Translating Science
Into Survival

SCIENTIFIC REPORT **2022**

Behind the cover

The image on the cover is an artist's rendition of an activated T cell visualized by electron microscopy overlaying a depiction of protein-protein interactions in nutrient signaling networks. St. Jude investigators continue to advance our understanding of T cell development, identity, and function. Their findings set the foundation for optimizing T cell mediated immunity, vaccine engineering, and immunotherapy for patients with cancer. The image echoes the institution's commitment to cutting-edge technologies, bioinformatics, and advanced microscopy.

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

Our culture and campus foster the free exchange of ideas to promote creative, collaborative science.

PHOTOGRAPHY DISCLAIMER:

All images were obtained either before the COVID-19 pandemic was declared or per COVID-19 safety guidelines at the time of the photo shoot.

During the past 60 years, St. Jude Children's Research Hospital has honored one noble mission and the promise of its foundation.

From modest beginnings, the institution has forged a path in science and medicine, advancing knowledge and lifesaving care for countless children. With a pioneering spirit that has only grown stronger since the doors of St. Jude opened, we are pursuing the most extensive strategic expansion in our institution's history. This bold plan is being fulfilled in laboratories, clinics, and institutions around the world, with the unifying goal of accelerating progress toward curing pediatric catastrophic diseases.

This *Scientific Report* details some recent advances that are turning the tide against pediatric cancer and other catastrophic diseases. In the first feature, we report the progress made by immunology groups studying how key metabolism-associated signals affect T-cell development. The extent to which T cells differentiate into specific subsets influences the effectiveness of a person's immune system; however, the mechanisms that drive T cell–subtype specification are largely unknown. Recent findings from St. Jude immunologists are inspiring new research. This ripple effect has the potential to identify novel approaches to enhance the immune system's ability to clear infections and improve cancer immunotherapy.

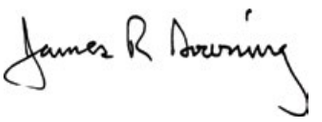
COVID-19 has dramatically changed the world and renewed our focus on the devastation that infectious diseases can cause. Over the past 2 years, researchers have studied SARS-CoV-2, the virus that causes COVID-19, to understand its pathogenesis and learn how variants have evolved and altered the disease landscape. In the second feature story, we present work by St. Jude scientists monitoring the virus, looking for new ways to combat it, and gaining knowledge to help chart a path forward in the coming years. One team spearheaded a study that examined viral genetics and immune responses to infection at the start of the pandemic and later studied the effects of vaccination. Other groups investigated whether past exposure to common-cold coronaviruses influences a person's response to SARS-CoV-2 infection. St. Jude Global led an assessment of the effects of SARS-CoV-2 on children with cancer and the provision of pediatric oncology care around the world.

Caused by a mutation in the *HBB* gene, sickle cell disease can lead to severe pain, multiorgan damage, and early death. Fetal hemoglobin (HbF), the early form of the protein, is unaffected by the *HBB* mutation. Understanding how HbF switches to adult hemoglobin can help us develop therapies that prevent this transition, thereby increasing HbF levels and protecting against sickle cell disease. In the third feature, we describe new insights into the mechanisms controlling HbF expression and improved gene-manipulation technologies. This understanding can help us reactivate HbF production, thereby curing sickle cell disease. As part of the Novel Gene Therapies for Sickle Cell Disease Research Collaborative, researchers at St. Jude and partner institutions have made major strides in these areas.

For pediatric patients with cancer, comprehensive assessments are crucial to advancing care and improving quality of life. By examining the short- and long-term physical and cognitive outcomes of diseases and anticancer treatments, we can identify risk factors that impair neurocognitive development and function. Ultimately, this information helps guide clinical decision-making and efforts to develop targeted interventions that address neurocognitive decline in this population. In the fourth feature article, we present findings from recent studies addressing the need for cognitive monitoring and intervention in patients and survivors of various childhood cancers.

In the final feature, we highlight progress made by St. Jude investigators studying the biological basis of the elevated risk for acute, highly aggressive leukemias. Their work focuses on hereditary bone marrow failure, myelodysplastic syndromes, rare lineage-ambiguous leukemias, and childhood cancer survivors whose treatment included cytotoxic agents. We also provide an update on the recently established multidisciplinary program that seeks to elucidate the genetic mechanisms influencing disease onset, progression, and evolution to high-risk leukemia while also providing the best clinical care possible for patients with these disorders.

From a heartfelt pledge in 1962 to a global symbol of hope in 2022, St. Jude is leading the way the world understands, cures, and defeats childhood cancer and other catastrophic diseases. It is our legacy, our future, and our promise to the children of the world.



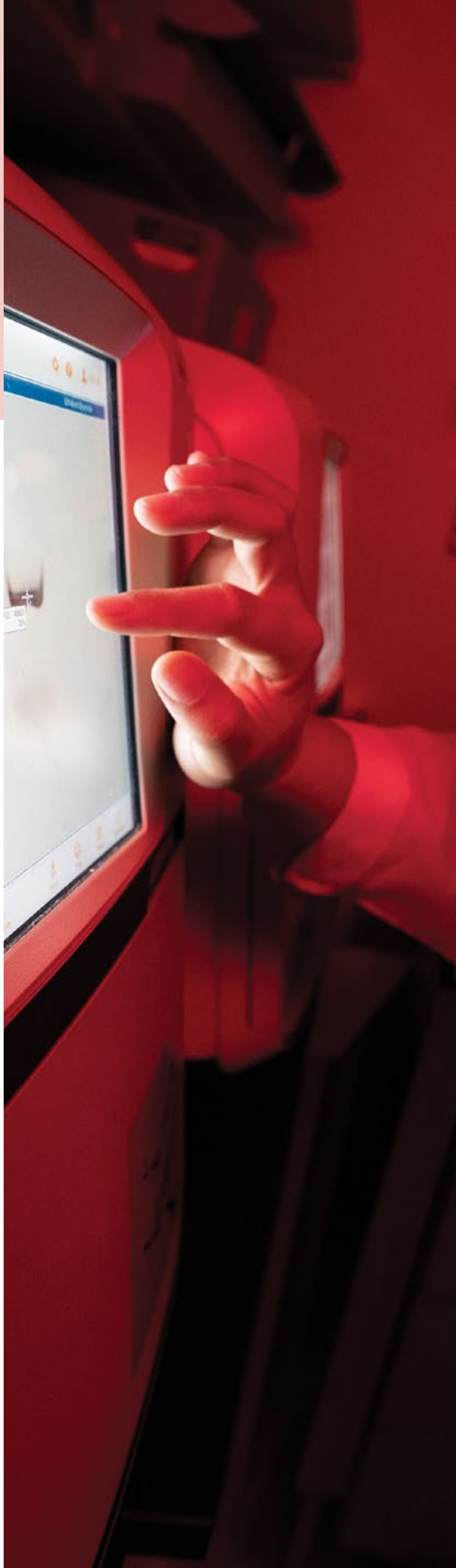
James R. Downing, MD

President and Chief Executive Officer

St. Jude Children's Research Hospital

METABOLIC SIGNALING DIRECTS T CELL–MEDIATED IMMUNITY

T cells orchestrate adaptive immunity by sensing pathogens or tumors and formulating responses specific to local conditions and needs. Although all T cells arise from the same progenitor cells in the thymus, subsets of T cells have specialized functions. These subsets form in response to stimuli received during the cells' activation and include short-lived effector T (T_{eff}) cells that may be cytotoxic and long-lived memory T (T_{mem}) cells that mediate long-term immunity. During activation, T cells may also become specialized to support specific immune responses or stimulate B cells that secrete antibodies. T cells may also develop into regulatory (T_{reg}) cells that suppress immune responses, thereby preventing inadvertent damage to self tissues due to overactive immune and inflammatory responses.



Lingyun Long, PhD

The extent to which T cells differentiate into specific effector and memory forms affects the overall effectiveness of a person's adaptive immune system; however, the mechanisms that drive subtype specification are largely unknown. By elucidating the molecular underpinnings of T-cell differentiation, researchers can provide an avenue to improve vaccines and therapies and expand our understanding of immune-mediated diseases.

Immunologists at St. Jude are studying how signals received by T cells influence their development into effector, memory, or regulatory forms and have identified important metabolism-associated signals in these processes. Their findings are inspiring new investigations into how T-cell differentiation, cell fate, and ultimately function are modulated and have the potential to reveal new approaches to enhance the immune system's ability to clear infections and improve immunotherapy for patients with cancer. Here we present key discoveries made by two laboratories over the last year.

A Metabolic Pathway Controls T Cell–Mediated Activation of Humoral Immunity

T cells orchestrate adaptive immune responses and support antibody production by B cells. The primary subset of T cells that engages B cells is called follicular helper (T_{FH}) cells. After a B cell recognizes a cognate antigen, T_{FH} cells activated by the same antigen interact with the B cell and provide signals fostering the B cell's maturation and production of antigen-specific antibodies. As such, T_{FH} cells form a bridge between T-cell immunity and antibody-based humoral immunity. Until recently, the underlying molecular mechanisms that control T_{FH}-cell differentiation and B-cell activation have been unclear. Hongbo Chi, PhD (Immunology), led an effort to better understand this process.

Although previous work showed that T_{FH} cells need nutrients for their proliferation and differentiation, immunologists knew little about the specific nutrient and metabolic requirements for priming humoral immunity. Dr. Chi's group conducted an unbiased screen of more than 3000 metabolism-associated genes in mouse $CD4^+$ T cells by using a CRISPR/Cas9-based deletion system. They knocked out genes of interest and then tested the ability of T_{FH} cells to induce a humoral response by using a viral infection as a trigger. This revealed the cytidine diphosphate (CDP)–ethanolamine metabolic pathway as a major determinant of T_{FH}-cell function. This metabolic pathway was not previously linked to T_{FH} cells and had been recognized primarily for its role in generating the phospholipid phosphatidylethanolamine, a building block of the cell membrane.

Dr. Chi's team reported in *Nature* how the CDP–ethanolamine pathway serves as an essential and nonredundant activator of T_{FH} cells. Three major enzymes (ETNK1, PCYT2, and SELENOI) are involved in this metabolic pathway and are needed in this process. The researchers found that these enzymes drive the synthesis of phosphatidylethanolamine in T_{FH} cells, which in turn stabilizes cell surface CXCR5, a receptor that is a hallmark of T_{FH} cells. They further determined that the CDP–ethanolamine pathway additionally acts by suppressing the formation of T_H1 cells, another $CD4^+$ helper T-cell subset that is induced during viral infections, thereby directing undifferentiated T cells into T_{FH} cells. Cells often

have redundant or compensatory mechanisms regulating their differentiation and function. The dependency of T_{FH} cells on the CDP–ethanolamine pathway makes its centrality that much more striking. This work represents a foundational change in the understanding of antibody responses by directly connecting T-cell metabolism to antibody formation.

Armed with this information, researchers and chemists can now develop drugs to either enhance or inhibit T_{FH} cell–dependent B-cell activation and antibody responses. By promoting T_{FH}-cell activation, researchers have the potential to improve vaccine-induced immune responses, leading to more durable antibody-based protection. Conversely, because T_{FH} cells selectively interact with B cells, inhibiting this T-cell subpopulation may be one approach to reducing antibodies involved in autoimmunity without affecting other immune functions.

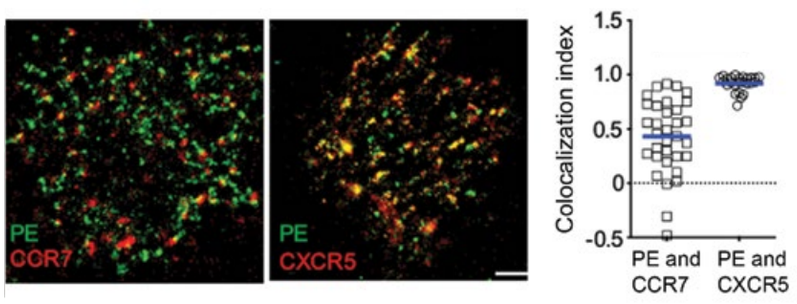


Figure. Phosphatidylethanolamine (PE) interacts with the chemokine receptor CXCR5 on the T_{FH}-cell membrane. TIRF–STORM imaging analysis and quantification reveals colocalization of PE and CXCR5, but not a control chemokine receptor CCR7, on the T_{FH}-cell membrane. Scale bar, 1 μm. TIRF: total internal reflection fluorescence; STORM: stochastic optical reconstruction microscopy. *Reprinted by permission from SNCSC GmbH: Springer Nature, Nature, 595:724-9. Metabolic control of T_{FH} cells and humoral immunity by phosphatidylethanolamine. Fu G et al, © 2021*

Nicole Chapman, PhD; Hongbo Chi, PhD

Peipei Zhou, PhD

Metabolic Signaling Machinery Determines the Cell Fate of CD8⁺ Memory T Cells

CD8⁺ T cells are essential for virus- and tumor-specific immune responses and can be subdivided into T_{eff} cells and T_{mem} cells. The balance of progenitor-cell differentiation into T_{eff} or T_{mem} cells is crucial. An adequate number of high-quality T_{eff} cells is needed to clear an acute infection. If too few T_{mem} cells form, then the same pathogen can cause a recurrent infection. Therefore, understanding T-cell fate determination is central to understanding immune protection and how it can become dysregulated in pathologic disorders or be circumvented by infections.

In the journal *Cell*, Dr. Chi and his colleagues reported their discovery of a major metabolic pathway essential to T-cell fate determination and mapped the biological machinery by which the immune system drives precursor cells toward a CD8⁺ T_{eff}- rather than T_{mem}-cell fate. The researchers first performed an in vivo pooled CRISPR-based screen of metabolism-related genes in primary CD8⁺ T cells from mice, leading to the discovery that the enzyme protein O-fucosyltransferase 1 (POFUT1) is a key regulator of CD8⁺ T-cell fate. They also identified a POFUT1-mediated nutrient-signaling axis as central to T-cell fate determination. This axis links GDP-fucose availability in the microenvironment to the Notch-Rbpj-signaling pathway, which by altering gene transcription connects nutrient sensing with cell-fate decisions.

To demonstrate the importance of the identified pathways, the investigators modulated T-cell fate decisions by blocking inhibitory pathways for T_{mem}-cell formation. During the process, they identified an intermediate population of T_{eff} cells (called T_{INT} cells), that can further differentiate into either a terminal population of T_{eff} cells (called TE′ cells) or T_{mem} cells. By deleting POFUT1, the investigators found that T_{eff} cells were better retained in the T_{INT} state. Altering the POFUT1-dependent nutrient-signaling axis in the T_{INT} cells promoted T_{mem}-cell differentiation and proliferation, leading to improved viral and tumor control.

This work suggests that nutrients play a more important role in controlling immune responses than was previously appreciated. It directly ties nutrients to T-cell differentiation in vivo and provides a strong foundation for future research on the influence of nutrient sensing in regulating immunity. Modulating this sensing has the potential to influence the immune response to pathogens, vaccines, or tumors.

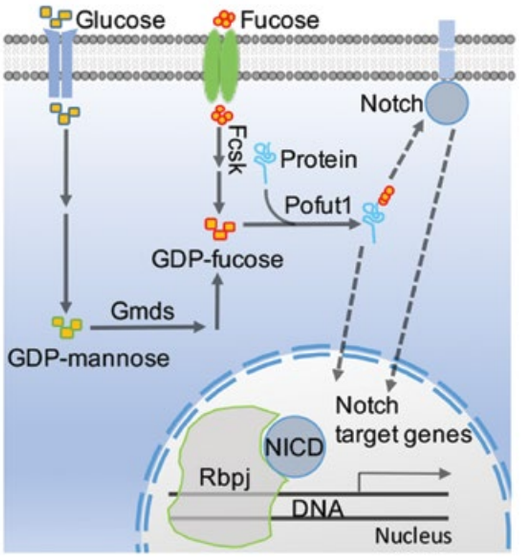


Figure. Pofut1-dependent fucosylation links Notch signaling with T-cell fate decisions. Upon synthesis or salvage of GDP-fucose by GDP-mannose 4,6-dehydatase (Gmds) and fucose kinase (Fcsk), respectively, Pofut1 transfers the fucose group from GDP-fucose to target proteins. Notch fucosylation by Pofut1 activates Notch signaling, which leads to transcriptional upregulation of target genes by the Notch intracellular domain (NICD) and the transcriptional regulator Rbpj. *Reprinted from Cell, 184, Huang H et al, In vivo CRISPR screening reveals nutrient signaling processes underpinning CD8⁺ T-cell fate decisions. 1245-61, © 2021, with permission from Elsevier.*

Mapping the Complex Nutrient-Signaling Network in T Cells

The immune system is often considered a surveillance system that aggressively responds to neutralize pathogens. It must simultaneously avoid uncontrolled immune activation and autoimmunity. This balance is linked to a T-cell's ability to detect nutrient status and establish specific cell fates and functions.

Scientists led by Dr. Chi created a comprehensive map of the nutrient-sensing networks that regulate T-cell function and growth. In an article published in *Nature*, the team began with a CRISPR screen of the entire genome (about 20,000 genes) in T_{reg} cells isolated from mice. They then looked for genes that specifically influence the activation of mTORC1 (mechanistic target of rapamycin complex 1), a key driver of cell growth and metabolism. Previous research had shown that mTORC1 is central to the interplay between nutrient signaling and immune response; however, the mechanisms underlying this integration were unknown.

Through the CRISPR screen, Dr. Chi's group identified 346 genes that affect mTORC1 activity in T_{reg} cells. Of these, 286 encoded proteins activated mTORC1, and 60 deactivated it. These proteins included well-known mTORC1 regulators (e.g., GATOR1 and GATOR2). However, the screen also identified many previously unknown regulators. The researchers evaluated how the proteins encoded by the implicated genes fit into larger regulatory networks, modeling how the proteins interact in cells. These protein–protein interaction analyses identified functional modules that constitute large regulatory networks involved in mTORC1 nutrient sensing in T cells.

Dr. Chi's team found that the chromatin-remodeling SWI/SNF complex reduces the expression of the amino acid–sensing protein CASTOR1, thereby leading to mTORC1 activation in T_{reg} cells. In contrast, CCDC101, a component of the SAGA chromatin-remodeling complex, inhibits mTORC1 by limiting the ability of cells to acquire nutrients. Moreover, CCDC101 promotes T-cell quiescence and the immunosuppressive actions of T_{reg} cells in vivo. Finally, the team identified SEC31A, a signaling protein that promotes mTORC1 activation by interacting with the GATOR2 component SEC13 (a

known regulator of mTORC1 activation) to protect it from proteasomal degradation. These interconnected systems suggest that mTORC1 activity is regulated by a three-tiered system—nutrient transport, nutrient sensing, and nutrient-mediated signal transduction—that "licenses" T-cell immunity (i.e., equips T cells with the capacity to alter their fate and function) and regulates immune reactions.

This work further supports the concept of "bidirectional metabolic signaling" in adaptive immunity. Dietary signals and invading microbes can trigger the immune system, and these activating signals can interface with nutrient-dependent metabolism and signal transduction. Together, these events propagate through functional modules that power the immune response. Identifying mTORC1-associated events can fuel the development of new interventions to modulate the immune response. Because the mTORC1 pathway supports T-cell priming (i.e., the initial activation of an immune response after the first contact between an antigen-presenting cell and a naïve T cell) during infection, characterizing how to manipulate this process has the potential to enhance treatments for infections and increase the immune response to vaccines. Conversely, the map can serve as a guide to modulate pathologic T-cell function. For example, intratumoral T_{reg} cells that protect tumors from the immune system's attack use the mTORC1 nutrient-sensing pathway. Impeding the immunosuppressive function of T_{reg} cells during immunotherapy may augment antitumor effects.

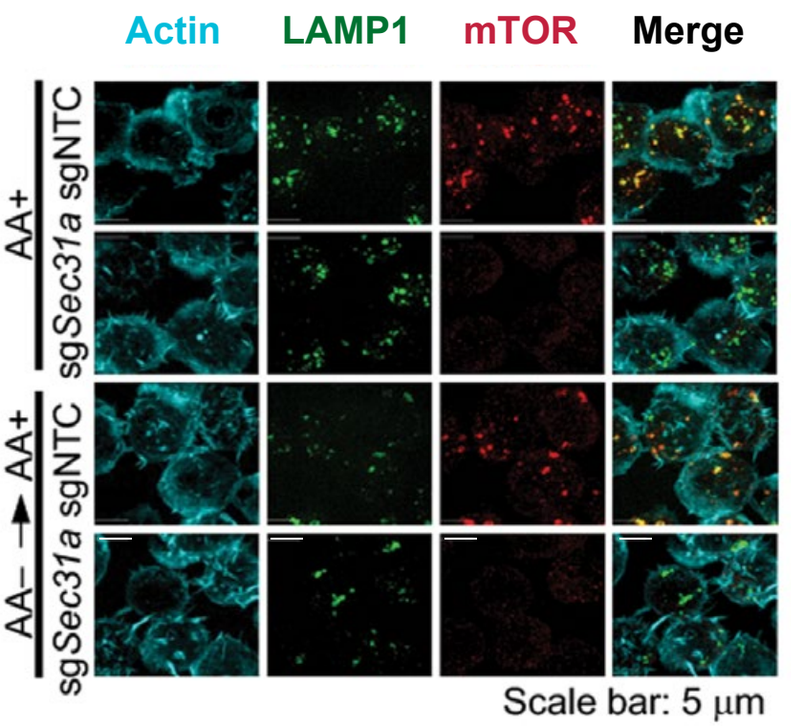
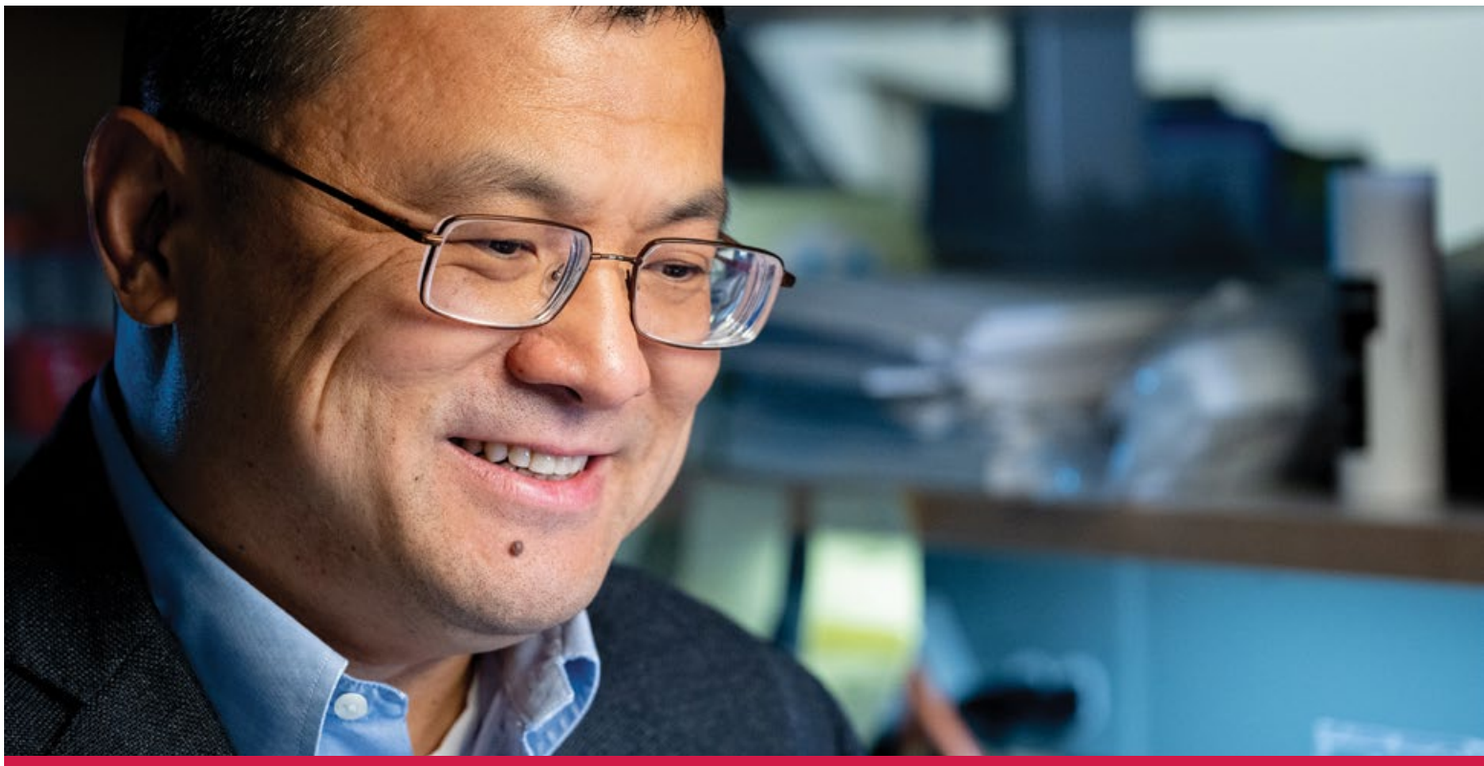


Figure. Sec31a integrates nutrient signals for mTORC1 activation in T_{reg} cells. Sec31a-null cells show decreased lysosome-associated mTor, and this is associated with a lack of response to amino acid stimulation. Control T_{reg} cells expressing a nontarget control single- guide RNA (sgNTC) recruit mTOR to the lysosome in nutrient-replete conditions (AA+) or upon amino acid starvation and refeeding (AA- → AA+), as evidenced by colocalization of LAMP1 (lysosome-associated membrane protein 1), a lysosomal marker, and mTOR. Deleting Sec31a (expressing sgSec31a) decreases lysosome-associated mTOR, indicative of impaired mTORC1 activation upon Sec31a inhibition. *Adapted with permission from SNCSC GmbH: Springer Nature, Nature, 600:308- 13. CRISPR screens unveil signal hubs for nutrient licensing of T cell immunity. Long L et al, © 2021*



Hongbo Chi, PhD

Lipid Signaling Is Central to Specifying T_{reg}-Cell Function in Tumors

T_{reg} cells create a local immunosuppressive environment that protects tumors from immune targeting. In the absence of T_{reg}-cell suppression, tumor-infiltrating lymphocytes can be activated to destroy the tumor and form a durable antitumor immune response. Identifying how T_{reg} cells are co-opted by tumors and selectively blocking their regulatory activities is a long-standing goal of immune-oncology research. Because global inhibition of T cells causes multiple immune-associated toxicities, identifying approaches to selectively target tumor-infiltrating T_{reg} cells is necessary.

Dr. Chi and his colleagues discovered a mechanism that tumors use to activate T_{reg} cells and protect themselves from other immune cells. The researchers challenged mice with melanoma tumors, collected the T_{reg} cells from the tumor and other locations, and analyzed which genes were selectively upregulated within the intratumoral T_{reg} subpopulation. In *Nature*, the team reported that a master genetic switch in intratumoral T_{reg} cells is centered on sterol regulatory element–binding proteins (SREBPs), a family of transcription factors involved in lipid synthesis and metabolic signaling.

After identifying the relation between T_{reg} cells and the SREBP pathway, Dr. Chi and his colleagues altered other proteins that regulate SREBP activity to determine whether this would also modulate T_{reg}-cell activity. Disrupting SREBP activity or its associated signaling pathways resulted in dysregulated phosphatidylinositol-3-kinase activity in intratumoral T_{reg} cells, thereby inhibiting their immunosuppressive function.

Dr. Chi's group challenged mice with melanoma or colon adenocarcinoma and then blocked the SREBP pathway in those animals. In conjunction, they used anti–PD-1 immunotherapy to treat the mice. PD-1 is an immune-checkpoint inhibitor that is upregulated on intratumoral T_{reg} cells and other T-cell populations. Mice normally do not respond robustly to anti–PD-1 therapy; however, in those animals in which the SREBP pathway was also blocked, the immune system's tumor-clearance response was rapidly activated. Importantly, no impact on peripheral T_{reg} cells that keep inflammation and autoimmunity in check was observed. Because the SREBP pathway was upregulated only in the intratumoral T_{reg} cells, the researchers concluded that it is a pathway activated selectively in the tumor microenvironment, thereby making it an ideal target for other immunotherapies.

Anti–PD-1 therapies work in fewer than 20% of patients with cancer, but those in whom the therapy is effective experience a durable remission. The findings from this study could serve as the basis for developing new approaches to enhance existing immunotherapies and to develop durable treatments for cancers that contain intratumoral T_{reg} cells. The same tumor-specific pathway is upregulated in T_{reg} cells in cancers of the skin, breast, and head and neck, indicating that this approach may be broadly applicable.

Controlling the Suppressive Capacity of T_{reg} Cells

Given the central role of T_{reg} cells in dampening the activity of effector T cells that target tumors and pathogens, immunologists have been investigating the genetic and epigenetic factors responsible for their development, maintenance, and suppressive function. The primary determinant of T_{reg}-cell lineage development is the expression of the *Foxp3* transcription factor. *Foxp3* defines the regulatory lineage, and its deficiency leads to lethal autoimmune disease due to uncontrolled effector T-cell activation. Previous research on T_{reg}-cell fate determination identified noncoding regions of DNA (or enhancers) near the *Foxp3* gene that promote *Foxp3* expression. Several enhancers, including conserved noncoding segment 0 (CNS0), CNS1, CNS2, and CNS3, modulate T_{reg}-cell development or lineage stability. Deficiency of one CNS causes minimal (if any) functional deficits, though it can affect T_{reg}-cell development or lineage stability. This result contrasts with the massive autoimmune dysregulation in fully *Foxp3*-deficient animals, raising the question of how *Foxp3* enhancer regions collectively function to influence T_{reg}-cell development, lineage stability, and immunosuppressive capacity.

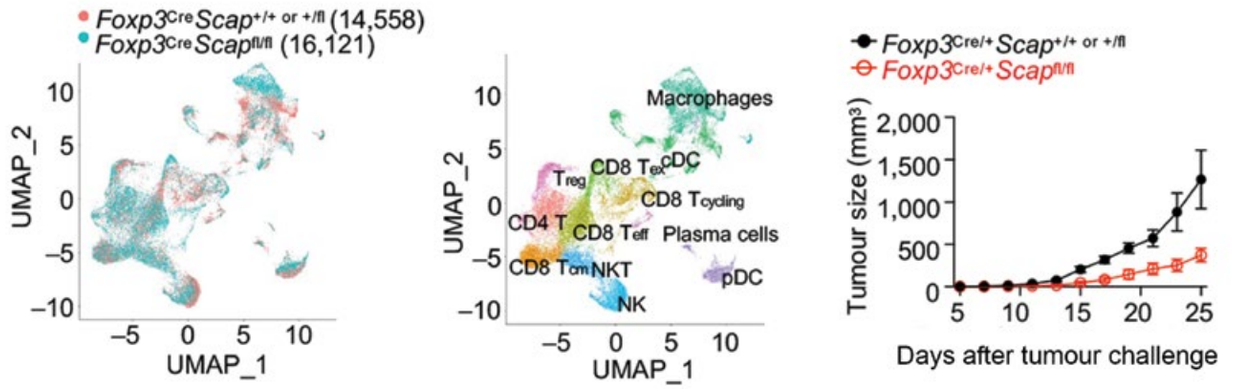
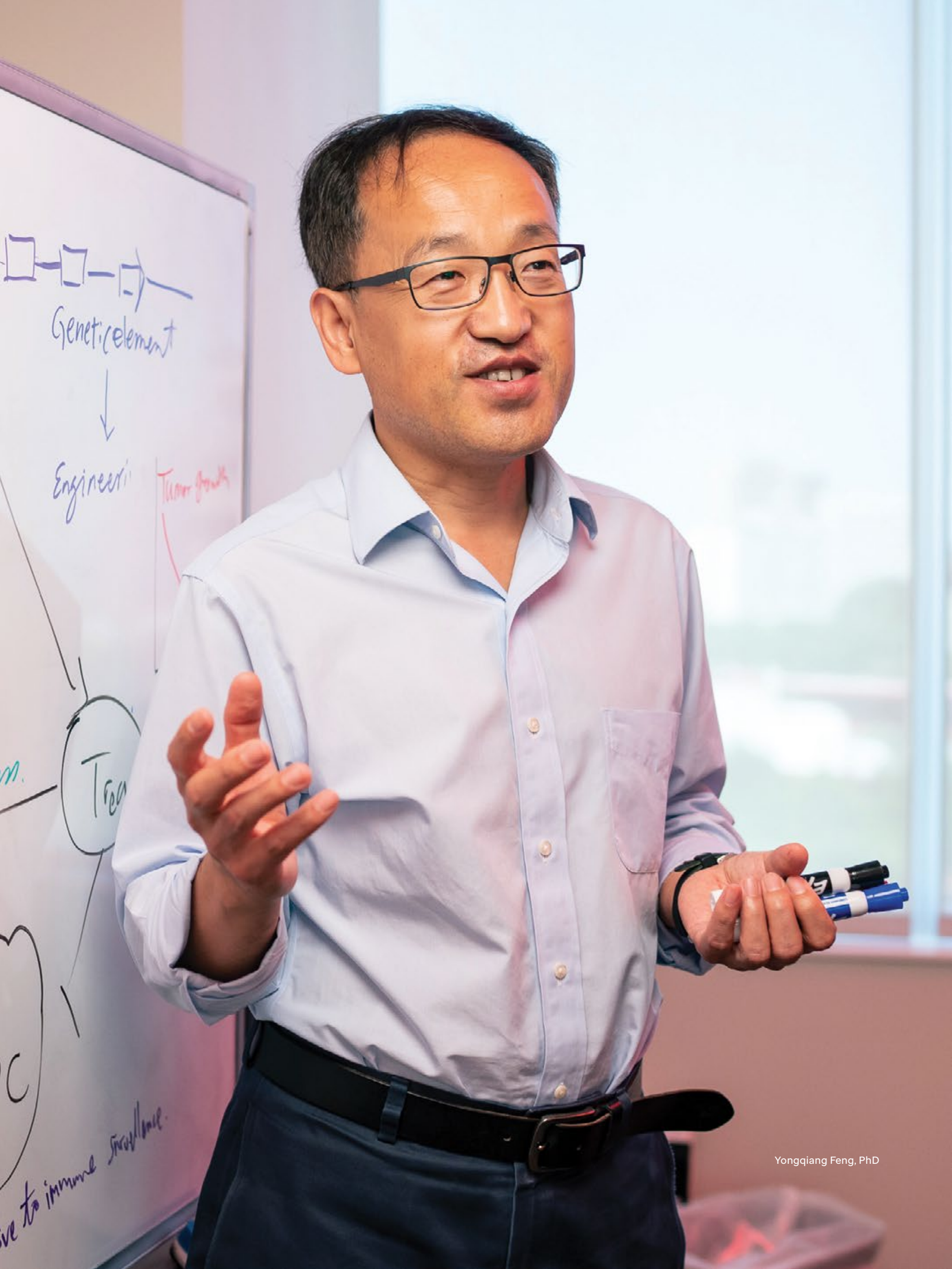


Figure. Sterol regulatory-element-binding proteins (SREBPs) maintain the functional fitness of T_{reg} in the tumor microenvironment, and cleavage-activating protein (Scap) binds to and is required for SREBP activity. Scap-SREBP signaling in T_{reg} cells impedes antitumor immunity. Unbiased scRNA-seq (single-cell RNA-sequencing) profiling and UMAP (uniform manifold approximation and projection)embedding demonstrate the effect of inhibiting Scap-SREBP signaling in T_{reg} cells on the immune cell composition of B16 melanoma (left and center panels). Growth of B16 melanoma is substantially inhibited in mice lacking Scap-SREBP signaling (right panel). *Reprinted by with permission from SNCSC GmbH: Springer Nature, Nature, 591:306-11. Lipid signalling enforces functional specialization of T_{reg} cells in tumours. Lim SA et al, © 2021*



Yongqiang Feng, PhD

Yongqiang Feng, PhD (Immunology), and his team sought to address this question by using epigenetic techniques, CRISPR screening, mouse genetics, and single-cell gene expression profiling to determine how *Foxp3* is regulated. They identified how pairs of enhancer elements act in concert to control T_{reg}-cell lineage commitment and stability. Interestingly, pairwise deletions led to lethal autoimmune diseases, whereas single deletions had more limited effects.

Dr. Feng's group showed that the different enhancer pairs influence different stages of the T_{reg}-cell life cycle. For example, deleting CNS0 and CNS3 caused a greater decrease in thymic T_{reg} cells than that caused by single deletion of either CNS, indicating that these two enhancers together drive the differentiation of an immature T-cell precursor into a mature T_{reg} cell. In contrast, deleting CNS0 with CNS2 impaired lineage stability. T_{reg} cells with these deletions did not sustain *Foxp3* expression, indicating that CNS0 and CNS2 in combination maintain T_{reg}-cell lineage identity during activation and proliferation. Without these two enhancers, T_{reg} cells progress either to an ex-T_{reg}-cell state or toward cell death, failing to suppress self-antigen-specific T_{eff} and killer T cells and leading to autoimmune diseases.

The investigators then quantified T_{reg}-cell development and lineage stability in the absence of single or paired enhancers and established a causal relationship between T_{reg}-cell development or lineage stability and immunosuppressive capacity. This established the extent to which T_{reg}-cell formation and lineage stability are each necessary to prevent susceptibility to autoimmune diseases.

These findings revealed fundamental principles controlling the suppressive capacity of T_{reg} cells and immune regulation. They serve as references to determine how factors affecting T_{reg}-cell development or lineage stability cause human autoimmune diseases. The genetic elements controlling *Foxp3* expression and their interacting proteins can be targeted or engineered to manipulate T_{reg}-cell suppressive capacity to treat autoimmune diseases or to enhance the antitumor immune response.

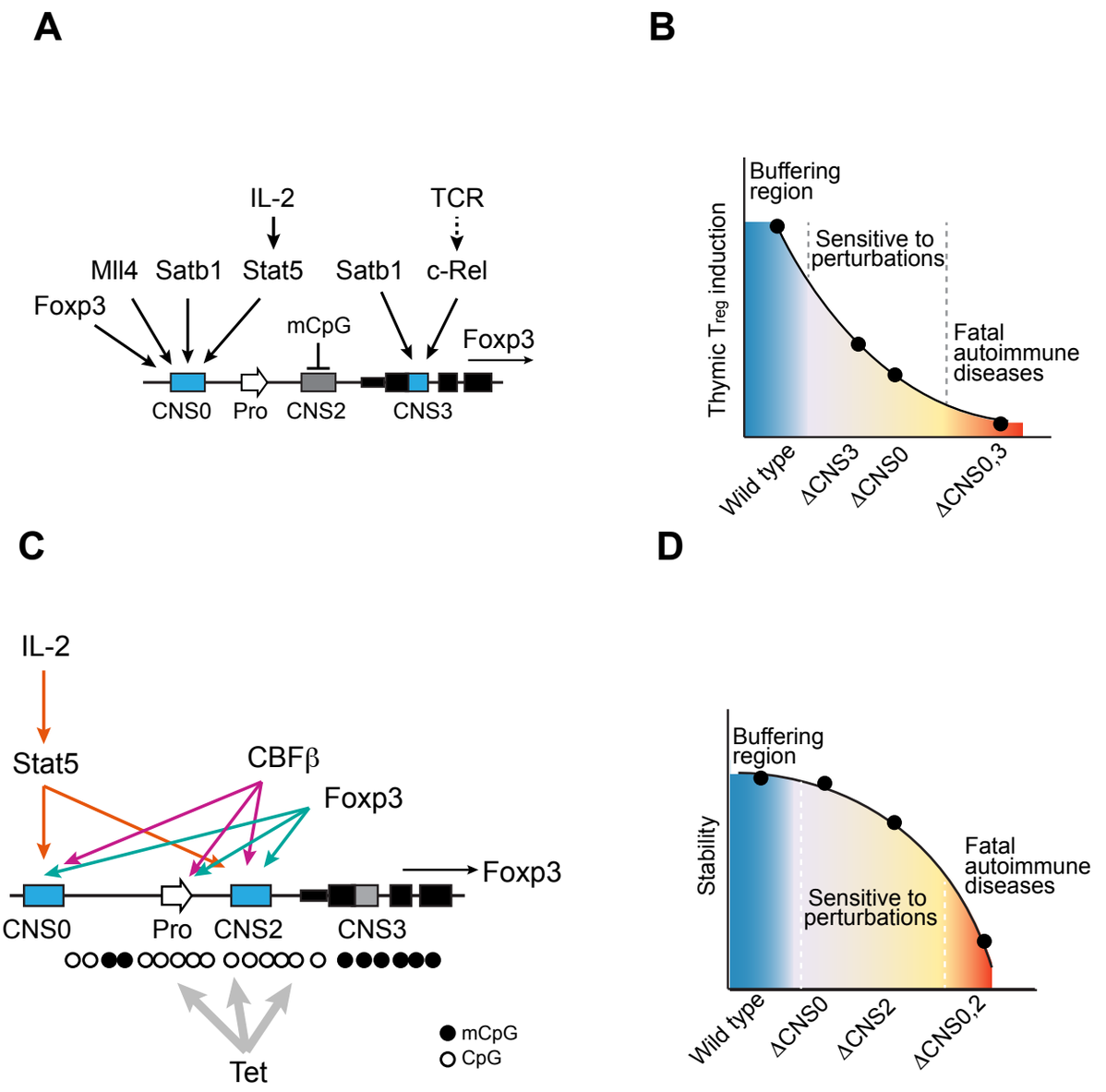


Figure. (**A**) Enhancers CNS0 and CNS3 are paired to optimize T_{reg}-cell development by promoting Foxp3 induction via different mechanisms. (**B**) Efficient T_{reg}-cell induction confers a suppressive capacity to buffer against immune perturbations and autoimmune diseases. Reduced T_{reg}-cell induction by the deficiency of CNS0 and CNS3, alone or together, impairs immune tolerance to various degrees. (**C**) In addition, CNS0 and CNS2 act through DNA demethylation–independent and –dependent pathways to reinforce T_{reg}-lineage identity characterized by *Foxp3* expression. (**D**) Coordination between CNS0 and CNS2 maximizes T_{reg}-lineage stability (blue) and suppressive capacity to oppose genetic variations and immune perturbations. Loss of both enhancers results in unstable T_{reg}-cell fate and fatal autoimmune diseases (red). *Republished with permission of Rockefeller University Press, from Journal of Experimental Medicine, Foxp3 enhancers synergize to maximize regulatory T cell suppressive capacity, Zong X et al, 218, 8, e20202415*

CONCLUSION

St. Jude immunologists are using cutting-edge genetic screens and functional analyses to reveal the molecular underpinnings of T-cell differentiation, function, and lineage stability. These studies set the foundation for discovering new ways to optimize T-cell immunity and to enhance vaccines and anticancer treatments.

Anastasia Minervina, PhD; Mikhail Pogorelyy, PhD; Paul G. Thomas, PhD

UNDERSTANDING THE HUMAN IMMUNE RESPONSE TO THE EVOLVING SARS-CoV-2 VIRUS

At the start of the pandemic, the St. Jude Tracking Study of Immune Responses Associated with COVID-19 (SJTRC; NCT04362995) was launched to monitor viral genetics and immune responses to infection and later vaccination. Gathering data from St. Jude employees who volunteered to participate, the SJTRC team examined the immune response to SARS-CoV-2 infection. They also studied whether past exposure to coronaviruses, like those that cause the common cold, influences the response of the immune system to SARS-CoV-2. Through St. Jude Global, another team of researchers assessed the effects of SARS-CoV-2 on pediatric patients with cancer and on the provision of pediatric oncology care around the world. Researchers have collaborated with scientists in other countries to monitor the evolution of the virus and assess the mechanisms underlying viral pathogenesis. The COVID-19 pandemic has dramatically changed the world. Here we present some recent work by St. Jude scientists who continue to closely monitor the virus, seek possible avenues to combat it, and gain knowledge to help chart a path forward in the coming years.

Thirumala-Devi Kanneganti, PhD; Rajendra Karki, PhD

Mechanisms of the Inflammatory Response During SARS-CoV-2 Infection and Cytokine Storms

Innate immunity provides the body's first line of defense against infection. One way in which the immune system responds to infection is by releasing cytokines, which are small proteins that relay signals between cells to help clear the pathogen. Cytokines can also spur inflammatory cell death, leading to further cytokine release and inflammation. This positive feedback loop between cytokines and inflammatory cell death can lead to an uncontrolled release of cytokines, causing a cytokine storm that can severely damage tissues and organs.

Infection with the SARS-CoV-2 virus is marked by increased levels of multiple cytokines in the blood. Cytokine storms can also contribute to severe COVID-19 disease. A lack of fundamental understanding of the underlying pathways that drive the dysregulated release of cytokines after COVID-19 infection has impeded the development of targeted therapies to prevent a cytokine storm.

To mechanistically characterize this release of cytokines after SARS-CoV-2 infection, Thirumala-Devi Kanneganti, PhD (Immunology), and her team studied the interaction of released cytokines with innate sensors that activate the immune system and mediate cytokine storms. Research by Dr. Kanneganti's group implicated proinflammatory

cytokines, specifically tumor necrosis factor (TNF)-α and interferon (IFN)-γ, in the induction of cytokine storm and inflammatory cell death during SARS-CoV-2 infection through a process termed PANoptosis (i.e., an inflammatory cell death pathway that integrates components from multiple cell death mechanisms). The factors that control the expression of inflammatory cytokines, including TNF-α and IFN-γ, during SARS-CoV-2 infection were unknown.

Inflammatory cytokine production can by stimulated through multiple signaling pathways in the cell. One such pathway is initiated by toll-like receptors (TLRs), which are innate immune sensors found on the cell surface and on endosomes that recognize pathogens like SARS-CoV-2. The specific sensors that activate the inflammatory signaling pathway during SARS-Cov-2 infection had not been identified. Dr. Kanneganti and her team reported in *Nature Immunology* the results of screening TLRs and their signaling adaptor proteins Myd88 and Trif to identify the receptors required to drive proinflammatory cytokine production during coronavirus infections. They found that TLR2 recognizes the SARS-CoV-2 envelope protein and drives inflammatory cytokine release during this infection. Blocking TLR2 protected cells from the lethal effects of SARS-CoV-2 in laboratory models, and treating mice with a TLR2 inhibitor reduced cytokine levels and mortality during SARS-CoV-2 infection. These findings suggest that TLR2 plays an essential role in the development of COVID-19 disease and in the cytokine storm and pathology that it mediates.

Knowing that TLR2 serves as an innate sensor required for the expression of inflammatory cytokines during coronavirus infection supports potential strategies for therapeutic intervention against this target. Such a therapeutic approach could also be used to treat other diseases in which TLR2-mediated cytokine production contributes to pathologic inflammation. Furthermore, although these results show that TLR2 is a cell-surface receptor that activates innate immune pathways and the production of cytokines, such as TNF and IL-6, by signaling through its adaptor Myd88, additional cytosolic sensors may be involved in cell death and the overall pathology in COVID-19. Dr. Kanneganti's team is continuing their long-standing efforts to identify novel innate sensors and signaling pathways. Through this and other fundamental studies, they are expanding our understanding of the molecular mechanisms that sense SARS-CoV-2 infection and induce inflammatory cytokine production and pathology.

SARS-CoV-2 mRNA Vaccine Elicits Long-Term Immunity via CD4$^+$ T_{FH} Cells

The most successful and widely adopted vaccines against SARS-CoV-2 are based on mRNA encoding the SARS-CoV-2 spike protein. Although much of the research on the immune response to mRNA vaccination has focused on the robust anti–spike protein antibody levels induced by the vaccine, Paul G. Thomas, PhD (Immunology), led a multisite study that examined how T cells respond to mRNA vaccines. Researchers at St. Jude and Washington University School of Medicine (St. Louis, MO) studied follicular

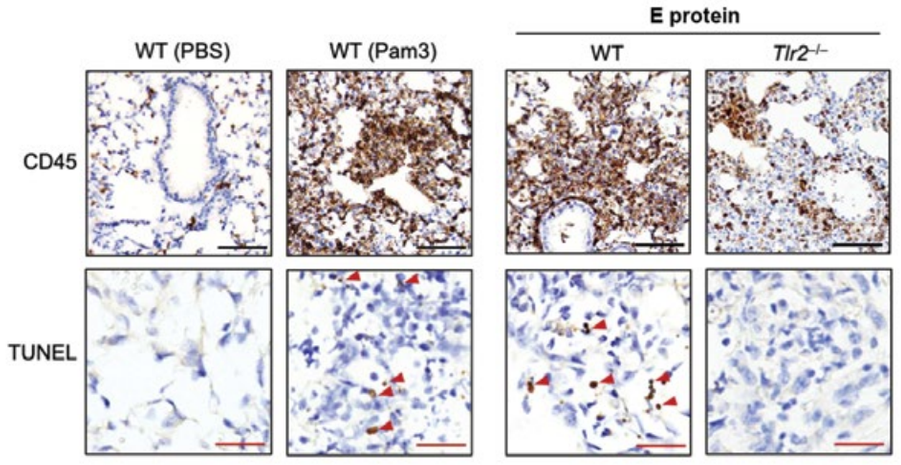


Figure. The SARS-CoV-2 envelope (E) protein induces cell death through TLR2. Images of mouse lung tissue stained for inflammatory cell infiltration (CD45) and cell death (TUNEL) in response to the SARS-CoV-2 E protein are shown. Treatment with Pam3, an activator of TLR2, provokes an inflammatory infiltrate and cell death in lung tissue (left panels). Treatment with E protein induces similar inflammation and cell death in WT but not TLR2-deficient lung tissue. Red arrows indicate TUNEL$^+$ cells. Abbreviations: Pam3, Pam3CSK4 ligand (activator) of TLR2; PBS, phosphate-buffered saline; WT, wild-type. Scale bars, 100 µm (black) or 25 µm (red). *Reprinted by permission from SNCSC GmbH: Springer Nature, Nat Immunol, 22:829–38. TLR2 senses the SARS-CoV-2 envelope protein to produce inflammatory cytokines. Zheng M et al, © 2021*

Joshua Wolf, PhD, MBBS; Paul G. Thomas, PhD

helper T (T_{FH}) cells circulating in the blood of 41 healthy participants who had received the BNT162b2 mRNA vaccine (Pfizer/BioNT). In addition, 15 participants underwent repeated fine-needle aspirations of draining axillary lymph nodes to extract T_{FH} cells from lymph up to 200 days after the first vaccine dose.

Dr. Thomas and his colleagues knew that responding T cells identify different regions of the virus due in part to the variability of their T-cell receptors (TCRs). They developed a new approach, termed "reverse epitope discovery," that uses TCRs to identify the virus epitope (i.e., the part of the virus that the immune system identifies). Reverse epitope discovery examines clusters of highly similar TCRs that recognize the virus in a similar way. The researchers showed that half the individuals studied reacted to the same epitope. This was a surprising finding that had previously been missed by other approaches. Furthermore, 10% of the $CD4^+$ T_{FH} cells, which help coordinate the immune response and support antibody production, recognized the same part of the virus, indicating a significant T-cell response to certain regions of the virus.

This work, which was published in *Cell*, showed that although the level of circulating T cells in the blood peaked 1 week after the second vaccination with BNT162b2 and waned 6 months after vaccination, T_{FH} cells in lymph nodes are still robust even beyond 6 months after vaccination, thereby indicating the lasting benefits of mRNA vaccines for SARS-CoV-2. The researchers also found that these levels of T_{FH} cells were often comparable to that at the peak of the immune response (i.e., immediately after vaccination).

Importantly, the dominant epitope identified by reverse epitope discovery was not altered in the major SARS-CoV-2 variants, including the Delta and Omicron variants. This work shows the enduring benefit of mRNA vaccination against SARS-CoV-2. By focusing on the T_{FH} cells, Dr. Thomas and his colleagues have provided evidence of long-term immunity elicited by the mRNA vaccine against SARS-CoV-2.

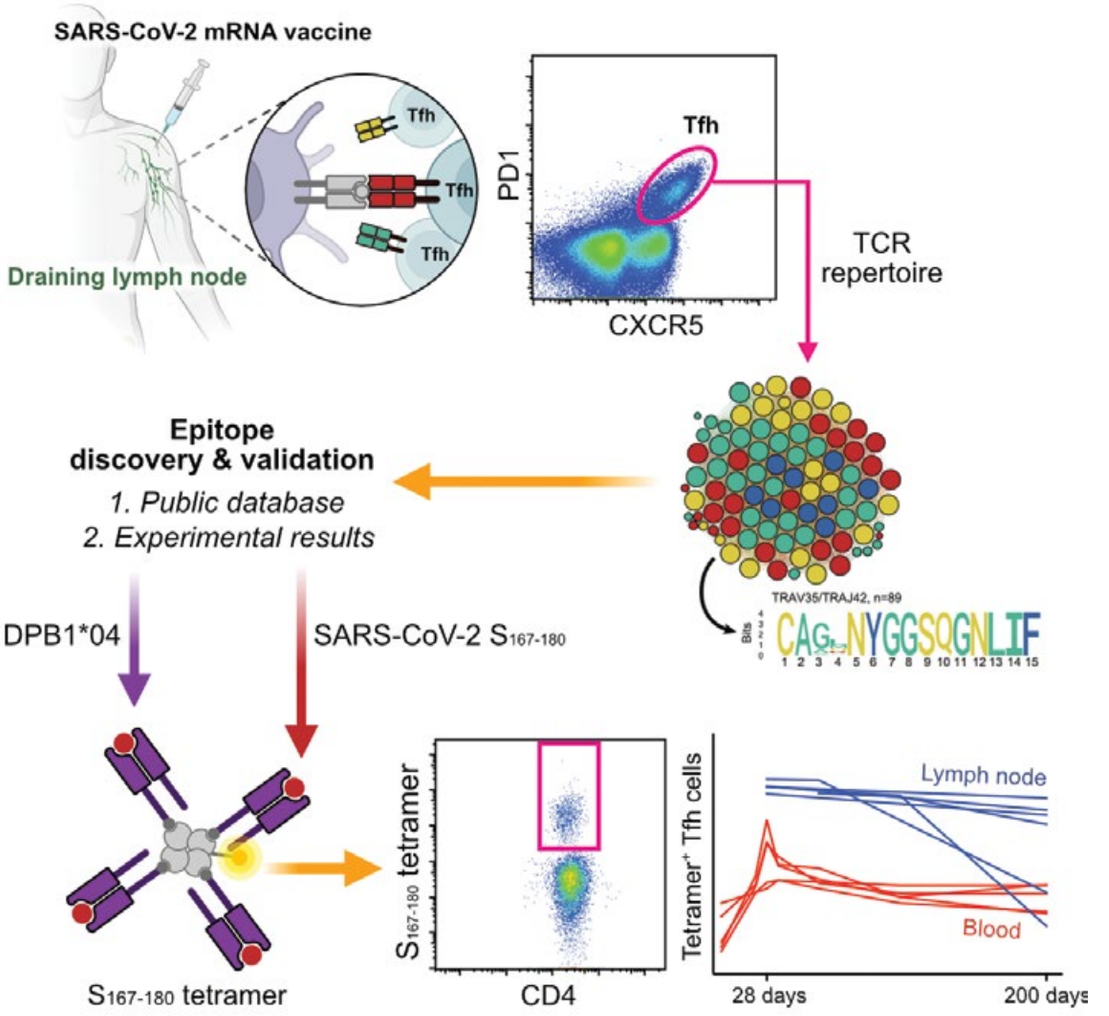


Figure. COVID-19 vaccine-induced follicular helper CD4+ T cells (T_{FH}) play a key role in establishing long-term immunity to SARS-CoV-2. Inoculation with the SARS-CoV-2 mRNA vaccine induces a population of T_{FH} cells, (as defined by surface expression of PD1 and CXCR5). Evaluating the resulting T_{FH}-cell receptor (TCR) repertoire revealed a response to a portion of the SARS-CoV-2 spike protein in individuals with the HLA-DPB1*04 allele, an HLA allele commonly found across multiple human populations. Furthermore, paired blood and lymph node samples showed that anti-spike (S-specific) circulating T_{FH} cells peak in number shortly after second immunization. S-specific T_{FH} cells persist in the lymph nodes for more than 6 months. These findings illustrate the importance of these T_{FH} cells in establishing and maintaining immunity to SARS-CoV-2 in humans. *Reprinted with permission from Elsevier, Cell, 185/4, Mudd PA et al. SARS-CoV-2 mRNA vaccination elicits a robust and persistent T follicular helper cell response in humans. 1-11 © 2021*

The Chronologic Order of SARS-CoV-2 Infection and Vaccination Influences the Immune System Response

Antigens are molecules on the surface of pathogens that the immune system uses to recognize a threat. The immune system is exposed to antigens by vaccinations and infections. Infections may occur in those who are unvaccinated (a primary infection) and in those who are vaccinated (a breakthrough infection). Certain T cells remember those antigens so they can effectively clear the pathogen upon re-exposure to virus or viral antigens in vaccines. However, through the introduction of multiple mutations, SARS-CoV-2 variants, such as Delta and Omicron, have changed their antigens, making it harder for the immune system to recognize the virus.

Dr. Thomas, Joshua Wolf, PhD, MBBS (Infectious Diseases), and their colleagues evaluated how vaccination against and infection with SARS-CoV-2 affects the immune system. During the pandemic, there has been a prevailing question in the public discourse—Do people who have so-called "natural immunity" as a result of contracting one of the SARS-CoV-2 variants need to be vaccinated? In *Nature Immunology*, Drs. Thomas, Wolf, and their colleagues reported on a study designed to answer this question.

Although much attention has been given to the antibody-mediated immune response to SARS-CoV-2 infection, $CD8^+$ T cells are thought to prevent severe COVID-19 disease. Thus, the researchers used new tools and approaches, including DNA-barcoded major histocompatibility complex (MHC) multimers, single-cell RNA sequencing (scRNA-seq), and single-cell T-cell receptor sequencing (scTCR-seq), to determine whether $CD8^+$ T-cell profiles differed based on a person's history of infection and vaccination.

A cohort of 55 participants from the SJTRC study were assigned to one of four groups based on their individual histories of SARS-CoV-2 infection and vaccination with BNT162b2: (1) those who were infected before vaccination, (2) those who were infected after the second dose of vaccine, (3) those who were vaccinated after infection, and (4) those who received both doses of vaccine and remained negative for SARS-CoV-2 infection.

The researchers detected some similarities in how the immune system responded in vaccinated versus infected individuals; however, the vaccine conferred additional benefit to infected individuals. The team found that the vaccine activates and expands the immune response to protect individuals previously infected with SARS-CoV-2. Even in persons who

Paul G. Thomas, PhD; Mikhail Pogorelyy, PhD; Joshua Wolf, PhD, MBBS; Anastasia Minervina, PhD

experience a breakthrough infection, the vaccine still provides protection and does not limit the immune system's ability to develop new immune responses to emerging variants.

The mRNA vaccines consist of mRNAs encoding spike proteins that are present on the virus' surface. Results from this study showed that the order of exposure, whether vaccination or infection came first, determines whether the immune response is directed toward the spike protein. Specifically, vaccination after primary infection further expands the spike protein–specific T cells, whereas breakthrough infections after vaccination cause robust non–spike-specific responses. The team concluded that breakthrough infections diversify memory T-cell responses.

This work supports the use of vaccines, regardless of whether the person has been infected with SARS-CoV-2 or not. Although some similarities exist between how the immune system responds to vaccination and infection, vaccination helps expand the T-cell response, ensuring a more robust immune reaction against infection.

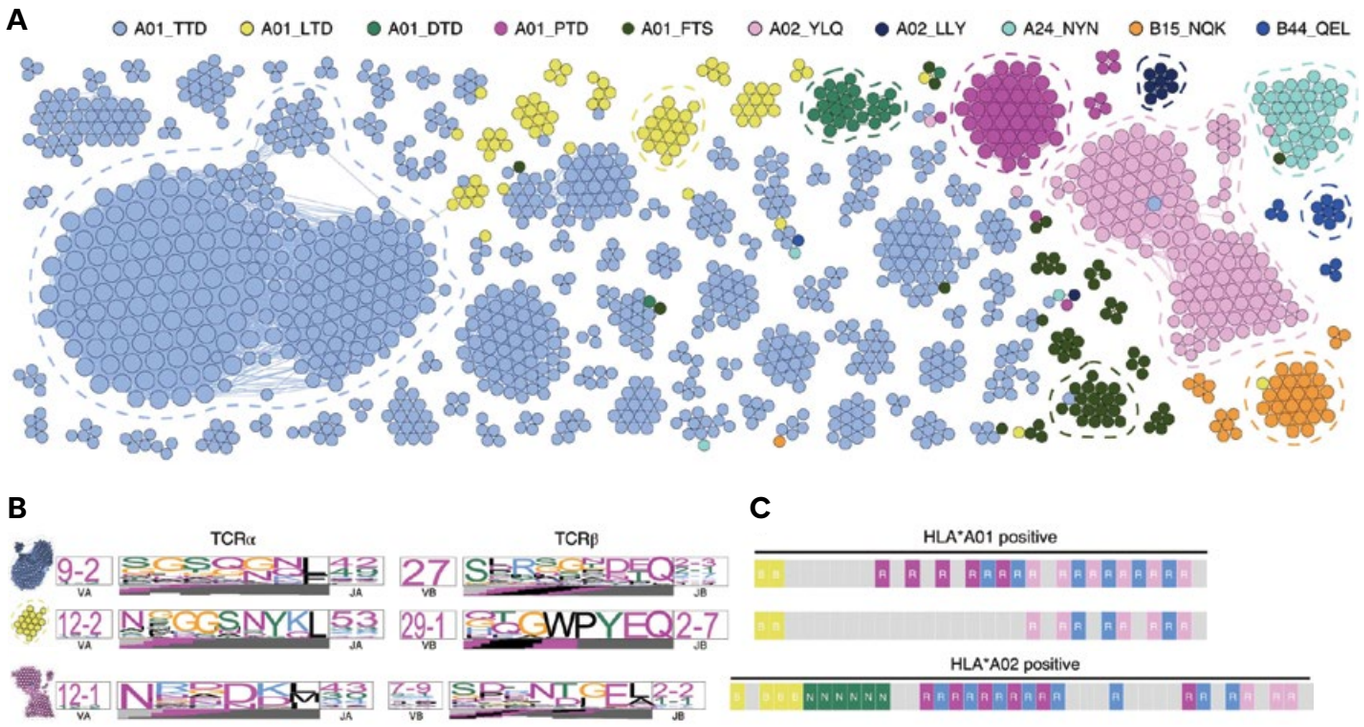


Figure. Similar SARS-CoV-2–specific *αβ* T cells are elicited by distinct exposure histories. (**A**) SARS-CoV-2–specific *αβ* T-cell receptors (TCRs) feature groups of highly similar sequences that share the same epitope specificity. Each node, or circle, is a unique paired *αβ* TCR amino acid sequence and an edge connects *αβ* TCRs with TCRdist score <110, allowing the identification of highly similar sequences. Each color represents a particular epitope specificity (as shown in the legend above the clusters), and the largest clusters of highly similar TCRs for each epitope are encircled with a dashed line. Only clusters with more than two members are shown. Spike protein–derived epitopes are in bold. (**B**) TCR amino acid sequence motifs of *α* and *β* chains (known as TCRdist logos) for the largest clusters of highly similar TCRs are shown for each epitope. Clusters from (**A**) are identified on the left for each amino acid sequence shown. These logos show that the clusters of similar sequences included TCRs of the same epitope specificity and largely share major components of the TCR, including V-region usage and certain amino acids in the CDR3 region. Collectively, (**A**) and (**B**) define the core features of SARS-CoV-2–specific TCRs targeting diverse regions of the virus. (**C**) TCRs with the same sequence motifs are found across individuals with all antigen-exposure histories. Occurrence of TCR motifs on the left is shown for all HLA-matching samples (rectangles). The color of the rectangles that have a TCR motif corresponds to the sample group: yellow = fully vaccinated and then infected, green = fully vaccinated, dark pink = infected, light pink = infected and then first vaccination, blue = infected and then fully vaccinated, and gray = TCR motif not present. The data suggest that epitopes are recognized by the same TCR–pMHC molecular interactions, regardless of the method of antigen exposure (infection, vaccination, etc.); thus, one could expect similar immune responses from memory T cells elicited by vaccination or natural infection. *Reprinted by permission from SNCSC GmbH: Springer Nature, Nat Immunol 23: 781-90. doi: 10.1038/s41590-022-01184-4. SARS-CoV-2 antigen exposure history shapes phenotypes and specificity of memory CD8 T cells. Minervina AA et al, © 2022*

Chun-Yang Lin; Li Tang, PhD; Joshua Wolf, PhD, MBBS

Determining Who Needs a Booster Shot

Dr. Wolf led the SJTRC team in a study of how antibodies against SARS-CoV-2 variants differ across individuals who were infected, individuals who were vaccinated but not infected, and those who had breakthrough infections after vaccination. In *Clinical Infectious Diseases*, the researchers reported the results of their analyses of plasma samples from 399 participants in the SJTRC study. Of these participants, 120 had the infection only, 237 were vaccinated with an mRNA vaccine but never infected, and 42 had a breakthrough infection after vaccination. The researchers measured the antibody levels against not only the original strain of the SARS-CoV-2 virus (Wuhan Hu-1) but also four variants (Alpha, Beta, Gamma, and Delta). The Omicron variant had not yet emerged at the time of the study.

Using an ELISA assay to measure the immunoglobin G (IgG) titers against the virus spike receptor–binding domain, Dr. Wolf and his colleagues found that the highest levels of cross-reactive antibodies were detected right after vaccination. This was especially true in individuals who were vaccinated after infection. Antibody levels were highest against the original strain and the Alpha variant. They also found that vaccinated participants had high antibody levels against the Delta variant, whereas those who had been infected and not vaccinated had low levels of antibodies against the Delta variant only.

The researchers investigated factors that could be used to predict antibody levels in people who had been infected and in those who had been vaccinated. Among the vaccinated participants, antibody levels were highest in those who were younger, had a healthy weight, or had been vaccinated more recently. This finding was consistent with results seen by the laboratory of Stacey L. Schultz-Cherry, PhD (Infectious Diseases), in their research on the responses to influenza vaccination. However, the researchers were surprised to find that in participants who had been infected with SARS-CoV-2, antibody responses were highest in those who had more severe infections, poor metabolic health, or obesity and in those who had received the vaccination after infection. Poor metabolic health is usually associated with worse immune responses, so the high IgG titers in those participants were puzzling. The researchers hypothesized that a higher viral load in these individuals leads to a greater stimulation of antibody-producing B cells or that baseline inflammation primes these individuals for antibody production.

The results of this work will help determine who might most benefit from booster vaccinations. People are considered fully vaccinated if they have had two doses of the mRNA vaccine against SARS-CoV-2, but booster shots are currently recommended to help increase immunity, particularly against the new viral variants. People who are older or obese might be more likely to benefit from a booster shot.

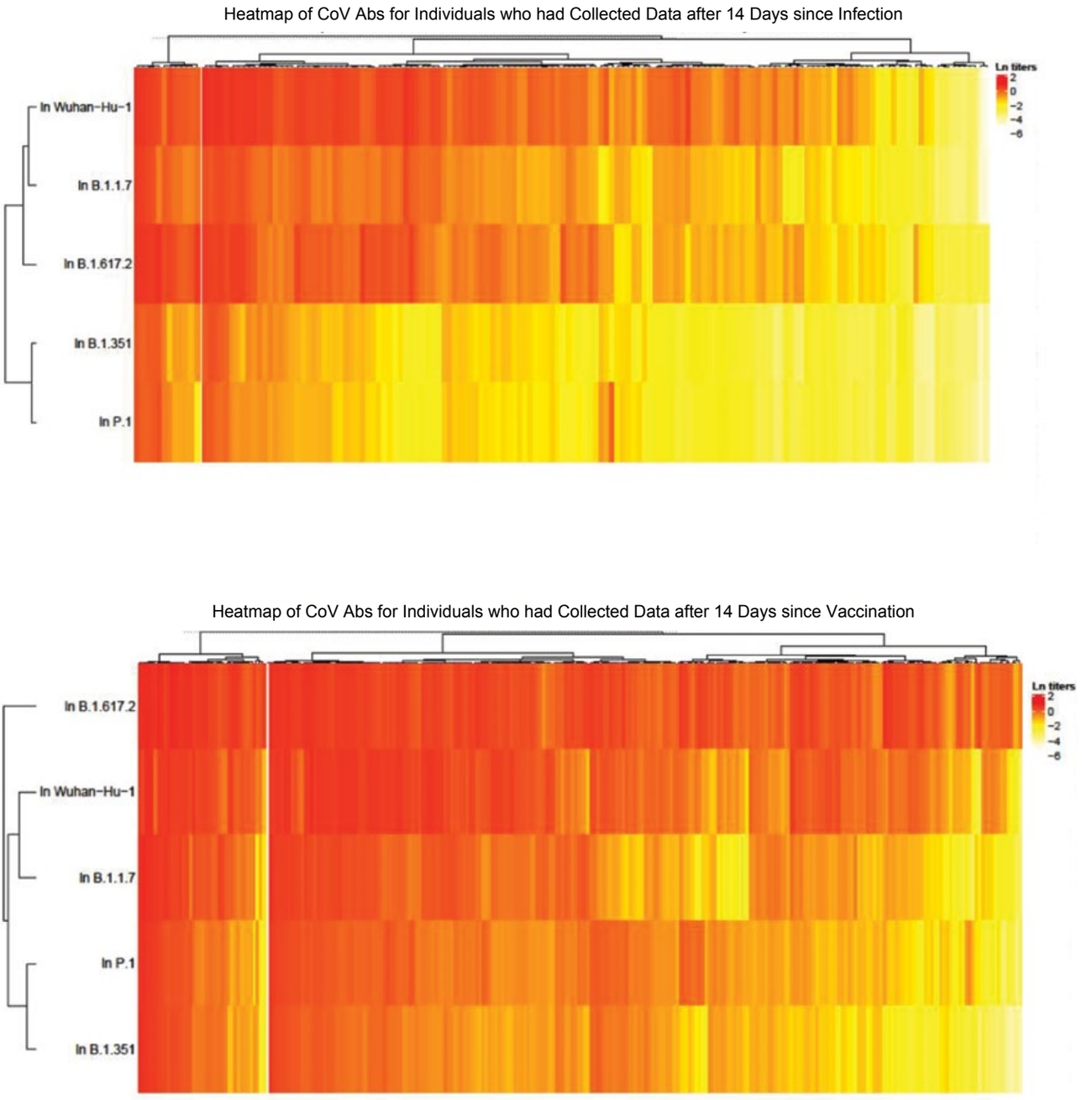


Figure. Colors in the heatmap represent the level of the spike receptor-binding domain (RBD). IgG antibodies (Abs) that recognize variants of SARS-CoV-2 (CoV) in individuals who were infected (top) or vaccinated (bottom). Vaccination induces a better antibody response to the variants than did infection. Additionally, the time after infection and severity of infection affected the response to variants of concern. These data show that participants who were vaccinated, younger, and of a healthy weight had the highest antibody levels against multiple virus variants. (variants of concern: B.1.1.7 – Alpha, B.1.351 – Beta, P.1 – Gamma, and B.1.617.2 – Delta). *Reprinted from Tang L et al, Host predictors of broadly cross-reactive antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern differ between infection and vaccination. Clin Infect Dis, 75:e705-e714, © 2022, doi: 10.1093/cid/ciab996 by permission of the Infectious Diseases Society of America.*

Richard J. Webby, PhD

Influenza Researchers Join the International Effort to Identify SARS-CoV-2 Variants

For decades, health officials in the U.S. and around the world have relied on St. Jude influenza researchers to identify and assess the pandemic potential of influenza and other novel respiratory viruses. The need for risk assessment has intensified since the COVID-19 pandemic started. In 2021, the National Institute of Allergy and Infectious Diseases requested that St. Jude researchers with expertise in infectious diseases, immunology, and computational biology join an international scientific team to provide comprehensive, real-time risk assessments of the emerging SARS-CoV-2 variants.

Richard J. Webby, PhD (Infectious Diseases), and Drs. Schultz-Cherry, Thomas, and McGargill are members of the SARS-CoV-2 Assessment of Viral Evolution (SAVE) Program, and Gang Wu, PhD (Pathology), and his team in the Center for Applied Bioinformatics are supporting this effort. The SAVE Program was created to provide crucial data to officials crafting the national public health response and to enhance rapid data sharing with global partners. SAVE focuses on how changes to the virus could affect transmissibility, virulence, and infection- or vaccine-induced immunity. The Program includes three working groups that focus on early detection, variant analysis, and in vitro and in vivo characterization. Their mandate is to identify SARS-CoV-2 variants that warrant closer scrutiny in terms of the immune response they trigger, vaccine efficacy, viral transmission, and more.

Chun-Yang Lin; Maureen A. McGargill, PhD

The Common Cold Limits the Immune Response to SARS-CoV-2

The SARS-CoV-2 virus belongs to a family of coronaviruses that includes the human common cold coronaviruses. Although SARS-CoV-2 is a new virus, four common cold corona viruses (HKU1, OC43, 229E, and NL63) have been circulating worldwide for decades. Since the common cold coronaviruses share homology with SARS-CoV-2, a major unresolved question was whether prior immunity to the common cold coronaviruses affected the likelihood of becoming infected with SARS-CoV-2, or if existing immunity to common cold coronaviruses influenced the severity of SARS-CoV-2 infection.

Maureen A. McGargill PhD (Immunology), and her team examined whether prior exposure to the common cold coronavirus influenced susceptibility to SARS-CoV-2 infection. Using samples from the SJTRC cohort, the researchers measured antibody levels to all four common cold coronaviruses in samples collected from the same individuals before and after SARS-CoV-2 infection or vaccination. The study showed that although the levels of pre-existing antibodies to common cold coronaviruses varied among participants, every individual had antibodies reactive against all four common cold coronaviruses.

In *Cell Host & Microbe*, the team showed that antibodies recognizing two of the common cold coronaviruses increased rapidly after infection with SARS-CoV-2, indicating that infection with the novel coronavirus amplified levels of antibodies generated during prior exposure to common cold coronaviruses. However, individuals with high levels of antibodies to

common cold coronaviruses were just as likely to be infected with SARS-CoV-2 as were individuals with lower antibody levels, suggesting that existing immunity to common cold coronaviruses was not protective against becoming infected with SARS-CoV-2. Therefore, although SARS-CoV-2 infection boosts pre-existing coronavirus antibodies, those antibodies do not block SARS-CoV-2 entry into host cells and, thus, are not protective.

Unexpectedly, the team found that individuals with higher levels of pre-existing common cold coronavirus antibodies had more severe disease after SARS-CoV-2 infection, as indicated by higher levels of SARS-CoV-2 antibodies at later time points after infection, a correlate of disease severity. Thus, the authors proposed a model in which high levels of pre-existing common cold coronavirus antibodies impede the immune response to SARS-CoV-2. Antibodies that bind regions conserved among common cold coronaviruses and SARS-CoV-2 can hinder SARS-CoV-2 immunity because the antibodies to conserved regions can be generated more rapidly than the antibodies that recognize the novel regions of SARS-CoV-2, which are required to neutralize SARS-CoV-2 and generate effective immunity.

Importantly, Dr. McGargill's team found that pre-existing immunity to common cold coronaviruses did not affect the generation of SARS-CoV-2 antibodies after vaccination against SARS-CoV-2. This finding suggests that the mRNA vaccines induce an immune response against SARS-CoV-2 that is strong enough to override the antibody-production advantage of common cold coronavirus memory.

Most people have been exposed to all four of the common cold coronaviruses during their lifetime. These data suggest that the level of pre-existing immunity to common cold coronaviruses is one factor that can contribute to the divergent outcomes of SARS-CoV-2 infection. Furthermore, vaccination overrides the negative impact of pre-existing immunity.

Sheena Mukkada, MD, MPH; Carlos Rodriguez-Galindo, MD

The COVID-19 Pandemic Has Affected Pediatric Patients with Cancer and Their Care

In Spring 2020, St. Jude researchers realized that they needed to quickly learn how SARS-CoV-2 virus affects children with cancer. To that end, Sheena Mukkada, MD, MPH (Global Pediatric Medicine, Infectious Diseases), and Carlos Rodriguez-Galindo, MD (Global Pediatric Medicine, Oncology), collaborated with colleagues at St. Jude and in the International Society of Paediatric Oncology to create the Global Registry of COVID-19 in Childhood Cancer. The Registry contains data on pediatric patients who have cancer or have received a hematopoietic stem cell transplant and who have had a laboratory-confirmed SARS-CoV-2 infection. It is being used to gather data on the pandemic's effect on this distinct patient population.

As reported in *The Lancet Oncology*, the team analyzed Registry data from 1500 pediatric oncology patients (median age, 8 years; range, 4–13 years) treated at 131 hospitals in 45 countries. Data were collected for the period of April 15, 2020, to February 1, 2021. Follow-up data at 30 days after symptom onset or COVID-19 diagnosis were available for 1319 patients. Most (82.9%) patients were actively receiving cancer-directed treatment at the time of SARS-CoV-2 infection.

The Registry revealed that 658 (49.9%) patients were hospitalized during the course of their COVID-19 infections; 231 (17.5%) required admission or transfer to a higher level of care; and 50 of 83 (60.2%) deaths that occurred during the study period were caused by SARS-CoV-2. This mortality represents 3.8% of the total cohort, which was substantially higher than the mortality reported by other studies in the general pediatric population (0.01%-0.7%). Due to the COVID-19 pandemic, anticancer treatment was modified for 609 of 1092 (55.8%) patients: 487 (80.0%) had chemotherapy withheld, 41 (6.7%) had surgery delayed, and 25 (4.1%) had radiotherapy delayed while their SARS-CoV-2 infections were treated.

This analysis was conducted before vaccinations were approved for children aged 5 years or older, before they became available in many parts of the world, and before the emergence of the Delta and Omicron variants. At that time, studies showed that just 1%-6% of the general pediatric population experienced severe SARS-CoV-2 infections, whereas 19.9% of the patients in the Registry had severe disease.

The COVID-19 pandemic continues to affect children, and for those with cancer, the effects have been particularly severe. Pediatric oncology patients in low- and middle-income countries have been most acutely affected by the pandemic, where the odds of severe or critical COVID-19 disease were nearly six times higher than that in high-income countries. Results from the Registry are a call to action to address critical needs for access to protective and effective treatment measures against SARS-CoV-2 infection among children with cancer worldwide.

CONCLUSION

From the early days of the COVID-19 pandemic, St. Jude infectious diseases and immunology researchers have gained invaluable insight about the virus and COVID-19 disease. Their work continues to support global efforts to navigate the pandemic. Regardless of what the future holds, St. Jude scientists will continue to contribute to global research efforts to ensure that we are able to optimally respond to SARS-CoV-2 and its variants.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Mitchell J. Weiss, MD, PhD; Phillip Doerfler, PhD

GENE EDITING HOLDS PROMISE FOR TREATING SICKLE CELL DISEASE

Sickle cell disease (SCD) is a common and deadly genetic disorder that affects hundreds of thousands of children born each year. Approximately 900 pediatric patients with SCD receive care in the Hematology Clinic at St. Jude. This autosomal-recessive disease is caused by a missense mutation in the *HBB* gene, which encodes the β-subunit of adult hemoglobin. Normal erythrocytes (or red blood cells) are pliable discs containing hemoglobin that transport oxygen through our bodies. SCD transforms these pliable discs into brittle, sickle-shaped cells that impede blood flow and stimulate inflammation, leading to severe acute and chronic pain, progressive multiorgan damage, and early death.

Fetal hemoglobin (HbF), the early form of the hemoglobin protein that is optimized for functioning in the low-oxygen environment of the womb, is unaffected by the mutation that causes SCD. HbF is normally replaced by the β-hemoglobin subunit after birth, and if that β subunit has the SCD mutation, then symptoms ensue. In a benign condition termed hereditary persistence of fetal hemoglobin (HPFH), genetic variants cause some individuals to express high levels of HbF into adulthood. When an individual coinherits an HPFH variant with SCD alleles, the elevated HbF level prevents erythrocytes from sickling and protects against symptoms of SCD. Understanding how HbF switches to adult hemoglobin can, therefore, help us develop therapies that prevent this transition, increase the levels of HbF, and protect against SCD.

Here we describe how insights into the mechanisms controlling HbF expression and improved technologies for gene manipulation have enabled us to develop approaches to manipulate the switch from fetal to adult hemoglobin or to convert the SCD mutation into a benign variant. There are many hurdles to overcome in transforming these insights into a curative therapy for SCD. Only a few of the genetic variants and regulatory elements that account for HbF's transition have been defined. In addition, modulating HbF expression by transplanting genetically modified bone marrow cells back into a patient carries the risk of insertional mutagenesis from gene therapy vectors and/or chromosomal structural changes caused by conventional gene-editing approaches. As part of the Novel Gene Therapies for Sickle Cell Disease Research Collaborative, researchers at St. Jude and partner institutions have made groundbreaking strides in overcoming these obstacles.

Chromothripsis Is an On-Target Consequence of CRISPR–Cas9 Genome Editing

Gene-editing technologies use molecular tools such as CRISPR (clustered regularly interspaced short palindromic repeats)–Cas9 to introduce defined mutations at specific genomic regions and can be used to introduce variants that maintain HbF production and prevent sickling of SCD erythrocytes. CRISPR–Cas9 is directed by a guide RNA to create specific DNA double-stranded breaks (DSBs), and these breaks are repaired through the process of nonhomologous end-joining or homology-directed repair. Using CRISPR–Cas9, researchers propose to ameliorate the symptoms of β-hemoglobinopathies by disrupting the DNA regions that suppress the expression of HbF in erythrocytes. However, the consequences of the DNA DSBs caused by CRISPR–Cas9 genome editing are not fully understood.

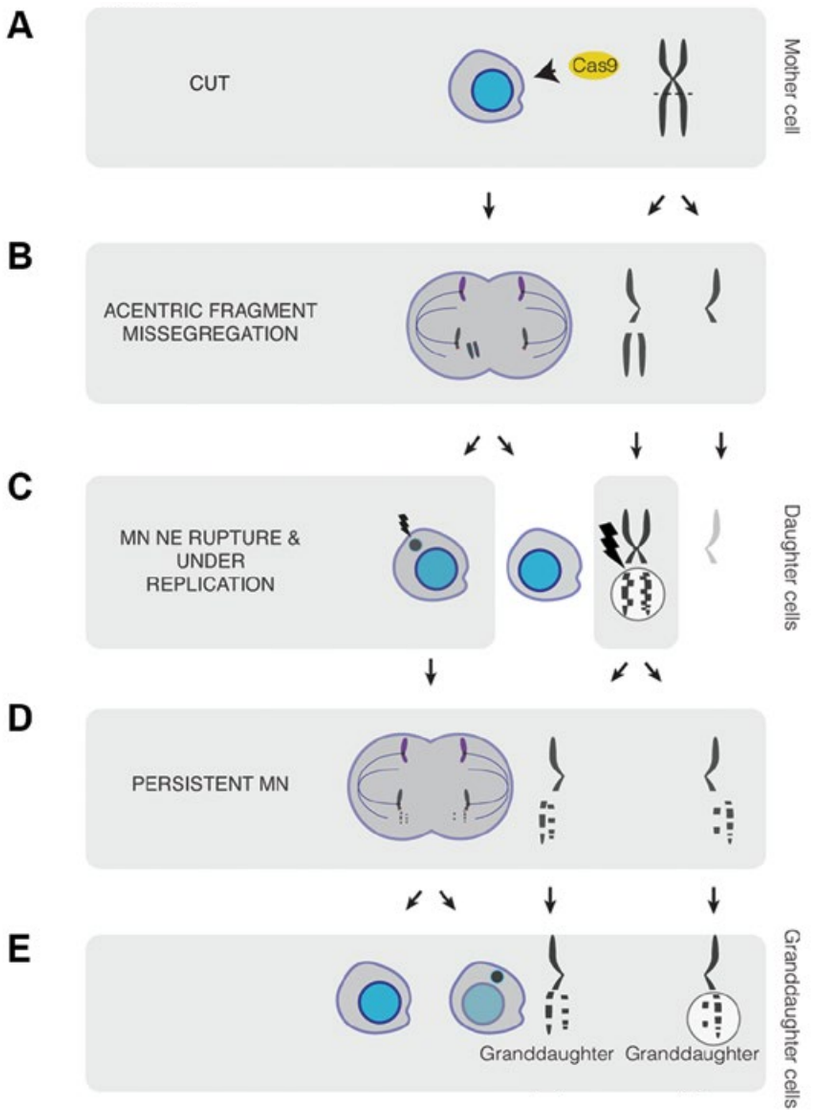


Figure. Events leading to CRISPR–Cas9-induced chromothripsis are shown, with cells on the left and chromosomes on the right. (**A**) CRISPR–Cas9 generates a double-stranded break that splits the target chromosome into "centric" and "acentric" fragments, with or without the centromere, respectively. (**B**) If the break is not repaired before the cell divides, the acentric fragment of the cleaved chromosome may mis-segregate into one daughter cell. (**C**) The acentric chromosomal fragment can form a micronucleus, shown on the left as a black dot. (**D**) DNA in the micronucleus is unstable and can undergo extensive, complex chromosomal rearrangements characteristic of chromothripsis, shown on the right. (**E**) Upon the next round of cell division, the rearranged chromosome segment is reincorporated into genomic DNA of a granddaughter cell, resulting in clustered chromosomal rearrangements that can lead to cell death or cancer. In this way, the formation of micronuclei followed by large-scale chromosomal rearrangements represents a potentially serious genotoxicity of CRISPR–Cas9 genome editing. Lightning bolts indicate DNA damage. MN, micronucleus; NE, nuclear envelope. *Reprinted by permission from SNCSC GmbH: Springer Nature, Nat Genet, 53:895–905. Chromothripsis as an on-target consequence of CRISPR–Cas9 genome editing. Leibowitz ML et al, © 2021*

Mitchell J. Weiss, MD, PhD (Hematology), David Pellman, MD (Dana-Farber Cancer Institute, Boston, MA), and other members of the St. Jude Novel Gene Therapies for Sickle Cell Disease Research Collaborative examined the on-target consequences of CRISPR–Cas9 genome editing in a stable human cell line. This work revealed that CRISPR–Cas9 genome editing can generate structural defects in the nucleus, such as micronuclei and chromosome bridges. This in turn initiates chromothripsis, a catastrophic mutational process that is defined by extensive chromosomal rearrangements occurring in association with a single event in one or a few chromosomes. Chromothripsis causes multiple oncogenic mutations to arise quickly and simultaneously. Furthermore, the initial errors caused by on-target genome editing are then amplified during subsequent cell divisions, thereby creating far more extensive genetic alterations that increase the risk of cancer.

Targeted manipulation of these DNA-binding motifs has practical implications for autologous hematopoietic stem cell therapies for

Novel Gene Therapies for Sickle Cell Disease Research Collaborative

In 2017, St. Jude established the Research Collaboratives Program, with oversight from the Comprehensive Cancer Center, to fund 5-year consortium agreements that leverage the insights and capabilities of renowned scientists and clinicians at St. Jude and other institutions to create collaborative teams committed to tackling groundbreaking projects that accelerate research.

The Novel Gene Therapies for Sickle Cell Disease Collaborative was organized by Dr. Weiss. This effort unites experts in erythroid biology, globin gene expression, genome editing, hematology, and clinical bone marrow transplantation/gene therapy to synergistically develop novel cures for SCD. The partner institutions in this Collaborative include Harvard Medical School, Boston Children's Hospital, Massachusetts General Hospital, the Broad Institute of MIT and Harvard (all of Boston, MA), the National Heart, Lung, and Blood Institute (Bethesda, MD), the Dana-Farber Cancer Center (New York, NY), and the Children's Hospital of Philadelphia (Philadelphia, PA).

The discoveries presented in this feature represent some of the early outcomes of this comprehensive multidisciplinary effort.

This study, which was published in *Nature Genetics*, raises concerns about the clinical use of genome-editing approaches involving DNA DSBs because such breaks can cause cells to quickly acquire oncogenic mutations. Dr. Weiss' team is further motivated to develop genome-editing strategies that do not rely on the generation of DNA DSBs, which should minimize the risk of chromothripsis and other chromosomal abnormalities.

Deciphering the Hereditary Persistence of Fetal Hemoglobin Expression

The fetal-expressed γ-globin genes (*HBG1* and *HBG2*) are normally shut off at birth. However, their expression can be sustained in adult red blood cells by naturally occurring rare variants in the γ-globin gene promoters in HPFH. Although rare variants are generally considered detrimental, HPFH is benign and actually beneficial to patients with β-hemoglobinopathies, such as SCD or β-thalassemia, because the underlying symptoms and pathologies are alleviated or eliminated by elevated levels of HbF in red blood cells. Thus, researchers have long envisioned recreating HPFH to inhibit the switch from fetal to adult hemoglobin in patients with β-hemoglobinopathies, thereby advancing the treatment of these nonmalignant hematologic diseases.

In a second article in *Nature Genetics*, Dr. Weiss and colleagues at St. Jude and the University of New South Wales (Sydney, Australia) mapped the fetal γ-globin promoter sequences at the nucleotide level by using CRISPR–Cas9 genome editing and base-editing approaches to create HPFH variants in an immortalized human erythroid cell line and in primary erythroblasts (i.e., red blood cell precursors extracted from umbilical cord blood or peripheral blood samples from adult donors). Phillip A. Doerfler, PhD (Hematology), a postdoctoral fellow working in Dr. Weiss' laboratory, led this effort and defined two pairs of closely spaced DNA-binding motifs that compete for binding of transcriptional activators or repressors to regulate fetal γ-globin expression. During the fetal stage, the binding of activators GATA1 and NF-Y predominates, and the gene is turned on. After birth, the repressors ZBTZ7A and BCL11A displace GATA1 and NF-Y, respectively, to shut off expression. HPFH mutations tip the balance to favor γ-globin expression in adult red blood cells, either by disrupting a repressor–binding element or by creating new binding sites for transcriptional activators.

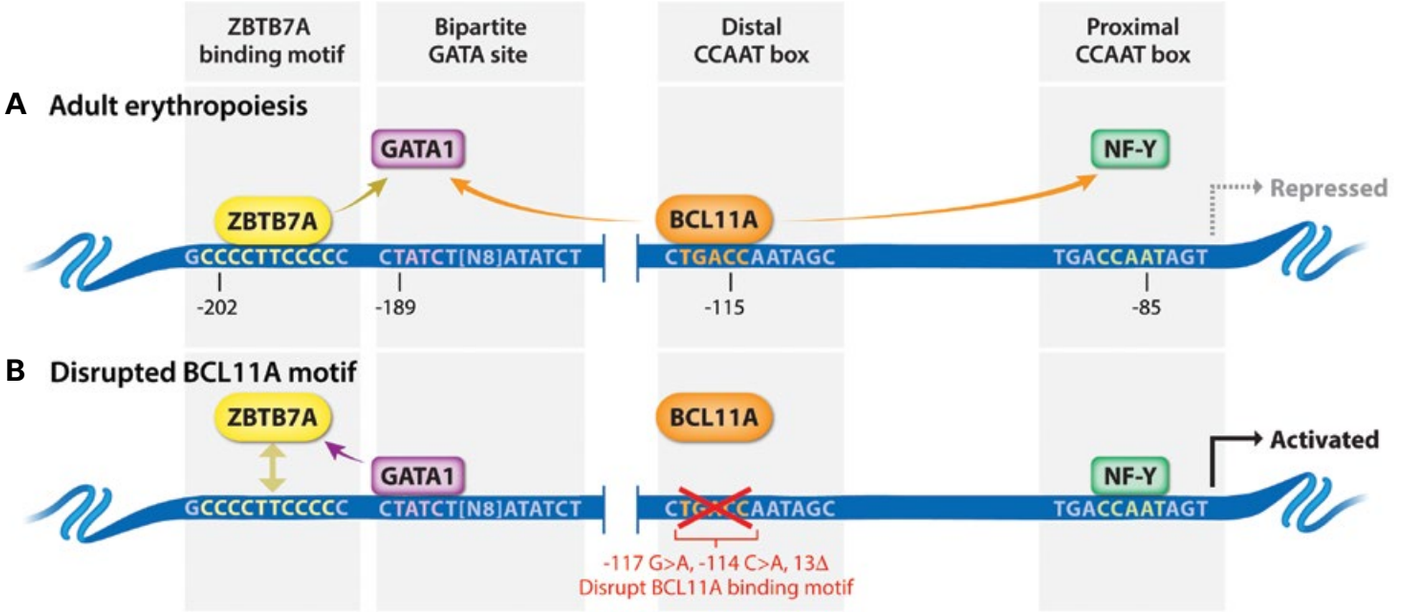


Figure. Transcriptional repressors and activators compete for the γ-globin promoter in hereditary persistence of fetal hemoglobin (HPFH). (**A**) In adult-stage red blood cells, ZBTB7A and BCL11A bind their indicated motifs to inhibit the recruitment of the transcriptional activators GATA1 and NF-Y. (**B**) HPFH mutations disrupt the BCL11A-binding motif, which leads to GATA1 and NF-Y chromatin occupancy and transcriptional activation. ZBTB7A may still bind its motif to partially inhibit the effect. *Reprinted by permission from SNCSC GmbH: Springer Nature, Nat Genet, 53:1177–86. Activation of γ-globin gene expression by GATA1 and NF-Y in hereditary persistence of fetal hemoglobin. Doerfler PA et al, © 2021*

β-hemoglobinopathies. However, as described above, the downstream implications of deletions induced by genome editing are unpredictable. Dr. Weiss and his colleagues believe that elucidating the landscape of gene regulatory switches at a more granular level and exploiting new approaches, such as base editing, will be central to developing new strategies to treat β-hemoglobinopathies.

ABEmax Screening Guides the Mapping of the Gene Regulatory Landscape of Fetal Hemoglobin

Genomic DNA sequences are transformed into gene expression profiles by cis-regulatory elements (CREs) present within noncoding regions of the genome. Nearly 90% of disease-associated genetic variants occur within these CREs. Common and rare genetic variants that control residual expression of HbF in adult red blood cells act by regulating CRE function. However, the current repertoire of known variants accounts for less than half of the heritability of HbF levels.

A team of researchers led by Yong Cheng, PhD (Hematology, Computational Biology), and Dr. Weiss developed an integrated, high-throughput system to map noncoding DNA functions at single-nucleotide resolution, which revealed previously unappreciated complexities of HbF. This new study, published in *Nature Genetics*, combines bioinformatics algorithms and the adenine base–editing tool ABEmax to introduce precise base-pair substitutions in targeted regions of the genome and determine the effect of these perturbations on HbF expression. In addition to validating known HbF CREs, this work revealed a complex regulatory network of novel CREs that regulate HbF levels by controlling the expression of the transcription factor genes *BCL11A, KLF1,* and *MYB*.

The investigators demonstrated the biological relevance of their findings by showing that rare variants in the newly discovered CREs are associated with relatively high levels of HbF in 454 individuals with SCD analyzed by whole-genome sequencing. Additionally, they showed that ABEmax-mediated disruption of a newly discovered CRE in hematopoietic progenitor cells from a patient with SCD caused a two-fold increase in HbF expression in red blood cell progeny, with reduced sickling under low-oxygen conditions. The authors are encouraged that their ABEmax-screening strategy can be used to better define the genetics of HbF expression and to identify new CREs that can be targeted therapeutically to recreate HPFH.

Yichao Li; Yong Cheng, PhD

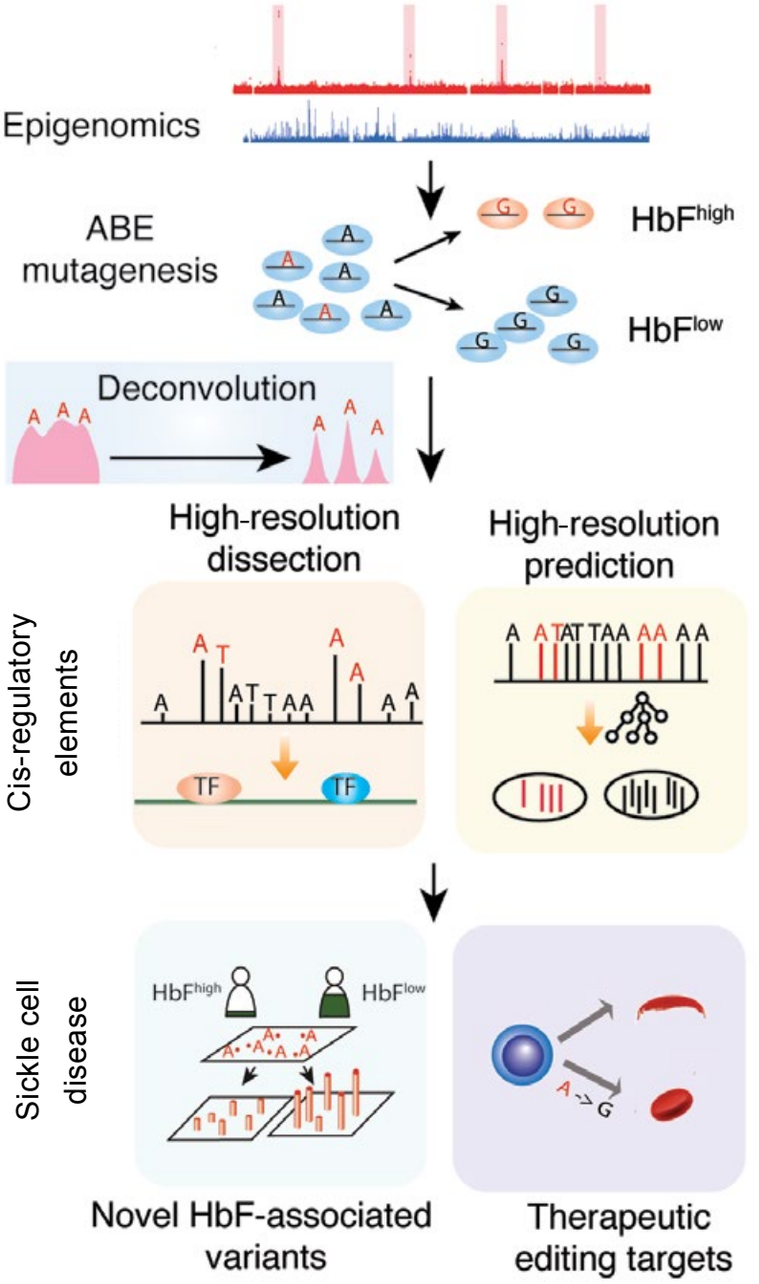
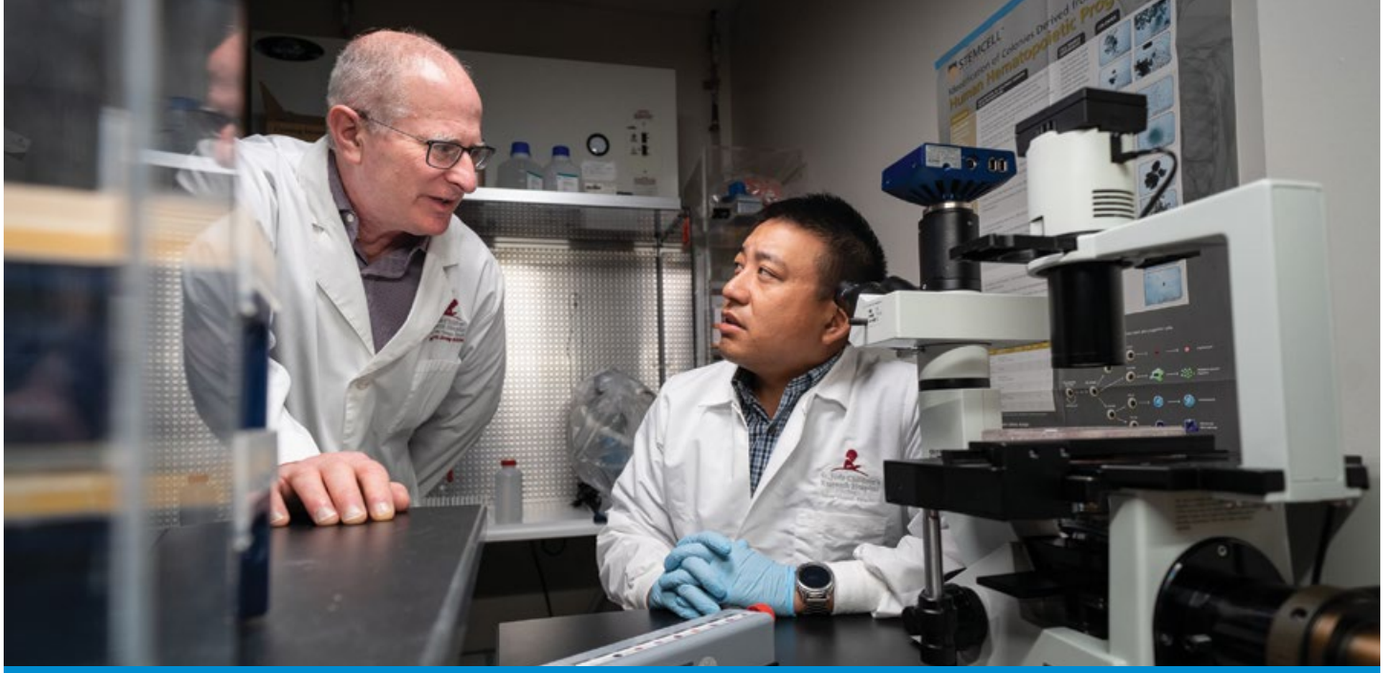


Figure. Workflow for a high-throughput mutational screen to identify novel cis-regulatory elements (CREs) that control fetal hemoglobin (HbF) expression. Potential CREs were identified by integrative population genetics and functional genomics approaches and mutagenized in a human erythroid cell line by using a custom guide RNA library and the adenine base editor ABEmax, which creates precise A-to-G transitions. The targeted CREs were analyzed by next-generation sequencing. Computational deconvolution was applied to quantitatively assess how ABE-induced mutations affect HbF levels. This approach discovered 45 new CREs that regulate HbF expression. Whole-genome sequence analysis of approximately 800 patients with sickle cell disease showed that rare, naturally occurring genetic variants in the newly discovered CREs are associated with high HbF levels. ABEmax disruption of a novel CRE in patient-derived $CD34^+$ hematopoietic progenitors raised HbF levels in erythroid progeny. Thus, identification and analysis of novel HbF-associated CREs explained natural variation of a health-related trait (HbF) and identified novel targets for genetic therapies to raise HbF levels in patients with hemoglobinopathies. Abbreviations: A, adenine; G, guanine; TF, transcription factor. *Reprinted by permission from SNCSC GmbH: Springer Nature, Nat Genet, 53:869–80. Single-nucleotide-level mapping of DNA regulatory elements that control fetal hemoglobin expression. Cheng L et al, © 2021*



Mitchel J. Weiss, MD, PhD; Jonathan Yen, PhD

Accelerating the Therapeutic Pipeline for Sickle Cell Disease

Currently, the only established cure for SCD is allogeneic hematopoietic stem cell transplantation (HSCT). However, matched related donors are available for only about 20% of patients, and there are inherent tissue incompatibility–related risks for the transplant recipient. Autologous HSCT (i.e., transplantation of cells into the same individual from whom they were obtained) of genetically modified hematopoietic stem cells (HSCs) represents a promising alternative. However, the process of gene editing introduces DSBs that can lead to potentially oncogenic large deletions, chromosomal rearrangements, and chromothripsis. A multidisciplinary collaboration led by Jonathan S. Yen, PhD, Thiyagaraj Mayuranathan, PhD (both of Hematology), Dr. Weiss, and David R. Liu, PhD (Broad Institute of MIT and Harvard University, Cambridge, MA), has advanced a new therapeutic strategy based on adenine base editing with distinct advantages over conventional approaches.

Using ABE8e-NRCH, a custom base editor designed by protein evolution, the investigators converted the mutated portion of the *HBB* gene (i.e., the SCD codon) of patient-derived hematopoietic stem and progenitor cells (HSPCs) into a nonpathogenic variant termed Hb Makassar; 80% of cells subjected to the screen were successfully modified. Those cells were then transplanted into immunodeficient mice, and 16 weeks later, the modified HSPCs still produced healthy blood cells: 68% of the cells still expressed the nonpathogenic HBB variant, and the donor red blood cells exhibited a five-fold decrease in sickling after exposure to hypoxia. In additional experiments, similar gene correction was performed in HSCs from a humanized mouse model for SCD, followed by autologous transplantation. These experiments revealed a remarkably protective and durable response at 16 weeks posttransplantation and demonstrated that 20% editing of HSCs is sufficient to mitigate the blood abnormalities of SCD.

This study, which was published in *Nature*, offers the promise of a one-time treatment and perhaps even a cure for SCD. Base editing introduces precise base-pair alterations into HSCs at high efficiency and reduces the genotoxicity risk of DSBs associated with CRISPR–Cas9 editing. The multidisciplinary team is leveraging its vast expertise in protein engineering, fundamental hematology, and genomic technologies to create a safer, more efficient treatment for patients with SCD. Their new approach also has therapeutic potential across β-hemoglobinopathies and other genetic blood diseases.

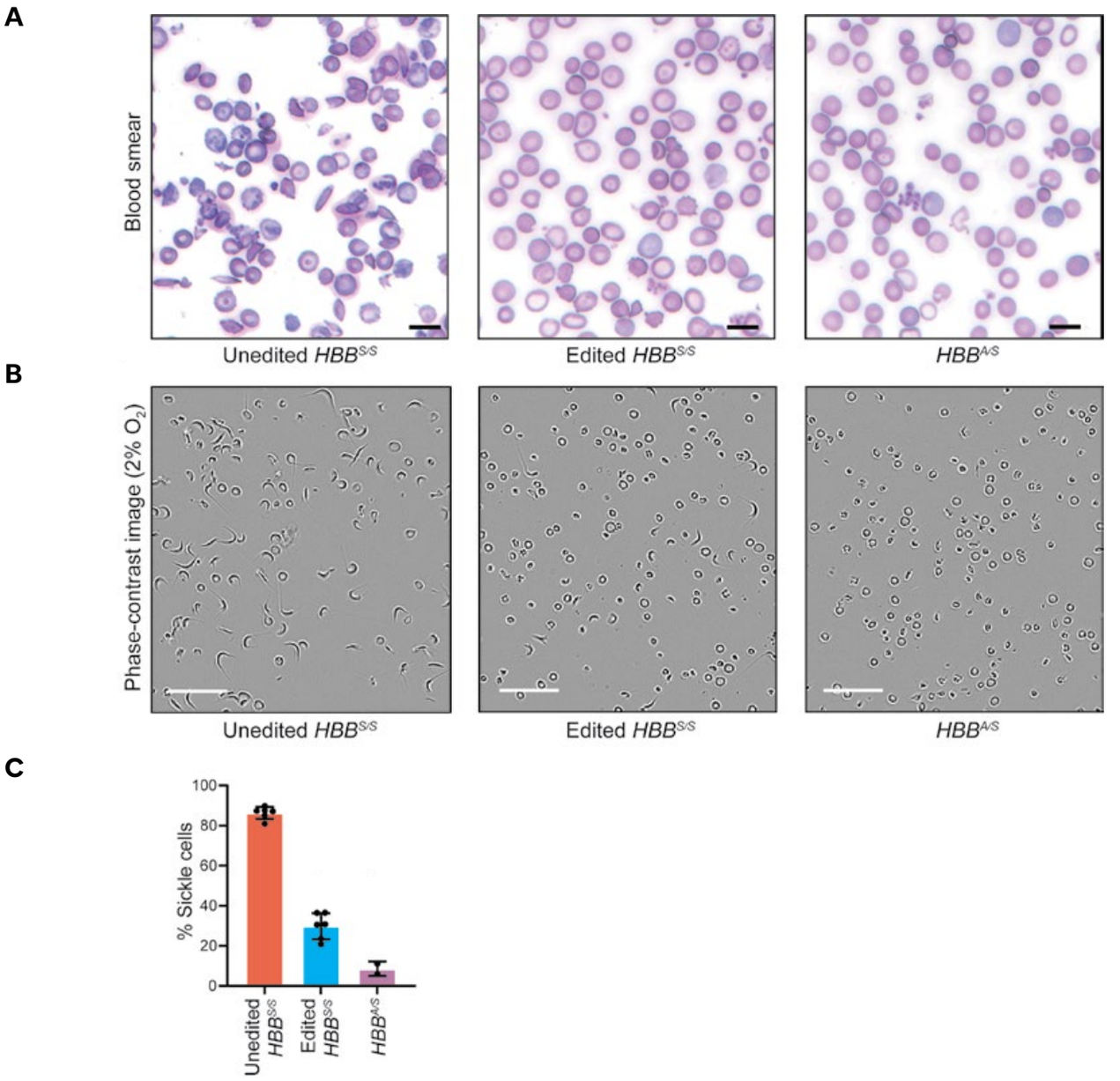


Figure. Base editing of hematopoietic stem cells (HSCs) rescues sickle cell disease (SCD) in mice. HSCs from a humanized mouse model of SCD were edited with ABE8e and single-guide RNA to convert the SCD mutation (HBB^S) into an allele encoding a benign β-globin variant called Hemoglobin Makassar (HBB^G); the HSCs were then transplanted into lethally irradiated congenic mouse hosts. Controls included mice transplanted with unedited HSCs from mice that were either homozygous ($HBB^{S/S}$) or heterozygous ($HBB^{A/S}$) for the SCD mutation. (**A**) Representative images of blood smears obtained from host mice 16 weeks after transplantation. The unedited $HBB^{S/S}$ smear contains a high proportion of deformed, sickled red blood cells (RBCs), whereas most RBCs derived from base-edited $HBB^{S/S}$ HSCs have a normal appearance, similar to those in the $HBB^{A/S}$ smear. Scale bars, 25 µm. (**B**) RBCs obtained from the mice described in (**A**) were incubated in low (2%) oxygen to promote sickling. The phase-contrast images show a marked reduction in sickled cells from mice that received base-edited HSCs compared to those in mice that received unedited $HBB^{S/S}$ HSCs. Scale bars, 50 µm. (**C**) Quantification of results shown in (**B**). These findings identify ABE-mediated conversion of HBB^S to HBB^G as a therapeutic approach for SCD. *Adapted with permission from SNCSC GmbH: Springer Nature, Nature, 595:295–302. Base editing of haematopoietic stem cells rescues sickle cell disease in mice. Newby GA et al, © 2021*

CONCLUSION

Discoveries made at St. Jude and in collaboration with investigators around the world are rapidly advancing our understanding of the genomic regulatory landscape, the development of safe and effective gene-editing approaches, and a capacity to implement new technologies in a therapeutics-development pipeline. The insights gained from these studies hold promise to transform the way we treat and, it is hoped, cure SCD and other genetic disorders that affect hemoglobin genes.

EFFORTS TO PREVENT COGNITIVE DECLINE AFTER CHILDHOOD CANCER

For pediatric patients with cancer, comprehensive assessments of the short-term and long-term physical and cognitive outcomes of their diseases and anticancer treatments are crucial to advancing care and improving their quality of life. As many as 35% of childhood cancer survivors may experience declines in cognitive function that interfere with academic achievement, independence, social interaction, work productivity, and quality of life. However, our understanding of how cancer and anticancer treatments alter cognitive development and function is limited. Identifying how disease-related and treatment-related risk factors impair neurocognitive development and function will help guide clinical decision-making and the design of targeted interventions to address neurocognitive decline in this population.


Victoria W. Willard, PhD

Investigators at St. Jude are studying the need for cognitive monitoring and intervention in patients and survivors of various childhood cancers, including brain tumors, retinoblastoma, and Hodgkin lymphoma. Cross-sectional analyses of physiologic frailty and neurocognition also show the need for interventions that prevent neurocognitive decline in young adult survivors of different types of cancer. The work presented here calls for the development of targeted interventions that will improve long-term quality of life for patients and survivors of childhood cancer.

Cognitive Performance in Young Children after Treatment for Brain Tumors as Infants

Central nervous system (CNS) malignancies are the second-most common pediatric cancer. These diseases require aggressive treatments, including neurosurgery, chemotherapy, and radiation therapy, that pose substantial risk to the developing brain. Thus, children with CNS tumors are at increased risk of neurocognitive deficits after diagnosis and treatment. Yet, little is known about the neurocognitive trajectories of young children with CNS tumors; the literature is limited and presents conflicting findings. Earlier studies did not examine specific cognitive domains, nor did they identify disease- and treatment-related factors most predictive of cognitive risk.

To address these limitations, Heather M. Conklin, PhD (Psychology), led a multi-institutional team that monitored the cognitive outcomes of children treated in a clinical trial for CNS tumors diagnosed during infancy. Their objective was to assess neurocognitive function longitudinally to identify disease- and treatment-related predictive factors contributing to cognitive risk.

The SJYC07 trial (NCT00602667) included 139 very young children with CNS tumors who underwent surgical resection at diagnosis and then received risk-stratified care. Nearly half (43.9%) received chemotherapy only, and the rest received chemotherapy and either focal proton radiation therapy (29.5%) or focal photon radiation therapy (26.6%). Participants underwent neurocognitive testing at baseline (after surgical resection), 6 months after baseline, at the end of treatment, and then annually for as long as 5 years. Neurocognitive assessments included intellectual functioning [i.e., intelligence quotient (IQ)] and parental ratings of attention, executive functioning (e.g., working memory), behavioral functioning, and adaptive functioning (i.e., age-appropriate self-care, communication, and socialization). Demographic traits, including socioeconomic status were also assessed.

The study, which was published in the *Journal of Clinical Oncology*, showed that infants treated for CNS tumors scored significantly lower than the age-matched normative population. Although IQ did not decrease over time, there was an increase in parent-reported problems in attention and executive function. Factors such as tumor location (i.e., supratentorial tumor) and the need for cerebral spinal fluid shunting were also associated with increased cognitive problems. Although demographic factors, such as young age at diagnosis and lower socioeconomic status, were associated with poorer cognitive outcomes, treatment exposure was not.

Heather M. Conklin, PhD

In infants with brain tumors, an early disease-related impact on neurocognitive function can diminish quality of life. The declines in attention and executive functioning call for increased cognitive monitoring and intervention for this vulnerable population. The results of this study may serve to guide treatment planning and indicate targets for cognitive monitoring and preventative intervention to increase quality of life in young children with brain tumors.

Longitudinal Investigation of Cognitive and Adaptive Functioning in Children with Retinoblastoma

Retinoblastoma (a cancer of the eye) is typically diagnosed in pediatric patients younger than 2 years, and most patients with retinoblastoma have a high probability of survival. However, the literature on the longitudinal cognitive functioning of these patients is limited. To address this gap in knowledge, Victoria W. Willard, PhD (Psychology), and her colleagues expanded upon their first longitudinal report of patients with retinoblastoma, which was published in the *Journal of Clinical Oncology* in 2014. In that

Victoria W. Willard, PhD

study, Dr. Willard's team assessed patients with retinoblastoma who participated in the St. Jude protocol RET5 (NCT00186888) for cognitive and adaptive functioning from diagnosis through 5 years of age. The findings from the initial study were consistent with the growing literature at the time—children with retinoblastoma need to be followed to determine whether the disease and/or its treatment affect their developmental trajectory beyond age five.

Key questions of the current study, which was also published in the *Journal of Clinical Oncology*, were whether patients with retinoblastoma whose sole treatment was enucleation (i.e., surgical removal of the diseased eye) would show improved cognitive function over time and whether disease-related or treatment-related factors affect cognitive outcome trajectories.

Of the 98 patients with retinoblastoma who completed psychological assessments through 5 years of age as part of their enrollment in the initial protocol, 73 (74.5%) completed an additional assessment at 10 years of age. The assessments evaluated adaptive functioning and cognitive functioning. Assessments from the 2014 study showed a decline in function from diagnosis to 5 years, but the current study shows a subsequent increase in function by 10 years. Adaptive functioning was in the average range and consistent with the normative mean. For cognitive functioning, the mean estimated IQ for patients was within the average range by 10 years of age, thus, patients showed a significant improvement after 5 years of age.

The rare genetic disorder 13q deletion syndrome is associated with increased risk of retinoblastoma. The *RB1* gene, the loss of which leads to retinoblastoma, is located on chromosome 13. Children with 13q deletion syndrome show a range of congenital problems, including developmental

delay and cognitive impairment, that depend on the size and location of the deletion. In the current study, only four of the 10 patients with 13q-deletion syndrome completed the assessment at 10 years; those data were analyzed separately because the means for both measures, estimated IQ and adaptive behavior, were well below the normative means. Dr. Willard's team found no significant change in the cognitive-functioning trajectory in the 13q deletion subgroup.

After treatment for retinoblastoma, children show a return to an average range of cognitive and adaptive functioning by 10 years of age. However, functioning ability varies based on treatment history. For patients who received enucleation only, the estimated IQs were lower than expected, and for those who received enucleation and subsequent adjuvant therapies, estimated IQs were consistent with normative means. The findings of this study support clinical recommendations that patients with retinoblastoma receive early intervention services to ensure appropriate development.

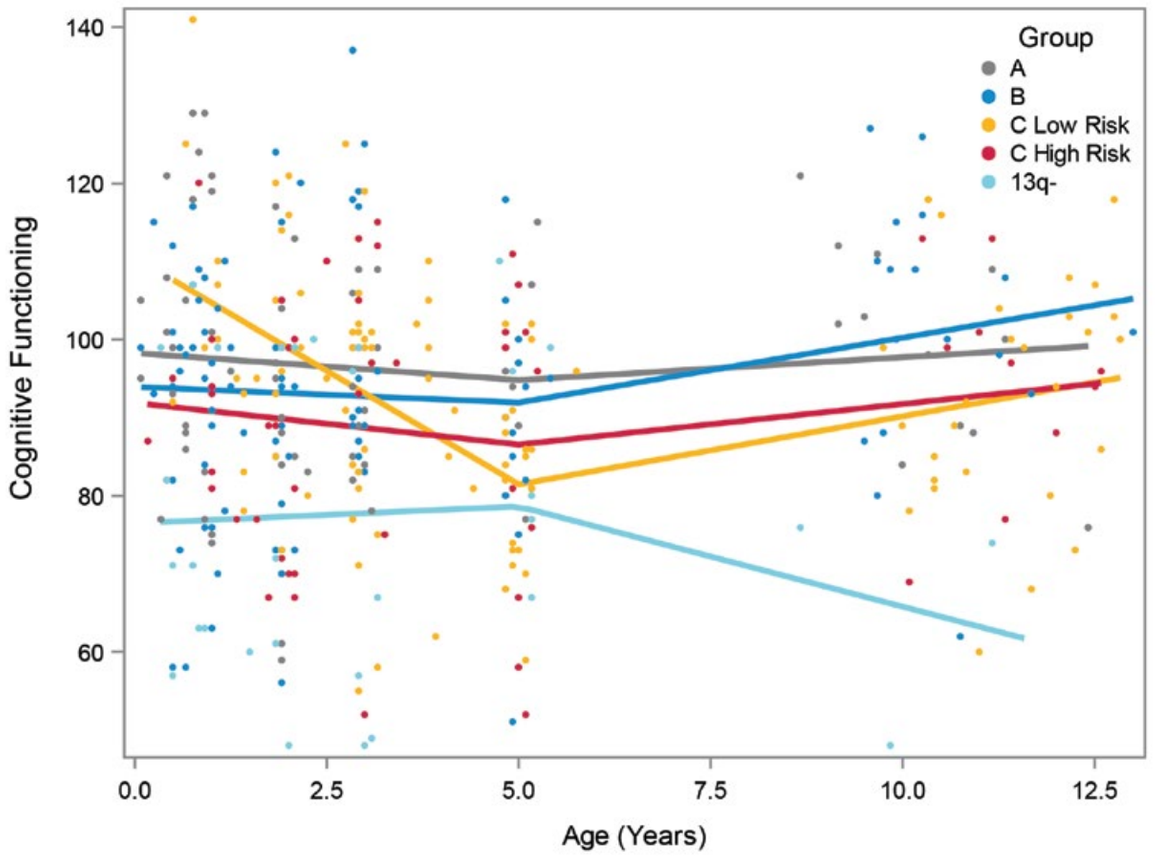


Figure. Longitudinal trajectories of cognitive functioning in patients with retinoblastoma were measured using the Early Learning Composite of the Mullen Scales of Early Learning through 5 years of age. At 10 years of age, the Estimated IQ from the Wechsler Abbreviated Scales of Intelligence (second edition) was used. Data were analyzed by treatment strata: Patients in Group A had unilateral or bilateral retinoblastoma (stage I-III) and those in Group B had bilateral retinoblastoma (stage IV or V); both groups received neoadjuvant chemotherapy comprising various agents. All patients in Group C had unilateral retinoblastoma (stage IV or V) and underwent enucleation. Based on the pathologic analysis of the enucleated eyes, patients in the low-risk subgroup were monitored only, and those in the high-risk subgroup received chemotherapy and external-beam radiation therapy, as indicated. Cognitive functioning declined in patients from diagnosis through age 5 but returned to the average range by 10 years. Primary diagnosis, treatment, and demographic factors contributed to data variability. *Willard VW et al., Cognitive and adaptive functioning in youth with retinoblastoma: a longitudinal investigation through 10 years of age. J Clin Oncol, 39, 24, 2676–84. Reprinted with permission. © 2021 American Society of Clinical Oncology. All rights reserved.*

Kirsten K. Ness, PT, PhD

Physiologic Frailty and Neurocognitive Decline in Young Adult Survivors of Childhood Cancer

In the general population, physiologic frailty is associated with aging and poor health, and in the elderly, it is associated with neurocognitive decline and dementia. Among childhood cancer survivors, frailty notes a person's physical condition and is characterized by having at least three of the following five criteria: fatigue, weakness, low lean-muscle mass, low energy expenditure, and slow walking speed. As childhood cancer survivors age, the risk of physiologic frailty increases. Although 8% of young-adult survivors meet the criteria for frailty, little is known about the effects of frailty among childhood cancer survivors.

Kirsten K. Ness, PT, PhD (Epidemiology & Cancer Control), led a team of investigators at St. Jude to characterize the association between frailty and neurocognitive impairment in 845 young-adult survivors (mean age, 30 years; mean time since cancer diagnosis, 22 years) recruited from the St. Jude Lifetime Cohort study (NCT00760656). Participants completed a comprehensive neurocognitive assessment at two times separated by 5 years. These assessments included tests of intelligence, attention, processing speed, memory, and executive function. They also completed a comprehensive physical examination. Those who exhibited two of the symptoms associated with frailty were deemed "prefrail," and those who exhibited three symptoms were deemed "frail." In the study cohort, 51 (6.1%) survivors were frail, 154 (18.2%) were prefrail, and 640 (75.7%) were nonfrail.

In the cross-sectional analysis of the association between frailty and neurocognitive function at baseline, the investigators noted that the prevalence of neurocognitive impairment was significantly higher among frail and prefrail survivors than among nonfrail survivors. Additionally, those survivors who were frail at baseline demonstrated significant declines in memory, processing speed, and executive function 5 years later, compared to those survivors who were nonfrail at baseline. The results of the study, which were published in the *Journal of Clinical Oncology*, show that frailty is associated with neurocognitive impairment and continued neurocognitive decline in young-adult survivors of childhood cancer. Both frail and prefail survivors experience declines in memory, attention, and executive function, compared with those measures in nonfrail survivors. Dr. Ness and her colleagues concluded that targeted interventions that prevent or improve physiologic frailty can also prevent neurocognitive decline in survivors of childhood cancer. However, more research is needed to better understand the relation between frailty and neurocognition.

Kevin R. Krull, PhD

Modifiable Risk Factors Affect Neurocognitive and Psychosocial Problems in Hodgkin Lymphoma Survivors

Survivors of childhood Hodgkin lymphoma have a high burden of chronic health morbidities, including cardiac, pulmonary, and endocrine problems. Yet, neurocognitive and psychosocial morbidity have not been well established in these survivors. To fill this gap in knowledge, Kevin R. Krull, PhD (Epidemiology & Cancer Control, Psychology), led a team of investigators from St. Jude, MD Anderson Cancer Center (Houston, TX), Duke Cancer Institute (Durham, NC), National Cancer Institute (Bethesda, MD), and Fred Hutchinson Cancer Research Center (Seattle, WA) who conducted a cross-sectional study of the risk of neurocognitive and psychosocial problems in Hodgkin lymphoma survivors.

The study, which was published in *Blood*, enrolled 1760 Hodgkin lymphoma survivors (mean age, 37.5 years; mean time since Hodgkin lymphoma diagnosis, 23.6 years) and 3180 siblings (mean age, 33.2 years), all of whom are participating in the Childhood Cancer Survivor Study (NCT01120353). All study participants completed surveys that evaluated neurocognitive function, emotional distress, quality of life, social attainment, smoking history, physical activity, and chronic health morbidities. Analysis of the surveys showed that, compared with the siblings, survivors are at significantly higher risk of neurocognitive and psychosocial impairment, anxiety, depression, chronic health morbidities, and poorer physical and mental quality of life. The neurocognitive and psychosocial impairment was associated with modifiable factors, such as smoking and reduced physical activity, and with chronic health conditions (e.g., hypertension and stroke). Structural-equation modeling demonstrated that chest and neck irradiation and the use of beomycin chemotherapy were directly associated with cardiovascular, endocrine, and respiratory problems, and these chronic health morbidities were associated with neurocognitive and psychosocial impairment. Smoking and lower physical activity were also associated with neurocognitive and psychosocial impairment.

Dr. Krull and his colleagues concluded that early identification and treatment of chronic health morbidities combined with increased positive health behaviors could be targets for interventions to improve long-term functional outcomes and quality of life for survivors of childhood Hodgkin lymphoma.

CONCLUSION

Clinical investigators in the Psychology and Epidemiology & Cancer Control departments at St. Jude are establishing associations between neurocognitive impairment and disease-related and treatment-related factors in childhood cancer. This work is imperative to establish targeted interventions that aim to preserve neurocognitive function and maximize quality of life as childhood cancer survivors grow and age.

Charnise Goodings Harris, PhD

GENETIC DISCOVERIES FOR PATIENTS WITH BONE MARROW FAILURE AND HIGH-RISK LEUKEMIAS

Although a cancer diagnosis during childhood is rare, cancer remains the leading cause of death by disease among children in the United States. The cause of most pediatric cancers is still unknown, but researchers at St. Jude and other institutions have identified a growing number of risk factors for these catastrophic diseases.

Here we highlight recent progress made by St. Jude investigators who seek to understand the biological basis of the elevated risk for acute, highly aggressive leukemias. These studies focused on children with hereditary bone marrow failure (BMF) and myelodysplastic syndromes (MDS), those with pediatric or adult lineage-ambiguous leukemias, and childhood cancer survivors whose cancer-directed treatment included cytotoxic agents that predispose to the development of secondary malignancies.

Marcin W. Wlodarski, MD, PhD; Sushree S. Sahoo, PhD

Discoveries from the Bone Marrow Failure and Myelodysplastic Syndromes Program

Bone marrow failure syndromes are a group of rare conditions resulting in the loss or dysfunction of hematopoietic stem cells and an increased risk of cancer. Most BMF syndromes are caused by inherited (germline) mutations that affect basic cellular pathways. Along with anemia, increased risk of bleeding, and infections, BMF syndromes predispose children to MDS and leukemia.

Marcin W. Wlodarski, MD, PhD (Hematology), from the St. Jude BMF and MDS Program in the Department of Hematology, and his international collaborators have published several papers focused on the genomic basis of BMF syndromes and MDS. Dr. Wlodarski's team has identified new causative genes, genetic biomarkers, and genotype/phenotype correlations related to pediatric BMF and MDS and has reported on promising new treatment strategies for secondary MDS and leukemias. They have also found evidence that somatic genetic rescue (SGR) is more common in hematopoietic disorders than previously recognized. SGR events are spontaneously arising gene- or genome-level alterations that compensate for the deleterious effect of germline mutations. This work provides a foundation for research to understand the mechanisms of SGR and its potential utility as a biomarker for therapy stratification in BMF and MDS syndromes. The studies also emphasize the need for worldwide collaborations that are essential to the success of research on rare catastrophic diseases.

Trajectories of Clonal Hematopoiesis in *SAMD9/SAMD9*L MDS-Predisposition Syndromes

Dr. Wlodarski, Sushree S. Sahoo, PhD (Hematology), a postdoctoral fellow working in his laboratory, and their colleagues from 19 countries published a landmark study in *Nature Medicine* demonstrating that germline mutations in the genes *SAMD9* and *SAMD9L* are among the most common causes of pediatric MDS. The study included an analysis of 669 children and adolescents enrolled prospectively in the registry of the European Working Group for MDS in Childhood (NCT00047268, NCT00662090). *SAMD9/SAMD9L* mutations account for 8% of MDS cases and are mutually exclusive with germline *GATA2* mutations, another common cause of pediatric MDS in 7% of patients.

The high prevalence of germline *SAMD9/SAMD9L* mutations is consistent with previous work published in 2017 by the laboratory of Jeffery M. Klco, MD, PhD (Pathology); however, the biology of these mutations and its impact on disease course was unclear. In the current study, the authors have demonstrated that the overall survival and outcome after hematopoietic stem cell transplantation are comparable between patients with germline *SAMD9/SAMD9L* mutations and those without any known predisposition. There was also no difference in outcomes between patients with *SAMD9* mutations and those with *SAMD9L* mutations, who had a 5-year overall survival of 84% and 93%, respectively.

Genetic mosaicism is a condition in which a person has two or more sets of genetically distinct cells. In BMF and MDS, the germline mutations drive the development of SGR, which leads to mosaicism in the hematopoietic system. The team reported that SGR occurred in 61% of the pediatric patients with MDS and *SAMD9* and *SAMD9L* mutations. In patients with SGR, 95% of the somatic changes in blood cells were maladaptive, and the patients had either monosomy 7 alone (i.e., one copy of chromosome 7 with germline *SAMD9* or *SAMD9L* mutation lost) or monosomy 7 with leukemia-driver mutations representing leukemic progression. However, the occurrence of multiple independent clones was common; in 51% of the patients with SGR, clonal hematopoiesis of a protective nature (termed "adaptive") was also discovered. Among the adaptive clones, uniparental disomy of chromosome 7q (i.e., when through a mitotic recombination event in a hematopoietic stem cell, the long arm [q] of chromosome 7 is duplicated) was found mostly in young children with germline *SAMD9L* mutations and resulted in the replacement of the *SAMD9L* mutation with the wild-type gene.

This "natural gene therapy" phenomenon is seen as a benign repair process that can outcompete other clones in the bone marrow and potentially result in life-long remission, as observed in some patients in the study.

For this project, the authors established an innovative single-cell DNA-sequencing assay that resolved not only mutations but also chromosomal aberrations in the bone marrow and blood with very high sensitivity. Using this method, they discovered that multiple competing SGR events in an individual patient lead to a plethora of novel clones in the blood, highlighting the extreme plasticity of hematopoiesis in children. Single-cell DNA sequencing also enabled the researchers to determine how different clones fare over time based on their frequency in the bone marrow. Early detection of SGR events has potential utility in disease surveillance and may help identify patients who would do well without hematopoietic stem cell transplantation, which is standard treatment for pediatric MDS.

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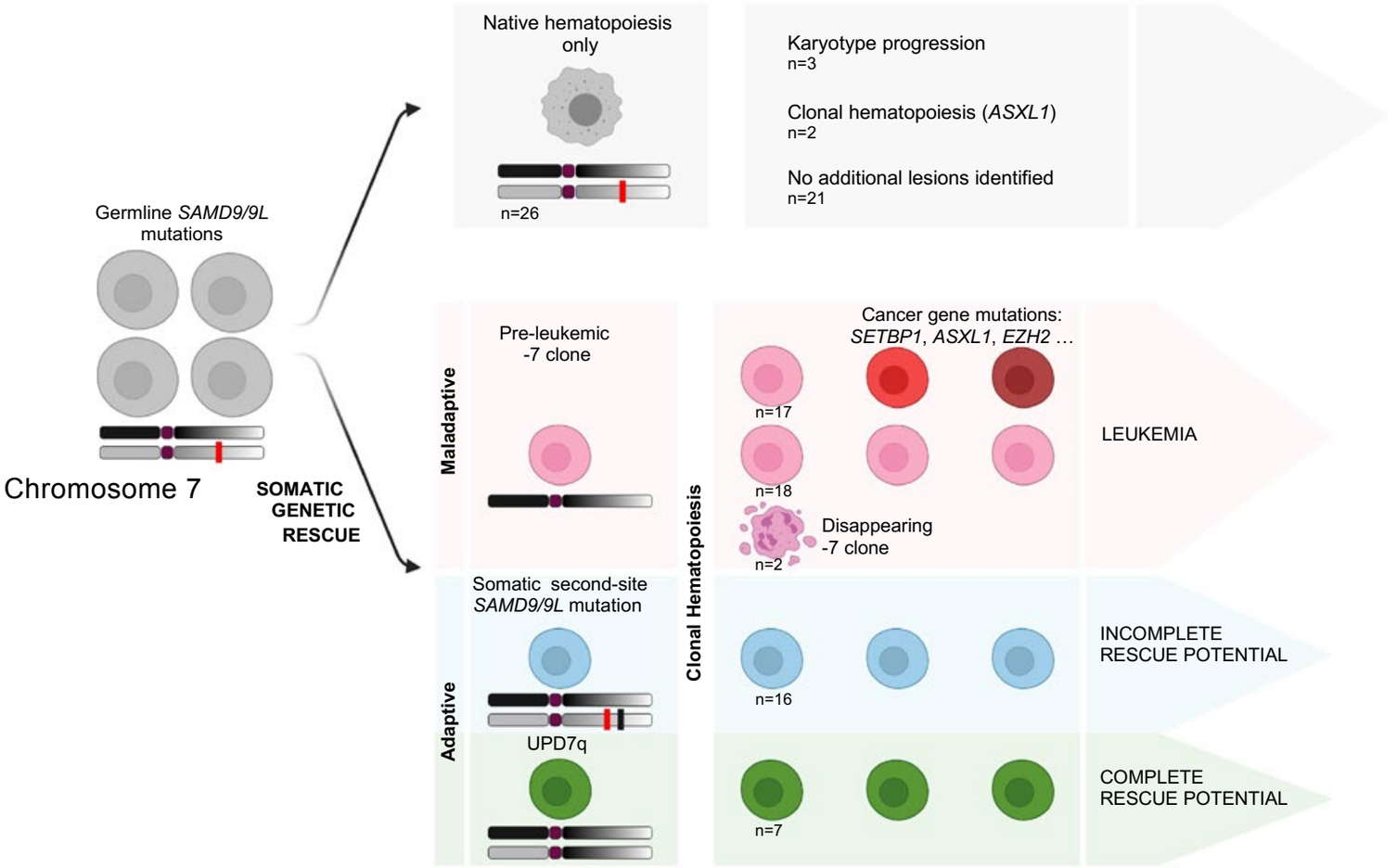


Figure. The four major trajectories of clonal hematopoiesis arising from mutations in the *SAMD9* and *SAMD9L* (*SAMD9/9L*) genes, as inferred from comprehensive molecular and cytogenetic characterization of bone marrow samples from 67 pediatric patients with myelodysplastic syndromes (MDS). The top panel depicts 26 (39%) patients with native-state hematopoiesis only; no somatic genetic rescue (SGR) occurred at chromosome 7 or within the *SAMD9/L9* locus (red bar), and the rate of clonal progression was low. The lower panel depicts the three trajectories of the 41 (61%) patients in whom SGR occurred. The first trajectory resulted in maladaptive clones, such as monosomy 7 (-7), that can gain additional oncogenic mutations and result in leukemia. The remaining two trajectories resulted in adaptive (benign) clones that involved either a second-site *SAMD9/9L* mutation (black bar) and resulted in incomplete rescue potential or clones, such as uniparental isodisomy 7q (UPD7q), and complete rescue potential. Overlapping SGR events were detected in 26 patients. These results show that SGR is common in children with *SAMD9/9L*-mutated MDS. *Reprinted by permission from SNCSC GmbH: Springer Nature, Nat Med, 27,1806–17, Clinical evolution, genetic landscape and trajectories of clonal hematopoiesis in SAMD9/SAMD9L syndromes, Sahoo SS et al, © 2021*

Der(1;7) Translocation Is Associated with Germline *GATA2* Mutations

GATA2 deficiency is another common germline predisposition for pediatric MDS; however, no specific markers of clonal evolution exist. Dr. Wlodarski worked with collaborators in the United States, Europe, and Japan to identify new clonal markers associated with disease progression. They found that MDS and germline *GATA2* mutations often carry a chromosomal translocation known as der(1;7)(q10;p10). This unbalanced whole-arm chromosomal translocation results in trisomy of 1q (i.e., three copies of chromosome 1q are present) and deletion of 7q.

In this study, which was reported in *Blood*, the researchers first reviewed the cytogenetic data of 1620 children and adolescents with MDS. Genomic-sequencing data were available for 811 patients with MDS. Der(1;7) was present in 8 of 87 (9.2%) patients with MDS and *GATA*2 deficiency, compared with 3 of 724 (0.4%) patients with MDS and wild-type *GATA2*. When the researchers expanded the study cohort to include additional cases with *GATA2* mutations and der(1;7), including patients enrolled in the St. Jude INSIGHT biobanking protocol (NCT02720679), they found that 18 of 19 (95%) patients tested also had somatic mutations in genes associated with myeloid malignancy (e.g., *SETBP1, ASLX1, STAG2, RUNX1, EZH2,* and *KRAS*). The patients had leukemic progression and could be cured only by hematopoietic stem cell transplantation.

These data suggest that der(1;7) is a strong predictor of a *GATA*2 deficiency, a finding that is relevant for diagnosis, surveillance, and treatment. The authors recommend surveillance via cytogenetic and deep-sequencing analyses to detect chromosomal aberrations and leukemia-driver mutations in patients with *GATA2* deficiency to identify those at risk of developing advanced MDS.

Germline *RPA1* Mutations Cause a New Telomere Biology Disorder with Bone Marrow Failure

Telomeres are the repetitive DNA sequences that protect the ends of chromosomes, and telomere biology disorders (TBDs; also called short-telomere syndromes) share a common biology but exhibit widely different phenotypes, including BMF and MDS. By exploring mutations present in patients with BMF that are associated with shortened telomeres, Dr. Wlodarski and his colleagues expanded the genetic spectrum of TBDs and identified a new BMF syndrome. They discovered three germline heterozygous missense mutations in the *RPA1* gene: $RPA1^{E240K}$, $RPA1^{V227A}$, and $RPA1^{T270A}$. RPA1 is a single-strand DNA-binding protein that is required for DNA replication and repair, as well as for telomere maintenance.

Dr. Wlodarski and Richa Sharma, MD (Hematology), a physician–scientist instructor working in the Wlodarski laboratory, detailed clinical manifestations consistent with TBD (e.g., BMF, MDS, lymphopenia, and pulmonary fibrosis) in four unrelated individuals. They also reported evidence of unique gain-of-function effects of the $RPA1^{E240K}$ and $RPA1^{V227A}$ proteins that involved increased DNA binding and telomere unfolding. Furthermore, induced pluripotent stem cells modified with CRISPR–Cas9 to express the *RPA1* mutations showed defective hematopoiesis and telomere shortening. The researchers also discovered two independently acquired somatic rescue events in the hematopoietic stem cells of one patient; these benign events inactivated the germline *RPA1* mutation either by acquired uniparental disomy or by cis-inactivating mutations that resulted in allelic loss of the germline *RPA1*-mutant allele and were associated with long-term stabilization of blood counts.

This study was published in *Blood* and drew from patient registries in the United States, Germany, Greece, and France. The findings suggest that *RPA1* missense variations should be carefully considered during a clinical workup of patients with symptoms suggesting a TBD. This study also showcases the power of international collaboration facilitated by biobanking protocols in defining the biology of rare diseases (e.g., the INSIGHT protocol).

St. Jude Establishes the Bone Marrow Failure and Myelodysplastic Syndromes Program

Despite major advances in the fields of pediatric hematology and oncology, BMF disorders and MDS in children remain poorly understood, difficult to treat, and frequently fatal. The BMF and MDS Program, which is in the Department of Hematology and led by Dr. Wlodarski, cares for patients with these devastating disorders and conducts related laboratory-based and clinical research.

The Program's mission is to provide the best multidisciplinary clinical care possible for patients with BMF or MDS and to better understand the genetic mechanisms that influence disease onset, progression, and evolution to leukemia. To facilitate the care of these patients, Dr. Wlodarski and his colleagues have established the multidisciplinary BMF/MDS Clinic that includes advanced practice providers, nurses, and a psychosocial care team. Clinical pathologists and computational biologists perform state-of-the-art molecular and genetic testing to ensure accurate diagnoses and optimal clinical management of each case. To facilitate research in BMF and MDS, a research biobank has been established, and Program members are engaged in numerous national and international collaborations and BMF/MDS consortia. They also work closely with the St. Jude Affiliate Network.

The long-term vision of the BMF and MDS Program is to improve the lives of pediatric patients who have these catastrophic diseases by developing innovative therapies and cures through mechanism-based research.

BMF and MDS Program Members

Marcin W. Wlodarski, MD, PhD
Program Leader

Nathan Gray
Physician Assistant

Michelle Boals
Nurse Practitioner

Jessica Uhrich
Program Coordinator

Sara Lewis
Genetic Counselor

Melvanique Hale
Nursing Care Coordinator

Richa Sharma, MD
Physician–Scientist Instructor

Senthil Bhoopalan, MD
Physician–Scientist Instructor

Swapna Thota, MD
Consultant, Adult BMF Specialist

Amanda Pullen
Social Worker

Tamanna Shamrin
Research Data Specialist

Sushree S. Sahoo, PhD
Postdoctoral Research Associate

Masanori Yoshida, MD, PhD
Postdoctoral Research Associate

Charnise Goodings-Harris, PhD
Scientist

Kelsey Ray
Clinical Research Associate

Richa Sharma, MD

CPX-351–Mediated Cytoreduction in Patients with Secondary Myeloid Malignancies Motivates a New St. Jude Clinical Trial

Myeloid malignancies that arise after treatment for primary oncologic or hematologic diseases have been termed secondary myelodysplastic syndromes or acute myeloid leukemia (sMDS/AML). It is rare for pediatric patients to experience sMDS/AML, but those who do have a poor prognosis, with a probability of survival less than 50%. The traditional approach to treating these patients is intensive chemotherapy, followed by hematopoietic cell transplantation. Because most have already received a significant amount of chemotherapy or have been chronically ill, early mortality and morbidity are high.

In August 2017, the U.S. Food and Drug Administration (FDA) approved the use of CPX-351 for older adults with myeloid leukemia or secondary myeloid neoplasms. CPX-351 contains daunorubicin and cytarabine (two agents commonly used during induction chemotherapy in myeloid leukemias) packaged inside nanometer-sized, lipid-based bilayer vesicles that minimize release/damage of healthy cells and maximize delivery to leukemia cells. In September 2017, St. Jude investigators submitted a compassionate use request to use CPX-351 to treat a secondary myeloid leukemia in an adolescent previously treated for osteosarcoma. The patient's leukemia showed a remarkable response to the compound, prompting CPX-351 treatment of additional patients with sMDS/AML at St. Jude.

Dr. Wlodarski, Raul C. Ribeiro, MD (Oncology), and their colleagues from the Departments of Bone Marrow Transplantation & Cellular Therapy and Pathology conducted a retrospective case-series study of patients who received CPX-351 at St. Jude between 2017 and 2021.The cohort of seven patients included six with sMDS/AML and one with primary AML with MDS-related changes and multiorgan failure. The mean age at diagnosis was 17 years (range, 13–23 years). Patients received one to three cycles of CPX-351. Treatment was well tolerated, and all patients experienced a morphologic remission with a substantial reduction in bone marrow cellularity.

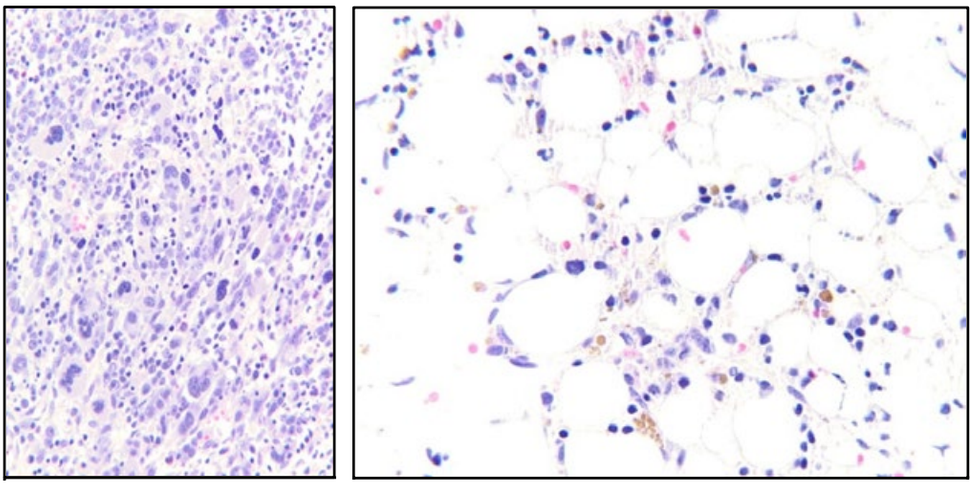


Figure. Images of bone marrow from a patient at diagnosis of secondary acute myeloid leukemia with myelodysplastic syndrome–related changes (left; original magnification, ×200) and 1 month after one cycle of CPX-351 treatment (right; original magnification, ×600). Bone marrow was stained with hematoxylin and eosin. The results support the need for larger prospective trials to assess the long-term benefits of CPX-351 in pediatric secondary myeloid malignancies. *Reprinted from Hu Y et al, CPX-351 induces remission in newly diagnosed pediatric secondary myeloid malignancies. Blood Adv, 6, 521–7, 2022, © 2022 by the American Society of Hematology, http://creativecommons.org/licenses/by-nc-nd/4.0/*

At last follow-up, six patients were alive and in remission (median duration, 12.5 months; range, 6–39 months) and one died of disease progression. This work was published in *Blood Advance*s and has resulted in the development of a St. Jude–initiated clinical trial of CPX-351 in patients with sMDS/AML entitled, CPXSMN, a Prospective, Multicenter, Single-Arm Pilot Study of CPX-351 (Vyxeos) in Individuals <22 Years with Secondary Myeloid Neoplasms Acute Myeloid Leukemia and Myelodysplastic Syndrome (NCT pending). Drs. Wlodarski and Ribeiro will serve as co-principal investigators on this study, which will open to accrual in Fall 2022.

Identifying the Mutations that Drive Therapy-Related Myeloid Neoplasms in Childhood Cancer Survivors

Children whose cancer-directed treatment includes cytotoxic therapy are at increased risk of therapy-related myeloid neoplasms (tMNs). These secondary cancers arise in 0.5%-1% of pediatric cancer survivors, and patients with tMNs have poorer 5-year survival than those with primary disease. The association between these secondary cancers and certain cytotoxic agents is well known. However, key details are lacking about tMN pathogenesis in children, including the somatic and/or germline genomic alterations that drive the disease.

Jeffery M. Klco, MD, PhD (Pathology), and Xiaotu Ma, PhD (Computational Biology), led an effort to complete whole-genome, whole-exome, and RNA sequencing in a cohort of 84 patients with an initial diagnosis of hematologic, solid tumor, or central nervous system malignancies. Their goal was to determine the genomic profiles of patients with tMNs. This research benefited from new computational tools, including CleanDeepSeq and SequencErr, that were developed by Dr. Ma's group. These methods increase the resolution and accuracy when identifying mutations in large sequencing data sets.

The study cohort included 28 patients with therapy-related MDS and 56 patients with therapy-related AML. The median age at diagnosis of tMN was 13.6 years (range, 1.2–24.6 years), and the period between diagnosis of primary disease and tMN varied greatly (median, 2.9 years; range, 0.7–16.2 years). Tumor and nontumor tissues were both sequenced in 62 cases, whereas nontumor tissues only were sequenced in 22 cases.

The team identified rearrangements in the *KMT2A* gene as the most common driver mutations in the study cohort. Somatic alterations in the Ras/MAPK pathway, *RUNX1*, and/or *TP53* were also frequent, and the transcription factor *MECOM* was often overexpressed due to enhancer hijacking (i.e., a process in which genomic rearrangements move an enhancer from its natural context to be in proximity to another gene and ectopically activate it). The researchers also found that, unlike tMNs in adults, most secondary cancers in children are caused by cytotoxic therapy rather than pre-existing tMN clones.

These findings, published in *Nature Communications*, may have implications for early intervention of tMNs. Drs. Klco and Ma and their team found that tMN clones can be identified as early as 2 years before the neoplasms develop.

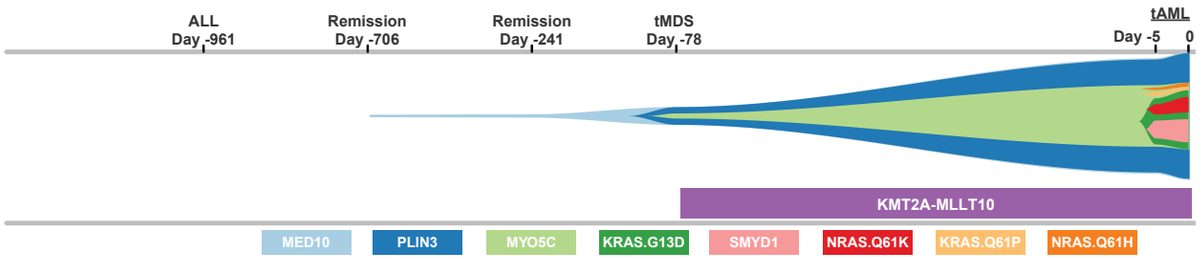
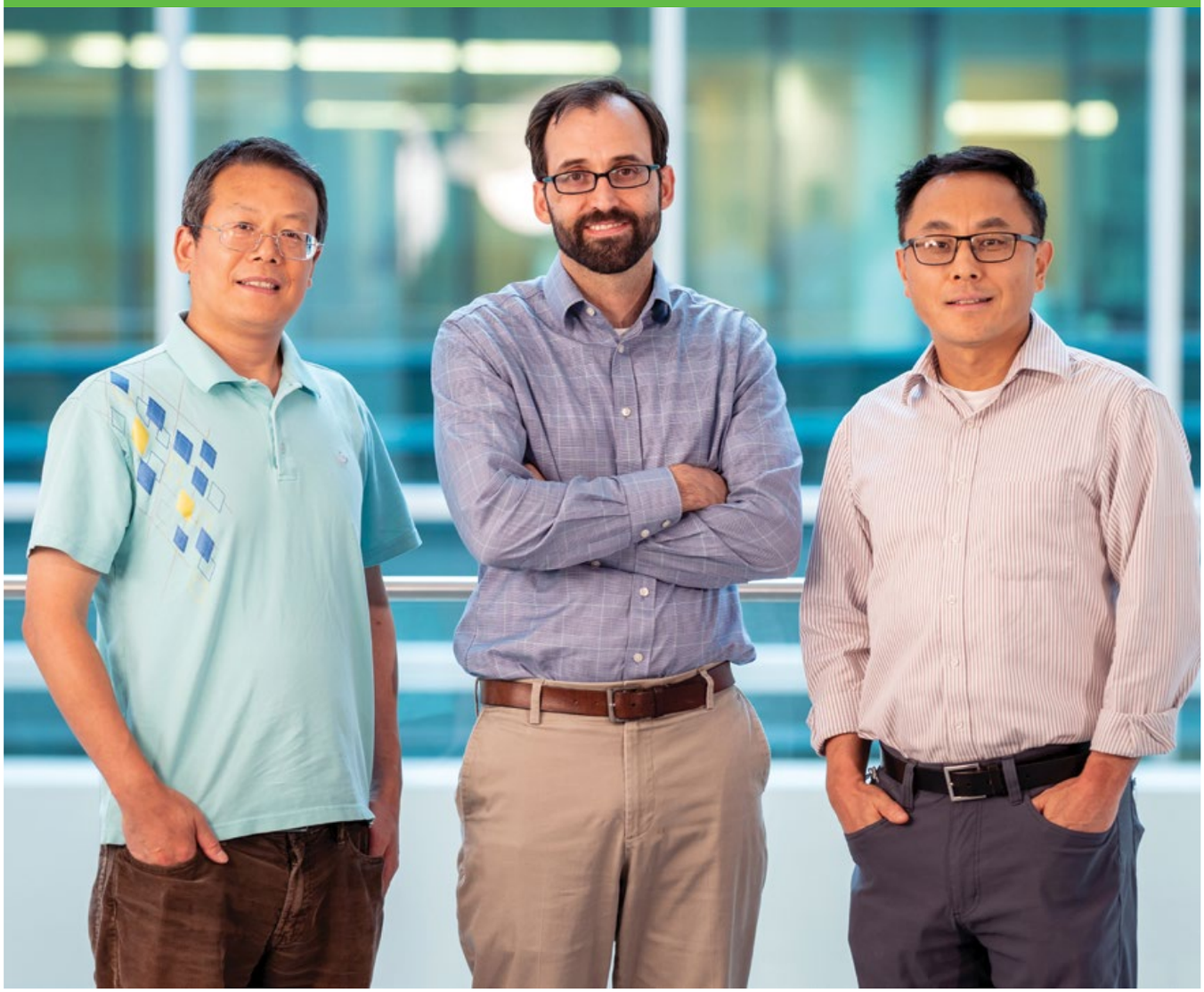


Figure. A river plot of a therapy-related myeloid neoplasm (tMN) arising in a patient who had a primary diagnosis of acute lymphoblastic leukemia (ALL). The tMN variants, which are depicted in various colors below the plot, occurred only after cytotoxic therapy. The founding clone variant in *MED10* (light blue) was detectable 628 days before the morphologic diagnosis of therapy-related myelodysplastic syndrome (tMDS) and 706 days before the diagnosis of therapy-related acute myeloid leukemia (tAML), both of which also had a KMT2A–MLLT10 fusion (purple). These results show that most pediatric tMN variants are caused by cytotoxic therapy, and they can be identified by comprehensive sequencing studies more than a year before any neoplasm is detected. *Reprinted from Schwartz JR, et al, The acquisition of molecular drivers in pediatric therapy-related myeloid neoplasms. Nat Commun, 12, 985, 2021, © 2021, http://creativecommons.org/licenses/cc by/*

Xiaotu Ma, PhD; Jeffery Klco, MD, PhD; Jing Ma, PhD



Loss of the LKB1/*STK11* Tumor Suppressor Drives the Progression of Myeloproliferative Neoplasms

Myeloproliferative neoplasms (MPNs) are a group of rare, closely related hematopoietic stem cell disorders that are characterized by overproduction of red blood cells, platelets, or other myeloid-lineage cells. The causes, symptoms, and outcomes of MPNs vary, but in as many as 20% of cases, MPN leads to acute leukemia, including a very aggressive form of AML called blast-phase myeloproliferative neoplasm (MPN-BP), which has a median survival of 3–5 months.

Sequencing studies of MPNs and MPN-BPs have identified mutations and gene variants related to myeloid malignancies, yet the mechanisms of transformation from chronic MPN to AML remained unclear. John D. Crispino, PhD, MBA (Hematology), and his colleagues focused on how the loss of tumor-suppressor genes affects the disease trajectory of MPNs. Using a CRISPR-Cas9 screen in murine MPN cells, Dr. Crispino's team looked for gene deletions that enhance self-renewal of hematopoietic stem and progenitor cells with MPN mutations.

The study, which was reported in *Cancer Discovery*, led the investigators to the tumor-suppressor gene serine threonine kinase 11 (*Stk11*), which is also known as liver-inducible kinase (Lkb1). The researchers showed that deletion of Lkb1/*Stk11* reduced differentiation and increased self-renewal in murine MPN cells. In human MPN-BP cells, LKB1/*STK11* loss was associated with increased reactive oxygen species and stabilization of hypoxia-inducible factor 1 alpha (HIF1α) protein, which has been linked to cancer. RNA sequencing of samples from 11 patients with progressive MPNs identified LKB1/*STK11* loss as a potential driver of blast-phase AML.

LKB1/*STK11* is a recognized tumor suppressor in solid malignancies. Dr. Crispino's team showed that in hematopoietic cells with enhanced JAK/

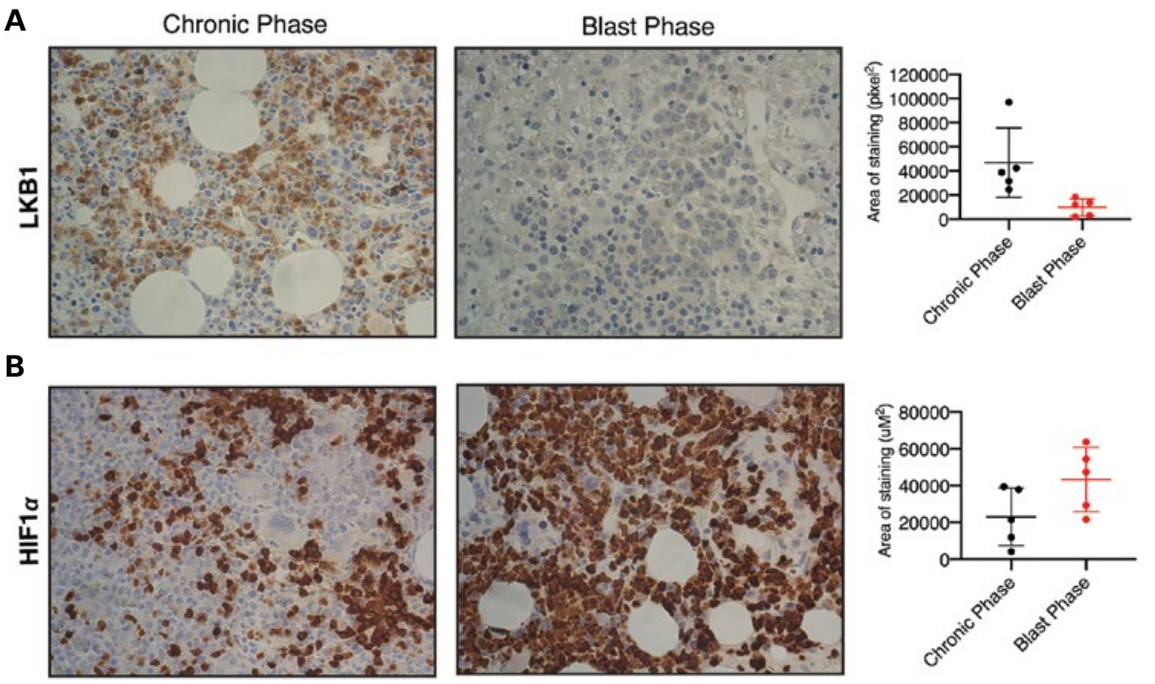


Figure. The loss of LKB1 (liver-inducible kinase) is a feature of myeloproliferative neoplasms (MPNs). Representative immunohistochemical analysis of LKB1, which suppresses disease progression (**A**), and HIF1α (inducible factor 1 alpha), which enhances the self-renewal of cells (**B**), in bone marrow sections from a patient with MPN. Bone marrow samples were obtained during the chronic (less severe) and blast (more aggressive) phases of the disease. All images are from the same patient. Changes in the areas of staining between the two MPN phases were quantified in five paired samples. Original magnification, 400×. *Reprinted from Cancer Discovery, © 2021, 11, 1398–410, Marinaccio C et al, LKB1/STK11 is a tumor suppressor in the progression of myeloproliferative neoplasms, with permission from AACR.*

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

STAT signaling, the loss of LKB1 stabilizes HIF1α, which in turn promotes self-renewal of MPN cells. The researchers also found that HIF inhibitors that are currently in development for renal cancer selectively inhibit colony formation by human MPN-BP cells. These findings suggest that HIF small-molecule inhibitors are also an effective treatment for MPN leukemias.

Integrated Genomic Analysis Reveals the Origin and Identity of Lineage-Ambiguous Acute Leukemias

After decades of research, 4% of acute leukemia cases are still difficult to classify. Lineage ambiguity makes diagnosis and treatment challenging; thus, these patients are at increased risk of poor outcomes. Such high-risk malignancies are termed mixed-phenotype acute leukemia (MPAL), acute leukemias of ambiguous lineage (ALAL), or early T-cell precursor acute lymphoblastic leukemia (ETP-ALL). To better understand the molecular and cellular basis of these rare leukemias, researchers assembled an international cohort of 2574 pediatric and adult cases of acute leukemia. Dr. Klco and Charles G. Mullighan, MBBS(Hons), MSc, MD (Pathology), led this research in partnership with Dr. Claudia Haferlach (Munich Leukemia Laboratory, Germany).

Using integrated genomic analysis and experimental modeling, the investigators identified a distinct subgroup of ALALs driven by deregulation of the *BCL11B* gene, which encodes a master transcription factor that plays a central role in T-cell differentiation but whose expression is normally repressed in uncommitted hematopoietic stem and progenitor cells.

This work, which was published in *Cancer Discovery*, revealed various structural DNA rearrangements that deregulated *BCL11B* expression. The rearrangements included multiple chromosomal regions that harbor enhancers active in hematopoietic stem cells. Drs. Mullighan and Klco and their colleagues also identified a new enhancer, BETA (*BCL11B* enhancer tandem amplification), that is generated by amplification of DNA downstream of *BCL11B*. The rearranged stem cell enhancers contact *BCL11B* in leukemic cells, and the resulting premature *BCL11B* expression fuels the transformation of hematopoietic progenitor cells into leukemic cells. Rather than a cell with a committed lineage, a hematopoietic stem or progenitor cell is the cell of origin of *BCL11B*-deregulated leukemia. Collectively, the project determined that about 30% of acute leukemia cases previously diagnosed as MPAL or ETP-ALL should be reclassified as a new ALL subtype termed *BCL11B*-deregulated ALAL.

CONCLUSION

St. Jude researchers are forging institutional and international partnerships to hasten progress toward understanding the biology of rare hematologic disorders that can give rise to aggressive myeloid disorders or acute leukemias. In the process, they are developing new tools and approaches to efficiently translate their discoveries to the clinic.

SCIENTIFIC HIGHLIGHTS

Deciphering Molecular Events that Control Early Translocation on the Ribosome

Translation is the process of converting the information in RNA into a specific string of amino acids. It is the basis of protein synthesis. Translation is an exquisitely orchestrated molecular process involving the interplay of messenger RNA (mRNA), aminoacyl transfer RNA (aa-tRNA), and the ribosome. Each molecule must move rapidly, with respect to each other, in a precisely defined series of events. As the ribosome moves along mRNA in discrete increments, aa-tRNAs are sequentially recruited and shifted (or translocated) in an efficient, accurate manner across three binding sites: A (aminoacyl), P (peptidyl), and E (exit). Despite advances in our knowledge of translocation, we know relatively little about the events that occur during this essential process.

In bacteria, the ribosome's translocation along mRNA is mediated by the highly conserved protein GTPase called elongation factor G (EF-G). Interactions between the ribosome and EF-G have been studied using various assays, including smFRET (single-molecule fluorescence energy transfer). Briefly, EF-G binding to the pre-translocation (PRE) ribosome complex brings about large-scale conformational changes among the large and small ribosomal subunits and tRNAs. This is accompanied by positional changes of deacyl and peptidyl tRNAs within the PRE ribosome to achieve highly transient states, including multiple structurally distinct hybrid states (PRE-H). These conformational changes involve the unlocking and relocking of tRNA and mRNA molecules at specific sites on the ribosome. The relation between these structural events and EF-G–catalyzed GTP hydrolysis has remained obscure, despite decades of research by multiple groups around the world.

A team led by Scott C. Blanchard, PhD (Structural Biology, Chemical Biology & Therapeutics), used smFRET methods to identify and enable the capture, via cryo-electron microscopy (cryo-EM), of specific ribosomal states during early translocation events, immediately before and after EF-G binding. Their results, which were published in *Nature*, showed that PRE-H conformations are spontaneously achieved without EF-G and thus require only thermal energy from the surrounding environment to form. EF-G then binds to PRE-H ribosomes in its active, GTP-bound conformation to initiate the movement of the peptidyl tRNA by unlocking it and mRNA from the small subunit. This never-before-seen ribosome complex was referred to as "intermediate state 1." Formation of this initial environment- and context-sensitive state triggers downstream translocation events that enable EF-G–catalyzed GTP hydrolysis. It also triggers further tRNA and mRNA movement, with respect to the ribosome, to reach intermediate state 2. The precision of the smFRET and cryo-EM methods enabled Dr. Blanchard's team to definitively show that tRNAs in intermediate state 2 are still incompletely translocated. This finding revealed that additional conformational processes, also independent of GTP hydrolysis, must take place within the EF-G–bound ribosome to complete translocation. As such, the authors concluded that a second set of events is needed to finish the process, ultimately regulating the rate of translocation. Follow-up investigations of these final rate-limiting events are underway in the Blanchard laboratory.

This work highlights how static high spatial-resolution microscopy can be paired with and complement high temporal-resolution dynamics spectroscopy to uncover the fundamental workings of molecular machines. These observations are also the first to show in molecular detail the multiple crucial processes that regulate the rate of protein synthesis, including those that occur within the PRE ribosome, before EF-G binding and after the energy of GTP hydrolysis has been expended. These translocation events are most likely sensitive to temperature, cellular context, and the physical composition of the ribosome, prompting exciting hypotheses about translation control in cellular contexts that Dr. Blanchard's group is actively pursuing. *Rundlet EJ et al, Nature 595:741–5, 2021*

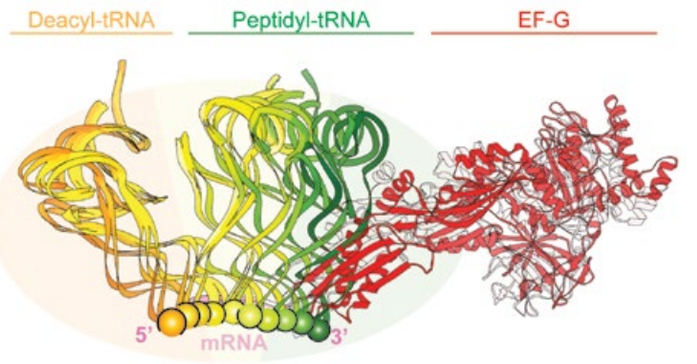
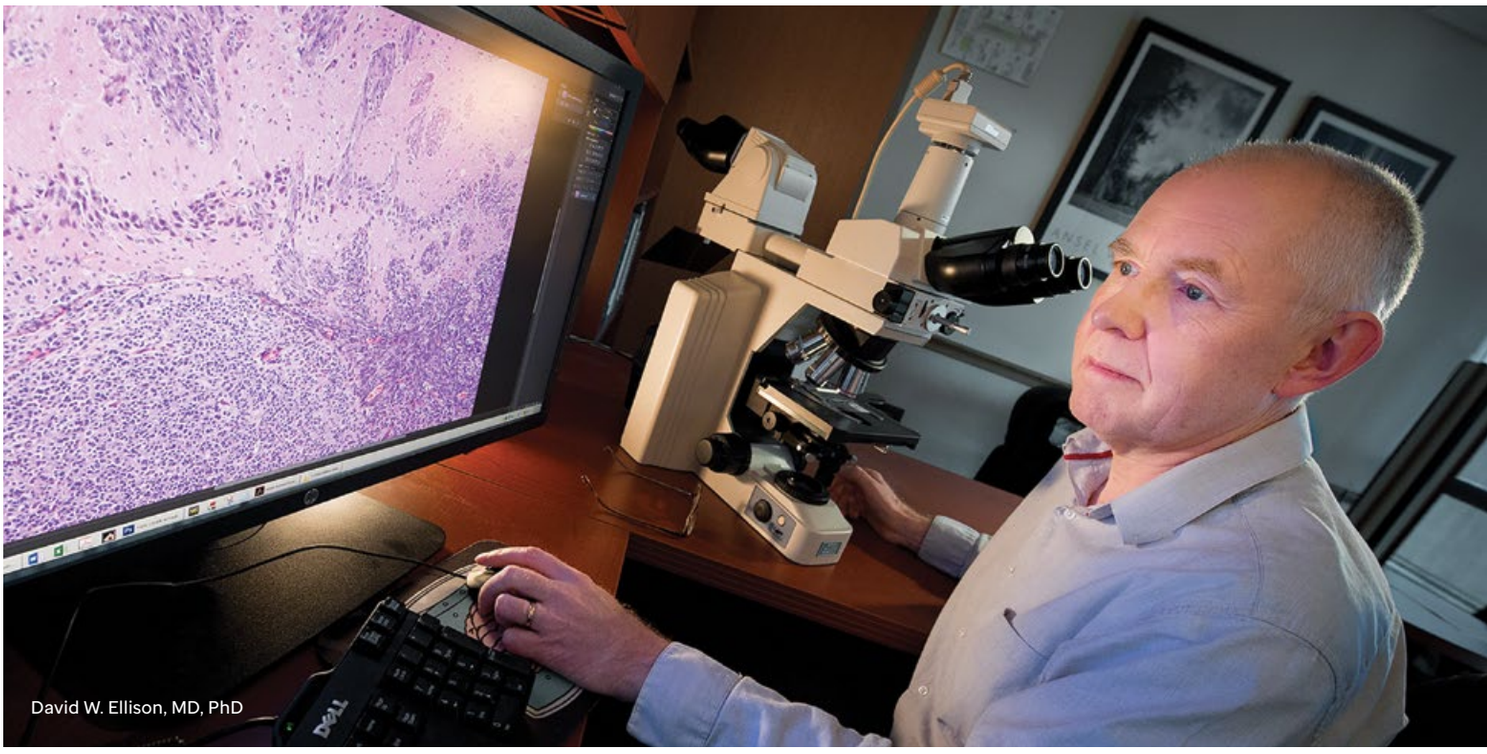


Figure. Elongation factor G–catalyzed movement of mRNA and tRNA through the ribosome during protein synthesis, as captured by cryo-electron microscopy. Abbreviations: EF-G, elongation factor G; mRNA, messenger ribonucleic acid, tRNA, transfer ribonucleic acid. *Reprinted from Rundlet EJ et al, Structural basis of early translocation events on the ribosome. Nature, 595:741–5, © 2021, http://creativecommons.org/licenses/cc by/*

WHO's New Classification of Central Nervous System Tumors

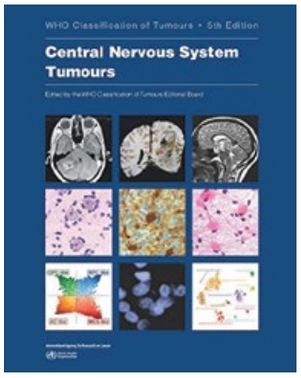


David W. Ellison, MD, PhD

The gold standard for the diagnosis of cancer types is the series of World Health Organization (WHO) tumor classifications. This 18-volume series of books is organized by anatomic site or organ system, such as the digestive system or central nervous system (CNS), and is used by clinicians and scientists across the world. New editions are launched every 5–7 years, and the WHO is currently publishing volumes in the fifth edition. A notable feature of the latest classifications is the substantial use of genetic or epigenetic characteristics to classify tumor types, supplementing traditional morphologic approaches.

A team of neuropathologists from St. Jude, comprising David W. Ellison, MD, PhD; Brent A. Orr, MD, PhD; and Jason Cheng-Hsuan Chiang, MD, PhD (all of Pathology), has contributed significantly to the *WHO Classification of Central Nervous System Tumours*, *Fifth Edition*, which focuses on the brain and spinal cord and was published as a book and an online resource in 2021. Dr. Ellison was one of four senior editors for the fourth edition of the WHO classification in 2016 and was on the enlarged editorial team for the fifth edition. He was also on the cIMPACT (Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy) committee that developed recommendations for the genetic classification of CNS tumors in preparation for the fifth edition. Dr. Ellison's role in cIMPACT included preparing articles on behalf of the committee, recommending new ways of classifying pediatric-type gliomas, including ependymomas, and co-organizing a meeting in Europe that brought together an international group of 25 neuropathologists to discuss the principles to be used in the new WHO classification. This meeting included Dr. Orr, who was one of five young neuropathologists to be co-opted into the group. Both Drs. Ellison and Orr wrote sections on tumor types for the fifth edition, and Dr. Ellison was the principal editor for many of the sections on pediatric tumors.

Research conducted by the laboratories of all three neuropathologists at St. Jude was central to providing novel data for the new classification. As part of the Pediatric Cancer Genome Project, Dr. Ellison's studies provided crucial information on genetic alterations in low-grade gliomas and ependymomas. This work has been used to distinguish several new molecularly defined tumor types. Dr. Orr's group discovered four new tumor types among those in the broad category of CNS primitive neuroectodermal tumors, all of which are included in the new classification, and Dr. Chiang's research helped to clarify the status of several new WHO tumor types among pediatric low-grade gliomas and glioneuronal tumors. *Brat D et al (eds), WHO Classification of Central Nervous System Tumours Edition 5, Volume 6. Lyon, France: IARC; 2021*



Early Inclusion of an Anti-GD2 Monoclonal Antibody in Combination with Chemotherapy Improves the Outcome of Pediatric Patients with High-Risk Neuroblastoma


Sara M. Federico, MD

High-risk neuroblastoma, a cancer of the sympathetic nervous system, is the most common solid tumor in children; it accounts for 15% of mortality among children with cancer. Children younger than 18 months with neuroblastoma and the amplified *MYCN* oncogene and those older than 18 months with metastatic neuroblastoma are classified as having high-risk disease. Treatment strategies for high-risk neuroblastoma include three stages: (1) Induction, which includes chemotherapy and surgery; (2) Consolidation, which includes stem cell rescue and radiation therapy; and (3) Post-consolidation, which involves immunotherapy using monoclonal antibodies (mAbs) primarily targeted to the disialoganglioside GD2, GM-CSF (granulocyte macrophage colony-stimulating factor), and isotretinoin. Despite this intense multimodal treatment approach, nearly 50% of pediatric patients with high-risk neuroblastoma experience relapse and succumb to the disease.

Preclinical neuroblastoma studies have shown that early inclusion of mAbs with chemotherapy can provide synergistic benefits with better outcomes. In the St. Jude NB2012 study (NCT01857934), Sara M. Federico, MD (Oncology), and her colleagues tested the benefits of administering hu14.18k322A, a humanized anti-GD2 mAb, concurrently with chemotherapy during induction in patients with newly diagnosed high-risk neuroblastoma in a Phase II single-institution setting. The authors had previously shown significant responses and clinical benefit in a small number of patients who had recurrent or refractory disease. In the NB2012 study, they extended their previous research to include 64 patients in their analysis of end-of-induction responses, estimates of event-free survival and overall survival, and the development of human-antihuman antibodies (HAHAs).

Dr. Federico and her colleagues showed that the regimen was well tolerated; approximately 67% of the patients showed significantly improved responses, which is almost twice that of a historical control group that received chemotherapy only. Patients who received the mAB also showed a median reduction of 75% in their primary tumor volume. This chemoimmunotherapy induction regimen also improved Curie scores (a prognostic marker of response to therapy) in 87% of the patients. Notably, no patient experienced disease progression during induction. Three-year event-free survival of 73.7% and overall survival of 86.0% were comparable to the survival seen in other neuroblastoma studies. Substantial HAHA responses developed in five of 64 (7.8%) patients; this incidence rate was substantially lower than that seen in Phase I trials. Furthermore, HAHA responses appeared weaker in the current study, and the HAHA did not reduce the peak levels of the mAb. These results suggest that a longer in vivo exposure to an anti-GD2 mAb, in conjunction with induction chemotherapy, significantly improves outcomes.

Improved early response, reductions in tumor volume, and increased survival with the addition of hu 14.18k322A to induction therapy suggests that this mAb improves the outcome of treating high-risk pediatric neuroblastoma.
Furman WL et al, J Clin Oncol 40:335-44, 2021

Sustained Function of CAR.GM18 T cells May Improve Treatment of Solid Tumors

Chimeric antigen receptor (CAR) T cells have been used successfully to treat a broad range of hematologic malignant neoplasms, including lymphoma, leukemia, and multiple myeloma. However, CAR T-cell therapy for solid tumors has been less effective, with the infused cells displaying only limited antitumor activity. CAR T cells require CAR-mediated, antigen-specific activation and costimulation, which result in the production of cytokines that promote the killing of tumor cells. However, chronic or repeated exposure to tumor antigens causes CAR T cells to become exhausted, limiting their ability to expand, persist, or continue producing cytokines.

Stephen M. Gottschalk, MD (Bone Marrow Transplantation & Cellular Therapy), and his colleagues, in parallel with other researchers, had previously shown that an inducible costimulatory molecule that activates MYD88, the central signaling hub for toll-like receptor, and the interleukin 1 (IL-1) and IL-18 receptors can sustain CAR T-cell effector function in the setting of chronic antigen exposure. Building on this finding, Dr. Gottschalk's group created a novel chimeric cytokine receptor that combines the extracellular components of the receptor for granulocyte–macrophage colony-stimulating factor (GM-CSF), a cytokine that is secreted upon CAR T-cell activation, with the transmembrane and signaling domains of the IL-18 receptor. The resulting chimeric receptor, designated GM18, binds GM-CSF and signals through the IL-18 receptor to activate MYD88, thereby creating an autocrine loop that links activation-dependent GM-CSF production by CAR T cells to the MYD88-signaling pathway. The group published the results of their evaluation of GM18 in the journal *Cancer Discovery*.

The researchers genetically modified CAR T cells targeting tumor antigens (e.g., EPHA2 tyrosine kinase) to also express GM18 (CAR.GM18 T cells). These cells recognized tumor cells in an antigen-dependent manner and exhibited sustained and improved effector function in sequential stimulation assays, which mimic chronic antigen exposure. In these assays, the CAR.GM18 T cells continued to expand and produce cytokines to kill tumor cells for at least six stimulations, whereas these abilities declined in their non–GM18-expressing counterparts after only two or three stimulations. In xenograft mouse models of Ewing sarcoma or osteosarcoma, CAR.GM18 T cells induced tumor regression at doses at which standard CAR T cells were ineffective, indicating that the CAR.GM18 T cells retain more function in the harsh tumor microenvironment.

This study showed that hijacking cytokines, such as GM-CSF, that are secreted by T cells in an antigen-dependent manner is a viable option for improving CAR T-cell therapy for solid tumors. *Lange S et al, Cancer Discov 11:1661–71, 2021*

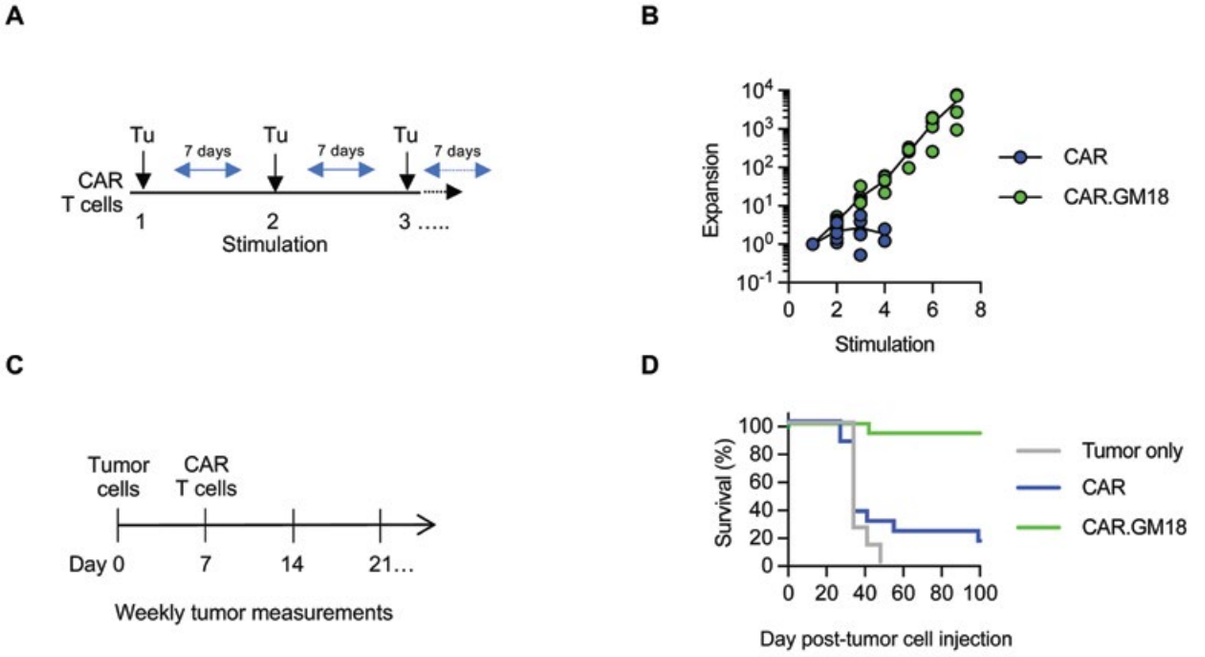


Figure. (**A**) Scheme of the repeat stimulation experiment in which CAR T or CAR.GM18 T cells were stimulated every 7 days with fresh Ewing sarcoma tumor cells (Tu). (**B**) The results show that only CAR.GM18 T cells are able to expand after multiple rounds of tumor cell stimulations. (**C**) Scheme of the animal experiment. Mice were injected with Ewing sarcoma tumor cells, and on Day 7 received CAR T or CAR.GM18 T cells. Thereafter, the tumor size was measured weekly. (**D**) Survival curves for mice treated as indicated. These results show that the chimeric GM18 receptor improves the antitumor activity of CAR T cells in preclinical models of pediatric sarcoma. *Adapted from Cancer Discov, © 2021, 11, 1661–71, Lange S et al, A chimeric GM-CSF/IL18 receptor to sustain CAR T-cell function, with permission from AACR.'*

The AIM2 PANoptosome Drives PANoptosis and Defense Against Pathogens

The innate immune system and inflammatory mechanisms play important roles in the pathogenesis of many diseases. Inflammasomes are multiprotein complexes that function as sentinels for innate immune defenses, sensing pathogens and inducing cell death in infected cells. There are several inflammasome sensors, each of which detects and responds to specific pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs). After exposure to PAMPs and DAMPs, inflammasome sensors form a multiprotein complex that activates the enzyme caspase-1, leading to cleavage of its substrates, inflammatory signaling, and a form of inflammatory cell death called pyroptosis.

The absent in melanoma 2 (AIM2) inflammasome detects double-stranded DNA and plays essential roles in development, infectious diseases, inflammatory diseases, and cancer. However, given that pathogens carry multiple PAMPs and induce the release of diverse DAMPs, a major question in the field has been how the specificity of a single sensor recognizing a single PAMP/DAMP is maintained during infection and whether multiple inflammasome sensors can integrate their responses to these varying triggers. To address this, a group led by Thirumala-Devi Kanneganti, PhD (Immunology), investigated the mechanism of AIM2-dependent inflammatory signaling during infection with herpes simplex virus type 1 (HSV1) and the bacterium *Francisella novicida*, both of which activate the AIM2 inflammasome. Their findings were published in the journal *Nature*.

To determine whether immune cells exposed to multiple PAMPs and DAMPs during infection with HSV1 or *F. novicida* could simultaneously engage multiple inflammasome sensors, the researchers infected bone marrow–derived macrophages (BMDMs) from wild-type mice and BMDMs that were singly deficient in several inflammasome sensors. Infecting BMDMs with HSV1 or *F. novicida* induced AIM2-dependent and NLRP3- and NLRC4-independent cleavage of caspase-1, the release of inflammasome-dependent cytokines (IL-1µand IL-18), and cell death. However, these effects were markedly reduced in mouse BMDMs lacking the *Mefv* gene that encodes pyrin, suggesting that infection activates pyrin to drive AIM2-mediated inflammatory signaling and cell death. As there was some residual AIM2-mediated caspase-1 cleavage in *Mefv*$^{-/-}$ cells, the researchers screened several other innate immune sensors to determine their involvement. HSV1 or *F. novicida* infection caused less caspase-1 cleavage and cell death in BMDMs lacking ZBP1, and these effects were further reduced when pyrin activation in *Zbp1*$^{-/-}$ cells was inhibited with colchicine or in *Mefv*$^{-/-}$ *Zbp1*$^{-/-}$ cells, which suggests that ZBP1 and pyrin cooperate to drive AIM2-dependent inflammatory signaling and cell death during infection with these pathogens.

The innate immune sensors AIM2, pyrin, and ZBP1 were subsequently found to drive the assembly of a large AIM2-mediated multiprotein complex that also contains the proteins ASC, caspase-1, caspase-8, RIPK3, RIPK1, and FADD. This complex of multiple inflammasome sensors and cell death regulators drives PANoptosis, a unique inflammatory cell death pathway identified by Dr. Kanneganti's group that cannot be accounted for by pyroptosis. Thus, Dr. Kanneganti's team termed this complex the "AIM2 PANoptosome."

Elucidating these interactions among AIM2, pyrin, and ZBP1 has defined a mechanism by which infection with pathogens releasing PAMPs and DAMPs can lead to inflammatory cell death. These findings also establish that inflammasomes can act as integral components of PANoptosomes in response to specific triggers. Together these mechanistic insights reveal potential therapeutic targets for diseases mediated by inflammasomes and PANoptosomes. *Lee SJ et al, Nature* 597:415–9, 2021

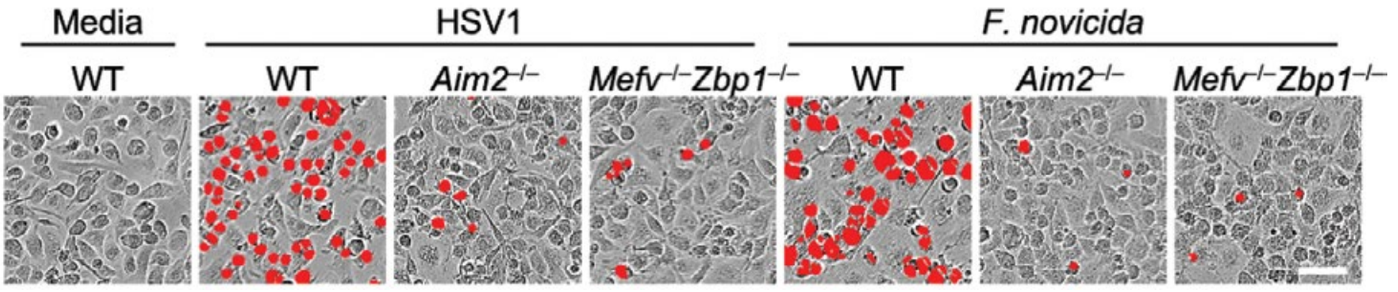


Figure. Cell death in wild-type (WT), *Aim2*$^{-/-}$, or *Mefv*$^{-/-}$ *Zbp1*$^{-/-}$ bone marrow–derived macrophages 16 h after infection with herpes simplex virus type 1 (HSV1) or the bacterium *F. novicida*, both of which activate the *AIM2* (absent in melanoma 2)-PANoptosome. *Aim2*$^{-/-}$ cells lack the gene that encodes AIM2, whereas *Mefv*$^{-/-}$ *Zbp1*$^{-/-}$ cells lack both the *Mefv* gene that encodes Pyrin and the *Zbp1* gene that encodes Z-DNA-binding protein 1 (ZBP1). Red indicates dead cells. As a consequence of infection with HSV1 or *F. novicida*, cell death is dramatically reduced in *Aim2*$^{-/-}$ cells and *Mefv*$^{-/-}$ *Zbp1*$^{-/-}$ cells, as compared to WT cells. These results indicate that *Aim2* alone is necessary for cell death to occur, while *Mefv* and *Zbp1* are functionally redundant during this AIM2-mediated cell death. Data represent at least three independent experiments. Scale bar, 50 µm. *Reprinted by permission from SNCSC GmbH: Springer Nature, Nature 597:415–9. AIM2 forms a complex with pyrin and ZBP1 to drive PANoptosis and host defense. Lee SJ, et al, © 2021*

Medulloblastoma Liquid Biopsies Can Detect Measurable Residual Disease, Monitor Treatment Response, and Predict Progression

Biomarkers are used to detect and characterize disease, monitor treatment response, and determine patients' health status during follow-up. For decades, clinicians have successfully assessed biomarkers to guide the clinical management of childhood leukemias, but such tools have been lacking for pediatric brain tumors.

Medulloblastoma, which is the most common malignant embryonal pediatric brain tumor, is a highly heterogeneous disease comprising multiple subgroups that have distinct characteristics and prognoses, ranging from favorable to very poor. Most (~70%) children with medulloblastoma respond to contemporary treatment regimens, but about 30% of patients experience disease progression and die. The typical monitoring scheme for patients with medulloblastoma includes magnetic resonance imaging and cytologic assessment of the cerebrospinal fluid (CSF) from lumbar punctures for the presence/absence of tumor cells. Paul A. Northcott, PhD (Developmental Neurobiology), Giles W. Robinson, MD (Oncology), and their colleagues evaluated copy number variations in cell-free DNA (cfDNA) fragments in the CSF of patients with medulloblastoma at St. Jude and its collaborating institutions as a potential surrogate biomarker of measurable residual disease (MRD).

The study involved a combination of low-coverage whole-genome sequencing and a computational framework optimized in the Northcott lab that was capable of detecting copy number variations to measure MRD in CSF specimens from 123 children who were at least 3 years old, had newly diagnosed medulloblastoma, and had been enrolled in the SJMB03 clinical trial (NCT00085202). CSF samples obtained at baseline, after radiotherapy, during chemotherapy, and at the end of therapy were analyzed and compared with the results of traditional imaging and cytology analyses performed at the same time points. As expected, less tumor-derived cfDNA was detected in the liquid biopsies after treatment started; however, in CSF samples obtained during and at the end of therapy, tumor-derived cfDNA was more often persistent or re-emergent in patients whose disease eventually progressed than it was in those whose disease did not return.

Drs. Northcott and Robinson and their colleagues reported that detection of MRD at baseline was not of prognostic value. However, at the end of therapy, MRD detection, based on the presence of tumor-derived copy number variations in CSF, was more sensitive than the current approach of imaging and cytologic analyses. MRD was also significantly associated with poorer progression-free survival at all study time points in patients with average-risk disease but only at the end of therapy in patients with high-risk disease. The authors concluded that MRD can be detected in children with medulloblastoma via serial assessments of cfDNA in CSF and that such detection holds promise as a tool for noninvasive characterization and longitudinal monitoring of medulloblastoma. Thus, they recommended that cfDNA measurements be evaluated in future prospective medulloblastoma trials as a step toward personalizing therapy based on MRD for pediatric patients with medulloblastoma and potentially for those with other types of brain tumors.

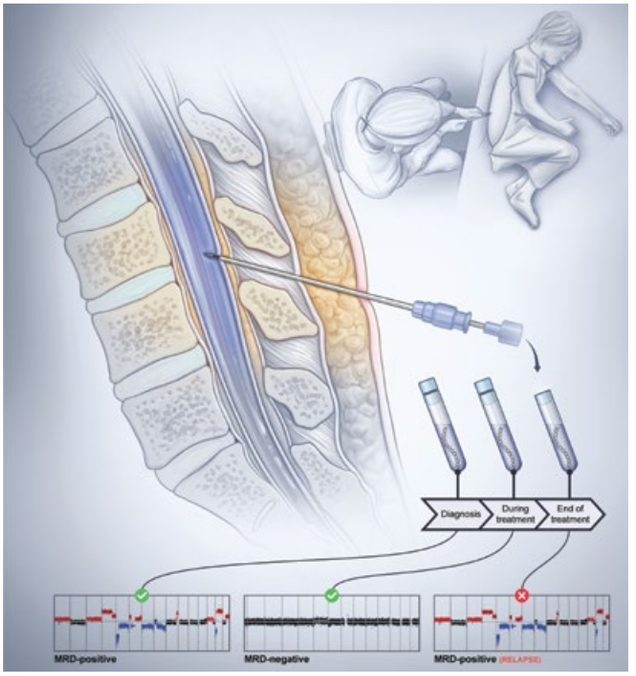


Figure. Scheme of the experimental workflow. Serial lumbar puncture procedures were done in each patient enrolled in the SJMB03 trial. The cerebral spinal fluid samples were banked, and tumor-derived cell-free DNA was extracted and quantified. The extracted DNA was then subjected to low-coverage whole-genome sequencing, and copy number variations were identified to determine the measurable residual disease (MRD) status of each patient at that point in the study. *Reprinted from Cancer Cell, 39, Liu APY et al, Serial assessment of measurable residual disease in medulloblastoma liquid biopsies, 1519–30, © 2021, with permission from Elsevier.*

This approach (i.e., assessing MRD during follow-up), which has been successful in pediatric leukemias, provides new hope for advancing treatment and improving the outcomes of children with treatment-resistant medulloblastoma. Serial assessments of cfDNA in CSF might be used to ensure that patients with high-risk disease receive adequately intense therapy and that those with low- or average-risk disease are spared unnecessarily intense treatments that can adversely affect their long-term quality of life.

This work was reported in *Cancer Cell*; the journal noted it among their "Top 10 Editors' Picks of 2021" and featured it in a Preview article that appeared in the same volume. The study was subsequently featured in a News & Views article published in *Nature Reviews Clinical Oncology* in February 2022. *Liu APY et al, Cancer Cell 39:1519–30, 2021*

Low-Risk Acute Lymphoblastic Leukemia May Not Warrant Long-Term Pulse Therapy with Vincristine and Dexamethasone

Ching-Hon Pui, MD

For the past 20 years, maintenance therapy for patients with acute lymphoblastic leukemia (ALL) has included pulses of vincristine and a steroid, such as dexamethasone or prednisone, throughout treatment. However, studies of the clinical benefit of such prolonged pulse therapy, which causes neuropsychological side effects and peripheral neuropathy in patients with intermediate-risk ALL, have yielded conflicting results, and randomized trials had not been conducted in patients with low- or high-risk ALL.
To determine whether pulse therapy with vincristine and dexamethasone is necessary for all risk groups of pediatric ALL, Ching-Hon Pui, MD (Oncology, Pathology, Global Pediatric Medicine), and his colleagues in the Chinese Children's Cancer Group conducted a randomized Phase III, open-label trial among patients enrolled in the CCCG-ALL 2015 (ChiCTR-IPR-14006706) study. Patients from each ALL risk group were enrolled at 20 medical centers in China, and the overall survival and event-free survival were compared among those patients in continuous remission for 1 year after initial treatment who did or did not receive the vincristine and dexamethasone treatment pulses during the latter half of maintenance. In a recent *Lancet Oncology* article, the researchers reported the findings from this study.

The study was designed to evaluate whether the seven vincristine and dexamethasone pulses typically administered during the second year of maintenance therapy can be safely eliminated for any risk group of pediatric patients with newly diagnosed ALL. Each participant's ALL risk group was determined based on minimal residual disease and specific biologic features of the leukemic cells. Event-free survival and overall survival were estimated using the Kaplan-Meier method. Data analysis included 5054 pediatric patients (aged 0–18 years) in whom ALL was newly diagnosed during 2015–2020 and who had a median follow-up of 3.7 years (range, 2.8–4.7 years).

Dr. Pui and his colleagues found that the vincristine and dexamethasone pulses after the first year of maintenance therapy could safely be omitted in patients with low-risk ALL without affecting relapse risk, event-free survival, or overall survival. However, noninferiority of administering fewer pulses was not firmly established in patients with intermediate- or high-risk ALL. Thus, further study is warranted to verify the safety and efficacy of this approach in patients with higher-risk disease. *Yang W et al, Lancet Oncol 22:1322–32, 2021*

Activation of Pantothenate Kinase Restores Mitochondrial Function in Mice with Propionic Acidemia

Propionic acidemia (PA) is a congenital metabolic disorder associated with substantial morbidity and mortality in newborns. PA is characterized by metabolic imbalances resulting from the mutation of the mitochondrial enzyme propionyl-coenzyme A (CoA) carboxylase, which causes a buildup of propionyl-CoA (C3-CoA) that is ultimately converted to propionyl-carnitine (C3-carnitine), the biomarker for PA. Newborns with PA have symptoms of vomiting, poor appetite, weak muscle tone, and lethargy, which may progress to cardiac and neurologic dysfunction. Metabolic imbalances in PA are poorly defined, and there are no approved therapies for the disease. Liver transplantation may improve quality of life, but this approach does not always prevent complications. In a recent article in *Science Translational Medicine*, a team of St. Jude scientists reported the therapeutic potential of a first-in-class allosteric activator of pantothenate kinase (PanK) discovered and developed at St. Jude in a preclinical model of PA.

Suzanne Jackowski, PhD (Infectious Diseases), Richard E. Lee, PhD (Chemical Biology & Therapeutics), Charles O. Rock, PhD (Infectious Diseases), and Stephen W. White, DPhil (Structural Biology), initially demonstrated that mouse models of PA have elevated C3-carnitine, the hallmark biomarker associated with the human disease. Their results confirmed that mutations in C3-CoA carboxylase directly result in the accumulation of C3-CoA in mouse liver at the expense of nonesterified CoA (CoASH), a key cofactor for mitochondrial energy generation and intermediary metabolism. The PanK enzyme catalyzes the rate-limiting step in CoASH biosynthesis, and the buildup of C3-CoA not only sequesters CoASH but also inhibits PanK, thereby exacerbating the depletion of CoASH. The researchers showed that the accumulation of a tricarboxylic acid (TCA) cycle intermediate, commonly detected in the urine of patients with PA, is a new biomarker for compromised mitochondrial function in mice with PA. The team also identified methylmalonyl–CoA hydrolysis as a novel pathway in the body's response to metabolic imbalances in PA, which it counteracts by liberating CoASH.

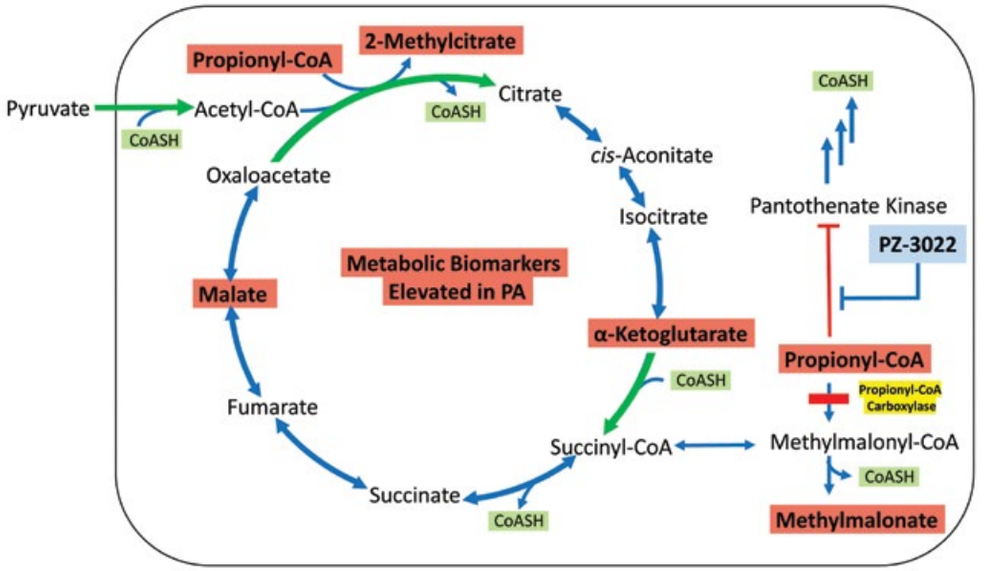


Figure. Schematic of the mitochondrial tricarboxylic acid (TCA) cycle. The irreversible, coenzyme A (CoA)-dependent steps in the TCA cycle (green arrows), nonesterified CoA (CoASH; light green boxes), and the metabolic biomarkers of TCA cycle dysfunction that accumulate in priopionic acidemia (PA) (red boxes) are highlighted. Low cellular CoASH in PA tissues arises from its sequestration as propionyl-CoA, which accumulates due to the block at propionyl-CoA carboxylase (yellow box). Propionyl-CoA is a potent inhibitor of pantothenate kinase and thus prevents the cells from correcting the problem by producing more CoA. PZ-3022 (blue box) relieves the inhibition of pantothenate kinase, which elevates CoASH and restores TCA cycle function. *From Subramaniam C et al, Pantothenate kinase activation relieves coenzyme A sequestration and improves mitochondrial function in mice with proprionic acidemia. Sci Transl Med, 13:eabf5965, © 2021. Reprinted with permission of AAAS.*

The team demonstrated that CoASH sequestration is alleviated by stimulating PanK with the allosteric activator PZ-3022. PZ-3022 belongs to a family of drug-like molecules called pantazines, which were developed as allosteric ligands that prevent feedback inhibition of PanK by C3-CoA. Pantazines elevate intracellular CoA concentrations. Treatment of the mouse model of PA with PZ-3022 normalized the depressed levels of CoASH and acetyl-CoA in the liver. PZ-3022 therapy reduces the concentration of circulating C3-carnitine, and the excretion of TCA cycle overflow metabolites in the urine indicates the restoration of mitochondrial function and the normalization of intermediary metabolism. Rapid rescue of CoASH levels after treatment with PZ-3022 also suggests the possibility of using pantazines to elevate CoA in other metabolic diseases, such as the inborn errors in fatty acid ß-oxidation, where mitochondrial function is compromised. Based on these exciting results, an optimized pantazine derived from PZ-3022 is currently in clinical trials for the treatment of PA (NCT04836494). *Subramaniam C et al, Sci Transl Med 13:eabf5965, 2021*

The High-Resolution Structure of Human LRRK2 Provides a Possible Template for Treating Parkinson Disease

The leucine-rich repeat kinase 2 (LRRK2) protein regulates key cellular processes involving membranous organelles. The protein molecule contains seven domains, sequentially designated ARM, ANK, LRR, ROC, COR, KIN, and WD40. LRRK2 normally exists as a monomer or dimer, but it can form microtubule-based filaments under pathogenic conditions. Mutations in the *LRRK2* gene are the most frequent cause of inherited Parkinson disease, accounting for at least 5% of cases. *LRRK2* mutations are also implicated in the pathogenesis of idiopathic Parkinson disease, whereas a different mutation in *LRRK2* confers susceptibility to Crohn disease. However, despite the clinical relevance of these mutations, the underlying structure–function relations have remained largely unknown because of a lack of high-resolution structures for the protein.

A team led by Ji Sun, PhD, (Structural Biology), used mass-spectrometry analysis, cryoelectron microscopy, and computer modeling to create detailed structures of full-length human LRRK2 in three physiologically important forms: the wild-type protein in its monomeric and dimeric states and the mutant LRRK2^{G2019S} form that is most commonly associated with Parkinson disease. The researchers published their results in the journal *Cell*.

Structures of the protein in its monomeric and dimeric states were captured at resolutions of 3.7 Å and 3.5 Å, respectively. This high resolution enabled the team to characterize the architecture of the protein in both states and to identify key interdomain interactions and scaffolding elements that are affected by disease-causing mutations. Notably, the ROC–COR interface, through which the protein forms functionally important homodimers, was a hotspot for mutations that cause Parkinson disease, and the mutation that confers a risk for Crohn disease was localized to a site on the KIN domain.

The KIN domain of LRRK2 displayed key features of an inactive kinase; this conformation was also found in LRRK2^{G2019S}, which has increased kinase activity. This structural similarity of wild-type LRRK2 and LRRK2^{G2019S} suggests that the mutation in the latter affects the kinase kinetics rather than the conformation, making inhibitors targeting this mutation of pharmacologic interest. The researchers also determined that the ROC–COR dimer interface was vital for pathogenic LRRK2 filamentation. They abolished this filamentation in HEK293 cells by introducing single-point mutations at the dimer interface. Overall, this study has yielded mechanistic insights into the physiologic and pathologic roles of LRRK2, and it has established a framework for designing conformation-specific inhibitors to treat Parkinson disease. *Myasnikov A et al, Cell 184:3519–27, 2021*

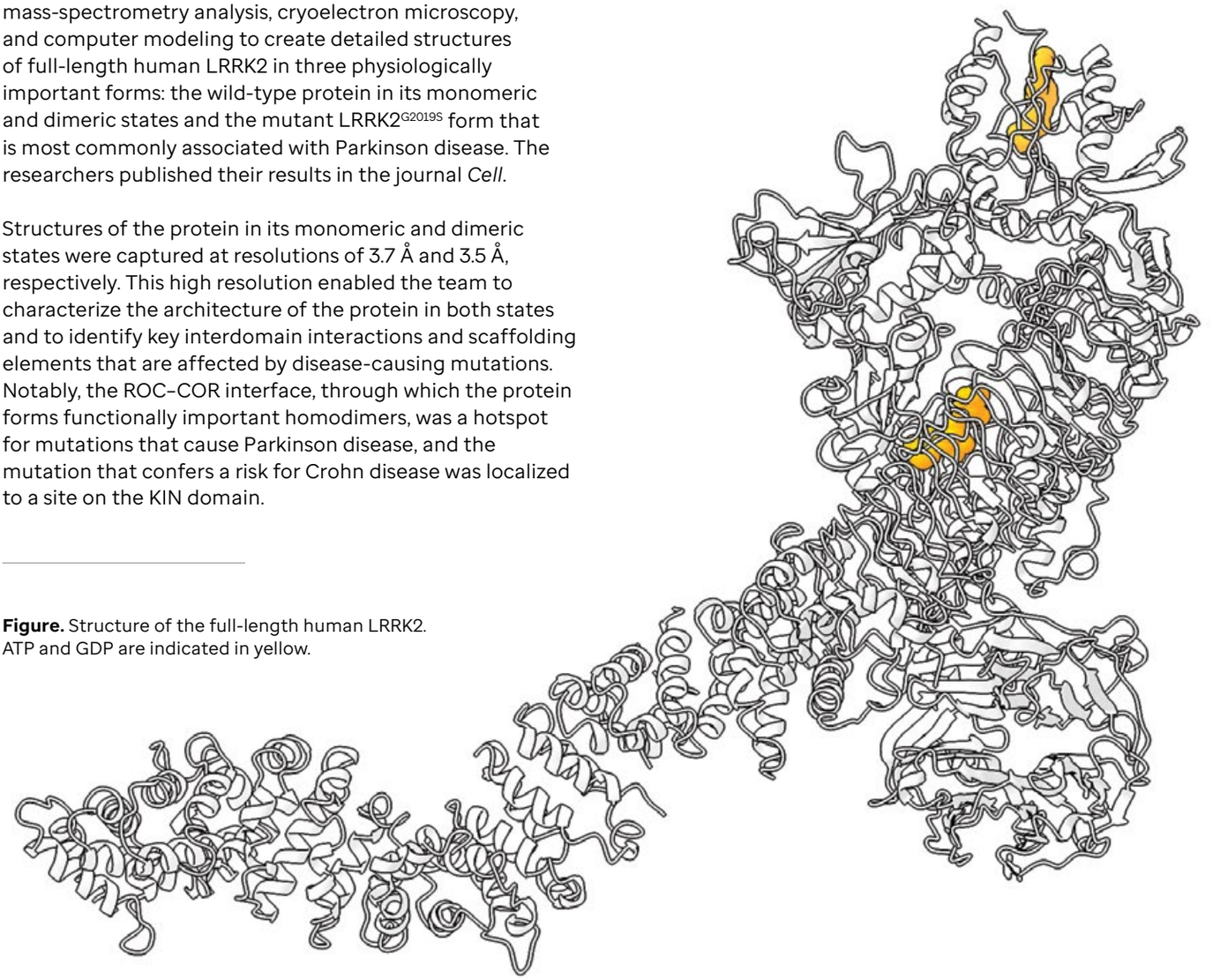


Figure. Structure of the full-length human LRRK2. ATP and GDP are indicated in yellow.

St. Jude Cloud Is the Largest Data-Sharing Ecosystem for Pediatric Cancer Genomic Data


Jinghui Zhang, PhD

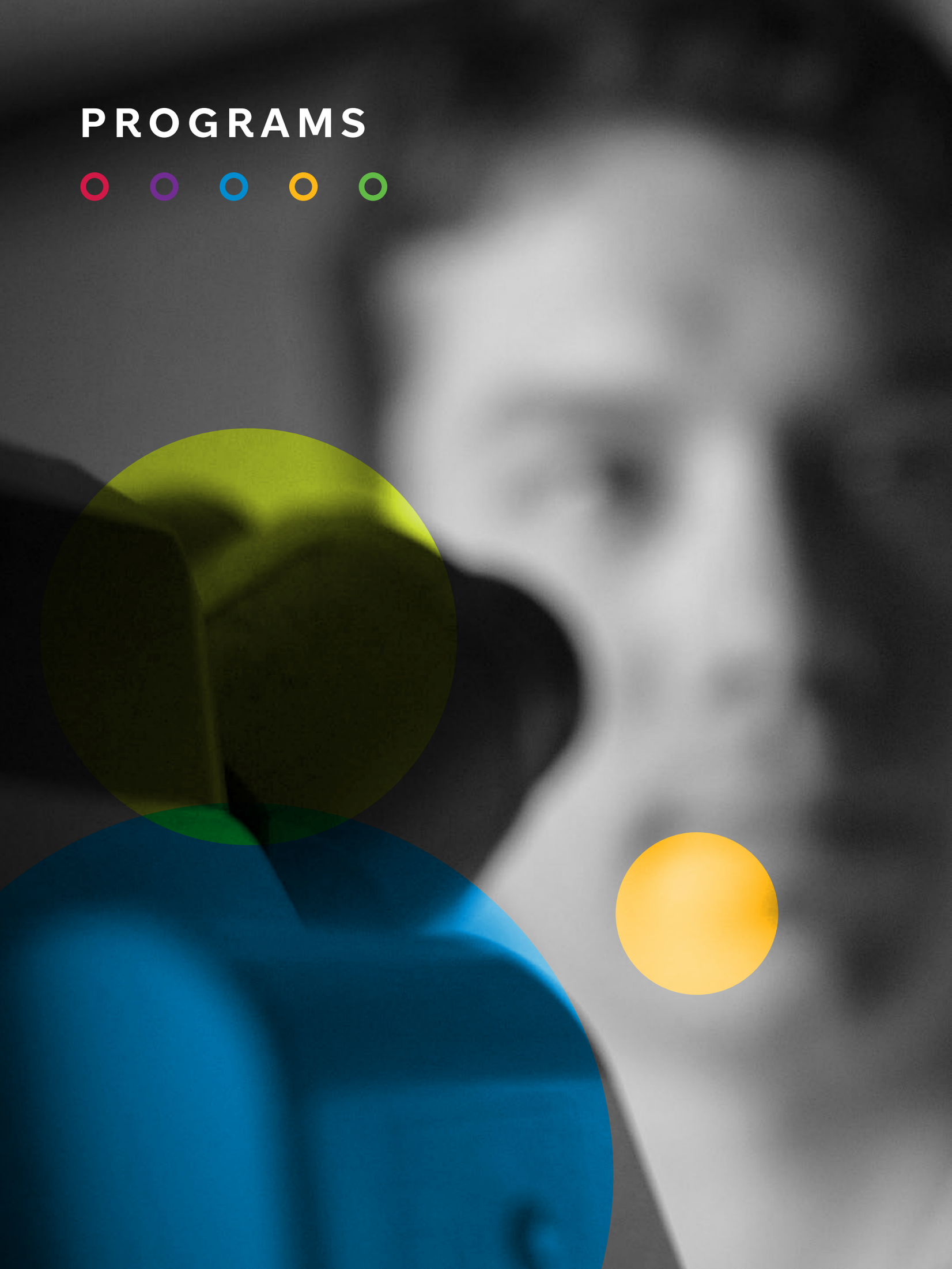
Pediatric cancer is the leading cause of death in children; more than 15,000 new cases are diagnosed each year in the United States. A key challenge to treating pediatric cancers is that many pediatric cancer subtypes are so rare that patient data from a single institute, a single research initiative, or, in some instances, even a single nation lack sufficient power for genomic discovery and clinical correlative analysis. Therefore, effective data sharing is essential to accelerating research to improve diagnostic precision, treatment efficacy, and long-term survival in pediatric cancer and other childhood catastrophic diseases.

Traditionally, individual researchers are required to build their own local data repositories by downloading large amounts of data from public repositories. Within this model, only institutions with large budgets and extensive infrastructure can afford to store large data cohorts. To democratize the accessibility of pediatric cancer genomic data, Jinghui Zhang, PhD (Computational Biology), conceptualized the St. Jude Cloud—a data-sharing platform that would enable researchers to run analyses on the shared cloud-based platform without needing to build up their own infrastructure. With help from Microsoft and DNAnexus, Dr. Zhang and her team developed St. Jude Cloud as an ecosystem, enabling access to raw data, the pediatric cancer knowledge base, and dynamic visualization, as reported in *Cancer Discovery*.

St. Jude Cloud hosts the genomic data of more than 10,000 pediatric patients with cancer and more than 800 pediatric patients with sickle cell disease. This freely available database provides access to more than 1.5 petabytes of genomic data, including 13,775 whole genomes, 9835 whole exomes, and 4425 transcriptomes, making it the largest publicly available genomic database for pediatric cancer. St. Jude Cloud is an ever-expanding resource to which data from clinical genomic programs at St. Jude are regularly added. To support researchers without formal computational training, end-to-end genomic workflows enable sophisticated genomic analyses in a point-and-click interface. Dr. Zhang and her team demonstrated the power of this approach by showing (1) cancer-subtype classification maps created from the transcriptome data, which have become an important reference for cancer diagnosis in recent years, and (2) the mutational burden and signatures across 35 major subtypes of pediatric cancers, which provide critical insight on cancer etiology, drug-resistance mechanisms, and patient eligibility for immunotherapy.

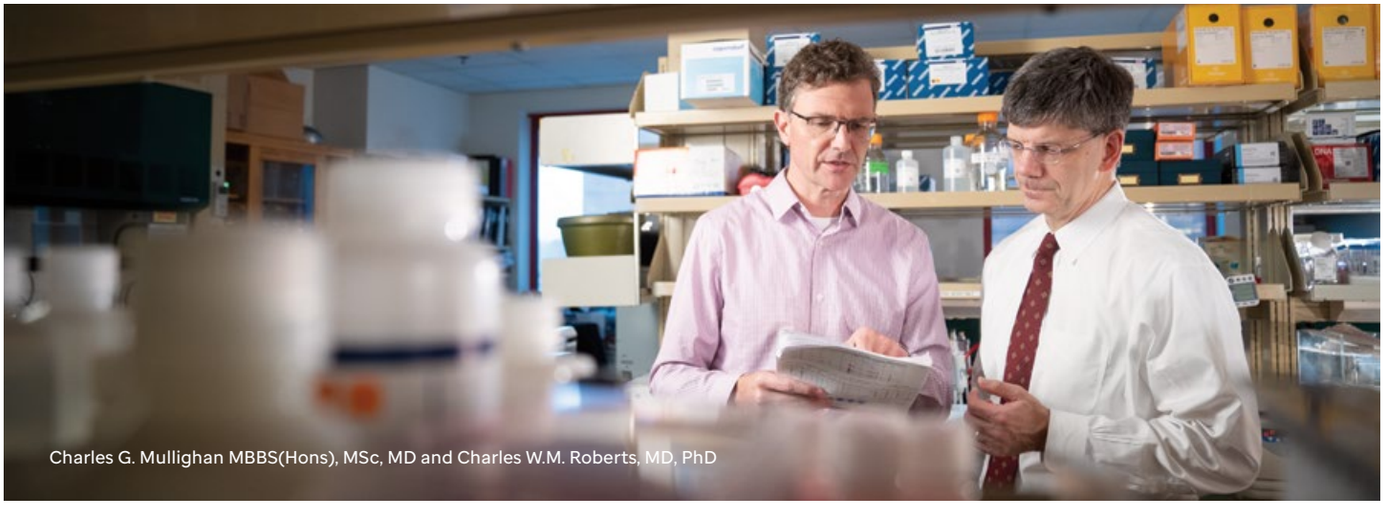
Since its debut in 2020, St. Jude Cloud has become a crucial global resource with which to accelerate research that can advance cures in pediatric cancer. Currently, 2952 users are registered on the St. Jude Cloud, with thousands of unique visitors leveraging the ecosystem monthly. As of May 20, 2022, 390 requests for access to raw genomic data have been made by 195 researchers at 125 institutes across 25 countries. Furthermore, the dimensionality of data sharing is increasing, as the St. Jude Cloud recently expanded to data generated from model systems and clinical imaging. *McLeod C et al, Cancer Discov 11:1082–99, 2021*

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.



Charles G. Mullighan MBBS(Hons), MSc, MD and Charles W.M. Roberts, MD, PhD

CANCER BIOLOGY PROGRAM

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

The diverse nature of pediatric cancers, coupled with the complex molecular, genetic, and developmental contexts in which they form, necessitates a broad spectrum of basic research to build a strong foundation for translational studies. The goal of this program is 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.

CANCER CONTROL & SURVIVORSHIP PROGRAM

Co-leaders: Gregory T. Armstrong, MD, MSCE; Melissa M. Hudson, MD

As treatments of 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 the conduct of 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 conducting research on a wide range of health-related and quality-of-life outcomes.

DEVELOPMENTAL BIOLOGY & SOLID TUMOR PROGRAM

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

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

HEMATOLOGICAL MALIGNANCIES PROGRAM

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

The overall goal of this program is 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 approaches 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.

NEUROBIOLOGY & BRAIN TUMOR PROGRAM

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

Brain tumors are the leading cause of cancer-related death in children. The goal of the Neurobiology & Brain Tumor Program is to improve survival and reduce morbidity for children with brain tumors by developing effective, relatively nontoxic therapies through a better understanding of pathogenesis. By integrating the latest genomic and genetic technologies into studies of the developing nervous system, members of this program are efficiently translating laboratory findings into opportunities for new treatments. Key advances include the identification of the cells of origin of important pediatric brain tumors and the modeling of 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.

Shared Resources

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

St. Jude Affiliate Program

Carolyn L. Russo, MD

The mission of the Affiliate Program at St. Jude is two-fold: first, to allow children to receive St. Jude pediatric oncology and hematology care close to home, and second, to encourage enrollment in St. Jude clinical research trials. The eight affiliate clinics are located throughout the Southeast and Midwest regions of the United States. Together, these clinics contribute 35%-40% of the patients enrolled in St. Jude–led clinical trials. The affiliate clinics serve rural and suburban communities with diverse racial and ethnic demographics.

The Affiliate Program teams have completed several quality-improvement projects aimed at ensuring high-quality care and improving the patient experience. One recent initiative was led by Lauren Raney, MD, from the Baton Rouge affiliate and JoAnne McManaman, MD, from the Charlotte affiliate. They conducted a multisite project to address the issue of documentation in the electronic medical record, which had been identified as a factor in provider burnout. Using quality-improvement methods, they analyzed the potential causes in three affiliate clinics and developed mitigation strategies. Drs. Raney and McManaman improved the outcomes in the three clinics and co-authored a report on their work in the *Journal of Oncology Practice*.

ADMINISTRATION

Medical Director • Carolyn L. Russo, MD
Nursing Director – Jennifer Morgan, MSN

ST. JUDE AFFILIATE SITES

Baton 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
Lauren Raney, MD
Sakshi Bami, MD
Katherine Helo, NP
Jessica Templet, PA-C
Joseph Kent, PA

Charlotte, NC

Novant Health Hemby Children's Hospital
Medical Director • Christine Bolen, MD
Jessica Bell, MD
Jenny McDaniel, MD
Joanne McManaman, MD
Felipe Bautista, MD
Courtney Saine, NP
Jennifer Weisner, NP
Andria Kokoszka, NP
Courtney Carr, NP

Huntsville, AL

Huntsville Hospital for Women & Children – Huntsville Hospital
Medical Director • Marla Daves, MD
Sana Mohiuddin, MD
Heidi Simpson, NP

Johnson City, TN

Niswonger Children's Hospital – Ballard Health
East Tennessee State University
Medical Director • Marcela Popescu, MD
Myesa Emberesh, MD
Angela Willocks, RN, MSN, CFNP
Lauren Wyatt, 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
Prerna Kumar, MD
Jaime Libes, MD
Mary Beth Ross, MD, PhD
Kay Saving, MD
Beth Speckhart, NP
Sue Gaitros, NP
Diana Simmons, NP

Shreveport, LA

Ochsner LSU Health – Shreveport
Medical Director • Majed Jeroudi, MD
Elizabeth Wadhwa, MD
Diana Townsend, NP

Springfield, MO

Mercy Children's Hospital – Springfield – Mercy Health System
Medical Director • Francisca Fasipe, 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
Samantha Zeller, NP
Alison Taylor, NP

St. Jude Global

Carlos Rodriguez-Galindo, MD

In 2021, St. Jude Global was proud to announce publicly the Global Platform for Access to Childhood Cancer Medicines. With the World Health Organization (WHO), St. Jude will create a first-of-its-kind solution to provide an uninterrupted supply of quality-assured medicines to treat children with cancer in low- and middle-income countries. This collaborative platform was developed with the support of the International Society of Paediatric Oncology (SIOP) and Childhood Cancer International. Our goal is to reach 25% of all children with cancer and nearly 70% of those in low- and lower-middle income countries by 2027.

RESEARCH

The Global COVID-19 Observatory and Resource Center for Childhood Cancer expanded as the pandemic evolved. In January, St. Jude and the SIOP hosted a COVID Conversation with data and initial findings from the COVIMPACT study and the Global Registry of COVID-19 in Pediatric Cancer. More than 1800 COVID-19+ cases from 51 countries have been entered into the Registry. The COVIMPACT study, which was published in *Lancet Child and Adolescent Health*, showed a significant decrease in the number of newly diagnosed pediatric cancer cases and an increase in abandonment and disruption of cancer-directed care during the pandemic.

EDUCATION

Several important milestones were reached in St. Jude Global's educational initiatives last year. In May, the St. Jude Global Academy partnered with the retinoblastoma program to launch a new certificate-based seminar: 38 centers from 21 countries enrolled 242 participants. In July, St. Jude Global and Unidad Nacional de Oncologia Pediatrica (UNOP) in Guatemala received confirmation that the ACGME-I (Accreditation Council for Graduate Medical Education International) would accredit UNOP as a sponsoring institution for fellowship training. Fellowship opportunities continued to expand as Shanghai Children's Medical Center launched a new fellowship program with St. Jude Global in September.

In November, a commencement ceremony was held to celebrate the successful completion of the Masters of Science in Global Child Health (MSc-GCH) degree by the first cohort of global scholars. Those graduates will now begin work on their approved capstone projects. The MSc-GCH Program continues to grow substantially: 69 individuals from 37 representing countries in all seven St. Jude Global regions applied to the program in 2021.

PROGRAM BUILDING

Through the end of 2021, 121 institutions participated in the abbreviated PrOFILE (Pediatric Oncology Facility Integrated Local Evaluation) assessment, and 17 participated in the full version. As the pandemic continued, virtual and hybrid workshops for PrOFILE were launched, with the first events held in Ethiopia, Chile, and Cameroon. As the tool has gained momentum, new components have been added, including critical care (PROACTIVE), pediatric hematology-oncology fellowship (EPAT), and neuro-oncology. Components for surgery, rehabilitation services, and palliative care are in progress.

The SJCARES Registry continues to grow, as 102 institutions have now signed the data-transfer rider, are working through the training process, and are beginning to enter data. More than 2000 cases have been entered into the Registry.

Throughout the year, the St. Jude Global Alliance accelerated. By the end of December, 177 medical institutions in 61 countries had applied for membership, and 127 had finalized membership agreements. The 2021 St. Jude Global Alliance Convening included more than 1000 registrants from 90 countries. Participants collaborated in 38 sessions, which were available in six languages, on the theme "Empower Everyone." Although less than a year since its launch, the online community has increased to more than 2000 registered users and more than 200 collaborative groups.

WHO ACTIVITIES

Finally, the St. Jude – WHO Global Initiative for Childhood Cancer concluded Phase I. On April 28, 2021, the WHO Director-General, Dr. Tedros Adhanom Ghebreyesus, and Dr. James Downing met virtually to reiterate their mutual commitment to support the Global Initiative for Childhood Cancer and to express their shared excitement about expanding the scope of work with St. Jude as the WHO Collaborating Centre for Childhood Cancer, aligning with St. Jude's ambitious 6-year Strategic Plan (FY2022–2027).

Graduate School of Biomedical Sciences

Mackenzie Bloom, PhD

The St. Jude Children's Research Hospital Graduate School of Biomedical Sciences includes three degree-granting programs. The first is a Doctorate of Philosophy in Biomedical Sciences (PhD-BMS) that trains young scientists to advance our understanding of the molecular basis of disease and therapy. The second is a Master's of Science in Global Child Health (MSc-GCH) that is developing a global community of agents of change and leaders dedicated to improving children's health worldwide. The third is a Master's of Science in Clinical Investigations (MSc-CI) that trains clinicians and medical professionals on how to perform clinical research and conduct clinical trials. Approximately 185 faculty members and staff at St. Jude are now formal members of the Graduate School faculty—teaching, mentoring, serving on committees, and helping to plan the school's future. To date, 65 PhD-BMS students, 30 MSc-GCH students, and four MSc-CI students have matriculated.

The COVID-19 pandemic continued to substantially affect Graduate School operations during 2021, and lectures and mentoring were largely conducted via distance learning. However, as a result of the experience gained in 2020, all academic activities were completed on schedule, student research proceeded with minimal disruption, and outstanding students were successfully recruited into all three programs. The PhD-BMS students brought productivity, creativity, and energy to the research environment; 58% of those who applied for F-31 fellowships sponsored by the National Institutes of Health were selected for funding, thereby demonstrating the excellence of our students.

The MSc-GCH students were particularly affected by the pandemic. Nevertheless, they performed superbly while working on the frontlines of health care in their home countries and demonstrated exemplary resilience and indomitable commitment. Although the MSc-GCH students were unable to visit the St. Jude campus for their matriculation, orientation, and summer intersession, they have continued to engage productively in online sessions and training. Ten MSc-GCH students of the inaugural cohort completed their studies in 2021 and graduated from the program.

During 2021, the Graduate School re-evaluated its structure as the student body expanded and the new MSc-CI program started. An Associate Dean and an Assistant Dean were appointed to each program, and Stacey L. Schultz-Cherry, PhD, was named Associate Dean for Student Affairs. Dr. Schultz-Cherry will manage all student issues and act as an intermediary between the Graduate School Administration and the student body. Having awarded its first doctorate and master's degrees, the Graduate School is now eligible to apply for accreditation through the Southern Association of Colleges and Schools Commission on Colleges (SACSCOC). Accreditation is an important process that confirms that 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 provided by this group of dedicated volunteers.

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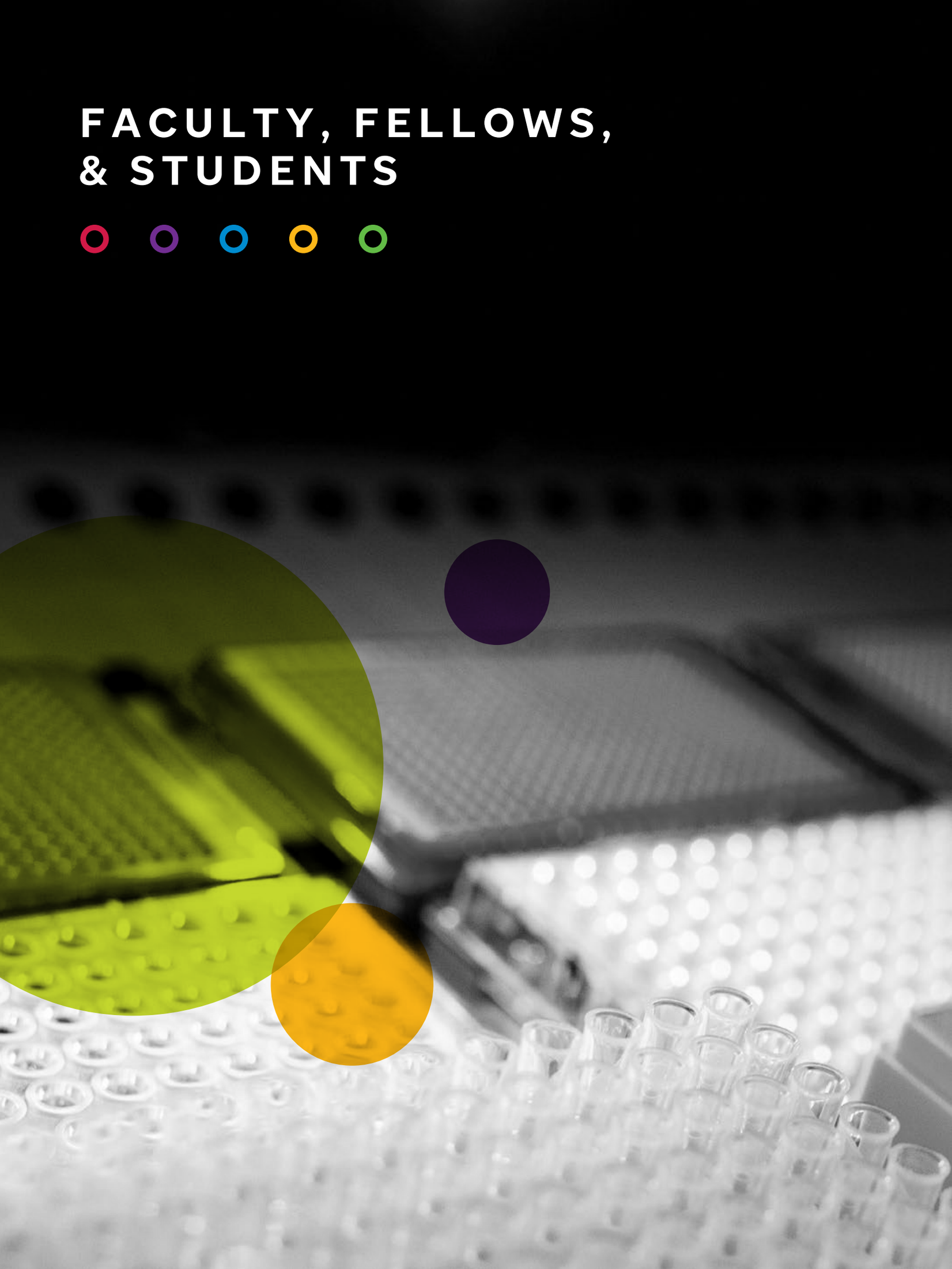
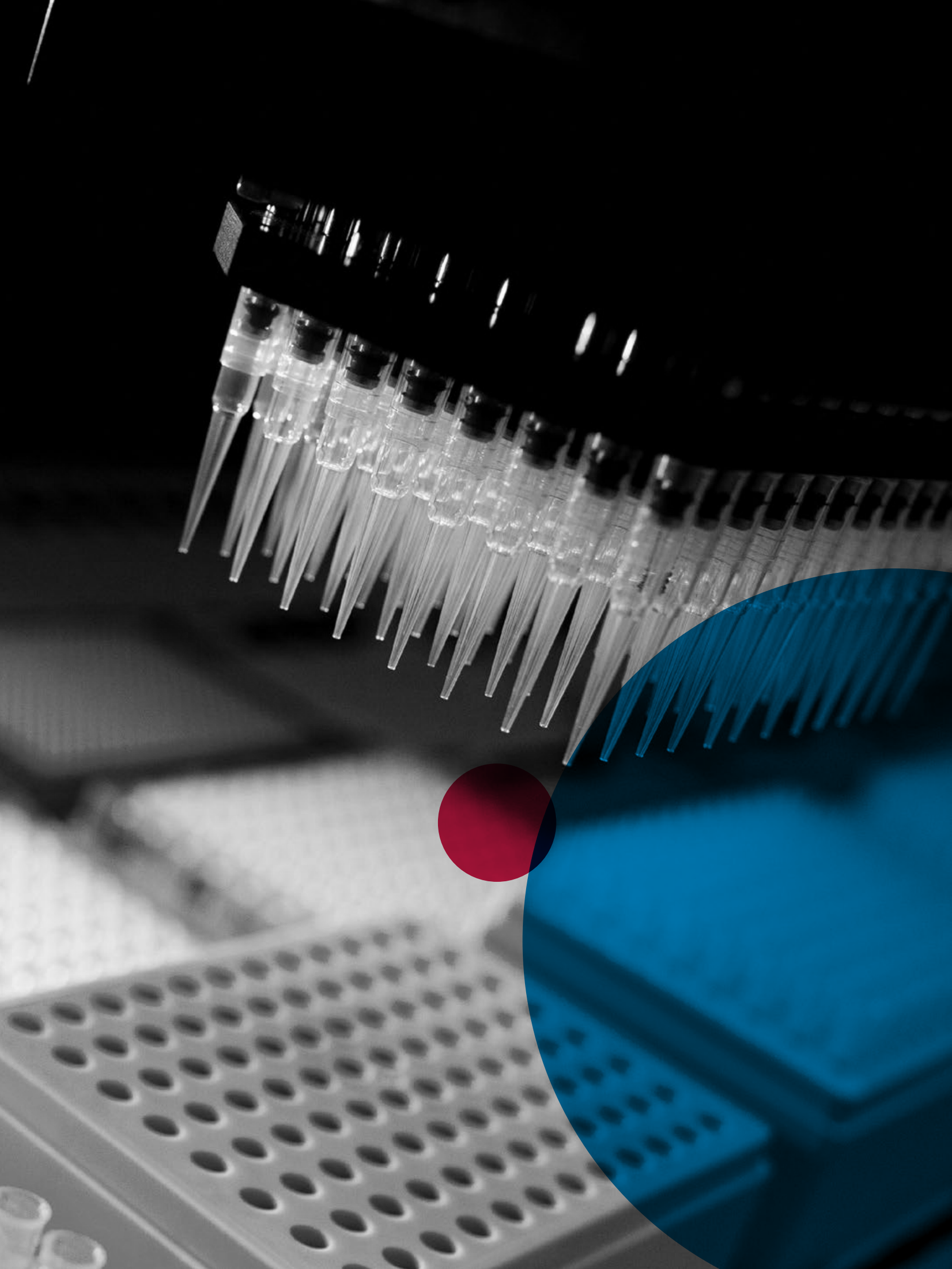
St. Jude Children's Research Hospital Graduate School of Biomedical Sciences

FACULTY, FELLOWS, & STUDENTS





BIOSTATISTICS

CHAIR
Motomi Mori, PhD, MBA; Endowed Chair in Biostatistics • Design and analysis of early phase clinical trials, biomarker discovery and validation, risk prediction models

MEMBERS
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Meenakshi Devidas, PhD, MBA[1,2] • Biostatistics, pediatric hematology and oncology
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Stanley B. Pounds, PhD[1] • Statistical cancer multi-omics; statistical pharmacogenomics
Deo Kumar S. Srivastava, PhD • Clinical trials, robust methods, survival analysis

ASSOCIATE MEMBERS
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Yimei Li, PhD • Statistical analysis of complex imaging data, survival data analysis & clinical trial design
Li Tang, PhD[1] • Prediction, validation, diagnostic testing, microbiome analysis

ASSISTANT MEMBERS
Cai Li, PhD • Statistical learning and computing methods for neurodegeneration
Qian Li, PhD • High-dimensional multi-omics, longitudinal modeling, statistical learning
Zhaohua Lu, PhD[3]
Haitao Pan, PhD • Bayesian dose-finding clinical trials design, adaptive design for single-arm and randomized clinical trials, pediatric extrapolation
Sedigheh Mirzaei Salehabadi, PhD[1] • Statistical methods for incomplete survival data, cancer survivorship
Yiwang Zhou, PhD • Statistical methods for precision medicine studies

BONE MARROW TRANSPLANTATION & CELLULAR THERAPY

CHAIR
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Ashok Srinivasan, MD • Hematopoietic cell transplantation and infections in the immune-compromised host
Brandon M. Triplett, MD[1] • Hematopoietic cell transplantation

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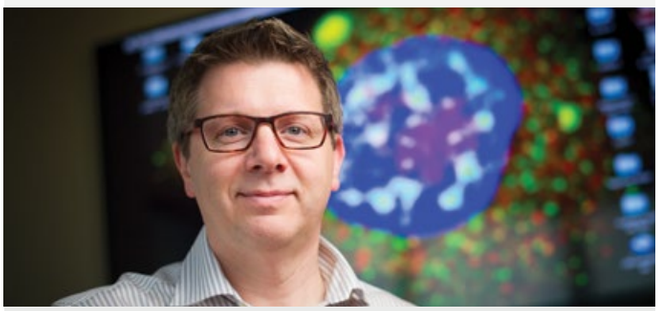
Caitlin E. Hurley, MD[2] • Onco-critical care, hematopoietic cell transplantation, long-term care
Giedre Krenciute, PhD[1] • Cellular therapy for brain tumors
Swati Naik, MBBS • Cellular therapy for hematologic malignancies, hematopoietic cell transplantation
Amr Qudeimat, MD • Hematopoietic cell transplantation
Akshay Sharma, MBBS • Gene therapy and transplantation for nonmalignant hematologic diseases
Aimee C. Talleur, MD[1] • Cellular therapy for hematologic malignancies
Paulina Velasquez, MD[1] • Cellular therapy for hematologic malignancies

INSTRUCTORS
Rebecca Epperly, MD • Cellular therapy for pediatric malignancies
Ali Y. Suliman, MD, MSc • Hematopoietic cell transplantation
Caitlin C. Zebley, MD, PhD • Cellular therapy and T-cell differentiation



CELL & MOLECULAR BIOLOGY

CHAIR
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MEMBERS
Mondira Kundu, MD, PhD[1] • Autophagy-related proteins in health & human disease
Peter J. McKinnon, PhD[1]; Endowed Chair in Pediatric Neurological Diseases • DNA damage responses in the nervous system
Heather C. Mefford, MD, PhD • Genetics of pediatric neurological disease

ASSOCIATE MEMBERS
Stacey K. Ogden, PhD[1] • Mechanisms of Hedgehog signal transduction
Joseph T. Opferman, PhD[1] • Regulation of cell death & mitochondrial function
Shondra M. Pruett-Miller, PhD • Genome-editing technologies

ASSISTANT MEMBERS
Chi-Lun Chang, PhD • Dynamic regulation of inter-organelle communication
Hans-Martin Herz, PhD[1] • Regulation of transcription & enhancer activity
Andrew T. Kodani, PhD[1] • Human genetics underlying neurodevelopmental disorders

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CHEMICAL BIOLOGY & THERAPEUTICS

CHAIR

Aseem Z. Ansari, PhD[1]; R. J. Ulrich Endowed Chair in Chemical Biology & Therapeutics • Synthetic gene regulators for personalized medicine, artificial transcription factors to control stem cell fate choices

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

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

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Philip M. Potter, PhD • Anticancer drug hydrolysis by carboxylesterases

Anang A. Shelat, PhD[1] • Translational research & chemical biology

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

Tudor Moldoveanu, PhD[1,2] • Programmed cell death in health & disease

COMPUTATIONAL BIOLOGY

CHAIR

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Zhaoming Wang, PhD[1,2] • Genetic epidemiology of pediatric cancer & survivorship

Jiyang Yu, PhD[1] • Systems biology, systems immunology, & translational oncology

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Xiang Chen, PhD[1] • OMICS integration & tumor heterogeneity by machine learning approaches

Yong Cheng, PhD[1,2] • Cis-regulatory modules in hematopoiesis & its disorders

Paul Geeleher, PhD[1] • Computational methods and drug repositioning

Xiaotu Ma, PhD • Mathematical modeling of cancer-initiating events

Xin Zhou, PhD • Data visualization and real-time analysis

ADJUNCT MEMBER

D. Neil Hayes, MD, MS, MPH • Translational biomarkers, genomics, & clinical trials

DEVELOPMENTAL NEUROBIOLOGY

CHAIR

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

MEMBERS

Suzanne J. Baker, PhD[1]; Endowed Chair in Brain Tumor Research • Genetic and epigenetic drivers of pediatric high-grade glioma

James I. Morgan, PhD; Executive Vice President and Scientific Director; Edna & Albert Abdo Shahdam Endowed Chair in Basic Research • Control of neuronal death & differentiation

Junmin Peng, PhD[1,2] • Proteomics & metabolomics in human disease

David J. Solecki, PhD[1] • Cell polarity in neuron precursor differentiation

Stanislav S. Zakharenko, MD, PhD[1] • Neural circuits of learning, memory, and their dysfunction in neurodevelopmental psychiatric disorders

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Stephen C. Mack, PhD • Pediatric brain tumors, cancer epigenetics, therapeutics, models

Paul A. Northcott, PhD[1] • Genomics & developmental biology of childhood brain tumors

Jamy C. Peng, PhD[1] • Epigenetic regulation of stem cell functions

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Myriam Labelle, PhD[1] • The role of the microenvironment in cancer metastasis

Lindsay A. Schwarz, PhD[1] • Mechanisms of neuromodulatory circuit organization

Elizabeth A. Stewart, MD[1,2] • Translational research of pediatric solid tumors

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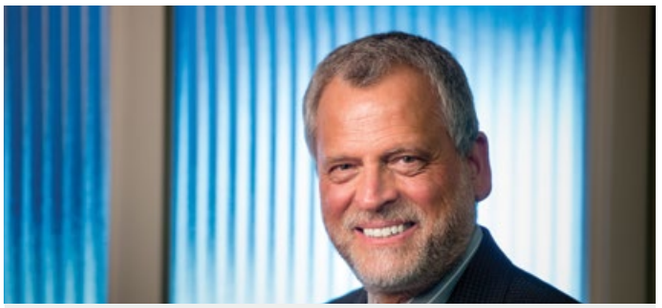

DIAGNOSTIC IMAGING

CHAIR
Zoltán Patay, MD, PhD; Endowed Chair in Diagnostic Imaging • Imaging genomics & radiomics in pediatric CNS tumors, cerebellar mutism syndrome

MEMBERS
Sue C. Kaste, DO • Skeletal toxicities in childhood cancer
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Noah D. Sabin, MD, JD • Imaging of brain tumors & side effects of therapy

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Puneet Bagga, PhD • Metabolic imaging, MR spectroscopy, molecular MRI, & cancer metabolism
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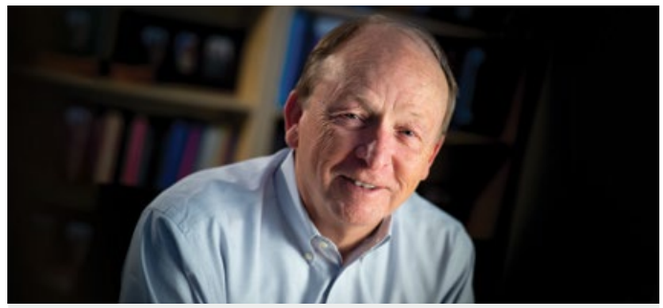
Cara E. Morin, MD, PhD • Novel MR body & cardiac imaging techniques

INSTRUCTOR
Zachary R. Abramson, MD, DMD • Quantitative imaging, computer-aided 3D modeling



EPIDEMIOLOGY & CANCER CONTROL

CHAIR
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Heather M. Brandt, PhD • HPV vaccination and cervical cancer screening
I-Chan Huang, PhD • Patient-reported outcomes measurement after pediatric cancer
Melissa M. Hudson, MD[2]; The Charles E. Williams Endowed Chair of Oncology–Cancer Survivorship • Health outcomes after childhood cancer
Kevin R. Krull, PhD; Endowed Chair in Cancer Survivorship • Cognitive neuroscience approaches to outcomes and interventions in pediatric cancer survivors
Kirsten K. Ness, PT, PhD[1] • Physical health and accelerated aging in childhood cancer survivors
Yutaka Yasui, PhD[1] • Genetics & risk of therapy-related outcomes

ASSOCIATE MEMBERS
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Wassim Chemaitilly, MD[3]
Daniel A. Mulrooney, MD, MS[1,2] • Cardiovascular outcomes of cancer therapy
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Nickhill Bhakta, MD, MPH[1,2] • Global health, survivorship, epidemiology, childhood leukemias
Angela Delaney Freedman, MD[2] • Hypothalamic/pituitary dysfunction in childhood cancer survivors
Matthew J. Ehrhardt, MD, MS[2] • Late effects of childhood cancer therapy
Yadav Sapkota, PhD • Genomic basis of pediatric cancer outcomes
Carmen L. Wilson, PhD[1] • Late effects of childhood cancer therapy

RESEARCH ASSOCIATE
Nicholas Phillips, MD, PhD • Neurocognitive late effects, cancer survivorship, functional and structural neuroimaging

GENETICS

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

MEMBER
Alessandra d'Azzo, PhD[1]; Jewelers for Children Endowed Chair in Genetics and Gene Therapy • Lysosomal/proteasomal function in health & disease

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GLOBAL PEDIATRIC MEDICINE

CHAIR

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Gaston K. Rivera, MD[4]
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Catherine G. Lam, MD, MPH[1,2] • Global health, health systems, pediatric solid tumors
Ibrahim A. Qaddoumi, MD, MS • Global health, brain tumors, telemedicine, retinoblastoma
Jeremy Slone, MD, MPH •Global pediatric cancer epidemiology

ASSISTANT MEMBERS

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Asya Agulnik, MD, MPH[1,2] • Global health, pediatric onco-critical care, quality improvement
Nickhill Bhakta, MD, MPH[1] • Global health, survivorship, epidemiology, childhood leukemias
Paola Friedrich, MD, MPH[1] • Global health, health disparities, health services, pediatric solid tumors
Dylan Graetz, MD • Global health, patient-centered care, solid tumors
Saman K. Hashmi, MD • Capacity building in global pediatric oncology
Sheena Mukkada, MD, MPH[1] • Global health, infection care & control
Teresa C. Santiago, MD[2] • Laboratory quality improvement & assessment

INSTRUCTOR

Daniel Moreira Ridsdale, MD • Global pediatric oncology, evidence-based education, pediatric CNS tumors

HEMATOLOGY

CHAIR

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

MEMBERS

John D. Crispino, PhD, MBA; The Wall Street Committee Endowed Chair • Mechanisms of leukemogenesis, benign & malignant blood disorders
Jane S. Hankins, MD, MS[1] • Sickle cell disease, transition to adult care & health outcomes during adolescence & young adulthood
Ellis J. Neufeld, MD, PhD; Executive Vice President; Clinical Director; John & Lorine Thrasher Endowed Chair in Pediatric Medicine • Patient-oriented studies in nonmalignant hematology
Arthur W. Nienhuis, MD[5]
Clifford M. Takemoto, MD; Lemuel Diggs Endowed Chair in Sickle Cell Disease • Hemostasis & thrombosis, vascular malformations, bone marrow failure
Winfred C. Wang, MD[4]

ASSOCIATE MEMBERS

Wilson K. Clements, PhD[1] • Hematopoietic development & leukemia
Jeremie H. Estepp, MD[1,2] • Sickle cell disease, novel therapies, translational studies
Shannon L. McKinney-Freeman, PhD[1] • Mechanisms of hematopoietic stem cell development & transplantation
Ulrike M. Reiss, MD[1] • Bleeding disorders, gene therapy for hemophilia, bone marrow failure
Carolyn Russo, MD • Quality improvement in clinical networks

ASSISTANT MEMBERS

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

INSTRUCTORS

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

RESEARCH ASSOCIATE

Christophe Lechauve, PhD • Hemoglobin biology, globin evolution, & protein dynamics

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IMMUNOLOGY

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• Cell death, autophagy, & immune function

VICE-CHAIR
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Peter C. Doherty, PhD[4]; Nobel Laureate
Paul G. Thomas, PhD[1] • Mechanisms of antiviral and antitumor immunity

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

ASSISTANT MEMBER
Yongqiang Feng, PhD[1] • Epigenetic & transcriptional basis of T-cell immunity

INFECTIOUS DISEASES

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

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Miguela A. Caniza, MD, MPH[1,2] • Global health, infection care, & control
Patricia M. Flynn, MD[1]; Deputy Clinical Director; Arthur Ashe Endowed Chair in Pediatric AIDS Research • HIV/AIDS in children & infections in children with cancer
Aditya H. Gaur, MD, MD, MBBS[1] • Clinical research in HIV prevention & treatment
Walter T. Hughes, MD[5]
Julia L. Hurwitz, PhD[1] • Pathogen/vaccine-induced immunity, nuclear hormones
Charles O. Rock, PhD[1] • Membrane phospholipid metabolism
Stacey L. Schultz-Cherry, PhD[1] • Pathogenesis of influenza & enteric virus infections
Richard J. Webby, PhD[1] • Influenza virus pathogenicity
Robert G. Webster, PhD[4]

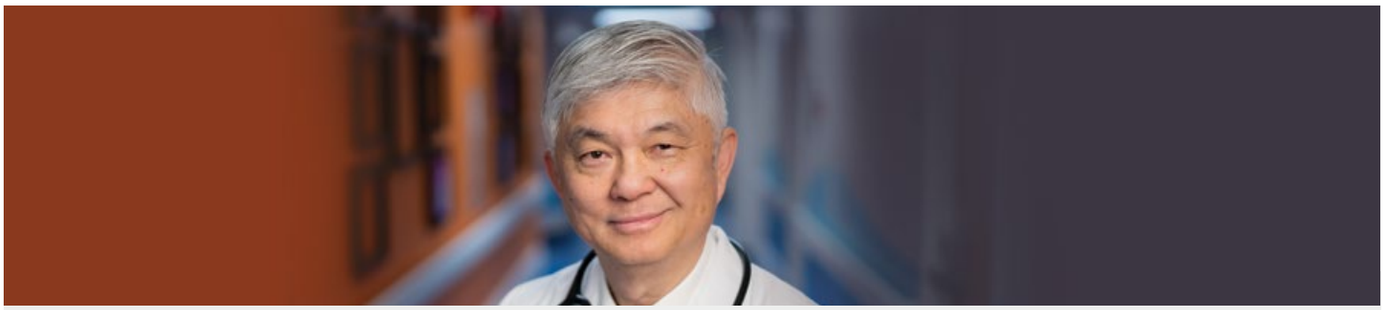
ASSOCIATE MEMBERS
Elisabeth E. Adderson, MD[1] • Epidemiology & treatment of infections
Hana Hakim, MD • Infection prevention & control
Katherine Knapp, MD • Perinatal HIV exposure/HIV clinical trials
Gabriela M. Marón Alfaro, MD • Infectious complications in transplant patients
Nehali Patel, MD • HIV clinical care
Jason W. Rosch, PhD[1] • Bacterial genomics & pathogenesis
Charles J. Russell, PhD[1] • Respiratory viruses: disease, cures, & prevention
Megan L. Wilkins, PhD[2] • Clinical & research psychological services for youth with HIV/AIDS
Joshua Wolf, PhD, MBBS[1] • Prediction, prevention, & treatment of infections in immunocompromised children

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

INSTRUCTOR
Timothy Flerlage, MD • Pathogenesis of severe lung infections

ADJUNCT MEMBER
Jonathan A. McCullers, MD • Interactions between viruses & bacteria

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



ONCOLOGY

CHAIR

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CO-CHAIR

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

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Justin N. Baker, MD[1] • Quality of life/palliative care & ethics
Elizabeth Fox, MD • Developmental therapeutics in pediatric oncology
Wayne L. Furman, MD[5]
Daniel M. Green, MD[1] • Adverse hepatic, renal, & reproductive effects of therapy
Melissa M. Hudson, MD; The Charles E. Williams Endowed Chair of Oncology–Cancer Survivorship • Health outcomes after childhood cancer
Hiroto Inaba, MD, PhD[1] • New therapeutic strategies for leukemia
Sima Jeha, MD[1,2] • Global health, childhood leukemias, developmental therapeutics
Sue C. Kaste, DO[2] • Skeletal toxicities in childhood cancer
Monika L. Metzger, MD[1,2] • Global health, Hodgkin & non-Hodgkin lymphomas
Kim E. Nichols, MD[1] • Heritable cancers & primary immunodeficiency syndromes
Alberto S. Pappo, MD[1]; Alvin Mauer Endowed Chair • New therapies for sarcomas & rare pediatric cancers
Raul C. Ribeiro, MD[1] • Hematological malignancies
Charles W. M. Roberts, MD, PhD[1]; Executive Vice President, Lillian R. Cannon Comprehensive Cancer Center Director Endowed Chair • SWI/SNF (BAF) chromatin remodeling/tumor suppressor
Carlos Rodriguez-Galindo, MD[1,2]; Four Stars of Chicago Endowed Chair in International Pediatric Outreach • Global medicine, pediatric solid tumors
Jeffrey E. Rubnitz, MD, PhD[1] • Treatment of acute myeloid leukemia
Victor M. Santana, MD[1,2]; Charles Pratt Endowed Chair in Solid Tumor Research • Novel therapeutics, neuroblastoma, research ethics
Jun J. Yang, PhD[1,2] • Pharmacogenomics of anticancer agents & drug resistance

ASSOCIATE MEMBERS

Richard A. Ashmun, PhD[2] • Applications of flow cytometry & cell separation
Rachel C. Brennan, MD[1] • Retinoblastoma, novel therapeutics, renal tumors
Patrick K. Campbell, MD, PhD • Histiocytic disorders, clinical informatics, patient safety
Sara M. Federico, MD[1] • Drug development, pediatric soft-tissue sarcomas
Mark E. Hatley, MD, PhD[1] • Origins of pediatric sarcomas
Liza-Marie Johnson, MD, MPH, MSB • Ethical issues in pediatrics
Catherine G. Lam, MD, MPH[1] • Global health, health systems, pediatric solid tumors
Deena R. Levine, MD • Pediatric palliative & end-of-life care
Daniel A. Mulrooney, MD, MS[1] • Cardiovascular outcomes of cancer therapy
Ibrahim A. Qaddoumi, MD, MS[2] • Global health, brain tumors, telemedicine, retinoblastoma
Giles W. Robinson, MD[1] • Origin & genomics of medulloblastoma, translational studies
Carolyn Russo, MD[2] • Quality improvement in clinical networks

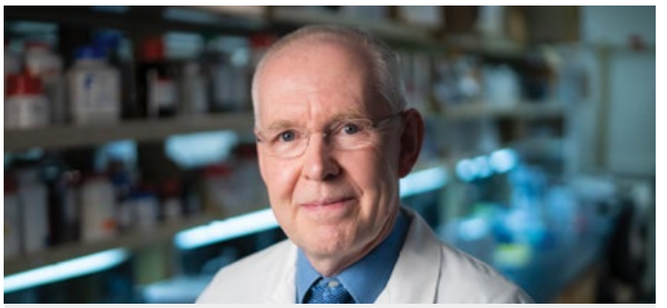
ASSISTANT MEMBERS

Kelsey C. Bertrand, MSc, MBBS • Understanding ependymoma and high-grade glioma
Nickhill Bhakta, MD, MPH[1,2] • Global health, survivorship, epidemiology, childhood leukemias
Michael W. Bishop, MD[1] • Osteosarcoma, Ewing sarcoma, soft-tissue sarcomas
Kari L. Bjornard, MD, MPH[3]
Stephanie B. Dixon, MD • Pediatric cancer survivorship
Adam D. Durbin, MD, PhD • Molecular biology of high-risk pediatric cancers
Matthew J. Ehrhardt, MD, MS • Late effects of childhood cancer therapy
Jamie E. Flerlage, MD, MS[1] • Reduction of the late effects for Hodgkin lymphoma survivors
Paola Friedrich, MD, MPH[1,2] • Global health, health disparities, health services, pediatric solid tumors
Dylan Graetz, MD[2] • Global health, patient-centered care, solid tumors
Kellie B. Haworth, MD[3]
Sara Helmig, MD • Sarcoma, thyroid carcinoma, & quality improvement
Zhongbo Hu, MD, PhD • Targeted leukemia therapy and clinical trials
Lauren P. Jerkins, MD • Cellular therapy, quality improvement, and patient safety
Seth E. Karol, MD • Toxicity reduction during acute leukemia therapy
Erica C. Kaye, MD • Prognostic communication, early integration of palliative care in oncology
Esther A. Obeng, MD, PhD[1] • Myeloid malignancies & bone marrow failure syndromes
Kimberly E. Sawyer, MD, MS • Shared decision-making, ethics, pediatric palliative care
Jitsuda Sitthi-Amorn, MD[3]
Holly L. Spraker-Perlman, MD, MS • Pediatric palliative care, symptom-management strategies
Elizabeth A. Stewart, MD[1] • Translational research of pediatric solid tumors
Linda Stout, MD • Pediatric oncology
Santhosh Upadhyaya, MD • Atypical teratoid rhabdoid tumor & ependymoma
Anna Vinitsky, MD, MS • Pediatric neuro-oncology & process improvement
Liqin Zhu, PhD[1,2] • Stem cells in normal & malignant development

INSTRUCTORS

Allison Ast, MD • Integrative therapies in pediatric hematology-oncology patients
Aditi Bagchi, MD, PhD • Molecular and genomic characteristics of pediatric brain tumors
Andrea Cuviello, MD • Early palliative care integration in pediatric oncology
Jessica Gartrell, MD • Early phase clinical trial development, sarcomas, liver tumors
Arshia Madni, MD • Hospice and palliative medicine
Daniel Moreira Ridsdale, MD[2] • Global pediatric oncology, evidence-based education, pediatric CNS tumors
Anand Patel, MD, PhD[1] • Tumor recurrence in pediatric rhabdomyosarcoma
Melissa R. Perrino, MD • Germline predisposition and genetic drivers of cancer

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



PATHOLOGY

CHAIR
David W. Ellison, MBBChir, MA(hons), MSc, MD, PhD;
Joan & Roy Gignac Endowed Chair in Pathology & Laboratory Medicine • Pathologic/molecular classification of CNS tumors

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

ASSOCIATE MEMBERS
Larissa V. Furtado, MD • Clinical genomics and data management systems
Gabriela Gheorghe, MD • Pediatric leukemias and lymphomas, histiocytic lesions
Laura J. Janke, DVM, PhD • Pathology of mouse models of disease
Jeffery M. Klco, MD, PhD[1] • Genomic & functional characterization of pediatric myeloid neoplasms
Yen-Chun Liu, MD, PhD • Hematologic malignancies
Mihaela Onciu, MD[3]
Brent A. Orr, MD, PhD • Molecular classification of tumors of the nervous system
Harshan Pisharath, DVM, PhD • Animal models of human diseases, preclinical safety
András Sablauer, MD, PhD • Imaging informatics & computerized tumor modeling
Teresa C. Santiago, MD • Laboratory quality improvement & assessment
Heather S. Tillman, DVM, PhD • Comparative pathology
Lu Wang, MD, PhD • Genomic profiling & functional analysis of genetic alterations in pediatric tumors

ASSISTANT MEMBERS
Paula Arnold, PhD • HLA and hematopoietic cell transplantation
Patrick R. Blackburn, PhD • Clinical laboratory genetics and genomics
Jason Cheng-Hsuan Chiang, MD, PhD • Diagnosis & classification of CNS tumors
Mohammed K. Eldomery, MD • Molecular oncology, cancer-predisposition syndromes
Heather L. Glasgow, PhD • Novel diagnostics for clinical microbiology
Mahsa Khanlari, MD • Diagnosis and classification of pediatric hematopoietic neoplasms
Selene C. Koo, MD, PhD • Molecular classification of pediatric solid tumors
Julieann C. Lee, MD, MS • Clinicopathologic and molecular characterization of pediatric brain tumors
Gang Wu, PhD • Genome instability, neurodegeneration, brain transcriptomics
Yan Zheng, MD, PhD • Red blood cell genotyping & alloimmunization, cancer Immunotherapy

INSTRUCTOR
Priya Kumar, MD • Diagnostic capacity building for hematologic malignancies in resource-limited settings

PEDIATRIC MEDICINE

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

MEMBERS
Shannon M. Dean, MD, MMM; Chief Medical Information Officer
Ellis J. Neufeld, MD, PhD; Executive Vice President; Clinical Director; John & Lorine Thrasher Endowed Chair in Pediatric Medicine • Patient-oriented studies in nonmalignant hematology

ANESTHESIOLOGY
Michael J. Frett, MD; Division Director • Pediatric anesthesia
Doralina L. Anghelescu, MD[1] • Pain management, anesthesia risks, palliative care
Angela Camfield, MD, MS[3]
Wasif H. Dweik, DO[3]
Kyle J. Morgan, MD[3]
Kavitha C. Raghavan, MBBS, FRCA • Patient safety & quality of care in pediatric anesthesia
Michael G. Rossi, DO • Patient safety & cognitive effects of anesthesia
Luis A. Trujillo Huaccho, MD • Regional anesthesia & anesthetic approach in high-risk cases
Becky B. Wright, MD[3]
Tzipa Zweig, MD, MS • Pediatric pain and palliative care

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

CRITICAL CARE MEDICINE
R. Ray Morrison, MD[1]; Division Director • Pediatric critical care, myocardial protection
Asya Agulnik, MD, MPH[1,2] • Global health, pediatric onco-critical care, quality improvement
Anita V. Arias Prado, MD • Capacity building in pediatric critical care
Lama Elbahlawan, MD • Pediatric critical care, acute lung injury
Saad Ghafoor, MD • Improvement of pediatric critical care outcomes
Melissa R. Hines, MD • Pediatric critical care, hemophagocytic lymphohistiocytosis
Caitlin E. Hurley, MD • Onco-critical care, HSCT/immunotherapy patients, long-term care
Jennifer A. McArthur, DO • Improving outcomes in critically ill pediatric patients

ENDOCRINOLOGY
Wassim Chemaitilly, MD[3]
Angela Delaney Freedman, MD; Division Director • Hypothalamic/pituitary dysfunction in childhood cancer survivors

NEUROLOGY
Raja B. Khan, MD; Division Director • Effect of cancer on central & peripheral nervous systems

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

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

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

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

PHARMACY & PHARMACEUTICAL SCIENCES

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

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

MEMBERS
William E. Evans, PharmD[4]
James M. Hoffman, PharmD; Chief Patient Safety Officer • Medication safety & outcomes
Mary V. Relling, PharmD[1] • Leukemia therapy & clinical pharmacogenetics
Erin G. Schuetz, PhD[1] • Mechanisms of human variation in drug response
John D. Schuetz, PhD[1] • Regulation & function of ABC transporters
Clinton F. Stewart, PharmD[1] • Pharmacology of anticancer drugs in children

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

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

PSYCHOLOGY

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

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

ASSOCIATE MEMBERS
Tara M. Brinkman, PhD[2] • Psychosocial outcomes of pediatric cancer
Jennifer L. Harman, PhD • The psychosocial functioning of young children with cancer
Niki Jurbergs, PhD • Psychological & cognitive impact of pediatric cancer
Jerlym S. Porter, PhD, MPH • Transition from pediatric to adult care in SCD
Megan L. Wilkins, PhD • Clinical & research psychological services for youth with HIV/AIDS

ASSISTANT MEMBERS
Jennifer M. Allen Lischwe, PhD • Pain management, adolescent/young adults, health behavior
Kristin E. Canavera, PhD • Pediatric bioethics
Lisa M. Jacola, PhD • Neurobehavioral outcomes in children treated for cancer
Kendra R. Parris, PhD • Coping & adjustment in youth with cancer
Brian S. Potter, PsyD • Neurocognitive outcomes in children with cancer
Darcy Raches, PhD • Acute neurological injury & cognitive outcomes associated with childhood cancer treatment
Rachel N. Webster, PhD • Promotion of healthy lifestyle behaviors in children with cancer & survivors of childhood cancer
Victoria W. Willard, PhD • Social outcomes in children with cancer

INSTRUCTORS
R. Elyse Heidelberg Kenney, PsyD • Pain and symptom management in pediatric hematology/oncology
Andrew M. Heitzer, PhD • Neurocognitive outcomes in sickle cell disease
Anna M. Jones, PhD • Transition off therapy for oncology patients and families
Jennifer Longoria, PhD • Neurocognitive outcomes in sickle cell disease
Katianne M. Sharp, PhD • Cancer predisposition & adjustment in families of children with cancer

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

RADIATION ONCOLOGY

CHAIR

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

MEMBERS

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

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

ASSOCIATE MEMBERS

John T. Lucas Jr., MS, MD • Brain tumors, neuroblastoma, proton therapy, clinical trial design

Christopher L. Tinkle, MD, PhD[1] • Preclinical evaluation of novel combination therapies and clinical trial development for high-risk brain tumors and sarcomas

ASSISTANT MEMBERS

Sahaja Acharya, MD[3]

Austin M. Faught, PhD • Proton therapy, biological modeling, adaptive therapy

INSTRUCTORS

Lydia J. Wilson, PhD • Predictive risk modelling, radiation late effects

Wenjun Yang, PhD • Neuroscience approaches to outcomes and interventions in pediatric cancer survivors

STRUCTURAL BIOLOGY

CHAIR

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

MEMBERS

M. Madan Babu, PhD, FRSC[1]; Endowed Chair in Biological Data Science • Data science for discovery and personalized medicine

Scott C. Blanchard, PhD[1]; Endowed Chair in Molecular Imaging • Examining structure–function relations in macromolecular assemblies

Richard W. Kriwacki, PhD[1] • Structural basis of tumor suppressor function

Tanja Mittag, PhD[1] • Molecular basis of liquid–liquid phase separation

Junmin Peng, PhD[1] • Proteomics & metabolomics in human disease

Stephen White, DPhil[1]; Endowed Chair-President, Dean of St. Jude Children's Research Hospital Graduate School of Biomedical Sciences • DNA repair, catalysis & structure-based drug discovery

ASSOCIATE MEMBERS

Eric J. Enemark, PhD[3]

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

ASSISTANT MEMBERS

Marcus Fisher, PhD[1,2] • Protein conformational ensembles

Chia-Hsueh Lee, PhD • Molecular mechanisms of membrane-signaling complexes

Tudor Moldoveanu, PhD[1] • Programmed cell death in health & disease

Ji Sun, PhD • Structural and pharmacological studies of membrane proteins

ADJUNCT MEMBER

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

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

SURGERY

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

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

ASSISTANT MEMBERS
Abdelhafeez H. Abdelhafeez, MD • Fluorescence-guided, minimally invasive, & subamputative pediatric surgical oncology
Andrew Jackson Murphy, MD • Renal tumors, neuroblastoma, Wilms tumorigenesis, cancer stem cells
Lindsay J. Talbot, MD • Sarcomas, immunotherapeutic strategies against sarcoma & solid tumor metastases
Jun Yang, MD, PhD • Cancer epigenetics & targeted therapy

ADJUNCT MEMBERS
Frederick Boop, MD[3]
Jeremiah L. Deneve, DO • Pediatric general surgery
Joseph M. Gleason, MD • Pediatric urology
Mary Ellen Hoehn, MD • Pediatric ophthalmology
Paul D. Klimo Jr, MD • Pediatric neurosurgery
Michael Neel, MD • Pediatric orthopedic oncology
Anthony Sheyn, MD • Pediatric otolaryngology
Jerome Thompson, MD, MBA • Pediatric otolaryngology
Matthew W. Wilson, MD; St. Jude Chair in Pediatric Ophthalmology • Pediatric ophthalmology

TUMOR CELL BIOLOGY

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

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

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

ADJUNCT MEMBER
Brenda A. Schulman, PhD[2] • Cellular regulation by ubiquitin-like proteins

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

Endowed Chairs

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

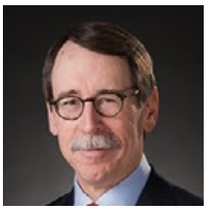
M. Madan Babu, PhD, FRSC
Endowed Chair in Biological Data Science

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

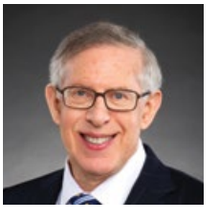
Scott C. Blanchard, PhD
Endowed Chair in Molecular Imaging

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

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

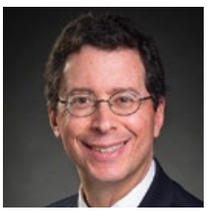


James R. Downing, MD
Dr. Donald Pinkel Endowed Chair in
Childhood Cancer Treatment

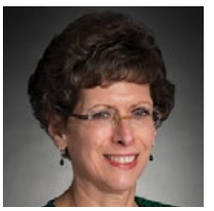


Richard S. Finkel, MD
Endowed Chair in Neurotherapeutics

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



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



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

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

Kevin R. Krull, PhD
Endowed Chair in Cancer Survivorship

Richard E. Lee, PhD
Endowed Chair in Medicinal Chemistry

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

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

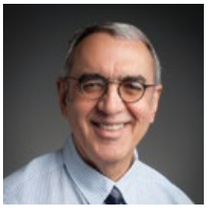
Charles G. Mullighan, MBBS(Hons), MD
William E. Evans Endowed Chair

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

Alberto S. Pappo, MD
Alvin Mauer Endowed Chair

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

Martine F. Roussel, PhD
Endowed Chair in Molecular Oncogenesis



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

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

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

Fellows & Students

POSTDOCTORAL FELLOWS

Diana Acevedo, PhD, Developmental Neurobiology
Adeleye Adeshakin, PhD, Bone Marrow Transplantation & Cellular Therapy
Aditi, PhD, Cell & Molecular Biology
Anup Aggarwal, PhD, Structural Biology[3]
Lisa Alcock, PhD, Pathology[1]
Tyler Alexander, PhD, Epidemiology & Cancer Control[1]
Gizem Altan, PhD, Diagnostic Imaging
Shelby Anderson, PhD, Chemical Biology & Therapeutics
Kavya Annu, PhD, Chemical Biology & Therapeutics[1]
Shariq Ansari, PhD, Cell & Molecular Biology
Sasi Arunachalam, PhD, Computational Biology
Gitanjali Asample, PhD, Structural Biology
Emilia Asante, PhD, Center for Pediatric Neurological Diseases Research
David Baggett, PhD, Structural Biology
Lu Bai, PhD, Immunology
Balaji Banoth, PhD, Immunology[2]
Juan Martin Barajas, PhD, Oncology
Stefanie Baril, PhD, Pharmacy & Pharmaceutical Sciences
Aditya Barve, PhD, Hematology
Katelyn Baumer, PhD, Chemical Biology & Therapeutics
Simran Bawa, PhD, Structural Biology
Swarna Beesetti, PhD, Immunology
Akshita Bhatt, PhD, Developmental Neurobiology
Kashi Bhattarai, PhD, Pharmacy & Pharmaceutical Sciences
Laure Bihannic, PhD, Developmental Neurobiology[2]
Emilio Boada Romero, PhD, Immunology
Shannon Boi, PhD, Immunology[1]
Nancy Bolous, MD, Global Pediatric Medicine
Wade Borcherds, PhD, Structural Biology
Austin Boucher, PhD, Hematology
David Boyd, PhD, Immunology[1]
Anne Bremer, PhD, Structural Biology
David Brice, PhD, Immunology
Mark Allan Brimble, PhD, Immunology
Cameron Buchman, PhD, Chemical Biology & Therapeutics[1]
Monicah Bwayi, PhD, Chemical Biology & Therapeutics[2]
Ratnakar Bynigeri, PhD, Immunology
Kirby Campbell, PhD, Developmental Neurobiology[2]
Deviprasanna Chakka, PhD, Structural Biology[2]
Shinjini Chakraborty, PhD, Immunology[1]
Bappaditya Chandra, PhD, Structural Biology
Phillip Chapman, PhD, Developmental Neurobiology
Kanokporn Chattrakun, PhD, Structural Biology
Deepti Chaturvedi, PhD, Structural Biology[1]
Meixia Che, PhD, Oncology[1]
Po-Ling Chen, PhD, Infectious Diseases
Xiaolong Chen, PhD, Computational Biology
Surendhar Reddy Chepyala, PhD, Structural Biology[2]
Peter Chockley, PhD, Bone Marrow Transplantation & Cellular Therapy
Hyo Young Choi, PhD, Computational Biology[1]
Shelbi Christgen, PhD, Immunology
Chia-Lung Chuang, PhD, Developmental Neurobiology
Elizabeth Cleverdon, PhD, Cell & Molecular Biology
Leslie Climer, PhD, Cell & Molecular Biology
Elizabeth Coffey, PhD, Hematology
Valerie Cortez, PhD, Infectious Diseases[1]
Chenxi Cui, PhD, Structural Biology
Yixin Cui, PhD, Structural Biology
Preeti Dabas, PhD, Chemical Biology & Therapeutics
Mahmoud Dabbah, PhD, Hematology
Yaxin Dai, PhD, Structural Biology
Adithi Danda, PhD, Chemical Biology & Therapeutics
Victoria Dardov, PhD, Cell & Molecular Therapy[1]
Emily Darrow, PhD, Developmental Neurobiology[1]
Jitendra Das, PhD, Structural Biology
Sarmistha Das, PhD, Biostatistics
Tapojyoti Das, PhD, Structural Biology
Christian DeJarnette, PhD, Pharmacy & Pharmaceutical Sciences
Ian Delahunty, PhD, Oncology
Kaushik Dey, PhD, Pharmacy & Pharmaceutical Sciences
Rachayata Dharmat, PhD, Cell & Molecular Biology[2]
Kirsten Dickerson, PhD, Pathology
Karissa Dieseldorff Jones, PhD, Computational Biology
Phillip Doerfler, PhD, Hematology
Priyanka Dogra, PhD, Collaborative Research Program
Qian Dong, PhD, Epidemiology & Cancer Control
Xingrong Du, PhD, Immunology[1]
Yongming Du, PhD, Structural Biology
Asaf Elazar, PhD, Structural Biology
Lana Elkins, PhD, Tumor Cell Biology
Abdelrahman Elsayed, PhD, Pathology
Rabeh Elshesheny, PhD, Infectious Diseases[1]
Carolin Escherich, MD, Pharmacy & Pharmaceutical Sciences
Daniel Estevez Prado, PhD, Structural Biology
Myron Evans, PhD, Developmental Neurobiology[1]
Li Fan, PhD, Pharmacy & Pharmaceutical Sciences
Esmat Fathi, PhD, Center for Pediatric Neurological Diseases Research
Feng Feng, PhD, Developmental Neurobiology
Daniel Ferguson, PhD, Pharmacy & Pharmaceutical Sciences[1]
Carlos Fernandez Pena Acuna, PhD, Developmental Neurobiology
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Diane Flasch, PhD, Computational Biology
Elizabeth Foley, PhD, Epidemiology & Cancer Control[1]
Leigh Fremuth, PhD, Genetics
Adolfo Frias, PhD, Immunology
Guotong Fu, PhD, Immunology[1]
Yingxue Fu, PhD, Structural Biology
Katherine Gadek, PhD, Oncology
Kellen Gandy, PhD, Epidemiology & Cancer Control
Debolina Ganguly, PhD, Chemical Biology & Therapeutics[1]
Dusan Garic, PhD, Developmental Neurobiology
Pragya Gautam Poudel, PhD, Epidemiology & Cancer Control
Clifford Gee, PhD, Chemical Biology & Therapeutics
Mohamed Ghonim, PhD, Immunology
Eric Gibbs, PhD, Structural Biology
Elizabeth G. Gibson, PharmD, PhD, Pharmacy & Pharmaceutical Sciences[1]
Vanshita Goel, PhD, Tumor Cell Biology
Lina Gonzalez Martinez, PhD, Developmental Neurobiology
Chelsea Goodenough, PhD, Epidemiology & Cancer Control
Scott Gorman, PhD, Structural Biology
Tomoka Gose, PhD, Pharmacy & Pharmaceutical Sciences
Flávia Graça Zuanazzi, PhD, Developmental Neurobiology
Wezley Griffin, PhD, Structural Biology
Jessica Gullett, PhD, Infectious Diseases[1]
Omer Gullulu, PhD, Structural Biology
Peter Gunnarsson, PhD, Structural Biology
Ao Guo, PhD, Immunology
Chuansheng Guo, PhD, Immunology
Youngdae Gwon, PhD, Cell & Molecular Biology
Kohei Hagiwara, MD, Computational Biology
Priyanka Halder, PhD, Genetics
Eric Hall, PhD, Cell & Molecular Biology
Trent Hall, PhD, Hematology
Lindsay Hammack, PhD, Structural Biology[1]
Joo-Hui Han, PhD, Immunology
Xiaolei Hao, PhD, Immunology
Virginia Hargest, PhD, Infectious Diseases2
Walter Harrington, PhD, Infectious Diseases
Dalia Haydar, PhD, Bone Marrow Transplantation & Cellular Therapy
Minghong He, PhD, Immunology
Roketa Henry, PhD, Genetics
Carl Mikael Holm, PhD, Structural Biology[2]
Rebekah Honce, PhD, Infectious Diseases[1]
Madeline Horan, PhD, Epidemiology & Cancer Control
Seyed Mohammad Hosseini, PhD, Structural Biology
Laura Hover, PhD, Developmental Neurobiology[1]
Meng Hu, PhD, Infectious Diseases
Hongling Huang, PhD, Immunology[1]
Wenjun Huang, PhD, Hematology
Xin Huang, PhD, Computational Biology
Yan Huang, PhD, Structural Biology
Andrew Huber, PhD, Chemical Biology & Therapeutics
Michael Hughes, PhD, Cell & Molecular Biology
Liam Hunt, PhD, Developmental Neurobiology[2]
Anna Huskey, PhD, Pathology
Jongchan Hwang, PhD, Oncology
Jorge Ibanez, PhD, Bone Marrow Transplantation & Cellular Therapy
Yoonjeong Jang, DVM, PhD, Hematology[2]
Meiqin Jiang, PhD, Structural Biology
Yajun Jiang, PhD, Structural Biology[1]
Yanbo Jiang, PhD, Developmental Neurobiology
Kasey Jividen, PhD, Hematology
Barbara M. Jonchere, MD, PhD, Tumor Cell Biology[1]
Jason Jones, PhD, Structural Biology
Zachary Jones, PhD, Developmental Neurobiology
Seughyun Jung, PhD, Developmental Neurobiology
Halime Kalkavan, MD, Immunology
Balabhaskararao Kancharana, PhD, Immunology
Ahmed Kandeil, PhD, Infectious Diseases
Suresh Kandikonda, PhD, Chemical Biology & Therapeutics
Tae Gun Kang, PhD, Immunology
Mangesh Kaulage, PhD, Chemical Biology & Therapeutics
Hari Khatri Neupane, PhD, Chemical Biology & Therapeutics[2]
Hanane Khoury, PhD, Hematology
Hyunsuh Kim, PhD, Infectious Diseases
Yunjung Kim, PhD, Immunology[1]
Shunsuke Kimura, MD, PhD, Pathology
Evan Kingsley, PhD, Developmental Neurobiology
Kaitlin Koreski, PhD, Cell & Molecular Biology[2]
Casey Langdon, PhD, Oncology
Shannon Lange, PhD, Bone Marrow Transplantation & Cellular Therapy
Ana Leal Cervantes, PhD, Oncology
Dong Geun Lee, PhD, Structural Biology
Natalie Lee, PhD, Infectious Diseases[1]
SangJoon Lee, PhD, Immunology
Shawn Lee, MD, Pharmacy & Pharmaceutical Sciences
Shaohua Lei, PhD, Computational Biology[2]

[1] No longer at St. Jude [2] Promoted to staff position [3] Promoted to faculty position [4] Promoted to postdoctoral fellow position

William Letsou, PhD, Epidemiology & Cancer Control
Dongfang Li, PhD, Cell & Molecular Biology
Jun Li, PhD, Immunology
Miaomiao Li, PhD, Oncology
Shuting Li, PhD, Immunology
Wei Li, PhD, Immunology
Yizhen Li, PhD, Pharmacy & Pharmaceutical Sciences
Yongtao Li, PhD, Chemical Biology & Therapeutics
Zhenrui Li, PhD, Immunology
Swantje Liedmann, PhD, Immunology
Bitna Lim, PhD, Developmental Neurobiology
Seon Ah Lim, PhD, Immunology
Danielle Little, PhD, Developmental Neurobiology
Beiyun Liu, PhD, Immunology
Danting Liu, PhD, Structural Biology
Fengming Liu, PhD, Developmental Neurobiology
Jingjing Liu, PhD, Computational Biology
Yiwei Liu, PhD, Pharmacy & Pharmaceutical Sciences[1]
Lingyun Long, PhD, Immunology
Marybeth Lupo, PhD, Developmental Neurobiology[2]
William MacCain, PhD, Infectious Diseases
Joelle Magne, PhD, Immunology
Kelsey Maher, PhD, Computational Biology
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Efran Maldonado, PhD, Chemical Biology & Therapeutics
Deepshikha Malik, PhD, Structural Biology
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Luigi Mari, PhD, Immunology
Erik Martin, PhD, Structural Biology[1]
Maxwell Martin, PhD, Structural Biology
Masihuzzaman, PhD, Structural Biology
Cecile Mathieu, PhD, Cell & Molecular Biology[1]
Yurika Matsui, PhD, Developmental Neurobiology
Jayadev Mavuluri, PhD, Pathology
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Benjamen Minden-Birkenmaier, PhD, Developmental Neurobiology
Anastasia Minervina, PhD, Immunology
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Lindsey Montefiori, PhD, Pathology
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Tresor Mukiza, PhD, Cell & Molecular Biology
Haruko Nakamura, MD, PhD, Cell & Molecular Biology
Ambuja Navalkar, PhD, Structural Biology
Christopher Nevitt, PhD, Hematology
Lam Nguyen, PhD, Immunology[1]
Madeline Niederkorn, PhD, Hematology
Rina Nishii, PhD, Pharmacy & Pharmaceutical Sciences[2]
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Mingming Niu, PhD, Structural Biology[1]
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Jennifer Ocasio Adorno, PhD, Developmental Neurobiology
Bryan O'Flynn, PhD, Structural Biology
Cameron Ogg, PhD, Developmental Neurobiology
Chet Ojha, PhD, Infectious Diseases
Adedolapo Ojoawo, PhD, Structural Biology
Faten Okda, DVM, PhD, Infectious Diseases
Taren Ong, PhD, Developmental Neurobiology[1]
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Philippe Pascua, PhD, Infectious Diseases[1]
Avik Pati, PhD, Structural Biology
Mary Patton, PhD, Developmental Neurobiology
Janaka Peragaswaththe Liyanage, PhD, Biostatistics
Ivan Peran, PhD, Structural Biology[1]
Nicholas Phillips, MD, PhD, Epidemiology & Cancer Control
Shabareesh Pidathala, PhD, Structural Biology
Anna Pittman, PhD, Developmental Neurobiology
Kristine Faye Piza, PhD, Tumor Cell Biology[2]
David Place, PhD, Immunology[1]
Anustup Poddar, PhD, Structural Biology
Mikhail Pogorelyy, PhD, Immunology
Petri Polonen, PhD, Pathology
Pragya Poudel, PhD, Epidemiology & Cancer Control
Brooke Prinzing, PhD, Bone Marrow Transplantation & Cell Therapy
Honghu Quan, PhD, Pathology[1]
Waise Quarni, PhD, Surgery
Christopher Radka, PhD, Infectious Diseases
Sabina Ranjit, PhD, Pharmacy & Pharmaceutical Sciences
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Jana Raynor, PhD, Immunology
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Sarah Robinson-Thiewes, PhD, Chemical Biology & Therapeutics
Stephanie Rockfield, PhD, Cell & Molecular Biology
Ricardo Rodriguez-Enriquez, PhD, Cell & Molecular Biology
Jarrid Ronnebaum, PhD, Chemical Biology & Therapeutics
Ericka Roubidoux, PhD, Infectious Diseases
Sarayu Row, PhD, Cell & Molecular Biology
Jessica Rubino, PhD, Infectious Diseases[2]
Sebastian Ruehl, PhD, Immunology
Diana Sa da Bandeira, PhD, Hematology
Sushree Sahoo, PhD, Hematology
Parimal Samir, PhD, Immunology[2]
Julio Sanchez, PhD, Structural Biology
Andrea Sanchez Corzo, PhD, Diagnostic Imaging
Laura Sanchez Hernandez, PhD, Diagnostic Imaging
Manbir Sandhu, PhD, Structural Biology[2]
Jordy Saravia, PhD, Immunology
Ming Shao, PhD, Chemical Biology & Therapeutics
Maxwell Shapiro, PhD, Structural Biology
Piyush Sharma, PhD, Immunology
Jerremy Shaw, PhD, Immunology
Noha Shendy, PhD, Oncology
Hazheen Shirnekhi, PhD, Structural Biology
Lilian Silva, PhD, Pharmacy & Pharmaceutical Science
Jin-ah Sim, PhD, Epidemiology & Cancer Control[1]
Shivendra Singh, PhD, Surgery[2]
Nan Song, PhD, Epidemiology & Cancer Control[1]
Aisha Hegab Souquette, PhD, Immunology
Timothy Stachowski, PhD, Chemical Biology & Therapeutics
Jennifer Stripay, PhD, Tumor Cell Biology[2]
Wei Su, PhD, Immunology
Huan Sun, PhD, Structural Biology
Xiang Sun, PhD, Immunology
Xiaojun Sun, PhD, Structural Biology[2]
Balamurugan Sundarm, PhD, Immunology
Shannon Sweeney, PhD, Developmental Neurobiology
Ran Tao, PhD, Developmental Neurobiology
Kristen Thomas, PhD, Developmental Neurobiology
Melvin Thomas III, PhD, Pathology
Elizabeth Tinder, PhD, Infectious Diseases
Ricky Tirtakusuma, PhD, Immunology
Michele Tolbert, PhD, Structural Biology
Carolina Torres Rojas, PhD, Developmental Neurobiology
Quang Tran, PhD, Computational Biology
Olivia Travis, PhD, Developmental Neurobiology
Alexandra Trevisan, PhD, Developmental Neurobiology
Sanja Trifkovic, PhD, Infectious Diseases
Shraddha Tuladhar, PhD, Immunology
Masayuki Umeda, PhD, Pathology
Alanna Van Huizen, PhD, Hematology
Jessica Wagner, PhD, Bone Marrow Transplantation & Cellular Therapy
LaShanale Wallace, PhD, Oncology
Jingheng Wang, PhD, Chemical Biology & Therapeutics
Qinrui Wang, PhD, Structural Biology[1]
Xiaokang Wang, PhD, Cell & Molecular Biology[1]
Xiaoqing Wang, PhD, Biostatistics
Yan Wang, PhD, Immunology
Yaqiu Wang, PhD, Immunology
Zhen Wang, PhD, Structural Biology
Abubakar Wani, PhD, Immunology
Arjumand Wani, PhD, Structural Biology
Megan Ware, PhD, Epidemiology & Cancer Control
Sarah Whaley, PharmD, PhD, Infectious Diseases
Anna Lynn Williams, PhD, Epidemiology & Cancer Control
Lydia Wilson, PhD, Radiation Oncology[1]
Nicholas Wohlgemuth, PhD, Infectious Diseases[1]
Qiong Wu, PhD, Surgery
Stephanie Wu, PhD, Developmental Neurobiology
Jiyuan Yang, PhD, Computational Biology
Ka Yang, PhD, Structural Biology
Shu Yang, PhD, Structural Biology
Xu Yang, PhD, Cell & Molecular Biology[2]
Rajesh Yetirajam, PhD, Immunology
Siqi Yi, PhD, Hematology
Masanori Yoshida, PhD, Hematology
Tomoko Yoshida, MD, PhD, Epidemiology & Cancer Control
Zhiyuan You, PhD, Immunology
Sarah Young, PhD, Chemical Biology & Therapeutics
Kaiwen Yu, PhD, Structural Biology[2]
Sujing Yuan, PhD, Immunology
Fatima Zaidi, PhD, Structural Biology
Jingliao Zhang, MD, Pharmacy & Pharmaceutical Sciences1
Peipei Zhang, PhD, Cell & Molecular Biology[1]
Xue Zhang, PhD, Structural Biology
Lanying Zhao, PhD, Hematology
Xujie Zhao, PhD, Pharmacy & Pharmaceutical Sciences
Min Zheng, PhD, Immunology[1]
Peipei Zhou, MD, PhD, Immunology
Hanwen Zhu, PhD, Structural Biology
Zhexin Zhu, PhD, Oncology
Jaquelyn Zoine, PhD, Bone Marrow Transplantation & Cellular Therapy
Xinying Zong, PhD, Immunology

[1] No longer at St. Jude [2] Promoted to staff position [3] Promoted to faculty position [4] Promoted to postdoctoral fellow position

Fellows & Students

CLINICAL FELLOWS

Bone Marrow Transplantation & Cellular Therapy Fellow

Rebecca Epperly, MD[3]

Critical Care Fellow

Anita V. Arias Prado, MD[3]

Global Pediatric Medicine Fellows

Meghna Dua, MD

Dylan Graetz, MD, MPH[3]

Shahzadi Resham, MBBS

Ocular Oncology Fellow

Jacqueline Laplant, MD

Neuropsychology Fellows

Diana Cohen, PhD

Holly Hasler, PhD[1]

Nicole Salman, PhD

Pediatric Hematology-Oncology Fellows

Taylor Aglio, MD

Senthil Bhoopalan, MBBS[3]

Jessica Bodea, MD

Kenneth Caldwell, MD[1]

Georgios Christakopoulos, MD

Caitlyn Duffy, MD

Kayla Foster, MD[1]

Camille Keenan, MD

Justin Kirkham, MD, PhD

Michael McNeil, MD

Margaret Nagel, MD

Ayo Olanrewaju, MD

Matthew Rees, MD

Marta Salek, MD

Richa Sharma, MD[3]

Aurora Tarun, MD

Ruth Wang'ondu, MD, PhD

Pediatric Infectious Diseases Fellows

Amanda Green, MD

Melissa Shenep, MD

Pediatric Neuro-oncology Fellows

Aditi Bagchi, MD[3]

Richard Graham, MD[1]

Trisha Larkin, MD[1]

Pediatric Surgical Oncology Fellows

Oswaldo Gomez Quevedo, MD1

Sara Mansfield, MD

Pattamon Sutthatarn, MD[1]

Pharmacogenetics Resident

Sarah Morris, PharmD[2]

Pharmacy Fellows

Chelsea Drennan, PharmD[2]

Jaclyn Hopp, PharmD[2]

Katherine Robinson, PharmD[1]

Deann Tims, PharmD[1]

Psychology Fellows

Vanessa Aguilera, PhD[1]

Mallorie Gordon, PhD[1]

Dana Kamara, PhD

Melanie Morse, PhD

Megan Schafer, PhD[1]

Solid Tumor Fellow

Jessica A. Gartrell, MD[3]

GRADUATE STUDENTS

St. Jude Graduate Students

Alhassan Abdul-Mumin, MD, Global Child Health

Grace Adkins

Joaquim Caetano de Aguirre Neto, MD, Global Child Health

Alia Ahmad, MD, Global Child Health

Hamoud Hodeish Yahya F. Al-Hussaini, MD, Global Child Health

Ana Patricia Alcasabas, MD, Global Child Health[1]

Ahmad Alokl-Moussa, MD, Global Child Health[1]

Alexandra Beckett, Bone Marrow Transplantation & Cellular Therapy

Matthew Bell, Bone Marrow Transplantation & Cellular Therapy

Brennan Bergeron, Pharmacy & Pharmaceutical Sciences

Mackenzie Bloom, Oncology

Joseph Brett

Kaitlyn Budd, Developmental Neurobiology

Madeline Bush, Oncology

Jiaoyang Cai, MD, Global Child Health

Terri L. Cain, Oncology

Christina Daly, Cell & Molecular Biology

Yogesh Dhungana, Computational Biology

Rosdali Diaz Coronado, MD, Global Child Health

Mae C. Dolendo-Jarencio, MD, Global Child Health

Marygrace Duggar, Immunology

D. Andrew Elliott, MD, Clinical Investigation

Abigail Fish

Jake Friske

Jessica Gaevert, Immunology

Rebecca Gee, Chemical Biology & Therapeutics

Anne C. Gilmore, Developmental Neurobiology

Wendy Cristhyna Gomez Garcia, MD, Global Child Health

Jamuni Gunasekera, MD, Global Child Health[1]

Liam Hallada, Developmental Neurobiology

Pascale Y. Heurtelou Gassant, MD, Global Child Health

Victoria Honnell, Developmental Neurobiology

Diriba Hordofa, MD, Global Child Health

Alex Hughes, Developmental Neurobiology

Alissa Jackson

Yusuf Danasabe Jobbi, MD, Global Child Health

Christina Kackos, Infectious Diseases

[1] No longer at St. Jude [2] Promoted to staff position [3] Promoted to faculty position [4] Promoted to postdoctoral fellow position

Seth A. Karol, MD, Clinical Investigation
Matthew B. Kieffer, Developmental Neurobiology
Allison Kirk, Immunology
Roman Kizyma, MD, Global Child Health
Rahul Kumar, Developmental Neurobiology[1]
Christy LaFlamme, Cell & Molecular Biology
Randolph Larsen, Oncology
Andrea Lee, Hematology
JaQuel Maise
Hayden Malone, Oncology
Sanya Mehta, Global Child Health
Mora Mel, MD, Global Child Health[1]
Ramon A. Misla David, Cell & Molecular Biology
Sarah E. Moore, Bone Marrow Transplantation & Cellular Therapy
Doreen Terry Karimi Mutua, MD, Global Child Health
Yuliya Nogovitsyna, Global Child Health
Erienne Norton
Kiera O'Keefe
Trevor S. Penix, Infectious Diseases
Nicolas B. Peterson, Immunology
Gregory Phelps, Chemical Biology & Therapeutics
Brittany Pioso, Structural Biology
Adriana M. Porras, MD, Global Child Health[1]
Rehana Punjwani, MD, Global Child Health
Venkatraman Radhakrishnan, MD, Global Child Health[1]
Sandi Radko-Juettner, Oncology
Adriana Ramirez Negron, Global Child Health
Kirtikumar Rathod, MD, Global Child Health
Muhammad Rafie Raza, MD, Global Child Health
Isaiah Reeves, Surgery
Rawad Rihani, MD, Global Child Health[1]
Jocelyn Rivera, MD, Global Child Health[1]
Jordan T. Roach, Developmental Neurobiology
Juan Pablo Rodriguez Auad, MD, Global Child Health
Samuel Rovito
Lauren Rowland
Abideen Olurotimi Salako, MD, Global Child Health
Akshay Sharma, MD, Clinical Investigation
Melissa Shenep, MD, Clinical Iinvestigation
Sarah J. Sherman, Structural Biology
Jamaica F. Siwak, Cell & Molecular Biology
Maria Smith, Infectious Diseases
Hannah Snoke
Matthew So
Bradley T. Stevens, Oncology
Morgan Sutton, Bone Marrow Transplantation & Cellular Therapy
Liliana Vasquez, MD, Global Child Health[1]
Ana Vazquez-Pagan, Infectious Diseases
Thelma Velasquez Herrera, MD, Global Child Health[1]
Christina Wang, Cell & Molecular Biology
Kendall Whitt
Elizabeth Wickman, Bone Marrow Transplantation & Cellular Therapy
Kristin Wiggins, Infectious Diseases
Benjamin Wilander, Immunology
McLean Williamson, Hematology
Stephen Winston, Surgery
Tristen D. Wright, Cell & Molecular Biology
Arturo Manuel Zapata Lopez, MD, Global Child Health

External Graduate Students

Ahmed Abuzaid, Surgery
Donna Bartel, Social Work[1]
Jake Batchelder, Structural Biology
Tharwa Bilbeisi, Oncoloy[1]
Lauren Brakefield, Cell & Molecular Biology
Anthony Brown, Pharmacy & Pharmaceutical Sciences
Theresa Bub, Infectious Diseases
Jingjing Chen, Hematology
Brandi Clark, Immunology
Ashton Coker, Chemical Biology & Therapeutics
Nisha Das, Chemical Biology & Therapeutics[1]
Amy Davis, Infectious Diseases
Laura Doorley, Pharmacy & Pharmaceutical Sciences
Leigh Fremuth, Genetics[4]
Ashley Gray, Pharmacy & Pharmaceutical Sciences
Xian Han, Structural Biology
Taylor Hedgecock, Cell & Molecular Biology
Jianzhong Hu, Pharmacy & Pharmaceutical Sciences
Hannah Huth, Radiation Oncology[1]
Menglin Jiang, Immunology
Fatemeh Keramatnia, Chemical Biology & Therapeutics
William Kuenzinger, Developmental Neurobiology
Xin Lan, Immunology
Chun-Yang Lin, Immunology
Joseph Miller, Pharmacy & Pharmaceutical Sciences
Robert Neel, Surgery
Schyler Odum, Chemical Biology & Therapeutics
Christopher Patton, Infectious Diseases
Christopher Rogers, Hematology
Aaron Ross, Surgery
Emily Rundlet, Structural Biology
Claire Sentilles, Radiation Oncology
Dewan Shrestha, Hematology
Hailey Shwr, Social Work
Amber Smith, Pathology
Wei Su, Immunology[4]
Jennifer Toth, Pharmacy & Pharmaceutical Sciences
Patricia Umberger, Cell & Molecular Biology[1]
Nicole Vita, Chemical Biology & Therapeutics
Jason A. Weesner, Genetics
Taylor Wilson, Immunology
Rachael Wood, Tumor Cell Biology[1]
Jinjun Wu, Cell & Molecular Biology
Zhen Xie, Computational Biology
Zemin Yang, Cell & Molecular Biology
Jay Yarbro, Structural Biology
Satoshi Yoshimura, Pharmacy & Pharmaceutical Sciences
Ugur Yurtsever, Cell & Molecular Biology
Xujie Zhao, Pharmacy & Pharmaceutical Sciences[4]
Jingwen Zhu, Pharmacy & Pharmaceutical Sciences

[1] No longer at St. Jude [2] Promoted to staff position [3] Promoted to faculty position [4] Promoted to postdoctoral fellow position

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Theodore J. Hazer[6]
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Paul J. Marcus
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Manal B. Saab
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Terre Thomas
Pat Kerr Tigrett
Thomas C. Wertz
Robert P. Younes, MD
Ramzi T. Younis, MD

[1] January–June, 2021 [2] July–December, 2021 [3] Ex officio voting member [4] November–December, 2021 [5] Nonelected member [6] Deceased [7] Inactive

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This panel of physicians and scientists, serving during 2021, 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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Member, National Academy of Medicine

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Vice Chair of Pediatric Oncology Research, Dana-Farber Cancer Institute
Co-Director, Pediatric Hematologic Malignancy Program
Boston Children's Hospital and Dana-Farber Cancer Institute
Professor of Pediatrics, Harvard Medical School
Institute Member, Broad Institute of MIT and Harvard
Dana-Farber/Boston Children's Cancer and Blood Disorders Center

Smita Bhatia, MD, MPH
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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

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Department of Chemistry
The Scripps Research Institute
Member, National Academy of Medicine
Member, National Academy of Sciences

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Departments of Internal Medicine, Human Genetics, and Pediatrics
University of Michigan Medical School
Member, National Academy of Medicine

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Consultant, Princess Margaret Cancer Centre

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Harvard Medical School Chair, Department of Radiation Oncology
Dana-Farber Cancer Institute
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Chancellor's Professor
Professor of Molecular Biology and Professor of Chemistry
University of California at Berkley
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John M. Maris, MD
Giulio D'Angio Professor of Pediatric Oncology
Perelman School of Medicine at the University of Pennsylvania
Division of Oncology
Children's Hospital of Philadelphia

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Board of Directors, Chief Medical Officer
Princess Maxima Center for Pediatric Oncology

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Genentech
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Member, National Academy of Sciences

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Burke O'Reilly Family Endowed Chair in Immunotherapy
Professor, Department of Medicine
Fred Hutchinson Cancer Research Center

Michael K. Rosen, PhD
Investigator, Howard Hughes Medical Institute
Mar Nell and F. Andrew Bell Distinguished Chair in Biochemistry
University of Texas Southwestern Medical Center
Member, National Academy of Sciences

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Harvard University
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American Cancer Society Research Professor
Roma and Marvin Auerback Distinguished Professorship in Pediatric Molecular Oncology
University of California, San Francisco

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Epidemiology & Cancer Control, Oncology

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Director, Center of Excellence for Data Driven Discovery
Structural Biology

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Oncology

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Hematology

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Pediatric Medicine

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Medical Director, Quality & Patient Care
Infectious Diseases

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Co-Chair, Oncology

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Director, Division of Cancer Survivorship
Oncology, Epidemiology & Cancer Control, Psychology

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Chief Administrative & Financial Officer

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Structural Biology

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Chair, Pediatrics, University of Tennessee Health Science Center
Pediatrician-in-Chief, Le Bonheur Children's Hospital

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Director, Center for Neurological Disease Research
Cell & Molecular Biology

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Scientific Director

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Pathology

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Chief Nursing Executive

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Executive Vice President
Clinical Director
Physician-in-Chief

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Ching-Hon Pui, MD
Chair, Oncology

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Executive Vice President
Director, Comprehensive Cancer Center

Leslie R. Robison, PhD
Chair, Epidemiology & Cancer Control

Carlos Rodriguez-Galindo, MD
Executive Vice President
Chair, Department of Global Pediatric Medicine
Director, St. Jude Global

P. David Rogers, PharmD, PhD
Chair, Pharmacy & Pharmaceutical Sciences

Martine F. Roussel, PhD
Tumor Cell Biology

Charles J. Sherr, MD, PhD
Chair, Tumor Cell Biology

J. Paul Taylor, MD, PhD
Chair, Cell & Molecular Biology
Director, Pediatric Translational Neuroscience Initiative

Elaine I. Tuomanen, MD
Chair, Infectious Diseases

Mitchell J. Weiss, MD, PhD
Chair, Hematology

Stephen W. White, DPhil
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

OPERATIONS & STATISTICS

OPERATIONS	
Operating expenses[1]	$1.192 billion
Number of employees[2]	5317
RESEARCH STATISTICS	
Grant funding[1]	$133.8 million
Peer-reviewed publications[3]	814
Faculty members	348
Postdoctoral fellows	362
Clinical residents and fellows[4]	270
Graduate students	145
CLINICAL STATISTICS	
Number of beds open[5]	73
Total outpatient visits	217,328
Inpatient admissions	3381
Total inpatient days	17,153
Total protocol enrollments in 2021	5137
Patients enrolled in therapeutic trials	723
Patients enrolled in nontherapeutic trials	4414 3536 in prospective trials 878 in tissue-banking protocols
Total number of protocols that were open to accrual in 2021	644
Number of active therapeutic trials	163
Number of active nontherapeutic trials	481 159 prospective trials 313 retrospective trials 3 tissue-banking protocols 6 other protocols

[1] Data represent the period July 1, 2020, to June 30, 2021.

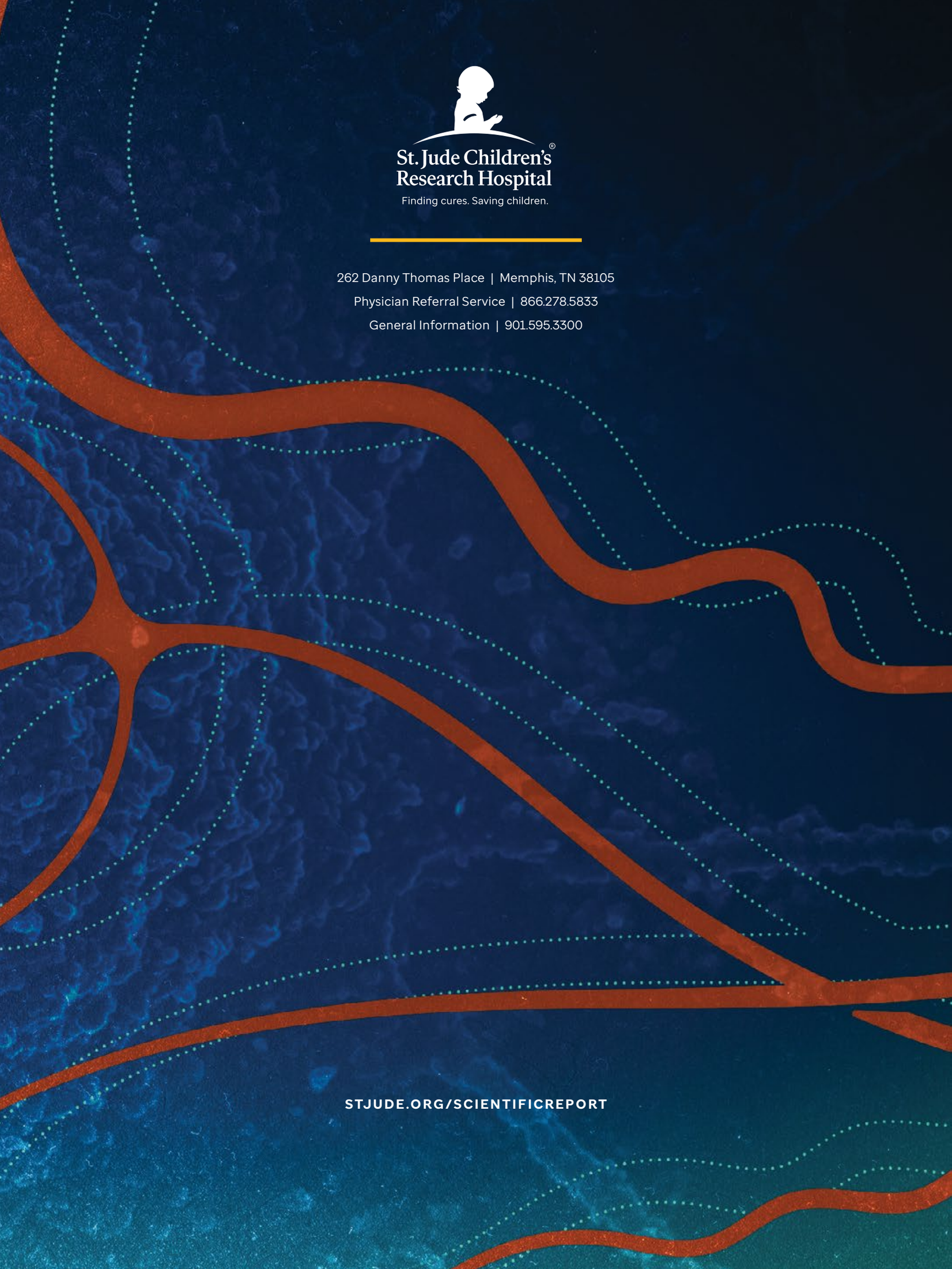
[2] Data are from July 1, 2021.

[3] Data include original data articles.

[4] Data include 71 full-time St. Jude fellows and 199 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.


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



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