Program. The former is a 2-year program that supports the training of 3 clinical fellows per year. The latter is a 1-year program that supports 3 scholars after completion of their clinical training. St Jude provides funding and mentorship for both programs.

MAS |+ Alliance Growth

2015—8 hospitals **2016**—11 hospitals **2019**—23 hospitals

Asia Pacific and China

The Asia Pacific regional program builds on a foundation that began in 2006, when St. Jude established partnerships in the Philippines and Singapore. Collaborative efforts have since expanded to include national programs in Cambodia, Myanmar, and the Philippines, with extended regional partnerships in Indonesia, Sri Lanka, Thailand, and Vietnam. Learning networks in the Asia Pacific region have engaged more than 200 multidisciplinary providers from 55 institutions across 20 countries. The network's clinical and educational platforms facilitate the exchange of evidence-based resources and best-practice teaching in oncology, surgery, pathology, and radiology; the network's smaller theme-based groups facilitate problem solving and advance regional projects.

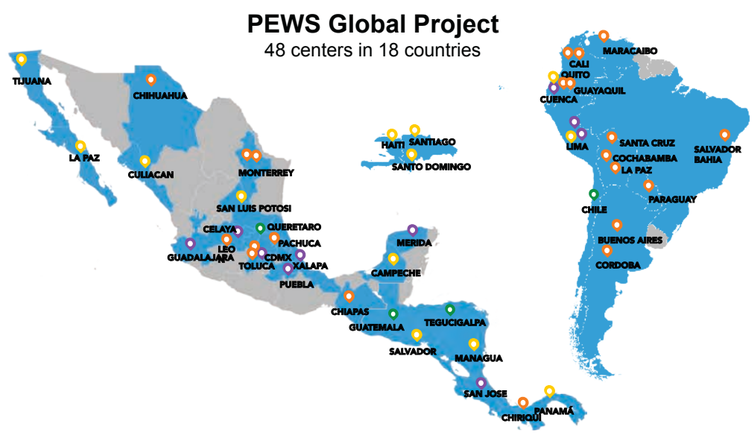
The most recent achievement of St. Jude Global is the March 2019 formation of an alliance between St. Jude and the VIVA Foundation for Children with Cancer (Singapore), VIVA China Children's Cancer Foundation (Hong Kong), KK Women's & Children's Hospital (Singapore), National University of Singapore, and Shanghai Children's Medical Center to improve the cure and treatment of childhood cancer in Singapore, China, and other countries in Asia. Extending across St. Jude Global's Asia Pacific and China regional programs, this agreement will leverage local leadership and regional strengths. Centers of Excellence in research and clinical care of children with cancer in Singapore and Shanghai will also serve as core training centers. An example of the progress made in the region and the potential to advance outcomes is the National Childhood ALL Study Group in China.

Asia Pacific collaborations have strengthened national health systems and increased the capacity for service delivery, workforce development, and research. Accomplishments across these areas include national strategic mapping and assessments initiated in Cambodia, Indonesia, Myanmar, Philippines, Sri Lanka, and Thailand. Regional case studies on critical gaps (e.g., shortages in essential medicines) have been completed to facilitate solutions. The region has also helped develop national cancer control programs that include children and adolescents in Myanmar and the Philippines. In Myanmar, a national childhood cancer network was launched; 17 sites were identified, mapped, and are now engaged in training. Sustainable strategies have been developed to cultivate a multidisciplinary workforce by providing local and cross-regional training programs, including new fellowships in pediatric oncology and multisite training for the first pediatric radiation oncologists in Cambodia and Myanmar. In Singapore, regional symposia on retinoblastoma, pathology, and surgery, with ongoing working groups, have been organized and funded. Regional nursing education and leadership development is being supported in Cambodia, and the St. Jude VIVA Asia Pacific Nursing Institute will be launched this year in Singapore, providing training for regional nurse educators, followed by continuing education and mentored implementation projects. Finally, the Asia Pacific regional program is building multicenter research capacity, including quality and implementation science research examining the local causes of treatment failure (e.g., treatment abandonment) and strategies to optimize capacity development and context-adapted treatment implementation.

Asya Agulnik, MD, MPH

Transversal Programs

As St. Jude's reach expands to more LMICs, interest in our transversal programs continues to grow. Currently, 8 transversal programs instill uniform interventions across regions and facilitate global research collaborations in Critical Care, Disease Burden and Simulation, Health Systems, Infectious Diseases, Metrics and Performance, Neuro-Oncology, Nursing, and Palliative Care. Here we briefly describe work in 3 of these programs.



Critical Care Transversal Program

The Global Critical Care Program strives to strengthen hospital care for critically ill children with cancer to improve overall survival. The Program identifies global problems in pediatric onco-critical care delivery and develops innovative solutions. Its initiatives include using evidence-based interventions to improve hospital care; educational initiatives to improve provider knowledge of the care of critically ill children; research on topics related to pediatric onco-critical care; and forming collaborative networks for providers to share knowledge, experience, and best practices to improve the care and survival of critically ill children with cancer.

One of the Program's initiatives, the Pediatric Early Warning System (PEWS), includes 48 pediatric cancer centers in 18 countries in Latin America. PEWS improves early identification of clinical deterioration in hospitalized patients to facilitate timely intervention and prevent complications and critical illness. PEWS has 2 components: a scoring tool calculated by the bedside nurse as part of routine care and an action algorithm that guides clinical teams responding to patients with deterioration. PEWS was first used in the Unidad Nacional de Oncologia Pediatrica (UNOP; Guatemala City, Guatemala), where it was successfully implemented and validated as an accurate tool for identifying clinical deterioration in children with cancer who are hospitalized in a resource-limited setting. A cost–benefit analysis showed a substantial net annual cost savings resulting from fewer unplanned transfers to the Pediatric Intensive Care Unit. Despite the impressive PEWS results at UNOP, whether this experience is generalizable to other centers in Latin America is unclear, because the centers vary in hospital organization, nursing staffing, and pediatric intensive care unit availability.

The Program also provides pediatric onco-critical care education. This year, the Program worked with the Division of Critical Care at St. Jude to sponsor the first Pediatric Onco-Critical Care Symposium (POCCS) in April 2019. St. Jude Global provided 30 scholarships to pediatric intensivists from all over the world to attend the conference at St. Jude. The conference was followed by the 2-day course "POCCS Basics," which teaches the practical aspects of providing high-quality care to critically ill children. The Program plans to launch the St. Jude Global Academy in Pediatric Onco-Critical Care in 2020.

The Global Critical Care Program also collaborates on research to better understand challenges in onco-critical care. Current work focuses on developing an evidence-based tool to assess the capacity and quality of pediatric onco-critical care in resource-limited settings. In collaboration with Dr. Anita Arias (Le Bonheur Children's Hospital, Memphis, TN), Dylan E. Graetz, MD (Oncology), a St. Jude Pediatric Hematology-Oncology Fellow, is evaluating how PEWS affects interdisciplinary communication about patient deterioration in hospitals with different resource levels.

Dylan E. Graetz, MD

Infectious Diseases Transversal Program

Infections and their complications are major contributors to treatment-related mortality in pediatric patients with cancer. The problem is exacerbated in low-resource settings, where most deaths during treatment are caused by infection. The Global Infectious Diseases Program was established to better understand the reasons for the high incidence of infections and poor treatment outcomes and to implement successful, sustainable solutions. Since its inception, the Program has worked with local health professionals to raise standards of care in infection control and prevention, augment the quality of the local clinical workforce, and collaborate in designing and conducting clinical and quality-improvement research to guide interventions based on evidence. Sustained improvement in the standards of infection care and prevention requires a robust local presence of infectious diseases experts and the support of hospital leaders. Therefore, the Program has established and manages 2 training tracks, one for infection preventionists and the other for infectious diseases physicians and leaders.

The Intensive Infection Control Course for infection preventionists targets staff responsible for institutional infection-control programs. The training covers all areas relevant to the infection preventionist, including the safety of patients and healthcare workers. The Spanish-language version of this course was created in 2005. It uses distance learning and in-person practicums on the essentials of infection control at selected regional sites. In 2018, an English-language version of the course with a similar curriculum and method was launched. To date, more than 400 participants from 150 institutions in 30 countries have been trained through this course.

The second training track targets physicians and leaders in pediatric infectious diseases. This track also combines distance learning and in-person learning. Participants learn the essentials of infections (especially those pertaining to immunocompromised children) leadership, team management, building and implementing research projects, and sharing results through scientific publications. This course is associated with the annual St. Jude/PIDS Pediatric Infectious Diseases Research Conference; graduates of the course present their work and connect with leaders in the field. To date, 103 participants from 77 institutions in 38 countries have completed the course.

Pediatric oncology units operate mostly in large public hospitals that have multiple competing needs and often limited resources. Optimizing the use of scarce resources and effectively communicating the needs of pediatric oncology units are essential to delivering safe health care. To date, the Program has helped establish 15 care teams at pediatric oncology institutions, mostly in Latin America. The teams are composed of St. Jude–trained leaders and infection preventionists who promote and deliver safe, high-quality infection care and prevention in pediatric oncology units. The Program collaborates with the local teams to improve standards for infection care and prevention, conduct on-site training, carry out surveillance of infections, implement quality improvement, and establish processes to maximize the use of local resources, incorporating such practices into routine institutional structures.

Finally, the Program establishes regional networks to enhance impact at the local level. The first network, PRINCIPAL, serves as a model for collaboration among infectious disease specialists, supporting the continuous exchange of knowledge and expertise. PRINCIPAL currently includes 29 institutions in 13 countries in Latin America and the Caribbean. Annual meetings at St. Jude strengthen the network and facilitate collaboration in research and quality-improvement projects.

Miguela A. Caniza, MD

Disease Burden and Simulation Transversal Program

The Disease Burden and Simulation Program provides actionable data and toolkits to support clinicians, health administrators, and health policy stakeholders in better allocating resources to treat pediatric cancer and hematological diseases. The Program includes faculty, staff, and collaborators with expertise in statistics, decision sciences, cancer survivorship, health economics, and epidemiology.

Due to the lack of cancer registration systems in LMICs, an accurate accounting of disease burden is impossible. Without knowing how many children need help, governments and nongovernment organizations cannot plan or advocate for increased resources to meet the affected children's needs. Because statistical data are missing, many children who die of cancer are not accounted for. To address this, St. Jude and the Institute for Health Metrics and Evaluation (IHME) at the University of Washington (Seattle, WA) began a formal partnership to advance knowledge and understanding of childhood cancer around the world.

The IHME is the coordinating center for the Global Burden of Disease (GBD) study, which aims to provide a comprehensive, comparable picture of what kills or disables people. The GBD study is quantifying total health loss from the hundreds of diseases, injuries, and risk factors for 195 countries from 1990 to the present. Until recently, childhood cancers were not a major focus of the GBD study. Recognizing that more work needed to be done, Nickhill Bhakta, MD, MPH (Global Pediatric Medicine, Epidemiology & Cancer Control, Oncology) and Lisa Force, MD (Oncology), a St. Jude Pediatric Hematology-Oncology Fellow, collaborated with Drs. Tina Fitzmaurice and Christopher Murray (both of IHME) to introduce methods to better quantify the global childhood cancer disease burden. Their goal is to generate the best-possible data needed to enable all stakeholders—policymakers, health advocates, and public and global health communities—to improve outcomes for pediatric patients with cancer around the world.

Lisa Force, MD; Nickhill Bhakta, MD, MPH

Shaloo Puri, MD

Strategic Educational Initiatives

Key components of St. Jude Global are training a global workforce, building the clinical and research initiatives needed to advance programs, and training the next generation of leaders to improve care for all children with childhood cancers or other catastrophic diseases. St. Jude Global builds human resources capacity through strategic educational programs. These include online seminars, guided courses, medical training programs, and a new MSc degree program in Global Child Health.

Certificate-Based Seminars

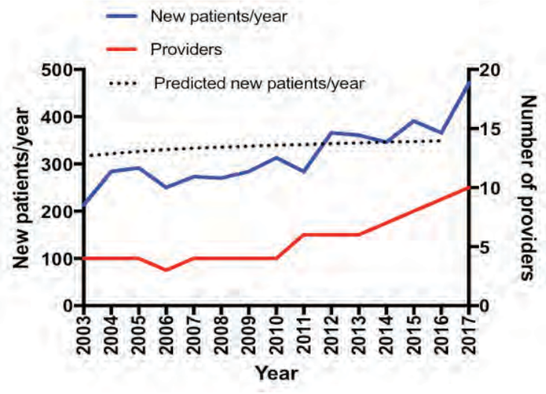
The St. Jude Global Academy provides short, competency-driven seminars in areas such as leadership, palliative and end-of-life care, neuro-oncology, infectious diseases, and infection prevention and control. These seminars deliver a structured curriculum to improve the knowledge and skills of participants by using a “train the trainer” model to maximize impact. The seminar format includes distance-learning modules and a residential practicum; scholars and clinicians from all St. Jude Global regions have participated.

Masters of Science in Global Child Health

The MSc in Global Child Health degree program is a collaboration between the St. Jude Graduate School of Biomedical Sciences and the Department of Global Pediatric Medicine. The Tennessee Higher Education Commission approved the program in January 2019. Shaloo Puri, MD (Global Pediatric Medicine), serves as the graduate school assistant dean and global pediatric medicine graduate studies director. In her position, Dr. Puri helped develop the interdisciplinary curriculum. The degree will be offered as a 2-year program that incorporates online and onsite learning. The program offers students around the world a transformative educational experience that will enable them to realize their potential to advance the treatment and care of childhood cancers and other catastrophic illnesses in global settings. It will provide training in basic and applied research, global health systems and innovation, and population sciences, all tailored to child health. The inaugural class will begin in July 2019.

Education Program Fellowship Support and Assessment Tool

St. Jude currently collaborates with medical training programs in 6 countries (Brazil, Guatemala, Jordan, Lebanon, Mexico, and Uruguay) to increase the number of specialists who provide care around the world. Plans are being developed to replicate these models in all regions. The institution’s participation in these fellowship programs includes input in curriculum design, hosting fellows for clinical rotations, and financial support. The programs span 2–3 years and follow competency-based training of physicians who have completed pediatrics residency programs. The Education Program Assessment Tool objectively assesses the quality of pediatric hematology-oncology fellowship programs. Twenty-three pediatric hematologists-oncologists from 8 countries have completed training at UNOP in Guatemala; they represent more than 90% of the new graduates trained in the region. The number of new pediatric patients at facilities in the region has also increased more than 2 fold since the program was initiated in 2003.



Ching-Hon Pui, MD

Building Research Capacity—Acute Lymphoblastic Leukemia Trials

St. Jude Global promotes the gradual implementation of research activities at international sites through the St. Jude Global Alliance. Local and regional research expertise is developed through St. Jude Global Fellowships, St. Jude Global Scholars, and the St. Jude Global Academy. The regional networks are adopting consortium-like functions with a solid clinical research infrastructure to provide foundational support for research activities.

For example, under the leadership of Ching-Hon Pui, MD (Oncology, Pathology), St. Jude has been extensively involved in an advisory role in the development of a National Childhood ALL Study Group in China. Their ALL-2015 trial (a version of St. Jude Total Therapy XV tailored to Chinese patients) accrued 5225 patients from November 2014 to September 2018. At 3 years after completion of treatment, the probability of patient survival was 93.3%. This consortium now accrues approximately 1300 patients per year. Its progress has helped foster the Chinese government's decision to approve the development of National Health Centers in Shanghai and Beijing for research, education, and patient care. Raul C. Ribeiro, MD (Oncology), and Gaston Rivera, MD (Global Pediatric Medicine), in collaboration with investigators at Children's Cancer Hospital Egypt 57357 (Cairo, Egypt) and the Instituto Materno Infantil de Pernambuco (Recife, Brazil) and former St. Jude faculty member Dr. Dario Campana, designed 2 studies (RECIFE ALL-2005 and Egypt VLR ALL 2011) to reduce treatment intensity for patients with very low–risk pediatric B-lineage ALL. Disease risk is identified by a simple, inexpensive measurement of minimal residual disease at Day 19 of induction therapy. Children whose residual leukemic cell level is less than 0.01% at that time point are candidates for therapy reduction. The 2 studies demonstrated that a simple, low-cost strategy can be used to measure leukemia and identify children for whom therapy can be reduced without compromising cure.

Jun J. Yang, MD, PhD (Pharmaceutical Sciences), is working with the Department of Global Pediatric Medicine to develop research programs focused on the biology of racial/ethnic differences in ALL. Through collaborations with colleagues in China, Guatemala, Japan, and Singapore, Dr. Yang has identified novel ALL genomic features unique to different ethnic groups and clinically actionable biomarkers of drug toxicity with racial disparities.

Paola Friedrich, MD, MPH; Miriam Gonzalez-Guzman

Childhood Cancer Analytics Resource and Epidemiological Surveillance System

Models and estimates alone are not sufficient to manage or resolve the global health disparities attributable to childhood cancer. Better data, cancer registries, and measurements of the quality of care and the strength of health systems are essential. To capture this information, new tools specifically designed for childhood cancer are required. In addition, healthcare workers will need to be educated to collect these data and ensure they are of the highest quality. Finally, it is paramount that we create a global repository and process for storing and integrating all the information, so that ultimately children will benefit from it.

To drive St. Jude Global growth, the St. Jude Global Childhood Cancer Analytics Resource and Epidemiological Surveillance System (SJCARES) was developed. SJCARES is an integrated solution to support evidence-based pediatric cancer care and decision making in LMICs. The system represents a new philosophy that aims to continuously identify, target, and monitor vital health metrics that affect patient outcomes. SJCARES is defined by 3 modules: (1) a hospital-based pediatric cancer registry, which ensures that descriptive epidemiology and outcomes are reported in a standard format; (2) the PrOFILE tool, which provides quantitative health facility data; and (3) Systems Analysis, an integrated solution to support evidence-based pediatric cancer care decision making in LMICs.

Module 1, the hospital-based pediatric cancer registry network, is being led by the Disease Burden and Simulation Transversal Program. The SJCARES registry is a free, cloud-based, secure tool specifically designed for LMIC contexts, where trained personnel are limited and guidance on what data to collect is lacking. We expect this electronic data-capture process to provide key information to physicians, hospital administrators, and government policy makers to enable them to design and track quality-improvement initiatives and provide data for population-based cancer registries. The Disease Burden and Simulation team has worked closely with global partners to ensure that the registry meets local needs and is easy to use. Importantly, all data in the registry will be owned by the hospitals using it but sharable in a deidentified manner to help advance global cancer-control efforts.

To ensure that patient information is safe and the platform complies with data privacy laws around the world, the registry is built on top of the OmniComm TrialMaster application, the same program that St. Jude uses to conduct clinical trials. Data are protected by multiple features (e.g., data encryption and segmentation, site- and role-based security, and deidentification). All system users will be required to use industry-standard second-factor authentication to ensure compliance with regulatory requirements.

Because many hospitals lack a workforce educated on how to enter these data, St. Jude Global's registry team has developed a curriculum to train users in how to register children with cancer. As a requisite to having access to the registry, users will be required to complete training and be given access to an SJCARES Registry Operations Manual and SJCARES Data Dictionary to support and guide effective tool utilization. They will also be asked to participate in regularly scheduled online conferences to discuss difficult cases or common data-entry errors.

Module 2 of SJCARES, PrOFILE, is a dynamic evaluation of health-services delivery that helps define an improvement strategy for increasing survival. It also acts as a diagnostic tool, identifying key issues requiring attention and improvement. PrOFILE is not a survey; it is a platform on which to build local capacity in quality improvement and a community of quality-improvement experts. It emphasizes the development of metrics and the assessment of performance but recognizes and embraces the expected differences across centers, promotes equity and integration with general child health services, and aims to reduce barriers to pediatric hematology-oncology care. Finally, PrOFILE's data-driven approach facilitates decision making within the limits of economic feasibility, and its repeated use will facilitate insightful benchmarking and local tracking of progress.

Implementation of PrOFILE

PHASE 1: PREPARATION

Step 1: Engage pediatric hematology-oncology leadership
Step 2: Identify an assessment team
Step 3: Confirm good fit of the site coordinator and MD Lead
Step 4: Enroll site coordinator to PrOFILE Train the Trainer
Step 5: Enroll participants to the PrOFILE Portal and educational website

PHASE 2: ASSESSMENT

A **PrOFILE module** consists of
1. Electronic forms
2. Educational training modules
3. Mentoring sessions
4. Exercises

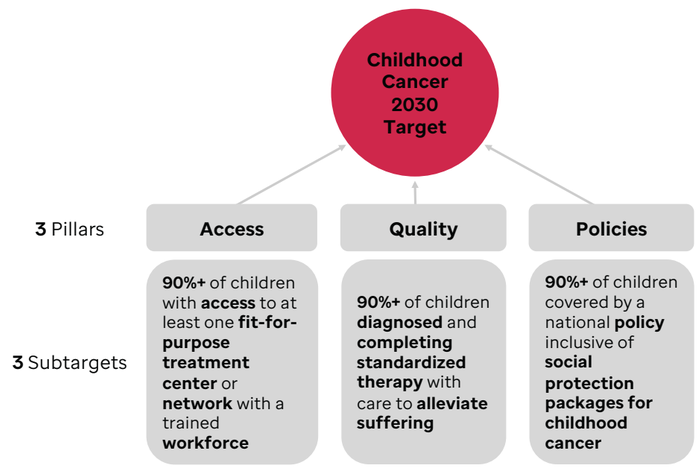
PHASE 3: INTERPRETATION AND ACTION

The **PrOFILE team** will assist with
1. Action plans based on the facility's priorities
2. Score-based analysis (internal, external, regional)
3. Ongoing monitoring and reporting of progress

James R. Downing, MD

The First WHO Collaborating Center for Childhood Cancer

The World Health Organization (WHO) designates collaborating centers to carry out specific activities to support WHO programs. These collaborations create opportunities for sharing technology and exploiting the expertise and institutional capacity of designated centers and the visibility and leadership of the WHO. In March 2018, St. Jude, through the Department of Global Pediatric Medicine, became the first WHO Collaborating Center for Childhood Cancer.



By 2030, ensure **at least 60% survival** of children with cancer worldwide **and alleviation of suffering for all.**

WHO Global Initiative for Childhood Cancer

In accordance with the recent World Health Assembly Resolution 70.12, *Cancer Prevention and Control in the Context of an Integrated Approach*, and the 2019–2023 WHO General Programme of Work, the WHO is committed to promoting health and equity for all, including children with cancer. As mandated by the resolution, the WHO will work with nongovernment partners to establish and implement comprehensive cancer prevention and control programs for managing cancers in children and adolescents.

In September 2018, at an inaugural side event titled, "Ensuring a Right to Cure: Improving Childhood Cancer Care and Decreasing Global Survival Disparities," in conjunction with the United Nations (UN) General Assembly, the WHO announced a new effort—the WHO Global Initiative for Childhood Cancer—with the aim of reaching at least a 60% survival rate for children with the most common cancers by 2030, thereby saving an additional 1 million lives. This new target represents more than a doubling of the global survival rate for children with cancer. The Initiative will facilitate increased prioritization of childhood cancer through awareness raising at the global and national levels and expand the capacity of countries to deliver childhood cancer care. Cross-cutting efforts will engage global partners across 3 pillars: access, quality, and policies. The UN event was hosted by the Permanent Missions to the United Nations of the Republic of Uzbekistan and the Hashemite Kingdom of Jordan, in partnership with St. Jude, the WHO, and the Permanent Missions to the United Nations of El Salvador, the Republic of Moldova, the Kingdom of Morocco, the Republic of the Philippines, the Russian Federation, and the United States.

The WHO will support governments in assessing current capacities in cancer diagnosis and treatment, including the availability of the workforce, medicines, and technologies; setting and cost prioritizing cancer diagnostic and treatment programs; and integrating childhood cancer into national strategies, health benefits packages, and social insurance schemes.

St. Jude as a WHO Implementing Partner

In addition to being a WHO Collaborating Center, in July 2018, St. Jude executed a 5-year agreement with the WHO to measurably and sustainably improve outcomes for children with cancer worldwide. Per the agreement, St. Jude is providing resources to create a childhood cancer–focused WHO program, with dedicated personnel to advance the development of childhood cancer care and control capacity through a novel global initiative. This collaboration synergizes the authority of the WHO (working with governments, nongovernment agencies, and leaders across health systems) with the implementation expertise of St. Jude Global (working with partners, including multidisciplinary providers and hospital administrators).

St. Jude and the WHO have committed to an action plan inclusive of in-country assessments and implementation efforts that will be supported by St. Jude Global and extend to linked global initiative deliverables. During 2019, at least 6 focus countries with WHO regional and national offices will be identified to receive tailored support from the WHO and St. Jude. The countries will demonstrate early measurable progress in childhood cancer care and serve to illustrate advances in one or more pillars of the initiative (access, quality, policies), while providing feedback for the refinement of tools to be used in the broader global initiative.

The WHO Global Initiative for Childhood Cancer creates an unprecedented opportunity to address the disparities in global cancer outcomes. By transforming facility-based efforts into national programs embedded in the health systems and enforced in government policies, this initiative will accelerate improvements in patient outcomes across diagnostic, demographic, and country borders, and it has the potential to have a global impact not previously thought possible.

Reimagining the Future of Pediatric Care Worldwide

St. Jude Global is seamlessly integrating research, innovation, and advanced education. Using programs and capacity building, we are creating a new paradigm in pediatric oncology in which global programs are incorporated into academic medicine and disparities in access to modern treatments are narrowed. Through partnerships with governments and the WHO, we will develop sustainable, scalable models that ensure that all children with cancer or other catastrophic diseases can access quality care, wherever they are.

Carlos Rodriguez-Galindo, MD

The St. Jude Affiliate Program has 8 affiliate clinics. Under the leadership of Carolyn L. Russo, MD, this network of affiliated clinics works with the St. Jude Clinical Trials Administration to extend the institution's mission. Physicians and staff at each clinic participate in St. Jude treatment and research programs by enrolling and providing care to patients on St. Jude clinical protocols. The clinics also provide patients with the opportunity to receive part of their care at a facility near their home community.

Victor M. Santana, MD; Carolyn L. Russo, MD

THE AFFILIATE PROGRAM EXTENDS ST. JUDE CLINICAL RESEARCH

Baton Rouge, LA

Our Lady of the Lake Children's Hospital – Our Lady of the Lake Regional Medical Center

Peoria, IL

Children's Hospital of Illinois OSF Healthcare System, University of Illinois College of Medicine at Peoria

Charlotte, NC

Novant Health Hemby Children's Hospital

Shreveport, LA

Feist-Weiller Cancer Center LSU Health Sciences Center

Huntsville, AL

Huntsville Hospital for Women & Children – Huntsville Hospital

Springfield, MO

Mercy Children's Hospital Springfield – Mercy Health System

Johnson City, TN

Niswonger Children's Hospital – Johnson City Medical Center, East Tennessee State University

Tulsa, OK

The Children's Hospital at Saint Francis

SHARED RESOURCES CONTRIBUTE EXPERTISE AND SUPPORT TO ST. JUDE RESEARCH

These 19 Shared Resources, including 9 supported by the St. Jude Comprehensive Cancer Center (indicated by an *), provide expertise and cutting-edge technologies in support of all research at St. Jude. The nearly 400 scientists and technologists who staff the facilities described here not only process samples but also contribute to the design, performance, and analysis of experiments.

Animal Resource Center

Director: Harshan Pisharath, DVM, PhD

The Center provides a comprehensive animal care program that includes technical services (resource procurement, drug delivery, and biological sample collection), husbandry and specialized care, cryopreservation and storage of biological specimens, and veterinary services to ensure the well-being and clinical care of laboratory animals.

Biorepository

Director: Charles G. Mullighan, MBBS, MD

Technical Director: Matthew Lear

Biorepository services include the processing and archiving of normal human tissues and disease specimens for future research studies. Cryopreserved specimens include cells, tissues, DNA, and body fluids. The Biorepository staff processes more than 5000 specimens per month, and more than 370,000 specimens have been archived.

Biostatistics*

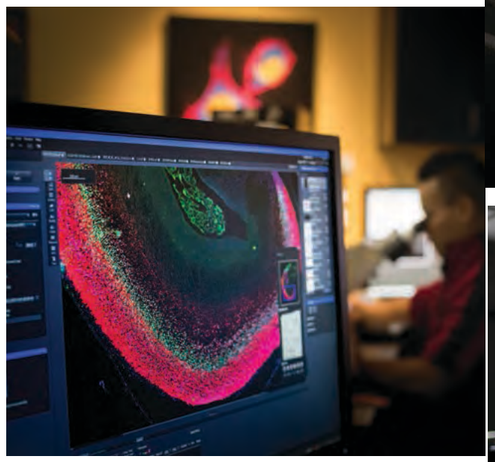
Director: Deo Kumar Srivastava, PhD

The Biostatistics Shared Resource within the Department of Biostatistics provides innovative statistical support to all research initiatives at St. Jude. This support includes designing and analyzing studies and performing expert analyses of large datasets, such as those generated by genomic or imaging studies. Biostatistics staff also provide biostatistical education, a centralized randomization system, statistical software, and technical support for hardware and software infrastructure.

Center for Advanced Genome Engineering

Director: Shondra M. Miller, PhD

The Center provides expertise in introducing investigator-defined mutations into mammalian cells or human pluripotent stem cells. The staff collaborate with our preclinical resources to produce knockout and knockin models and to generate validated genotyping protocols. The Center also has a strong focus on research and development, identifying, validating, and delivering new genome-editing applications and technologies.



Cell and Tissue Imaging Center*

Director of Electron Microscopy: Camenzind Robinson, PhD

Director of Light Microscopy: Victoria C. Frohlich, PhD

Staff in Cell and Tissue Imaging offer consultation on the design and execution of optical-imaging experiments; assist with image acquisition, analysis, quantification, presentation, and publication; and educate investigators about the theory and practice of imaging technologies. The Division of Light Microscopy houses laser-scanning imaging systems, spinning-disk confocal imaging systems, super-resolution imaging, sheet plane illumination microscopy, and widefield imaging and automated scanning. The Division of Electron Microscopy houses transmission and scanning electron microscopes, including a Helios NanoLab DualBeam for 3-dimensional imaging. Other technologies available include negative staining of single particles and immunoelectron microscopy.

Center for Bioimage Informatics

Director: Khaled Khairy, PhD

The Center offers state-of-the-art bioimage technologies to extract accurate, usable information from complex data sets generated by advanced imaging technologies. The Center provides expertise in processing, registration, and segmentation of biological images, as well as machine learning, computer vision, and image-based data quantitation and visualization.

Center for In Vivo Imaging and Therapeutics*

Director: Walter Akers, DVM, PhD

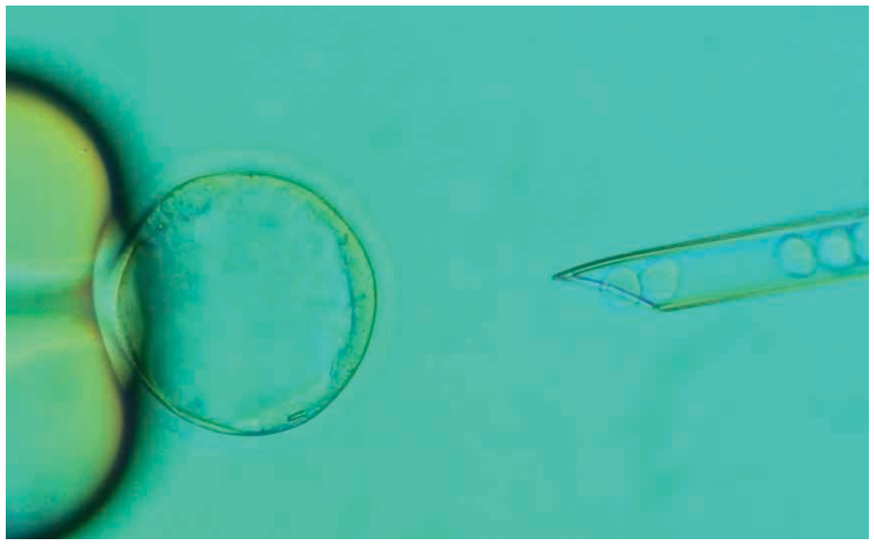
The Center provides cutting-edge imaging, surgery, and image-guided therapeutic services for preclinical studies. The technologies available include magnetic resonance imaging, positron emission tomography, high-frequency ultrasound, bioluminescence imaging, intravital multiphoton microscopy, and image-guided radiation therapy. The staff also assist investigators with planning and performing experiments to ensure that preclinical studies are conducted at the highest standard.

Center for Proteomics and Metabolomics

Director: Junmin Peng, PhD

Research Coordinator: Anthony High, PhD

In support of basic and clinical research, the proteomics and metabolomics staff deliver a range of mass spectrometry–based analyses, including protein identification and characterization, posttranslational-modification analysis, affinity purification, comprehensive profiling of the proteome and phosphoproteome, and metabolite profiling.



Cytogenetics*

Director: Marcus Valentine

Cytogenetics performs G-band karyotyping and spectral karyotyping of tumor or targeted embryonic cell lines, patient-derived orthotopic xenografts, and somatic cell hybrids for preclinical studies. Various fluorescence in situ hybridization (FISH) analyses, including tissue-section, protein, DNA, and RNA FISH, are also available.

Diagnostic Biomarkers

Director: Ruth Tatevossian, MD, PhD
Technical Director: Paul Mead, PhD
Diagnostic Biomarkers provides expert advice and technical and experimental support for conducting molecular assays (e.g., nucleic acid extraction, PCR, RT-PCR) in prospective clinical trials. Staff members consult with researchers to design assays, optimize and validate methods, execute experiments, and analyze data.

Flow Cytometry and Cell Sorting*

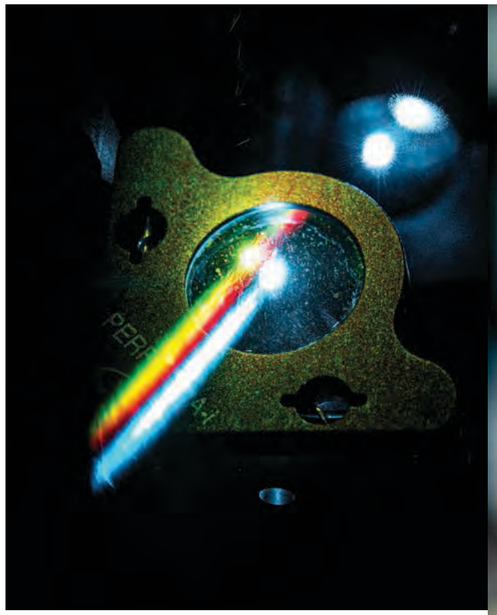
Director: Richard A. Ashmun, PhD
This Shared Resource provides access to sophisticated flow cytometry equipment, services, and expertise. The staff actively trains St. Jude investigators in flow cytometry theory and applications, so that they can conduct flow cytometry analyses independently. Other technologies available include high-end cell sorting, magnetic cell separation, and a repository of more than 500 validated reagents.

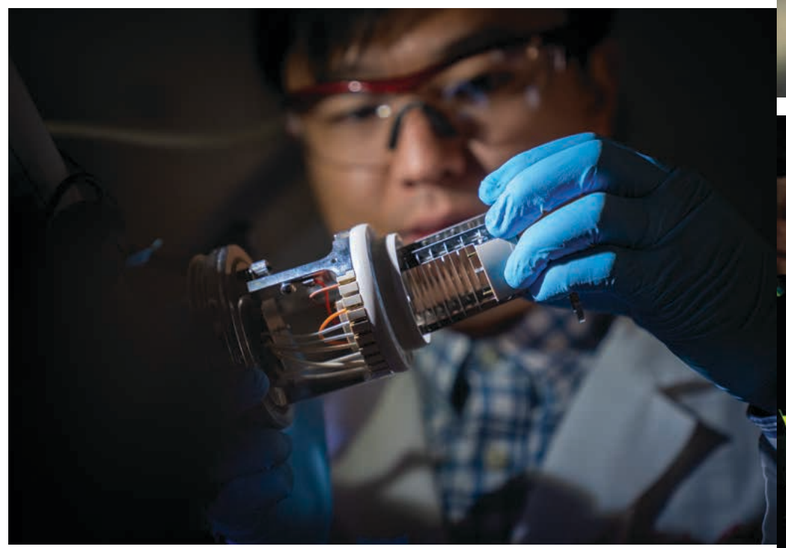
Hartwell Center for Bioinformatics and Biotechnology

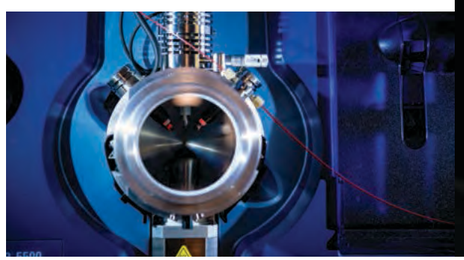
Director: Geoffrey Neale, PhD
The Hartwell Center provides services in a wide variety of high-throughput biotechnology platforms, including Sanger DNA sequencing, DNA microarray analysis, genome sequencing, genotype analysis, functional genomics, and macromolecular synthesis. Investigators working with the Hartwell Center can interface with the Bioinformatics and Biotechnology Core* to perform high-end analytics required for data interpretation.

Molecular Interaction Analysis

Director: Amanda Nourse, PhD
Staff in this Shared Resource assist investigators by using biophysical approaches for molecular interaction–based research. The technologies available include analytical ultracentrifugation, surface plasmon resonance, isothermal iteration calorimetry, multiangle light scattering, and microscale thermophoresis.







Pharmacokinetics*

Director: Mary V. Relling, PharmD
Co-Director: Kristine Crews, PharmD
Pharmacokinetics staff provide study design, modeling, and assay implementation for investigator-initiated studies. They also perform clinical pharmacokinetic and pharmacodynamic analyses and modeling. The goal of this Shared Resource is to develop new drugs and optimize drug scheduling and dosing for clinical studies.

Protein Production*

Director: Richard Heath, PhD
Staff in Protein Production express and purify proteins from bacterial, insect, or mammalian producer cells. These proteins are then used in biochemical or structural analyses, high-throughput screening, or as reagents or antigens. This facility expresses and purifies approximately 110 proteins per year.

Vector Development

Director: Byoung Ryu, PhD
The Vector Development staff develop and provide research-grade viral vectors and maintain an archive of well-characterized cellular and plasmid reagents. They also help investigators transition promising preclinical vectors into clinical-grade viral vectors that are then produced in the Children's GMP, LLC, for gene therapy clinical trials.

Preclinical Pharmacokinetics

Director: Burgess Freeman III, PharmD
Staff in this Shared Resource support pharmacokinetic and pharmacodynamic studies executed in the preclinical setting, particularly in the context of disease modeling. Preclinical Pharmacokinetics enhances basic and translational research through the development and validation of bioanalytical methods, preclinical study design, and pharmacometric analyses.

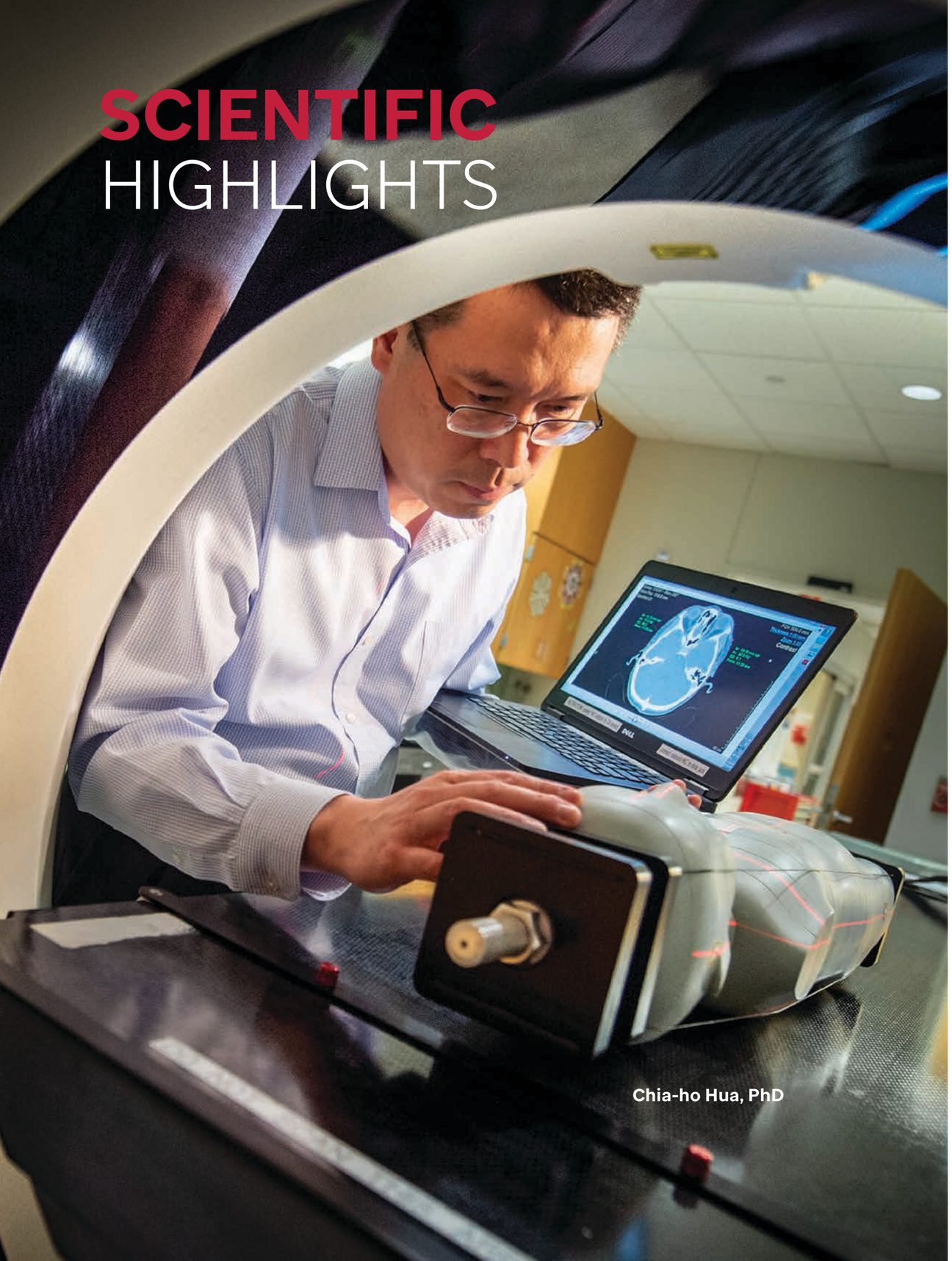
Transgenic and Gene Knockout*

Director: Hartmut Berns, PhD
This Shared Resource uses cutting-edge transgenic and gene-targeting technologies to generate genetically engineered preclinical models for investigators. It also offers various additional services in support of model development, including expertise in traditional embryonic stem cell targeting and culture.

Veterinary Pathology Core

Director: Peter Vogel, DVM, PhD
The Core's services include diagnostic analysis of biological fluids and necropsy (e.g., tissue collection and perfusion), histology (e.g., immunohistochemistry and antibody optimization), and pathology (e.g., laser-capture microdissection and image analysis) of preclinical models.

SCIENTIFIC HIGHLIGHTS



Chia-ho Hua, PhD

Dual-Energy Computed Tomography Holds Promise to Improve the Accuracy of Radiation Therapy Planning

Radiation therapy planning based on computed tomography (CT) images conventionally uses calibration curves to convert the value in Hounsfield Units of each pixel in the images to the electron density (ED), in the case of photon therapy, or the proton stopping power, in the case of proton therapy, of the tissue. However, concern over deviations from the calibration conditions often prompts the restriction of patient scans to fixed parameters, potentially resulting in suboptimal image quality. For proton therapy, the conversion process also introduces range uncertainties that typically necessitate the use of an expanded target margin or increased plan robustness. These strategies are not ideal and may result in more normal tissues being irradiated.

Dual-energy CT (DECT) allows direct calculation on a pixel-by-pixel basis of the ED, the effective atomic number (Z_{eff}), and subsequently the proton stopping power. This approach holds promise to eliminate the need for calibration-curve mapping for photon therapy and to improve the range accuracy for proton therapy. Another advantage of DECT is that it enables the iodine concentration in tissues to be estimated. Iodinated contrast agent is often administered to patients undergoing CT simulation to better visualize tumors and blood vessels, but the contrast agent may cause side effects; therefore, reducing the dose required would be beneficial.

St. Jude is pioneering the use of DECT in radiation therapy. Because DECT was originally developed for diagnostic radiology applications, early adopters in the radiation oncology community are working to define its roles in radiation therapy and provide guidelines for its use. As an initial contribution to this effort, Chia-ho Hua, PhD (Radiation Oncology), and colleagues studied the accuracy of the ED, Z_{eff}, and iodine concentration values determined with a new dual-layer DECT (DL-DECT) system (IQon Spectral CT, Philips Healthcare) and examined the dependence of the accuracy on the scan and reconstruction parameters used. Their findings were published in *Medical Physics*.

The accuracy measurements were performed on polymer test phantoms with various tissue-equivalent inserts and iodine inserts of different concentrations. The expected values of the ED and Z_{eff} were derived from the chemical composition of the phantoms. With scan conditions of 120-kVp tube potential and 20-mGy CTDIvol, the accuracies of the measured ED and Z_{eff} were on the order of ± 1% and ± 2%, respectively, for both soft-tissue and bone-equivalent materials, with somewhat larger percentage deviations for lung-mimicking materials. For iodine quantification, the median absolute deviations from the nominal values were 0.3 mg/mL or less for concentrations of 2-20 mg/mL, with an overall median deviation of –0.1 mg/mL. The accuracies appeared to be unaffected by changes in the tube potential, radiation dose, gantry rotation time, or spectral reconstruction level. The researchers thus demonstrated the high accuracy of the ED, Z_{eff}, and iodine concentration values derived from DL-DECT.

Direct derivation of the ED and Z_{eff} from DL-DECT scans can potentially improve the accuracy of radiation therapy planning, especially for proton therapy. If the proton stopping power can be calculated with greater confidence, the current conservative safety margins and plan robustness may no longer be required. Furthermore, because DECT enhances iodine contrast, it should be possible to reduce the dose of iodinated contrast agent for pediatric patients. Work is ongoing at St. Jude to bring these potentials to realization. *Hua C et al, Med Phys 45:2486–97, 2018*

Risk-Stratified Therapy for Young Children with Medulloblastoma: Results of the Phase II Trial SJYC07

Medulloblastoma, the most common malignant brain tumor in children, accounts for 18%-20% of childhood brain tumors. Young patients with medulloblastoma have a lower overall survival than do older children, mainly because radiation therapy (RT) is reduced or omitted in young children due to severe long-term sequelae. Medulloblastoma is classified into 4 molecular subgroups—WNT, sonic hedgehog (SHH), group 3, and group 4—that have distinct clinical, genetic, and prognostic characteristics. In infants and young children, medulloblastoma has not been systematically studied; molecular classification has not been uniformly applied; and outcomes have not been assessed by subtype or subgroup.

Giles W. Robinson, MD (Oncology), Amar J. Gajjar, MD (Pediatric Medicine, Oncology), and Paul A. Northcott, PhD (Developmental Neurobiology), led the effort to analyze the therapeutic and molecular outcomes of early childhood medulloblastoma in the Phase II trial SJYC07, which was reported in *The Lancet Oncology*. SJYC07 enrolled 81 children younger than 3 years with newly diagnosed medulloblastoma or aged 3–5 years with newly diagnosed nonmetastatic medulloblastoma without high-risk features at 6 centers in the U.S. and Australia. All patients received identical induction chemotherapy (methotrexate, vincristine, cisplatin, and cyclophosphamide; vinblastine was added for high-risk disease). Risk was assigned based on the clinical characteristics, and risk-adapted consolidation (cyclophosphamide, etoposide, carboplatin) was given for low-risk; focal RT, for intermediate-risk; and chemotherapy (topotecan and cyclophosphamide), for high-risk disease. Maintenance consisted of cyclophosphamide, topotecan, and erlotinib for all patients. To refine the stratification, a molecular cohort of 190 patient samples with methylation and matched germline and tumor-sequencing data were analyzed. Primary endpoints were event-free survival (EFS) and methylation-profiling patterns associated with progression-free survival (PFS).

At a median follow-up of 5.5 years, 5-year EFS was 31.3%, 55.3%, 24.6%, and 16.7% for the entire, low-, intermediate-, and high-risk cohorts, respectively. The team identified 2 infant molecular subtypes within the SHH subgroup: iSHH-I and iSHH-II. Infants with iSHH-II had better 5-year PFS than did those with iSHH-I (75.4% vs. 27.8%). The 5-year PFS of patients with low-risk iSHH-II was 90.9% versus 22.2% for those with high-risk iSHH-I. Most progressions or relapses occurred during therapy; 55% occurred during maintenance. Therapy was well tolerated, and there were no protocol-related deaths.

This study provides a comprehensive landscape of medulloblastoma in infants and young children and advocates the use of molecular risk-adapted models in future trials. Although treatment was well tolerated and primary outcomes differed by clinically risk-stratified groups, EFS did not improve. However, improved PFS in patients with the iSHH-II subtype without RT or ventricular/high-dose chemotherapy supports the notion that patients with this subtype can receive radiation-sparing therapy, and molecular classification will improve risk stratification in future trials of childhood medulloblastoma. *Robinson GW et al, Lancet Oncol 19:768–84, 2018*

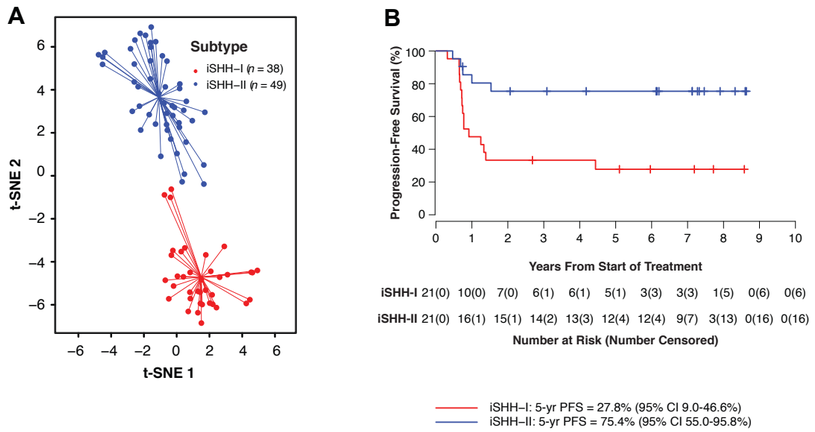


Figure. (**A**) The t-distributed stochastic neighbor embedding (t-SNE) plot showing the separation of the iSHH-I and iSHH-II subtypes of medulloblastoma. (**B**) Progression-free survival (PFS) analysis of iSHH-I and iSHH-II subtypes. *Reprinted from Lancet Oncol, 19, Risk-adapted therapy for young children with medulloblastoma (SJYC07): therapeutic and molecular outcomes from a multicenter, phase 2 trial. Robinson GW et al, 768–84, © 2018, with permission from Elsevier.*

Pan-Cancer Study Reveals the Genomic Architecture of Pediatric Cancers

The transformation of a normal cell into a cancer cell involves the dysregulation of key biological processes driven by specific genes and proteins. Pan-cancer analysis, which studies molecular aberrations across multiple cancer types, yields vital information on commonalities and differences across tumor lineages. To date, pan-cancer studies have been performed for adult but not pediatric cancers.

To unravel the genetic repertoire of childhood cancers, with the goal of developing targeted, safe therapies for this population, Jinghui Zhang, PhD (Computational Biology), and her team analyzed paired tumor and normal samples from 1699 patients (aged 21 years or younger) enrolled in clinical trials by the Children's Oncology Group (COG). This study, reported in *Nature*, analyzed samples from 6 tumor histotypes. Patient samples were obtained through the COG and the Therapeutically Applicable Research to Generate Effective Treatments project of the National Cancer Institute. The researchers used whole-genome sequencing (WGS), whole-exome sequencing (WES), and transcriptome sequencing to analyze data on somatic mutation rates and signatures and process it under a uniform analytical pipeline. Somatic mutations analyzed included single-nucleotide variations, small insertions/deletions, copy number alterations (CNAs), and structural variations.

The median somatic mutation rate ranged from 0.17 per million bases in acute myeloid leukemia and Wilms tumor to 0.19 per million in osteosarcomas, which was lower than that for many adult cancers. Eleven genome-wide mutational signatures were identified. Notably, 1 signature matched that generated by ultraviolet light (UV) exposure and was present in 8 B-lineage acute lymphoblastic leukemia samples, suggesting that UV exposure or other mutational processes could lead to pediatric leukemogeneis. Enrichment of somatic alterations in individual histotypes or the pan-cancer cohort revealed 142 mutated driver genes in pediatric cancer. Strikingly, 78 (55%) of those genes were not found in adult pan-cancer studies. Furthermore, CNAs and structural variations, which are often driving events in childhood cancers, made up 62% of events and were more efficiently detected by WGS than by WES. Dr. Zhang's team identified 21 recurrently altered biological pathways in 682 leukemia and 236 solid tumor samples. Point mutations affecting signaling pathways were mostly subclonal, indicative of subclonal mutations contributing to tumorigenesis. Analysis of 6959 coding mutations with matching WGS and RNA-sequencing data showed that mutant alleles were expressed in 34% of the mutations, and 20% of the mutations had allele-specific expression.

This landmark study provides a detailed overview of the mutational landscape in childhood cancer. It reveals that only 45% of driver genes are common in childhood and adult cancers. Thus, the genetic basis for childhood cancer is distinct from that of adult cancer, and gene panels used to detect genomic abnormalities in adults with cancer are not sufficient for genomic profiling of pediatric patients with cancer. Datasets developed in this pan-cancer study will provide a roadmap for functional validation and implementation of genomics to facilitate precision medicine in children with cancer. *Ma X, Nature 555:371–6, 2018*

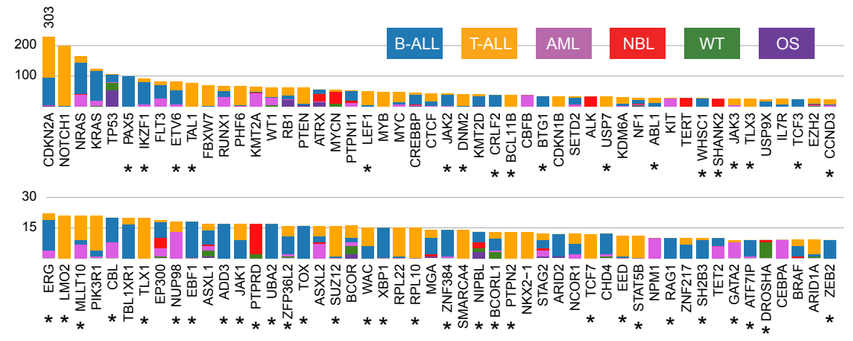


Figure. Top 100 recurrently mutated genes in childhood cancer. The case count for each histotype is shown in the same color as the legend. Asterisks indicate genes not reported in previous adult pan-cancer analyses. **Abbreviations:** B-ALL, B-lineage acute lymphoblastic leukemias; T-ALL, T-lineage acute lymphoblastic leukemias, AML, acute myeloid leukemias; NBL, neuroblastomas; WT, Wilms tumor; OS, osteosarcoma. *Reprinted by permission from SNCSC GmbH: Nature, 555:371–6, Ma X et al, Pan-cancer genome and transcriptome analyses of 1,699 paediatric leukaemias and solid tumours. © 2018 Springer Nature*

CIRCLE-Seq: a New Technique for Identifying the On-Target and Off-Target Effects of CRISPR–Cas9

Genome editing by CRISPR–Cas9 is now widely used for specifically directing mutations in genomic DNA. However, CRISPR–Cas9 is limited by the introduction of off-target mutations within the genome that may be deleterious to the organism. Identifying such off-target mutations is imperative for clinical applications of CRISPR–Cas9, because unknown off-target mutations may drive oncogenic transformation of cells.

Several methods are available for defining the off-target effects of CRISPR–Cas9-mediated genome editing. However, these methods are generally limited by low sensitivity, high background, and a reliance on cellular DNA damage–repair pathways for detection. To address these shortcomings, Shengdar Q. Tsai, PhD (Hematology), and colleagues developed a novel approach to identify the on-target and off-target mutations resulting from CRISPR–Cas9-based genome editing. Circularization for in vitro reporting of cleavage effects by sequencing (CIRCLE-seq) is a cell-free method that uses circularization of randomly sheared genomic DNA fragments containing both on- and off-target CRISPR–Cas9 sites, which are then subjected to nuclease cleavage, adaptor ligation, and selective sequencing.

In *Nature Protocols*, Dr. Tsai's team reported the specific method by which CIRCLE-seq is performed to identify genome-wide on- and off-target mutations introduced by CRISPR–Cas9. The protocol consists of 97 steps that are performed over the course of 2 weeks. These CIRCLE-seq protocol steps are divided into 8 distinct stages: (1) Cells or tissues are harvested. (2) Genomic DNA is extracted. (3) Single-guide RNAs (sgRNAs) are cloned and transcribed in vitro. (4) The Cas9–sgRNA ribonuclear protein complexes are tested for their ability to cleave a PCR amplicon containing the intended CRISPR–Cas9 target site. (5) The genomic DNA is sheared into fragments. (6) A CIRCLE-seq library is prepared by circularizing the genomic DNA fragments and degrading any residual linear DNA. (7) The circularized DNA fragments containing the CRISPR–Cas9 on- and off-target sites are cleaved with an optimized Cas9–sgRNA ribonuclear protein complex. (8) Adapters are added to the cleaved ends of the genomic DNA fragments, which are then PCR amplified and subjected to paired-end high-throughput sequencing.

In comparison with previously reported methods for detecting the off-target effects of genome editing, CIRCLE-seq provides numerous advantages. CIRCLE-seq requires a relatively small number of sequencing reads (3-5 × 10^6 reads) and reduces the uniformly high background of random reads associated with other cell-free methods. In contrast with cell-based methods of off-target detection, CIRCLE-seq does not rely on DNA damage–repair machinery for detection, is not affected by the method of Cas9 delivery, and has greatly improved sensitivity. Moreover, CIRCLE-seq does not require alignment with a reference genome to identify potential Cas9-mediated DNA double-stranded breaks, permitting detection of off-target mutations in the genomes of organisms lacking complete sequencing or annotation or in genomes with high genetic variability. CIRCLE-seq greatly reduces the sequencing coverage requirements required by other methods. Therefore, CIRCLE-seq is easily adaptable and can be performed in any laboratory with high-throughput sequencing capability.
Lazzarotto CR et al, Nat Protoc 13:2615–42, 2018

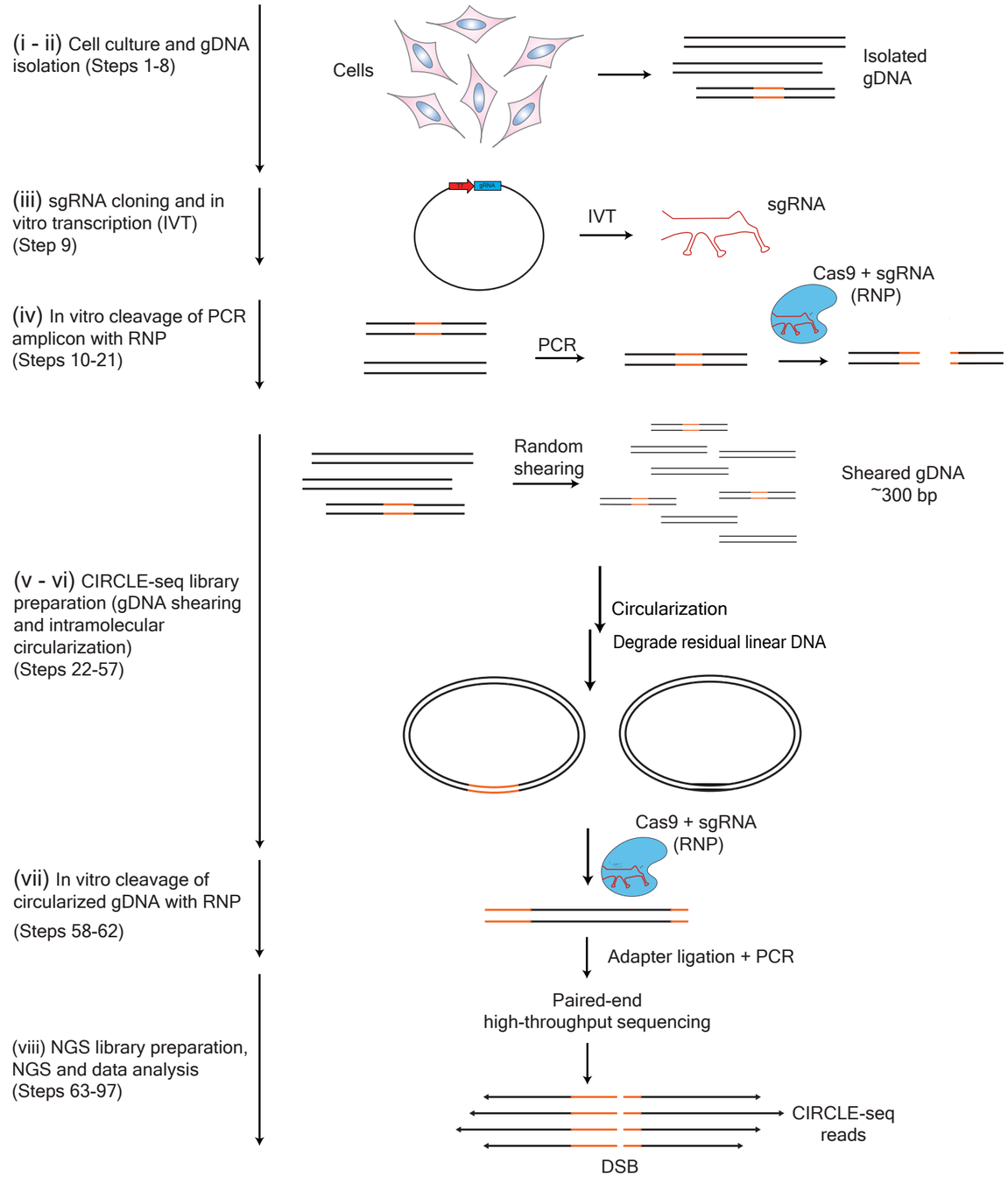


Figure. Overview of the CIRCLE-seq workflow. *Reprinted by permission from SNCSC GmbH: Nat Protoc, 13:2615–42, Lazzarotto CR et al, Defining CRISPR-Cas9 genome-wide nuclease activities with CIRCLE-seq. © 2018 Springer Nature*

A Novel Druggable Target to Selectively Modulate Androgen Receptor Activity for the Treatment of Spinal Bulbar Muscular Atrophy

Spinal bulbar muscular atrophy (SBMA) is a debilitating motor neuron disease affecting 1 in 40,000 men worldwide. It is caused by a CAG-repeat expansion in the androgen receptor (*AR*) gene, which confers a toxic gain of function. This gain of function requires activation of the AR by its cognate ligands testosterone or dihydrotestosterone (DHT), in addition to binding of various activating or repressing cofactors. One domain within the AR in which such cofactors bind is termed the activation function 2 (AF2) domain. A previous study in a *Drosophila* model of SBMA by J. Paul Taylor, MD, PhD (Cell & Molecular Biology), and colleagues revealed that cofactor binding specifically to the AF2 domain is required for driving neurodegeneration in SBMA. Because cofactor binding to the AF2 domain can be selectively modulated by small-molecule compounds that bind a nearby motif termed binding function 3 (BF3), the BF3 motif is an ideal druggable target for simultaneously mitigating the toxic gain of function resulting from CAG-repeat expansion in *AR* and preserving its native function as a transcription factor.

In a follow-up study published in *Nature Medicine*, Dr. Taylor's group screened several potential SBMA therapeutic compounds that specifically bind to the BF3 motif of the AR and modulate cofactor binding to the AF2 domain in a *Drosophila* model of SBMA. This screen revealed 2 compounds, tolfenamic acid (TA) and 1-[2-(4-methylphenoxy)ethyl]-2-[(2-phenoxyethyl)sulfanyl]-1H-benzimidazole (MEPB), that restored several indicators of DHT-dependent neurodegeneration, including viability, motor control, and neuromuscular junction architecture. To further characterize the efficacy of these 2 compounds for treating SBMA, the researchers generated a novel mouse model of SBMA that recapitulated the symptoms and pathology of the human disease. When TA and MEPB were administered to the SBMA mice, MEPB was more effective than TA at diminishing SBMA phenotypic symptoms and pathology. Pharmacokinetic analysis of TA and MEPB in mice revealed that MEPB exhibits superior bioavailability compared with TA, suggesting that MEPB is a more beneficial therapeutic because it has optimal duration and penetration in the tissues affected by SBMA pathology. In a large, blinded preclinical trial in SBMA mice, MEPB improved several phenotypic outcomes and quality-of-life parameters, including body weight, motor control and coordination, and muscle strength. Moreover, spinal cord, muscle, and testicular degeneration were reduced in a dose-dependent manner in the SBMA mice.

To glean insight into the mechanism of action of MEPB on CAG repeat–expanded AR, the researchers conducted several in vitro assays of AR functional activity. MEPB treatment did not affect DHT-dependent translocation of the AR to the nucleus or its transcriptional activity, indicating that MEPB does not inhibit AR-mediated transcription of target genes. Indeed, the transcription of 8 known motor neuron–specific target genes was unaffected by MEPB treatment. However, MEPB specifically increased the recruitment of nuclear receptor corepressor 1 to the AF2 domain, suggesting that the selective modulation of CAG repeat–expanded AR by MEPB is mediated by recruiting corepressors, rather than coactivators, to the AF2 domain. Together, these findings provide proof-of-principle evidence for the subtle modulation of cofactor binding to the AR AF2 domain by BF3-binding compounds for SBMA therapy without complete androgen-signaling ablation. *Badders NM et al, Nat Med 24:427-37, 2018*

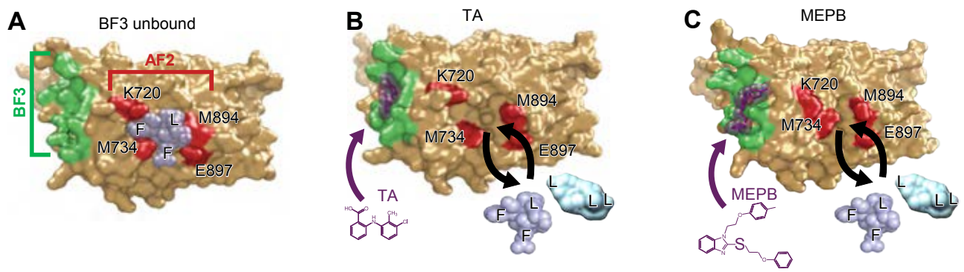


Figure. Structural depiction of the AR ligand–binding domain unbound (**A**) or in complex with TA (**B**) or MEPB (**C**). The AF2 domain is shown in red; the BF3 domain, in green; and TA and MEPB, in purple. *Reprinted by permission from SNCSC GmbH: Nature Med, 24:427-37, Badders NM et al, Selective modulation of the androgen receptor AF2 domain rescues degeneration in spinal bulbar muscular atrophy. © 2018 Springer Nature*

Mixed Phenotype Acute Leukemia Study Motivates the Expansion of the WHO Classification Scheme for Acute Leukemias

Mixed phenotype acute leukemia (MPAL) represents 2%-3% of pediatric acute leukemias, and children with this rare disease typically experience poor survival (i.e., 20%-40%). Clinicians have yet to determine the optimal treatment for patients with MPAL, which has features similar to those of both acute lymphoblastic leukemia (ALL) and acute myeloid leukemia. Although some MPAL cases have a classic *MLL* rearrangement or *BCR–ABL* fusion, the genetic basis of most cases has remained unknown.

To improve the treatment and ultimately the survival of children with this rare leukemia, Charles G. Mullighan, MBBS, MD (Pathology), and an international group of collaborators analyzed data from 115 patients with MPAL and identified the disease's genetic basis. In a recent *Nature* article, the researchers reported the distinct genomic profiles of the 3 most common subtypes of MPAL—T/myeloid, B/myeloid, and *KMT2A* (*MLL*)-rearranged MPAL—as determined by sequencing of exomes, transcriptomes, and whole genomes, among other analyses.

Dr. Mullighan's team found that the *ZNF384* gene was rearranged in 48% of B/myeloid MPAL cases and the *WT1* gene was frequently altered in T/myeloid MPAL. T/myeloid MPAL resembled early T-cell precursor ALL (ETP-ALL), in that it carried mutations that affected hematopoietic development and signaling. Differences also existed among specific signaling pathways and epigenetic regulators in the different subtypes of MPAL.

During their search for the MPAL cell of origin, the researchers discovered that the founding genetic lesions arose in early hematopoietic progenitors and that individual subpopulations of cells could regenerate the immunophenotypic diversity. Thus, MPAL cells are primed for lineage promiscuity by their cell of origin and founding lesions and not by secondarily acquired genomic alterations.

These findings prompted Dr. Mullighan and his collaborators to propose that the World Health Organization update the classification scheme for acute leukemias to include the 3 subtypes of MPAL. This work has implications for risk stratification and tailoring of treatments based on genomic data and immunophenotyping of the acute leukemia. *Alexander TB et al, Nature 562:373-9, 2018*

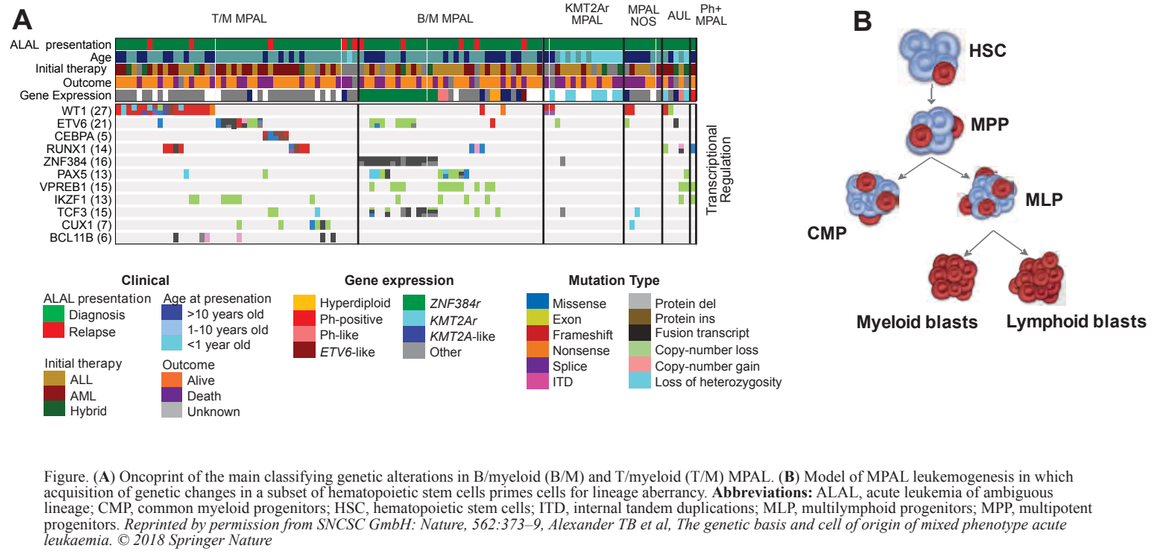


Figure. (**A**) Oncoprint of the main classifying genetic alterations in B/myeloid (B/M) and T/myeloid (T/M) MPAL. (**B**) Model of MPAL leukemogenesis in which acquisition of genetic changes in a subset of hematopoietic stem cells primes cells for lineage aberrancy. **Abbreviations:** ALAL, acute leukemia of ambiguous lineage; CMP, common myeloid progenitors; HSC, hematopoietic stem cells; ITD, internal tandem duplications; MLP, multilymphoid progenitors; MPP, multipotent progenitors. *Reprinted by permission from SNCSC GmbH: Nature, 562:373–9, Alexander TB et al, The genetic basis and cell of origin of mixed phenotype acute leukaemia. © 2018 Springer Nature*

Pantazine PZ-2891 Is a Promising Therapeutic for Patients with Pantothenate Kinase–Associated Neurodegeneration

Pantothenate kinase (PANK) is a key regulator of coenzyme A (CoA), a cofactor required for many enzymatic and metabolic processes. In humans, 3 *PANK* genes express 4 closely related isoforms, and inactivating mutations in *PANK2* lead to PANK-associated neurodegeneration (PKAN), a rare disorder marked by iron deposition in the basal ganglia. Symptoms of PKAN include progressive movement abnormalities, speech problems, vision loss, behavioral issues, and intellectual deterioration.

PANK is the first and rate-limiting enzyme in the CoA biosynthesis pathway, and CoA supports oxidative metabolism, ketone utilization, and lipid and glucose metabolism. CoA deficiency in neurons most likely leads to the symptoms of PKAN. However, no effective treatment has been developed to combat the debilitating symptoms of the disease. Compounds that bypass a *PANK* genetic deficiency and increase CoA production have been tested, but they fail to cross the blood–brain barrier (BBB) efficiently and do not affect brain CoA levels.

To develop an optimal treatment for PKAN, Suzanne Jackowski, PhD (Infectious Diseases), and her team used a novel therapeutic strategy to develop a drug that allosterically activates PANK isoforms PANK1α,β,βand PANK3 to compensate for the loss of PANK2. In a study reported in *Nature Communications*, the group used hit-to-lead optimization and studied the hit list by using an alternative approach to filter compounds, with lipophilic ligand efficiency as the primary metric. This optimization approach identified the pantazine PZ-2891, which is about 800 times more potent than the initial hit, penetrates the BBB, and increases the concentration of CoA in neural tissues. PZ-2891 activates all 4 mouse and human PANK isoforms. Kinetic and thermal stabilization studies revealed that PZ-2891 occupies the pantothenate pocket and bound tightly to the PANK•ATP•Mg^{2+} complex. Crystal structures of the PANK3•ATP•Mg^{2+}•PZ-2891 complex showed that PZ-2891 bound across the PANK-dimer interface to stabilize the active PANK conformation. PZ-2891 acts as an allosteric activator at subsaturating concentrations and as an orthosteric inhibitor at very high concentrations. The activation by PZ-2891 prevents the natural feedback regulation inhibition of PANK3 and increases CoA levels.

A human liver–derived cell line treated with PZ-2891 had elevated CoA levels. Increasing pantothenate in the cell culture medium without adding PZ-2891 did not affect CoA content, supporting the notion that PANK is the rate-controlling factor in the CoA pathway. In mice, PZ-2891 plus pantothenate increases the CoA content in the brain and liver. Finally, a mouse model of brain CoA deficiency revealed that PZ-2891 treatment increases weight and longevity and improves locomotor activity.

Although the pharmaceutical properties of PZ-2891 remain to be optimized, these studies provide compelling proof that this PANK activator has excellent oral bioavailability, target affinity, and BBB permeability. These studies validate the activations of alternative PANK isoforms as a promising approach to treating PKAN, and PZ-2891 should be further explored as a therapeutic agent in the clinic. *Sharma LK et al, Nat Commun 9:1–15, 2018*

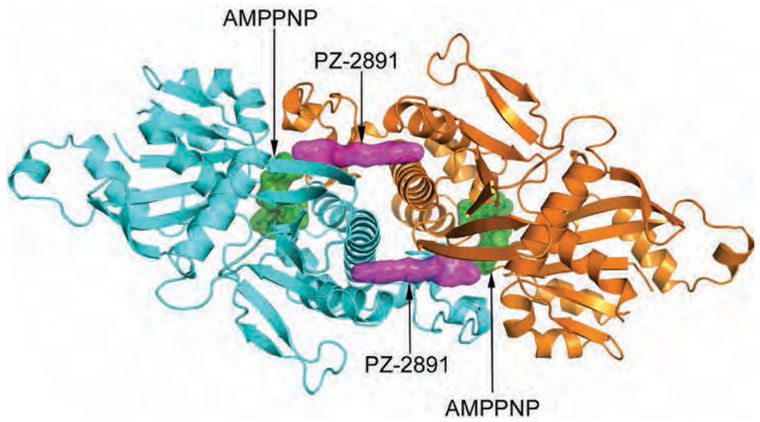


Figure. Diagram showing that PZ-2891 (pink) binds with AMPPNP (green) across the PANK3 protomers (cyan and gold). *Reprinted by permission from SNCSC GmbH: Nat Commun, 9:1–15, Sharma LK et al, A therapeutic approach to pantothenate kinase associated neurodengeration. © 2018 Springer Nature*

The NetBID Algorithm Reveals Coupling of the Metabolic State and Immune Function of CD8α⁺ Dendritic Cells

Dendritic cells (DCs) are antigen-presenting cells whose primary function is to process antigens into peptide fragments and present them to T cells to activate them. DCs that express the glycoprotein CD8αβchain on their surface (CD8α⁺ DCs) preferentially present antigens to $CD8^+$ T cells and elicit cytotoxic T-cell responses to viruses, bacteria, and tumors. In contrast, DCs that do not express the CD8αβchain (CD8α⁻ DCs) are more efficient at priming $CD4^+$ T cells (T helper cells). Although some lineage-specific transcriptional regulators of CD8α⁺ DC development have been identified, the molecular pathways that orchestrate CD8α⁺ DC function remain elusive. Metabolic reprogramming is important for DC development and activation, but the metabolic regulation of specific DC subsets has been poorly defined.

Hongbo Chi, PhD (Immunology), and Jiyang Yu, PhD (Computational Biology), led a team to develop a data-driven systems biology tool called Network-based Bayesian Inference of Drivers (NetBID), which integrates transcriptomic, whole-proteomic, and phosphoproteomic data. They used this algorithm to determine the role of kinases of the Hippo signaling pathway in the selective reprogramming of CD8α⁺ DC function and metabolism, and they published their findings in *Nature*.

The NetBID analysis of DCs revealed that the activities of Hippo-pathway kinases were enriched in CD8α⁺ DCs, as compared to CD8α⁻ DCs. The researchers then engineered mice with DC-specific deletions of the Hippo-pathway kinases Mst1 and Mst2 (Mst1/2), Lats1 and Lats2 (Lats1/2), or Yap and Taz (Yap/Taz). They found that DC-specific depletion of Mst1/2 disrupted the homeostasis and function of $CD8^+$ T cells and, thus, antitumor immunity in the mice, whereas DC-specific depletion of Lats1/2 or Yap/Taz, which mediate canonical Hippo signaling, had no effect. Mst1/2-deficient CD8α⁺ DCs were impaired in their presentation of antigens to $CD8^+$ T cells, whereas CD8α⁻ DCs that lacked Mst1/2 had essentially normal function. Compared to CD8α⁻ DCs, CD8α⁺ DCs exhibited much stronger oxidative metabolism and depended on Mst1/2 signaling to maintain the bioenergetic activities and mitochondrial dynamics that are necessary to their function. In a subsequent experiment, the selective expression by CD8α⁺ DCs of the cytokine interleukin 12 (Il-12), which serves as a signal for $CD8^+$ T-cell activation, depended on Mst1/2 and crosstalk with noncanonical NF-κB signaling.

In summary, the researchers defined a noncanonical Hippo signaling pathway that coordinates mitochondrial activity, noncanonical NF-κB signaling, and cytokine signaling in CD8α⁺ DCs, and they showed that Mst1/2 kinases are crucial and selective regulators of CD8α⁺ DC function. This interplay between immune signaling and metabolic reprogramming underlies the unique functions of DC subsets. Accordingly, strategies that modulate the activities of DC subset–specific Mst1/2 signaling and metabolic regulation are attractive candidates for therapeutic interventions against cancers and immune-mediated diseases. Furthermore, the NetBID algorithm has demonstrated its advantage over conventional analysis methods by successfully identifying "hidden" kinase drivers. This approach can now be extended to other drivers and biological questions. *Du X et al, Nature 558:141–5, 2018*

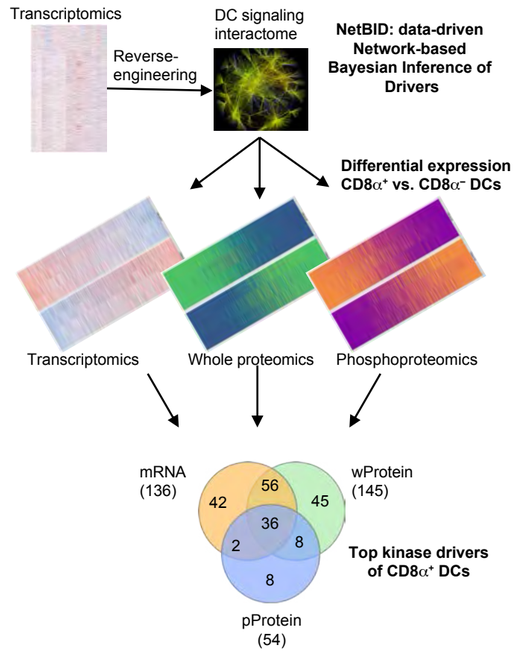


Figure. Overview of NetBID. *Reprinted by permission from SNCSC GmbH: Nature, 558:141–5, Du X et al, Hippo/Mst signalling couples metabolic state and immune function of CD8α⁺ dendritic cells. © 2018 Springer Nature*

Apurinic Endonuclease 1 Suppresses Oxidative DNA Damage in the Neural Genome

Genome stability is crucial for the development and functioning of organisms. DNA-repair enzymes prevent the accumulation of DNA lesions, which can affect several organ systems and are linked to disease pathologies. High oxygen consumption in the nervous system makes it susceptible to oxidative damage, caused mainly by reactive oxygen species (ROS). Given that neurons consume a large quotient of oxygen, DNA repair of ROS damage is essential in the nervous system.

Oxidative damage–related DNA lesions are repaired by the base excision repair (BER) pathway, in which DNA glycosylases recognize and remove base damage to generate apurinic/apyramidinic (AP) sites. AP endonuclease 1 (APE1, also known as redox effector factor) recognizes AP sites and nicks the phosphodiester backbone 5′ to the lesion to generate a single-stranded break. Several components of the BER pathway play key roles in the nervous system, but the role of APE1 remains unknown.

To characterize the physiological role of APE1 in the nervous system, Peter J. McKinnon, PhD (Genetics), and his group generated a conditional-knockout *Ape1* (*Ape1*$^{Nes\text{-}cre}$) murine model to study neurogenesis during embryonic and postnatal stages and in neural homeostasis. Their findings were reported in the *Proceedings of the National Academy of Sciences U S A*. Embryonic neural development occurred, despite the absence of APE1 during neurogenesis. However, after birth [postnatal day (P) 5 onward], *Ape1*$^{Nes\text{-}cre}$ mice had a decline in vigor, stunted growth, low body weight, and ataxia, and they died after 3 weeks. Brains of P9 *Ape1*$^{Nes\text{-}cre}$ mice showed a conspicuous defect in cerebellar development, marked by widespread loss of granule neurons and decrease in interneurons. By studying DNA damage with the marker γH2AX and apoptosis by TUNEL, the group concluded that DNA damage–induced apoptosis leads to cellular atrophy. Furthermore, cortex size was markedly reduced postnatally in *Ape1*$^{Nes\text{-}cre}$ mice, confirming that APE1 is required for cortical homeostasis.

APE1 loss also resulted in other neural defects, such as loss of myelination in oligodendrocyte-rich regions of the brain and disruption of upper cortical layers. In neural cells, APE1 was crucial for repairing oxidative DNA lesions to maintain genome stability and sensitize cells to genotoxins. *Ape1*$^{Nes\text{-}cre}$ mice exhibited shivering, and using heating pads extended their survival. The thermoregulatory defect compromising survival in the shivering phenotype was traced to the loss of thermoregulatory serotonergic neurons in the rostral medullary Raphe nuclei.

Apart from its DNA-repair activity, APE1 controls the redox status and DNA-binding activity of transcription factors. This redox effector factor role was confirmed by kainic acid–induced hippocampal stimulation, which activated binding of the transcription factor AP-1. Notably, APE1 and p53 inactivation made mice susceptible to brain tumors (e.g., glioblastoma and medulloblastoma), supporting the hypotheses that APE1 is a potent tumor suppressor, and oxidative DNA lesions initiate events in tumorigenesis.

This study shows key roles for APE1 in maintaining postnatal neurodevelopment and genomic integrity in mature neurons. These results are clinically important for understanding the underlying pathology of diseases related to oxidative DNA damage in the nervous system and developing effective therapeutics for them. *Dumitrache LC et al, Proc Natl Acad Sci U S A 115:E12285–94, 2018*

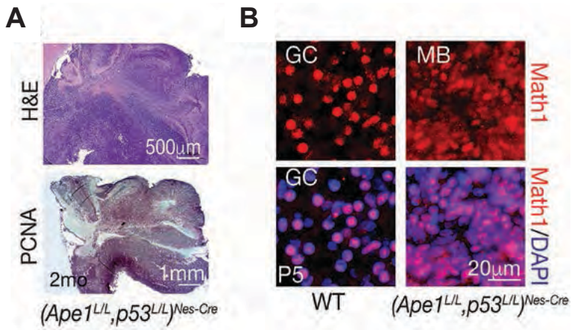


Figure. Mice with inactivation of APE1 and p53 develop medulloblastoma within 1–3 months. (**A**) Hematoxylin and eosin (H&E) staining and proliferating cell nuclear antigen (PCNA) immunostaining of medulloblastomas in the cerebellum indicate tumor cell proliferation in 2-month-old mice. (**B**) Math1 immunostaining of immature granule cells (GC) in wild-type (WT) P5 cerebellum and medulloblastoma (MB) indicates that the tumor is derived from granule cell precursors. *Reprinted from Proc Natl Acad Sci U S A 115: E12285–94. © 2018 Dumitrache LC et al*

Nonmyogenic Progenitors Give Rise to Fusion-Negative Rhabdomyosarcoma

Rhabdomyosarcoma is the most common pediatric soft-tissue sarcoma; however, the cell of origin of this common tumor has remained unknown. The tumor cells resemble skeletal muscle–derived cells, and rhabdomyosarcoma occurs throughout the body, including areas devoid of skeletal muscle. Because these tumors often express PAX3–FOXO1 or PAX7–FOXO1 fusion proteins, which are linked to poorer prognosis, rhabdomyosarcoma is classified as being either fusion-negative or fusion-positive.

Mark E. Hatley, MD, PhD (Oncology), and his colleagues performed in-depth analyses of the cellular origins of fusion-negative rhabdomyosarcoma by using their previously designed mouse model of the disease. The model includes a conditional constitutively active *Smoothened* mutant (SmoM2) that is activated by *aP2-Cre*. In *Cancer Cell*, the researchers reported their findings from a series of genetic fate-mapping experiments. Their model recapitulated fusion-negative rhabdomyosarcoma in nonmuscle cells exclusively in the head and neck, which is the most common site of rhabdomyosarcoma in patients. To their surprise, SmoM2 was activated in aP2-Cre–expressing endothelial cells within muscle interstitium.

The group also examined the role of the Sonic hedgehog pathway in the murine rhabdomyosarcoma model, because this pathway is vital to skeletal muscle formation outside the head and neck. They found that the abnormal activation of the Sonic hedgehog pathway caused SmoM2 expression in Cre-expressing endothelial progenitor cells that were predestined to become blood vessel cells, causing them to instead transdifferentiate into muscle-like cells. Therefore, rhabdomyosarcoma can arise from nonmyogenic cells.

A better understanding of the cellular origins and molecular drivers of this tumor might provide insight into the mechanisms of tumorigenesis and enable the use of more personalized therapy, thereby benefitting patients with fusion-negative rhabdomyosarcoma. *Drummond CJ et al, Cancer Cell 33:108–24, 2018*

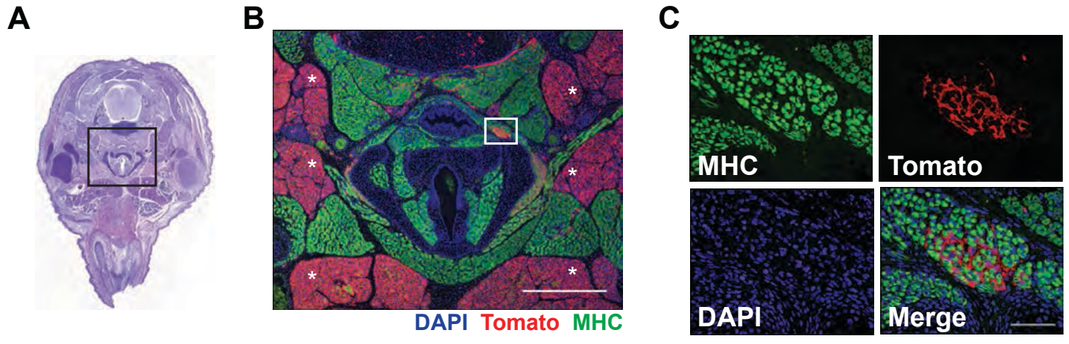


Figure. (**A**) Transverse section of an E17.5 murine model of rhabdomyosarcoma. (**B**) Magnification of boxed inset in A. Asterisks indicate regions of Tomato-positive adipose tissue (red) between developing myosin heavy chain (MHC)–positive myofibers (green). Scale bar, 500 μm. (**C**) Magnification of boxed inset in B. Scale bar, 50 μm. *Reprinted from Cancer Cell, 33, Drummond CJ et al, Hedgehog pathway drives fusion-negative rhabdomyosarcoma initiated from non-myogenic endothelial progenitors, pp. 108–24, © 2018 with permission from Elsevier.*

Interferon Regulatory Factor 8 Is a Crucial Regulator of NLRC4 Inflammasome Activation

Inflammasomes are molecular platforms that assemble in response to threat-associated intracellular stimuli to process caspase-1 into its active form, enabling the production of interleukin 1β (IL-1β) and interleukin 18 (IL-18) and ultimately inducing pyroptosis, a form of inflammatory cell death. Inflammasome activation is an essential component of the host defense against many microbial infections.

The NLRC4 inflammasome is crucial for protection against flagellated bacterial pathogens such as *Salmonella* or *Legionella* species. This inflammasome is unusual, in that it requires another sensor for ligand recognition and activation. Specifically, it requires NLR-family apoptosis-inhibitory proteins (NAIPs) to detect bacterial flagellin or type-III secretion system (T3SS) components in the cytosol. However, the mechanism by which this activation pathway is regulated was unknown. Mutations in NLRC4 and NAIPs are associated with autoinflammatory diseases such as infantile enterocolitis and recurrent macrophage activation syndrome.

Thirumala-Devi Kanneganti, PhD (Immunology), and her colleagues studied the regulation of the NLRC4 inflammasome in bone marrow–derived macrophages (BMDMs) from mice and published their findings in *Cell*. Interferon regulatory factors 1 and 8 (IRF1 and IRF8) are both present in macrophages, and IRF1 is required for the activation of the AIM2 inflammasome in response to bacterial infection. Thus, the researchers investigated whether IRF8 had a similar role in the inflammasome's activation. They first exposed BMDMs from wild-type (WT) mice and from mice lacking the *Irf8* gene (*Irf8*$^{-/-}$ mice) to ligands that prompt the activation of specific inflammasomes in WT cells. When the cells were exposed to stimulators of activation of the AIM2, NLRP3, and pyrin inflammasomes, the levels of caspase-1 activation, cytokine production, and cell death in *Irf8*$^{-/-}$ BMDMs were comparable to those in WT cells. However, when WT and *Irf8*$^{-/-}$ BMDMs were infected with *Salmonella* Typhimurium, a stimulator of NLRC4 inflammasome activation, the levels of caspase-1 activation, cytokine production, and cell death were substantially lower in the *Irf8*$^{-/-}$ cells than in the WT cells. Similar results were obtained when WT and *Irf8*$^{-/-}$ BMDMs were infected with *Pseudomonas aeruginosa* or *Burkholderia thailandensis*, which also engage the NLRC4 inflammasome. Thus, IRF8 is required for optimal activation of the NLRC4 inflammasome in murine BMDMs infected with various bacterial species but is dispensable for activation of the NLRP3, AIM2, and pyrin inflammasomes.

Dr. Kanneganti's team then performed transcription-based analyses of the differential regulation of innate immune sensors in WT and *Irf8*$^{-/-}$ BMDMs infected with *S.* Typhimurium. In *Irf8*$^{-/-}$ cells, they found reduced expression of 4 Naip genes (*Naip1*, *Naip2*, *Naip5*, and *Naip6*) and of the gene encoding NLRC4, whereas an analysis of ChIP-seq data from WT cells showed IRF8 binding to the promoters of the *Naip2*, *Naip5*, and *Naip6* genes and to the intronic region of the *Nlcr4* gene. Thus, IRF8 regulates the transcription of Naip genes and, consequently, the detection of flagellin or T3SS proteins to mediate NLRC4 inflammasome activation.

In a subsequent experiment, WT and *Irf8*$^{-/-}$ mice were infected with *S.* Typhimurium or *B. thailandensis*. Compared to WT mice, *Irf8*$^{-/-}$ mice exhibited markedly accelerated weight loss and mortality after infection, indicating that IRF8 confers protection against bacterial infection in vivo. In summary, these findings suggest that IRF8 is a crucial regulator of NAIPs and NLRC4 inflammasome activation for defense against infection by bacterial pathogens. *Karki R et al, Cell 173:920–33, 2018*

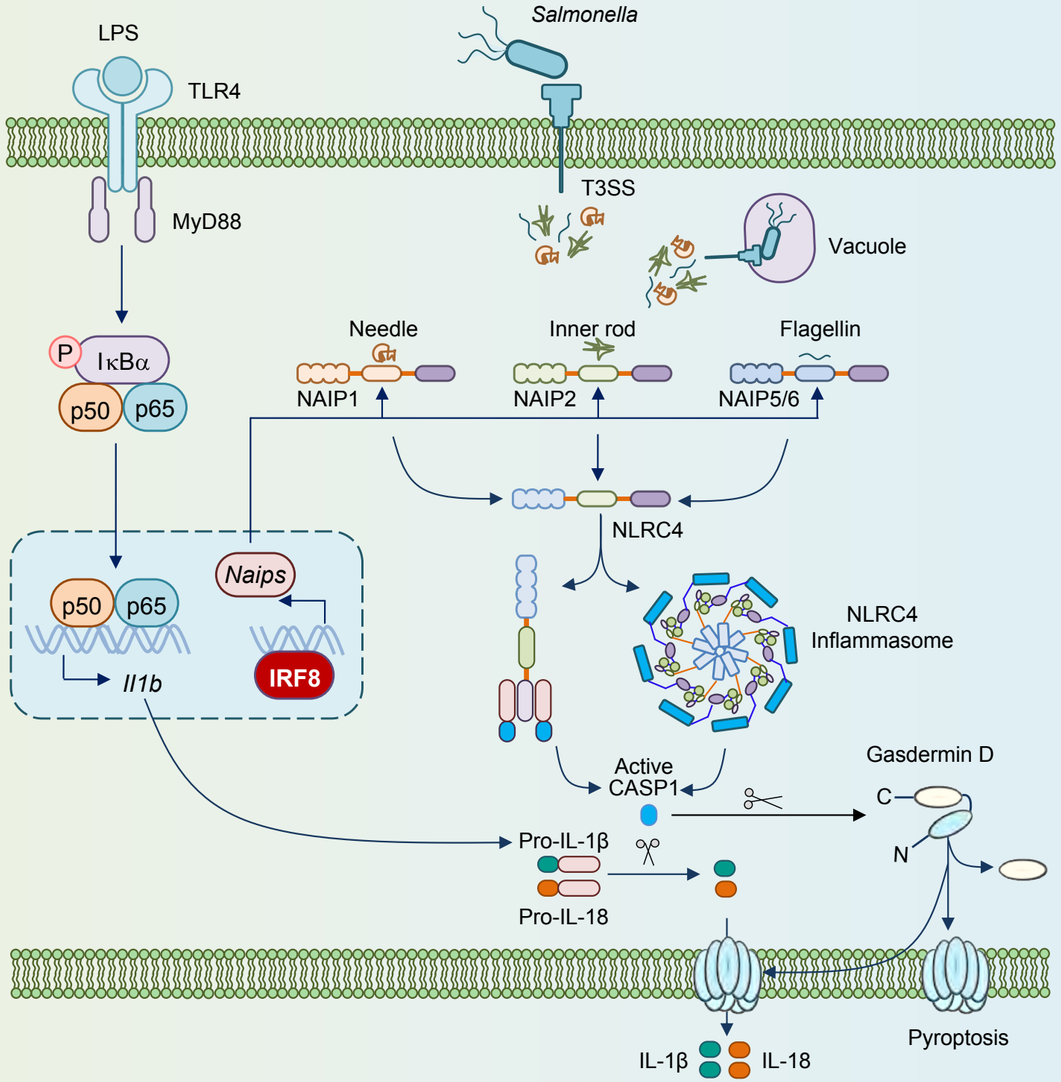


Figure. Model showing that the optimal activation of the NLRC4 inflammasome in response to pathogenic bacteria depends on IRF8. *Reprinted from Cell, 173, Karki R et al, IRF8 regulates transcription of Naips for NLRC4 inflammasome activation, 920–33, © 2018 with permission from Elsevier.*

MAGE-F1–NSE3 E3 Ubiquitin Ligase Controls Flux Through the Cytosolic Iron–Sulfur Cluster Assembly Pathway by Ubiquitinating and Degrading MMS19

The cytosolic iron–sulfur (Fe–S) cluster assembly (CIA) pathway is an evolutionarily conserved process that is vital for many cellular functions. For cytoplasmic and nuclear Fe–S proteins, Fe–S clusters are generated by coordinated activity of the CIA machinery. In humans, the CIA pathway has at least 9 components and is the pipeline through which iron- and sulfur-containing cofactors are generated from a precursor and processed for incorporation into cytosolic or nuclear proteins that need the Fe–S cluster as a structural, enzymatic, or electron-transfer component. MMS19 is a key component and end-target binding factor for the CIA Fe–S complex, and its loss in human cells can increase their susceptibility to DNA-damaging agents. However, the mechanisms by which the CIA pathway is regulated in normal and disease states and those by which MMS19 is targeted during this process have not yet been elucidated.

In humans, the melanoma antigen gene (MAGE) protein family is highly expressed in cancer and plays a role in tumorigenesis. In a study reported in *Molecular Cell*, Ryan Potts, PhD (Cell & Molecular Biology), and his team pinpointed the mechanism regulating the CIA pathway by studying MAGE-F1. MAGE-F1 is amplified in several types of cancer, but its specific functions had remained unknown. Pull-down experiments and in vitro binding assays for partners interacting with MAGE-F1 identified the E3 ubiquitin ligase NSE1, a member of the MAGE–RING ligase family, bound to MAGE-F1. Unlike MAGE-G1, MAGE-F1 did not incorporate into the SMC5/6 complex, which plays a central role in maintaining genomic stability. In a search for targets of MAGE-F1–NSE1, Dr. Potts' team identified MMS19 and showed that an increase in its ubiquitination and degradation controls flux through the CIA pathway. They also found that MAGE-F1 decreases the incorporation of iron into MMS19 targets; thus, the protein regulates iron homeostasis. The group then used homologous recombination assays to determine whether this decreased incorporation of iron affects cellular DNA-repair mechanisms in HeLa-Cas9 cells with overexpression or knockout of the *MAGE-F1* gene. Indeed, downregulation of MMS19 by MAGE-F1–NSE1 inhibited homologous recombination, reduced the DNA-repair capacity, and sensitized cells to DNA-damaging agents.

The team also unexpectedly found that adaptive pseudogenization (i.e., conversion of a gene to a pseudogene) of *MAGE-F1* occurred multiple times in specific mammalian lineages and most likely altered MMS19 and CIA-pathway function. Furthermore, genomic analysis of tumors in The Cancer Genome Atlas revealed that several cancer types, prominently lung squamous cell carcinomas, had amplification of *MAGE-F1*. Overexpression of *MAGE-F1* in a squamous carcinoma cell line increased tumor xenograft rates, suggesting that *MAGE-F1* amplification or overexpression triggers tumorigenesis.

This study provides strong evidence that the CIA pathway can be posttranslationally regulated by ubiquitination and degradation of the MMS19 protein. These results have potential clinical implications for patients with cancer or genomic instability and provide the basis for altering the CIA pathway in cancer, especially smoking-induced cancers (e.g., lung squamous cell carcinoma, esophageal carcinoma, and head and neck squamous carcinoma), in which *MAGE-F1* is amplified. *Weon JL et al, Mol Cell 69:113–25, 2018*

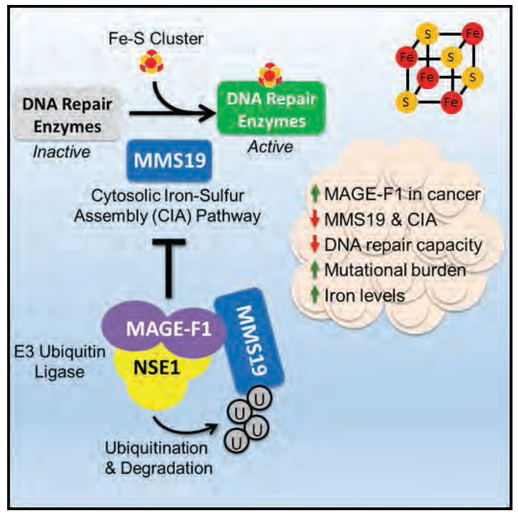


Figure. Scheme showing how MAGE-F1 specifies the cytosolic iron–sulfur assembly (CIA) pathway protein MMS19 for ubiquitination and degradation. *Reprinted from Molecular Cell, 69, Weon JL et al, Cytosolic iron–sulfur assembly is evolutionarily tuned by a cancer-amplified ubiquitin ligase, 113–25, © 2018, with permission from Elsevier.*

Social and Functional Independence Among Adult Survivors of Childhood Central Nervous System Tumors

Tara M. Brinkman, PhD

The survival of children with central nervous system (CNS) tumors has increased dramatically since the 1980s, when the 5-year survival was less than 60%; today the survival is approximately 74%. However, long-term survivors of childhood cancer are at risk for neurocognitive impairment, physical limitations, and other devastating ill effects that may adversely affect their social participation and functional independence. Previous results from the ongoing Childhood Cancer Survivor Study, which includes follow-up of 5-year survivors of childhood cancer whose primary disease was initially diagnosed from 1970 through 1999, show that survivors of CNS tumors are much less likely to be employed than their siblings and are also far less likely to live independently than other childhood cancer survivors. Tara M. Brinkman, PhD (Epidemiology & Cancer Control, Psychology), and her colleagues analyzed additional data from adult survivors participating in the St. Jude Lifetime Cohort Study (SJLIFE) to assess the independence of survivors of CNS tumors and the impact of independence on survivors' health-related quality of life.

In a recent article in the *Journal of Clinical Oncology*, Dr. Brinkman and her colleagues report results of analyses of 306 survivors of childhood CNS tumor survivors who were older than 18 years and at least 10 years from diagnosis. The study examined 6 validated indicators of functional and social independence: full-time employment, living independently, assistance with routine needs, assistance with personal care needs, obtaining a driver's license, and history of marriage or partnership. Overall, 123 (40%) pediatric CNS tumor survivors were independent as adults; 104 (34%) were moderately independent, and 79 (26%) were nonindependent. Craniospinal irradiation and younger age at diagnosis were associated with increased risk of nonindependence, as were limitations in key measures of physical performance (i.e., aerobic capacity, strength, flexibility, balance, mobility, and adaptive physical function). Despite the need for more assistance, nonindependent survivors reported mental health–related quality of life comparable to that reported by independent survivors.

The prevalence of medulloblastoma (for which treatment with craniospinal irradiation is essential for cure) among the participants may have increased the prevalence of nonindependence. Nevertheless, these findings indicate that a substantial percentage of survivors need continued assistance in adulthood. Vocational rehabilitation and physical performance interventions may be particularly useful in assisting the moderately independent survivors toward increased social and functional independence. *Brinkman TM et al, J Clin Oncol 36:2762–9, 2018*

Pathogenic Mutations in Cancer-Predisposition Genes Increase the Risk of Subsequent Neoplasms in Survivors of Childhood Cancer

The discovery of new anticancer therapies and improvement of existing therapies has increased the number of long-term survivors of childhood cancer. As this population continues to expand and age, the incidence of long-term therapy- or disease-related sequelae is also increasing. Subsequent neoplasms (SNs) are a relatively common long-term outcome for survivors of childhood cancers. Anticancer therapies, especially radiation therapy, increase the risk of SNs. However, the contribution of pathogenic mutations in cancer-predisposition genes to SNs in these patients is unknown. To determine whether germline mutations in cancer-predisposition genes play a role in the development of SNs in survivors of childhood cancer, Jinghui Zhang, PhD (Computational Biology), and Leslie L. Robison, PhD (Epidemiology & Cancer Control), led a collaborative study of the prevalence of pathogenic/likely pathogenic mutations in 60 cancer-predisposition genes in 3006 long-term survivors of childhood cancer.

In the *Journal of Clinical Oncology*, the researchers reported their findings from whole-genome and/or whole-exome sequencing of DNA derived from blood samples from patients who had survived at least 5 years after their cancer diagnoses. The initial cancer types that occurred in these survivors included leukemias (35%), lymphomas (19%), tumors with CNS involvement (11%), and other solid tumors (35%). The team classified the pathogenicity of single-nucleotide variants, copy-number variations, and small insertions and deletions in the cancer-predisposition genes according to guidelines set forth by the American College of Medical Genetics and Genomics. They also assessed the independent contribution of these pathogenic/likely pathogenic mutations to the risk of a specific SN after adjusting for initial cancer therapy.

Among 439 long-term survivors of childhood cancer, 1120 SNs occurred, including nonmelanoma skin cancer, meningioma, thyroid cancer, sarcoma, and breast cancer. In these patients, 175 pathogenic/likely pathogenic mutations were present in 32 cancer-predisposition genes. Although the cumulative incidence of an SN was the same for survivors with or without germline mutations who received radiation therapy, the incidence of SNs for those who did not receive radiation therapy was higher in survivors with pathogenic/likely pathogenic mutations than in those without. Nevertheless, the statistically inferred relative rate of developing any SN was higher when pathogenic/likely pathogenic mutations were present. Furthermore, the relative rate of breast cancer and sarcoma was highest among survivors who received radiation therapy, suggesting that these survivors are particularly vulnerable to radiation-induced neoplasms.

Genetic heterogeneity and pleiotropy were also prevalent among the long-term survivors. Specifically, mutations within different genes frequently resulted in the same SN type, and mutations within the same gene often resulted in different SN types. Together, these findings indicate that referrals for genetic counseling for all survivors and genetic testing, cancer screening recommendations, and risk-reduction strategies should be prioritized for a specific subset of patients with pathogenic/likely pathogenic mutations in cancer-predisposition genes to reduce the long-term risks associated with survival of childhood cancers. *Wang Z et al, J Clin Oncol 36:2078–87, 2018*

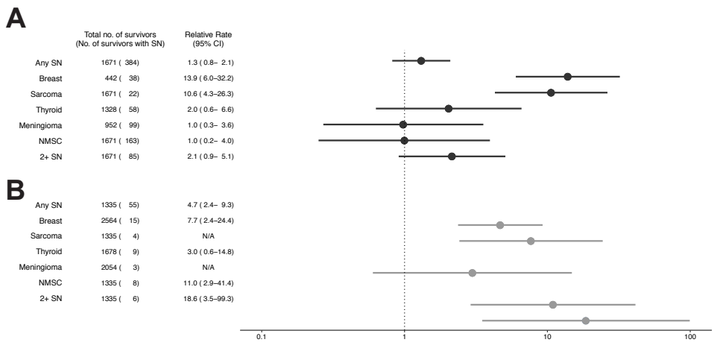


Figure. Multivariable piecewise exponential regression was used to calculate the relative rate (RR) of subsequent neoplasms (SNs) and 95% confidence intervals (CI) for mutation status stratified by (**A**) exposure to radiation or (**B**) no exposure to radiation. RR and 95% CI are plotted along the X-axis in a $\log_{10}$ scale. **Abbreviations:** NA, not applicable; NMSC, nonmelanoma skin cancer. *Wang Z et al, Genetic risk for neoplasms among long-term survivors of childhood cancer. J Clin Oncol 36, 20, 2078–87. Reprinted with permission. © 2018 American Society of Clinical Oncology. All rights reserved.*

Ethanol-Lock Therapy Is Not Recommended for Preventing Central Line–Associated Bloodstream Infections in Children

Children undergoing anticancer treatment or hematopoietic cell transplantation often require the long-term insertion of a central venous catheter (CVC), known as a central line, to facilitate the administration of chemotherapy drugs, blood products, and fluids. Although CVCs are essential to cancer care, they can give rise to serious infections. Approximately 25% of pediatric patients with cancer in high-income countries experience at least 1 episode of central line–associated bloodstream infection (CLABSI), which often necessitates the removal of the CVC and can cause life-threatening sepsis. Even after apparently successful treatment with antibiotics, the infections often return.

CLABSI is attributed to microorganisms that form "biofilms" on the surface of the CVC lumen and then spread to the bloodstream. These biofilms are resistant to systemic antibiotic therapies and immune clearance; to address this, adjunctive antimicrobial catheter-lock therapy has been used with the aim of eradicating or preventing biofilm-associated CLABSI. In this technique, an antimicrobial agent is allowed to dwell inside the CVC for a set period to kill the biofilm organisms. At high concentrations, ethanol kills organisms in biofilms. Ethanol-lock therapy (ELT) has been proposed as a likely effective preventative measure. However, no trials had been conducted to evaluate its efficacy as treatment and secondary prophylaxis for patients who already have CLABSI, though ELT is used for this purpose around the world.

Joshua Wolf, MBBS (Infectious Diseases), and colleagues designed and conducted the ETHEL Study, a randomized, double-blinded, placebo-controlled trial of the efficacy and tolerability of ELT as treatment and secondary prophylaxis for CLABSI in children and adolescents receiving treatment for cancer or hematologic disorders. The results of the trial were published in *The Lancet Infectious Diseases*.

The trial was conducted at St. Jude and at the Royal Children's Hospital Melbourne (Parkville VIC, Australia). Of the 94 evaluable patients enrolled in the trial, 48 received ELT with 70% ethanol and 46 received heparinized saline placebo locks. Treatment was administered for 2–4 hours per lumen per day for 5 days (the treatment phase) and then up to 3 nonconsecutive days per week for 6 months (the prophylaxis phase). Most participants

Joshua Wolf, MBBS

had very high adherence to the protocol therapy, with 85% receiving at least 75% of their scheduled doses. The incidence of treatment failure (defined as CVC removal or patient death attributable to infection, new or persistent infection, a need for additional lock therapy during the treatment phase, or recurrent CLABSI during the prophylaxis phase) was similar in both groups, occurring in 21 (44%) of the ELT recipients and 20 (43%) of the placebo recipients. However, adverse events attributable to lock therapy were more frequent in the ELT group. Notably, catheter occlusion requiring thrombolytic therapy occurred in 28 (58%) of the ELT recipients but in only 15 (33%) of the placebo recipients.

Dr. Wolf and his colleagues thus showed that ELT was ineffective as treatment and secondary prophylaxis for CLABSI in the pediatric populations studied; ELT demonstrated no advantage over placebo. Furthermore, such therapy increased the risk of catheter occlusion requiring thrombolytic therapy. This is important because the treatment has been used in many centers without high-quality evaluation of its safety or efficacy. The researchers concluded that ELT should not be used routinely in children with cancer or hematologic disorders. *Wolf J et al, Lancet Infect Dis 18:854–63, 2018*

Molecular Diversity and Alterations in the Uncharacterized Gene *CXorf67* in Posterior Fossa Group A Ependymomas

Wilda Orisme, PhD; David W. Ellison, MD, PhD

Ependymomas account for nearly 30% of central nervous system tumors in infants, and targeted therapies could reduce morbidity and mortality in patients whose tumors are inoperable. Previous DNA-methylation profiling studies undertaken, in part, to uncover such targets revealed that ependymomas from the supratentorial, spinal, and posterior fossa regions of the central nervous system can be separated into molecular groups, with posterior fossa group A (PFA) being the most common form of the disease.

Following up on their previous work, David W. Ellison, MD, PhD (Pathology), and his collaborators at St. Jude, the German Cancer Research Center, the Hospital for Sick Children (Toronto, Canada), and the University of Nottingham, U.K., performed DNA-methylation profiling on 675 PFA ependymomas to discover novel molecular subtypes with distinct clinical characteristics.

In *Acta Neuropathologica*, Dr. Ellison and his team reported that PFA ependymomas are molecularly diverse and can be categorized into 2 subgroups (PFA-1 and PFA-2) that are composed of 9 subtypes and may arise from separate anatomic locations. To determine whether this hierarchical molecular classification is clinically relevant, the researchers analyzed patient data and tumor profiles from 569 cases. They found that PFA-1 ependymomas were associated with local recurrence and PFA-2 ependymomas were associated with distant relapse. Furthermore, PFA subtypes were associated with distinct outcomes; in particular, OTX2-overexpressing PFA-2c tumors appeared to have very favorable rates of progression-free and overall survival.

In a reanalysis of published sequencing data of ependymomas, Dr. Ellison's team found novel recurrent mutations in the uncharacterized gene *CXorf67*. This gene was mutated only in PFA tumors, at a frequency of 9.2%. They also noticed that *CXorf67* is highly expressed in PFA ependymomas but not in other ependymoma molecular groups. Using immunoprecipitation and mass spectrometry studies to show that CXorf67 binds to core components of the polycomb repressive complex 2 (PRC2) and by modulating levels of CXorf67 in cell lines to show that CXorf67 can inhibit PRC2, they also discovered a mechanism for the depletion of H3 K27-trimethylation in PFA ependymoma tumor cells. These studies implicate CXorf67 as an oncogenic driver in PFA ependymomas and suggest that targeting of CXorf67's inhibition of PRC2 may be a useful therapeutic strategy in children with PFA ependymomas. *Pajtler KW et al, Acta Neuropathol 136:211–26, 2018*

Improving Immunohistochemistry Capability in Central America and the Caribbean

The Asociacíon de Hemato-Oncología Pediátrica de Centro América (AHOPCA) is a consortium of pediatric oncology centers in low- and middle-income countries (LMICs) in Central America and the Caribbean. St. Jude collaborates with AHOPCA in multidisciplinary educational activities to improve the quality of health care for children with cancer in those countries.

One area requiring improvement is access to immunohistochemistry (IHC) resources, which are essential for the proper diagnosis and treatment of cancer. Whereas IHC is widely available in anatomic pathology laboratories in high-income countries, its availability in LMICs is limited or nonexistent. Even when IHC is available in LMICs, the results may be of suboptimal or inconsistent quality, leading to incorrect diagnoses. Accordingly, for many years, St. Jude pathologists have provided second-opinion diagnoses to AHOPCA members. However, it would be preferable if pathologists in LMICs were able to provide high-quality IHC services at their respective institutions.

In an article published in the *Journal of Global Oncology*, Teresa Santiago, MD (Pathology), and her colleagues reported on a 5-day training workshop on IHC techniques that was organized by the AHOPCA Pathology Working Group for pathologists and histotechnologists from 7 Central American and Caribbean countries.

The workshop was held at the Hospital Nacional de Niños Benjamin Bloom (HNNBB) in San Salvador, El Salvador. This institution was chosen as the training center because its pathologists perform their IHC assays manually but obtain results of excellent overall quality. Therefore, their IHC techniques were considered suitable for adoption by other pathology laboratories for which the cost of acquiring and maintaining an automated IHC-staining system is prohibitive.

The workshop participants comprised a pathologist and a histotechnologist from each of 8 centers in Costa Rica, the Dominican Republic, Guatemala, Haiti, Honduras, Nicaragua, and Panama. The participants from 3 centers had never performed IHC staining in their daily practice. The training team consisted of 2 histotechnologists and a pathologist from the HNNBB and a pathologist (Dr. Santiago) from St. Jude. In addition to providing

Teresa Santiago, MD

an overview of their laboratory operations and assets, the participants were asked to bring paraffin-embedded tissue specimens from patients with non-Hodgkin lymphoma, corresponding hematoxylin and eosin–stained slides, and previously stained IHC slides, where available. After intensive didactic and practical training in IHC, the participants applied the techniques to new slides prepared from the same specimens, and the results were compared to those obtained before the workshop.

Poor antigen retrieval, nonspecific staining, and intense background staining were some of the problems identified in the IHC slides prepared before the workshop; inadequate fixation and processing of tissue were also noted in some cases. Strategies to correct these deficiencies were addressed during the training sessions, and the participants received personalized recommendations on their IHC technique and laboratory practices.

Based on an assessment of the participants' performance during the workshop and comparisons of their original IHC slides with the slides they prepared during the practical sessions, the organizers concluded that intensive workshops of this kind can train participants to perform manual IHC assays that yield high-quality, reproducible results comparable to those obtained with automated IHC systems and that this is a useful strategy for improving IHC capability and proficiency in regions with limited resources. *Santiago T et al, J Global Oncol 4:1–9, 2018*

ACADEMIC DEPARTMENTS

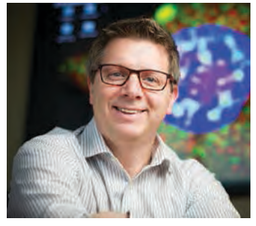
BIOSTATISTICS

Interim Chair
Deo Kumar S. Srivastava, PhD • Clinical trials, robust methods, survival analysis

Members
Cheng Cheng, PhD • Statistical methods in cancer biology, clinical & translational studies
Arzu Onar-Thomas, PhD[1] • Phase I/II designs, survival analysis, Bayesian statistics
Stanley B. Pounds, PhD[1] • Statistical methods for genomics studies

Associate Members
Guolian Kang, PhD • Statistical genetics/genomics, modeling of complex data
Yimei Li, PhD • Statistical analysis of complex imaging data, survival data analysis & clinical trial design
Li Tang, PhD • Prediction, validation, diagnostic testing, microbiome analysis
Hui Zhang, PhD • Longitudinal missing discrete data & computational neuroscience

Assistant Members
Zhaohua Lu, PhD • Statistical analysis of neuroimaging & genetic data, longitudinal & functional data analysis
Sedigheh Mirzaei Salehabadi, PhD • Statistical methods for incomplete survival data, epidemiologic study designs
Haitao Pan, PhD • Bayesian adaptive designs for clinical trials, graphical modeling, microbiome data modeling
Natasha A. Sahr, PhD • Variable classification, screening, selection in high-dimensional data



CELL & MOLECULAR BIOLOGY

Chair
J. Paul Taylor, MD, PhD[1]; Edward F. Barry Endowed Chair in Cell & Molecular Biology • Molecular genetics of neurological diseases

Associate Members
Mondira Kundu, MD, PhD[1,2] • Autophagy-related proteins in health & human disease
Stacey K. Ogden, PhD[1] • Mechanisms of Hedgehog signal transduction
Joseph T. Opferman, PhD[1] • Regulation of cell death & mitochondrial function
Ryan Potts, PhD[1] • Biochemical & molecular characterization of MAGE proteins

Assistant Members
Hans-Martin Herz, PhD[1] • Regulation of transcription & enhancer activity
Malia B. Potts, PhD[1] • Higher-order regulation of autophagy
Shondra M. Miller, PhD • Genome-editing technologies

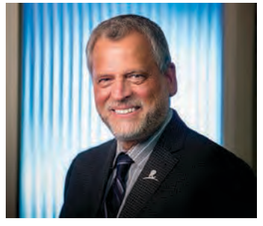
COMPUTATIONAL BIOLOGY

Chair
Jinghui Zhang, PhD[1]; Endowed Chair in Bioinformatics • Cancer genomic variant analysis & visualization

Associate Member
Zhaoming Wang, PhD[2] • Genetic epidemiology of pediatric cancer & survivorship

Assistant Members
Xiang Chen, PhD • OMICS integration & tumor heterogeneity by machine learning approaches
Yong Cheng, PhD[1,2] • *Cis*-regulatory modules in hematopoiesis & its disorders
Charles Gawad, MD, PhD[2] • Cellular & genetic origins of childhood cancers
Jiyang Yu, PhD • Systems biology, systems immunology, & translational oncology

Adjunct Member
Neil Hayes, MD, MS, MPH • Translational biomarkers, genomics, & clinical trials



DIAGNOSTIC IMAGING

Chair
Zoltán Patay, MD, PhD; Endowed Chair in Diagnostic Imaging • Imaging genomics & brain tumor characterization by quantitative MRI

Members
Sue C. Kaste, DO • Skeletal toxicities in childhood cancer
Robert A. Kaufman, MD[4]
Mary E. (Beth) McCarville, MD[1] • Solid tumor imaging & contrast-enhanced ultrasonography
Wilburn E. Reddick, PhD • White matter injury in leukemia & CNS tumors
Barry L. Shulkin, MD, MBA • PET imaging evaluation of pediatric tumors

Associate Members
Asim K. Bag, MBBS, MD • Response assessment of immunotherapy & radiation therapy, assessment of cancer therapy–related brain damage
Mikhail Doubrovin, MD, PhD[5]
Julie H. Harreld, MD[1] • Magnetization transfer MR imaging & cerebral perfusion
Claudia M. Hillenbrand, PhD • Novel MR techniques in solid tumors & sickle cell disease
Robert J. Ogg, PhD • Imaging assessments of brain function in CNS & ocular tumors
Noah D. Sabin, MD, JD • Imaging of brain tumors & side effects of therapy
Scott E. Snyder, PhD[1] • Design of radioactive diagnostic agents for molecular imaging

Assistant Member
Scott N. Hwang, MD, PhD • Brain tumors, quantitative imaging, computational modeling

Instructor
Cara E. Morin, MD, PhD • Novel MR body & cardiac imaging techniques

BONE MARROW TRANSPLANTATION & CELLULAR THERAPY

Chair
Stephen M. Gottschalk, MD[1]; Endowed Chair in Bone Marrow Transplantation & Cellular Therapy • Cancer immunotherapy, cell therapy, stem cell transplantation

Member
William E. Janssen, PhD • Therapeutic use of intact cell products

Associate Members
Ashok Srinivasan, MD • Infections in the immune-compromised host
Brandon M. Triplett, MD[1] • Hematopoietic cell transplantation

Assistant Members
Christopher DeRenzo, MD, MBA • T-cell therapy for patients with solid tumors
Caitlin Hurley, MD[2] • Onco-critical care, HSCT/immunotherapy patients, long-term care
Ewelina K. Mamcarz, MD • Transplantation in patients with nonmalignant diseases
Amr Qudeimat, MD • Transplant for bone marrow failure syndromes
Paulina Velasquez, MD[1] • Immunotherapy of hematologic malignancies

Instructors
Giedre Krenciute, PhD • CAR T-cell immunotherapy for pediatric brain tumors
Akshay Sharma, MBBS • Gene therapy & transplantation for nonmalignant hematological diseases
Aimee C. Talleur, MD • Cancer immunotherapy & cellular therapy

CHEMICAL BIOLOGY & THERAPEUTICS

Interim Chair
Richard E. Lee, PhD[1]; Endowed Chair in Medicinal Chemistry • Discovery of new antibiotic agents and structure-based drug design

Member
Taosheng Chen, PhD, PMP[1] • Xenobiotic receptors and therapeutic responses

Associate Members
Naoaki Fujii, PhD[3]
Philip M. Potter, PhD • Anticancer drug hydrolysis by carboxylesterases
Anang A. Shelat, PhD[1] • Translational research & chemical biology
Scott E. Snyder, PhD[1,2] • Design of radioactive diagnostic agents for molecular imaging

Assistant Members
Marcus Fischer, PhD[1] • Protein conformational landscapes for ligand discovery
Tudor Moldoveanu, PhD[1,2] • Programmed cell death in health & disease
Fatima R. Rivas, PhD[1] • Organic chemistry synthesis/natural product discovery

DEVELOPMENTAL NEUROBIOLOGY

Chair
Michael A. Dyer, PhD[1]; Richard C. Shadyac Endowed Chair in Pediatric Cancer Research • Retinal development, retinoblastoma, & pediatric solid tumor translational research

Members
Suzanne J. Baker, PhD[1]; Endowed Chair in Brain Tumor Research • Genetic and epigenetic drivers of pediatric high-grade glioma
James I. Morgan, PhD; Scientific Director, Edna & Albert Abdo Shahdam Endowed Chair in Basic Research • Control of neuronal death & differentiation
Junmin Peng, PhD[1,2] • Proteomics & metabolomics in human disease
Stanislav S. Zakharenko, MD, PhD[1] • Learning & memory, synaptic mechanisms of schizophrenia
Jian Zuo, PhD[3]

Associate Members
Xinwei Cao, PhD[1] • Growth control during neural tube development
Young-Goo Han, PhD[1] • Regulatory mechanisms of neural progenitors in brain development, diseases, & evolution
Khaled Khairy, PhD[1] • Biomechanics-based computational models as priors for biological image analysis
David J. Solecki, PhD[1] • Cell polarity in neuron precursor differentiation

Assistant Members
Jay B. Bikoff, PhD • Neural circuits controlling movement
Fabio Demontis, PhD[1] • Protein homeostasis & stress sensing in skeletal muscle aging
Myriam Labelle, PhD[1] • The role of platelets in cancer metastasis
Paul A. Northcott, PhD[1] • Genomics & developmental biology of childhood brain tumors
Jamy C. Peng, PhD[1] • Epigenetic regulation of stem cell functions
Lindsay A. Schwarz, PhD • Mechanisms of neuromodulatory circuit organization
Elizabeth A. Stewart, MD[1,2] • Translational research of pediatric solid tumors

EPIDEMIOLOGY & CANCER CONTROL

Chair
Leslie L. Robison, PhD; Endowed Chair in Epidemiology & Cancer Control • Pediatric cancer epidemiology & outcomes

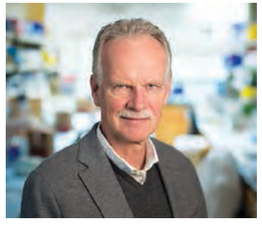
Members
Gregory T. Armstrong, MD, MSCE[1] • Cancer survivorship & long-term follow-up
Melissa M. Hudson, MD[2]; The Charles E. Williams Endowed Chair in Oncology–Cancer Survivorship • Health outcomes after childhood cancer
Kevin R. Krull, PhD • Cognitive neuroscience approaches to outcomes and interventions in pediatric cancer survivors
Kirsten K. Ness, PT, PhD • Physical health and accelerated aging in childhood cancer survivors
Yutaka Yasui, PhD • Genetics & risk of therapy-related outcomes

Associate Members
Wassim Chemaitilly, MD[2] • Endocrine sequelae in childhood cancer survivors
I-Chan Huang, PhD • Patient-reported outcomes measurement after pediatric cancer
Daniel A. Mulrooney, MD, MS[1,2] • Cardiovascular outcomes of cancer therapy
Zhaoming Wang, PhD • Genetic epidemiology of pediatric cancer & survivorship

Assistant Members
Nickhill Bhakta, MD, MPH[1,2] • Global pediatric medicine
Tara M. Brinkman, PhD • Psychosocial outcomes of pediatric cancer
Matthew J. Ehrhardt, MD, MS[2] • Late effects of childhood cancer therapy
Todd M. Gibson, PhD • Risk factors for late effects after pediatric cancer
Carmen L. Wilson, PhD • Late effects of childhood cancer therapy

[1]Graduate school faculty member; [2]Secondary appointment; [3]No longer at St. Jude; [4]Emeritus; [5]Deceased

ACADEMIC DEPARTMENTS



GENETICS

Chair
Gerard C. Grosveld, PhD[1]; Albert & Rosemary Joseph Endowed Chair in Genetic Research • Unraveling mTORC3's role in development & cancer

Members
Alessandra d'Azzo, PhD[1]; Jeweler's Charity Fund Endowed Chair in Genetics and Gene Therapy • Lysosomal/proteasomal function in health & disease
Peter J. McKinnon, PhD[1] • DNA damage responses in the nervous system

HEMATOLOGY

Chair
Mitchell J. Weiss, MD, PhD[1]; Arthur Nienhuis Endowed Chair in Hematology • Blood development & associated diseases

Members
Ellis J. Neufeld, MD, PhD; Clinical Director; John & Lorine Thrasher Endowed Chair in Pediatric Medicine • Patient-oriented studies in nonmalignant hematology
Arthur W. Nienhuis, MD[4]
Brian P. Sorrentino, MD[5]
Clifford M. Takemoto, MD • Hemostasis & thrombosis, vascular malformations, bone marrow failure
Winfred C. Wang, MD[4]

Associate Members
Wilson K. Clements, PhD[1] • Hematopoietic development & leukemia
Jane S. Hankins, MD, MS[2] • Sickle cell disease, transition to adult care & health outcomes during adolescence & young adulthood
Shannon L. McKinney-Freeman, PhD[1] • Mechanisms of hematopoietic stem cell development & transplantation
Ulrike M. Reiss, MD[1] • Bleeding disorders, gene therapy for hemophilia, bone marrow failure
Carolyn Russo, MD • Quality improvement in clinical networks
Byoung Ryu, PhD • Stem cell gene therapy for blood disorders

Assistant Members
Yong Cheng, PhD[1] • *Cis*-regulatory modules in normal & pathologic gene expression
Jeremie H. Estepp, MD[1] • Sickle cell disease, novel therapies, translational studies
Latika Puri, MD • Sickle cell disease, thrombocytopenias, chronic transfusion
Shengdar Q. Tsai, PhD[3] • Genome engineering technologies for therapeutics
Marcin W. Wlodarski, MD, PhD • Inherited bone marrow failure & MDS predisposition syndromes

Instructors
Nidhi Bhatt, MD • Health communication & implementation science
Parul Rai, MD • Cardiac injury in sickle cell disease
Jason R. Schwartz, MD, PhD • Pediatric MDS & bone marrow failure

GLOBAL PEDIATRIC MEDICINE

Chair
Carlos Rodriguez-Galindo, MD[1]; Four Stars of Chicago Endowed Chair in International Pediatric Outreach • Global medicine, pediatric solid tumors

Members
Sima Jeha, MD[1] • Global health, childhood leukemias, developmental therapeutics
Monika L. Metzger, MD[1] • Global health, Hodgkin & non-Hodgkin lymphomas
Ching-Hon Pui, MD[1,2]; Fahad Nassar Al-Rashid Endowed Chair in Leukemia Research • Biology & treatment of childhood leukemia
Victor M. Santana, MD[2]; Charles B. Pratt Chair in Solid Tumor Research • Global health, novel therapeutics, neuroblastoma, research ethics

Associate Members
Miguela A. Caniza, MD[1] • Global health, infection care & control
Catherine G. Lam, MD, MPH[2] • Global health, health systems, pediatric solid tumors
Ibrahim A. Qaddoumi, MD, MS[1] • Global health, brain tumors, telemedicine, retinoblastoma

Assistant Members
Asya Agulnik, MD, MPH[1] • Global health, pediatric onco-critical care, quality improvement
Nickhill Bhakta, MD, MPH[1] • Global health, survivorship, epidemiology, childhood leukemias
Paola Friedrich, MD, MPH[1] • Global health, health disparities, health services, pediatric solid tumors

Instructors
Abdelhafeez Abdelhafeez, MD[2]• Global health, fluorescence-guided minimally invasive & subamputative pediatric surgical oncology
Sheena Mukkada, MD, MPH[1] • Global health, infection care & control

IMMUNOLOGY

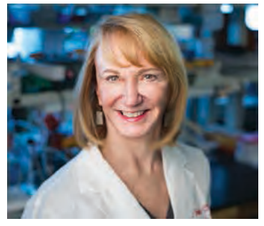
Chair
Douglas R. Green, PhD[1]; Peter C. Doherty Endowed Chair in Immunology • Cell death, autophagy, & immune function

Vice-Chair
Thirumala-Devi Kanneganti, PhD[1]; Rose Marie Thomas Endowed Chair in Immunology • Mechanisms of host defense & inflammation

Members
Hongbo Chi, PhD[1]; Robert G. Webster Endowed Chair in Immunology • Immune signaling and metabolism
Peter C. Doherty, PhD[1]; Nobel Laureate; Michael F. Tamer Endowed Chair in Immunology
Paul G. Thomas, PhD[1] • Mechanisms of antiviral and antitumor immunity

Associate Members
Maureen A. McGargill, PhD[1] • Regulation of the immune response
Benjamin A. Youngblood, PhD[1] • T-cell memory differentiation, T-cell exhaustion, and immunotherapy

Assistant Members
Yongqiang Feng, PhD • Epigenetic & transcriptional basis of T-cell immunity
Rhea M. Sumpter Jr, MD, PhD • Selective autophagy, innate immunity, inflammation



INFECTIOUS DISEASES

Chair
Elaine I. Tuomanen, MD[1]; Endowed Chair in Infectious Diseases • Pathogenesis of pneumococcal infection

Members
Patricia M. Flynn, MD; Deputy Clinical Director; Arthur Ashe Endowed Chair in Pediatric AIDS Research • HIV/AIDS in children & infections in children with cancer
Aditya H. Gaur, MD, MBBS[2] • Clinical research in HIV prevention & treatment
Walter T. Hughes, MD[4]
Julia L. Hurwitz, PhD[1] • Pathogen/vaccine-induced immunity, nuclear hormones
Suzanne Jackowski, PhD[1] • Coenzyme A in health & disease, regulation of membrane phospholipids
Charles O. Rock, PhD • Membrane phospholipid metabolism
Stacey L. Schultz-Cherry, PhD[1] • Pathogenesis of influenza & enteric virus infections
Richard J. Webby, PhD[1] • Influenza virus pathogenicity
Robert G. Webster, PhD[4]

Associate Members
Elisabeth E. Adderson, MD • Epidemiology & treatment of infections
Miguela A. Caniza, MD[1,2] • Global health, infection care & control
Hans Haecker, MD, PhD[1] • Signal transduction of Toll-like & TNF receptors
Hana Hakim, MD • Infection prevention & control
Diego R. Hijano, MD • Host–pathogen interactions of respiratory virus
Katherine Knapp, MD • Perinatal HIV exposure/HIV clinical trials
Jason W. Rosch, PhD[1] • Bacterial genomics & pathogenesis
Charles J. Russell, PhD[1] • Respiratory viruses: disease, cures, & prevention
Megan L. Wilkins, PhD[2] • Clinical & research psychological services for youth with HIV/AIDS

Assistant Members
Elisa Margolis, MD, PhD • Microbiome dynamics in immunocompromised patients
Gabriela M. Marón Alfaro, MD • Infectious complications in transplant patients
Joshua Wolf, MBBS[2] • Prediction, prevention, & treatment of infections in immunocompromised children

Instructor
Sheena Mukkada, MD, MPH[1,2] • Global health, infection care & control

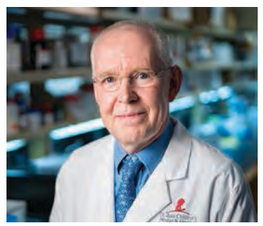
Adjunct Member
Jonathan A. McCullers, MD • Interactions between viruses & bacteria

ONCOLOGY

Chair
Ching-Hon Pui, MD; Fahad Nassar Al-Rashid Endowed Chair in Leukemia Research • Biology & treatment of childhood leukemia

Co-Chair
Amar J. Gajjar, MD[2]; Scott & Tracie Hamilton Endowed Chair in Brain Tumor Research • Novel treatments for children with brain tumors

Members
Gregory T. Armstrong, MD, MSCE[1,2] • Pediatric neuro-oncology & cancer survivorship
Justin N. Baker, MD • Quality of life/palliative care & ethics
Wayne L. Furman, MD • New drug development, neuroblastoma, liver tumors
Daniel M. Green, MD[1] • Adverse hepatic, renal, & reproductive effects of therapy
Melissa M. Hudson, MD; The Charles E. Williams Endowed Chair in Oncology–Cancer Survivorship • Health outcomes after childhood cancer
Hiroto Inaba, MD, PhD[1] • New therapeutic strategies for leukemia
Sima Jeha, MD[1,2] • Global health, childhood leukemias, developmental therapeutics
Sue C. Kaste, DO[2] • Skeletal toxicities in childhood cancer
Monika L. Metzger, MD[1,2] • Global health, Hodgkin & non-Hodgkin lymphomas
Kim E. Nichols, MD[1] • Heritable cancers & primary immunodeficiency syndromes
Alberto S. Pappo, MD[1]; Alvin Mauer Endowed Chair • New therapies for sarcomas & rare pediatric cancers
Raul C. Ribeiro, MD[1] • Hematological malignancies
Charles W. M. Roberts, MD, PhD[2]; Lillian R. Cannon Comprehensive Cancer Center Director Endowed Chair • SWI/SNF (BAF) chromatin remodeling/ tumor suppressor
Carlos Rodriguez-Galindo, MD[1,2]; Four Stars of Chicago Endowed Chair in International Pediatric Outreach • Global medicine, pediatric solid tumors
Jeffrey E. Rubnitz, MD, PhD • Treatment of acute myeloid leukemia
John T. Sandlund, MD[1] • Clinical & biologic investigation of NHL & ALL
Victor M. Santana, MD; Charles B. Pratt Endowed Chair in Solid Tumor Research • Novel therapeutics, neuroblastoma, research ethics



PATHOLOGY

Chair
David W. Ellison, MD, PhD; Joan & Roy Gignac Endowed Chair in Pathology & Laboratory Medicine • Pathologic/ molecular classification of CNS tumors

Members
James R. Downing, MD; President and Chief Executive Officer; Dr. Donald Pinkel Chair of Childhood Cancer Treatment • The molecular pathology of acute leukemia
Terrence L. Geiger, MD, PhD[1]; Deputy Director for Academic and Biomedical Operations; Endowed Chair in Pediatrics • T-cell regulation, adoptive immunotherapy
Randall T. Hayden, MD • Clinical microbiology of immunocompromised hosts
Michael M. Meagher, PhD[1]; President, Children's GMP, LLC • Cell culture, fermentation, protein purification, process scale-up, & GMP manufacturing
Charles G. Mullighan, MBBS, MD[1]; William E. Evans Endowed Chair • Genomic, experimental, & preclinical studies of acute leukemia
Ching-Hon Pui, MD[2]; Fahad Nassar Al-Rashid Endowed Chair in Leukemia Research • Biology & treatment of childhood leukemia
Susana C. Raimondi, PhD • Cytogenetics & FISH of leukemias, lymphomas, & solid tumors
Jerold E. Rehg, DVM • Preclinical models of infectious diseases & cancer
A. Peter Vogel, DVM, PhD • Pathology of animal models of human disease
Gerard P. Zambetti, PhD[1] • The function of p53 in tumor suppression & tumorigenesis

Associate Members
Armita Bahrami, MD[1] • Molecular pathogenesis of sarcomas and melanoma
John K. Choi, MD, PhD[1] • Transcription factors in acute leukemias
Laura Janke, DVM, PhD • Pathology of mouse models of disease
Mondira Kundu, MD, PhD[1] • Autophagy-related proteins in health & human disease
Brent A. Orr, MD, PhD • Molecular classification of tumors of the nervous system
Janet F. Partridge, PhD[1] • Chromosome segregation, heterochromatin assembly
Harshan Pisharath, DVM, PhD • Animal models of human diseases, preclinical safety
Richard Rahija, DVM, PhD • Animal models of human disease

ONCOLOGY- *cont*

Associate Members
Richard A. Ashmun, PhD • Applications of flow cytometry & cell separation
Rachel C. Brennan, MD[1] • Retinoblastoma, novel therapeutics, renal tumors
Sara M. Federico, MD[1] • Drug development, pediatric soft-tissue sarcomas
Tanja A. Gruber, MD, PhD • Pathogenesis of infantile ALL & pediatric AMKL
Mark E. Hatley, MD, PhD[1] • Origins of pediatric sarcomas
Catherine G. Lam, MD, MPH[1,2] • Global health, health systems, pediatric solid tumors
Daniel A. Mulrooney, MD, MS[1] • Cardiovascular outcomes of cancer therapy
Ibrahim A. Qaddoumi, MD, MS[1,2] • Global health, brain tumors, telemedicine, retinoblastoma
Jun J. Yang, PhD[1,2] • Pharmacogenomics of anticancer agents & drug resistance

Assistant Members
Nickhill Bhakta, MD, MPH[1,2] • Global health, survivorship, epidemiology, childhood leukemias
Michael W. Bishop, MD • Osteosarcoma, Ewing sarcoma, soft-tissue sarcomas
Patrick K. Campbell, MD, PhD • Histiocytic disorders, clinical informatics, patient safety
Matthew J. Ehrhardt, MD, MS • Late effects of childhood cancer therapy
Jamie E. Flerlage, MD, MS • Reduction of the late effects for Hodgkin lymphoma survivors
Paola Friedrich, MD, MPH[1,2] • Global health, health disparities, health services, pediatric solid tumors
Charles Gawad, MD, PhD • Cellular & genetic origins of childhood cancers
Kellie Haworth, MD • Immunotherapies for pediatric neurogenic tumors
Sara Helmig, MD • Sarcoma, thyroid carcinoma, & quality improvement
Liza-Marie Johnson, MD, MPH, MSB • Ethical issues in pediatrics
Seth E. Karol, MD • Toxicity reduction during acute leukemia therapy
Erica C. Kaye, MD • Prognostic communication, early integration of palliative care in oncology
Chimene Kesserwan, MD • Cancer predisposition
Deena R. Levine, MD • Pediatric palliative & end-of-life care
Esther A. Obeng, MD, PhD • Myeloid malignancies & bone marrow failure syndromes
Giles W. Robinson, MD[1] • Origin & genomics of medulloblastoma, translational studies
Jitsuda Sitthi-Amorn, MD • Quality improvement & patient safety
Holly Spraker-Perlman, MD, MS • Pediatric palliative care, symptom-management strategies
Elizabeth A. Stewart, MD[1] • Translational research of pediatric solid tumors
Linda Stout, MD • Pediatric oncology
Anna Vinitsky, MD, MS • Pediatric neuro-oncology & process improvement
Liqin Zhu, PhD[1,2] • Stem cells in normal & malignant development

Instructor
Santhosh Upadhyaya, MD • Atypical teratoid rhabdoid tumor (ATRT) and ependymoma

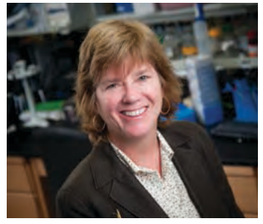
[1]Graduate school faculty member; [2]Secondary appointment; [3]No longer at St. Jude; [4]Emeritus; [5]Deceased

ACADEMIC DEPARTMENTS

PATHOLOGY- *cont*

András Sablauer, MD, PhD; Chief Medical Information Officer • Imaging informatics & computerized tumor modeling
Lu Wang, MD, PhD • Genomic profiling & functional analysis of genetic alterations in pediatric tumors

Assistant Members
Elizabeth M. Azzato, MD, PhD[3]
Jason Cheng-Hsuan Chiang, MD, PhD • Diagnosis & classification of CNS tumors
Michael R. Clay, MD • Molecular & histologic classification of pediatric solid tumors & sarcomas, DNA-methylation profiling of pediatric malignancies
Jeffrey M. Klco, MD, PhD[1] • Genomic & functional characterization of pediatric myeloid neoplasms
Vasiliki Leventaki, MD[3]
Teresa C. Santiago, MD • Laboratory quality improvement & assessment
Heather S. Tillman, DVM, PhD • Comparative pathology
Yan Zheng, MD, PhD • Red blood cell genotyping & alloimmunization, cancer immunotherapy



PHARMACEUTICAL SCIENCES

Chair
Mary V. Relling, PharmD[1]; Endowed Chair in Pharmaceutical Sciences • Leukemia therapy & clinical pharmacogenetics

Members
William E. Evans, PharmD[1]; Endowed Chair in Pharmacogenomics • Pharmacogenomics of antileukemic agents in children
William L. Greene, PharmD; Chief Pharmaceutical Officer • Optimizing pharmacotherapy
Erin G. Schuetz, PhD[1] • Mechanisms of human variation in drug response
John D. Schuetz, PhD[1] • Regulation & function of ABC transporters
Clinton F. Stewart, PharmD[1] • Pharmacology of anticancer drugs in children

Associate Members
James M. Hoffman, PharmD; Chief Patient Safety Officer • Medication safety & outcomes
Jun J. Yang, PhD[2] • Pharmacogenomics of anticancer agents & drug resistance

Assistant Members
Daniel D. Savic, PhD[1] • Pharmacogenomics & *cis*-regulatory architecture of pediatric leukemia
Liqin Zhu, PhD[1] • Stem cells in normal & malignant liver development

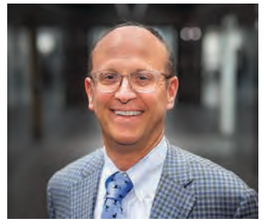
RADIATION ONCOLOGY

Chair
Thomas E. Merchant, DO, PhD[1]; Baddia J. Rashid Endowed Chair in Radiation Oncology • Proton radiotherapy for CNS tumors & radiation-related CNS effects

Member
Matthew J. Krasin, MD • Developing radiation therapy strategies & toxicity profiles for pediatric sarcomas

Associate Member
Chia-ho Hua, PhD • Improving proton therapy accuracy, advanced imaging for radiation therapy, normal tissue complication modeling

Assistant Members
Sahaja Acharya, MD • Brain tumors, proton therapy, image-guided radiation
Austin M. Faught, PhD • Proton therapy, biological modeling, adaptive therapy
John T. Lucas Jr, MS, MD • Brain tumors, neuroblastoma, proton therapy, clinical trial design
Christopher L. Tinkle, MD, PhD[1] • Preclinical evaluation of novel combination therapies and clinical trial development for high-risk brain tumors and sarcomas
Weiguang Yao, PhD[5]



SURGERY

Chair
Andrew M. Davidoff, MD[1]; Endowed Chair in Surgical Research • Surgical management of solid tumors, gene therapy, angiogenesis inhibition, neuroblastoma, Wilms tumor

Members
Bhaskar N. Rao, MD[4]
Stephen J. Shochat, MD[4]

Assistant Members
Kevin W. Freeman, PhD[3]
Andrew Jackson Murphy, MD • Renal tumors, neuroblastoma, Wilms tumorigenesis, cancer stem cells
Jun Yang, MD, PhD • Cancer epigenetics & targeted therapy

Instructors
Abdelhafeez Abdelhafeez, MD • Fluorescence-guided minimally invasive & subamputative pediatric surgical oncology
Lindsay J. Talbot, MD • Sarcomas, immunotherapeutic strategies against sarcoma & solid tumor metastases

Adjunct Members
Frederick Boop, MD; St. Jude Chair in Neurosurgery • Pediatric neurosurgery
Joseph M. Gleason, MD • Pediatric urology, Wilms tumor, pelvic RMS
Mary Ellen Hoehn, MD • Pediatric ophthalmology
Paul D. Klimo Jr, MD • Pediatric neurosurgery
Michael Neel, MD • Pediatric orthopedic oncology
Anthony Sheyn, MD • Pediatric otolaryngology
Jerome Thompson, MD, MBA • Pediatric otolaryngology
Robert D. Wallace, MD • Pediatric plastic surgery
Matthew W. Wilson, MD; St. Jude Chair in Pediatric Ophthalmology • Pediatric ophthalmology

PEDIATRIC MEDICINE

Chair
Amar J. Gajjar, MD; Scott & Tracie Hamilton Endowed Chair in Brain Tumor Research • Novel treatments for children with brain tumors

Anesthesiology
Michael G. Rossi, DO; Division Director • Patient safety & cognitive effects of anesthesia
Doralina L. Anghelescu, MD[1] • Pain management, anesthesia risks, palliative care
Wasif H. Dweik, DO • Patient safety, regional anesthesia, acute pain management
Michael J. Frett, MD • Pediatric anesthesia
Kyle J. Morgan, MD • Pain management for pediatric cancer & sickle cell disease
Kavitha C. Raghavan, MBBS, FRCA • Patient safety & quality of care in pediatric anesthesia
Luis A. Trujillo Huaccho, MD • Regional anesthesia & anesthetic approach in high-risk cases
Becky B. Wright, MD • Pain management techniques, peripheral nerve blocks

Critical Care Medicine
R. Ray Morrison, MD[1]; Division Director • Pediatric critical care, myocardial protection
Asya Agulnik, MD, MPH[1,2] • Global health, pediatric onco-critical care, quality improvement
Lama Elbahlawan, MD • Pediatric critical care, acute lung injury
Melissa R. Hines, MD • Pediatric critical care, hemophagocytic lymphohistiocytosis
Caitlin Hurley, MD • Onco-critical care, HSCT/immunotherapy patients, long-term care
Jennifer A. McArthur, DO • Improving outcomes in critically ill pediatric patients

Endocrinology
Wassim Chemaitilly, MD[1]; Division Director • Endocrine sequelae in childhood cancer survivors

Neurology
Raja B. Khan, MD; Division Director • Effect of cancer on central & peripheral nervous systems
Zsila Sadighi, MD[3]

Nursing Research
Belinda N. Mandrell, PhD, RN, CPNP[1]; Division Director • Biological mechanism of symptoms associated with cancer & cancer therapy

PSYCHOLOGY

Chair
Sean Phipps, PhD[1]; Endowed Chair in Psychology • Coping & adjustment in children with cancer

Members
Heather M. Conklin, PhD[1] • Cognitive outcomes of childhood cancer treatment
Melissa M. Hudson, MD[2]; The Charles E. Williams Endowed Chair in Oncology–Cancer Survivorship • Health outcomes after childhood cancer
Kevin R. Krull, PhD[2] • Neurocognitive outcomes of pediatric cancer

Associate Members
Valerie M. Crabtree, PhD[1] • Sleep disruptions and fatigue in pediatric oncology
Niki Jurbergs, PhD • Psychological & cognitive impact of pediatric cancer
Megan L. Wilkins, PhD • Clinical & research psychological services for youth with HIV/AIDS

Assistant Members
Nicole M. Alberts, PhD • Pain, psycho-social outcomes, & eHealth/mHealth in psycho-oncology & sickle cell disease
Tara M. Brinkman, PhD[2] • Psychosocial outcomes of pediatric cancer
Kristin E. Canavera, PhD • Pediatric bioethics
Jennifer L. Harman, PhD • Psychosocial functioning of young children with cancer
Lisa M. Jacola, PhD • Neurobehavioral outcomes in children treated for cancer
Kendra R. Parris, PhD • Coping & adjustment in youth with cancer
Jerlym S. Porter, PhD, MPH • Transition from pediatric to adult care in SCD
Brian Potter, PhD • Neurocognitive outcomes in children with cancer
Darcy Raches, PhD • Acute neurological injury & cognitive outcomes associated with childhood cancer treatment
Victoria W. Willard, PhD • Social outcomes in children with cancer

Instructors
Jennifer Allen, PhD • Pain management, adolescent/young adults, health behavior
Daniel Garrison, PhD[3]
Katianne Sharp, PhD • Cancer predisposition & adjustment in families of children with cancer
Rachel N. Tillery, PhD • Promotion of healthy lifestyle behaviors in children with cancer & survivors of childhood cancer

STRUCTURAL BIOLOGY

Chair
Charalampos Babis Kalodimos, PhD[1]; Joseph Simone Endowed Chair in Basic Research • Functional mechanisms of protein machineries

Members
Richard W. Kriwacki, PhD[1] • Structural basis of tumor suppressor function
Junmin Peng, PhD[1] • Proteomics & metabolomics in human disease
Stephen White, DPhil[1]; Endowed Chair–Dean of St. Jude Children's Research Hospital Graduate School of Biomedical Sciences • DNA repair, catalysis, & structure-based drug discovery

Associate Members
Eric J. Enemark, PhD[1] • Molecular mechanisms of DNA replication
Mario Halic, PhD • Regulation of genome expression
Tanja Mittag, PhD[1] • Molecular basis of liquid–liquid phase separation

Assistant Members
Marcus Fischer, PhD[1,2] • Protein conformational ensembles
Tudor Moldoveanu, PhD[1] • Programmed cell death in health & disease

Adjunct Member
Brenda A. Schulman, PhD • Cellular regulation by ubiquitin-like proteins

TUMOR CELL BIOLOGY

Chair
Charles J. Sherr, MD, PhD; Herrick Foundation Endowed Chair in Tumor Cell Biology • Tumor suppressor–dependent signaling networks

Members
Linda M. Hendershot, PhD[1] • ER quality control in development & disease
Martine F. Roussel, PhD[1]; Endowed Chair in Molecular Oncogenesis • Genomics & epigenomics in pediatric brain tumors

Assistant Member
Chunliang Li, PhD[1] • 3D genome and transcriptional regulation in cancer

Adjunct Member
Brenda A. Schulman, PhD • Cellular regulation by ubiquitin-like proteins

[1]Graduate school faculty member; [2]Secondary appointment; [3]No longer at St. Jude; [4]Emeritus; [5]Deceased

ENDOWED CHAIRS

Alessandra d'Azzo, PhD
Jewelers Charity Fund Endowed Chair in Genetics & Gene Therapy

Suzanne J. Baker, PhD
Endowed Chair in Brain Tumor Research

Hongbo Chi, PhD
Robert G. Webster Endowed Chair in Immunology

Peter C. Doherty, PhD
Nobel Laureate
Michael F. Tamer Endowed Chair in Immunology

James R. Downing, MD
Dr. Donald Pinkel Endowed Chair in Childhood Cancer Treatment

William E. Evans, PharmD
Endowed Chair in Pharmacogenomics

Patricia M. Flynn, MD
Arthur Ashe Endowed Chair in Pediatric AIDS Research

Terrence L. Geiger, MD, PhD
Endowed Chair in Pediatrics

Melissa M. Hudson, MD
The Charles E. Williams Endowed Chair in Oncology-Cancer Survivorship

Thiramala-Devi Kanneganti, PhD
Rose Marie Thomas Endowed Chair in Immunology

James I. Morgan, PhD
Edna & Albert Abdo Shahdam Endowed Chair in Basic Research

Charles G. Mullighan, MBBS, MD
William E. Evans Endowed Chair

Ellis J. Neufeld, MD, PhD
John & Lorine Trasher Endowed Chair in Pediatric Medicine

Alberto S. Pappo, MD
Alvin Mauer Endowed Chair

Charles W. M. Roberts, MD, PhD
Lillian R. Cannon Comprehensive Cancer Center Director Endowed Chair

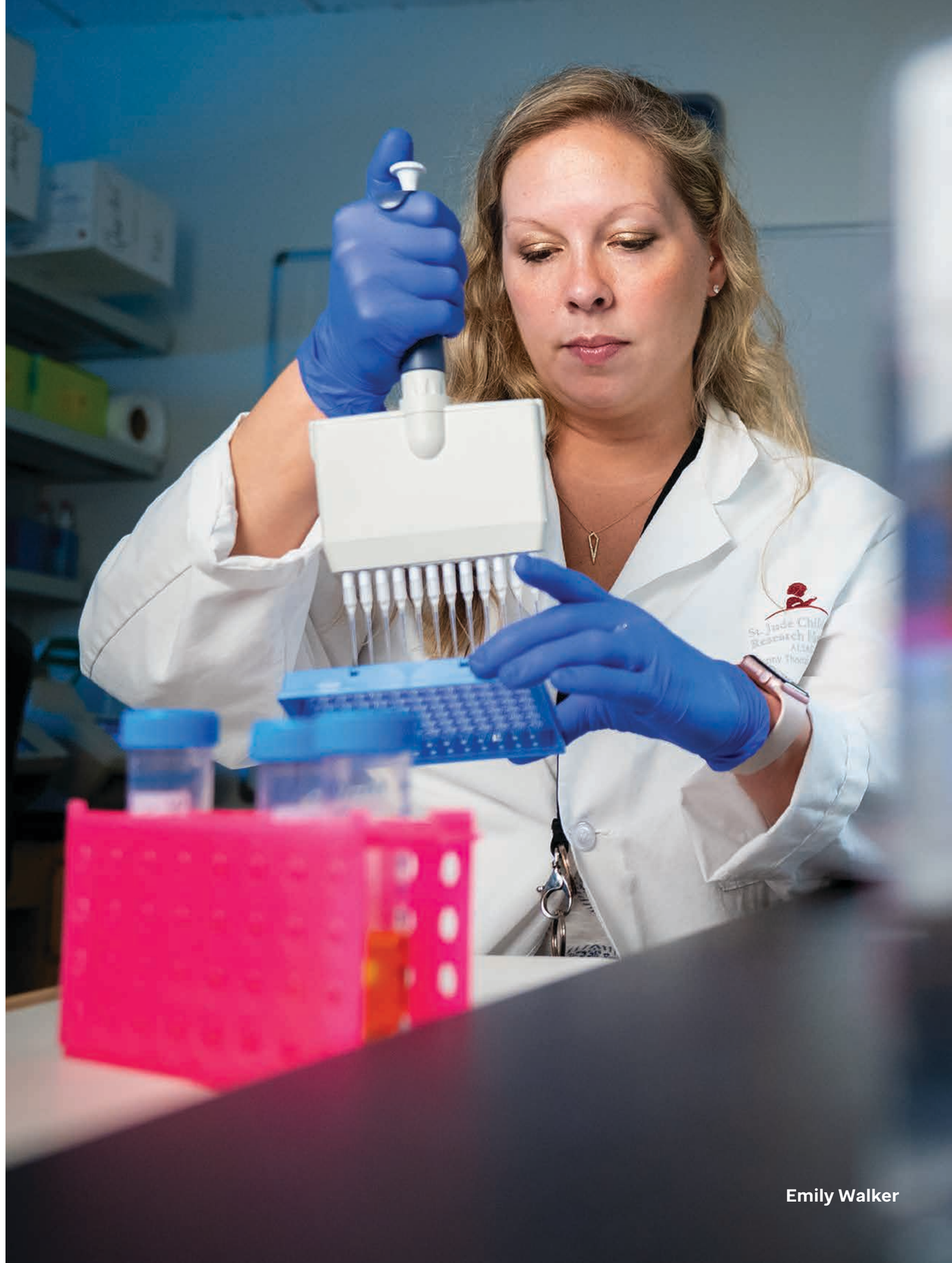
Martine F. Roussel, PhD
Endowed Chair in Molecular Oncogenesis

Victor M. Santana, MD
Dr. Charles B. Pratt Endowed Chair in Solid Tumor Research

Brian P. Sorrentino, MD[1]
Wall Street Committee Endowed Chair in Bone Marrow Transplant Research

Stephen W. White, DPhil
Endowed Chair – Dean, St. Jude Children's Research Hospital Graduate School of Biomedical Sciences

[1]Deceased



Emily Walker

FELLOWS & SCHOLARS

POSTDOCTORAL FELLOWS
Hossam Abdelsamed, PhD, Immunology
Aditi, PhD, Genetics
Issam Al Diri, PhD, Developmental Neurobiology[1]
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Shariq Ansari, PhD, Cell & Molecular Biology
David Arroyo, PhD, Developmental Neurobiology
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Stefanie Baril, PhD, Pharmaceutical Sciences
Justin Batte, PhD, Infectious Diseases
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Randall Binder, PhD, Chemical Biology & Therapeutics
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Farimah Salami, PhD, Diagnostic Imaging[1]
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Jun Wei, PhD, Immunology[2]
Jing Wen, PhD, Immunology[1]
Sarah Whaley, PharmD, PhD, Infectious Diseases
Michael White, PhD, Structural Biology
Juwina Wijaya, PhD, Pharmaceutical Sciences
Justin Williams, PhD, Computational Biology
Laura Wilt, PhD, Chemical Biology & Therapeutics
Nicholas Wohlgemuth, PhD, Infectious Diseases
Lara Megan Wood, PhD, Developmental Neurobiology[1]
Boer Xie, PhD, Structural Biology
Jia Xie, PhD, Radiation Oncology[2]
Tao Xie, PhD, Structural Biology[2]
Qiong Xing, PhD, Structural Biology
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Peiguo Yang, PhD, Cell & Molecular Biology[2]
Seung Wook Yang, PhD, Cell & Molecular Biology
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Janet Huimei Zheng, PhD, Structural Biology
Min Zheng, PhD, Immunology
Wenting Zheng, PhD, Pathology
Peipei Zhou, MD, PhD, Immunology
Jiahua Zhu, PhD, Radiation Oncology
Jing Zhu, PhD, Structural Biology[2]
Zhexin Zhu, PhD, Oncology
Xinying Zong, PhD, Immunology

CLINICAL FELLOWS

BONE MARROW TRANSPLANTATION & CELLULAR THERAPY FELLOWS
Mansi Sachdev, MD[1]
Ali Suliman, MD, MSc

CANCER SURVIVORSHIP FELLOWS
Neel Bhatt, MBBS, MD
Alia Zaidi, MD[2]

INFECTIOUS DISEASES IN IMMUNOCOMPROMISED CHILDREN AND ADOLESCENTS FELLOWS
Sujittra Chaisavaneeyakorn, MD, PhD
Maria Garcia-Fernandez, MD[1]

INFECTIOUS DISEASES PEDIATRIC HIV FELLOW
Dana Sanders, MD[1]

OCULAR ONCOLOGY FELLOW
Benjamin King, MD[1]

NEUROPSYCHOLOGY FELLOWS
Jeanelle Ali, PhD
Traci Olivier, PsyD[1]
Marita Partanen, PhD

PEDIATRIC HEMATOLOGY-ONCOLOGY FELLOWS
Maggie Besler, MD
Senthil Bhoopalan, MBBS
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Kenneth Caldwell, MD
Steven Carey, MD, PhD[2]
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Jonathan J. Miller, MD, PhD
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Jessica M. Valdez, MD[1]
Caitlin C. Zebley, MD

PEDIATRIC INFECTIOUS DISEASES FELLOWS
Ruba Barbar, MD
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Patrick Gavigan, MD
Kathryn Goggin, MD
Amanda Green, MD

PEDIATRIC NEURO-ONCOLOGY FELLOWS
Anthony Liu, MD
Daniel Moreira Ridsdale, MD
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Hafeez Abdelhafeez, MD[2]
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PHARMACOGENETICS RESIDENTS
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Chuang Jiang, Pharmaceutical Sciences
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Nick Keeling, Pharmaceutical Sciences
Xin Lan, Hematology
Shelby Lane, Radiation Oncology
Anna Lee, Cell & Molecular Biology
Ein Lee, Immunology[1]
Victoria Liddle, Oncology[1]
Jock Lillard, Surgery[2]
Victoria Loudon-Hossler, Chemical Biology & Therapeutics[2]
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Christina Moore, Nursing Research[2]
Alex Mugengana, Chemical Biology & Therapeutics
Richard Grant Muller, Surgery[1]
Christina Oikonomou, Tumor Cell Biology
Majek Olaleye, Global Pediatric Medicine[1]
Aurora Peck, Infectious Diseases[1]
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Ashlin Philip, Oncology[1]
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Lee Pribyl, Genetics
Brooke Prinzing, Bone Marrow Transplantation & Cellular Therapy
Spencer Richardson, Immunology
Jordan Roach, Surgery
Sushree Sahoo, Hematology
Anjelica Saulsberry, Hematology
Hao Shi, Immunology
Kenneth Shiao, Oncology
Geetika Singh, Structural Biology
Kaitlyn Smith, Cell & Molecular Biology
Aisha Souquette, Immunology
Wei Su, Immunology
Parker Tumlin, Radiation Oncology
Patricia Umberger, Cell & Molecular Biology
Mitra Varedi Kolaei, Epidemiology & Cancer Control[2]
Elena Varotto, Oncology
Nicole Vita, Chemical Biology & Therapeutics
Anh Vo, Infectious Diseases[1]
Xinyu von Buttlar, Oncology
Megan Walker, Hematology
Kirby Wallace, Surgery[1]
Miranda Wallace, Chemical Biology & Therapeutics
Amber Ward, Pathology
Jason A. Weesner, Genetics
Rachael Wood, Tumor Cell Biology
Kaitly Woodard, Hematology
William Charles Wright, Chemical Biology & Therapeutics
Tianhua Wu, Pathology[1]
Zemin Yang, Cell & Molecular Biology
David Yanishevski, Surgery
Jay Yarbro, Structural Biology
Sarah Youssef, Oncology[1]
Xujie Zhao, Pharmaceutical Sciences
Yumei Zheng, Structural Biology
Qifan Zhu, Immunology[1]
Tony Zhuang, Oncology
Chan Zou, Pharmaceutical Sciences

[1]No longer at St. Jude; [2]Promoted to staff position

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[1]Ex officio voting member; [2]January 2017–June 2018; [3]Nonelected member; [4]July–December 2018; [5]Deceased

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This panel of physicians and scientists, serving during 2018, fostered the institution's development through discussion with faculty members, reports to the Board of Governors, and advice to the President and CEO on scientific and clinical research directions.

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Medical Director, Princess Margaret Cancer Centre
University Health Network, University of Toronto

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Dana-Farber Cancer Institute

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Dana-Farber Cancer Institute

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The Ohio State University Health System

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Professor, Department of Biology
Massachusetts Institute of Technology
Core Member and Chair of the Faculty
Director, Cell Circuits Program and Klarman Cell Observatory
Broad Institute

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Mar Nell and F. Andrew Bell Distinguished Chair in Biochemistry
University of Texas Southwestern Medical Center

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Director, Center for Cell Engineering
Memorial Sloan-Kettering Cancer Center

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Jeff C. Tarr Professor of Molecular and Cellular Biology
Paul J. Finnegan Family Director, Center for Brain Science
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Associate Professor of Pediatrics, Harvard Medical School
Samuel E. Lux IV Chair in Hematology/Oncology
Director, Bone Marrow Failure and Myelodysplastic Syndrome Programs
Dana-Farber Cancer Institute
Boston Children's Cancer & Blood Disorders Center

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Professor of Pediatrics, Harvard Medical School
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Principal Investigator, Pediatric Oncology
Dana-Farber Cancer Institute
Co-Director, Pediatric Hematologic Malignancy Program
Boston Children's Hospital and Dana-Farber Cancer Institute
Ted Williams Chair, Pediatric Oncology, Dana-Farber Cancer Institute
Dana-Farber/Boston Children's Cancer & Blood Disorders Center

OPERATIONS & STATISTICS

OPERATIONS	
Operating expenses[1]	$937.2 million
Number of employees[2]	4682
RESEARCH STATISTICS	
Grant funding[1]	$94.4 million
Peer-reviewed publications	764
Faculty members	296
Postdoctoral fellows	313
Clinical residents and fellows[3]	359
Graduate research scholars	121
CLINICAL STATISTICS	
Number of beds open[4]	73
Outpatient encounters[5]	294,798
Inpatient admissions	3472
Total inpatient days	18,921
Total protocol enrollments in 2018	7265
Patients enrolled in therapeutic trials	844
Patients enrolled in nontherapeutic trials	6421
	5020 in prospective trials
	1401 in tissue-banking protocols
Number of protocols open to accrual in 2018	338
Number of active therapeutic trials	174
Number of active nontherapeutic trials	164
	162 prospective trials
	2 tissue-banking protocols

[1]Data represents the period July 1, 2017–June 30, 2018.
[2]Data is from July 1, 2018.
[3]Data includes 183 full-time St. Jude fellows and 176 rotating fellows from the University of Tennessee Health Science Center or other medical schools.
[4]Data represents the number of beds in use. St. Jude is licensed for 80 beds.
[5]Data represents the total number of ambulatory or ancillary encounters not daily visits.

To cure one child at St. Jude is to cure countless children worldwide.