Translating Science into Survival

SCIENTIFIC REPORT 2023
St. Jude researchers, backed by extraordinary resources and support teams, are focused on making big discoveries.
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
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ince 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), 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.

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.

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.
CAR targeting the glucose-regulated
detailed their engineering of a novel
Communications, the researchers
In a paper published in
Nature
specific antigens.
inside-out approach to select AML-
overcome this, researchers used an
finding an antigen specific to AML
therapy for AML. Using
Velasquez’s lab is also investigating
therapy
for AML
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
persistance 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
may 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,
stores the ability of AML-specific T cells
to recognize tumor cells that express
low levels of the target antigen and
function in chronic antigen exposure
settings. This resulted in improved
antitumor activity in several
preclinical solid tumor models.

Molecularly, the absence of RASA2
modulated the transcriptional
programs of activator protein 1 (AP-
1), nuclear factor-kappa B (NF-kB),
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,
are able 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
persistance 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 this 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 of CD19-CAR T cells. They published their findings in Cancer Discovery.

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 immunooncology 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.

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 of Cellular Therapy, highlighting its commitment to producing high-quality therapeutic products. It features SS 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 asset 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 therapeutic. 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.
Of the estimated 20,000 genes in the human genome, more than one-third are expressed in the brain.
F or 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.

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.
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,” 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 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 a transcription factor, Gtf2ird1, encoded by one of the 27 genes lost in WBS, regulates the expression of a neuropeptide receptor, VIPR1, in the auditory cortex. Deletion or overexpression of 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 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.

“Recording electrophysiological activity on the auditory cortex provides a unique opportunity to study the development of the auditory cortex in 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
Department of Developmental Neurobiology

**Paul Northcott, PhD**
Developmental Neurobiology
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 and group-level lives. For example, treating cancer 5, 10, 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 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 survivors who 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 76% 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 6.53 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.

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 4.5 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.

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.”

Zhaoming Wang, PhD
Epidemiology and Cancer Control

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

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

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Yadav Sapkota, PhD
Epidemiology and Cancer Control
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 there 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, including genetic ancestry of 2,428 children 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 step up to see if we can develop therapies focusing on children of color for 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 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.

They looked for associations between clinical factors and gene-by-treatment interactions – 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, carbustine, leucovorin, 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 with these 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 pharmacogenomic PRS (surPRS) predicted RVD better than any other score.

The surPRS achieved good discriminatory power with an Area Under the Curve (AUC) validation of 0.82, 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 doubt 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 survivorship outcomes 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 face a higher risk 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 impairments 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 certain survivors, based on their disease, genetics, and treatment, are at higher risk of health conditions developing later in life; in many cases, survivors who smoked experienced a higher risk of adverse health outcomes. Clinical cardiovascular and neurologic conditions were also associated with impairments in nearly every aspect tested.

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...
used epigenome-wide association studies to identify epigenetic 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 socioeconomic 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 socioeconomic markers may have fueled the disparities through epigenetic changes. Epigenetics encompasses how genes are regulated, which can be affected by the 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 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 socioeconomic factors 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 the epigenetic 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 simultaneous symptoms of moderate-to-severe intensity.

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 271 times higher if they have less than a high school education. These trends like this, but the magnitude of the difference was us to say, ‘St. Jude is the place where the old principles of care are being improved survival, as opposed to looking at the long-term consequences of treatment.’

Robison identified and characterized that 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 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.”
Radiation therapy is a cornerstone of care for many types of pediatric cancer.
Radiation therapy for cranioophyngioma

With rare CNS tumors that have high survival rates, such as cranioophyngioma, 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.

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 cranioophyngioma.”

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 survival and overall survival, factors that need further study.

The researchers determined that given the likelihood of long-term survival in patients with cranioophyngioma 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.

Cranioophyngioma 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 cranioophyngioma. 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 cranioophyngioma.

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 cranioophyngioma 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.

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

Thomas Merchant, DO, PhD
Radiation Oncology
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.

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

Amar Gajjar, MD
Pediatric Medicine

Radiation therapists conduct proton therapy from the control room.
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 and perceptual speed by 10%-15% and 8%-12%, respectively. The results suggest 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.”

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?

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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
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.

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 Global 5 study, which attained 50% survival. Through the work of Pui and others, the Total studies helped boost survival past 70% in the 1990s.

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 16, which Pui led. The study pioneered measuring minimal residual disease (MRD) in cerebrospinal fluid. Remarkably, this central nervous system (CNS)-directed treatment approach successfully removed cranial irradiation from the standard of care for 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.

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.”

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.

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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 in Blood Cancer Discovery, looked at ALL subtypes such as DTUB4-rearranged, MXD1-like, BCR-ABL1-like, ETMY-RMK1-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 effective therapies.

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.”

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 Jin 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 calls 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
enom 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 complexity 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 plays a major role in 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 impact gene regulation. Researchers have discovered many abnormalities and these may be tied to individual mutations throughout the genome, and cancer.

Researchers are digging through the genome of cancer cells to understand how genes are controlled and express 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 genetic 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 the origin of leukemia.

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

### 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 oncprotein in ALL development and demonstrated 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 consequences.

### Beyond leukemia, coding and non-coding genetic variants remain a discovery area of focus.

Researchers continue to make discoveries 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 result is published in Blood; showed 33 coding and 11 noncoding variant risks in 28 of the families.

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

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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.”

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 TFIABP. To alter oncogenic transcription in neuroblastoma, the team developed a PROTAC compound to target and disrupt EP300. The compound, QJAD1, causes the loss of HK274 (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.”

The POWER OF PROTACS: PROTEIN DEGRADATION FOR TARGETED ANTICANCER THERAPY

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 continually 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.

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, ES 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-glutamidamide, 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 L1 other kinase, 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.

SAFER Ukraine partners include non-governmental organizations (NGOs) or foundations, such as Fundacja Herosi and Tabletchiki 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. 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."

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.

* 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), which could be due to treatment-related changes or tumor progression. Accurate differentiation between these 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 [11C] 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.

Scientists at St. Jude are changing that, recently publishing a study in the Journal of Nuclear Medicine on using [11C] 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.

PET imaging with MET gives an advantage in brain imaging because the tracer is not dependent on glucose metabolism for 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.

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, [18F]-2-fluoro-2-deoxy-D-glucose, or [18F]FDG. This is because heavily glucose-dependent normal brain tissue accumulates a high amount of [18F]FDG. Compared to [18F]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 [11C]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 halflife 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 analyzing T-cell specificity 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, 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 programs. 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 complex, scientists continue to work on refining methods and tools that researchers learn about the interplay between T-cell specificity and function across different disease states. CoNGA is not limited to 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.

If the patient has the right cell to respond

How are the patient’s cells responding?
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 new next-generation sequencing techniques, such as single-nucleus RNA sequencing and epigenetic profiling, on matched patient and orthotopic patient-derived xenografts that are available from the St. Jude Childhood 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,” said Dyer. “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 normal developmental 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.”

Charting the genomic landscape of ALL fuels precision medicine

S. 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-responding author Charles Mullighan, MD, PhD, 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 for us 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 co-regulatory regions. Broadly, the findings implicate a previously unknown pathway in the development of ALL.

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

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’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 Borchers, 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, and the way proteins can change the driving force for phase separation. Multiple phosphorylation events occur across a protein sequence, which 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.

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

Scientists led by Tanja Mittag, PhD, Department of Structural Biology, and Roby 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 region, 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 and the spacers model for phase separation. Knowing the stickers’ identity and the protein’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.

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Investigators have teased apart how three physical/molecular properties — sticker interaction strength, sticker charge, and spacers — determine the volume and net charge per residue — drive phase separation, an important biological process for forming condensates.
A new therapeutic target for alveolar rhabdomyosarcoma

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.

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

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 see this instrument be further adapted 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.

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.

“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 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.
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’s 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 temperature, 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 had 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.”

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, human babies born with another hemoglobin, gamma-globin, which is expressed instead of beta-globin during fetal development.

Gammaglobin combines with alpha-globin to form fetal hemoglobin (HbF). Typically around the time of an infant’s birth, their gamma-globin-gamma-globin expression is turned off and beta-globin is turned on, resulting in a switch from HbF to adult hemoglobin.

The researchers showed that a drug that activates 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 HIFα 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 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 HIFα 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 HIFα-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.

“Ideation of gamma-globin as a HIF target gene supports the notion that HIF 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

Charles W. M. Roberts, MD, PhD
Director

Charles G. Mullighan, MBBS(Hons), MSc, MD
Deputy Director

Suzanne J. Baker, PhD
Associate Director, Basic Science

Heather M. Brandt, PhD
Co-Associate Director, Outreach

Elizabeth Fox, MD, MS
Associate Director, Clinical Research

Melissa M. Hudson, MD
Associate Director, Population Sciences

Shondra M. Pruett-Miller, PhD
Associate Director, Shared Resources

Carlos Rodriguez-Galindo, MD
Co-Associate Director, Outreach

Victor M. Santana, MD
Interim Associate Director, Diversity, Equity & Inclusion

Dana Wallace, MS
Associate Director, Administration

Gerald P. Zambetti, PhD
Associate Director, Education & Training

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 BIOLOGY 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.

CANCER CONTROL & SURVIVORSHIP 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 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.

NEUROBIOLOGY & BRAIN TUMOR PROGRAM

Co-leaders: Suzanne J. Baker, PhD; Ambar 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 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. Papalo, 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
- Cytophenetics
- Flow Cytometry and Cell Sorting
- Pharmacokinetics
- Protein Production
- Transgenic/Gene Knockout

Therapeutics

• Transgenic/Gene Knockout

• Protein Production

• Pharmacokinetics

• Flow Cytometry and Cell Sorting

• Cytophenetics

• Cell and Tissue Imaging

• Biostatistics

• Bioinformatics and Biotechnology

• Shared Resources

• Developmental Biology & Solid Tumor Program

• Cancer Control & Survivorship Program

• Cancer Biology Program

• Hematological Malignancies Program

• Neuroscience & Brain Tumor Program

• Scientific Report 2023
The St. Jude Affiliate Program has a two-fold mission:
1. To extend St. Jude care and research to more children
2. 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.

ST. JUDE AFFILIATE SITES

Batson Rouge, LA
Our Lady of the Lake Children’s Hospital
Our Lady of the Lake Regional Medical Center
Medical Director • Jeffrey Deyo, MD, PhD
Kacie Sims, MD
Sasky Bani, MD
Katherine Helo, NP
Jessica Templet, PA-C
Joseph Kent, PA

Charlotte, NC
Novant Health Hemby Children’s Hospital
Medical Director • Christina Bolen, MD
Jessica Bell, MD
Jenny McDaniel, MD
Joanne McManaman, MD
Felipe Bautista, MD
Holly Edington, MD
Courtney Saine, NP
Jennifer Weisner, NP
Andria Kokoszka, NP
Courtney Carr, PA

Huntsville, AL
Huntsville Hospital for Women & Children
Huntsville Hospital
Medical Director • Marla Daves, MD
Sana Mohiuddin, MD
Medical Director • Emily Clawson, NP

Johnson City, TN
Niswonger Children’s Hospital – Ballard Health
East Tennessee State University
Medical Director • Marcela Popescu, MD
Myesa Embereishi, MD
Angela Willocks, RN, MSN, CFNP
Lauren Wyatt, NP
Amy Shaw, NP

Peoria, IL
Children’s Hospital of Illinois – OSF Healthcare System
University of Illinois College of Medicine at Peoria
Medical Director • Brinda Mehta, MD
Pedro de Alarcon, MD
Amber D’Souza, MD
Sabrina Kimrey, MD
Prema Kumar, MD
Jaime Libes, MD
Mary Beth Ross, MD, PhD
Kay Savin, MD
Beth Speckhart, NP
Sue Gaitros, RN
Diana Simmons, NP
Colleen Kirr, NP

Shreveport, LA
Ochsner LSU Health – Shreveport
Medical Director • Majed Jeroudi, MD
Elizabeth Wadhwa, MD
Diana Townesid, NP
Amanda Saunders, NP

Springfield, MO
Mercy Children’s Hospital – Springfield
Mercy Health System
Medical Director • Franciska Fastie, MD
Batzel El-Atoum, MD
Carolyn Sullivan, NP
Danielle Lee, NP

Tulsa, OK
The Children’s Hospital of Saint Francis
Medical Director • Greg Kirkpatrick, MD
Martina Hum, MD
Shilpa Shukla, MD
Jill Salo, MD
Sara Mednansky, MD
Cori Ryan, NP
Allison Taylor, NP

St. Jude Affiliate Program

ST. JUDE GLOBAL

CAPACITY BUILDING

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.

ADMINISTRATION

Medical Director
Carolyn L. Russo, MD
Nursing Director
Jennifer Morgan, MSN
Clinical Operations Director
Nicra Graunke, MPH

St. Jude Affiliate Program
The St. Jude Children’s Research Hospital Graduate School of Biomedical Sciences (Graduate School) is comprised of 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 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.
Faculty, Fellows & Students
**BIOSTATISTICS**

**CHAIR**
M. Gaborieau, PhD, M.D.: Endowed Chair in biostatistics • Design and analyses of phase I-II clinical trials; biomarker discovery and validation, risk prediction models

**MEMBERS**
Geng Gao, PhD • Statistical methods in cancer biology; clinical & translational studies
Ekaterina Prokhorova, PhD • Biostatistics
Gosia Kang, PhD • Statistical genetics/geneomics, modeling of complex data

**ASSISTANT MEMBERS**
Li Tang, PhD1 • Prediction, validation, diagnostic testing, machine learning

**ASSISTANT MEMBERS**
Gao Li, PhD1 • Statistical learning and computing methods for biological discovery

**INSTRUCTOR**
Sudesh R. Sekular, PhD • Design and sequential monitoring of clinical trials

**BONE MARROW TRANSPLANTATION & CELLULAR THERAPY**

**CHAIR**
Stephen W. Gottschalk, MD: Endowed Chair in Bone Marrow Transplantation & Cellular Therapy • Cancer immunotherapy, cellular therapy, hematopoietic cell transplantation

**MEMBER**
Brandon L. Truitt, MD: Hematopoietic cell transplantation

**ASSOCIATE MEMBERS**
Eswick V. Kottapalli, MD • Gene therapy & transplantation for nonmalignant hematologic diseases
Amita Srinivasan, MD • Hematopoietic cell transplantation and infections in the immuno-compromised host

**ASSISTANT MEMBERS**
Christopher Porteus, MD, M.D.: Cellular therapy for solid tumors
Alex E. Ibrahim, MD: Gene therapy for brain tumors
Gao Li, PhD: Statistical methods for incomplete survival data

**INSTRUCTORS**
Rebecca A. Spiller, MD • Cellular therapy for pediatric malignancies
Gavin C. Zeddy, MD, PhD: Cellular therapy and T-cell differentiation

**CELL & MOLECULAR BIOLOGY**

**CHAIR**
J. Paul Taylor, MD, PhD, FACP: Executive Vice President and Scientific Director; Edward J. Boyer Endowed Chair in Cell & Molecular Biology • Molecular genetics of neurological diseases

**MEMBER**
Stacey K. Ogden, PhD1 • Mechanisms of Hedgehog signal transduction

**ASSISTANT MEMBERS**
Maryam Q. Naghavi, MD, PhD1 • Mechanisms of Hedgehog signal transduction

**INSTRUCTORS**
Paulina Velasquez, MD1 • Cellular therapy for hematologic malignancies

**CHEMICAL BIOLOGY & THERAPEUTICS**

**CHAIR**
A. Z. Anapel, PhD, R. J. Ulrich Endowed Chair in Chemical Biology & Therapeutics • Synthetic gene regulation for personalized medicine, anticancer transcription factors to control stem cell fate choices

**MEMBERS**
Takahiro Chang, PhD, PhD1: Antibiotic resistance and therapeutic responses
Richard E. Lee, PhD, Endowed Chair in Medicinal Chemistry • Discovery of new therapeutic drugs, structure-based drug design

**ASSOCIATE MEMBERS**
Philip M. Potter, PhD1 • Translational research & chemical biology

**ASSISTANT MEMBERS**
Daniel J. Biao, PhD • Covalent inhibitors and automated synthesis

**INSTRUCTORS**
Hai T. Dao, PhD1 • Discovery of new antibiotic agents and structure-based drug design

1 Graduate school faculty members; 2 Secondary appointment; 3 No longer at St. Jude; 4 Emeritus; 5 Deceased
GENETICS
CHAIR
Carlos Rodriguez-Galindo, MD, Vice President and Executive Director, St. Jude Children’s Research Hospital

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

ASSOCIATE MEMBERS
Ulrike M. Reiss, MD1 • Bleeding disorders, gene therapy for hemophilia, bone growth

ASSISTANT MEMBERS
Parul Rai, MD • Cardiac injury in sickle cell disease

INSTRUCTORS
Winfred C. Wang, MD4 • Blood development; red cell biology; novel therapeutic approaches to pediatric solid tumors

IMMUNOLOGY
CHAIR
Douglas B. Green, PhD • Peter C. Doherty Endowed Chair in Immunology - Cell death, apoptosis & immune function

VICE-CHAIR
Thanh-Dien Duong-Khong, PhD, Rose Marie Thomas Endowed Chair in Immunology - Immune signaling and metabolism

ASSOCIATE MEMBERS
Wenjiang Feng, PhD1 • Dynein & transcytotic barriers of T-cell immunity

ADJUNCT MEMBERS
Diana C. Mccall, MD • Immunology

GLOBAL PEDIATRIC MEDICINE
CHAIR
Igor I. Bud depos, MD, PhD, 2014 Nobel Laureate in Physiology or Medicine, Executive Vice President & Chief Scientific Officer, St. Jude Children’s Research Hospital

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

ASSOCIATE MEMBERS
Christophe Lechauve, PhD3 • Translational studies in nonmalignant hematology

ASSISTANT MEMBERS
Noureen L. Fawzy, MD, MPH • Global health, pediatric oncology, education, pediatric CNS tumors

INSTRUCTORS
Johannes W. Stickney, MD1; The Wall Street Committee Endowed Chair in Clinical Oncology - Mechanisms of leukemogenesis, benign & malignant blood disorders

HEMATOLOGY
CHAIR
Michael J. Morse, MD, PhD, PFI • Arthur Nechemias Endowed Chair in Hematology - Blood development, red cell biology, novel therapies to pediatric solid tumors

MEMBERS
John D. Gergis, MD, PhD, MPH • The Wall Street Committee Endowed Chair - Mechanisms of leukemogenesis, congenital & malignant blood disorders

ASSOCIATE MEMBERS
Jessica A. Boyan, MD, MPH • Global health, childhood leukemias, developmental diseases

ASSISTANT MEMBERS
Parul Rai, MD • Cardiac injury in sickle cell disease

INSTRUCTORS
Robert A. De Angelis, MD • Health communication & implementation science

RESEARCH ASSOCIATES
Philip A. Dowbenko, MD, MPH • Gene therapy & genome editing

ADJUNCT MEMBERS
Friederike Heine, MD • Leukemia, lymphoma, hemoglobinopathies, and acute myeloid leukemia

ADJUNCT MEMBERS
Michelle Pajak, MD • Congenital hematological disorders

GLOBAL INFECTIOUS DISEASES
CHAIR
Ursula M. Corbett, MD, 2015 Nobel Laureate in Physiology or Medicine, Chief and Director, St. Jude Children’s Research Hospital

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

ASSOCIATE MEMBERS
Gaston K. Rivera, MD4 • Global medicine, subamputative pediatric surgical oncology

ASSISTANT MEMBERS
Nalini Mokhe, MD, MPH • Global health, novel therapeutics, neuroblastoma, research ethics

INSTRUCTORS
Benjamin A. Youngblood, PhD1 • T-cell memory differentiation, deletion, & immunotherapy

RESEARCH ASSOCIATES
Hongbo Chi, PhD1; Robert G. Webster Endowed Chair in Immunology - Immune signaling and metabolism

ADJUNCT MEMBERS
Michael F. Crow, PhD • Cell death, autophagy, & immune function

GLOBAL ONCOLOGY
CHAIR
Nasser J.Warning, PhD, MSc, FACS • Vice President of Clinical Development for Oncology, St. Jude Children’s Research Hospital

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

ASSOCIATE MEMBERS
Ulrike M. Reiss, MD1 • Bleeding disorders, gene therapy for hemophilia, bone growth

ASSISTANT MEMBERS
Parul Rai, MD • Cardiac injury in sickle cell disease

INSTRUCTORS
Winfred C. Wang, MD4 • Blood development; red cell biology; novel therapeutic approaches to pediatric solid tumors

RESEARCH ASSOCIATES
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ADJUNCT MEMBERS
Friederike Heine, MD • Leukemia, lymphoma, hemoglobinopathies, and acute myeloid leukemia

ADJUNCT MEMBERS
Michelle Pajak, MD • Congenital hematological disorders

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ASSISTANT MEMBERS
Parul Rai, MD • Cardiac injury in sickle cell disease

INSTRUCTORS
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RESEARCH ASSOCIATES
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STRUCTURAL BIOLOGY

CHAIR
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MEMBERS
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Scott C. Blackard, PhD; Endowed Chair in Molecular Imaging – Imaging structure-function relations in macromolecular assemblies
Richard W. Kriegel, PhD; Structural basis of tumor suppressor function
Tanja Mittag, PhD; Molecular basis of liquid–liquid phase separation
Junmin Peng, PhD; Proteomics & metabolomics in human disease

ASSOCIATE MEMBER
Stephen White, DPhil

ASSISTANT MEMBERS
Marcus Fisher, PhD; Protein conformational ensembles
Chia-Hsueh Lee, PhD; Molecular mechanisms of membrane signaling
Tudor Moldoveanu, PhD; Structural and pharmacological studies of membrane proteins

ADJUNCT MEMBERS
Brenda A. Schulman, PhD; Cellular regulation by ubiquitin-like proteins

SURGERY

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Stephen J. Shochat, MD; Surgical oncology – Neurosurgery, neuroblastoma, Wilms tumor

ASSOCIATE MEMBER
Andrew Jackson Murphy, MD; 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; Sarcoma, immunotherapeutic strategies against sarcomas & solid tumor metastases
Jun Yang, MD, PhD; 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 otorhinolaryngology
Jerome Thompson, MD, MBA; Pediatric otorhinolaryngology
Matthew W. Wilson, MD; St. Jude Chair in Pediatric Ophthalmology – Pediatric ophthalmology

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

MEMBERS
Linda M. Henderson, PhD; EBV quality control in development & diseases
Stephan J. Shochat, MD; Endowed Chair in Molecular Oncogenesis – Genomics & epigenetics in pediatric brain tumors

ASSISTANT MEMBER
Charles L. Levy; 3D genome and transcriptional regulation in cancer

¹ Graduate school faculty members; ² Secondary appointment; ³ No longer at St. Jude; ⁴ Emeritus; ⁵ Deceased
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Phillip D. Rogers, PharmD, PhD
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Frederick M. Azar, MD
Paul J. Ayoub
Steven J. Allen MD
Joyce A. Aboussie
Officers are indicated by the titles under their names.

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This panel of physicians and scientists, serving during 2022, fostered the institution’s development through discussion with faculty members, reports to the Board of Governors, and advice to the President and CEO on scientific and clinical research directions.

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Professor of Pediatrics, Harvard Medical School
Institute Member, Broad Institute
Dana-Farber/Boston Children’s Cancer and Blood Disorders Center
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Perelman School of Medicine at the University of Pennsylvania
Division of Oncology
Children’s Hospital of Philadelphia
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Professor, Pediatric Oncology
Vice Chair for Outcomes Research, Department of Pediatrics
Director, Institute for Cancer Outcomes and Survivorship
University of Alabama at Birmingham
School of Medicine
University of Alabama at Birmingham
Daphne A. Haas-Kogan, MD
Professor of Radiation Oncology, Harvard Medical School
Chair, Department of Radiation Oncology
Dana-Farber Cancer Institute
Member, National Academy of Medicine
David Ginsburg, MD
James V. Neel Distinguished University Professor
Departments of Internal Medicine, Human Genetics, and Pediatrics
Investigator, Howard Hughes Medical Institute
University of Michigan Medical School
Member, National Academy of Medicine
Mary K. Gospodorowicz, MD, FRCP, FRCR (Hon)
University Professor, University of Toronto
Consultant, Princess Margaret Cancer Centre
Nathaniel S. Gray, PhD
Member, CHI-M-H
Program Leader, Small Molecule Drug Discovery for the Innovative Medicines Accelerator
Co-Director, Cancer Drug Discovery
Co-Leader, Cancer Therapeutics Research Program
Krishnan-Shah Family Professor, Chemical and Systems Biology
Stanford University
John Kuriyan, PhD
Investigator, Howard Hughes Medical Institute
Distinguished Professor Molecular & Cell Biology and Chemistry
University of California at Berkeley
Member, National Academy of Sciences
Joshua R. Sanes, PhD
Jeff C. Tarr Professor of Molecular and Cellular Biology
Founding Director, Center for Brain Science
Harvard University
Department of Molecular and Cellular Biology
Member, National Academy of Sciences
Kevin M. Shannon, MD
American Cancer Society Research Professor
Roma and Marvin Auerback Distinguished Professorship in Pediatric Molecular Oncology
University of California, San Francisco
Helen Diller Family Comprehensive Cancer Center
Sarah A. Teichmann, FMedSci FRS
Head of Cellular Genetics
Senior Group Leader
Wellcome Sanger Institute
Wellcome Genome Campus

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Joseph G. Shaker
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Michael C. Simon
Tony Thomas
Richard M. Unes
Paul H. Wein
Susan R. Windham-Bannister
Tama H. Zaydon

1November–December 2022
2January–June 2022
3Ex officio voting member
4July–December 2022
5Inactive
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Chair, Immunology

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Chair, Genetics

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Charalampos G. Kalodimos, PhD
Chair, Structural Biology

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Structural Biology

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Senior Vice President Chief Nursing Executive

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Executive Vice President Clinical Director Physician-in-Chief

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Oncology

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Executive Vice President Chair, Department of Global Pediatric Medicine Director, St. Jude Global

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Tumor Cell Biology

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Chair, Tumor Cell Biology

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Chair, Infectious Diseases

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Chair, Hematology

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President and Dean, St. Jude Graduate School of Biomedical Sciences Structural Biology

Kelvin Womack
Vice President Chief Diversity & Inclusion Officer

Jinghui Zhang, PhD
Chair, Computational Biology

1Deceased, *Emeritus, **No longer at St. Jude
Operations & Statistics

<table>
<thead>
<tr>
<th>OPERATIONS</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Operating expenses(^1)</td>
<td>$1.249 billion</td>
</tr>
<tr>
<td>Number of employees(^2)</td>
<td>5,699</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>RESEARCH STATISTICS</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Grant funding(^3)</td>
<td>$130.3 million</td>
</tr>
<tr>
<td>Peer-reviewed publications(^3)</td>
<td>826</td>
</tr>
<tr>
<td>Faculty members</td>
<td>334</td>
</tr>
<tr>
<td>Postdoctoral fellows</td>
<td>370</td>
</tr>
<tr>
<td>Clinical residents and fellows(^4)</td>
<td>241</td>
</tr>
<tr>
<td>Graduate students</td>
<td>109</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CLINICAL STATISTICS</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Number of beds open(^5)</td>
<td>73</td>
</tr>
<tr>
<td>Total outpatient visits</td>
<td>230,234</td>
</tr>
<tr>
<td>Inpatient admissions</td>
<td>3,328</td>
</tr>
<tr>
<td>Total inpatient days</td>
<td>17,175</td>
</tr>
<tr>
<td>Total protocol enrollments in 2021</td>
<td>4,877</td>
</tr>
<tr>
<td>Patients enrolled in therapeutic trials</td>
<td>685</td>
</tr>
<tr>
<td>Patients enrolled in nontherapeutic trials</td>
<td>4,192</td>
</tr>
<tr>
<td>3,215 in prospective trials</td>
<td></td>
</tr>
<tr>
<td>975 in tissue-banking protocols</td>
<td></td>
</tr>
</tbody>
</table>

Total number of protocols that were open to accrual in 2021 | 755

Number of active therapeutic trials | 200
Number of active nontherapeutic trials | 555

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.