Translating Science into Survival

SCIENTIFIC REPORT **2023**

St. Jude researchers, backed by extraordinary resources and support teams, are focused on making big discoveries.

This report reflects the activities of St. Jude Children's Research Hospital during 2022.

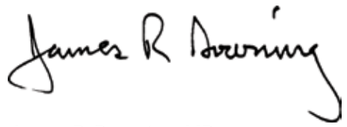
For more than 60 years, the culture of St. Jude has inspired visionaries and trailblazing pioneers to take on the field's biggest challenges with dedication and passion. Our focus has been to accelerate progress against pediatric catastrophic diseases through research and treatment.

This past year has been filled with new discoveries, continued growth, and transformative collaborations and partnerships. This Scientific Report highlights the latest advancements in scientific and clinical research made by St. Jude faculty and staff during 2022.

Within this report, you will learn about advances in the use of CAR T cells for the treatment of pediatric leukemia. Recent work by faculty within the Department of Developmental Neurobiology highlights how the study of normal brain development can contribute to our understanding of diseases pathogenesis, including medulloblastoma. Work focused on the St. Jude Lifetime Cohort Study (St. Jude LIFE) and the Childhood Cancer Survivor Study (CCSS) illustrates the power of the exploration of large datasets using advanced data science applications. These analyses help to better understand some of the factors associated with an increased risk of long-term complications that can result from cancer treatments. Recent work from the Department of Radiation Oncology also highlights how more tailored radiation therapy can be used to provide effective treatment for pediatric brain tumors while decreasing the possibility of long-term toxicities. Additionally, St. Jude scientists are studying the science of gene regulation to identify novel therapeutic opportunities.

We also recognize the exceptional career of Ching-Hon Pui, MD. Over his 45-plus-year career at St. Jude, Dr. Pui has done more than any other individual to improve the outcome for children with acute lymphoblastic leukemia (ALL). He began his career as a trainee at St. Jude in 1977 after graduating from medical school in Taiwan. He rapidly became a key member of the ALL team and helped to improve survival rates through the 'Total' family of ALL clinical trials. His research was instrumental in translating discoveries from St. Jude laboratories to personalizing treatment approaches based on the underlying biology of each patient's leukemia. In 2006, he took on the position of chair of the Department of Oncology and served in this position for more than 17 years. As he steps down as chair in early 2023, Dr. Pui will continue his work on ALL, focusing on advancing cures for children around the globe as the St. Jude Global China Region director.

While we celebrate our progress in treating and understanding childhood cancer and other catastrophic diseases in the Scientific Report 2023, we remain steadfast in our commitment to the dream of St. Jude founder Danny Thomas—that no child should die in the dawn of life.



James R. Downing, MD
President and Chief Executive Officer
St. Jude Children's Research Hospital

ENGINEERING A BREAK THROUGH

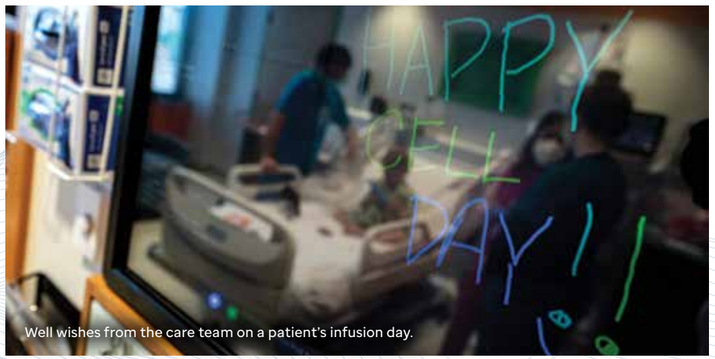
Nurse Emily Oakhill prepares a patient for CAR T-cell infusion therapy.

Since initially proposing the idea of harnessing the immune system to fight cancer in 1891, scientists have made enormous headway in understanding cancer biology, the immune system, and the interplay between them. Today, immunotherapy is a Nobel Prize–winning concept and a beacon of hope for many patients. Unfortunately, the promise of immunotherapy has yet to be realized for most pediatric cancers.

At St. Jude, scientists are investigating a type of immunotherapy called synthetic T-cell therapy. In this immunotherapy, researchers genetically modify T cells with genes that, when expressed, can improve T-cell function and redirect T cells to target cancer.

The most well-known example of this strategy is the chimeric antigen receptor (CAR). CAR T cells are immune cells engineered in a laboratory to contain a CAR that targets an antigen, a protein expressed on the surface of cancer cells. When physicians give these modified T cells to patients, the CAR binds to cancer cells expressing the cognate antigenic ligand — the antigen it was engineered to recognize. This activates the therapeutic T cell, which then kills the antigen-bearing target.

This immunotherapy is now used clinically to treat acute lymphoblastic leukemia (ALL), often in patients whose disease has relapsed or is not responding to other treatments. However, its use has been limited in many other types of pediatric cancer.



Well wishes from the care team on a patient's infusion day.

Understanding the roadblocks for **CAR T-cell therapy**

CAR T cells' limited success in treating acute myeloid leukemia (AML), solid tumors, and brain tumors is multifactorial. Several issues impede therapeutic success, including a limited array of targeting antigens, toxicity, limited expansion and persistence of therapeutic T cells, hostile tumor microenvironments that suppress immune responses, and the inability of CAR T cells to home in on and penetrate tumors.

Many limitations of CAR T-cell therapy can be traced back to issues with the cells' design. Researchers must carefully craft CAR T cells to optimize their function. However, engineering CAR T cells is no simple task. CARs typically contain three domains (regions or components). These include extracellular antigen-binding, transmembrane, and intracellular signaling domains.

Once the engineered CARs are inserted into T cells, the extracellular CAR domain, typically composed of a modified portion of an antibody, identifies and binds a specific antigen on the surface of the cancer cells. This step triggers the intracellular signaling domain, which activates the T cells similarly to how antigenic ligands, such as viral components, typically activate a T cell. Activating the intracellular signaling domain results in the T cells killing the cancer cells.

CAR T-cell therapy is successful when the modified cells persist after infusion, precisely target cancer cells with few off-target effects, and stimulate the immune system without causing adverse reactions, including dangerous inflammatory responses such as cytokine release syndrome.

Finding ways to remove roadblocks and develop successful CAR T-cell therapies relies on multidisciplinary collaboration, at which St. Jude excels. By leveraging valuable collaborations with St. Jude experts in immunology, hematological malignancies, brain tumors, and solid tumors, investigators in the Department of Bone Marrow Transplantation and Cellular Therapy have made remarkable advances in fundamental and translational immuno-oncology research to improve T-cell immunotherapy, including CAR T-cell therapy. Additionally, partnering with the Children's GMP, LLC, at St. Jude has enabled the on-campus production of CAR T-cell therapies for active clinical trials, a unique advantage that is fueling progress.

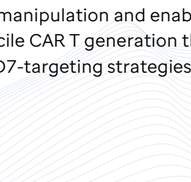
Care team members Toni Temples, Christina Smith, and Eleanor McDonald perform verification check on CAR T-cell product for infusion therapy.

With fresh insights and cutting-edge experiments, scientists at St. Jude are leading the charge to design the next generation of CAR T cells so that more pediatric cancers can be treated with these "living drugs."

Hiding in plain sight: **CD7$^-$ T cells advance treatment for ALL**

The protein CD7 has been recognized as an attractive target for T-cell malignancies because it is expressed on over 95% of T-cell acute lymphoblastic leukemia (T-ALL) cells and T-cell lymphomas. However, this protein is also expressed on healthy T cells. Because of this, targeting CD7 with a CAR causes the therapeutic CAR T cells to attack, not only the cancer cells but also each other.

To overcome this, researchers use a variety of strategies, including gene editing of CD7 with CRISPR–Cas9, sequestering CD7 to the cytoplasm, and preventing CD7 protein expression on the CAR T cells. However, these approaches can be time-intensive and costly, requiring additional cell modifications during the engineering process by implementing a new approach that was published in *Blood*, Paulina Velasquez, MD, Department of Bone Marrow Transplantation and Cellular Therapy, and colleagues sidestepped these additional CAR modifications and, instead, focused on a subset of naturally occurring CD7$^-$ T cells.



What started as a simple strategy to bypass gene editing led us to this interesting subset of T cells that can be harnessed as an adoptive cell therapy for T-ALL.

Paulina Velasquez, MD
Bone Marrow Transplantation and Cellular Therapy

The investigators found that in healthy donors and patients with cancer, CD7$^-$ T cells comprise, on average, 5%-6% of all T cells. Velasquez isolated these CD7$^-$ cells and used them to engineer CAR T cells that were highly effective against CD7$^+$ T-ALL in preclinical models. Altogether, Velasquez's work resulted in an effective preclinical CAR T-cell therapy that required less cellular manipulation and enabled a more facile CAR T generation than other CD7-targeting strategies.

Robert Throm, PhD, inspecting cells during the production of viral vector preparations.

Monicah Bwayi performs a visual inspection of a GMP-manufactured cellular therapy product.

"What started as a simple strategy to bypass gene editing led us to this interesting subset of T cells that can be harnessed as an adoptive cell therapy for T-ALL," said Velasquez.

As this novel CAR T-cell strategy progresses to clinical trials, it stands to decrease the time, cost, and resources needed to manufacture the necessary immunotherapeutic products. This, ultimately, has the potential to accelerate the T-ALL treatment timeline.

Engineering advances in cellular therapy **for AML**

Velasquez's lab is also investigating CAR T-cell therapy for AML. Using CAR T cells to treat AML has been difficult, partly because finding an antigen specific to AML cells has been challenging. To overcome this, researchers used an inside-out approach to select AML-specific antigens.

In a paper published in *Nature Communications*, the researchers detailed their engineering of a novel CAR targeting the glucose-regulated protein 78 (GRP78) as a specific AML target. Though typically sequestered in the endoplasmic reticulum, GRP78 moves to the cell surface in cancer cells. Compared to that in healthy tissue, GRP78 expression is often increased in cancer cells, which makes it a promising candidate for CAR T-cell therapy. Scientists found that cell-surface GRP78 is overexpressed in pediatric AML but is not expressed on the surface of important lymphoid and myeloid cells such as T cells, granulocytes, monocytes, natural killer cells, natural killer T cells, and hematopoietic stem cells.

Investigators designed a panel of GRP78-CAR T cells and determined the optimal configuration of the CAR to promote antileukemia activity. They also demonstrated that GRP78-CAR T cells do not recognize and kill healthy hematopoietic stem cells, a common and concerning target of other CARs for treating AML. Finally, they showed that the antileukemia activity of GRP78-CAR T cells could be further enhanced by adding the drug dasatinib during production. Dasatinib, a U.S. Food and Drug Administration–approved drug for treating leukemia, blocks CAR signaling and prevents the cells from entering terminally differentiated states. Ultimately, this engineering strategy has afforded researchers at St. Jude another immunotherapeutic option against AML.

Additionally, the Velasquez lab is exploring genetically modifying AML-specific T cells with an inducible co-stimulatory system to activate the immune system and enhance anti-AML activity. One such approach is to target CD123, a component of the IL-3 receptor present on most AML cells. One way to target this AML-specific antigen is by modifying T cells to secrete bispecific engagers (ENGs). These CD123-ENGs have two ligand-binding domains: one that binds CD123 on the tumor cell and another that binds to CD3 on T lymphocytes. Therefore, CD123-ENGs act as adaptors for healthy T cells and tumor cells. This elegant solution is, however, restricted by the limited persistence of engager T cells, given the lack of additional co-stimulation.

To enhance the persistence of CD123-ENG T cells, Velasquez and collaborators showed that an inducible co-stimulatory system, including MyD88 and CD40 molecules, significantly improved the ability of AML-specific T cells to kill tumor cells. This system provides additional co-stimulation that can be modulated, and it fosters T-cell expansion. Published in *Haematologica*, the results show that engineering CD123-ENG T cells to include MyD88 and CD40 enhances their effector function and antitumor activity.

CAR T-cell therapy for solid tumors: **A focus on *RASA2***

T-cell therapy for solid tumors presents unique challenges for researchers. The immunosuppressive nature of the tumor microenvironment can impair CAR T-cell function. To increase T-cell treatment options, Giedre Krenciute, PhD, Department of Bone Marrow Transplantation and Cellular Therapy, in collaboration with others, harnessed the power of CRISPR-Cas9 gene editing to identify a gene that, when disrupted, increased CAR T-cell success.

The work, published in *Nature*, identified RASA2, a GTPase-activating protein, as a signaling checkpoint in T cells that impacted the efficacy of CAR T cells in solid tumors. Removing *RASA2* from CAR T cells enabled these cells to recognize tumor cells that express even low levels of the target antigen and to function in chronic antigen exposure settings. This resulted in improved antitumor activity in several preclinical solid tumor models.

Removing *RASA2* from CAR T cells enabled them to exhibit long-term antitumor responses in preclinical models, even after tumor rechallenge.

Giedre Krenciute, PhD
Bone Marrow Transplantation and Cellular Therapy

Molecularly, the absence of *RASA2* modulated the transcriptional programs of activator protein 1 (AP-1), nuclear factor-kappa B (NF-κB), and nuclear factor of activated T cells (NFAT) in such a way that the T cells' ability to repeatedly recognize and kill tumor cells is improved.

Cells without *RASA2* also had an altered metabolic state. T-cell activation and differentiation require a substantial amount of cellular energy, and active T cells obtain this energy through a process called glycolysis. However, inactive T cells, or those in quiescence, aquire the energy to maintain metabolic homeostasis through a process called oxidative phosphorylation. Research has recently shown that metabolism regulates the transition between T-cell quiescence and activation. Therefore, changes in the metabolic states of T cells are important. In this study, cells without *RASA2* were skewed more towards oxidative phosphorylation, which, researchers believe, helped prevent their dysfunction.

"Removing *RASA2* from CAR T cells enabled them to exhibit long-term antitumor responses in preclinical models, even after tumor rechallenge," Krenciute said. "It's exciting because limited T-cell persistence is a major limitation to creating a successful CAR T-cell therapy."

Reverse translation — learning from **clinical studies**

Analyzing samples from cellular therapy research has the potential to provide clues on how these cells work and how to design next-generation studies.

Stephen Gottschalk, MD, Department of Bone Marrow Transplantation and Cellular Therapy chair, and Paul Thomas, PhD, and Jeremy Crawford, PhD, Department of Immunology, analyzed samples from a clinical study that evaluated the safety and anti-ALL activity of CD19-CAR T cells. They published their findings in *Cancer Discovery.*

Using single-cell gene expression and T-cell receptor (TCR) sequencing data, the researchers tracked individual CAR T cells from the infused cellular therapy product and post-infusion samples from the blood and bone marrow of pediatric patients with B-cell acute lymphoblastic lymphoma. The researchers identified a unique transcriptional profile in specific subsets of infused CAR T cells that produce most of the enduring anti-ALL activity. In particular, three genes within that transcriptional profile encoded cell surface proteins that proved to be important for anti-ALL activity. If T cells expressed a specific combination of these three cell surface proteins, they had a strong effector function and did not become exhausted or functionally ineffective.

The methodological framework created by the researchers has identified distinct functional potential in subpopulations of manufactured CAR T cells. It serves as a template to improve other CAR T–cell therapies and the T cells' quality in these complex immunotherapies.

"Before our study," Thomas said, "almost everything for CAR products was assessed at a bulk level. We showed that you need to look at the single-cell level to define the phenotypes of those cells that will be the critical effectors in the patient."

Making synthetic T-cell therapy **an option for more patients**

St. Jude investigators have embarked on a concerted effort to develop effective T-cell therapies for more types of pediatric cancer and, therefore, for more pediatric patients. By using multi-omics and systems approaches, scientists can better understand how tumor cells interact with nonmalignant cells in the tumor microenvironment, enabling them to decipher the immune landscape and immunosuppressive network. Functional genomics tools, such as CRISPR screening, are also helping to dissect mechanisms of tumor–immune cell interactions, discover druggable immuno-oncology targets, and develop combinatorial therapies. Investigators are also optimizing cellular and genetic engineering strategies to translate discoveries into curative immunotherapies or combination therapies for pediatric cancer.

"Immunotherapy with genetically engineered T cells holds the promise not only to improve outcomes for patients — who currently cannot be cured — but also to reduce side effects for all patients," Gottschalk said. "Likewise, the advent of single omics approaches will allow us to study the immune system at an unprecedented resolution, holding the promise of future curative therapies."

With this progress and more on the horizon, scientists at St. Jude are at the forefront of engineering effective cellular immunotherapies and bringing these to even more patients with childhood cancer.

...the advent of single omics approaches will allow us to study the immune system at an unprecedented resolution, holding the promise of future curative therapies.

Stephen Gottschalk, MD
Bone Marrow Transplantation and Cellular Therapy

GMP-manufactured cellular therapy product undergoing quality control.

FROM CONCEPT TO CAR T:
Good Manufacturing Practice team brings therapies to life

Cellular and gene therapies provide novel treatments and cures for many diseases. These "living drugs" target diseases by altering a person's cells or genes. However, these therapies must be manufactured in accordance with strict regulations and standards. The manufacturers of these drugs must follow current Good Manufacturing Practice (GMP) rules as established by the Federal Drug Administration and European Medicines Agency.

To enable the production of therapeutics specifically for catastrophic pediatric diseases, the Children's GMP, LLC, opened its doors on the St. Jude campus in 2003. This facility provides St. Jude with a key advantage: the ability to develop and produce innovative pediatric treatments quickly.

Sixty employees staff the 50,000-square-foot facility, vetted by the Foundation for Accreditation for Cellular Therapy, highlighting its commitment to producing high-quality therapeutic products. It features 30 processing and support rooms, International Standards Organization (ISO) 7- and ISO 5-rated cleanrooms, and Biosafety Level 3–approved laboratory capabilities.

The Children's GMP, LLC, has unparalleled product depth and breadth. It manufactures cellular therapy products such as chimeric antigen receptor (CAR) T cells used in clinical trials for acute leukemias and solid tumors. It also produces gene therapy products such as the adeno-associated viral vector used to treat factor IX hemophilia. The GMP has modified natural killer cells for treating B-cell acute lymphoblastic leukemia and produced a breakthrough treatment for X-linked severe combined immunodeficiency. The GMP facility's gene-corrected blood stem cells provided a landmark cure for this rare, life-threatening genetic disorder.

Fifteen zoonotic candidate vaccine viruses have been produced to combat diseases that threaten to spread from animals to humans, as have several multicomponent viral vaccines and two human challenge viruses. These viruses help scientists understand how pathogens infect humans and guide vaccine development. Monoclonal antibodies for neuroblastoma have been manufactured, as have recombinant proteins, such as Cas9, that are crucial for gene editing strategies.

The GMP facility, led by Frank Fazio, is a cross-institutional collaborative powerhouse enabling investigator-generated concepts to come to fruition. The GMP facility has strong partnerships with the Human Applications Laboratory (HAL) led by Salem Akel, PhD, the Department of Vector Development led by Robert Throm, PhD, and the Experimental Cell Therapeutics Lab (ECTL) led by Sheng (Albert) Zhou, PhD, which facilitate concurrent product design, testing, and manufacturing. "The GMP, in combination with many collaborating institutional departments, provides a great asset to the investigators at St. Jude," says Fazio. "The subject-matter experts who develop robust manufacturing processes, reliable analytical methods, and deliver a therapeutic agent to the investigators are all on-site. This results in the acceleration of the time required to translate the discovery from the laboratory into the clinic."

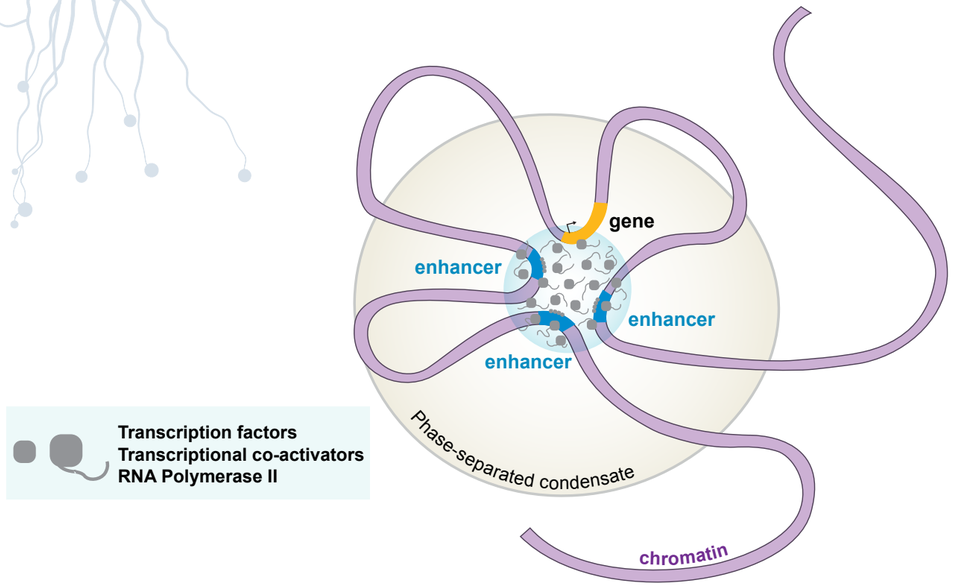
When an idea for a therapy is born, each division provides input on GMP-compatible engineering strategies for therapeutics. For example, to develop a CAR T-cell therapy, Throm's team assists with designing, optimizing, and producing vectors, which carry the CARs that reprogram T cells to fight certain cancers. Vectors are passed to the ECTL to determine the best conditions for their growth and manufacture. The HAL liaises between the GMP facility and the clinics, first coordinating the collection and transfer of patient samples, such as T cells, to the GMP facility and subsequently overseeing the preservation, dosing, and delivery of finished GMP-manufactured products to the clinics.

As investigators reimagine the possibilities of cellular therapies, the GMP facility and its strong partnerships bring these ideas to life and provide life-saving treatments and cures for a broader population of pediatric patients.

THE DEVELOPING BRAIN

FROM LINEAGE TO PATHOLOGY

Of the estimated 20,000 genes in the human genome, more than one-third are expressed in the brain.



Super-enhancers – regulatory DNA sequences that include multiple enhancers – can drive the expression of genes crucial to regulating cell identity and function.

For genes to be expressed, they must be transcribed into messenger RNA (mRNA). The information in these mRNA transcripts is then translated into proteins that direct the developing brain. The expression of genes must occur in a highly coordinated manner across space and time to ensure normal development and function.

How and when gene expression should occur depends on a cell's origin. Changes in this origin-mediated pattern of expression can lead to cancers and diseases. Understanding which factors regulate the transcription of genes, especially in the context of the complex lineage and cell development pathways of the brain, provides valuable insight into disease pathology.

Scientists in the Department of Developmental Neurobiology investigate the fundamental processes that govern normal brain development and function to understand what can go awry and cause disease.

Researchers recently traced the cell lineages of the developing brain to identify how gene expression and the mechanisms that control it contribute to retinoblastoma, medulloblastoma, and Williams-Beuren syndrome. Their work provides new ways to study these rare but devastating disorders and opens new avenues for potential treatments.

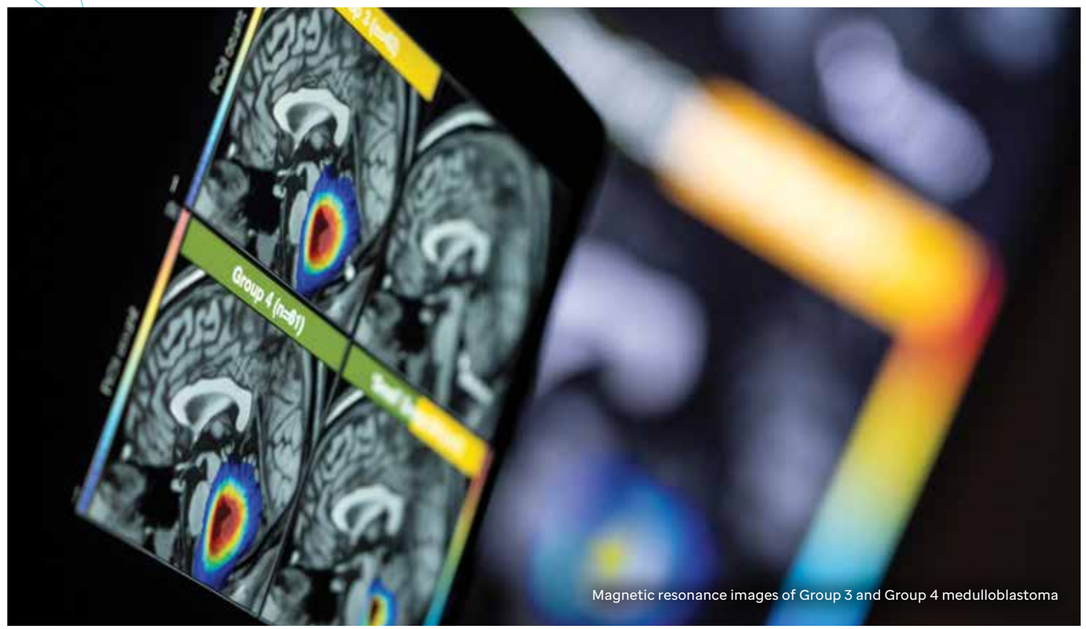
Origins of retinal development and **retinoblastoma**

Transcription factors regulate gene expression and play essential roles in development. In the retina, the Vsx2 transcription factor is expressed in established bipolar neurons, Müller glia, and progenitor cells and is required for retinal progenitor cell proliferation.

Michael Dyer, PhD, Department of Developmental Neurobiology chair, previously identified a regulatory DNA sequence – called a super-enhancer – that controls *Vsx2* expression. Only recently discovered, super-enhancers can drive the expression of genes important in regulating cell identity and function.

In a paper published in *Nature Communications*, Dyer and his team identified the domains of the *Vsx2* super-enhancer, elucidating four distinct regions. Three of the regions are involved in retinal development. This study is the first to demonstrate independent functions of distinct regions within a super-enhancer, a phenomenon Dyer's group calls a "modular" super-enhancer.

> **When you can fully understand how one of these modular super-enhancers works, you can go globally to all the super-enhancers with a framework to understand them more broadly.**
>
> **Michael Dyer, PhD**
> Developmental Neurobiology



Magnetic resonance images of Group 3 and Group 4 medulloblastoma

Because functional regions of modular super-enhancers can be independently manipulated, alterations of these regions enable scientists to change the expression of individual transcription factors in particular cell types at specific stages of development. This allows them to study gene expression in ways that were previously unattainable when using traditional knockout models. When *Vsx2* expression is knocked out, the eye does not form; therefore, researchers needed the ability to fine-tune *Vsx2* expression at different times and locations during retina formation.

Modifications in the *Vsx2* super-enhancer make this possible and provide a proof of concept for how modification of modular super-enhancers can provide models for studying complex gene expression patterns that occur during brain development. The analysis of *Vsx2* demonstrated that different subdomains of the super-enhancer differentially support the development of specific cell types, such as retinal progenitor cells and bipolar neurons.

"When you can fully understand how one of these modular super-enhancers works, you can go globally to all the super-enhancers with a framework to understand them more broadly," Dyer said.

This discovery also lays the foundation for a better understanding of retinoblastoma, an eye cancer that forms in utero, highlighting the importance of early development in the disease.

Origins of **medulloblastoma**

Tracing cell lineages within the developing brain has allowed St. Jude researchers to make significant advances in understanding the origins of medulloblastoma. Their discoveries could reveal novel treatment options for certain subgroups of this aggressive brain cancer.

Medulloblastoma is the most common malignant pediatric brain tumor and is categorized into four subgroups: WNT, SHH, Group 3, and Group 4.

Investigators at St. Jude and elsewhere categorized the disease in this way by analyzing patterns of transcription and other distinguishing characteristics. Researchers named the WNT and SHH subgroups for the characteristic mutations that drive them, and their origins are well known. However, researchers need more information about the origins of Group 3 and Group 4, which can be challenging tumors to treat.

To gain insights into these subgroups' biology, create better research models, and identify new areas for therapeutic development, St. Jude scientists molecularly defined the developmental origins of Group 3 and Group 4 medulloblastoma.

Led by Paul Northcott, PhD, Department of Developmental Neurobiology, researchers tracked the origin of Group 3 and Group 4 medulloblastoma to the rhombic lip, a structure present during early cerebellum development. Their findings were published in *Nature*. This is the first identification of a specific origin for Group 3

Recording electrophysiological activity in the auditory cortex

medulloblastoma and reinforces prior findings about Group 4.

Northcott's team leveraged the first-ever atlas of human cerebellar development to look for transcriptomic signatures of medulloblastoma subgroups. In addition to implicating the rhombic lip in Group 3 and Group 4 origins, they found that cells differentially branch off from this shared path, explaining why Group 3 and Group 4 tumors have both overlapping and unique characteristics.

> We've had evidence that these groups had some kind of common ancestry that then likely diverged, depending on the genetic events driving those tumors, but we couldn't say that definitively until now.
>
> **Paul Northcott, PhD**
> Developmental Neurobiology

"We've had evidence that these groups had some kind of common ancestry that then likely diverged, depending on the genetic events driving those tumors, but we couldn't say that definitively until now," said Northcott.

Origins of enhanced auditory processing in **Williams-Beuren syndrome**

Beyond cancer, scientists at St. Jude are also investigating how gene expression plays a role in the developmental origins of rare neurological disorders. Williams-Beuren syndrome (WBS) is a rare disorder that causes neurocognitive and developmental deficits. Yet, the disease is also characterized by an unexplained gain of function; an above-average auditory processing ability.

In WBS, the loss of approximately 27 contiguous genes causes developmental and cognitive deficits. However, it also preserves and even enhances musical and auditory abilities. How the loss of so many genes provides a gain of function in auditory processing was a mystery St. Jude scientists have now solved.

The part of the brain that processes sound, the auditory cortex, plays a role in this enhanced auditory ability. Still, researchers knew little about the molecular underpinnings of how this occurs. Using RNA sequencing in mouse models of WBS, scientists led by Stanislav Zakharenko, MD, PhD, Department of Developmental Neurobiology, showed that hyperexcitable interneurons cause the enhanced ability to discriminate tones of different frequencies in the auditory cortex.

In work published in *Cell*, the researchers identified a neuropeptide receptor, VIPR1, the expression of which is reduced in the auditory cortex of individuals with WBS. They also found reduced *VIPR1* expression in cerebral organoids, advanced models made with human induced pluripotent stem cells. The transcription factor Gtf2ird1, encoded by one of the 27 genes lost in WBS, regulates VIPR1. Deleting or overexpressing *Vipr1* in the auditory cortex can mimic or reverse the auditory effects observed in WBS. Thus, it is Gtf2ird1 downregulating *Vipr1* that is responsible for the impact of WBS on auditory ability.

> This work opens up new directions to learn about musicality and how our brain differentiates sounds based on these findings in models of WBS.
>
> **Stanislav Zakharenko, MD, PhD**
> Developmental Neurobiology

"This work suggests that reducing the hyperexcitability of interneurons might be a general mechanism for treating WBS through targeting VIPR1," Zakharenko said. "It also opens up new directions to learn about musicality and how our brain differentiates sounds based on these findings in models of WBS."

Cellular origin: **a roadmap for disease**

Scientists must know where development takes a detour to understand how a disease may progress and where to look for potential treatments and cures. By elucidating the origins of neurological cell types and tracking their development, St. Jude scientists are creating roadmaps to better understand the point of origin of pediatric diseases.

SURVIVORSHIP IN THE ERA OF BIG DATA

What does it mean for patient care to be “**data-driven**” at St. Jude?

SURVIVORSHIP RESEARCH *IS AT THE FOREFRONT OF THE BIG DATA REVOLUTION.*

What does it mean for patient care to be "data-driven" at St. Jude? For the scientists investigating the long-term health problems experienced by childhood cancer survivors, it means leaning heavily into the vast information provided by large-cohort studies of survivors. With access to world-class data, these scientists are gaining new insight into the genetic underpinnings of pediatric cancer survivors' unique health challenges.

In 2022, researchers at St. Jude leveraged the large and robust genetic and clinical information datasets generated by the St. Jude Lifetime Cohort and the Childhood Cancer Survivor Study to discover associations, develop algorithms, and design computer models that tell a more wholistic story about cancer survivors. Survivorship research is at the forefront of the big data revolution. The amounts of data generated by research are immense, and the insights gained may change individual lives. For people treated for cancer 5, 10, 20, or more years ago, data are driving progress in understanding their health and how they can improve it.

Collecting data starts with survivors

St. Jude leads two unparalleled survivorship resources. These cohort studies have a high level of participation by childhood cancer survivors. The desire to learn more about their health while helping scientists make discoveries that could improve care for all patients – past and future – inspires these participants.

The St. Jude Lifetime Cohort Study (St. Jude LIFE) is a flagship clinical study of more than 10,000 survivors that tracks long-term survivorship outcomes. Hundreds of childhood cancer survivors, who were once treated at St. Jude, choose to come back annually for a health and wellness checkup and to participate in the study. Because the survivors are former St. Jude patients, their medical records and follow-up care are well documented, providing a robust and detailed data source. In addition, participants have both of their germline (inherited) genomes studied with whole-genome sequencing and other forms of sequencing. St. Jude LIFE is a magnifying glass that supplies scientists with a strong lens to look deep into these survivors' health details.

St. Jude also leads the Childhood Cancer Survivor Survey (CCSS), a massive National Cancer Institute (NCI)-funded international study. The CCSS is a retrospective cohort of more than 38,000 childhood cancer survivors who are at least 5 years post-therapy and were treated at one of 31 institutions in the United States or Canada. The CCSS is the largest North American cohort of survivors, representing about 22% of all childhood cancer survivors whose cancer was diagnosed between 1970 and 1999.

Childhood cancer survivors develop chronic disease earlier

A significant finding derived from both St. Jude LIFE and the CCSS data is that survivors experience chronic diseases much earlier in life than their peers. One such chronic condition is obesity, which survivors disproportionately experience when compared to the general population. St. Jude researchers combined genetic and clinical risk factors to design a model that they can use to predict which patients are most likely to develop severe or "morbid" obesity as adults. In the future, the tool will give physicians and survivors information to help motivate positive lifestyle changes early in life to avoid later obesity. The research was published in *Nature Medicine*.

"It is important for childhood cancer survivors to know if they are at risk for developing various chronic conditions," said first and co-corresponding author Yadav Sapkota, PhD, Department of Epidemiology and Cancer Control. "We have developed a prediction model that can help healthcare providers identify which survivors are likely to develop severe obesity."

The scientists generated a model that took genetic variants associated with obesity, then created a polygenic risk score for an individual. The aggregate score is derived from approximately 2.1 million common genetic variants associated with body mass index in individuals of European ancestry in the general population. The model had up to a 75% success rate in predicting adult obesity when it included this information.

Using the tool, the researchers calculated that survivors with the highest genetic risk score had a 53 times greater risk of severe obesity than survivors with the lowest score. This risk was independent of other general risk factors. After creating the tool by using St. Jude LIFE data, the researchers validated it with data from the CCSS, which produced similar findings.

It is important for childhood cancer survivors to know if they are at risk for developing various chronic conditions.

Yadav Sapkota, PhD
Epidemiology and Cancer Control

Finally, by adding the new risk score to traditional lifestyle factors and treatment factors commonly used to assess obesity risk, the researchers improved their ability to determine high-risk survivors, identifying 4.3 times more survivors who fall in this category. Therefore, the tool identifies survivors at high risk of severe obesity due to genetics who are missed by current methods but could benefit from individualized advice and motivation from clinicians regarding weight and healthy lifestyle management.

"This is a really important advance for the care of survivors," said co-corresponding author Yutaka Yasui, PhD, Department of Epidemiology and Cancer Control. "We can identify the highest-risk survivors with this method – a genetic method. We can know which childhood cancer patients are at high risk for severe or other obesity early on in life, so we can give personalized advice to them."

Epigenetic age acceleration in childhood cancer survivors

In addition to obesity, survivors develop many other age-related chronic conditions earlier than their peers. St. Jude scientists are studying the genetic risk factors that underlie these age-related conditions to identify the survivors most at risk, so that they can be offered early interventions.

In a study published in *Genome Medicine*, scientists at St. Jude analyzed the link between common genetic variants and epigenetic age acceleration (EAA) in St. Jude LIFE participants. EAA is a measure of the difference between the "biological" and chronological age of each survivor, and it is associated with the development of age-related diseases. The researchers relied on the whole-genome sequencing data available through St. Jude LIFE.

Our work can help determine subgroups at the highest risk for accelerated aging among childhood cancer survivors.

Zhaoming Wang, PhD
Epidemiology and Cancer Control and Computational Biology

"This is one of a series of studies my lab has undertaken to investigate aging biomarkers in childhood cancer survivors," said corresponding author Zhaoming Wang, PhD, of the Departments of Epidemiology and Cancer Control and Computational Biology. "We previously evaluated nongenetic risk factors, including cancer treatments, health behaviors, and chronic health conditions contributing to age acceleration. Our study focuses on the underlying genetic factors among these patients."

Wang's group found variants in two genomic regions associated with the development of accelerated aging. Both gene regions are involved in age-related diseases, offering a plausible mechanism. For example, one is near the gene for selectin P (SELP), a protein upregulated in Alzheimer's disease.

"Our work can help determine subgroups at the highest risk for accelerated aging among childhood cancer survivors," Wang said. "The findings can also identify potential drug targets for future invention studies."

Predicting patient prognosis through genetics

Studying treatment outcomes of pediatric patients with cancer can help inform therapy in the future. Choosing the right drugs or interventions for each patient remains difficult because even those with the same type of cancer and treatment plan can experience different outcomes. For decades, this disparity has suggested that their is a genetic component to how patients respond to treatments, but only recently have scientists gained enough data and computational expertise to understand this.

St. Jude researchers showed that genetic ancestry is a much more significant factor contributing to treatment outcomes – independent of other factors – for children with acute lymphoblastic leukemia (ALL), the most common childhood cancer, than was previously realized. The findings were published in *JAMA Oncology*.

Genetic studies of ALL systematically underrepresent African, Latin American, and Asian populations, even though they comprise the bulk of global pediatric ALL cases. Therefore, St. Jude researchers used RNA sequencing to characterize the molecular subtype of ALL and the genetic ancestry of 2,428 children and adolescent patients, including those of underrepresented genetic ancestries. The scientists found associations between ancestry, clinical features, and treatment outcomes. This work was possible because the researchers assembled a robust cohort that provided quality data on these underrepresented ancestries.

The researchers found that of 21 known ALL subtypes, eight were associated with ancestry. East Asian ancestry was positively associated with subtypes with a good prognosis, such as *DUX4* rearrangements, and negatively associated with those with a poor prognosis, including BCR–ABL1-like ALL and T-ALL.

In contrast, Native American ancestry was linked to *CRLF2* rearrangements, which mark particularly aggressive ALL cases. Children with African ancestry showed the highest incidence of T-ALL cases, which was seven-fold higher than in those of Native American descent (e.g., certain Hispanic groups). African and Native American ancestries were both associated with lower event-free survival and overall survival than seen in other groups. The work serves as an initial step towards understanding the connection between genetic ancestry and leukemia biology and treatment outcomes.

"As a field, we really need to put diversity front and center in our research going forward," said corresponding author Jun J. Yang, PhD, Departments of Pharmacy and Pharmaceutical Sciences and Oncology. "We need to stop assuming we can develop therapies focusing on children of one race or ethnicity, and then they can just be extrapolated to others.

We need to be more cognizant and understanding of the needs of children with cancer across the world. As we look to the next generation of therapies for ALL, it will be essential to consider the diversity of patients with this cancer on a global scale."

The intersection of treatment and genetic risk

The genetic variants in a person's DNA can affect their cancer treatment outcomes. This understanding enables scientists and clinicians to evaluate genetic data to find such variants, thereby identifying patients who might experience treatment complications such as lung problems. In a polygenic risk score (PRS), certain variants are best looked at collectively as a group of many genes.

Some survivors are at a greater risk of developing lung issues, especially those exposed to chest-directed radiotherapy. These lung complications are also one of the leading causes of mortality in survivors.

Therefore, understanding who is and is not at risk for these complications could lead to life-saving changes in treatment regimens.

St. Jude researchers examined the relationships between particular genetic variants and the therapies used to treat childhood cancer. This study included more than 9 million single-nucleotide variants, insertions, or deletions, which were represented at more than 1% in their sample.

Future clinicians can use these scores to choose effective treatments that cause less long-term damage in survivors.

Yutaka Yasui, PhD
Epidemiology and Cancer Control

They looked for associations between clinical factors and gene-by-treatment interaction effects – to determine the power of polygenic scores to predict lung complications – in the context of specific treatments. These treatments included radiation therapy to part or all of the chest; medications including bleomycin, busulfan, carmustine, lomustine and anthracyclines; and thoracic or pulmonary surgery. The first score, the clinical risk score, used clinical factors and these treatments to predict restrictive ventilatory defects (RVDs).

The researchers created another score by employing a genome-wide association study to develop a PRS for lung complications without considering treatments. Then they combined approaches to account for gene-by-treatment effects, which resulted in a composite PRS. The final and novel survivor-specific pharmaco/radiogenomic PRS (surPRS) predicted RVD better than any other score.

The surPRS achieved good discriminatory power with an Area Under the Curve (AUC) validation of 0.81, significantly outperforming the next best prediction model, with clinical risk scores only, with an AUC of 0.78. In addition, the survivors at the highest risk were considered approximately 20 times higher risk than those at the lowest risk. Therefore the PRS has double the ability of the next best score to identify the difference in risk between the low and high groups.

The scientists strategically used St. Jude LIFE's unique mix of whole-genome sequencing results, treatment data and patient outcomes to create a PRS to better predict which survivors were at the highest risk of lung complications (particularly RVDs) as a late effect of their cancer treatment. The study, led by Yasui, was published in *Cancer Research*.

Discovering disease-specific risks in childhood cancer survivors

The data researchers can gather from childhood cancer survivors is not limited to their genes. Scientists at St. Jude are studying cancer survivors' neurocognitive and psychosocial outcomes based on data collected through long-term follow-up studies.

In addition to therapy-specific risks, some cancers come with their own long-term health risks. For example, childhood survivors of Hodgkin lymphoma experience a range of poor outcomes later in life. A study led by Kevin Krull, PhD, Department of Psychology and Biobehavioral Sciences chair, and published in *Blood* found that survivors experienced more significant neurocognitive impairment, depression, unemployment, and a lower quality of life than their peers. In many categories, survivors who smoked experienced a higher risk of adverse health outcomes. Clinical cardiovascular and neurologic conditions were also associated with impairment in nearly every aspect tested.

The study also found a reason for hope. Survivors who met the Centers for Disease Control and Prevention's exercise guidelines were at a lower risk of depression and had better outcomes in multiple quality-of-life domains. The research showed that although certain survivors, based on their disease, genetics, and treatment, are at higher risk of health conditions developing later in life, they can make choices to reduce that risk. In addition, clinicians should address treatable cardiovascular and neurological conditions to improve the lives of these survivors.

Social and health inequalities physically impact survivors more

Even though all childhood cancer survivors are at a higher risk of poor health outcomes, these burdens are not shared equally. Scientists also found considerable ancestry and socioeconomic disparities among survivors who experienced severe outcomes.
St. Jude scientists examined lung impairment in St. Jude LIFE survivors of European or African ancestry to assess whether there was a disparity and, if so, why. They

Genetics, passed from parent to child, can be used to predict survivors' risks.

used epigenome-wide association studies in tandem with observing social determinants of health. Social determinants of health were a significant source of the observed disparity in lung impairment between survivors of African vs. European ancestry. The scientists assessed personal educational attainment, personal income, and neighborhood deprivation. They determined socioeconomic neighborhood deprivation by using the Area Deprivation Index (ADI), which includes factors for income, education, employment, and housing quality in every census block of the United States.

The researchers found that these social determinants may have fueled the disparities through epigenetic changes. Epigenetics encompasses how genes are regulated, which can be affected by their environment, as in the case of DNA methylation. The study analyzed 130 DNA methylation 5'-cytosine-phosphate-guanine-3' (CpG) sites, a set of epigenetic modifications already associated with social determinants of health. The scientists found that certain epigenetic markers previously correlated to social determinants of health linked potential cellular changes to the association between social determinants of health and lung impairment. This indicates that the impoverished environment may have directly affected these survivors' gene expression and downstream health outcomes.

The study, led by Wang, and published in *Cancer Communications*, is part of a growing body of evidence showing that genetic ancestry and socioeconomics are significant determinants of survivors' health. Importantly, epigenetic markers can be tracked, suggesting that researchers can objectively evaluate the efficacy of future social support interventions by assessing these correlative markers in survivors.

Similarly, a study in the *Journal of Clinical Oncology* found that survivors who experience health equity issues, such as a lack of health insurance or education, are more likely to have a higher burden of severe symptoms as adults due to the late effects of their childhood care. The St. Jude study also discovered that nearly half of the survivors experience multiple simultaneous symptoms of moderate-to-severe intensity.

We found a survivor's risk of experiencing severe symptom burden in all three symptom areas, physical, somatic, and psychological, was 7.71 times higher if they have less than a high school education.

I-Chan Huang, PhD
Epidemiology
and Cancer Control

These symptoms include physical (sensation, movement, cardiac, and pulmonary), somatic (pain, fatigue, and nausea), and psychological (memory, anxiety, and depression) symptoms, which all childhood cancer survivors experience at higher levels than do those who have not had cancer.

"We found a survivor's risk of experiencing severe symptom burden in all three symptom areas, physical, somatic, and psychological, was 7.71 times higher if they have less than a high school education," said corresponding author I-Chan Huang, PhD, Department of Epidemiology and Cancer Control. "Based on previous research, we expected trends like this, but the magnitude was beyond our imagination."

In addition to education, the investigation showed an association between a lack of health insurance and the risk of severe symptom burden. Survivors' sex, relationship status, and cancer treatment significantly correlated with moderate-to-severe symptom burden.

"I want to emphasize this really is a health equity issue," Huang said. "Health care providers need to pay specific attention to this vulnerable population. Survivors with lower educational attainment, without insurance, female and single – including divorced – have a higher risk of experiencing a high symptom burden than their counterparts."

Moving survivorship forward

Access to data means progress. Without it, scientists would not understand the factors, whether they be genetic, epigenetic, social, or environmental, that influence the health of childhood cancer survivors. By using St. Jude LIFE, the CCSS, and other cohorts, St. Jude researchers have continued to improve diagnostics, treatments, and care to make a difference in the health and lifespans of childhood cancer survivors.

With an approach to science that relies on data-driven investigations, researchers at St. Jude are poised to make even more breakthroughs in understanding childhood cancer survivorship. Investigators are already diving deeper into how healthy lifestyles can help survivors, how socioeconomic deprivation can be harmful, how understanding genetic ancestry can improve treatments, and much more. With data making a difference, St. Jude is breaking down barriers to our understanding of childhood cancer survivors so that they can live as long and remain as healthy as possible.

A GIANT

IN THE FIELD OF EPIDEMIOLOGY AND CANCER CONTROL

Leslie (Les) Robison, PhD, was a part of the St. Jude faculty for 18 years, serving as the inaugural chair of the Department of Epidemiology and Cancer Control until he retired in early 2023. Throughout his career, Robison was a leader in the fields of pediatric oncology and cancer survivorship research.

During Robison's undergraduate years, he began a research assistant job with the National Cancer Institute (NCI) Children's Cancer Study Group at the University of Southern California Medical School.

"As I was exposed to pediatric cancer research," Robison said, "I realized how little epidemiology had looked at survivors. The focus until that point had been improving survival, as opposed to looking at the long-term consequences of treatment."

Robison earned his master's and doctoral degrees in public health and epidemiology at the University of Minnesota. As a faculty member at the University of Minnesota Medical School, he proposed tracking a cohort of more than 20,000 patients and thousands of their siblings – the Childhood Cancer Survivor Survey (CCSS).

"It wasn't an easy process to get CCSS up and running," Robison said. "We had to propose it, do pilot studies, write grants, and convince the NCI to invest in a cohort of childhood cancer survivors."

When he moved to St. Jude, Robison brought the CCSS with him. Since its launch, the CCSS has produced over 300 peer-reviewed scientific papers, many reporting practice-changing discoveries. Robison sees it as more than that.

"There are many things that CCSS identified and characterized that would never have come to light as quickly without the cohort," Robison explained. "Another benefit, though, is the collaborative structure that brought together a large number of investigators, all working on a common goal."

After starting CCSS, Robison looked for a change. "What really drew me to St. Jude," Robison said, "is that we proposed the St. Jude Lifetime Cohort Study. I said, 'If we can do that, if we can set up a cohort that is different than CCSS, because these patients are going to be clinically assessed as opposed to relying heavily on self-reported outcomes, that would advance the field.' And so, it was the institution's willingness to make this significant commitment that made the decision easy for me to say, 'St. Jude is the place I should be.'"

In 2005, Robison partnered with Melissa Hudson, MD, St. Jude Division of Survivorship director, to lay the foundation for the St. Jude Lifetime Cohort (St. Jude LIFE). The study launched in 2007 and continues to publish high-impact results pushing the field of survivorship forward.

"In St. Jude LIFE, we were able to focus on the most important questions," Robison said, "as opposed to the most fundable with grants. We were able to do the most important research because of the resources and cohorts we had at St. Jude."

Robison has been succeeded by Gregory Armstrong, MD, MSCE, department chair and head of the CCSS.

"Dr. Robison was the department's founding Chairman, and his leadership in population sciences facilitated St. Jude advancing from an NCI-designated Cancer Center to an NCI-designated Comprehensive Cancer Center status," Armstrong reflected. "His real legacy, however, is that he trained the next generation of survivorship researchers who are leading across the world with tremendous impact, CCSS and St. Jude LIFE, results from which have undoubtedly improved care for long-term survivors of childhood cancer."

RETHINKING THE ROLE OF RADIATION THERAPY

Radiation therapy is a cornerstone of care for many types of pediatric cancer.


Radiation therapists Mary Beth Wainwright and Randi Carter prepare a patient for proton therapy.


A patient begins her proton therapy.

For cancers of the central nervous system (CNS), radiation therapy, in combination with chemotherapy and surgery, is a core component of the therapeutic strategy. Due to this centrality, a tremendous amount of research has focused on the safe and optimal use of radiation to treat pediatric cancer. However, advancements in the understanding of CNS disease variability have elevated the need for a more nuanced assessment of the role of radiation therapy as part of personalized treatment plans.

Through clinical trials and other outcomes-focused research, St. Jude is leading efforts to study radiation therapy in the context of CNS disease subtype, accompanying treatment modalities, and long-term effects. Extending beyond mere efficacy measurements to consider radiation therapy's impact on quality of life, the research provides field-shaping recommendations to improve care for patients who have rare and difficult-to-treat CNS tumors.

Radiation therapy for craniopharyngioma

With rare CNS tumors that have high survival rates, such as craniopharyngioma, a benign brain tumor, there is still an urgent need to investigate how to improve treatments, minimize the risk of adverse late effects, and improve patients' quality of life.

There is nothing published that matches the breadth and depth of our late effects research, especially for rare tumors such as craniopharyngioma.

Thomas Merchant, DO, PhD
Radiation Oncology

To examine the ability of radiation therapy to reduce tumor volume safely, a team of scientists led by Thomas Merchant, DO, PhD, Department of Radiation Oncology chair, designed a long-term clinical trial. The phase II trial, called RT1, collected 10 years of follow-up data from 101 patients treated with photon-based conformal radiation therapy (CRT, a radiation delivery method that conforms the radiation beam to match the tumor's shape) or intensity-modulated radiation therapy and surgery at St. Jude.

"We made radiation more acceptable because we could show how we spared normal tissues when treating our patients. The RT1 protocol was one in a portfolio of St. Jude protocols that comprehensively evaluated patients before and after treatment," said Merchant. "There is nothing published that matches the breadth and depth of our late-effects research, especially for rare tumors such as craniopharyngioma."

The results, published in *Neuro-Oncology*, showed that at 10 years post-treatment, the respective overall survival, progression-free survival, and event-free survival rates were 96%, 79%, and 77%, respectively. There was a low incidence of severe complications, including vasculopathy, necrosis, and secondary malignancies, which showed that limited surgery and photon-based CRT can achieve excellent tumor control. Twenty patients experienced tumor progression, and data showed that race, shunt status, and tumor volume significantly affect progression-free survivaland overall survival, factors that need further study.

The researchers determined that given the likelihood of long-term survival in patients with craniopharyngioma and the high efficacy of radiation therapy, reducing target volume margins for irradiation should be a priority to manage long-term adverse effects of tumors and treatment.

Beyond assessing the efficacy of radiation therapy as part of the therapeutic regimen for this rare brain tumor, researchers also examined the incidence and onset of hormonal deficiencies in relation to tumor-related and other treatment-related factors.

Craniopharyngioma arises in the region of the hypothalamus and pituitary gland. It is not unusual for a child to undergo evaluation for growth delay, only to learn that they have craniopharyngioma. Standard treatments, such as surgery and radiation therapy, can likewise impact hormonal activity. Surgery can injure the hypothalamus–pituitary axis (HPA), and the target volumes for radiation therapy often encompass the HPA, both resulting in hormone deficiencies. Because of these factors, there is a high incidence of endocrinopathy among patients with craniopharyngioma.

In a paper published in *Neuro-Oncology*, Merchant and his colleagues reported the incidence and time to onset of specific hormone deficiencies. Their results were based on hormone levels measured before and after radiation therapy. The research provided clear examples of how endocrinopathy can be attributed to tumors, surgery, and radiation therapy.

Given the excellent survival when craniopharyngioma is treated with radiation therapy, the ability to predict endocrinopathy could lead to new strategies that will improve patients' long-term quality of life. These results were later used to show that early growth hormone replacement leads to improved cognitive test scores. This work was published in the *International Journal of Radiation Oncology, Biology, Physics*.

For rare CNS tumors, developing therapeutic plans that consider the quality of life and establish a balance between risk and benefit is critical. As investigators continue to examine the nuances of radiation therapy in treating pediatric cancer, additional disease-specific information can help to guide areas of study.

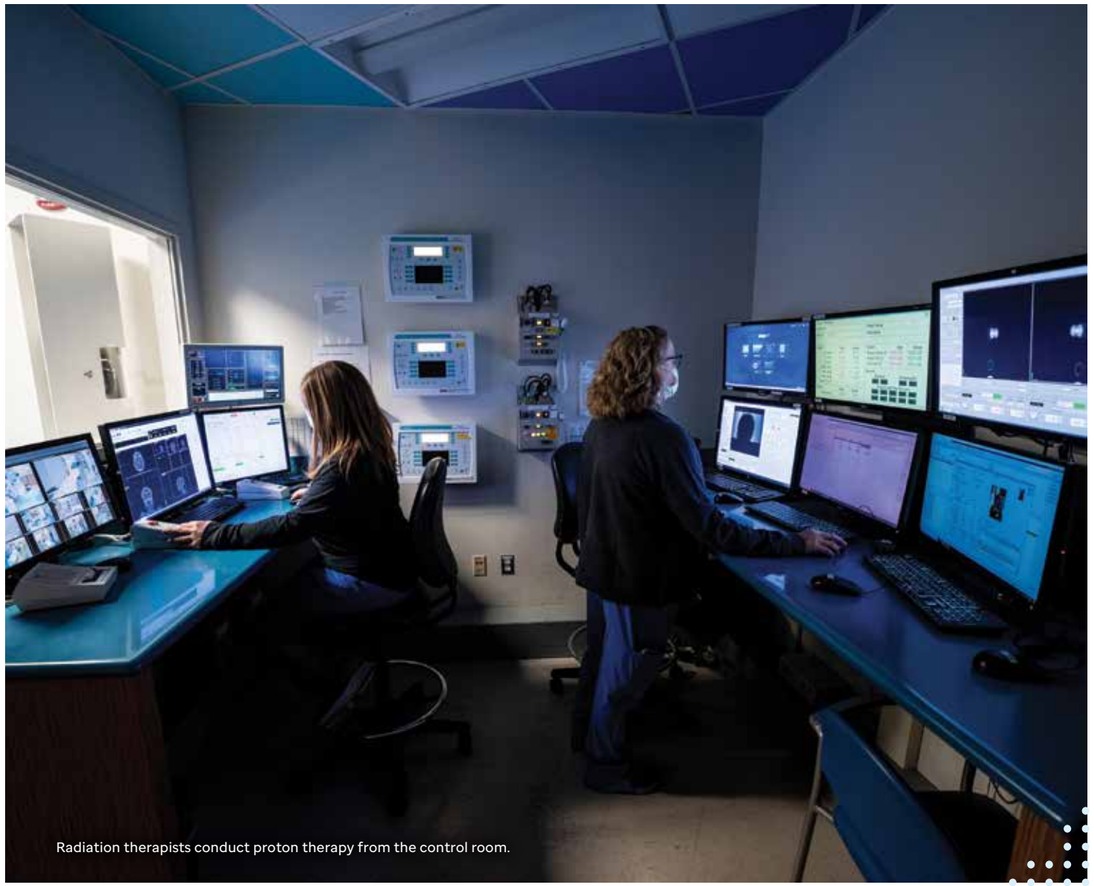
Molecular heterogeneity shapes treatment needs

The use of molecular profiling has provided insights into disease subtypes that can direct therapies for pediatric CNS tumors. Researchers previously used methylation profiling (the characterization of methyl group additions to DNA that dictate gene expression) to better understand central nervous system primitive neuro-ectodermal tumors (CNS-PNETs). They found CNS-PNETs to be a diversely heterogeneous entity of their own, instead of another subgroup of medulloblastoma, as previously thought. Based on this, CNS-PNETs have been reclassified as a heterogeneous collection of tumors, as documented in the 2021 World Health Organization CNS Tumor Classification. With a new classification, what is the best method of treatment?

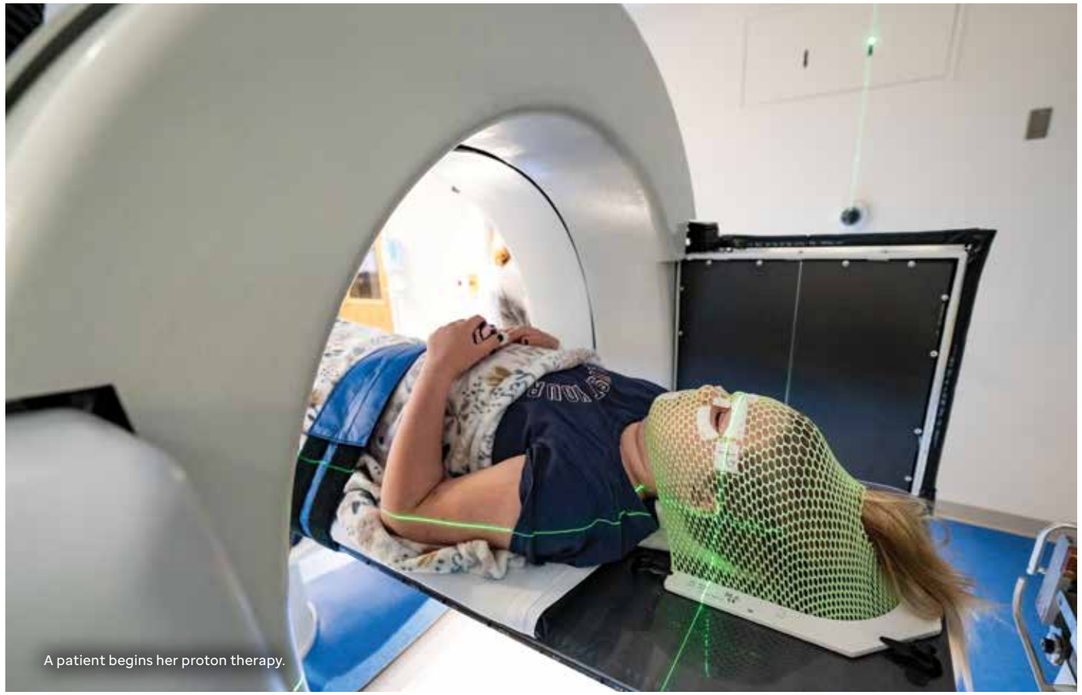
Investigators led by Amar Gajjar, MD, Department of Pediatric Medicine chair and Neuro-Oncology Division director, reported clinical outcomes associated with molecular profiles of CNS-PNETs in two multi-center clinical trials, SJMB03 and SJYC07. The results, published in *Acta Neuropathologica*, chronicled the response to conventional therapy options, with respect to cohort characteristics.

With a refined understanding of our patients' clinical risk and molecular profile, we can assign them a risk-adapted treatment plan that will help reduce short- and long-term toxicities.

Amar Gajjar, MD
Pediatric Medicine



Radiation therapists conduct proton therapy from the control room.



A patient begins her proton therapy.

The researchers used a combination of approaches, including next-generation sequencing, to find alterations in DNA and methylation profiling to analyze the patterns of methyl group additions to DNA in available samples. By analyzing 70 tumors collected over 20 years, Gajjar and his team found two highly aggressive tumor subtypes with poor survival rates independent of treatment: embryonal tumors with multilayer rosettes (ETMR) and high-grade glioma. The remainder of the tumor subtypes had more favorable survival, which suggests that, with better diagnostic tools, clinicians can tailor treatment to improve outcomes or provide predictions that limit therapy to precisely what is needed, thus reducing side effects caused by treatments such as craniospinal irradiation.

"New molecular techniques, combined with traditional cellular morphology and immunohistochemistry, have made it easier for us to accurately diagnose and classify pediatric brain tumors. With a refined understanding of our patients' clinical risk and molecular profile, we can assign them a risk-adapted treatment plan that will help reduce short- and long-term toxicities," said Gajjar.

Tailoring radiation therapy based on **molecular groups**

Medulloblastoma is the most common malignant pediatric brain tumor, and molecular profiling has revealed the diverse molecular heterogeneity of this tumor. Medulloblastoma can be classified into four distinct molecular subgroups consisting of 13 subtypes with various characteristics, drivers, and prognoses. With this knowledge, investigators sought to define the optimal role of radiation in treating this tumor.

Using data from the SJMB03 clinical trial, Merchant and his investigators studied risk-adapted radiation therapy and dose-intensive chemotherapy with autologous stem cell rescue (a transplantation procedure in which the patient's own healthy stem cells from blood or bone marrow are administered after chemotherapy or radiation therapy) in 155 patients with newly diagnosed medulloblastoma. They conducted methylation profiling on samples to stratify disease subtypes and risk profiles. Published in *Neuro-Oncology*, the study reveals the influence of methylation subgroups and demonstrates potential treatment strategies, according to clinical and molecular risk profiles. For molecularly low-risk medulloblastomas, lower cumulative doses and tighter margins of radiation therapy are beneficial. In contrast, molecularly high-risk tumors may require alternative strategies, such as using chemotherapeutic agents that act as

Radiation therapist Randi Carter checks the patient positioning before proton therapy commences.

radiation sensitizers to enhance the effectiveness of radiation treatment.

Merchant and his team conducted an additional study, published in the *Journal of Clinical Oncology*, to evaluate the impact of radiation on cognitive outcomes for this cohort of patients with high-risk medulloblastoma. The goal was to assess the association between the radiation therapy dose to the hippocampus, corpus callosum, and frontal white matter areas of the brain and long-term effects on memory and processing speed. These areas are particularly prone to injury during radiation therapy; a better understanding of the relation between the radiation therapy dose and cognitive outcomes could result in radiation therapy plans that preserve neurocognition.

The results showed a decline in processing speed correlated with a dose increase to the corpus callosum and frontal white matter. Increasing the radiation dose to these areas by 1 Gray (the unit of measurement for absorbed energy in tissue, used to assess radiation exposure) increases the risk of a meaningful decline in composite processing speed and perceptual speed by 10%-15% and 8%-12%, respectively. The results suggests an opportunity to shift radiation therapy planning to a form that is substructure-informed in future medulloblastoma protocols.

By providing evidence supporting a treatment planning paradigm shift that couples biological and clinical understanding with advances in radiation protocols, the team offers a planning recommendation that can improve the quality of life for medulloblastoma survivors.

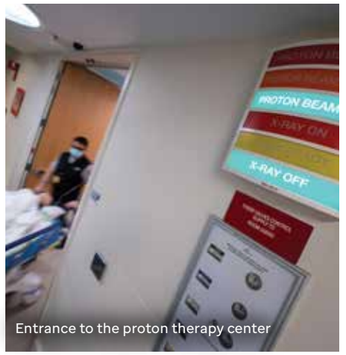
Optimizing radiation therapy **for future patients**

Although many standard-of-care protocols for pediatric CNS tumors involve radiation therapy, the research led by St. Jude investigators provides the opportunity to further understand the risk and benefit of this treatment modality and to develop treatment plans that put the patient, not just the tumor, at the center of treatment.

Reflecting on the impact of radiation therapy on care at St. Jude, Merchant said, “We have methodically evaluated the use of radiation therapy approaches for all diagnoses and conditions that require radiation. Advances in radiation therapy, such as the use of protons as opposed to photons, have impacted diverse patients with varied therapeutic needs. The radiation oncology team at St. Jude is heartened by comments from other care teams when it is reported that their patients experience fewer anticipated side effects during treatment or after years of follow-up and show little or no signs of adverse effects from treatment.”

SIX YEARS OF PROTON THERAPY AT ST. JUDE

In the middle of the St. Jude campus, 60 feet below ground, is a radiation therapy center unlike any other. Harnessing the power of positively charged subatomic particles – protons – the Proton Therapy Center at St. Jude is the first proton therapy center in the world dedicated to treating childhood cancer. What makes protons such a powerful and effective radiation therapy for cancer?



Entrance to the proton therapy center

Traditional radiation therapy uses X-rays delivered to the body in beams of high-energy photons, which are bundles of electromagnetic energy. This conventional approach targets a tumor and sends the beams of photons through the body, exiting on the other side. This complete passthrough delivers high-energy radiation to not only the tumor but also the surrounding healthy tissue, causing an array of adverse side effects.

Since 2016, St. Jude has offered an innovative approach to radiation therapy that delivers proton-based radiation beams directly to a tumor. Unlike photons, protons slow and stop at the tumor, where they deposit their energy. Because protons do not fully pass through the body, they are able to spare much of the healthy tissue around the tumor. This limits some of the adverse effects of radiation therapy in children treated for brain tumors or solid tumors.

The state-of-the-art proton center occupies more than 25,000 square feet, with a design that optimizes not only care delivery and research but also patient comfort. A musical stairwell leads to the core of the building. There, housed beyond a rainforest-themed waiting room, is a 100-ton, three-story-high gantry that rotates around the patient and directs a high-energy proton beam to target malignancies precisely. In its six years of operation, the center has treated 1,274 patients and delivered 1,335 courses of treatment.

St. Jude was one of the early adopters of the newest form of proton therapy called intensity-modulated proton therapy, or pencil-beam scanning proton therapy, which uses a tumor’s unique shape, size, and location to precisely deliver a pattern of protons to the target area. When St. Jude designed the center, the decision to commit the entire operation to this newer method was based on years of methodological research. Six years later, the St. Jude Proton Therapy Center and the institution’s treatment protocols remain cutting edge. The center is a testament to the hospital’s commitment to innovative treatments and research initiatives that advance cures for pediatric cancer.

“Regardless of what is happening above ground, 60 feet underneath the Kay Research and Care Center, protons are being accelerated to high energies and directed at the most difficult-to-treat tumors in an effort to cure our patients,” said Thomas Merchant, DO, PhD, Department of Radiation Oncology chair.

A view inside the proton beam gantry

CHING-HON PUI

TRAILBLAZER:

HOW CHING-HON PUI, MD, CHANGED ONCOLOGY

> **As we consider the history of St. Jude, Dr. Pui is among the visionaries who created a trajectory of discovery and innovation that persists to this day.**
>
> **James Downing, MD**
> President and CEO

Ching-Hon Pui, MD, with St. Jude patient in 1981.

Imagine standing at the edge of a dense forest. You must get through it, but there is no visible way forward. Giving up isn't an option; you must blaze a trail yourself. As you work through the forest, you start to break a path. Over time, your path becomes a well-trod road as others follow in your footsteps. You have become a trailblazer. When it comes to pediatric leukemia, few deserve this moniker as much as Ching-Hon Pui, MD.

Ching-Hon Pui, MD and St. Jude founder Danny Thomas in 1987.

Since 1977, Pui has called St. Jude home, leading the Department of Oncology as chair for the last 17 years. He stepped down from this leadership role in January 2023, welcoming Julie Park, MD, who arrived at St. Jude from Seattle Children's Hospital. Pui's efforts, not just to cure patients – though he has done that time and time again – have optimized treatment for childhood leukemia here and around the world.

L to R: Joseph Mirro, MD; Geoffrey R. Kitchingman, PhD; Ching-Hon Pui, MD

Whether reducing the late effects of treatment, building bridges between the lab and the clinic, or working with colleagues around the world to raise the global cure rate, Pui embodies the trailblazer spirit, paving the way for critical breakthroughs.

"Total" clinical trials set the standard

When St. Jude opened in 1962, the probability of survival for patients with acute lymphoblastic leukemia (ALL) was 4%. Donald Pinkel, MD, established the St. Jude Total Therapy series of clinical trials to treat ALL with a combination of approaches that included chemotherapy and radiation. The hospital achieved acclaim for the Total 5 study, which attained 50% survival. Through the work of Pui and others, the Total studies helped boost survival past 70% in the 1990s.

> Pui embraced the genomic era to understand ALL biology better and identify targetable lesions of various disease subtypes.

Key factors behind these advances were more precise risk stratification, including DNA indexing (using flow cytometry to quantify the DNA from cancer cells), incorporation of reinduction treatment, and a marked reduction in the use of prophylactic cranial irradiation (given to fewer than 20% of patients) to reduce toxicity.

The Total Therapy trials have continued – each with a new approach designed to boost survival rates, while expanding existing knowledge about treatment and response. A key discovery stemmed from Total 15, which Pui led. The study pioneered measuring minimal residual disease (MRD), the submicroscopic quantity of cancer cells that remain in the body after initial therapy. Total 15 resulted in the highest cure rate reported for the disease as a result of the stringent risk classification based on MRD and dose adjustments according to pharmacogenetic and pharmacodynamic characteristics.

Total 15 applied several measures to optimize intrathecal therapy, which was intensified in patients with blasts (abnormal, immature white blood cells that multiply uncontrollably) in the cerebrospinal fluid. Remarkably, this central nervous system (CNS)-directed treatment approach successfully removed cranial irradiation from the standard of care of all patients. This seminal discovery, published in 2009 in the *New England Journal of Medicine*, was a landmark achievement because cranial irradiation carries the risk of cognitive deficits, hormone imbalances (including stunted growth), and secondary brain cancers.

Pui and his colleagues followed this clinical trial with Total 16, which the *Journal of Clinical Oncology* featured in 2019. The results of that study continued to show that it is feasible and safe to eliminate cranial irradiation and that additional intrathecal therapy during early induction further improves CNS control without causing excessive toxicity for patients with high-risk disease.

The right treatment for the right patient

In addition to working on the series of Total clinical trials, Pui embraced the genomic era to understand ALL biology better and identify targetable lesions of various disease subtypes. Pui incorporated this increasingly nuanced understanding of childhood leukemia genetics into therapy so that patients can receive novel molecular therapeutics and immunotherapy to improve cure rates while minimizing long-term side effects.

"One of the smartest things I did was seek Dr. Pui out as a collaborator, ultimately co-authoring over 200 papers together, and there are many St. Jude faculty who can say the same," said William Evans, PharmD, former St. Jude president and CEO. "Undoubtedly, Dr. Pui's leadership was instrumental in pushing the cure rate for ALL beyond 90% while reducing the side effects of treatment. His eagerness to collaborate with basic scientists of all disciplines is why St. Jude excelled at translational research long before the term was coined."

Ching-Hon Pui, MD, and St. Jude patient in 1987.

Ching-Hon Pui, MD and Charles Mullighan, MBBS(Hons), MSc, MD

One of Pui's collaborators is Charles Mullighan, MBBS(Hons), MSc, MD, Comprehensive Cancer Center deputy director. In 2014, they published a study in the *Journal of Clinical Oncology* on a subtype of ALL called *BCR–ABL1*–like ALL. This subtype typically has poor outcomes and exhibits a gene expression profile like that of *BCR–ABL1*–positive ALL while lacking the characteristic BCR–ABL1 fusion protein. The researchers examined the outcome of children with *BCR–ABL1*–like ALL treated with risk-directed therapy based on their MRD levels. The findings showed that patients who have *BCR–ABL1*–like ALL with poor initial treatment response can be salvaged with MRD-based risk-adapted therapy and may benefit from targeted therapies.

In 2021, Pui, Mullighan, and their colleagues continued their work on MRD, evaluating the clinical significance of novel subtypes of ALL in the context of MRD-directed therapy. The study, published i*n Blood Cancer Discovery*, looked at ALL subtypes such as *DUX4*-rearranged, *PAX5alt, BCR–ABL1*–like, *ETV6–RUNX1*–like, *MEF2D*-rearranged, and *ZNF384*-rearranged, among others. Their work further demonstrated that genomic analysis and MRD should be used together for optimized risk-adapted treatment of childhood ALL. The scientists determined that this combined analysis could have prognostic and therapeutic significance in the context of contemporary treatment and the availability of new and more effective therapies.

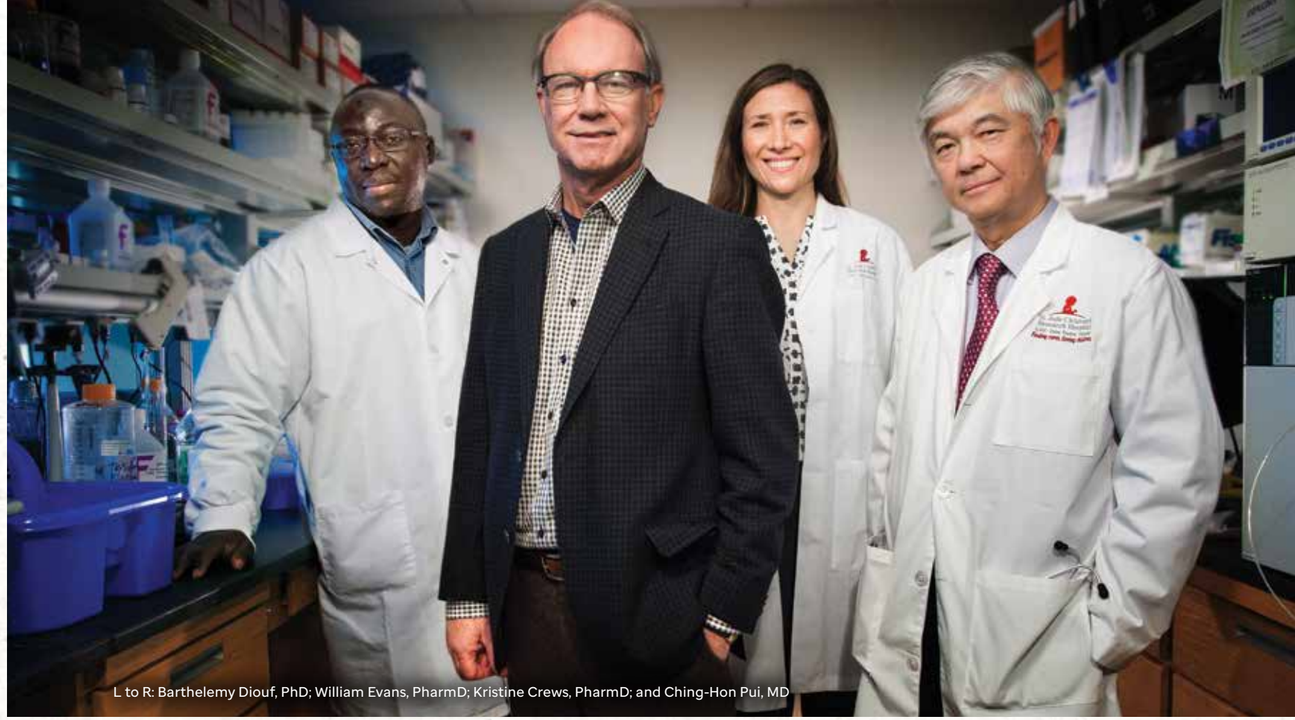
"It is difficult to think of a clinician who has had a greater impact on the lives of children with cancer," Mullighan said. "Dr. Pui has worked tirelessly as an innovator of more effective, safer treatment approaches for children with acute lymphoblastic leukemia and implemented some of the most profound changes in the treatment of children, often against the tide of current thinking. These include MRD measurement to guide treatment intensity and the elimination of cranial irradiation in treating ALL."

Building bridges, removing obstacles

Pui's work extends beyond the bounds of St. Jude. Through his scientific and administrative leadership in various organizations, and now through St. Jude Global, Pui has paved the way for improved leukemia treatment worldwide. Perhaps no example better demonstrates his passion for helping children with ALL than his work in China. Decades ago, he showed that children with ALL could be saved with minimal investment. Before this, children with the disease often died without access to treatment. Based on his work, the country adopted a national insurance plan to fund the treatment of pediatric patients with ALL in 2010. Since then, Pui has helped to launch several collaborative trials, adding volumes to what the world knows about leukemia and its treatment.

"Countless children at St. Jude and around the globe have received exceptional and lifesaving care because of Dr. Pui's commitment over the past 46 years," said Carlos Rodriguez-Galindo, MD, Department of Global Pediatric Medicine chair and St. Jude Global director. "That reach extends well beyond his career-defining work in the Oncology department. For more than 30 years, Dr. Pui has led the close collaboration between St. Jude and institutions in China to expand care to more children and greatly increase the probability of survival of those with ALL. These transformational initiatives have also influenced how we treat childhood leukemia globally.

His work as medical director of the St. Jude Global China Regional Program will continue this focus as we grow our partnerships in that region."



L to R: Barthelemy Diouf, PhD; William Evans, PharmD; Kristine Crews, PharmD; and Ching-Hon Pui, MD

A **trailblazing legacy**

When his colleagues think of Pui, the dogged nature of his pursuit for answers is one of the first qualities they cite as making him such a successful physician and researcher.

"Dr. Pui is the quintessential clinician–scientist, not only because he is one of the best pediatric oncologists in the world but also because of his unique scientific acumen," said Jun J. Yang, PhD, Departments of Oncology and Pharmacy and Pharmaceutical Sciences. "Many of us working in the lab gravitated toward him to tackle questions arising from his clinical observations. Working with him on a daily basis reminds me of what St. Jude is all about: clinicians and scientists side-by-side fighting to save our patients."

With a career that spans decades, Pui has seen ideas come and go, therapies succeed and fail. But those years of insight continue to pay dividends, as science advances and new discoveries are made.

"I remember that during his postdoc, Dr. Pui worked in the lab of a biochemistry faculty member, where it was discovered that children whose leukemia cells had low levels of the glucocorticoid receptor had a worse treatment outcome," Evans recalled. "Three decades later, we co-authored a *Nature Genetics* paper reporting the mechanism causing leukemia cells of some patients to have low glucocorticoid receptor levels. He never let go."

Everyone at St. Jude, from the researchers, clinicians, and patients to the staff, contributes to the story of St. Jude. As he blazed a trail to improve leukemia therapy, Pui wrote chapter after chapter of that story.

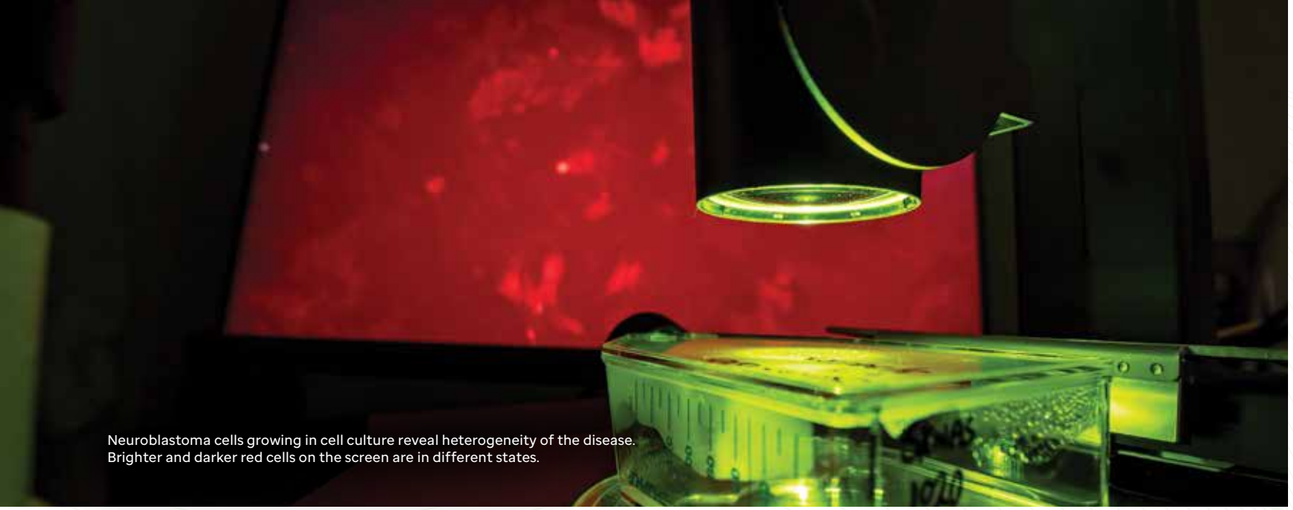
"Ching-Hon Pui is a tenacious researcher and a compassionate physician," said James Downing, St. Jude president and CEO. "He is also a dedicated educator and mentor, helping shape the careers of many investigators in pediatric oncology. For an investigator such as Dr. Pui, whose natural inclination is to move heaven and earth for a patient, being at St. Jude has meant incredible achievements for the field and in the lives of children."

He added, "As we consider the history of St. Jude, Dr. Pui is among the visionaries who created a trajectory of discovery and innovation that persists to this day."

GENE REGULATION:

THE NEXT FRONTIER

OF DISCOVERY IN PEDIATRIC CANCER



Neuroblastoma cells growing in cell culture reveal heterogeneity of the disease. Brighter and darker red cells on the screen are in different states.

Genomic changes drive pediatric cancers, but how these changes occur, trigger disease, and can be targeted for treatment has yet to be fully understood. Gene expression, where the code contained in the gene is used to create a product such as a protein, is a foundational biologic process that cells use to perform their functions. In the decade since the St. Jude–Washington University Pediatric Cancer Genome Project (PCGP) was initiated, St. Jude has led research to understand the relationship between abnormal gene expression and cancer.

Although the PCGP yielded many discoveries, one of the major insights concerned the relative genetic and mutational simplicity of many pediatric cancers compared to adult cancers. This highlighted the concept that other changes in the biology of cancer cells contribute to disease development. Recent studies have shown that the regulation of gene expression influences pediatric cancer more than was previously appreciated. Researchers have discovered many abnormalities and mutations throughout the genome, and these may be tied to individual genes or loci that more broadly regulate gene expression.

As the importance of understanding gene regulation comes to the forefront of pediatric cancer research, St. Jude is once again on the leading edge of discovery. Researchers are digging through the genome of cancer cells to understand how genes are controlled and expressed to identify potential vulnerabilities and weaknesses that therapies can exploit.

Exploring genetic predisposition in acute lymphoblastic leukemia

For many malignancies, both germline (inherited) and somatic (acquired) genetic variations contribute to the origin of the disease. Understanding how these genomic changes contribute to pathogenesis is critical as researchers examine factors predisposing children to cancer.

With the increasing evidence of an inherited susceptibility to acute lymphoblastic leukemia (ALL), the most common cancer in children, researchers at St. Jude are striving to understand how inherited mutations give rise to the disease. A team led by Jun J. Yang, PhD, Department of Pharmacy and Pharmaceutical Sciences and Department of Oncology, were specifically interested in noncoding variants – variations in portions of the genome that do not contain the code to make proteins.

The scientists examined the impact of noncoding germline variants in *ARID5B* and *GATA3* expression and on ALL onset.

Previous genome-wide association studies (GWAS) reported non-coding variants at the *ARID5B* gene locus but could not determine the molecular mechanisms that link *ARID5B* to leukemogenesis. By performing targeted sequencing in germline DNA of more than 5,000 patients with ALL, Yang and colleagues identified 54 common noncoding variants in *ARID5B* that were associated with leukemia risk. The results of the study were published in the *Journal of the National Cancer Institute*.

To understand the mechanisms linking these variants with gene expression, Yang collaborated with Chunliang Li, PhD, Department of Tumor Cell Biology, to develop CRISPR-based high-throughput screening to identify responsible *cis*-regulatory elements, such as promoters, enhancers, and silencers. These elements are part of the molecular machinery of gene regulation, controlling how genes are expressed (by promoting, enhancing, or silencing expression).

The results identified six *cis*-regulatory elements at the *ARID5B* gene, controlled by the blood transcription factor *MEF2C*, which activates *ARID5B*. This work shows how noncoding variants contribute to genetic susceptibility to ALL.

This study is a departure from many other cancer genomic projects... Adding the germline component provides a unique angle and opportunity for us to understand cancer biology.

Jun J. Yang, PhD
Pharmacy and Pharmaceutical Sciences and Oncology

To further elucidate the mechanisms of inherited susceptibility to ALL, St. Jude investigators performed targeted sequencing of another risk gene, *GATA3*, and found an inherited genetic variant associated with Philadelphia chromosome–like ALL (Ph-like ALL). Their findings were published in *Nature Genetics*. This noncoding variant resulted in a global chromatin change, positively regulated the oncogene *CRLF2,* and increased JAK–STAT pathway activity (a key signaling pathway in cancer and inflammation). This cascade of germline-associated events precipitated oncogenic effects during the initial development of ALL, providing further evidence for the role of inherited variants in this disease.

"This study is a departure from many other cancer genomic projects, most of which focus on somatic, or cancer, DNA," Yang said. "Adding the germline component provides a unique angle and opportunity for us to understand cancer biology."

Understanding **vulnerabilities** in ALL

Researchers studying how gene regulation can drive ALL are also investigating the role of methylation patterns. DNA methylation – the addition of a methyl group to a DNA molecule – is a necessary process that regulates gene expression. The process is stable and maintained in healthy cells but goes awry in cancer cells.

Researchers, led by Charles Mullighan, MBBS(Hons), MSc, MD, Comprehensive Cancer Center deputy director, performed whole-methylome sequencing across 82 ALL samples representing different subtypes such as T-ALL and B-ALL, as well as healthy hematopoietic cells (blood stem cells). In a paper published in *Nature Cancer*, Mullighan and colleagues demonstrated that a highly methylated genome is typical in ALL. As researchers look for vulnerabilities in ALL against which to develop new treatments, their work paves a path toward more focused examinations of the cancer methylome and underlying regulation.

Mullighan and his team also led the research, published in *Blood Cancer Discovery*, that established the role of ZNF384 as a fusion oncoprotein in ALL development, and demostrated its sensitivity to *FLT3* inhibition. Because *FLT3* is mainly expressed in hematopoietic stem cells and early progenitors, it plays a role in early blood cell formation, a stage in which abnormal expression can have oncogenic effects. Complementary work by Yang and Daniel Savic, PhD, Department of Pharmacy and Pharmaceutical Sciences, identified molecular mechanisms underlying *FLT3* activation in *ZNF384*-rearranged ALL. They published this work in *Nature Communications.* To understand the mechanisms driving this oncogene activation, the team examined the genomes of 1,988 patients with B-ALL and found that *FLT3* transcription can be turned on by the ZNF384 fusion protein in ALL.

The researchers also evaluated the therapeutic potential of gilteritinib, an FLT3 inhibitor. In patient-derived xenograft models of *ZNF384*-rearranged ALL, the drug exhibited significant anticancer efficacy. Yet in vitro models with downregulation of *ZNF384* and associated blunting of *FLT3* activation in ALL cells show decreased sensitivity to the drug.

Both studies suggest that *FLT3* and its regulatory mechanisms represent a critical vulnerability in ALL and provide another area of study for genomics-guided targeted therapy.

Identification of predisposing variants in Hodgkin lymphoma

Beyond leukemia, coding and non-coding genetic variants remain an area of discovery. For example, in Hodgkin lymphoma, large population studies demonstrate the potential for cancer to appear throughout families. Despite Hodgkin lymphoma accounting for 40%-50% of all lymph node cancers in children and adolescents, the roots of genetic susceptibility in this cancer are poorly understood.

Investigators at St. Jude, led by Yang and Jamie Flerlage, MD, Department of Oncology, performed whole-genome sequencing on 36 family pedigrees (234 individuals total) that feature two or more first-degree relatives with Hodgkin lymphoma. The results, published in *Blood*, showed 33 coding and 11 noncoding risk variants in 28 of the family pedigrees. Some variants were associated with known predisposing loci, such as *KDR* and *KLHDC8B*, or with novel predisposing loci, such as *PAX5*, *GATA3, IRF7, EEF2KMT,* and *POLR1E*. The study is the largest cohort of familial Hodgkin lymphoma assessed with whole-genome sequencing to date. Identifying novel genetic variants can help inform germline testing panels for at-risk family members, thereby improving care and outcomes for those genetically predisposed to Hodgkin lymphoma.

We took on this study because understanding what is causing cancer in these families will help us to better counsel people about their chances of passing on genetic risk to their offspring, as well as help us identify novel targets that might potentially be used to create new treatments.

Jamie Flerlage, MD
Oncology

"We've never been able to tell these families anything, other than it's just bad luck, because nobody knew why more than one family member would develop Hodgkin lymphoma," said Flerlage. "We took on this study because understanding what is causing cancer in these families will help us to better counsel people about their chances of passing on genetic risk to their offspring, as well as help us identify novel targets that might potentially be used to create new treatments."

Genetic drivers in brain tumors

Investigations to determine the causes of cancer continue to yield novel insights into the role of genomic factors, especially in pediatric brain tumors. For aggressive brain malignancies that can be resistant to treatment, such as high-grade glioma, understanding the cause of the disease is crucial for identifying molecular vulnerabilities that may spark new research areas or potential targets for therapy.

In the first study of its kind, co-authors Jason Chiang, MD, PhD, Department of Pathology, and Jinghui Zhang, PhD, Department of Computational Biology chair, examined the role of the long interspersed element-1 (LINE-1) transposon in the genesis of infant high-grade glioma. The study, published in *Acta Neuropathologica*, demonstrated how a transposon, a piece of DNA that "jumps" around in the genome, can donate its promoter to drive oncogene expression. LINE-1 is the only active transposon in humans and has been shown to disrupt gene function. The researchers revealed the mechanism underlying this transposon directly activates the transcription of oncogene *FOXR2*, which in turn drives cancer. The discovery provides new avenues for investigating genomic drivers in the development of brain tumors.

The potential of **genomics-guided targeted therapies**

Understanding the mechanisms that underlie the origin and proliferation of, and predisposition to, disease enables researchers to guide the development of targeted therapies for specific genetic vulnerabilities.

Adam Durbin, MD, PhD, Department of Oncology, guided his team's work to develop a novel proteolysis-targeting chimera (PROTAC) compound to attack genetic vulnerabilities in high-risk neuroblastoma. This rare pediatric solid tumor begins in peripheral nerve cells, such as those in the adrenal gland. The results of this study were published in *Cancer Discovery.* PROTACs work by using compounds to target proteins of interest and degrade them, thereby disrupting disease progression.

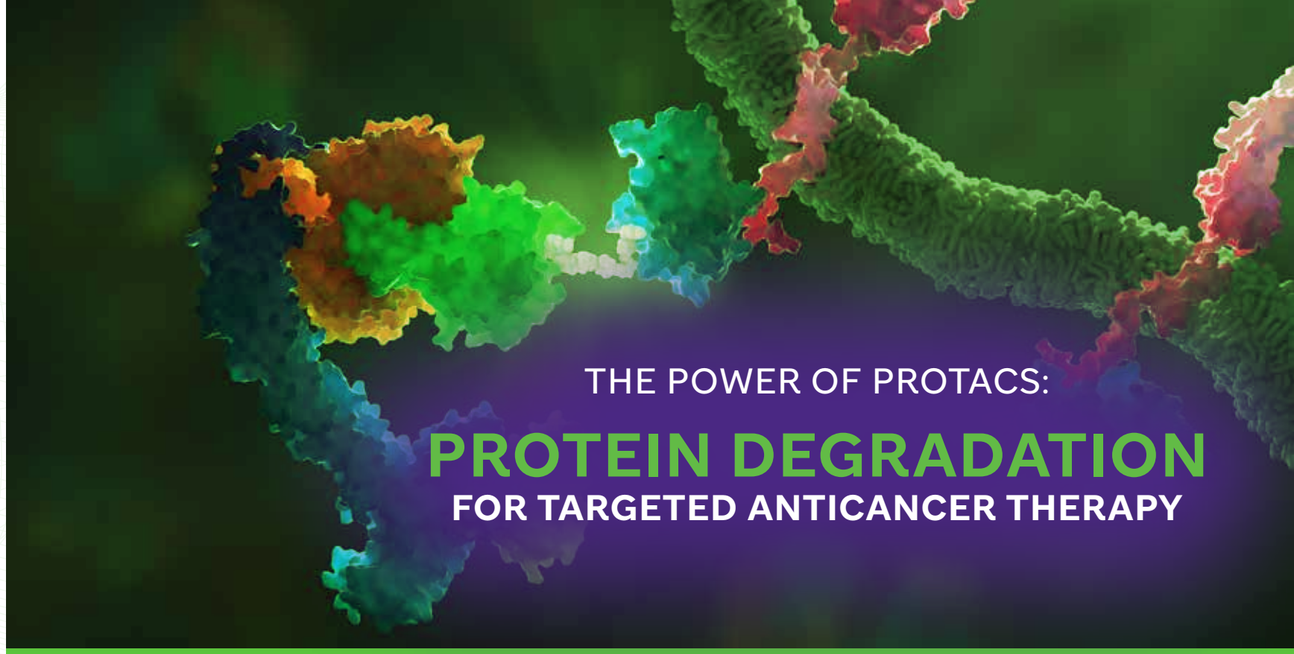
Building on knowledge previously developed by Durbin, the team identified that neuroblastoma depends on EP300, an enzymatic protein that controls oncogenic transcription in neuroblastoma by binding the transcription factor TFAP2β. To alter oncogenic transcription in neuroblastoma, the team developed a PROTAC compound to target and disrupt EP300. The compound, JQAD1, causes the loss of H3K27ac (a marker for gene enhancers that control gene expression) in neuroblastoma cells and prompts rapid neuroblastoma cell death with limited toxicity to other tissues.

"We saw that when we treated neuroblastoma cells with this molecule, EP300 was degraded, which caused loss of all the transcription factors we believe drive neuroblastoma," said Durbin. "The exciting part is that we've also found that EP300 is a sensitivity in nearly one-third of cancers. So, this PROTAC compound that can effectively target and disrupt EP300 has great potential not only in neuroblastoma but in other diseases as well."

Charting a new course toward **novel therapeutics**

Despite decades of research on cancer genomics, scientists have much to discover about the different factors and processes that fuel these diseases — especially in children. Gene regulation represents the next frontier in the search for novel targets and new therapies; St. Jude researchers constantly reveal more about how the machinery that governs gene expression can mutate and give rise to cancer.

Whether inherited or acquired genetic variation, the consequent perturbation in gene regulation can profoundly affect disease across cancers, from ALL and Hodgkin lymphoma to brain tumors and solid tumors. Findings from the laboratories at St. Jude are advancing the study of the genomic landscape across diseases to yield insights into vulnerabilities that researchers can use to create the next generation of therapeutics for childhood cancer.



THE POWER OF PROTACS: **PROTEIN DEGRADATION** FOR TARGETED ANTICANCER THERAPY

Is it better to block or destroy disease-causing proteins to keep disease from progressing? For cancer therapeutics, the ability to block disease-related proteins by using small-molecule inhibitors led to a new era of targeted therapeutics in which clinicians used inhibitors to hinder disease progression.

Small-molecule inhibitors, such as the chemotherapy drug dasatinib, can have a transient effect and lose efficacy as cancer cells mutate to resist the drug. Additionally, some proteins are difficult to drug or are simply undruggable. These limitations make small-molecule inhibitors ineffective at blocking cancer-driving proteins, but what if treatments could destroy target proteins instead of just inhibiting them?

Proteolysis-targeting chimeras (PROTACs) can aid in designing drugs that degrade, instead of block, disease-causing proteins. The PROTAC approach uses bifunctional molecules to hijack the ubiquitin–proteosome system (UPS), which targets and degrades proteins of interest. Cells maintain normal processes by creating proteins to perform specific tasks and recycling them when they are no longer needed. The UPS functions as the cell's garbage disposal system.

In the UPS, E3 ubiquitin ligases mark proteins that must be disposed of with a ubiquitin tag, as the system will degrade only the tagged protein. To leverage this process for cancer therapeutics, a PROTAC molecule is built with a ligand for the target protein and an E3-binding entity that connects via a linker. This draws the protein degradation machinery to the target, thus creating a highly effective, target-specific cancer treatment.

For aggressive malignancies with difficult targets, such as T-cell acute lymphoblastic leukemia (T-ALL), this innovative strategy holds therapeutic promise. T-ALL activates the lymphocyte-specific protein tyrosine kinase (LCK) and is responsive to LCK inhibitor therapy. However, current therapies are limited in their long-term efficacy, and LCK inhibition can reverse when small-molecule inhibitors are utilized.

Researchers at St. Jude, led by Zoran Rankovic, PhD, Department of Chemical Biology and Therapeutics, and Jun J. Yang, PhD, Department of Pharmacy and Pharmaceutical Sciences and Department of Oncology, developed a novel compound, SJ11646, to degrade LCK. They published their work to create a PROTAC for T-ALL in *Science Translational Medicine.*

To create the compound SJ11646, the investigators built LCK degraders by using dasatinib as the LCK ligand and phenyl-glutarimide, an improved E3-binding entity that Rankovic and colleagues previously developed. *In vivo* pharmacokinetic and pharmacodynamic profiling in patient-derived xenograft models of T-ALL showed that SJ11646 was significantly more effective in extending leukemia-free survival than was dasatinib alone.

By combining expertise in biology and chemistry and creating an LCK-targeted PROTAC, St. Jude researchers demonstrated the promise of protein degradation as a therapeutic approach to T-ALL. Because SJ11646 holds a high binding affinity for 51 other kinases, the PROTAC compound also provides a foundation for exploring degradation-based therapeutics for other cancers.

Scientific Highlights

Every year the breadth and depth of the research enterprise at St. Jude expands. The Scientific Highlights capture a snapshot of the diversity of fields, departments, and researchers charting new discoveries at St. Jude. These high-impact publications provide a window into the scientific accomplishments of St. Jude investigators in 2022.

SAFER Ukraine: a blueprint for global health crisis response

When Russian forces invaded Ukraine in February 2022, disruptions of civilian life (particularly of the health care system) created a dire situation for Ukrainian children with cancer or blood disorders. In response, the St. Jude Global initiative, together with many international partners, formed Supporting Action for Emergency Response in Ukraine (SAFER Ukraine). An account of SAFER Ukraine was published in *The Lancet Haematology* to share the blueprint for this unprecedented global response to an emerging health crisis.

Supporting Action for Emergency Response in Ukraine (SAFER Ukraine) facilitated the safe evacuation of more than 900 patients and families to re-establish medical care abroad after the outbreak of war in Ukraine in early 2022.

SAFER Ukraine partners include non-governmental organizations (NGOs) or foundations, such as Fundacja Herosi and Tabletochki Charity Foundation, the Polish Society of Pediatric Oncology and Hematology (PSPOH), the International Society for Pediatric Oncology–Europe, Childhood Cancer International–Europe, and government agencies, plus many other volunteers and contributors. The effort facilitated the safe evacuation of more than 900 patients* and families to re-establish medical care abroad.

"SAFER Ukraine demonstrates the importance of collaborative networks in global health, with participation from individuals, institutions, and governments, to facilitate both rapid responses to emergencies and ongoing capacity building to improve patient care and outcomes," said first and co-corresponding author Asya Agulnik, MD, MPH, Department of Global Pediatric Medicine and Division of Critical Care Medicine.

The SAFER Ukraine effort provides a proof of concept for global health that can be leveraged in future international emergency responses. Several unique and notable characteristics of SAFER Ukraine were determined to be important in the effort's success. These include the patient population, the geopolitical context, and well-established pre-war collaborations.

Asya Agulnik, MD, MPH, meeting with colleagues in Poland during the SAFER Ukraine effort.

For example, childhood cancer treatment can be effective but requires precise timing. Patients with interrupted care can benefit from a rapid evacuation and relocation to a hospital, thus providing continuity of care. Rapid resumption of treatment offers a substantial survival benefit. The war also galvanized support for Ukraine, with the European Union extending immediate protection and legal status to Ukrainian refugees. That status created the legal and financial framework that ultimately made it possible to refer patients for care throughout Europe. Additionally, St. Jude Global already had partnerships in the region.

The rapid repurposing of existing collaborative networks was key to the effort's success.

"We hope that lessons learned from SAFER Ukraine can guide future emergency responses to support medically complex, high-risk patients during man-made and natural disasters," Agulnik said. "This effort truly highlighted the importance of our pre-war collaborations. Without the existing and ongoing work with our partners through the St. Jude Global initiative and the St. Jude Global Alliance, this wouldn't have been possible. The supportive geopolitical environment in Europe and the unique patient population of children with cancer were also important factors in the success of SAFER Ukraine."

* At the time of publication

Innovative method clarifies ambiguous MRI findings

Often, after radiation therapy or surgery for a high-grade brain tumor, a radiologist may come across ambiguous findings on magnetic resonance imaging (MRI), that could be due to treatment-(surgery or radiation therapy) related changes or tumor progression. Accurate differentiation between the two is crucial as these situations necessitate different treatments.

At St. Jude, members of the Department of Diagnostic Imaging have been investigating an innovative way to clarify ambiguous MRI findings using a novel positron emission tomography (PET) scan approach that uses [^{11}C] methionine (MET).

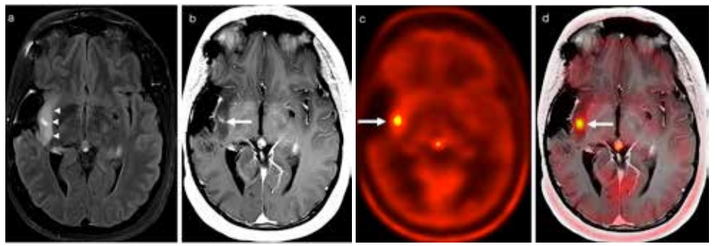


Image A: A signal from an anaplastic astrocytoma remained stable for 8 years after surgery. Image B: The tumor developed a small focus of enhancement that was not conclusive using MRI. Image C/D: However, ^{11}C-Methionine position emission tomography showed a clear focus that indicated tumor progression.

Methionine is a naturally occurring amino acid necessary for protein synthesis. As high-grade brain tumors grow rapidly, the formation of new proteins becomes essential to support amplified cellular growth. PET imaging with MET gives an overall estimate of amino acid uptake in a given tissue. Although researchers have explored MET and other amino acid PET tracers over the last few decades in evaluations of high-grade brain tumors, primarily in adults, they have done little to show their usefulness in children.

Scientists at St. Jude are changing that, recently publishing a study in the *Journal of Nuclear Medicine* on using [^{11}C] methionine PET (MET-PET) to identify recurrent pediatric high-grade gliomas (a type of high-grade brain tumor). Using MET-PET during follow-up visits, the researchers evaluated 27 lesions in 26 patients with new or worsening MRI abnormalities for whom tumor recurrence was a concern. They conducted quantitative and qualitative assessments of both MET-PET and MRI data to predict tumor recurrence.

Results showed that MET-PET has slightly higher sensitivity and accuracy for correctly predicting tumor recurrence when compared with MRI. Quantitative MET-PET can also predict overall survival. These findings suggest that MET-PET can be helpful for further evaluating MRI changes during surveillance of previously treated pediatric high-grade gliomas.

“Differentiating true tumor progression from pseudo-progression has been a challenge in neuro-oncology,” said corresponding author Asim Bag, MD, Department of Diagnostic Imaging. “Results of our study address that challenge.”

MET-PET is an excellent PET tracer for evaluating brain tumors in comparison to the more commonly used PET tracer, [^{18}F]-2-fluoro-2-deoxy-D-glucose, or [^{18}F]FDG, in oncologic imaging. This is because heavily glucose-dependent normal brain tissue accumulates a high amount of [^{18}F]FDG. Compared to[^{18}F] FDG, MET accumulation in healthy brain tissue is very low, but it does accumulate in tumor tissue, making it much easier to differentiate tumor tissue from nontumor tissue when using [^{11}C]MET.

“Imaging a brain with FDG is like looking for stars when the sun is shining,” said senior author Barry Shulkin, MD, Department of Diagnostic Imaging. “The stars are there, but we just can’t see them. Imaging with MET takes out the sun, and we can see them.”

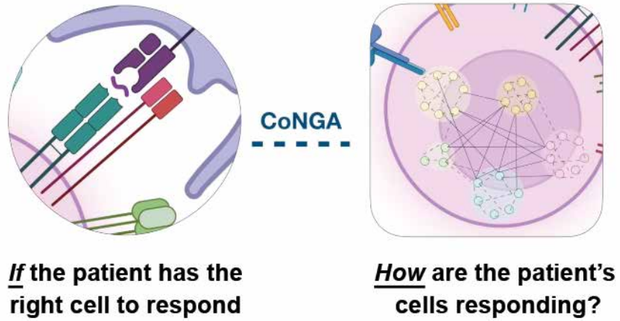
Since the MET tracer is labeled with radioactive carbon-11, which has a half-life of only 20 minutes, researchers can perform MET-PET studies only in hospitals with a nearby or onsite cyclotron and radiochemistry facility for MET preparation. For the benefit of St. Jude patients, the Department of Diagnostic Imaging installed such a facility, the Molecular Imaging Core, in 2007.

CoNGA algorithm improves T-cell analysis

If you have two different types of data and want to consider them at the same time, how do you do that efficiently? Scientists at St. Jude developed a new method for studying T cells called clonotype neighbor graph analysis (CoNGA), which leverages two ways of analyzing T cells: gene expression analysis and T-cell receptor (TCR) sequence analysis. Although methods already existed for analyzing gene expression, scientists lacked tools for systematically analyzing gene expression and TCR data simultaneously to find patterns that link functional potential, identifiable through gene expression data, with T-cell identification and specificity, identifiable through TCR sequence information.

The TCR is the part of the T cell that is used to visualize antigens, the molecules that the immune system recognizes as being out of place, for example, from a virus or tumor. Every T cell has a unique receptor that it uses to see and respond to its antigen. T cells recognizing the same antigens often use similar sets of TCR sequences.

Using single-cell RNA sequencing, scientists led by Paul Thomas, PhD, Department of Immunology, measured the gene expression and determined the receptor sequences for thousands of T cells simultaneously by using CoNGA. As reported in *Nature Biotechnology*, CoNGA allows scientists to quantify TCR information and groups cells with similar sequence features into “neighborhoods” of cells. For gene expression, they group cells near each other with similar profiles and put cells far away from dissimilar ones. Based on these clusters, the researchers can assign each cell its closest neighbors in either TCR or gene expression space.



CoNGA is an algorithm developed at St. Jude for simultaneously analyzing gene expression and T-cell receptor sequence. It enables researchers to identify groups of cells with shared features to draw conclusions about how cells may be related and how they function.

“Imagine that I’m a cell on a map,” Thomas explains. “If I’m a cell in Hawaii, my nearest neighbor might be in California because there are no other cells around me. But if I’m a cell in California, there’s no way that my nearest neighbor is in Hawaii. That Hawaiian cell isn’t going to be part of my neighborhood.”

By looking at cells in this way, the researchers can identify groups of cells that share features of their TCRs and their gene expression. This enables Thomas’ team to draw conclusions about how the cells might be related and how they function. They can also look for specific features to see whether a particular neighborhood of cells has high expression of a certain gene and compare that expression to other neighborhoods.

“We’ve known that T-cell receptors with similar specificities tend to reside in the same neighborhood – for example, the T-cell receptors that respond to a particular flu antigen,” said first author Stefan Schattgen, PhD, Department of Immunology. “However, through CoNGA, we’ve found that they’re also close to each other in gene expression. It makes sense that the same specificity would share features in their gene expression programs since they’re called on to do the same thing. But what was unexpected is how well these patterns are conserved across different people despite vast differences in their immune experiences during their lifetimes.”

CoNGA has already identified novel types of T cells. Still, as datasets continue to become larger and more complicated, it will help researchers learn about the interplay between T-cell specificity and function across different disease states, CoNGA is not limited to just T cells either. Scientists have recently added support for B-cell analysis, which may aid in identifying which cells are making antibodies against the same antigens. CoNGA is open source and works with other standard tools for analyzing these data types, so researchers worldwide can easily implement it.

EGFR inhibitors for preventing **rhabdomyosarcoma recurrence**

Rhabdomyosarcoma is the most common type of soft tissue sarcoma in children. Unfortunately, this disease has a high rate of recurrence, driven by cancer cells that persist despite aggressive therapy. With recurrence, outcomes are poor, and treatment options are limited. Therefore, it is crucial to understand why treatment fails so often.

Scientists at St. Jude studied the population of sarcoma cells that persists after therapy. They found that primary tumor cells exist in multiple developmental states, but recurrent tumor cells are enriched in cells that mirror an early developmental state. Cells in this state may respond to a type of targeted therapy.

The work presents a strategy for developing chemotherapy regimens that will, from the outset, treat tumor cells in all developmental states, including those that would otherwise lead to recurrence. This approach serves as a model for understanding tumor heterogeneity and may also apply to other pediatric cancers.

In the study published in *Developmental Cell*, the researchers used newly available techniques, such as single-nucleus RNA sequencing and epigenetic profiling, on matched patient samples and orthotopic patient-derived xenografts that are available from the St. Jude Childhood Solid Tumor Network. They found that these patient-derived models capture the biology and complexity of the human tumor more accurately than do other existing models.

“This project is rooted in the Pediatric Cancer Genome Project, which showed us that these populations of cells that survive therapy drive recurrence. In addition, working with our clinical colleagues revealed that understanding and being able to prevent recurrence is a major unmet need for this cancer,” said corresponding author Michael Dyer, PhD, Department of Developmental Neurobiology chair and co-leader of the Developmental Biology and Solid Tumor Program.

Embryonic cells express certain proteins and other factors that guide each cell toward an identity, such as a muscle cell. The researchers found that the population of cells driving the recurrence of rhabdomyosarcoma had features that mirrored an early stage of muscle development. Chemotherapy can eliminate most of the rhabdomyosarcoma cells in a patient’s tumor, but the cells with characteristics of early development persist.

“As a developmental biologist, I was impressed with the degree to which the tumor cells progress through the normal stages of muscle development,” Dyer said. “In fact, those normal developmental programs are contributing to rhabdomyosarcoma recurrence. The most immature cells survive treatment and then become re-activated to progress through the muscle development program and re-establish the tumor after treatment. Our goal is to kill all cells in the tumor with a particular focus on the rare cell population that seeds recurrence.”

The team further found that this population of cells depends on epidermal growth factor receptor (EGFR) signaling and is sensitive to EGFR inhibitors. EGFR inhibitors are a targeted therapy used to treat cancers with mutations in the *EGFR* gene, such as lung cancer in adults.

The work shows the importance of therapeutic strategies that treat the entirety of the tumor. Targeting the different developmental stages of the tumor cells is an approach that may apply to other types of pediatric cancer besides rhabdomyosarcoma.

“We were able to carefully pinpoint all of the different levels of development present among these cancer cells, going back to cells that recapitulate the earliest stages of development, and those are the cells that seem to survive treatment and can regrow the tumor,” said first author Anand Patel, MD, PhD, Department of Oncology. “We have a proof of concept that if you target those rare cells that persist with an EGFR inhibitor and combine that with chemotherapy, you get a much better outcome because you’re treating the entire tumor. This reflects a different way of thinking about therapy that isn’t focused just on the initial response.”

Scientists in the Developmental Neurobiology lab of Michael Dyer, PhD, published a study on rhabdomyosarcoma recurrence.

Charting the genomic landscape of **ALL fuels precision medicine**

St. Jude scientists have created a roadmap of the genetic mutations present in the most common childhood cancer, acute lymphoblastic leukemia (ALL). The study, published in *Nature Genetics*, is the first to supply a comprehensive view of the genomics of all subtypes of ALL.

As a result of the work of scientists and clinicians at institutions such as St. Jude, most children with ALL will survive. However, a fraction of those patients does not respond well to therapy. If researchers understand the impact of genetic differences on cancer outcomes, then physicians can adapt their treatment regimens to the specific mutations present.

For personalized therapies to take shape in the clinic, scientists need to map the different mutations that drive the development of leukemia across the landscape of diverse disease subtypes.

“In this study, we comprehensively defined the number and type of recurrently altered genes found in childhood ALL,” said co-corresponding author Charles Mullighan, MBBS(Hons), MSc, MD, Comprehensive Cancer Center deputy director.

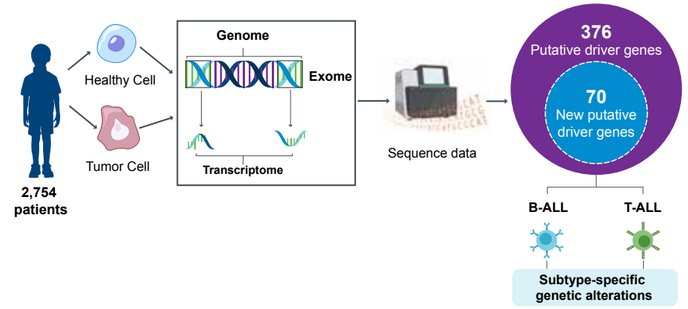
The research was unique because it included 2,754 pediatric ALL patient samples, the largest such cohort ever published. As a comparison, earlier studies have typically studied hundreds of samples or fewer. St. Jude investigators collaborated with the Children’s Oncology Group to collect samples over more than a decade. The large number of patient samples enabled the scientists to find novel disease drivers.

“The new drivers included a type of protein modification, which was really exciting because we have never anticipated that this group of proteins will be involved in disease initiation for leukemia,” said co-corresponding author Jinghui Zhang, PhD, Department of Computational Biology chair.

Some unexpected potential driver mutations are in genes involved with cellular processes, such as ubiquitination, SUMOylation, or noncoding *cis*-regulatory regions. Broadly, the findings implicate a previously unknown pathway in the development of ALL.

variation in the expression of genes, such as *CEBPA*, *FLT3,* and *NFATC4,* that stratified the outcomes of these cases. This observation may have clinical implications, as new FLT3 inhibitors are in clinical trials.

The researchers’ work revealed the sequence of mutation events in many ALL cases, with potential implications for treatment. In hyperdiploid B-cell ALL (B-ALL), cancer cells have at least five more



Scientists analyzed cells from pediatric patients with ALL and discovered 376 putative driver genes – including 70 new genes – that, when altered, may lead to the development of ALL. Many of these genetic alterations are associated with specific ALL subtypes.

Of these recurrent mutations, almost all affected protein modification pathways. These alterations involved multiple genes, and sequence and structural variants. The gene and type of alterations were frequently mutually exclusive and showed specific associations with ALL subtypes. Collectively, these observations suggest that the alterations have important roles in the pathogenesis of subtype-specific ALL.

Overall, the group identified 376 significantly mutated genes that potentially drive cancer development. Seventy of the genes have never been implicated in ALL.

The researchers also found differences in the mutations present within subtypes of ALL, which may affect clinical care. For example, subtypes with *KMT2A* (MLL) and *DUX4* rearrangements showed chromosomes than normal. A long-standing question has been the relative timing of chromosomal gains and other mutations in hyperdiploid ALL development. The researchers traced the order of events leading to hyperdiploid ALL by using computational modeling of the sequence of mutations and chromosomal gain data. This sequence showed that in most hyperdiploid B-ALL cases, the chromosomal gains appear to happen early and all at once—a chromosomal “big bang.” Then, the precancerous cells gain more mutations, partially due to ultraviolet (UV) light-induced DNA damage.

“The study demonstrates the power of the data,” Zhang said. “If you don’t have a sufficient number of patient samples, you lack the statistical power to find drivers present at a low prevalence.”

T-cell exhaustion is influenced by a **young host microenvironment**

> *What we have shown is that the kinetics for driving the T cell to a dysfunctional state are much faster in a young individual, and the way it's set up is through this interaction in the context of a tumor microenvironment.*
>
> *- Benjamin Youngblood, PhD*
> *Department of Immunology*

Immunotherapies are treatments that harness the power of the immune system to tackle diseases such as cancer. Currently, these therapies work only for certain patients with certain diseases. Expanding the benefit of immunotherapy to additional patients requires a more detailed understanding of the immune system and the factors that can influence how the body responds to immunotherapies and disease.

T cells are immune cells that can be used to target diseased cells for clearance by the immune system. However, when T cells are chronically exposed to an antigen (the structure on the surface of a cell that indicates to the immune system that it is diseased), their ability to respond to that antigen can decrease over time. This "T-cell exhaustion" occurs through a series of epigenetic changes that reprogram T cells, leading to reduced functionality. Exhausted T cells are one of the major obstacles that limit the success of immunotherapies.

Differences in the immune systems of children and adults can affect these processes. Scientists at St. Jude studied the fundamental differences between young and old immune microenvironments to better understand their distinct adaptive immune responses to tumors. In a study published in *Science Immunology*, the researchers transferred tumor-specific CD8 T cells to young and adult mice and tracked their expansion and function in response to tumors.

Results showed that the CD8 T cells primed in the young hosts acquired different characteristics than did cells primed in adult hosts, including heightened expression of inhibitory receptors and their regulating transcription factors. Tumor-infiltrating T cells in tumors implanted in young mice rapidly developed a dysfunctional immune response compared to T cells in tumors implanted in older mice. This was also associated with changes in myeloid cells.

Myeloid cells survey the body and eliminate stressed and transformed cells. The researchers found that these myeloid cells capture and present tumor antigens better in the young hosts. This ability led to enhanced priming of the T cells and to their eventual exhaustion, once they infiltrated the tumors. The scientists also analyzed immune cells from pediatric solid tumors, showing a relationship between exhausted CD8+ T cells and the frequency of PD-L1–expressing cells, which are also involved in T-cell exhaustion.

"When we think about immunotherapy for children with cancer, we rely on an understanding primarily based on how the immune system works in adults," said corresponding author Benjamin Youngblood, PhD, Department of Immunology. "What we have shown is that the kinetics for driving the T cell to a dysfunctional state are much faster in a young individual, and the way it's set up is through this interaction in the context of a tumor microenvironment."

Clinical trials and other research demonstrate that in certain cases, particularly in solid tumors, the protective potential of immunotherapy can be limited in pediatric patients. Although there are many possible reasons for this, these findings suggest that the robust nature of the immune system in children plays a role. T cells driven to dysfunction by prolonged activity will quickly become nonresponsive, limiting the window during which immunotherapy could be effective. This research provides new insight into the mechanisms limiting the efficacy of T-cell–based immunotherapies in pediatric patients and is guiding the efforts of St. Jude researchers to translate these discoveries into sustained protective responses.

Findings highlight the role of protein solubility and charge in phase separation

Scientists led by Tanja Mittag, PhD, Department of Structural Biology, and Rohit Pappu, PhD, Washington University in St. Louis, have dissected the fundamental principles of biological phase separation. This process is a major mechanism governing how cells are organized and function.

Interactions among intrinsically disordered proteins or protein regions, notable for their lack of structure, can drive the formation of localized cellular structures containing specific proteins and cellular content. This can occur dynamically, with subcellular structures forming and dissipating, depending on the cellular state guided by interactions of these intrinsically disordered protein domains. When this process of biological phase separation goes awry, it can contribute to cellular dysfunction, leading to diseases that include neurologic disorders and cancer.

In a previous study, the researchers created a so-called stickers-and-spacers model for phase separation. Stickers are adhesive elements in the protein sequence; all other amino acid residues are considered spacers. The new findings, published in *Nature Chemistry*, reveal in greater depth how specific stickers and spacers drive phase separation and the role of protein solubility and charge in guiding the process.

"We now have a concept that tells us what the stickers and spacers are doing in every sequence context, instead of having to study each individual sequence separately," said Mittag. "For the spacers, we wanted to understand what charged residues specifically do because previous studies reported different effects, but also how the physicochemical features determined by the conserved composition of the intrinsically disordered proteins drive phase behavior."

The team found that how the stickers are arranged in the sequence and interspersed by spacers is essential for phase separation. Knowing the stickers' identity and the protein chain's dimension allowed the team to determine the strength of the sticker-sticker interactions and thus predict protein phase separation. This new work also investigated the differences between the specific types of sticker and spacer residues.

The researchers identified differences in the behaviors of the stickers tyrosine and phenylalanine, showing that tyrosine is a stronger sticker. They also found that arginine can be a sticker in certain contexts.

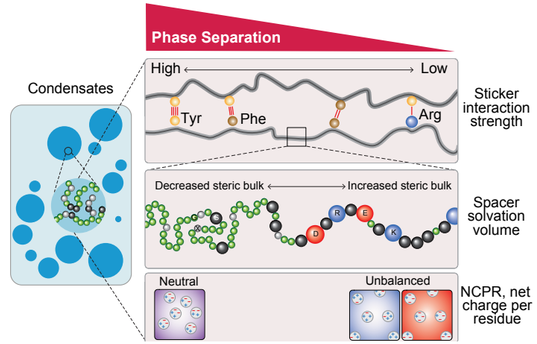
"The model is beautifully simple; there are stickers, and there are spacers," said co-first author Anne Bremer, PhD, Department of Structural Biology. "But there is hidden complexity encoded in the sequences. Not all spacers are equal, and they determine phase behavior by how much they like to interact with the solvent."

The researchers studied a type of intrinsically disordered protein region from RNA-binding proteins. This region tends to contain positively charged arginine residues. The scientists found that some negative charge aids phase separation, but too much reduces it because increased charge per residue increases solubility. These findings show that spacers contribute to phase behavior through their effects on solubility.

"When we originally tried to explain phase separation with this model, it wasn't clear why some proteins have stronger or weaker phase behavior," said co-first author Wade Borcherds, PhD, Department of Structural Biology, "but we found that the higher the overall net charge of a protein, whether net positive or net negative, the less readily it would phase separate."

This work also provides a conceptual basis for understanding modifications that happen after translation, so-called post-translational modifications, which regulate function in response to cell states. These include phosphorylation, which changes the net charge of a protein. Proteins are often aberrantly phosphorylated in disease processes. If multiple phosphorylation events occur across a protein sequence, this can change the driving force for phase separation.

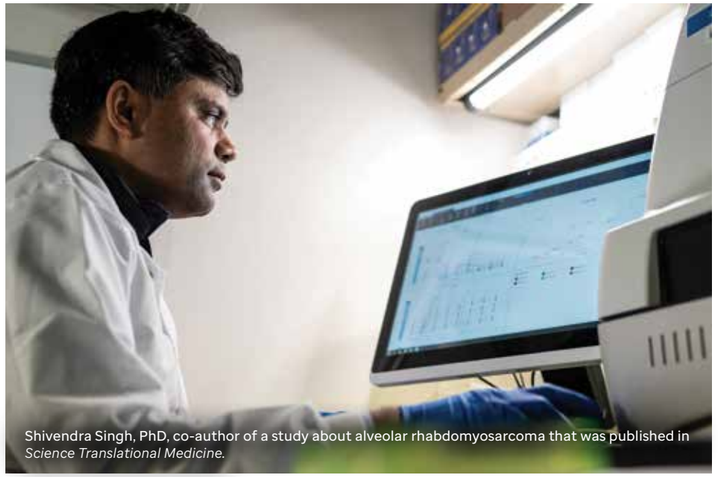
The research highlights the network fluid character of condensates and, therefore, has implications for future work delving into biochemical activity and disease processes associated with condensates.



Investigators have teased apart how three physical/molecular properties – sticker interaction strength, spacer solvation volume, and net charge per residue – drive phase separation, an important biological process for forming condensates.

A new therapeutic target for **alveolar rhabdomyosarcoma**

To find new treatment approaches for childhood cancer, scientists at St. Jude are focusing on disease biology and targeting a process long considered "undruggable" – transcription. Transcription factors are proteins involved in the process of "transcribing" or converting the information in DNA into RNA. Transcription is a highly regulated process, but normal regulation can be subverted in cancer cells. This dysregulation often leads cancer cells to become dependent on abnormally expressed or mutant transcription factors or other proteins.



Shivendra Singh, PhD, co-author of a study about alveolar rhabdomyosarcoma that was published in *Science Translational Medicine.*

The researchers, led by Jun Yang, MD, PhD, Department of Surgery, targeted transcription to reveal a new strategy for treating an aggressive form of rhabdomyosarcoma. Rhabdomyosarcoma is a type of cancer that arises in soft tissue, such as muscles. Soft tissue sarcomas comprise 7%-8% of all childhood cancers. There are two types of rhabdomyosarcoma: embryonal and alveolar. The alveolar type occurs in children of all ages and often affects the large muscles of the arms, legs, and trunk.

Gene fusions can drive alveolar rhabdomyosarcoma. When a piece of one gene abnormally attaches to another, a gene fusion occurs. Together, these genetic pieces encode a fusion oncoprotein as a chimeric transcription factor, a protein that plays a role in driving cancer.

Alveolar rhabdomyosarcoma that contains the *PAX3–FOXO1* fusion is more aggressive, has a higher rate of metastasis, and poorer prognosis than cancers without the fusion. This is because the *PAX3–FOXO1* fusion affects transcription factors essential for constructing a core regulatory circuit (CRC) network that drives rhabdomyosarcoma. CRC refers to a set of transcription factors that establish and maintain cell identity, in this case, cancer cell identity.

In a paper in *Science Translational Medicine*, Yang and his team demonstrated their new treatment strategy, which involves targeting a class of proteins called KDM4 histone demethylases that regulate chromatin structure and, thereby, gene expression. To study the *PAX3–FOXO1* fusion and tease out the roles of different network parts, researchers conducted in-depth analyses, including RNA-seq, CUT&TAG, and ATAC-seq. Through these efforts, they narrowed in on the protein KDM4B, revealing it to be an important node in the CRC of alveolar rhabdomyosarcoma driven by the fusion oncogene.

Historically, it has been challenging to develop treatments targeting transcription factors. However, their interaction with other proteins provides an opportunity to target their protein partners to disrupt their activity. By using genetic methods and a compound that inhibits KDM4B in the lab, the researchers could delay tumor growth substantially. Combining KDM4B inhibition with currently used chemotherapy regimens caused tumors to shrink in preclinical xenograft models of the disease.

"Rhabdomyosarcoma driven by this fusion is a dangerous disease that is very challenging to cure," said Yang. "It has few genetic mutations driving it, with limited treatment options for the fusion-positive version. By looking at a class of proteins that remove methylation marks from histones, we were able to identify a promising target that has been unappreciated until now. When combined with the standard of care, we saw a complete response in our models, which were often very resistant to chemotherapy alone."

Overturning dogma to renew a field of **hematopoietic stem cell research**

St. Jude scientists have changed the thinking on how hematopoietic stem cells (HSCs), the source of all blood cells, expand. Their study, published in *Nature Cell Biology*, challenges a long-standing assumption that these critical stem cells increase their number rapidly in the fetal liver before migrating to the bone marrow. Instead, the authors found that the cells increase only modestly before birth and rapidly expand their ranks in infant bone marrow.

"A better understanding of when and where stem cells expand might help us know how to expand them in a dish and create many more therapies with them," said corresponding author Shannon McKinney-Freeman, PhD, Department of Hematology. "Theoretically, this knowledge could improve bone marrow transplantation regimens and similar treatments."

Scientists have tried to figure out where HSCs expand for decades because of their therapeutic potential. Many emerging cellular therapies for diseases, ranging from cancer to anemia, would benefit from greatly increasing the number of HSCs, essentially creating higher doses for these treatments.

When HSCs divide, they can have one of two fates. Either they can head down a path toward differentiation to become specialized blood cells, such as red or white blood cells, or they can make more HSCs. HSCs maintain the potential to produce any type of blood cell, a property known as stemness.

Previous research found that HSCs must greatly expand their numbers during early development. Researchers in the HSC field believed this expansion occurred in the fetal liver because, during prior experiments, scientists found that the numbers of transplantable HSCs increased dramatically over time in the mouse fetal liver. Therefore, most follow-up research used fetal liver HSCs. However, this approach has failed to produce methods to meaningfully expand HSCs for clinical applications, such as bone marrow transplantation. Instead, the field has shifted from studying the developmental biology of HSCs to looking for small molecules that could trigger HSC expansion.

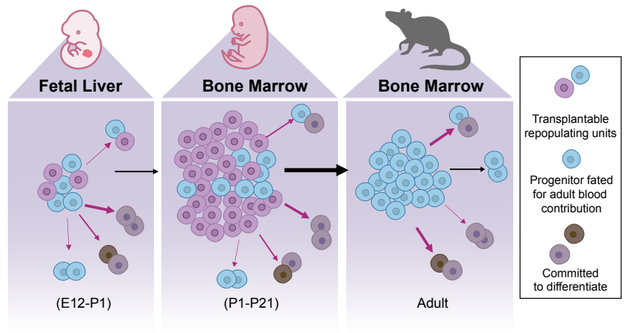
The study led by McKinney-Freeman may renew interest in looking at HSCs in early development. The group found that HSCs do not rapidly expand in the fetal liver. In fact, they only doubled, a much smaller increase than expected. Furthermore, when HSCs from the fetal liver divided, they differentiated into blood cells and did not maintain their stemness. When the scientists instead tracked HSCs in newborns, they found an explosion of HSCs in bone marrow.

"We showed the fetal liver is likely not the primary HSC expansion niche," McKinney-Freeman said. "That niche might instead be the early bone marrow."

The researchers made this discovery by using lineage tracing technology adapted to look at HSCs. They genetically modified mice so that their HSCs, and those HSCs' descendants, expressed one of four colors randomly. The scientists then used the number of cells and the different proportions of colors, to statistically analyze how much expansion had occurred. They followed this with an investigation of whether the cells were HSCs or differentiated blood cells. This system enabled the researchers to directly monitor cellular expansion and differentiation, avoiding the need for indirect inferences through more conventional transplant experiments. Although this study has the potential to overturn decades of dogma, it almost did not happen.

"What we've discovered here does have the potential to impact future translational efforts," McKinney-Freeman said. "We've made core observations that will change how people think about blood development and lead to a more intense study of a period of development that has been understudied."

"It's getting harder and harder to obtain external funding to support these basic science questions," she added. "Being at St. Jude gave us the freedom to pursue this type of fundamental basic science."



Researchers discovered that hematopoietic stem cells (HSCs) in the murine fetal liver are biased towards differentiation rather than self-renewal, disputing the current dogma. Instead, the murine neonatal bone marrow may be the primary HSC expansion niche.

Scientists test tool to measure health effects **in long-term survivors of childhood cancer**

Studies have shown that childhood cancer survivors can experience a variety of health effects later in life at higher rates than in individuals who never had cancer. St. Jude scientists tested a tool to measure how these physical, physiological, and behavioral effects can accumulate in childhood cancer survivors. The assessment provided evidence of accelerated aging-related deficits such as memory impairment and premature mortality.

"We were surprised to see that some survivors, even as young as 30 years old, can still experience advanced deficits," said Kevin Krull, PhD, Department of Psychology and Biobehavioral Sciences chair.

Krull led the study with postdoctoral fellow AnnaLynn Williams, PhD, who is now a faculty member at the University of Rochester. In the study, published in the *Journal of the National Cancer Institute*, the researchers used a type of analysis called a deficit accumulation index (DAI). The DAI combines clinical assessments and questionnaires and is used widely in various clinical aging measurement contexts, such as assessing patients with dementia. However, using the assessment tool in childhood cancer survivors was a novel context.

For the study, the researchers utilized the St. Jude Lifetime cohort study (SJLIFE), an unprecedented research study that brings long-term childhood cancer survivors back to St. Jude for regular health screenings throughout their adult lives. They applied the DAI to 4,000 former pediatric patients with cancer and more than 600 controls (community participants without a history of cancer) from the SJLIFE cohort. They focused their study on individuals in the 23- to 35-year age range who were 20 years postcancer diagnosis.

> *"Our paper is the first to use the DAI in childhood cancer survivors. Its flexible design made it possible for us to adapt it to this unique population."*
>
> *- Kevin Krull, PhD*
> *Department of Psychology and Biobehavioral Sciences chair*

"Our paper is the first to use the DAI in childhood cancer survivors," Krull said. "The DAI's flexible design made it possible for us to adapt it to this unique population. We'd like to take this index and further adapt it to use other measures that are easier to obtain by a general clinician so that it does not have to be done in a high-tech facility like St. Jude."

Once the assessment is administered, a DAI score is calculated from 44 aging-related items, including self-reported daily function, psychosocial symptoms, and existing health conditions. Items are weighted from 0 (if absent) to 1 (present and/or severe). The item rankings are summed and divided by the total number of items to yield a ratio, where a higher score correlates with a higher number of deficits.

One of the health effects that the study assessed was accelerated aging, in which the body exhibits biological characteristics more commonly seen in older individuals. In addition to finding that childhood cancer survivors can experience accelerated aging, the scientists found that survivors experienced different rates of deficit accumulation.

Among survivors, cranial and abdominal irradiation, treatment with alkylators or platinum drugs, and neurosurgery were associated with higher DAI scores and, therefore with higher levels of deficits. For all types of cancer studied, the researchers reported that no single chronic health condition could predict functional limitations; instead, the accumulation of deficits was more critical.

Once fully validated tools such as the DAI specifically for childhood cancer survivors will enable physicians to more readily identify survivors who may need additional treatment or monitoring to reduce or prevent the accumulation of health effects later in life.

Cardiac MRI can find "silent" heart problems **associated with sickle cell disease**

Scientists from St. Jude and Le Bonheur Children's Hospital showed that sickle cell disease (SCD) damages the hearts of young patients and that current standard-of-care treatments do not appear to prevent it, regardless of how early they begin. The study, published in *Blood*, challenges the belief that disease-modifying therapies, such as hydroxyurea, can protect against heart problems in patients if started earlier in life. The research also highlights the potential role of cardiac magnetic resonance imaging (MRI) in the diagnosis of heart damage, such as myocardial fibrosis, early to arm physicians and patients with that knowledge before it causes serious or irreversible damage.

"All organ systems get involved in sickle cell disease, and heart problems are quite common in patients with sickle cell disease," said co-first author Akshay Sharma, MBBS, Department of Bone Marrow Transplantation and Cellular Therapy. "We have been trying to figure out for many years, 'What can you do about it?' One of the easiest things to do is to treat these patients. People thought, 'If you can control their sickle cell disease, then maybe their heart problems will be prevented.'"

The study, co-led by Jane Hankins, MD, Department of Hematology and St. Jude Global Hematology Program director, found that fibrosis is prevalent in all patients with SCD, but starting therapy earlier in life is not protective. They also found that fibrosis starts very early in these patients.

"Myocardial fibrosis is mostly asymptomatic in these patients," Hankins said. "It's scary that it happens so early in life that we see school-age children and teenagers with this amount of fibrosis in the heart but no symptoms."

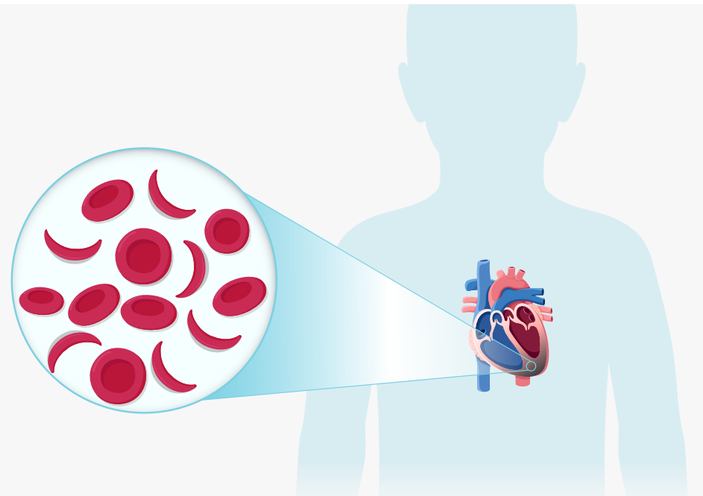
Even though fibrosis is asymptomatic for most of a patient's life, it can eventually lead to irreversible cardiac damage and early death.

"The number one cause of death in sickle cell disease in adulthood is heart disease," Hankins said. "They experience sudden death from their cumulative heart damage. We need a test sensitive enough to catch fibrotic changes early in life to know if they might progress and could become deadly in adulthood. That would allow us to monitor potential treatments."

The St. Jude group used cardiac MRI to evaluate heart muscle and function in patients with SCD. Cardiac MRI is the gold standard, as it is the only current modality that can do both evaluations, unlike echocardiograms, which are restricted to measuring function.

Although the study did not find a way to prevent fibrosis, it did show that cardiac MRI could be the right tool for detecting and measuring fibrosis, enabling early intervention and preventative measures.

The research was possible due to the close work of subspecialists from Le Bonheur and St. Jude. The study also builds on work by Winfred Wang, MD, Department of Hematology Emeritus member, who was the first to prove the safety and efficacy of using hydroxyurea in very young pediatric patients with SCD.



Heart problems, such as myocardial fibrosis, are drivers of early mortality in patients with sickle cell disease. By using cardiovascular magnetic resonance imaging (MRI), researchers discovered that early disease-modifying therapy does not protect pediatric patients from myocardial fibrosis.

Water networks are crucial for **ligand binding and discovery**

Marcus Fischer, PhD, and Timothy Stachowski, PhD, published research on water networks in protein–ligand interactions.

Three-dimensional protein structures are central to understanding protein function and developing drugs. Researchers typically derive these structures from samples cooled to cryogenic (frozen) temperatures, which makes them easier to study. Scientists at St. Jude created an algorithm to reveal when freezing proteins may create "artifacts" — errors that cause misleading structural features. The research also showcases the importance of water networks in protein–ligand interactions, and it challenges the common view that well-resolved cryogenic water positions can be assumed to be precise and accurate.

Ligands are molecules that bind to a receptor protein. When a ligand binds to a protein, the protein conformation (shape) can change, often initiating different cell activities. Protein–ligand binding and the resulting shape changes are crucial elements to consider during drug-development efforts.

Researchers often leverage available protein structures from the Protein Data Bank database. They capture around 95% of these structures cryogenically. Yet, drug discoverers rarely look closely at the raw experimental data, which is in the form of an electron density map. Interrogating these maps, rather than structural models, provides an unbiased approach to revealing new dynamic features and possible cryogenic artifacts.

Researchers led by Marcus Fischer, PhD, Department of Chemical Biology and Therapeutics and Department of Structural Biology, developed an algorithm called Flipper that looks at the raw experimental data in electron density maps. Flipper identifies map peaks (signals) that scientists often overlook. These peaks correspond to specific conformations of amino acid residues in the protein that researchers might not account for in the original structure. These residues respond to changes — for instance, in temperature — by changing the relative preference for one state over another. This "flip" in their electron density, moving between conformations, gave the algorithm its name.

In a study published in *Angewandte Chemie*, the researchers used this approach to identify residues in the important biomedical target Hsp90 that respond to temperature changes and to track the residues in a barcode-like system across the entire protein. This strategy enabled them to see how residues inside and outside the ligand-binding site respond to freezing or warming temperatures.

Armed with their new approach, the researchers conducted a systematic analysis that showed the importance of water networks. Water plays an active role in changes in protein conformation due to freezing. This is particularly true at protein–ligand-binding sites. Because the temperature and water network effects influence a vast number of structures, the findings may have a widespread impact on drug development.

"If you only look at the cryogenic data, the information being used for drug discovery has artifacts baked in that you wouldn't know were there," said Fischer. "We've developed a way to disentangle those artifacts. Using paired comparisons between cryogenic and room temperatures, you can pinpoint parts of the protein that are affected by temperature, which are often the sites we are trying to target with ligands."

"This is the first time that we have systematically shown the importance of temperature on water networks for modulating the ligand-binding interface, which is where biology happens," he added. "Water is often ignored in the drug-discovery process. Here, we've shown that in addition to having a profound effect on ligand binding, water also influences binding-site residues, capturing them in positions that differ depending on the temperature."

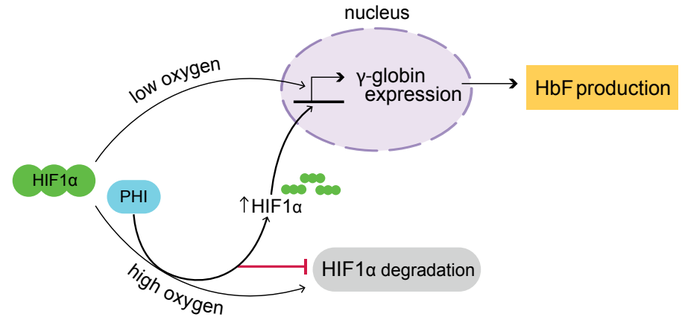
A new path to treating **sickle cell disease**

St. Jude scientists have discovered how a protein responsible for adapting to low-oxygen conditions (hypoxia) causes increased fetal hemoglobin (HbF) expression in adults. The findings, published in *Nature*, have implications for treating sickle cell disease and beta-thalassemia, serious blood disorders that affect millions of individuals.

Hemoglobin acts like a protein sponge that soaks up oxygen and enables red blood cells to ferry it throughout the body. Adult hemoglobin contains four protein subunits — two beta-globin and two alpha-globin subunits. Mutations in beta-globin cause sickle cell disease and beta-thalassemia. However, humans have another hemoglobin-subunit gene (gamma-globin), which is expressed instead of beta-globin during fetal development. Gamma-globin combines with alpha-globin to form fetal hemoglobin (HbF). Typically around the time of an infant's birth, their gamma-globin expression is turned off and beta-globin is turned on, resulting in a switch from HbF to adult hemoglobin.

Persistent HbF expression after birth can ameliorate symptoms of sickle cell disease and beta-thalassemia. Especially high levels of HbF can alleviate many symptoms of these diseases, despite the presence of defective beta-globin genes. Therefore, finding ways to increase HbF production could provide a novel way to treat these diseases.

In a study led by Mitchell Weiss, MD, PhD, St. Jude Department of Hematology chair, researchers showed that a key regulator of cellular adaptation to hypoxia termed "hypoxia-inducible factor 1α (HIF1α)" directly promotes transcription of the gamma-globin gene to enhance HbF production. HIF1α accumulates in many tissues in low-oxygen conditions and activates hundreds of genes, including the gene that encodes HbF in red blood cells.



Researchers showed that, under low-oxygen conditions, hypoxia-inducible factor 1α (HIF1α) enhances fetal hemoglobin (HbF) production in adults and that adding a proline hydroxylase inhibitor (PHI) causes HIF1α accumulation, leading to increased HbF production that reduces red blood cell sickling.

The researchers showed that a drug that activates part of the cellular hypoxia response also inhibits the sickling of red blood cells derived from adults with sickle cell disease. The drug, a proline hydroxylase inhibitor, caused HIF1α to accumulate and bind a DNA regulatory region near the gamma-globin gene. This accumulation activated transcription of the gene, inducing HbF production and inhibiting red blood cell sickling.

Proline hydroxylase inhibitors are currently in late-stage clinical development for treating anemia associated with chronic kidney disease. These drugs work by stabilizing HIF proteins to stimulate the production of erythropoietin, a hormone that drives red blood cell production.

"Our findings indicate that proline hydroxylase inhibitors might be useful for treating sickle cell disease or beta-thalassemia, where turning on HbF production has therapeutic benefits," Weiss said. "Approximately 20% of adult sickle cell disease patients develop kidney failure with related anemia. Proline hydroxylase inhibitors might serve a dual purpose in these individuals by stimulating the production of both erythropoietin and HbF."

The study establishes a direct connection between HIF1α-mediated hypoxia adaptation and HbF expression. This connection explains longstanding clinical observations that accelerated production of red blood cells induces HbF in response to hypoxia exposure or in some forms of anemia.

"Identification of gamma-globin as a HIF target gene supports the notion that HbF evolved as a protective mechanism against hypoxia," Weiss said. "Studies of hemoglobin over more than 50 years have established many general principles in biology and medicine. It is exciting and gratifying that investigations into hemoglobin and globin gene expression continue to produce new, clinically relevant discoveries."

Programs

Comprehensive Cancer Center

The National Cancer Institute (NCI) supports 71 Cancer Centers in the United States. The St. Jude Comprehensive Cancer Center, under the direction of Charles W. M. Roberts, MD, PhD, is the first and only NCI-designated Comprehensive Cancer Center solely focused on pediatric cancer. Charles G. Mullighan, MBBS(Hons), MSc, MD, serves as Deputy Director. Comprising five research programs and nine shared resources, the Comprehensive Cancer Center is designed to foster interdisciplinary basic and translational research, clinical trials, and population science focused on childhood cancer and survivorship.

SENIOR LEADERSHIP

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Deputy Director

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Heather M. Brandt, PhD
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CANCER BIOLOGY PROGRAM

Co-leaders: Douglas R. Green, PhD; Richard W. Kriwacki, PhD

The diverse nature of pediatric cancers, coupled with the complex molecular, genetic, and developmental contexts in which they form, necessitates a broad spectrum of basic research to build a strong foundation for translational studies. This program aims to explore and understand the fundamental biology of cancer. In working toward this goal, program members lead integrated and transdisciplinary efforts to define pathways related to cancer, identify driver mutations and genetic anomalies as new targets for translation into clinical trials, and advance understanding of the cancer microenvironment as a route to therapy.

HEMATOLOGICAL MALIGNANCIES PROGRAM

Co-leaders: Charles G. Mullighan, MBBS(Hons), MSc, MD; Ching-Hon Pui, MD

This program aims to improve the cure rates for childhood leukemias and lymphomas, while minimizing treatment-related adverse effects. This established, highly interactive, transdisciplinary program has a long track record of major discoveries in cancer biology. Translation of these findings into new diagnostic and treatment methods has changed the standard of care for children with hematological malignancies. The members of this program have used whole-genome approaches to identify novel subgroups of leukemias and the mutations that drive these diseases and translate these findings into innovative precision-medicine studies worldwide. The same genetic tools are being used to uncover genetic variations that dictate susceptibility to childhood cancers, as well as the response of patients to essential chemotherapies.

CANCER CONTROL & SURVIVORSHIP PROGRAM

Co-leaders: Gregory T. Armstrong, MD, MSCE; Kirsten K. Ness, PT, PhD, FAPTA

As treatments for childhood cancers improve, the number of long-term survivors of childhood cancer increases. This multidisciplinary program strives to improve the quality of life of individuals surviving childhood cancer by identifying and reducing treatment sequelae and promoting health-protective behaviors through innovative clinical, genetic, and observational research. Leading two of the world's largest pediatric survivorship research studies, the St. Jude Lifetime Cohort Study and the Childhood Cancer Survivor Study, program members are researching a wide range of health-related and quality-of-life outcomes.

NEUROBIOLOGY & BRAIN TUMOR PROGRAM

Co-leaders: Suzanne J. Baker, PhD; Amar J. Gajjar, MD

Brain tumors are the leading cause of cancer-related death in children. The Neurobiology & Brain Tumor Program aims to improve survival and reduce morbidity for children with brain tumors by developing effective, relatively nontoxic therapies through a better understanding of pathogenesis. By integrating the latest genomic and genetic technologies into studies of the developing nervous system, members of this program are efficiently translating laboratory findings into opportunities for new treatments. Significant advances include identifying the cells of origin of important pediatric brain tumors and modeling some of the most aggressive forms of these tumors, including high-grade gliomas. Close collaboration among the laboratory and clinical members of the program enables the rapid translation of high-throughput drug screens of mouse models to clinical trials.

DEVELOPMENTAL BIOLOGY & SOLID TUMOR PROGRAM

Co-leaders: Michael A. Dyer, PhD; Alberto S. Pappo, MD

Some of the most devastating and poorly understood cancers to affect children arise in the peripheral nervous system, muscles, and bones. Members of this program are working to understand how the normal development of these tissues goes awry, resulting in malignant diseases such as neuroblastoma, sarcomas, and retinoblastoma. Research in this program extends from basic mechanistic development studies to therapeutic studies in preclinical models and, ultimately, to testing new anticancer agents in clinical trials.

Shared Resources

- Bioinformatics and Biotechnology
- Biostatistics
- Cell and Tissue Imaging
- Center for In Vivo Imaging and Therapeutics
- Cytogenetics
- Flow Cytometry and Cell Sorting
- Pharmacokinetics
- Protein Production
- Transgenic/Gene Knockout

St. Jude Affliate Program

The St. Jude Affiliate Program has a two-fold mission:

- to extend St. Jude care and research to more children
- to encourage enrollment in St. Jude clinical research trials

Eight affiliate clinics in the Southeast and Midwest regions of the United States contribute 35% of the patients enrolled in St. Jude–led clinical trials. Providing equal access to care for pediatric patients with cancer regardless of their geographic location is a major goal of the Affiliate Program. The affiliate clinics support participant recruitment for clinical trials and the geographic extension of St. Jude clinical care. To ensure high-quality pediatric cancer care, the Affiliate Program conducts annual on-site clinical audits. Using a comprehensive approach that involves self-reflection, transparent sharing of quality metrics, local champions' development, and senior leaders' engagement, the Affiliate Program has improved quality across a broad geographic pediatric oncology network. Our work on re-inventing the clinical audit in a network of affiliated clinics was published this year in the *Journal of Pediatric Hematology & Oncology*.

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Jill Salo, MD
Sara Mednansky, MD
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Allison Taylor, NP

St. Jude Global

CAPACITY BUILDING

St. Jude Global continues to expand program offerings in areas identified as major gaps in patient care among Alliance members. The SJCARES platform has collected data from more than 150 institutions through the St. Jude Pediatric Oncology Facility Integrated Local Evaluation Tool (PrOFILE), and 137 institutions are contributing data on more than 5,000 patients to the Registry. The demand for PrOFILE has increased as our partners begin to understand the power of the tool to uncover learnings at an institutional and regional level and to assist with prioritization in improvements. Similarly, the Registry is seen as a viable solution for measuring and tracking the impact of interventions; it is considered one of the most reliable ways for the global health community to begin to understand the depth of disease burden in low-to middle-income countries (LMICs).

In parallel to the opportunities that emerged during 2022, world events challenged our partners in unexpected and dramatic ways. A significant example of this was the Russian invasion of Ukraine in February 2022, which led to the development of the SAFER Ukraine (Supporting Action for Emergency Responses in Ukraine) initiative. Based on the relationships established through the St. Jude Global Alliance and the understanding of regional capacity through tools like C5 and PrOFILE, the St. Jude Global team was able to convene a large-scale collaboration with dozens of foundations, medical institutions, and other international organizations to assist with the transition of families out of Ukraine and to find a safe location for the continuation of clinical care and treatment for more than 1,200 children. SAFER Ukraine demonstrates the importance of collaborative networks in global health as they enable a quick response to crises and continuation of capacity building to improve patient care and outcomes.

WORLD HEALTH ORGANIZATION COLLABORATIONS

Advances in two major initiatives strengthened the partnership between St. Jude and the World Health Organization (WHO) over the course of the year.

The Global Initiative for Childhood Cancer expanded to 65 countries. The year concluded with a CureAll Country Showcase that highlighted the work of 12 countries from all six WHO regions.

In partnership with the WHO, the Global Platform for Access to Childhood Cancer Medicines began its first development phase. Work on this initiative included establishing the governance and operational structures. The Platform has four active working groups focused on infrastructure, country selection, medicines (selection, formulation, and tender), and the last mile (the medication delivery process from the port of entry to the patient). Through the end of 2022, the Platform working groups identified a provisional list of pilot countries, selected the list of medicines for procurement, and designed two assessment tools for clinical capacity and procurement/supply management. Through the development process, the Platform has benefited from multisectoral input, with the guiding principle being co-creation with country-level stakeholders and technical experts.

Graduate School of Biomedical Sciences

Ana Vazquez-Pagan and Maria Smith

The St. Jude Children's Research Hospital Graduate School of Biomedical Sciences (Graduate School) is comprises three degree-granting programs, including a Doctor of Philosophy in Biomedical Sciences (PhD-BMS), training young scientists to advance our understanding of the molecular basis of disease and therapy; a Master of Science in Global Child Health (MSc-GCH), developing a global community of agents of change and leaders dedicated to improving children's health worldwide; and a Master of Science in Clinical Investigation (MSc-CI), training clinicians and medical professionals to perform clinical research and conduct clinical trials.

Approximately 185 faculty members and staff at St. Jude are now formal Graduate School faculty members involved in teaching, mentoring, serving on committees, and continuing to enhance the school's future. In 2022, 65 PhD-BMS students, 30 MSc-GCH students, and 12 MSc-CI students were actively enrolled.

In 2022, the Graduate School transitioned as the President and Dean, Dr. Stephen W. White, retired at the end of June. Dr. Stacey Schultz-Cherry, Associate Dean of Student Affairs, served as Senior Associate Dean while a national search was conducted for a new Dean. Dr. Steven Varga was later named Dean and took up the position in January 2023. In addition to his role as Dean, he will be a member of the Department of Infectious Diseases. Varga comes to St. Jude from the University of Iowa, where he served as Associate Dean of Academic Affairs and Graduate Student Development, a professor in the Department of Microbiology and Immunology and a professor in the Department of Pathology. Varga has more than 10 years of leadership experience in graduate education.

The MSc-GCH program has a mission to provide transformative education, facilitate collaborative opportunities, build capacities, and cultivate a diverse community of change agents to enhance equity, access, and quality of health care for children globally. The program completed its third academic year in 2022 and admitted another strong cohort of 10 health care professionals. The second cohort of students completed the coursework and successfully defended their theses. During the summer, students were welcomed back to campus for the first time since the start of the pandemic. A total of four cohorts (students and alumni) came to Memphis to participate in orientation, Summer Intersession, professional development/leadership training, Convocation, and Commencement. Nineteen students were able to participate in the Commencement ceremony and receive their diplomas.

Throughout the year, MSc-GCH students and alumni continued to lead their home institutions and health systems as agents of change and to collaborate through online classrooms, publications, and initiatives. Led by Associate Dean Dr. Shaloo Puri and Assistant Dean Julie Laveglia, the faculty and students of the MSc-GCH program worked collaboratively, making progress toward the program's vision of advancing child health globally.

The MSc-CI program officially launched in the 2021–22 academic year. The program leverages St. Jude faculty and staff expertise in designing, conducting, and supporting clinical research endeavors. It aims to develop a cadre of health care professionals who can transform human health through clinical investigation and evidence-based medical breakthroughs. Pat Flynn, MD, and Victor Santana, MD, two experienced clinical research principal investigators, lead the program as Associate Deans. The program is supported by an Assistant Dean, Sally Utech, who has extensive higher education administration experience. The second cohort of students matriculated in the Fall of 2022 and comprised eight students representing health care professionals and researchers employed as postdoctoral fellows, junior faculty, or medical staff.

During 2022, several new staff members were hired, including a recruiter, an event planner, an administrative coordinator, and an administrative specialist. Having awarded a sufficient number of initial doctorate and master's degrees, the Graduate School is now preparing to apply for accreditation through the Southern Association of Colleges and Schools Commission on Colleges (SACSCOC). Accreditation is an important process that ensures a school maintains the highest educational standards, as judged by peer institutions.

Finally, none of these activities and accomplishments would have been possible without the support of our Board of Trustees. The Graduate School relies heavily on the advice and insight that this group of dedicated volunteers provides.

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Yimei Li, PhD[1] • Statistical analysis of complex imaging data, survival data analysis & clinical trial design
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INSTRUCTORS
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Caitlin C. Zebley, MD, PhD • Cellular therapy and T-cell differentiation

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

CELL & MOLECULAR BIOLOGY

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Marcus Fischer, PhD[1] • Protein conformational landscapes for ligand discovery
Tudor Moldoveanu, PhD[3]

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Jason D. Vevea, PhD • Mechanisms of organelle quality control and organelle trafficking in neurons

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Dylan Graetz, MD • Global health, patient-centered care, solid tumors
Saman K. Hashmi, MD • Capacity building in global pediatric oncology
Daniel Moreira Ridsdale, MD • Global pediatric oncology, evidence-based education, pediatric CNS tumors
Sheena Mukkada, MD, MPH[1] • Global health, infection care & control
Teresa C. Santiago, MD[2] • Laboratory quality improvement & assessment

INSTRUCTORS
Michael J. McNeil, MD, MPH • Defining the state of palliative care for children with cancer in resource-constrained settings
Marta A. Salek, MD, MPH • Optimizing care and quality of life for children diagnosed with cancer on a global scale

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

HEMATOLOGY

CHAIR
Mitchell J. Weiss, MD, PhD[1]; Arthur Nienhuis Endowed Chair in Hematology • Blood development; red cell biology; novel therapeutic approaches to sickle cell disease and beta-thalassemia

MEMBERS
John D. Crispino, PhD, MBA[1]; The Wall Street Committee Endowed Chair • Mechanisms of leukemogenesis, benign & malignant blood disorders
Jane S. Hankins, MD, MS[1] • Sickle cell disease, transition to adult care & health outcomes during adolescence & young adulthood
Ellis J. Neufeld, MD, PhD; Executive Vice President; Clinical Director; John & Lorine Thrasher Endowed Chair in Pediatric Medicine • Patient-oriented studies in nonmalignant hematology
Clifford M. Takemoto, MD; Lemuel Diggs Endowed Chair in Sickle Cell Disease • Hemostasis & thrombosis, vascular malformations, bone marrow failure
Winfred C. Wang, MD[4]

ASSOCIATE MEMBERS
Wilson K. Clements, PhD[1] • Hematopoietic development & leukemia
Jeremie H. Estepp, MD[3]
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
Shengdar Q. Tsai, PhD[1] • Genome engineering technologies for therapeutics

ASSISTANT MEMBERS
Nidhi Bhatt, MD • Health communication & implementation science
Yong Cheng, PhD[1] • *Cis*-regulatory modules in hematopoiesis & its disorders
Rohith Jesudas, MBBS • Hemostasis, thrombosis, & immune cytopenias
Dirk Loeffler, PhD[1] • Cancer stem cells & clonal hematopoiesis
Parul Rai, MD • Cardiac injury in sickle cell disease
Marcin W. Wlodarski, MD, PhD[1] • Inherited bone marrow failure & MDS-predisposition syndromes

INSTRUCTORS
Senthil V. Bhoopalan, MBBS, PhD • Gene therapy & genome editing
Marta Derecka, PhD • Hematopoiesis & the bone marrow microenvironment
Yogindra Persaud, MD • Advancing the knowledge of sickle cell disease
Richa Sharma, MD • Telomere biology disorders, pediatric DNA-repair disorders

RESEARCH ASSOCIATES
Phillip A. Doerfler, PhD • Improving the safety of gene and cell therapy
Christophe Lechauve, PhD[3]

ADJUNCT MEMBERS
Francisca Fasipe, MD • Leukemia, lymphoma, hemoglobinopathies, and solid tumors
Marcela Popescu, MD • Clinical pediatric hematology

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[4]; Nobel Laureate
Paul G. Thomas, PhD[1] • Mechanisms of antiviral and antitumor immunity

ASSOCIATE MEMBERS
Yongqiang Feng, PhD[1] • Epigenetic & transcriptional basis of T-cell immunity
Maureen A. McGargill, PhD[1] • Regulation of the immune response
Benjamin A. Youngblood, PhD[1] • T-cell memory differentiation, exhaustion, & immunotherapy

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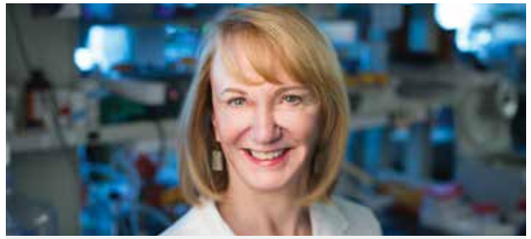


INFECTIOUS DISEASES

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

MEMBERS
Miguela A. Caniza, MD, MPH[1,2] • Global health, infection care, & control
Patricia M. Flynn, MD[1]; Deputy Clinical Director; Arthur Ashe Endowed Chair in Pediatric AIDS Research • HIV/AIDS in children & infections in children with cancer
Aditya H. Gaur, MD, MD, MBBS[1] • Clinical research in HIV prevention & treatment
Julia L. Hurwitz, PhD[1] • Pathogen/vaccine-induced immunity, nuclear hormones
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]

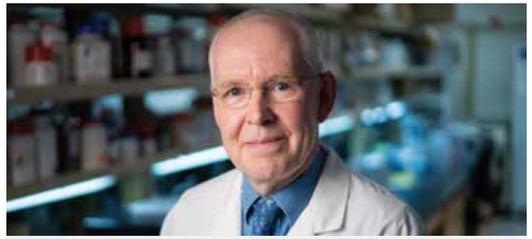
ASSOCIATE MEMBERS
Elisabeth E. Adderson, MD[1] • Epidemiology & treatment of infections
Hana Hakim, MD • Infection prevention & control
Katherine Knapp, MD • Perinatal HIV exposure/HIV clinical trials
Gabriela M. Marón Alfaro, MD[1] • Infectious complications in transplant patients
Nehali Patel, MD • HIV clinical care
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
Joshua Wolf, PhD, MBBS[1] • Prediction, prevention, & treatment of infections in immunocompromised children

ASSISTANT MEMBERS
Diego R. Hijano, MD, MSc[1] • Host–pathogen interactions of respiratory virus
Ellie B. Margolis, MD, PhD[1] • Microbiome dynamics in immunocompromised patients
Sheena Mukkada, MD, MPH[1,2] • Global health, infection care & control

INSTRUCTORS
Timothy Flerlage, MD • Pathogenesis of severe lung infections
Amanda M. Green, MD • Human immune responses to co-infection and chronic viruses, including HIV and CMV

RESEARCH ASSOCIATE
Christopher D. Radka, PhD • Anaerobic bacterial physiology & biosynthesis of bacterial immune modulators

ADJUNCT MEMBERS
Nicholas Hysmith, MD, MS, FAAP • Emerging infections & hospital epidemiology
Jonathan A. McCullers, MD • Interactions between viruses & bacteria



PATHOLOGY

CHAIR
David W. Ellison, MBBChir, MA (Hons), MSc, 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]; Endowed Chair in Pediatrics • T-cell regulation, adoptive immunotherapy
Randall T. Hayden, MD • Clinical microbiology of immunocompromised hosts
Mondira Kundu, MD, PhD[1,2] • Autophagy-related proteins in health & human disease
Michael M. Meagher, PhD[4]
Charles G. Mullighan, MBBS(Hons), MSc, MD[1]; William E. Evans Endowed Chair • Genomic, experimental, & preclinical studies of acute leukemia
Kim E. Nichols, MD[1,2] • Heritable cancers & primary immunodeficiency syndromes
Jerold E. Rehg, DVM[4]
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
Richard A. Ashmun, PhD • Applications of flow cytometry & cell separation
Jason Cheng-Hsuan Chiang, MD, PhD • Diagnosis & classification of CNS tumors
Jeremie H. Estepp, MD[3]
Larissa V. Furtado, MD • Clinical genomics and data management systems
Gabriela Gheorghe, MD • Pediatric leukemias and lymphomas, histiocytic lesions
Laura J. Janke, DVM, PhD • Pathology of mouse models of disease
Jeffery M. Klco, MD, PhD[1] • Genomic & functional characterization of pediatric myeloid neoplasms
Yen-Chun Liu, MD, PhD • Hematologic malignancies
Brent A. Orr, MD, PhD[1] • Molecular classification of tumors of the nervous system
Harshan Pisharath, DVM, PhD • Animal models of human diseases, preclinical safety
András Sablauer, MD, PhD[5]
Teresa C. Santiago, MD • Laboratory quality improvement & assessment
Heather S. Tillman, DVM, PhD • Comparative pathology
Lu Wang, MD, PhD • Genomic profiling & functional analysis of genetic alterations in pediatric tumors
Gang Wu, PhD[1] • Genome instability, neurodegeneration, brain transcriptomics

ASSISTANT MEMBERS
Paula Y. Arnold, PhD • HLA and hematopoietic cell transplantation
Patrick R. Blackburn, PhD • Clinical laboratory genetics and genomics
Mohammed K. Eldomery, MD • Molecular oncology, cancer-predisposition syndromes
Heather L. Glasgow, PhD • Novel diagnostics for clinical microbiology
Mahsa Khanlari, MD • Diagnosis and classification of pediatric hematopoietic neoplasms
Selene C. Koo, MD, PhD • Molecular classification of pediatric solid tumors
Priya Kumar, MD • Diagnostic capacity building for hematologic malignancies in resource-limited settings
Julieann C. Lee, MD, MS • Clinicopathologic and molecular characterization of pediatric brain tumors
Yan Zheng, MD, PhD • Red blood cell genotyping & alloimmunization, cancer immunotherapy

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ONCOLOGY

CHAIR
Ching-Hon Pui, MD[1]; 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[1] • Quality of life/palliative care & ethics
Sara M. Federico, MD[1] • Drug development, pediatric soft-tissue sarcomas
Elizabeth Fox, MD[1] • Developmental therapeutics in pediatric oncology
Wayne L. Furman, MD[4]
Daniel M. Green, MD[1] • Adverse hepatic, renal, & reproductive effects of therapy
Melissa M. Hudson, MD[1]; The Charles E. Williams Endowed Chair of 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[2,4]
Monika L. Metzger, MD[3]
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[1]; Executive Vice President, Lillian R. Cannon Comprehensive Cancer Center Director Endowed Chair • SWI/SNF (BAF) chromatin remodeling/tumor suppressor
Jeffrey E. Rubnitz, MD, PhD[1] • Treatment of acute myeloid leukemia
Jun J. Yang, PhD[1,2] • Pharmacogenomics of anticancer agents & drug resistance

ASSOCIATE MEMBERS
Asya Agulnik, MD, MPH[1,2] • Global health, pediatric onco-critical care, quality improvement
Richard A. Ashmun, PhD[2] • Applications of flow cytometry & cell separation
Nickhill Bhakta, MD, MPH[1,2] • Global health, survivorship, epidemiology, childhood leukemias
Rachel C. Brennan, MD[3]
Patrick K. Campbell, MD, PhD[1] • Histiocytic disorders, clinical informatics, patient safety
Matthew J. Ehrhardt, MD, MS • Late effects of childhood cancer therapy
Jamie E. Flerlage, MD, MS[1] • Reduction of the late effects for Hodgkin lymphoma survivors
Mark E. Hatley, MD, PhD[1] • Origins of pediatric sarcomas
Liza-Marie Johnson, MD, MPH, MSB • Ethical issues in pediatrics
Seth E. Karol, MD[1] • Toxicity reduction during acute leukemia therapy
Erica C. Kaye, MD[1] • Prognostic communication, early integration of palliative care in oncology
Catherine G. Lam, MD, MPH[1,2] • Global health, health systems, pediatric solid tumors
Deena R. Levine, MD • Pediatric palliative & end-of-life care
Daniel A. Mulrooney, MD, MS[1] • Cardiovascular outcomes of cancer therapy
Ibrahim A. Qaddoumi, MD, MS[1,2] • Global health, brain tumors, telemedicine, retinoblastoma
Giles W. Robinson, MD[1] • Origin & genomics of medulloblastoma, translational studies
Carolyn Russo, MD[2] • Quality improvement in clinical networks
Anna Vinitsky, MD, MS • Pediatric neuro-oncology & process improvement

ASSISTANT MEMBERS
Kelsey C. Bertrand, MSc, MBBS • Understanding ependymoma and high-grade glioma
Michael W. Bishop, MD[1] • Osteosarcoma, Ewing sarcoma, soft-tissue sarcomas
Steven S. Carey, MD, PhD • Management of central nervous system malignancies
Griffin S. Collins, MD • Integration of palliative care
Stephanie B. Dixon, MD • Pediatric cancer survivorship
Adam D. Durbin, MD, PhD[1] • Molecular biology of high-risk pediatric cancers
Paola Friedrich, MD, MPH[1,2] • Global health, health disparities, health services, pediatric solid tumors
Dylan Graetz, MD[2] • Global health, patient-centered care, solid tumors
Lillian M. Guenther, MD • Novel genomic targets in osteosarcoma
Sara Helmig, MD[1] • Sarcoma, thyroid carcinoma, & quality improvement
Zhongbo Hu, MD, PhD • Targeted leukemia therapy and clinical trials
Lauren P. Jerkins, MD • Cellular therapy, quality improvement, and patient safety
Myriam Labelle, PhD[1] • The role of the microenvironment in cancer metastasis
Esther A. Obeng, MD, PhD[1] • Myeloid malignancies & bone marrow failure syndromes
Kimberly E. Sawyer, MD, MS[3]
Holly L. 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
Santhosh Upadhyaya, MD • Atypical teratoid rhabdoid tumor & ependymoma
Liqin Zhu, PhD[2] • Stem cells in normal & malignant development

INSTRUCTORS
Aditi Bagchi, MD, PhD • Molecular and genomic characteristics of pediatric brain tumors
Andrea Cuviello, MD • Early palliative care integration in pediatric oncology
Matthew J. Davis, MD • Acute care of hematology and oncology patients
Jessica Gartrell, MD • Early phase clinical trial development, sarcomas, liver tumors
Emily M. Hanzlik, MD • Clinical pediatric neuro-oncology & neurologic complications of pediatric cancer
Arshia Madni, MD[3]
Michael J. McNeil, MD, MPH[2] • Defining the state of palliative care for children with cancer in resource-constrained settings
Daniel Moreira Ridsdale, MD[2] • Global pediatric oncology, evidence-based education, pediatric CNS tumors
Anand G. Patel, MD, PhD[1] • Tumor recurrence in pediatric rhabdomyosarcoma
Melissa R. Perrino, MD • Germline predisposition and genetic drivers of cancer
Ruth W. Wang'ondu, MD, PhD • Integration of genetic data from diverse populations to inform treatment of B-acute lymphoblastic leukemia

ADJUNCT MEMBERS
Francisca Fasipe, MD • Leukemia, lymphoma, hemoglobinopathies, and solid tumors
Marcela Popescu, MD • Clinical pediatric hematology

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

PEDIATRIC MEDICINE

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

MEMBERS
Justin N. Baker, MD[1,2]; Quality of life/palliative care & ethics
Shannon M. Dean, MD, MMM; Chief Medical Information Officer
Kirsten K. Ness, PT, PhD, FAPTA[1,2] • Physical health and accelerated aging in childhood cancer survivors
Ellis J. Neufeld, MD, PhD[2]; Executive Vice President; Clinical Director; John & Lorine Thrasher Endowed Chair in Pediatric Medicine • Patient-oriented studies in nonmalignant hematology

ANESTHESIOLOGY
Doralina L. Anghelescu, MD[3]
Michael J. Frett, MD; Division Director • Pediatric anesthesia
TeKesha Henry, DO • Pediatric anesthesia and pain management
Kavitha C. Raghavan, MBBS, FRCA • Patient safety & quality of care in pediatric anesthesia
Michael G. Rossi, DO • Patient safety & cognitive effects of anesthesia
Luis A. Trujillo Huaccho, MD • Regional anesthesia & anesthetic approach in high-risk cases
Tzipa Zweig, MD, MS • Pediatric pain and palliative care

CENTER FOR EXPERIMENTAL NEUROTHERAPEUTICS
Richard S. Finkel, MD[1]; Endowed Chair in Neurotherapeutics; Division Director • Pediatric neurologic and metabolic diseases

CRITICAL CARE MEDICINE
R. Ray Morrison, MD[1]; Division Director • Pediatric critical care, myocardial protection
Anita V. Arias Prado, MD • Capacity building in pediatric critical care
Lama Elbahlawan, MD • Pediatric critical care, acute lung injury
Saad Ghafoor, MD • Improvement of pediatric critical care outcomes
Melissa R. Hines, MD • Pediatric critical care, hemophagocytic lymphohistiocytosis
Caitlin E. Hurley, MD • Onco-critical care, HSCT/immunotherapy patients, long-term care
Jennifer A. McArthur, DO[1] • Improving outcomes in critically ill pediatric patients

ENDOCRINOLOGY
Angela Delaney Freedman, MD; Division Director • Hypothalamic/pituitary dysfunction in childhood cancer survivors
Christine Yu, MD • Fertility after gonadotoxic therapy

NEUROLOGY
Raja B. Khan, MD; Division Director • Effect of cancer on central & peripheral nervous systems
Emily M. Hanzlik, MD[2] • Clinical pediatric neuro-oncology & neurologic complications of pediatric cancer

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

PSYCHIATRY
D. Andrew Elliott, MD; Division Director • Psychiatric effects of cancer and its treatment

ADJUNCT MEMBERS
Mark Corkins, MD • Gastroenterology
Patricia Dubin, MD • Pulmonology
Terri H. Finkel, MD, PhD • Rheumatology
James Wheless, MD • Neurology

PHARMACY & PHARMACEUTICAL SCIENCES

CHAIR
P. David Rogers, PharmD, PhD[1]; Endowed Chair in Pharmaceutical Sciences • Molecular and genetic basis of antifungal drug resistance

VICE-CHAIRS
William L. Greene, PharmD; Chief Pharmaceutical Officer • Optimizing pharmacotherapy
Jun J. Yang, PhD[1] • Pharmacogenomics of anticancer agents & drug resistance

MEMBERS
William E. Evans, PharmD[4]
James M. Hoffman, PharmD; Chief Patient Safety Officer • Medication safety & outcomes
Markos Leggas, PhD • Pharmacometabolomic methods to improve therapeutic outcomes and minimize toxicity in the context of pediatric clinical trials
Mary V. Relling, PharmD • Leukemia therapy & clinical pharmacogenetics
Erin G. Schuetz, PhD[5]
John D. Schuetz, PhD[1] • Regulation & function of ABC transporters
Clinton F. Stewart, PharmD[1] • Pharmacology of anticancer drugs in children

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

INSTRUCTOR
Jeffrey M. Rybak, PharmD, PhD • Antifungal pharmacotherapy

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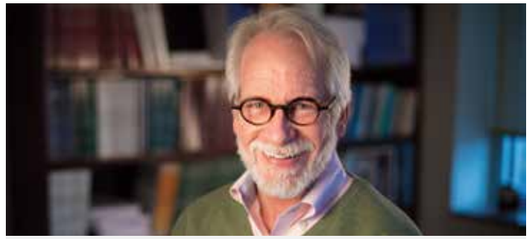

PSYCHOLOGY

CHAIR
Sean Phipps, PhD[4]

MEMBERS
Heather M. Conklin, PhD[1] • Cognitive outcomes of childhood cancer treatment
Valerie M. Crabtree, PhD[1] • Sleep disruptions and fatigue in pediatric oncology
Melissa M. Hudson, MD[1,2]; The Charles E. Williams Endowed Chair of Oncology–Cancer Survivorship • Health outcomes after childhood cancer
Kevin R. Krull, PhD[2]; Endowed Chair in Cancer Survivorship • Cognitive neuroscience approaches to outcomes and interventions in pediatric cancer survivors

ASSOCIATE MEMBERS
Tara M. Brinkman, PhD[2] • Psychosocial outcomes of pediatric cancer
Jennifer L. Harman, PhD • The psychosocial functioning of young children with cancer
Lisa M. Jacola, PhD • Neurobehavioral outcomes in children treated for cancer
Niki Jurbergs, PhD • Psychological & cognitive impact of pediatric cancer
Kendra R. Parris, PhD • Coping & adjustment in youth with cancer
Jerlym S. Porter, PhD, MPH[1] • Transition from pediatric to adult care in SCD
Megan L. Wilkins, PhD • Clinical & research psychological services for youth with HIV/AIDS
Victoria W. Willard, PhD[1] • Social outcomes in children with cancer

ASSISTANT MEMBERS
Kristin E. Canavera, PhD[3]
R. Elyse Heidelberg Kenney, PsyD • Pain and symptom management in pediatric hematology/oncology
Andrew M. Heitzer, PhD • Neurocognitive outcomes in sickle cell disease
Anna M. Jones, PhD • Transition off therapy for oncology patients and families
Jennifer M. Allen Lischwe, PhD[3]
Jennifer Longoria, PhD • Neurocognitive outcomes in sickle cell disease
Brian S. Potter, PsyD • Neurocognitive outcomes in children with cancer
Darcy Raches, PhD • Acute neurological injury & cognitive outcomes associated with childhood cancer treatment
Katianne M. Sharp, PhD • Cancer predisposition & adjustment in families of children with cancer
Rachel N. Webster, PhD • Promotion of healthy lifestyle behaviors in children with cancer & survivors of childhood cancer

INSTRUCTOR
Ryan N. James, PhD • Pediatric pain and somatic symptoms & trauma-informed care in adolescents and young adults

RADIATION ONCOLOGY

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

MEMBERS
Chia-ho Hua, PhD • Improving proton therapy accuracy, advanced imaging for radiation therapy, normal tissue complication modeling
Matthew J. Krasin, MD[1] • Developing radiation therapy strategies and toxicity profiles for pediatric sarcomas

ASSOCIATE MEMBERS
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

ASSISTANT MEMBERS
Ozgur Ates, PhD, DABR • Adaptive proton therapy & surface-guided radiation therapy
Austin M. Faught, PhD[3]

INSTRUCTORS
Lydia J. Wilson, PhD • Predictive risk modelling, radiation late effects
Wenjun Yang, PhD[3]

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

STRUCTURAL BIOLOGY

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

MEMBERS
M. Madan Babu, PhD, FRSC[1]; Endowed Chair in Biological Data Science • Data science for discovery and personalized medicine
Scott C. Blanchard, PhD[1]; Endowed Chair in Molecular Imaging • Examining structure–function relations in macromolecular assemblies
Richard W. Kriwacki, PhD[1] • Structural basis of tumor suppressor function
Tanja Mittag, PhD[1] • Molecular basis of liquid–liquid phase separation
Junmin Peng, PhD[1] • Proteomics & metabolomics in human disease
Stephen White, DPhil[4]

ASSOCIATE MEMBER
Mario Halic, PhD[1] • Regulation of genome expression

ASSISTANT MEMBERS
Marcus Fisher, PhD[1,2] • Protein conformational ensembles
Chia-Hsueh Lee, PhD[1] • Molecular mechanisms of membrane-signaling complexes
Tudor Moldoveanu, PhD[3]
Ji Sun, PhD[1] • Structural and pharmacological studies of membrane proteins

ADJUNCT MEMBER
Brenda A. Schulman, PhD • Cellular regulation by ubiquitin-like proteins

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]

ASSOCIATE MEMBER
Andrew Jackson Murphy, MD[1] • Renal tumors, neuroblastoma, Wilms tumorigenesis, cancer stem cells

ASSISTANT MEMBERS
Abdelhafeez H. Abdelhafeez, MD • Fluorescence-guided, minimally invasive, & subamputative pediatric surgical oncology
Lindsay J. Talbot, MD • Sarcomas, immunotherapeutic strategies against sarcoma & solid tumor metastases
Jun Yang, MD, PhD[1] • Cancer epigenetics & targeted therapy

ADJUNCT MEMBERS
Frederick Boop, MD • Pediatric neurosurgery
Jeremiah L. Deneve, DO • Pediatric general surgery
Joseph M. Gleason, MD • Pediatric urology
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
Matthew W. Wilson, MD; St. Jude Chair in Pediatric Ophthalmology • Pediatric ophthalmology

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

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

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

Endowed Chairs

Aseem Z. Ansari, PhD
Robert J. Ulrich Endowed Chair in Chemical Biology and Therapeutics

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

M. Madan Babu, PhD, FRSC
Endowed Chair in Biological Data Science

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

Scott C. Blanchard, PhD
Endowed Chair in Molecular Imaging

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

John D. Crispino, PhD, MBA
The Wall Street Committee Endowed Chair

Andrew Davidoff, MD
Endowed Chair in Surgical Research

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

Michael A. Dyer, PhD
Richard C. Shadyac Endowed Chair in Pediatric Cancer Research

David W. Ellison, MD, PhD
Joan and Roy Gignac Endowed Chair in Pathology and Laboratory Medicine

Richard S. Finkel, MD
Endowed Chair in Neurotherapeutics

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

Amar J. Gajjar, MD
Scott and Tracie Hamilton Endowed Chair in the Brain Tumor Program

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

Stephen M. Gottschalk, MD
Endowed Chair in Bone Marrow Transplantation and Cellular Therapy

Douglas R. Green, PhD
Peter Doherty Endowed Chair in Immunology

Gerard C. Grosveld, PhD
Albert and Rosemary Joseph Endowed Chair in Genetic Research

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

Charalampos G. Kalodimos, PhD
Joseph Simone Endowed Chair in Basic Research

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

Kevin R. Krull, PhD
Endowed Chair in Cancer Survivorship

Richard E. Lee, PhD
Endowed Chair in Medicinal Chemistry

Peter J. McKinnon, PhD
Endowed Chair in Pediatric Neurological Diseases

Thomas E. Merchant, DO, PhD
Baddia J. Rashid Endowed Chair in Radiation Oncology

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

Motomi Mori, PhD
Endowed Chair in Biostatistics

Charles G. Mullighan, MBBS(Hons), MSc, 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

Zoltan Patay, MD, PhD
Endowed Chair in Diagnostic Imaging

Sean Phipps, PhD
Endowed Chair in Psychology

Endowed Chairs

Ching-Hon Pui, MD
Fahad Nassar Al-Rashid Endowed Chair in Leukemia Research

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

Phillip D. Rogers, PharmD, PhD
Endowed Chair in Pharmaceutical Sciences

Leslie L. Robison, PhD
Endowed Chair in Epidemiology and Cancer Control

Martine F. Roussel, PhD
Endowed Chair in Molecular Oncogenesis

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

Charles J. Sherr, MD, PhD
Herrick Foundation Endowed Chair in Tumor Cell Biology

Clifford M. Takemoto, MD
Lemuel Diggs Endowed Chair in Sickle Cell Disease

J. Paul Taylor, MD, PhD
Edward F. Barry Endowed Chair in Cell and Molecular Biology

Elaine I. Tuomanen, MD
Endowed Chair in Infectious Diseases

Mitchell J. Weiss, MD, PhD
Arthur Nienhuis Endowed Chair in Hematology

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

Jun J. Yang, PhD
Endowed Chair in Pharmacogenomics

Jinghui Zhang, PhD
Endowed Chair in Bioinformatics

Fellows & Students

POSTDOCTORAL FELLOWS

Diana Acevedo, PhD, Developmental Neurobiology
Anushree Achari, PhD, Chemical Biology & Therapeuticss
Adeleye Adeshakin, PhD, Bone Marrow Transplantation & Cellular Therapy
Aditi, PhD, Genetics[1]
Shahbaz Ahmed, PhD, Structural Biology
Gizem Altan, PhD, Diagnostic Imaging[1]
Shelby Anderson, PhD, Chemical Biology & Therapeutics
Konstantin Andreev, PhD, Infectious Diseases
Shariq Ansari, PhD, Cell & Molecular Biology[2]
Gary Arevalo, PhD, Chemical Biology & Therapeutics
Sasi Arunachalam, PhD, Computational Biology[1]
Gitanjali Asampille, PhD, Structural Biology[1]
Emilia Asante, PhD, Center for Pediatric Neurological Disease Research
Anoop Babu Vasandan, PhD, Immunology
David Baggett, PhD, Structural Biology[2]
Lu Bai, PhD, Immunology
Juan Barajas, PhD, Oncology
Stefanie Baril, PhD, Pharmacy & Pharmaceutical Sciences
Aditya Barve, PhD, Hematology
Katelyn Baumer, PhD, Chemical Biology & Therapeutics
Simran Bawa, PhD, Structural Biology[1]
Swarna Beesetti, PhD, Immunology
Matthew Bell, PhD, Bone Marrow Transplantation & Cellular Therapy
Soumen Bera, PhD, Computational Biology
Akshita Bhatt, PhD, Developmental Neurobiology
Kashi Bhattarai, PhD, Pharmacy & Pharmaceutical Sciences
Khaggeswar Bheemanapally, PhD, Structural Biology
Mackenzie Bloom, PhD, Oncology
Emilio Boada Romero, PhD, Immunology[2]
Nancy Bolous, MD, Global Pediatric Medicine[2]
Wade Borcherds, PhD, Structural Biology
Austin Boucher, PhD, Hematology
Anne Bremer, PhD, Structural Biology[2]
David Brice, PhD, Immunology
Pam Brigleb, PhD, Infectious Diseases
Mark Brimble, PhD, Surgery
Christina Brunelle, PhD, Infectious Diseases
Ratnakar Bynigeri, PhD, Immunology
Zhongheng Cai, PhD, Biostatistics
Kasturee Chakraborty, PhD, Diagnostic Imaging
Bappaditya Chandra, PhD, Structural Biology
Chih-Chiang Chang, PhD, Diagnostic Imaging[1]
Phillip Chapman, PhD, Developmental Neurobiology[2]
Kanokporn Chattrakun, PhD, Structural Biology
Po-Ling Chen, PhD, Infectious Diseases
Wen Chen, PhD, Immunology
Xiaolong Chen, PhD, Computational Biology
Peter Chockley, PhD, Bone Marrow Transplantation & Cellular Therapy
Jaesung Choi, PhD, Epidemiology & Cancer Control
Sk Mohiuddin Choudhury, PhD, Immunology
Shelbi Christgen, PhD, Immunology[1]
Mengqi Chu, PhD, Structural Biology
Chia-Lung Chuang, PhD, Developmental Neurobiology
Elizabeth Cleverdon, PhD, Cell & Molecular Biology[1]
Leslie Climer, PhD, Cell & Molecular Biology
Jordan Cockfield, PhD, Oncology
Elizabeth Coffey, PhD, Hematology[1]
Francisco Cruz Navarrete, PhD, Structural Biology
Chenxi Cui, PhD, Structural Biology
Yixin Cui, PhD, Structural Biology
Preeti Dabas, PhD, Chemical Biology & Therapeutics
Mahmoud Dabbah, PhD, Hematology
Yaxin Dai, PhD, Structural Biology
Adithi Danda, PhD, Chemical Biology & Therapeutics
Anuska Das, PhD, Structural Biology
Jitendra Das, PhD, Structural Biology
Sarmistha Das, PhD, Biostatistics
Tapojyoti Das, PhD, Structural Biology
Abhijit Dasgupta, PhD, Structural Biology
Christian DeJarnette, PhD, Pharmacy & Pharmaceutical Sciences[1]
Ian Delahunty, PhD, Oncology
Ashish Deshmukh, PhD, Structural Biology
Kaushik Dey, PhD, Structural Biology
Rachayata Dharmat, PhD, Cell & Molecular Biology
Subhash Dhital, PhD, Immunology
Kirsten Dickerson, PhD, Pathology[1]
Karissa Dieseldorff Jones, PhD, Bone Marrow Transplantation & Cellular Therapy
Phillip Doerfler, PhD, Hematology[2]
Priyanka Dogra, PhD, Structural Biology
Qian Dong, PhD, Pharmacy & Pharmaceutical Sciences[2]
Yongming Du, PhD, Structural Biology
Meghan Dukes, PhD, Bone Marrow Transplantation & Cellular Therapy
Asaf Elazar, PhD, Structural Biology
Lana Elkins, PhD, Tumor Cell Biology[1]
Abdelrahman Elsayed, PhD, Biostatistics[1]
Carolin Escherich, MD, Pharmacy & Pharmaceutical Sciences
Mansoore Esmaili, PhD, Structural Biology
Daniel Estevez Prado, PhD, Structural Biology[1]
Li Fan, PhD, Pharmacy & Pharmaceutical Sciences
Esmat Fathi, PhD, Tumor Cell Biology
Feng Feng, PhD, Developmental Neurobiology
Carlos Fernandez Pena, PhD, Developmental Neurobiology
Lourds Fernando, PhD, Developmental Neurobiology
Martina Finetti, PhD, Developmental Neurobiology
Diane Flasch, PhD, Computational Biology[1]
Leigh Fremuth, PhD, Genetics
Adolfo Frias, PhD, Immunology[1]
Yingxue Fu, PhD, Structural Biology[1]
Katherine Gadek, PhD, Oncology
Kellen Gandy, PhD, Psychology
Kaustav Gangopadhyay, PhD, Structural Biology
Pritha Ganguly, PhD, Structural Biology
Karishma Gangwani, PhD, Computational Biology
Dusan Garic, PhD, Immunology
Clifford Gee, PhD, Chemical Biology & Therapeutics[1]
Mohamed Ghonim, PhD, Immunology
Eric Gibbs, PhD, Structural Biology
Kyla Gibney, PhD, Psychology
Milica Gilic, PhD, Structural Biology
Vanshita Goel, PhD, Tumor Cell Biology
Luisa Gomez Londono, PhD, Pharmacy & Pharmaceutical Sciences
Lina Gonzalez Martinez, PhD, Developmental Neurobiology[1]
Chelsea Goodenough, PhD, Epidemiology & Cancer Control
Scott Gorman, PhD, Structural Biology[1]
Tomoka Gose, PhD, Pharmacy & Pharmaceutical Sciences[2]
Flavia Graca Zuanazzi, PhD, Developmental Neurobiology
Wezley Griffin, PhD, Structural Biology
Qingqing Gu, MD, Hematology
Xinrui Gui, PhD, Structural Biology
Omer Gullulu, PhD, Structural Biology
Alexander Gunnarsson, PhD, Structural Biology[1]
Ao Guo, PhD, Immunology
Chuansheng Guo, PhD, Immunology
Youngdae Gwon, PhD, Cell & Molecular Biology[1]
Kohei Hagiwara, MD, Computational Biology[1]
Priyanka Halder, PhD, Genetics
Eric Hall, PhD, Cell & Molecular Biology
Trent Hall, PhD, Hematology
Rawan Hammoud, MD, Epidemiology & Cancer Control
Xiaolei Hao, PhD, Immunology
Walter Harrington, PhD, Infectious Diseases
Dalia Haydar, PhD, Bone Marrow Transplantation & Cellular Therapy[1]
Minghong He, PhD, Immunology
Elodie Henriet, PhD, Oncology
Roketa Henry, PhD, Genetics[2]
Madeline Horan, PhD, Epidemiology & Cancer Control
Keito Hoshitsuki, PharmD, Pharmacy & Pharmaceutical Sciences
Hadi Hosseini, PhD, Biostatistics
Jianzhong Hu, PhD, Pharmacy & Pharmaceutical Sciences
Meng Hu, PhD, Infectious Diseases[1]
Wenjun Huang, PhD, Hematology
Xin Huang, PhD, Cell & Molecular Biology
Yan Huang, PhD, Structural Biology
Michael Hughes, PhD, Cell & Molecular Biology
Anna Huskey, PhD, Pathology
Jongchan Hwang, PhD, Oncology
Jorge Ibanez, PhD, Bone Marrow Transplantation & Cellular Therapy[2]
Siri Manasa Ippagunta, PhD, Developmental Neurobiology
Katelyn Jackson, PhD, Structural Biology
Thilina Jayasinghe, PhD, Chemical Biology & Therapeutics
Meiqin Jiang, PhD, Structural Biology
Yanbo Jiang, PhD, Developmental Neurobiology
Kasey Jividen, PhD, Hematology
Cydney Johnson, PhD, Infectious Diseases
Jason Jones, PhD, Structural Biology[1]
Kamal Jouad, PhD, Diagnostic Imaging
Seunghyun Jung, PhD, Developmental Neurobiology
Halime Kalkavan, MD, Immunology[1]
Balabhaskararao Kancharana, PhD, Immunology
Ahmed Kandeil, PhD, Infectious Diseases
Suresh Kandikonda, PhD, Chemical Biology & Therapeutics
Tae Gun Kang, PhD, Immunology
Mangesh Kaulage, PhD, Chemical Biology & Therapeutics
Pranav Khade, PhD, Chemical Biology & Therapeutics[1]
Suparna Khatun, PhD, Structural Biology
Hanane Khoury, PhD, Hematology
Hyunsuh Kim, PhD, Infectious Diseases[1]
Shunsuke Kimura, MD, PhD, Pathology
Evan Kingsley, PhD, Developmental Neurobiology
Kaitlin Koreski, PhD, Cell & Molecular Biology
Damian Krzyzanowski, PhD, Hematology
Prasanth Kumar, PhD, Immunology
Jesyin Lai, PhD, Diagnostic Imaging
Casey Langdon, PhD, Oncology[1]
Shannon Lange, PhD, Bone Marrow Transplantation & Cellular Therapy[1]
Ana Leal Cervantes, PhD, Oncology[1]
Dong Geun Lee, PhD, Structural Biology
SangJoon Lee, PhD, Immunology[1]
Shawn Lee, MD, Pharmacy & Pharmaceutical Sciences[1]
William Letsou, PhD, Epidemiology & Cancer Control[1]
Dongfang Li, PhD, Cell & Molecular Biology
Jun Li, PhD, Immunology[2]
Miaomiao Li, PhD, Cancer Center Administration[1]
Shuting Li, PhD, Immunology[1]
Wei Li, PhD, Immunology[1]
Yizhen Li, PhD, Pharmacy & Pharmaceutical Sciences[2]
Zhenrui Li, PhD, Immunology
Swantje Liedmann, PhD, Immunology
Bitna Lim, PhD, Developmental Neurobiology[1]
Jennapher Lingo VanGilder, PhD, Radiation Oncology
Danielle Little, PhD, Developmental Neurobiology
Beiyun Liu, PhD, Immunology
Danting Liu, PhD, Structural Biology[1]
Fengming Liu, PhD, Developmental Neurobiology
Jingjing Liu, PhD, Computational Biology[2]
Xueying Liu, PhD, Computational Biology
Lingyun Long, PhD, Immunology[2]
Jianlin Lu, PhD, Immunology
William MacCain, PhD, Infectious Diseases
Joelle Magne, PhD, Immunology
Arun Maharaj, PhD, Epidemiology & Cancer Control
Kelsey Maher, PhD, Computational Biology
Maud Maillard, PhD, Pharmacy & Pharmaceutical Sciences
Snigdha Maiti, PhD, Structural Biology
Efren Maldonado, PhD, Chemical Biology & Therapeutics
Deepshikha Malik, PhD, Structural Biology
Alexandra Mandarano, PhD, Immunology
Luigi Mari, PhD, Immunology
Maxwell Martin, PhD, Structural Biology
Masihuzzaman, PhD, Structural Biology
Yurika Matsui, PhD, Developmental Neurobiology
Jayadev Mavuluri, PhD, Immunology[2]
Thiyagaraj Mayuranathan, PhD, Hematology
Johanna Melo-Cardenas, PhD, Hematology
Audrey Mercier, PhD, Tumor Cell Biology
Robert Mettelman, PhD, Immunology
Nicole Michmerhuizen, PhD, Pathology
Benjamin Minden-Birkenmaier, PhD, Developmental Neurobiology
Anastasia Minervina, PhD, Immunology
Priya Mittal, PhD, Oncology
Robert Jackson Mobley, PhD, Oncology[2]
Lindsey Montefiori, PhD, Pathology
Antonio Morales-Hernandez, PhD, Hematology[1]
Ardiana Moustaki, PhD, Bone Marrow Transplantation & Cellular Therapy[1]
Tresor Mukiza, PhD, Cell & Molecular Biology
Haruko Nakamura, MD, PhD, Cell & Molecular Biology[1]
Ambuja Navalkar, PhD, Structural Biology
Miguel Navarrete, PhD, Psychology
Christopher Nevitt, PhD, Hematology[2]
Madeline Niederkorn, PhD, Hematology
Andrew Nishimoto, PhD, Infectious Diseases
Jacqueline Norrie, PhD, Developmental Neurobiology
Shaikh Nurunnabi, PhD, Developmental Neurobiology
Jennifer Ocasio Adorno, PhD, Developmental Neurobiology
Brian O'Flynn, PhD, Structural Biology
Mary Cameron Ogg, PhD, Developmental Neurobiology
Chet Ojha, PhD, Infectious Diseases[1]
Adedolapo Ojoawo, PhD, Structural Biology[1]
Faten Okda, PhD, Infectious Diseases
Anasuya Pal, PhD, Chemical Biology & Therapeutics
Allison Palazola, PhD, Oncology[1]
Qingfei Pan, PhD, Computational Biology[1]
Ankit Pandeya, PhD, Immunology
Nagakannan Pandian, PhD, Immunology
Chiara Papini, PhD, Epidemiology & Cancer Control
Avik Pati, PhD, Structural Biology[1]
Mary Patton, PhD, Developmental Neurobiology
Janaka Peragaswaththe Liyanage, PhD, Biostatistics
Charles Perry, PhD, Developmental Neurobiology
Kateryna Petrykey, PhD, Epidemiology & Cancer Control
Shabareesh Pidathala, PhD, Structural Biology
Anna Pittman, PhD, Developmental Neurobiology
Noel-Marie Plonski, PhD, Epidemiology & Cancer Control
Anustup Poddar, PhD, Structural Biology[1]
Mikhail Pogorelyy, PhD, Immunology
Petri Polonen, PhD, Pathology
Pragya Poudel, PhD, Epidemiology & Cancer Control[1]
Brooke Prinzing, PhD, Bone Marrow Transplantation & Cellular Therapy[1]
Sashikantha Reddy Pulikallu, PhD, Structural Biology
Qiang Qin, PhD, Immunology
Zhuo Qu, PhD, Biostatistics
Waise Quarni, PhD, Surgery
Christopher Radka, PhD, Infectious Diseases[2]
Sabina Ranjit, PhD, Pharmacy & Pharmaceutical Sciences
Jana Raynor, PhD, Immunology[2]
Meghdad Razizadeh, PhD, Center for Bioimage Informatics
Stephanie Reeve, PhD, Chemical Biology & Therapeutics[1]
Sarah Robinson-Thiewes, PhD, Chemical Biology & Therapeutics
Stephanie Rockfield, PhD, Cell & Molecular Biology
Ricardo Rodriguez-Enriquez, PhD, Cell & Molecular Biology[1]
Ericka Roubidoux, PhD, Infectious Diseases
Sarayu Row, PhD, Cell & Molecular Biology
Sourav Roy, PhD, Chemical Biology & Therapeutics
Sebastian Ruehl, PhD, Immunology[1]
Emily Rundlet, PhD, Structural Biology
Diana Sa da Bandeira, PhD, Hematology
Sushree Sahoo, PhD, Hematology
Andrea Sanchez Corzo, PhD, Diagnostic Imaging
Julio Sanchez, PhD, Structural Biology
Laura Sanchez, PhD, Diagnostic Imaging
Jordy Saravia, PhD, Immunology[2]
Roman Sarkar, PhD, Immunology
Neha Sarodaya, PhD, Developmental Neurobiology
Anna Seffernick, PhD, Biostatistics
Justin Seffernick, PhD, Chemical Biology & Therapeutics
Ming Shao, PhD, Chemical Biology & Therapeutics
Maxwell Shapiro, PhD, Biostatistics[1]
Jeremy Shaw, PhD, Immunology
Noha Shendy, PhD, Oncology
Hazheen Shirnekhi, PhD, Structural Biology
Him Shrestha, PhD, Structural Biology
Rupesh Shrestha, PhD, Chemical Biology & Therapeutics
Lilian Silva, PhD, Pharmacy & Pharmaceutical Sciences[1]
Aisha Souquette, PhD, Immunology
Timothy Stachowski, PhD, Chemical Biology & Therapeutics
Wei Su, PhD, Immunology
Huan Sun, PhD, Structural Biology
Renqiang Sun, PhD, Immunology
Xiang Sun, PhD, Immunology
Balamurugan Sundaram, PhD, Immunology
Shannon Sweeney, PhD, Developmental Neurobiology
Kumari Sweta, PhD, Chemical Biology & Therapeutics
Katarzyna Szoltysek, PhD, Pathology
Justin Tanner, PhD, Epidemiology & Cancer Control
Ran Tao, PhD, Developmental Neurobiology[2]
Kristen Thomas, PhD, Developmental Neurobiology
Melvin Thomas III, PhD, Pathology[2]
Cheng Tian, PhD, Pharmacy & Pharmaceutical Sciences
Elizabeth Tinder, PhD, Infectious Diseases[2]
Ricky Tirtakusuma, PhD, Immunology
Michele Tolbert, PhD, Structural Biology[1]
Carolina Torres Rojas, PhD, Developmental Neurobiology
Halil Toy, PhD, Epidemiology & Cancer Control
Quang Tran, PhD, Computational Biology
Olivia Travis, PhD, Developmental Neurobiology
Alexandra Trevisan, PhD, Developmental Neurobiology
Sanja Trifkovic, PhD, Infectious Diseases
Vikas Trivedi, PhD, Structural Biology[1]
Shraddha Tuladhar, PhD, Immunology
Masayuki Umeda, MD, Pathology
Gintvile Valinciute, PhD, Tumor Cell Biology
Alanna Van Huizen, PhD, Hematology
Ashish Verma, PhD, Chemical Biology & Therapeutics
Paulina Villanueva, PhD, Diagnostic Imaging
Jessica Wagner, PhD, Bone Marrow Transplantation & Cellular Therapy[2]
Wahiduzzaman, PhD, Structural Biology
LaShanale Wallace, PhD, Oncology
Jingheng Wang, PhD, Chemical Biology & Therapeutics
Ju Wang, PhD, Structural Biology
Xiaoqing Wang, PhD, Biostatistics[1]
Yan Wang, PhD, Immunology
Yaqiu Wang, PhD, Immunology
Zhen Wang, PhD, Structural Biology
Abubakar Wani, PhD, Immunology
Arjumand Wani, PhD, Structural Biology[1]
Grace Ward, PhD, Hematology
Megan Ware, PhD, Epidemiology & Cancer Control
Zoe Watson, PhD, Structural Biology
Jayce Weesner, PhD, Genetics
Sarah Whaley, PhD, Infectious Diseases
Shyra Wilde, PhD, Infectious Diseases
Annalynn Williams, PhD, Epidemiology & Cancer Control1
Qiong Wu, PhD, Surgery
Stephanie Wu, PhD, Developmental Neurobiology
Hui Xia, PhD, Immunology
Jiyuan Yang, PhD, Computational Biology
Ka Yang, PhD, Structural Biology[1]
Shu Yang, PhD, Structural Biology
Rajesh Yetirajam, PhD, Immunology
Siqi Yi, PhD, Hematology
Masanori Yoshida, MD, PhD, Hematology
Tomoko Yoshida, MD, PhD, Epidemiology & Cancer Control
Zhiyuan You, PhD, Immunology
Sarah Young, PhD, Structural Biology
Sujing Yuan, PhD, Immunology
Ugur Yurtsever, PhD, Cell & Molecular Biology
Fatima Zaidi, PhD, Structural Biology
Ivica Zamarija, PhD, Structural Biology[1]
Xue Zhang, PhD, Structural Biology
Yifan Zhang, PhD, Chemical Biology & Therapeutics
Huanbin Zhao, PhD, Pharmacy & Pharmaceutical Sciences
Lanying Zhao, PhD, Hematology
Xujie Zhao, PhD, Pharmacy & Pharmaceutical Sciences[1]
Peipei Zhou, PhD, Immunology
Xuelin Zhou, PhD, Structural Biology
Hanwen Zhu, PhD, Structural Biology
Zhexin Zhu, PhD, Oncology
Jaquelyn Zoine, PhD, Bone Marrow Transplantation & Cellular Therapy
Xinying Zong, PhD, Immunology[1]

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

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

Fellows & Students

CLINICAL FELLOWS

Bone Marrow Transplantation & Cellular Therapy Fellow
Dua'a Zandaki, MD

Global Health Fellow
Caitlyn Duffy, MD

Infectious Diseases Fellows
Afreen Abraham, MBBS
Elspeth Bittle, MD
Sandra Castejon Ramirez, MD
Kate Shapiro, MD
Melissa Shenep, MD

Medication-Use Safety Resident
Madison Cole, PharmD

Neuropsychology Fellows
Rachel Bridges, PhD
Lakia Kearson, PhD
Bethany Schwandt, PhD

Ocular Oncology Fellow
Aleksandr Kruglov, MD

Pediatric Hematology-Oncology Fellows
Taylor Aglio, MD
Tarun Aurora, MD
Jessica Bodea, MD
La'Ron Browne, MD
Georgios Christakopoulos, MD
Margaret Cupit-Link, MD
Vidyasagar Jaiswal, MBBS, MP
Camille Keenan, MD, MPH
Justin Kirkham, MD, PhD
Megan Lilley, MD
Margit Mikkelsen, MD
Bradley Muller, MD
Devin Murphy, DO
Ayobami Olanrewaju, MBBS, MP
Matthew Rees, MD
Supriya Sarvode, MD
Jasmine Smith, MD
Shruthi Suryaprakash, MD

Pediatric Surgical Oncology Fellows
Huma Faiz Halepota, MBBS
Tarek Zaghloul, MD

Pharmacy Informatics Resident
Chad Compagner, PharmD

Pharmacy Oncology Resident
Katelyn Phillips, PharmD

Pharmacogenomics Resident
Rachael Stone, PharmD

Pediatric Psychology Fellow
Ayanna Johnson, PhD

Radiation Oncology Fellow
Carol Oliveira, MD, PhD

Sickle Cell Disease Fellow
Amie Patel, DO

Solid Tumor Fellow
Marija Kacar, MD

GRADUATE STUDENTS

St. Jude Graduate Students
Alhassan Abdul-Mumin, MD, Global Child Health[1]
Grace Adkins, Oncology
Alia Ahmad, MD, Global Child Health[1]
Hamoud Hodeish Yahya F. Al-Hussaini, MD, Global Child Health
Juan Pablo Rodriguez Auad, MD, Global Child Health[1]
Tarun Aurora, MD, Clinical Investigation
Alexandra Beckett, Bone Marrow Transplantation & Cellular Therapy
Matthew Bell, Bone Marrow Transplantation & Cellular Therapy
Brennan Bergeron, Pharmacy & Pharmaceutical Sciences
Elspeth Bittle, MD, Clinical Investigation
Mackenzie Bloom, Oncology[3]
Joseph Brett, Structural Biology
Kaitlin Budd, Developmental Neurobiology
Madeline Bush, Oncology
Jiaoyang Cai, MD, Global Child Health
Terri Cain, Oncology
Omar Chamdine, MD, Global Child Health
Rosdali Diaz Coronado, MD, Global Child Health[1]
Margaret Cupit-Link, MD, Clinical Investigation
Christina Daly, Cell & Molecular Biology
Ramon Misla David, Center for Pediatric Neurological Disease Research
Morgan Davis
Yogesh Dhungana, Computational Biology
Mae C. Dolendo-Jarencio, MD, Global Child Health
Liezl Du Plessis, MD, MMD, Global Child Health
Marygrace Duggar, Immunology
Christine Dunn
Angela Edwards, BHS, RT, Clinical Investigation
Darrell A. Elliott, MD, Clinical Investigation
Rebecca Epperly, MD, Clinical Investigation
Lauren Ezzell
Abigail Fish, Chemical Biology & Therapeutics
Jake Friske, Tumor Cell Biology
Jessica Gaevert, Immunology
Lily Saladana Gallo, MD, Global Child Health
Pascale Y. Heurtelou Gassant, MD, Global Child Health[1]
Wendy Cristhyna Gomez Garcia, MD, Global Child Health
Rebecca (Florke) Gee, Chemical Biology & Therapeutics
Anne Gilmore, Developmental Neurobiology
Chelsea Goodenough, PhD, Clinical Investigation
Liam Hallada, Developmental Neurobiology
Blake Holcomb
Victoria Honnell, Developmental Neurobiology
Diriba Hordofa, MD, Global Child Health[1]
Alex Hughes, Developmental Neurobiology
Alissa Jackson, Hematology
Yusuf Danasabe Jobbi, Global Child Health[1]
Christina Kackos, Infectious Diseases
Seth E. Karol, MD, Clinical Investigation
Matthew Kieffer, Develop Neurobiology
Sandra Kietlinska
Allison Kirk, Immunology
Roman Kizyma, MD, Global Child Health
Christy LaFlamme, Cell & Molecular Biology
Randolph Larsen, Oncology
Arturo Manuel Zapata Lopez, MD, Global Child Health
JaQuel Maise, Oncology
Hayden Malone, Oncology
Sanya Mehta, Bone Marrow Transplantation & Cellular Therapy
Pablo Gonalez Montalvo, MD, Global Child Health
Sarah Moore, Bone Marrow Transplantation & Cellular Therapy
Claudia Pascual Morales, MD, Global Child Health
Doreen Terry Karimi Mutua, MD, Global Child Health
Mariam Ndagire, RN, Global Child Health
Joaquim Caetano de Aguirre Neto, MD, Global Child Health
Yuliya Nogovitsyna, Global Child Health
Erienne Norton, Immunology
Hovaire Nsabimana, MD, Global Child Health
Kiera O'Keefe, Hematology
Athena Olszewski
Trevor Penix, Infectious Diseases
Nicolas Peterson, Immunology
Gregory Phelps, Chemical Biology & Therapeutics
Brittany Pioso, Structural Biology
Rehana Punjwani, MD, Global Child Health[1]
Bilal Qureshi, MBBS, FCPS, Global Child Health
Sandi Radko-Juettner, Oncology
Muhammad Rafie Raza, MD, Global Child Health
Revathi Rajagopal, MD, MMed, Global Child Health
Adriana Ramirez Negron, Infectious Diseases
Kirtikumar Rathod, MD, Global Child Health[1]
Isaiah Reeves, Surgery
Jordan Roach, Developmental Neurobiology
Samuel Rovito, Infectious Diseases
Lauren Rowland, Infectious Diseases
Abideen Olurotimi Salako, MD, Global Child Health
Kate Shapiro, MD, Clinical Investigation
Akshay Sharma, MD, Clinical Investigation
Melissa Shenep, MD, Clinical Investigation
Sarah Sherman, Structural Biology
Jamaica Siwak, Cell & Molecular Biology
Maria Smith, Infectious Diseases
Hannah Snoke, Chemical Biology & Therapeutics
Matthew So, Immunology
Bradley Stevens, Oncology
Morgan Sutton, Bone Marrow Transplantation & Cellular Therapy
Samantha Turk
Ana Vazquez-Pagan, Infectious Diseases
Dennis Voronin
Christina Wang, Cell & Molecular Biology
Nicholas Watkins, MD, Clinical Investigation
Kendall Whitt, Infectious Diseases
Elizabeth Wickman, Bone Marrow Transplantation & Cellular Therapy
Kristin Wiggins, Infectious Diseases
Benjamin Wilander, Immunology
McLean Williamson, Hematology
Stephen Winston, Surgery
Tristen Wright, Cell & Molecular Biology
Milugeta Yimer, MD, Global Child Health

External Graduate Students
Ahmed Abuzaid, Surgery
Osama Alaidi, Chemical Biology & Therapeutics
Amir Arabzade, Developmental Neurobiology
Ingmar Bastian, Chemical Biology & Therapeutics
Lauren Brakefield, Cell & Molecular Biology
Anthony Brown, Pharmacy & Pharmaceutical Sciences[2]
Theresa Bub, Infectious Diseases
Jingjing Chen, Hematology
Brandi Clark, Immunology
Ashton Coker, Chemical Biology & Therapeutics
Amy Davis, Infectious Diseases
Laura Doorley, Pharmacy & Pharmaceutical Sciences
Ashley Gray, Pharmacy & Pharmaceutical Sciences
Xian Han, Structural Biology
Alexander Jenner, Chemical Biology & Therapeutics
Menglin Jiang, Immunology
Alisha Kardian, Developmental Neurobiology
William Kuenzinger, Developmental Neurobiology
Genevieve Lambert, Epidemiology & Cancer Control
Xin Lan, Immunology
Chun-Yang Lin, Immunology
Michaela Meehl, Immunology
Joseph Miller, Pharmacy & Pharmaceutical Sciences
Kumar Niloy, Pharmacy & Pharmaceutical Sciences
Allison Norman, Immunology
Schyler Odum, Chemical Biology & Therapeutics
Christopher Patton, Infectious Diseases
Christopher Rogers, Hematology
Dilruba Sharmin, Chemical Biology & Therapeutics
Utsav Shrestha, Diagnostic Imaging
Dewan Shrestha, Hematology
Jason Weesner, Genetics[3]
Jinjun Wu, Cell & Molecular Biology
Zhen Xie, Computational Biology
Zemin Yang, Cell & Molecular Biology
Jay Yarbro, Structural Biology
Satoshi Yoshimura, Pharmacy & Pharmaceutical Sciences
Ugur Yurtsever, Cell and Molecular Biology
Jingwen Zhu, Pharmacy & Pharmaceutical Sciences

[1]No longer at St. Jude, [2] Promoted to staff position, [3]Promoted to postdoctoral fellow position

SCIENTIFIC REPORT **2023**

Boards & Executives

2022 Board of Governors

These volunteers served on the Board of Governors of St. Jude Children's Research Hospital during 2022. Officers are indicated by the titles under their names.

Joyce A. Aboussie
Steven J. Allen MD[1]
Joseph S. Ayoub Jr.
Paul J. Ayoub
Chair
Frederick M. Azar, MD
Martha Perine Beard
Sheryl A. Bourisk[2]
Robert A. Breit, MD
Terry L. Burman
Ann M. Danner
Joseph M. DeVivo
Lisa R. Diller, MD[1]
James R. Downing, MD[3]
St. Jude President and CEO
Joseph E. Eid, MD[1]
Fred P. Gattas III, PharmD
Ruth C. Gaviria[2]
Judy A. Habib
Vice Chair
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[1] November–December, 2022, [2] January–June, 2022 , [3] Ex officio voting member, [4] July–December, 2022, [5] Inactive

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[1]Deceased, [2]Emeritus , [3]No longer at St. Jude

Operations & Statistics

OPERATIONS	
Operating expenses[1]	$1.249 billion
Number of employees[2]	5,699
RESEARCH STATISTICS	
Grant funding[1]	$130.3 million
Peer-reviewed publications[3]	826
Faculty members	334
Postdoctoral fellows	370
Clinical residents and fellows[4]	241
Graduate students	109
CLINICAL STATISTICS	
Number of beds open[5]	73
Total outpatient visits	230,234
Inpatient admissions	3,328
Total inpatient days	17,175
Total protocol enrollments in 2021	4,877
Patients enrolled in therapeutic trials	685
Patients enrolled in nontherapeutic trials	4,192 3,215 in prospective trials 975 in tissue-banking protocols
Total number of protocols that were open to accrual in 2021	755
Number of active therapeutic trials	200
Number of active nontherapeutic trials	555 179 prospective trials 364 retrospective trials 3 tissue-banking protocols 9 other protocols

[1] Data represent the period July 1, 2021, to June 30, 2022.

[2] Data are from July 1, 2022.

[3] Data include original research articles only.

[4] Data include 39 full-time St. Jude fellows and 202 rotating fellows and residents from the University of Tennessee Health Science Center or other medical schools.

[5] Data represent the number of beds in use. St. Jude is licensed for 80 beds.