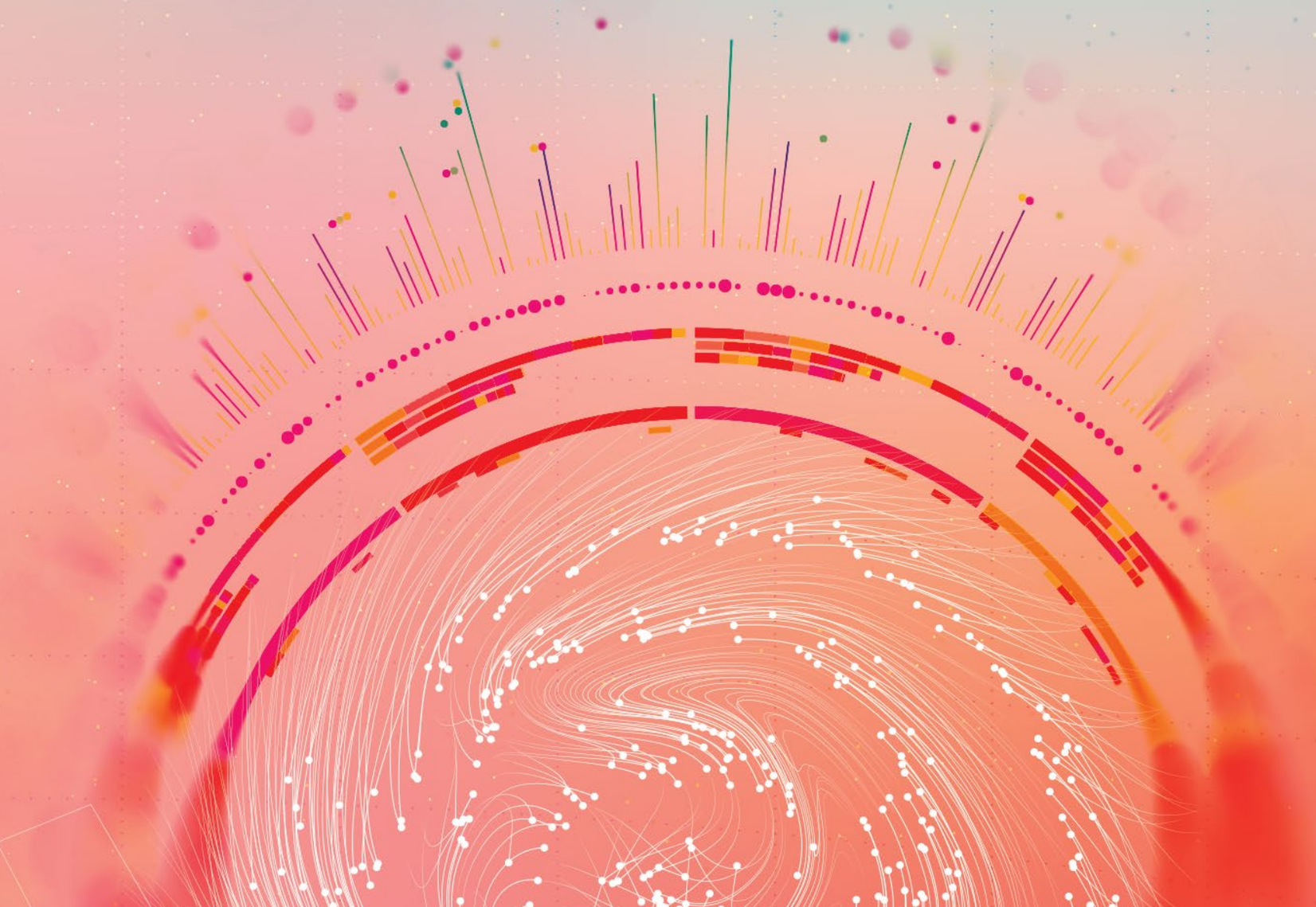
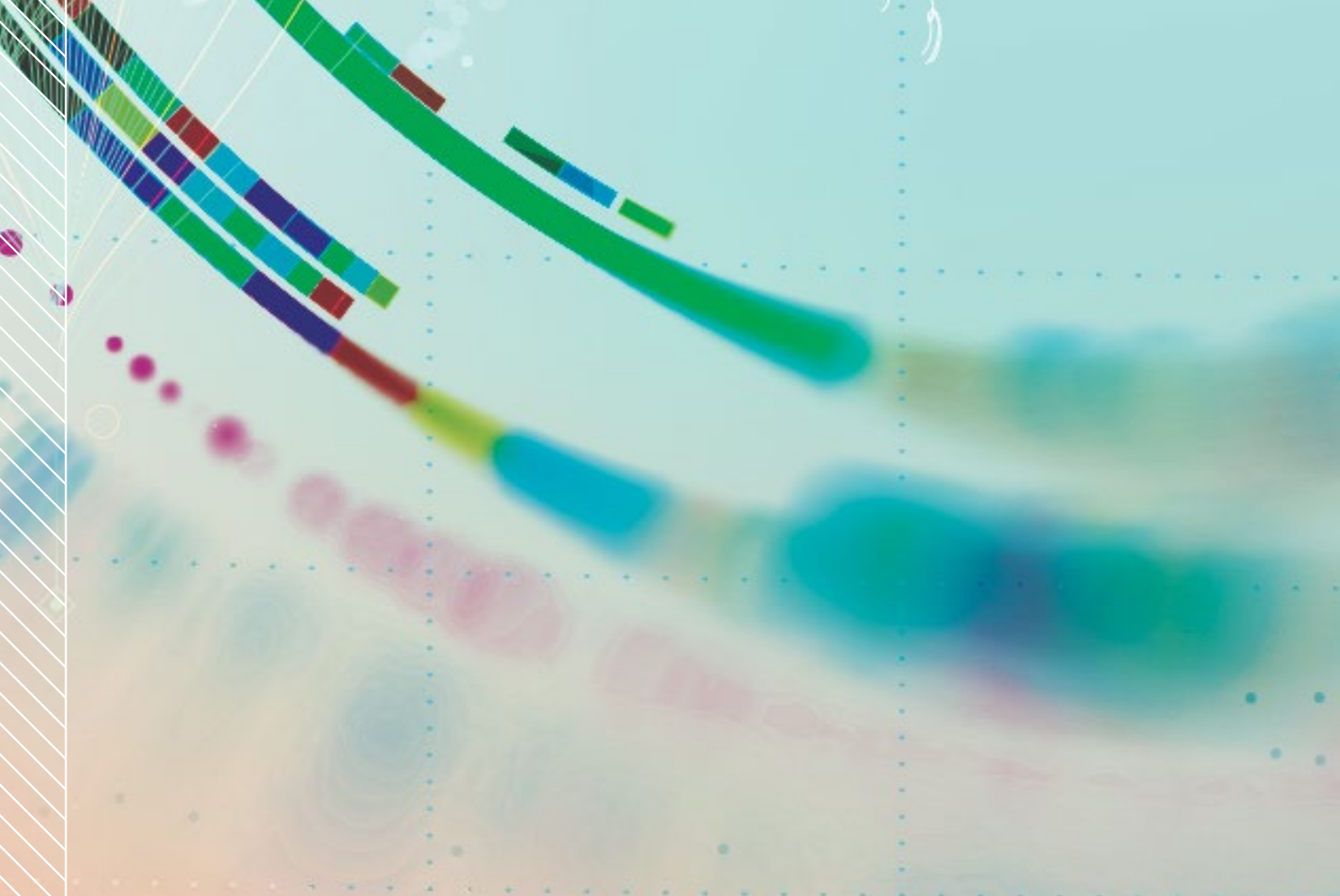
Translating Science
Into Survival

SCIENTIFIC REPORT

2021





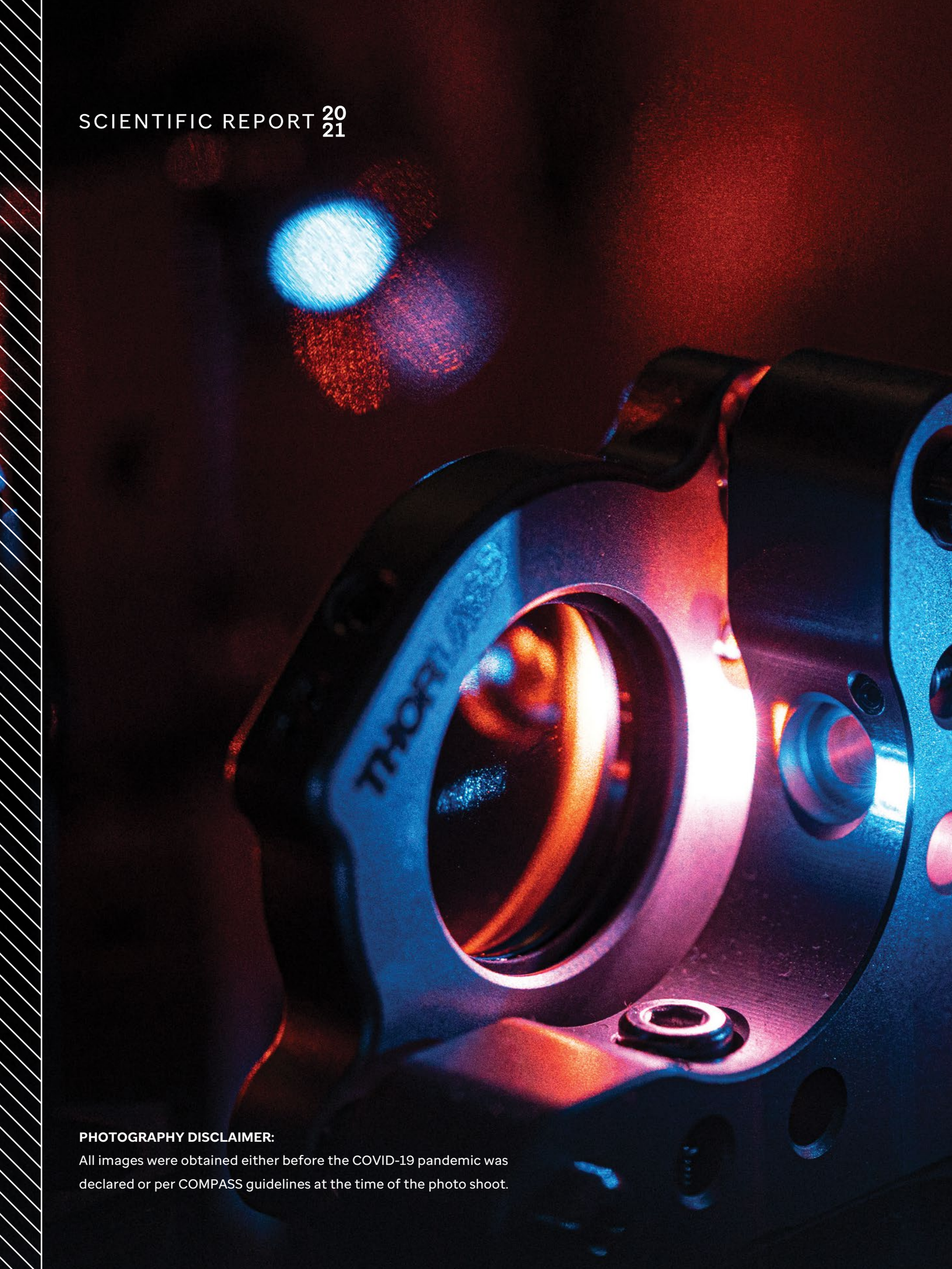
BEHIND THE COVER

The image on the cover is an artist's rendition of the high-tech graphics used to depict the relations and interactions of individual genes or proteins in a network. This graphic exemplifies some of the data generated by St. Jude investigators working on the Pediatric Cancer Genome Project (PCGP) for the past decade. The institutional growth resulting from the PCGP has included a new academic department and clinical divisions, computational tools, technologies, laboratories, and transformative research initiatives and collaborations.

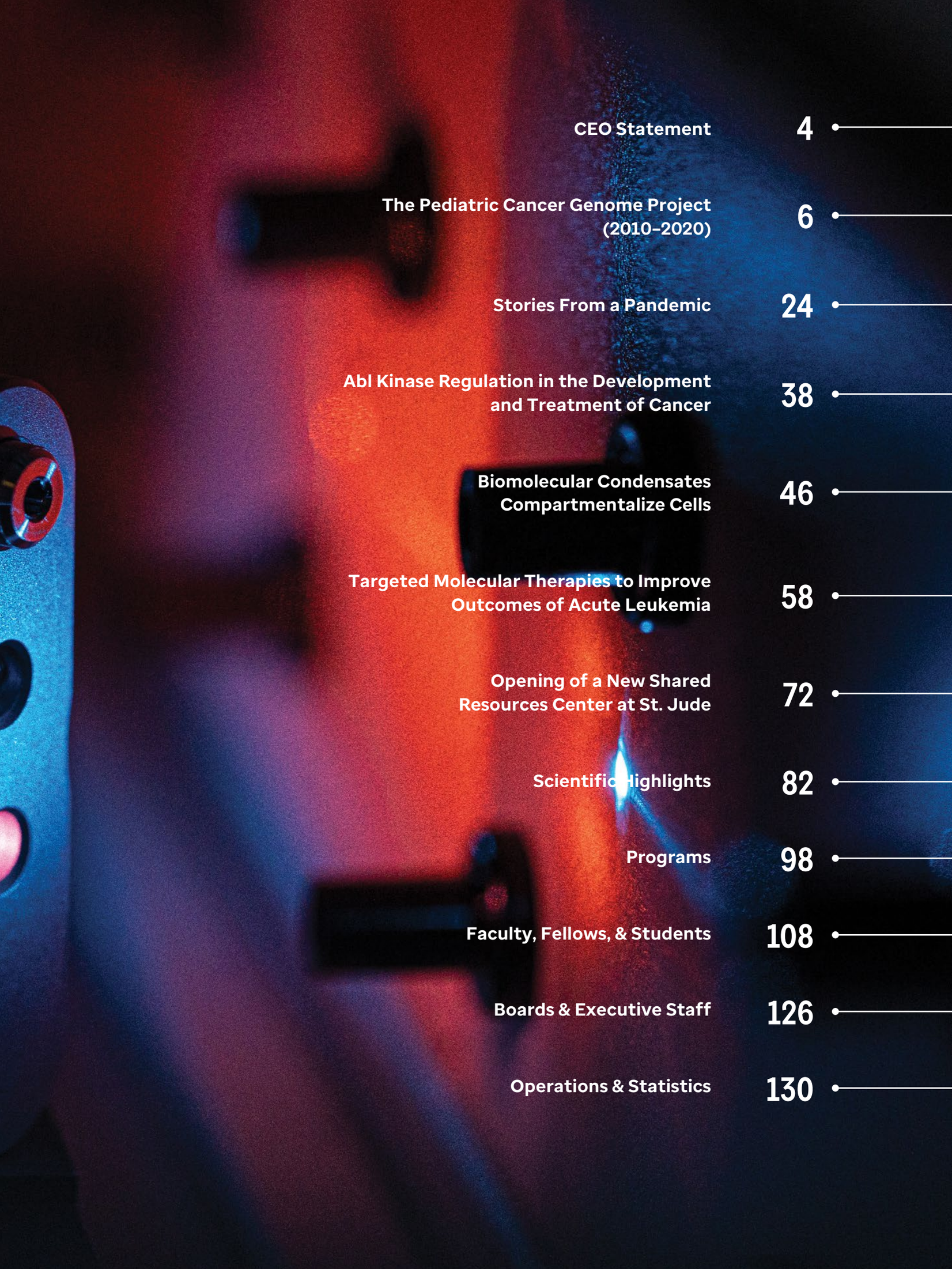
ST. JUDE RESEARCHERS, BACKED BY EXTRAORDINARY RESOURCES AND SUPPORT TEAMS, ARE FOCUSED ON MAKING BIG DISCOVERIES.

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

SCIENTIFIC REPORT 2021



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



Nearly 60 years ago, St. Jude Children's Research Hospital was founded on the belief that no child should die in the dawn of life.

At that time, a diagnosis of pediatric cancer or other childhood catastrophic disease was devastating. Today, children with life-threatening illnesses are surviving longer and with fewer complications. These gains were hard won by researchers who believed that children deserve hope for the future. Our work to deliver on this promise continues. This Scientific Report provides a glimpse into the research and treatment advances St. Jude faculty and staff made during the past year alone.

The first feature outlines the legacy of the Pediatric Cancer Genome Project, an unprecedented effort to understand the genetic landscape of childhood cancer. This project, which was launched in 2010 by St. Jude and Washington University (St. Louis, MO) researchers, uncovered why certain brain tumors, high-risk leukemias, and solid tumors arise, spread, and resist treatment. The data gleaned from this project ushered in a decade of transformative research that continues to spur the development of new computational tools, research programs, clinical trials, and initiatives.

The COVID-19 pandemic affected virtually every aspect of St. Jude operations. In the second feature story, we share personal stories about conducting science during the pandemic and how infectious diseases researchers are gaining knowledge about the SARS-CoV-2 virus and its effects on healthy children and those with catastrophic diseases.

Protein kinases have a central role in cellular physiology; their activity is generally regulated by a conformational switch between active and inactive protein states. In cancer, mutations in kinases can increase kinase activity, thereby promoting tumor cell growth, proliferation, survival, and migration. In the third narrative, we chronicle how St. Jude structural biologists are using the most advanced technologies available to study the structures and dynamics of protein kinases to identify more effective cancer-directed therapeutics.

Liquid–liquid phase separation (LLPS) compartmentalizes cells into two coexisting liquid phases—a dilute phase and a dense phase. During LLPS, biomolecules assemble into large networks, which then condense into liquid-like droplets called biomolecular condensates (or membrane-less organelles). LLPS functions in many fundamental biological processes, and dysregulation of this process can cause neurodegenerative diseases and some cancers. The fourth feature describes how St. Jude molecular biologists and structural biologists are changing the way scientists view cellular organization, with the goal of discovering new therapeutic opportunities.

The toxicity of many classic chemotherapy agents is caused by their deleterious effects on healthy cells, which can be avoided by using targeted molecular therapies. Therefore, such therapeutics represent a major advance in the treatment of cancer. The fifth feature highlights the work of St. Jude researchers to develop molecularly targeted therapies to advance the treatment of acute leukemias. These new approaches hold promise for decreasing treatment-related toxicities, improving the likelihood of survival, and enhancing long-term quality of life for survivors.

Last year, St. Jude completed construction of a new 30,000-ft^2 Shared Resources Center, which directly supports fundamental science, translational research, and preclinical trials. The Center brings together staff scientists and technologists with expertise in different fields and was designed to promote synergy and coordination among the various core laboratories. The final article describes how this place of interaction is leading to the exchange of ideas, improving best practices, and more effectively supporting the St. Jude mission.

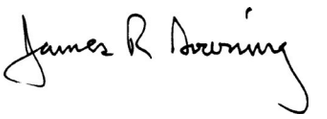
Beyond the work showcased in this Report, the past year was marked with opportunity and growth. St. Jude broke ground on a new six-story housing facility for patients and their families, neared completion of the 625,000-ft^2 Advanced Research Center, and opened an on-site clinic and pharmacy for employees. We also began hiring leaders for our newest research endeavor—understanding and treating pediatric neurological diseases. Lastly, St. Jude Global joined more than 85 institutions across 50-plus countries in an alliance focused on raising the international childhood survival rate.

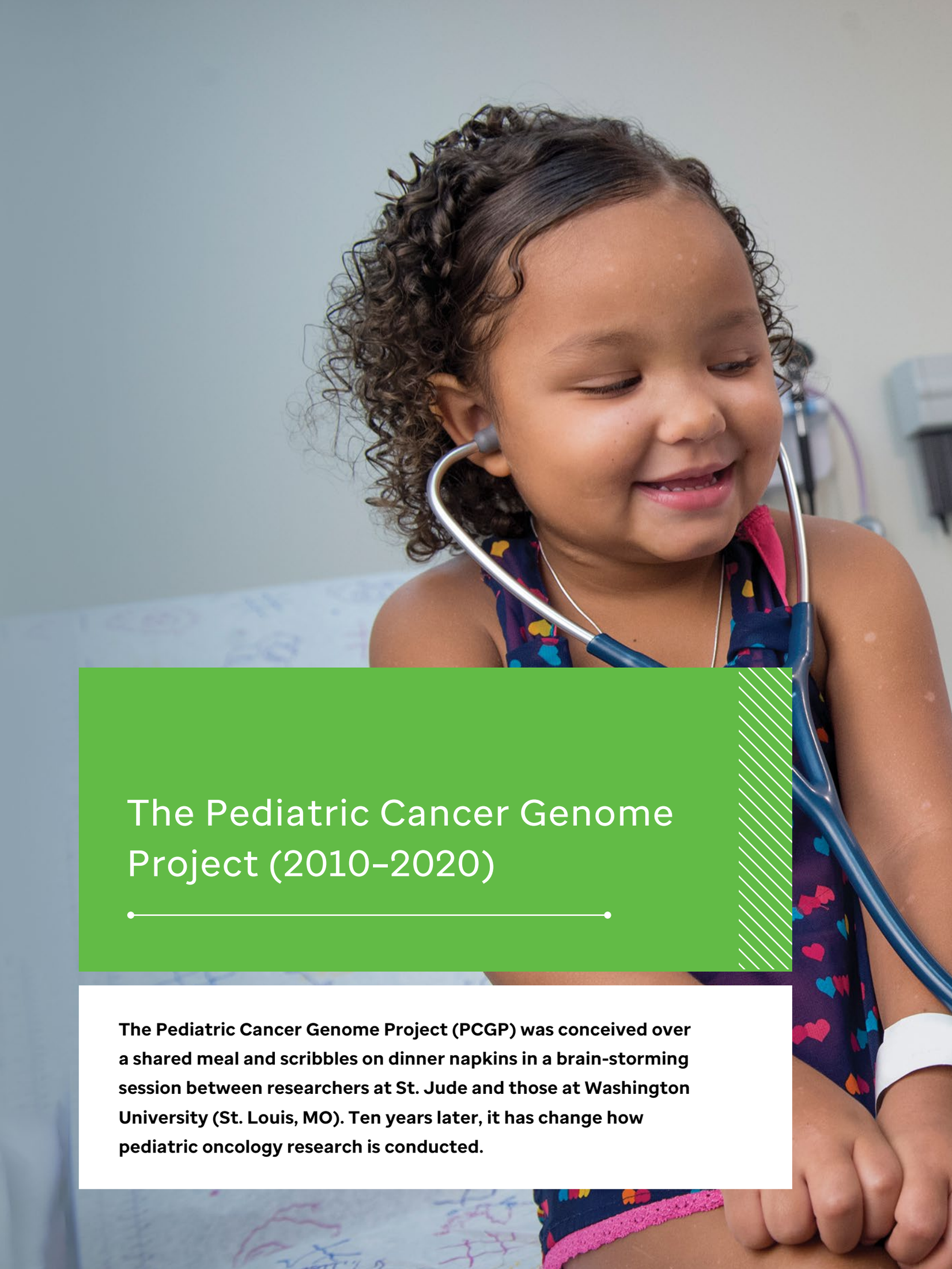
It has been more than half a century since St. Jude opened its doors to give children the chance of a brighter future. Through our work today and plans for tomorrow, we are committed to keeping this dream alive in communities near and far.

James R. Downing, MD

President and Chief Executive Officer

St. Jude Children's Research Hospital





The Pediatric Cancer Genome Project (2010-2020)

The Pediatric Cancer Genome Project (PCGP) was conceived over a shared meal and scribbles on dinner napkins in a brain-storming session between researchers at St. Jude and those at Washington University (St. Louis, MO). Ten years later, it has change how pediatric oncology research is conducted.

Kim E. Nichols, MD

The year 2020 came and went, with the COVID-19 pandemic silencing any celebration for the anniversary of the PCGP—no fanfare or shared meal to reflect on all that has been accomplished over the past decade and all that has been born out of that first shared meal. Here we celebrate the team of scientists who led this project; provide a sampling of the major discoveries resulting from those efforts; and speak to the new tools, resources, technologies, and initiatives at St. Jude produced through the PCGP.

Historic Perspective

As recently as a decade ago, the genetic aberrations that cause cancer, oncogenic drivers, remained elusive, especially in children. Genomic sequencing projects that were underway focused on adult cancers and not childhood diseases, and the lack of efforts in pediatric cancer did not go unnoticed by St. Jude researchers. At the same time, major advances were being made in sequencing technologies that resulted in lower costs and faster results. Hypothetical studies to sequence the whole genomes of cancer cells were formulated into formal research proposals, and the PCGP became a reality.

In 2010, St. Jude launched the 3-year collaboration with Washington University to uncover why childhood cancer arises, spreads, and resists treatment. Drs. Timothy Ley (Washington University), Richard Wilson, and Elaine Mardis (then Co-Directors of the McDonnell Genome Institute at Washington University) offered their expertise in high-speed, large-scale genomic sequencing. Under the direction of James R. Downing, MD (then Scientific Director), St. Jude would provide research and treatment experience and access to one of the world's largest collections of childhood cancer tissue samples.

By 2013, the PCGP had obtained whole-genome sequencing data of matched healthy cells and cancer cells from 800 pediatric patients whose illnesses included 23 types of cancer and one neurodegenerative disease. The PCGP data led to numerous discoveries in brain tumors, high-risk leukemias, solid tumors, and amyotrophic lateral sclerosis (also known as Lou Gehrig's disease). Through these efforts, St. Jude researchers learned that about 10% of children who have cancer were born with genetic anomalies that increase their risk of the disease.

On the basis of the success of the first 3 years of the PCGP, St. Jude extended the project for another year. During the second phase of the PCGP, investigators further explored the genomic makeup of pediatric cancers and generated new computational tools to identify key oncogenic mutations that other methods had missed. By 2014, a new era of clinical genomics was initiated, and St. Jude moved toward performing comprehensive genomic testing for all eligible patients. The PCGP served as a catalyst for a decade of transformative research at St. Jude and around the world, identifying the genetic underpinnings for cancer formation, spread, and resistance to treatment, and as the impetus for establishing new institutional initiatives and capabilities.

James R. Downing, MD; Jinghui Zhang, PhD

A DECADE OF DISCOVERY

Over the past decade, every volume of this Report has included feature stories or scientific highlights describing work from the PCGP. Here we briefly note some of the discoveries considered most important by the leaders studying hematologic malignancies, solid tumors, brain tumors, and computational biology.

2011

Jinghui Zhang, PhD (Computational Biology), led the development of the data-mining tool CREST (clipping reveals structure), which maps somatic structural variations in cancer genomes with base-pair resolution. *Wang J et al, Nat Methods 8:652–4, 2011*

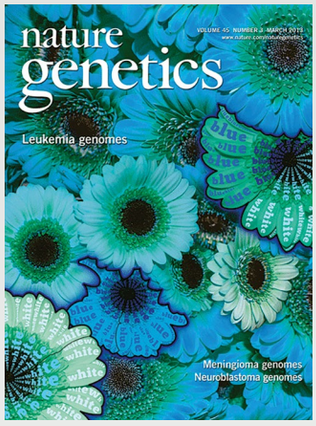
2012

Dr. Downing and Charles G. Mullighan, MBBS(Hons), MD (Pathology), and their colleagues reported the first genomic sequencing data from a pediatric cancer. They found unexpected genetic alterations in early T-cell precursor ALL, a high-risk form of the disease, that may improve diagnosis and treatment. *Zhang J et al, Nature 481:157–63, 2012*

Michael A. Dyer, PhD (Developmental Neurobiology), and his group used genomic and epigenetic analyses to elucidate the mechanisms of retinoblastoma development and identify a promising new treatment. *Zhang J et al, Nature 481:329–34, 2012*

Suzanne J. Baker, PhD (Developmental Neurobiology), led the first study to show the direct effect of epigenetic dysregulation in cancer. This work also identified histone mutations with distinct pathogenesis for diffuse pontine glioma (DIPG). *Wu G et al, Nat Genet 44:251–3, 2012*

Dr. Zhang and Richard J. Gilbertson, MD, PhD (Developmental Neurobiology), and their colleagues identified new recurrent mutations in medulloblastoma and illustrated the genomic landscape across subtypes of the disease. *Robison G et al, Nature 488:43–8, 2012*



2013

Dr. Mullighan's group found that hypodiploid ALL, a poorly understood disease subtype that includes multiple whole-chromosome losses, can be grouped into two main subtypes that have distinct mutations. This work also suggested a treatment strategy using drugs already in use to treat other cancers. *Holmfeldt L et al, Nat Genet 45:242–52, 2013*

David W. Ellison, MD, PhD (Pathology), led a comprehensive study that identified new mutations and potential therapeutic targets in low-grade gliomas, the most common pediatric brain tumor. *Zhang J et al, Nat Genet 45:602–12, 2013*

J. Paul Taylor, MD, PhD (Cell & Molecular Biology), and his laboratory defined the pathogenic mutations in prion-like domains of nuclear ribonucleoproteins in families with degenerative disorders affecting muscle, brain, motor neurons, or bone; one case involved familial amyotrophic lateral sclerosis. Their findings offer promise of advancing treatment of some common degenerative diseases. *Kim HJ et al, Nature 495:467–73, 2013*

2014

Drs. Zhang, Gilbertson, and Ellison and their colleagues identified novel *C11orf95–RELA* oncogenic fusions that are now used as a molecular classification for supratentorial ependymoma. *Parker M et al, Nature 506:451–5, 2014*

Dr. Baker and her group led an in-depth analysis of the genomic landscape of pediatric high-grade glioma. They identified *NTRK* fusions in infants with the disease and *ACVR1* mutations selectively in the youngest patients with DIPG. *Wu G et al, Nat Genet 46:444–50, 2014*

Dr. Mullighan and his colleagues demonstrated the genomic landscape of activating fusions and mutations in Ph-like ALL. This work resulted in major changes to ALL diagnostics and the development of new clinical trials. *Roberts KG et al, N Engl J Med 371:1005–15, 2014*

2015

Dr. Downing, Tanja A. Gruber, MD, PhD (Oncology, Pathology), and their team reported the most comprehensive analysis to date of ALL in infants. This highly aggressive form of leukemia has surprisingly few mutations, beyond the well-established *MLL* rearrangement. Therefore, targeting *MLL* may improve survival. *Andersson AK et al, Nat Genet 47:330–7, 2015*

A large-scale landmark study, led by Drs. Downing and Zhang, found that nearly one in 10 pediatric patients with cancer was born with an increased risk of the disease. The team also discovered unexpected links between pediatric cancers and adult cancers. *Zhang J et al, N Engl J Med 373:2336–46, 2015*

Alberto S. Pappo, MD (Oncology), and Armita Bahrami, MD (Pathology), reported the first genetic evidence that UV damage contributes to melanoma in children. This work underscores the importance of starting sun protection early. Also, some adolescents with melanoma harbor the same genetic alterations seen in adult melanoma; thus, they may respond to the same therapy. *Lu C et al, J Invest Dematol 135:816–23, 2015*

2016

In collaboration with the Children's Oncology Group, PCGP researchers reported that the deregulated expression of two genes, *DUX4* and *ERG*, leads to leukemogenesis of ALL, the most common childhood cancer. DUX4 and ERG control crucial genes in human blood cells; thus, this work may lead to new diagnostic approaches for ALL. *Zhang J et al, Nat Genet 48:1481–9, 2016*

PCGP investigators completed a detailed map of the genomic changes in a subtype of acute myeloid leukemia (AML) defined by rearrangements in the core-binding factor complex. This work identified new genetic changes that may cooperate with known oncogenes and highlights genes that may influence AML relapse. *Faber ZJ et al, Nat Genet 48:1551–6, 2016*

2017

Dr. Dyer led the development of a protocol to generate orthotopic patient-derived xenografts at diagnosis, recurrence, and autopsy to model recurrent childhood solid tumors. His team established 67 xenografts, representing 12 types of cancer. They performed genomic profiling of the tumors, including detailed clonal analysis, to determine whether the clonal population in the xenografts recapitulated the patients' tumors. *Stewart E et al, Nature 549:96–100, 2017*

2018

Drs. Downing, Zhang, and Ellison led the evaluation of a clinical test to detect somatic and germline mutations relevant to pediatric oncology. Their team performed three-platform sequencing (i.e., whole-genome, -exome, and -transcriptome) of tumors and healthy tissue from 78 pediatric patients with cancer. Their approach achieved 98% sensitivity; the then-current standard for precision oncology achieved only 78% sensitivity. *Rusch M et al, Nat Commun 9:3962, 2018*

2020

Dr. Dyer's group showed that amplification of the oncogene *MYCN* and inactivation of the tumor-suppressor gene *ATRX*, both of which are correlated with high-risk neuroblastoma, are mutually exclusive. Defects in the ATRX–histone complex and MYCN-mediated metabolic reprogramming cause replicative stress that leads to synthetic lethality. Therefore, synthetic lethality may be exploited to improve outcomes of high-risk neuroblastoma. *Zeineldin M et al, Nat Commun 11:913, 2020*

Dr. Mullighan's group analyzed the genomic landscape of relapsed childhood ALL to determine its genetic drivers. Evolutionary modeling and xenografting demonstrated that relapse-fated clones are present at diagnosis. Leukemias prone to repeated relapse exhibit hypermutation, resulting in heightened neoepitope burden and potential vulnerability to immunotherapy. This work provides a genomic framework for anticipating and preventing ALL relapse. *Waanders E et al, Blood Cancer Discov 1:96–111, 2020*

INSTITUTIONAL GROWTH DRIVEN BY THE PCGP

Paul Geeleher, PhD; Jinghui Zhang, PhD

Department of Computational Biology

For each pediatric patient included in the PCGP, genomics scientists at Washington University identified the sequences of 6 billion base pairs of DNA: 3 billion base pairs of normal genome data and 3 billion base pairs of cancer genome data. St. Jude quickly recognized the need to establish a Department of Computational Biology to facilitate the analysis of this unfathomable amount of new information being generated. Jinghui Zhang, PhD, a computational biologist who came to St. Jude to work on the PCGP, was appointed Chair. Over the past decade, her department has grown to include nine faculty members and nearly 100 staff.

Throughout the course of the PCGP, computational biologists at St. Jude created new data-mining tools to maximize discoveries. One early tool, CREST, outperformed all prior tools so well that it has been adopted by scientists worldwide. In 2015, two more novel computational tools were made freely available to the research community. The first, CONSERTING, was developed to identify a specific type of genetic mutation called a copy-number alteration. Many cancers involve copy number alterations, and CONSERTING identifies these aberrations with much higher accuracy and sensitivity than did previous tools. The second tool, ProteinPaint, is a web-based application that helps scientists visualize and explore cancer genome data. The ProteinPaint portal houses information on nearly 27,500 mutations from more than 1000 pediatric patients and includes 21 types of cancer.

Sabrin Albeituni, PhD; Kim E. Nichols, MD

Division of Cancer Predisposition

In 2014, St. Jude established the Division of Cancer Predisposition and appointed Kim E. Nichols, MD (Oncology), as the Director. The Division promotes cutting-edge clinical, translational, and basic research related to the genetic predisposition to childhood cancer. Germline mutations in cancer-susceptibility genes are associated with a substantial proportion of pediatric cancers. By further elucidating the heritable nature of pediatric cancers, researchers in the Division aim to improve the clinical care and overall outcomes for families with increased genetic risk of those diseases. Other research projects in the Division include identifying novel genetic causes of cancer and elucidating the factors that influence how parents and adolescents make decisions, communicate, and react to genetic testing for cancer risk.

The Cancer Predisposition Clinic, which is also led by Dr. Nichols, is staffed by certified genetic counselors, clinical research associates, and advanced care providers who identify patients with cancer-predisposing conditions and coordinate treatment (i.e., genetic counseling and testing) for those patients and, when appropriate, their parents and siblings. The staff also implement protocols for cancer surveillance and prevention.

PCGP-Motivated Clinical Trials

Insights gained from the PCGP studies have directly influenced many St. Jude clinical trials for children with cancer.

A *Clinical and Molecular Risk-Directed Therapy for Newly Diagnosed Medulloblastoma* (SJMB12) is an international Phase II clinical trial for pediatric patients with medulloblastoma that opened in 2013. Treatment is stratified based on not only clinical risk (low, standard, intermediate, or high), as determined by the amount of tumor remaining after surgical resection but also molecular subtype of disease (WNT, SHH, or non-WNT/non-SHH). Amar J. Gajjar, MD (Pediatric Medicine, Oncology), and Giles W. Robinson, MD (Oncology), are the co-principal investigators (PIs) of this trial; its National Clinical Trials (NCT) identifier is NCT01878617.

The *Genomes for Kids* (G4K) trial was initiated in 2015 as an observational protocol that anticipated enrolling 5000 patients over a 7-year period. Through the PCGP, investigators used next-generation sequencing approaches (e.g., whole-genome, whole-exome, and RNA sequencing) to determine how to classify tumors into pathologic and prognostic subtypes. These methods are further able to detect alterations in cellular pathways that may serve as novel therapeutic targets, guiding personalized treatments and/or preventive measures. As a result of the success of the initial phase of the G4K trial, clinical genomic sequencing of tumor and germline samples is now offered as part of standard care for pediatric oncology patients at St. Jude.

In 2018, the G4K trial was revised to include the storage and analysis of germline and tumor genome data, so that investigators can examine germline mutations in 150 cancer-predisposition genes and determine their influence on clinical presentation, tumor histology, tumor genomic findings, response to therapy, and long-term outcomes. These studies will enable more accurate genetic counseling and treatment strategies. Dr. Nichols is the PI of this trial (NCT02530658).

Total Therapy 17 for Newly Diagnosed Patients with Acute Leukemia and Lymphoma (TOT17) was opened in 2017. TOT17 is a Phase II/III clinical trial for pediatric patients with newly diagnosed ALL or acute lymphoblastic lymphoma (LLy). The overarching goal of the study is to use novel precision-medicine strategies based on inherited

Giles W. Robinson, MD

or acquired leukemia-specific genomic features and targeted treatment approaches to improve the cure rate and quality of life for children with ALL or LLy. TOT17 incorporates complementary, innovative objectives that address questions across risk groups and molecular subtypes of childhood ALL and LLy. Hiroto Inaba, MD, PhD (Oncology), is the PI of this trial (NCT03117751).

Study of GDC-0084 in Pediatric Patients with Newly Diagnosed Diffuse Intrinsic Pontine Glioma or Diffuse Midline Gliomas (SJP13K) opened in 2018. This Phase I clinical trial is a first-in-pediatrics study for patients with DIPG or diffuse midline glioma. The trial tests a new chemotherapeutic, GDC-0084, that targets a growth pathway overactive in most DIPGs and similar brain tumors. Unlike most other chemotherapies, GDC-0084 crosses the blood–brain barrier, thereby delivering its potent effects straight to malignant cells. This trial was informed, in part, by the finding that a single mutation in a gene that was not previously linked to cancer changes the expression of other genes to drive the development of DIPGs and similar brain tumors. Dr. Gajjar and Christopher L. Tinkle, MD, PhD (Radiation Oncology), are the co-PIs of this trial (NCT03696355).

The Childhood Solid Tumor Network

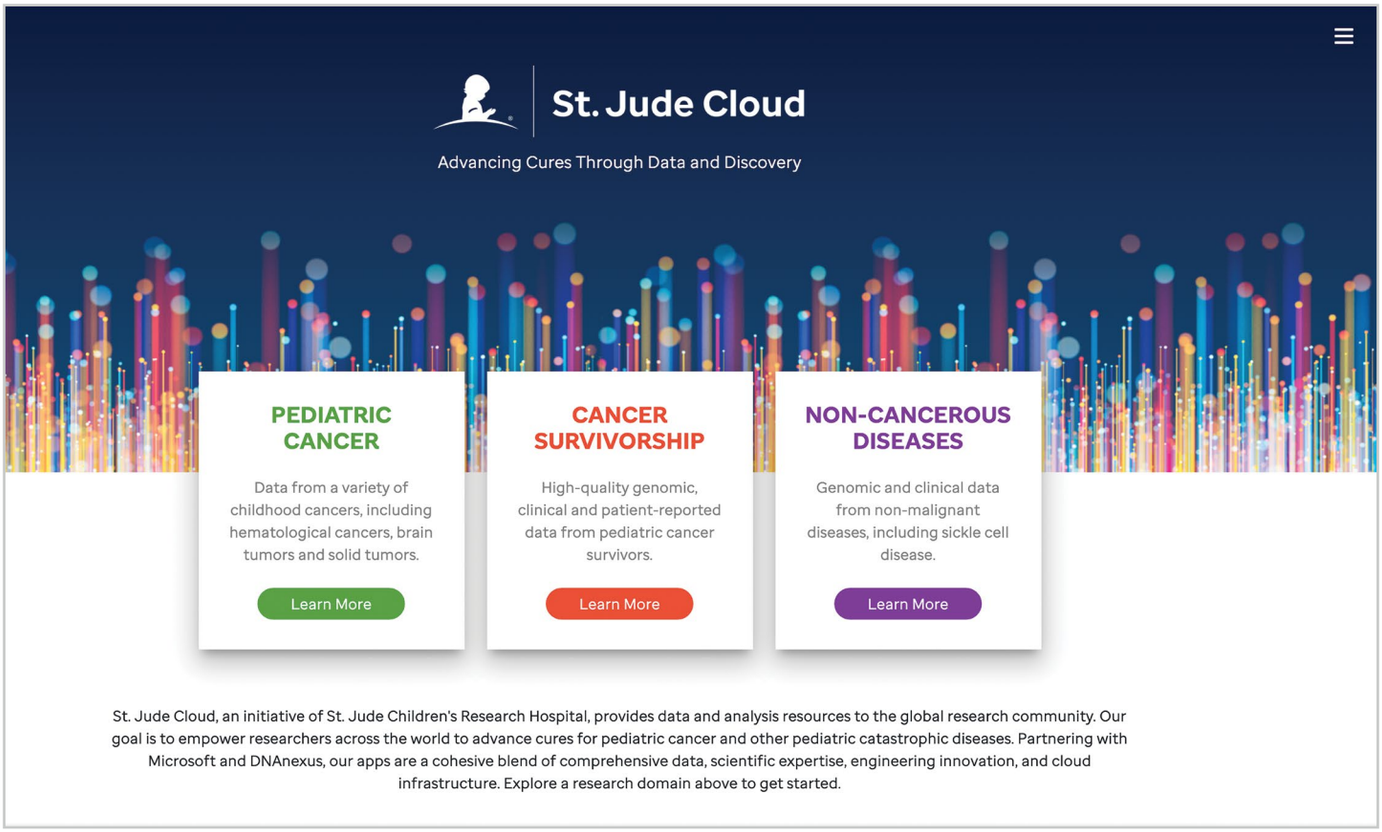
In collaboration with the Howard Hughes Medical Institute, St. Jude created the Childhood Solid Tumor Network (CSTN) in 2013 and released it to the research community in 2017. The CSTN is a data portal that includes preclinical solid tumor models (e.g., patient-derived xenografts) and detailed genomic and drug-sensitivity data on various solid tumors. This resource is freely available to researchers worldwide with no expectation of collaboration. The goal of the CSTN is to accelerate research and development of novel lifesaving therapies for children with solid tumors. The CSTN currently houses data on 170 patient-derived samples, representing 21 types of childhood solid tumor. Dr. Dyer led this initiative.

Elizabeth A. Stewart, MD; Michael A. Dyer, PhD

Charles G. Mullighan, MBBS(Hons), MD; Matthew Lear

Public Resource of Patient-Derived and Expanded Leukemias Database

Similar to the CSTN, the Public Resource of Patient-Derived and Expanded Leukemias (PROPEL) is a St. Jude repository for one of the world's largest collections of pediatric and adult leukemia xenografts. The portal houses samples of more than 20 subtypes of leukemia, including 22 matched samples obtained at diagnosis and disease relapse. The collection is continuously updated with recently engrafted samples, the associated genomic data, and other metadata (e.g., clinical information, pathology data, mouse models). PROPEL resources are freely available to researchers worldwide, with no obligation to collaborate. The goal of PROPEL is to advance fundamental research on leukemia biology and accelerate discoveries and cures for the disease. Dr. Mullighan leads this initiative.

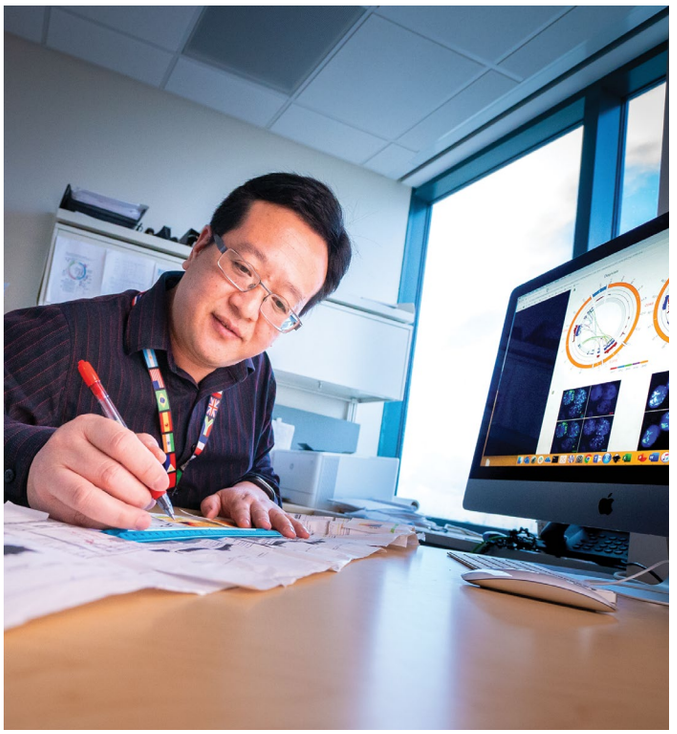


The St. Jude Cloud

To build upon the success of the PCGP, Dr. Zhang proposed creating an online data-sharing ecosystem for genomic data that would become the St. Jude Cloud.

In 2018, the St. Jude Cloud was launched to provide a platform for collaboration and access to the world's largest public repository of pediatric cancer genomics data. More than 1.2 petabytes of raw genomic data are available. The Cloud continues to expand as new genomic data are added regularly by the St. Jude Clinical Genomics Program. The platform offers whole-genome, -exome, and -transcriptome sequencing data from more than 10,000 pediatric patients with cancer. To accelerate cancer survivorship research, it also houses high-quality genomic, clinical, and patient-reported data from 7750 adult survivors of childhood cancer. The first non-cancer data set added to the platform is that from the Sickle Cell Genome Project, which includes data from more than 800 pediatric patients with sickle cell disease.

In 2020, established preclinical resources, i.e., the CSTN and PROPEL, were moved to the St. Jude Cloud. In addition, 37 orthotopic patient-derived xenograft models of various molecularly characterized pediatric brain tumors were uploaded. Necessary computational biology tools (e.g., CREST, CONCERTING, ProteinPaint) are available for analyzing data housed on the platform or data provided by the user. Interactive visualization applications enable users to explore more than 126,000 pediatric cancer–related gene mutations. The St. Jude Cloud initiative is supported by partnerships with DNAnexus® (Mountain View, CA) and Microsoft (Redmond, WA).



Gang Wu, PhD

Center for Applied Bioinformatics

The Center for Applied Bioinformatics (CAB) provides state-of-the-art bioinformatics support to St. Jude investigators. Under the leadership of Gang Wu, PhD (Pathology), the CAB staff provide customized bioinformatics analyses, consultations on experimental designs, and hands-on training and educational resources. They also develop and validate open-access computational methods and workflows, help departments and investigators optimize their data storage and computing resources, and maintain relevant reference data sets. The CAB is staffed by 18 bioinformatics scientists, engineers, and analysts working in five groups: Genetics, Epigenetics, Genomics, Transcriptomics, and Bioinformatics Development & Operations.

M. Madan Babu, PhD, FRSC

Center of Excellence for Data Driven Discovery

With the arrival of M. Madan Babu, PhD, FRSC (Structural Biology), the Center of Excellence for Data Driven Discovery was established in 2020. Dr. Babu is a pioneer in data science. He has developed state-of-the-art computational and machine learning–based approaches that interrogate large-scale, multidimensional data sets to address fundamental questions in biology and disease and to discover new biologic information. The diversity of data sets analyzed in the Center range from gene expression, protein structures, and chemical biology to higher-order biologic systems, cancer genomics, and clinical information. The challenge of such analyses is to develop computational approaches that derive actionable information from the data sets. The goal of the Center is to increase our understanding of the origins of disease and apply that knowledge to advance biotechnology, drug discovery, and personalized medicine.

Gregory T. Armstrong, MD, MSCE

The National Cancer Institute's Childhood Cancer Data Initiative

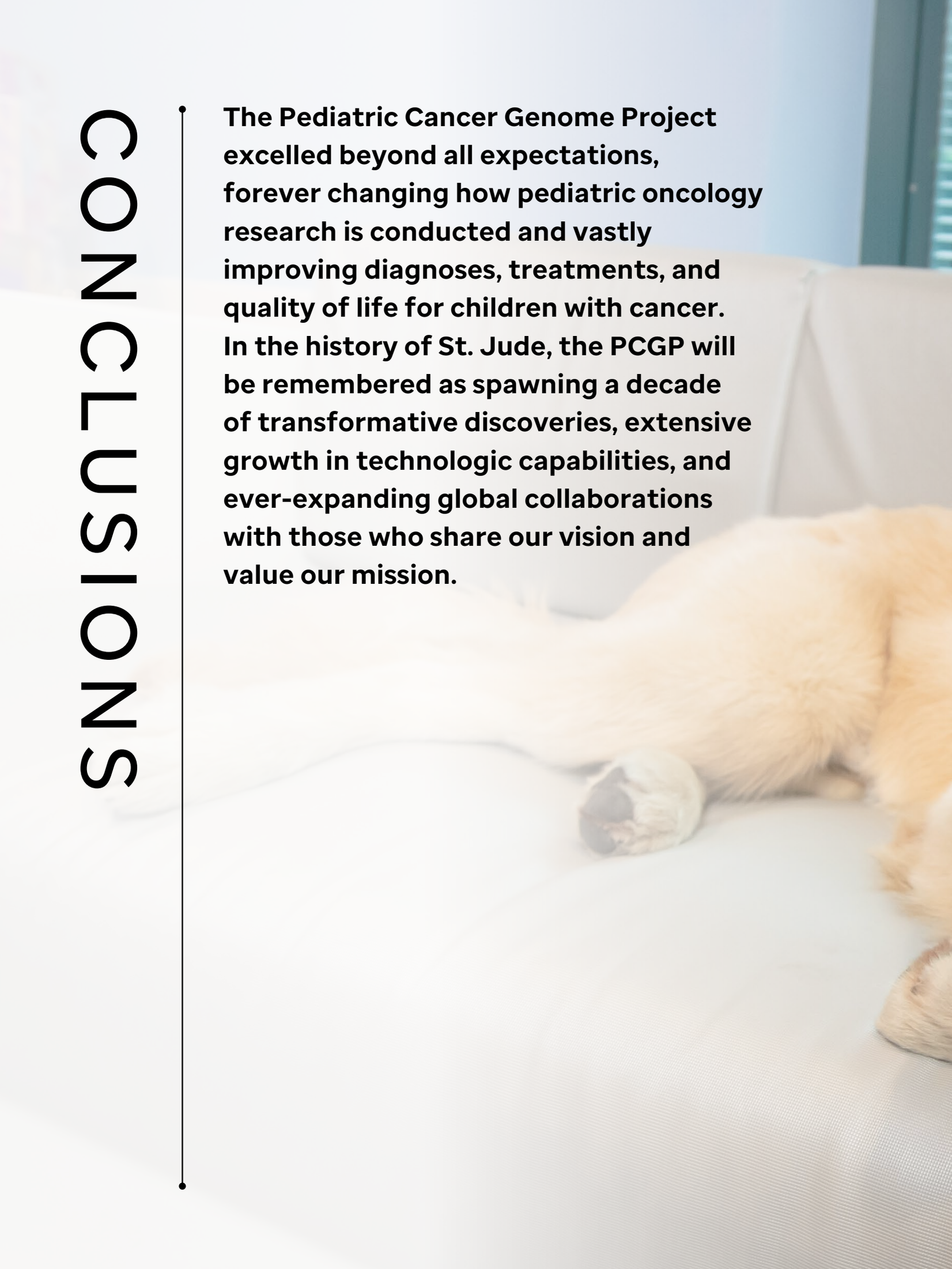
In 2019, the National Cancer Institute (NCI) introduced the Childhood Cancer Data Initiative (CCDI) to promote the efficient sharing of clinical care and research data among institutions to improve the outcomes of children with cancer and to better understand the biology of those diseases. Dr. Downing served as a member of the NCI Scientific Advisory Board's ad hoc working group assigned to guide the development and implementation of the CCDI.

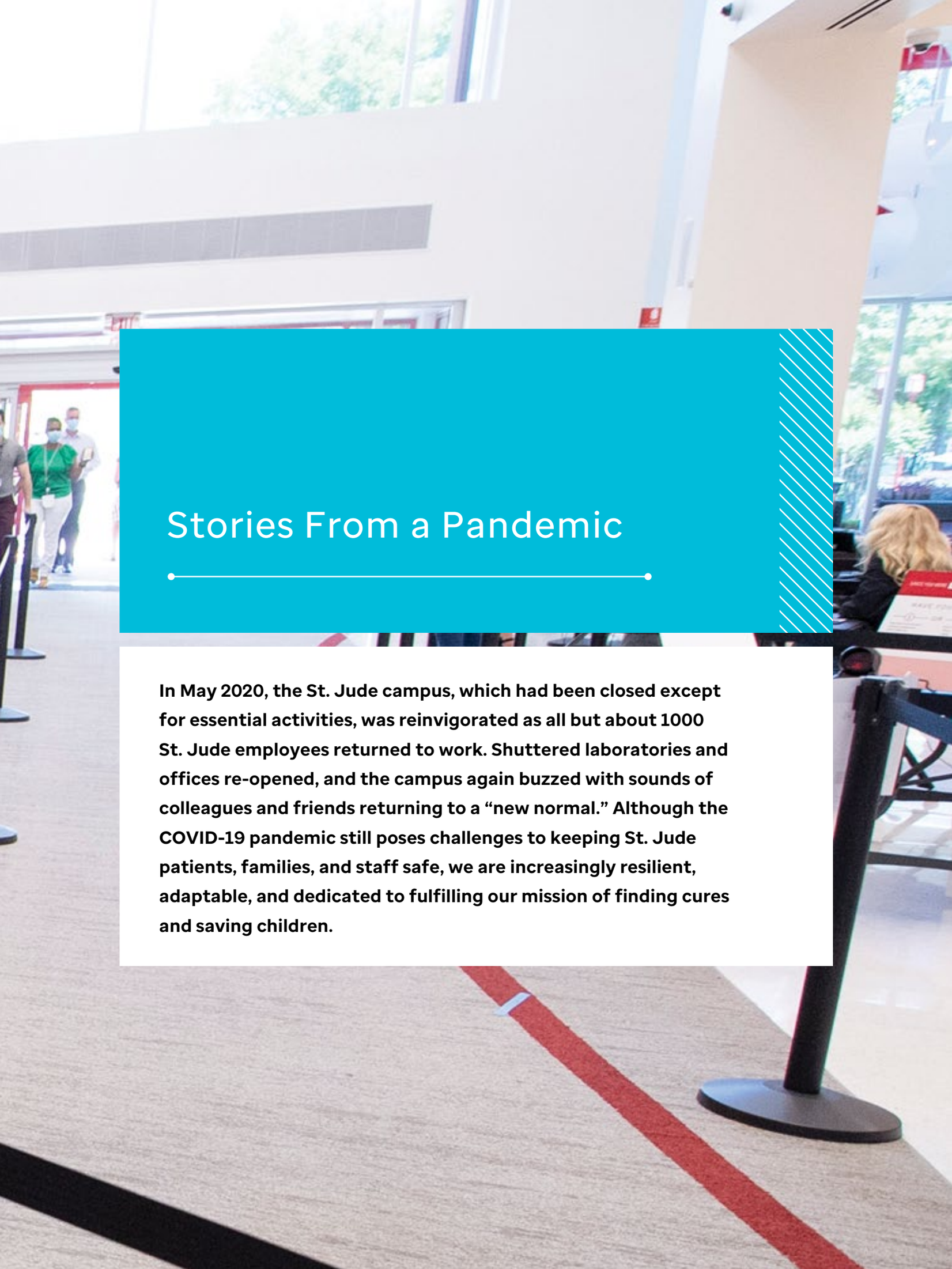
The working group recommended that pediatric oncology data be aggregated into six categories: (1) clinical treatments and outcomes data from clinical trials or electronic health records; (2) clinical molecular data and research sequencing data; (3) data on the availability and location of archived biospecimens (i.e., germline and tumor DNA); (4) longitudinal population data from patients and survivors of childhood cancers; (5) characteristics of cell lines, patient-derived xenografts, and genetically engineered mouse models of childhood cancers; and (6) any data generated in studies of those preclinical models.

The CCDI has three foundational goals: (1) Gather data from every child, adolescent, and young adult with pediatric cancer, regardless of where they receive care. (2) Create a national strategy of appropriate clinical and molecular characterization to speed diagnosis and inform treatment for all types of pediatric cancers. (3) Develop a platform and tools to compile clinical care and research data that will improve prevention, treatment, quality of life, and survivorship for pediatric patients with cancer. Dr. Zhang, Gregory T. Armstrong, MD, MSCE (Epidemiology & Cancer Control, Oncology), and Charles W.M. Roberts, MD, PhD (Oncology), are members of the CCDI Steering Committee and are leading the CCDI efforts at St. Jude.

CONCLUSIONS

The Pediatric Cancer Genome Project excelled beyond all expectations, forever changing how pediatric oncology research is conducted and vastly improving diagnoses, treatments, and quality of life for children with cancer. In the history of St. Jude, the PCGP will be remembered as spawning a decade of transformative discoveries, extensive growth in technologic capabilities, and ever-expanding global collaborations with those who share our vision and value our mission.





Stories From a Pandemic

In May 2020, the St. Jude campus, which had been closed except for essential activities, was reinvigorated as all but about 1000 St. Jude employees returned to work. Shuttered laboratories and offices re-opened, and the campus again buzzed with sounds of colleagues and friends returning to a "new normal." Although the COVID-19 pandemic still poses challenges to keeping St. Jude patients, families, and staff safe, we are increasingly resilient, adaptable, and dedicated to fulfilling our mission of finding cures and saving children.

The implementation of the COVID-19 Monitoring, Preparedness, Screening, and Surveillance (COMPASS) Program's safety guidelines; frequent COVID-19 testing; and an institutional vaccination program has enabled St. Jude researchers to continue to forge new directions in foundational, translational, and clinical research. Here we present personal stories about conducting science during a pandemic and how St. Jude is furthering the world's understanding of the novel SARS-CoV-2 virus, its disease trajectory, and effects of COVID-19 on healthy children and those with catastrophic diseases.

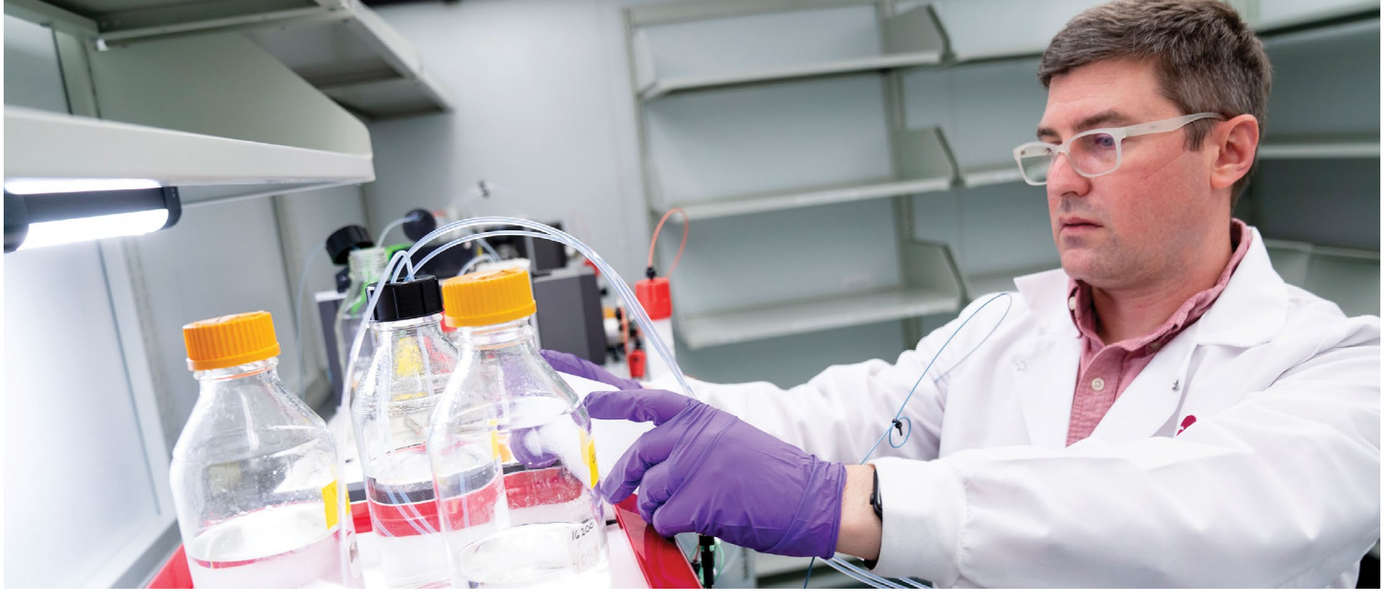
Jennifer Parris

Ensuring Research Progress and Personnel Safety

With nearly 150 staff, fellows, and students working in 14 faculty-led laboratories and seven core facilities, Developmental Neurobiology (DNB) is one of the largest academic departments at St. Jude. During the months of remote working, a few essential staff members from each laboratory and one person from each core were on campus to conduct essential long-term experiments, manage animal colonies, and maintain equipment that could not be shut down. Department Chair Michael A. Dyer, PhD, ensured that everyone working remotely had access to a computer, and the department used multiple platforms (WhatsApp, Webex, Teams) and an electronic DNB newsletter to maintain communication. This enabled employees to stay informed of the pandemic situation, combat challenges in experiments, and provide and receive emotional support.

Working with COMPASS Program leaders, Dr. Dyer and his team developed a strategy to bring DNB staff back to campus in a safe manner. Their plan included five phases, staggered every 2 to 3 weeks. Jennifer Parris, the Director of Research Operations for the DNB department, centralized the delivery of all supplies and equipment to her office and ensured that someone was onsite to receive perishable and/or hazardous items and store them appropriately. As the pandemic persisted, basic laboratory supplies became scarce, as they were being used worldwide for COVID-19 testing. Therefore, Ms. Parris coordinated efforts to share supplies among DNB groups and with other departments, while staff in Materials Management worked to find new sources of much-needed reagents and supplies.

Ms. Parris also organized shift work schedules for DNB staff. Physical-distancing guidelines reduced the maximum capacity of laboratory modules to three people; therefore, the department implemented two or three 4-hour shifts per day, depending on the number of people working in a laboratory or core. To minimize the risk of infection, each group wiped down



Ben Leslie, PhD

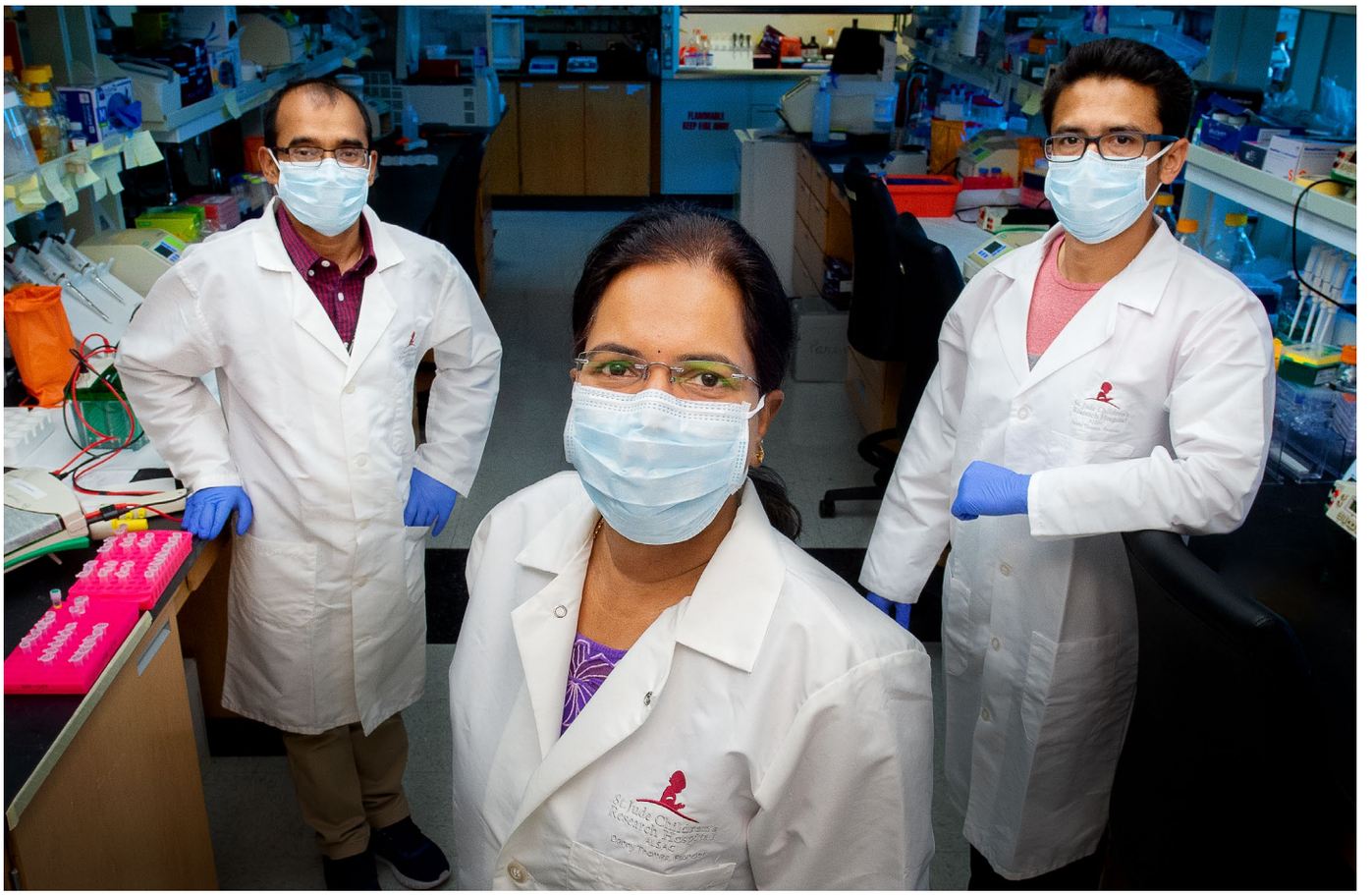
their work areas at the beginning and end of each shift. Staff members had months to adapt to performing data analysis remotely, so they were able to spend precious time in the laboratory more efficiently. Break rooms were closed, and common-use rooms were monitored via erasable sign-in sheets. These sheets facilitated contact tracing and prompt deep cleaning if a staff member received a COVID-19+ test result after using that room.

Establishing a New Research Laboratory During a Global Lockdown

Uprooting a laboratory and moving equipment, staff members, and their families across the Atlantic Ocean would be a monumental effort under normal circumstances; doing so when the entire world is locked-down due to a pandemic was nothing short of miraculous. M. Madan Babu, PhD, FRSC, FMedSci (Structural Biology), the Director of the Center of Excellence for Data Driven Discovery, faced this challenge last year as he prepared to leave the MRC Laboratory of Molecular Biology (Cambridge, U.K.) and assume a new faculty position at St. Jude. Ben Leslie, PhD (Structural Biology), the newly hired Director of Laboratory Operations for Dr. Babu's group, had vast experience moving staff and renovating and setting up multiple laboratories in new spaces. In September 2020, he arrived at St. Jude and began those efforts, while Dr. Babu and his staff remained in the U.K.

Given pandemic-related logistical delays at St. Jude, Dr. Leslie and two postdoctoral fellows, Asaf Elazar, PhD, and Manbir Sandu, PhD (both of Structural Biology), moved into temporary space in the Chili's Care Center. Although Dr. Babu's laboratory is mostly focused on computational studies, his staff also operates a wet lab to validate data-driven hypotheses in cellular assays and produce proteins for structural studies. With the invaluable help of Elisabetta Bini, PhD, the Director of Research Operations for the Department of Structural Biology, and Angie Williams, executive assistant to Dr Babu, Dr. Leslie converted empty lab modules into a fully functioning molecular biology wet laboratory. He predicted the needs of staff not yet hired or still in the U.K. due to the pandemic and worked with Information Sciences to provision workstations and mail them to staff in the U.K. Because of supply chain issues brought on by the pandemic, Dr. Leslie often had to weigh product availability against price and brand preferences to get the lab up and running as quickly as possible.

In November 2020, most of the computational staff arrived in Memphis but continued to work remotely. Dr. Babu and his remaining staff members arrived in April 2021. Dr. Babu's desire to build a sense of community culminated in the group's first in-person, physically distanced laboratory meeting in May 2021. His laboratory has continuously accelerated its discoveries in G-protein–coupled receptor signaling, regulation, and pharmacology; the biology of intrinsically disordered proteins; computational biology; and structural biology.



Raghvendra Mall; Thirumala-Devi Kanneganti, PhD; Rajendra Karki, PhD

COVID-19–Directed Research at St. Jude

Investigators in the Infectious Diseases, Immunology, and Structural Biology departments are conducting foundational research aimed at expanding knowledge of the novel SARS-CoV-2 virus, the disease it causes, optimal infection prevention strategies, and effective treatments for those infected. COVID-19 is characterized by an excessive production of proinflammatory cytokines and acute damage to the lungs that is associated with severe morbidity and mortality. Thirumala-Devi Kanneganti, PhD (Immunology), and her colleagues recently reported in the journal *Cell* that although multiple inflammatory cytokines are produced during SARS-CoV-2 infection, only two, tumor necrosis factor-α (TNF-α) and interferon-gamma (IFN-γ), are central to the disease's pathogenesis.

Synergism between TNF-α and IFN-γ drives the cytokine storm and PANoptosis, a form of cell death associated with COVID-19. Dr. Kanneganti's team found that TNF-α and IFN-γ cause a lethal cytokine shock in mice that replicates the tissue damage and inflammation seen in patients with severe COVID-19. Furthermore, treating the infected mice with neutralizing antibodies against the two cytokines protected them from cytokine shock and death. The researchers concluded that blocking the cytokine-mediated PANoptosis-signaling pathway may benefit patients with COVID-19.

Paul G. Thomas, PhD (Immunology), Stacey L. Schultz-Cherry, PhD, and Richard J. Webby, PhD (both of Infectious Diseases), are experts on various aspects of influenza virus infection, surveillance, and treatment; however, since the pandemic, these researchers and members of their laboratories have redirected efforts to conduct similar essential studies in SARS-related diseases. Dr. Thomas collaborated with Joshua Wolf, MBBS, PhD (Infectious Diseases), to conduct the SJTRC study, a 1-year prospective trial examining COVID-19–related host factors affecting the disease course and immune responses to infection. Dr. Thomas is also conducting multiple fundamental and collaborative clinical studies to further our understanding of the immune response to SARS-CoV-2 infection. Dr. Schultz-Cherry's group has several ongoing COVID-19–directed projects, including better understanding the natural history and transmissibility of SARS-CoV-2. Her laboratory is also examining the impact of obesity and other metabolic syndromes, major risk factors for COVID-19–associated morbidity, on the severity of SARS-CoV-2 infection by using unique model systems and samples from the SJTRC clinical study.

Dr. Webby's team is assessing antibody responses to SARS-CoV-2 infection to improve the safety and effectiveness of vaccines developed for the pandemic. In *Vaccines*, they reported highly variable antibody responses across a panel of 37 convalescent COVID-19 human serum samples. The magnitude of differences appeared to be independent of antibody levels to seasonal human coronaviruses. Analysis of serum samples from cats and dogs revealed that antibodies generated in these companion animals also showed cross-reactivity to endemic viruses. The researchers demonstrated the substantial interindividual variation in antibody responses generated in response to SARS-CoV-2 infection in humans and animals.

Scott C. Blanchard, PhD (Structural Biology, Chemical Biology & Therapeutics), and his colleagues at Yale University (New Haven, CT), reported in *Cell Host & Microbe* their structural analysis of the spike proteins on the SARS-CoV-2 virus. Spike proteins disrupt cell membranes, thus enabling the virus to enter and infect the cell. The researchers used single-molecule fluorescence energy transfer (smFRET) imaging to investigate the structure of SARS-CoV-2 spikes and determine the best approach to prevent the virus from entering host cells.

Their smFRET analysis revealed that SARS-CoV-2 spikes adopt four different conformational states, depending on whether they are activated by host receptor or attacked by host antibodies. SARS-CoV-2 spike proteins contain three receptor-binding domains, and the orientation of those domains determines the conformational state. This work sheds light on how to design small molecules or immunogens to stabilize the virus in its inactive ground state, thereby preventing its entry into host cells.

Richard J. Webby, PhD

Pandemic-Associated Changes May Improve Clinical Trials Operations

Childhood catastrophic diseases did not pause during the COVID-19 pandemic, though enrollment into St. Jude therapeutic clinical trials dramatically decreased during its early days, when stay-at-home orders were in place. Elizabeth Fox, MD, MS, began her new position as Senior Vice President of Clinical Trials Research a few months before the pandemic. Little did she know the challenges she would face as the SARS-CoV-2 virus affected medical care and clinical research and her staff members were forced to work remotely.

Clinical investigators critically assessed the number of campus visits included in their protocols and decreased them to the safest minimum. Through virtual research visits, clinical trials staff reached out to study participants and their families as needed. Dr. Fox believes that virtual research visits have been crucial to conducting clinical trials during the pandemic, and the benefits of this approach continue to be identified. In monthly meetings with various research groups, Dr. Fox has found that trials in Psychology, Epidemiology & Cancer Control, Symptom Management, and Quality of Life have progressed and are meeting a key objective—to support patients and their families—via virtual research visits.

Deciding whether to re-open a clinical trial required consideration of whether the potential benefits of the research to the patient outweighed its risks. For healthy adult survivors of childhood cancer enrolled in the SJLIFE study, traveling to St. Jude for annual evaluations during the pandemic would have increased their risk of contracting the virus and spreading it on campus. However, visits via the virtual research visit platform enabled staff to continue to meet with research participants. For some therapeutic protocols, participants received treatments at collaborative sites or St. Jude Affiliate clinics closer to their homes.

The biggest issue with bringing study participants back to campus has been physical distancing and managing patient schedules and staff capacity in the clinics. Clinic leaders, including physicians, nurses, and administrators, jointly plan clinic schedules 2 to 3 weeks in advance and then meet to negotiate and allocate clinical space to individual studies. This work is overseen by Clinical Director Ellis J. Neufeld, MD, PhD, the clinical operations triads, and the COMPASS team and has ensured optimal use of clinic space.

For Dr. Fox's staff, working remotely has been a successful experience. The Clinical Research Associates in the Comprehensive Cancer Center increased their productivity and improved their timelines for data entry. Research Patient Advocates flourished using virtual research visits. Before the pandemic, those staff members spent a lot of time tracking down patients and squeezing in meetings with families between clinic visits. Now, they schedule a virtual meeting or phone call at the family's convenience. Using this approach, the Advocates have increased the percentage of families they talk to at the time of consent and are spending more time with each family, explaining what it means to participate in a clinical trial. However, challenges have remained, including remote monitoring of activities and clinical trial data at collaborating sites. Setting up access to other sites' electronic systems and finalizing contracts to continue remote monitoring of clinical trials was an arduous task. Virtual site visits to activate new studies also take longer to complete than in-person visits.

Working remotely during the pandemic has helped clinical investigators better use electronic systems that are vital for tracking patient data and increasing study efficiency. The Clinical Research Informatics Services Program (CRiSP), led by Jason Morrison, JD, PhD (Cancer Center Administration), the Director of Clinical Research Informatics, has implemented and remotely trained investigators and study teams on new electronic clinical research systems. One project that was initiated by the

Elizabeth Fox, MD, MS

Clinical Trials Administration before the pandemic was to replace a paper-based process with a new electronic system for tracking regulatory documents and sponsor obligations for St Jude–initiated trials. This project was completed during the pandemic, ahead of schedule and under budget. In addition, the team initiated a new clinical trials management system for participant tracking and trial management. This system will go live throughout St. Jude and our collaborating sites on August 31, 2021.

The COVID-19 pandemic forced St Jude to suspend enrollment in nontherapeutic and noninterventional clinical trials. Therapeutic clinical trial enrollment decreased in April 2020 but quickly rebounded, as study teams and St. Jude clinical teams worked together to prioritize and provide innovative therapies. By July 21, 2021, restrictions on nontherapeutic and noninterventional trials were removed, and investigators and clinical operations were relied on to assess COVID-19 guidelines and clinical capacity for research visits. Clinical investigators carefully reviewed their protocols to determine the impact of protocol changes implemented due to the pandemic (e.g., fewer campus visits) on their research and ability to complete their trials. As a result, they are making some changes permanent to decrease the burden on study participants and their families.

Nehali Patel, MD; Aditya H. Gaur, MD, MBBS; Patricia M. Flynn, MD; Diego R. Hijano, MD, MSc

Infectious Diseases Clinicians Participate in COVID-19 Vaccine Trials

St. Jude belongs to the COVID-19 Prevention Network (COVPN) of the National Institute of Allergy and Infectious Diseases (NIAID). As part of Operation Warp Speed, the COVPN is conducting vaccine and monoclonal antibody trials. Under the leadership of Aditya H. Gaur, MD, MBBS, and Patricia M. Flynn, MD (both of Infectious Diseases), the Infectious Diseases Clinical Research Operations Team at St. Jude participated in COVPN's international double-blind, placebo-controlled Phase III trial ENSEMBLE (NCT04505722) to assess the safety and efficacy of the Johnson & Johnson investigational COVID-19 vaccine (Ad26.COV2.S). The study enrolled 43,783 adults (aged 18 years or older) in eight countries. Drs. Gaur and Flynn and a team of 75 colleagues from many departments at St. Jude and the University of Tennessee recruited 283 participants in Memphis in 6 weeks. Those enrolled were diverse: 40% were minorities, nearly 50% were older than 60 years, and 50% were female. With the support of the Department of Defense, the trial site was set up just outside the St. Jude campus. While the study participants are being followed for 2 years, early findings led to the U.S. Food and Drug Administration's emergency use authorization approval and the roll-out of this single-dose COVID-19 vaccine worldwide.

The Infectious Diseases Clinical Research Operations Team is now focused on clinical trials of investigational COVID-19 vaccines for pediatric patients. Nehali Patel, MD (Infectious Diseases), is leading the pediatric Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) trial in Memphis. This placebo-controlled, Phase II/III study (NCT04816643) is assessing the safety, tolerability, and immunogenicity of a SARS-CoV-2 RNA vaccine in an estimated 4644 healthy children younger than 12 years. Diego R. Hijano, MD, MSc (Infectious Diseases), will lead the BLAZE-1 trial (NCT04427501) to assess the effectiveness of two neutralizing antibodies, LY3819253 (LY-CoV555) and LY3832479 (LY-CoV016), from Eli Lilly in treating mild to moderate COVID-19 in immunocompromised pediatric patients.

KZ Zandani

BNT162b2 Vaccine Prevents SARS-CoV-2 Infection in the St. Jude Workforce

In a letter to the *Journal of the American Medical Association*, Li Tang, PhD (Biostatistics), and her colleagues reported that from December 17, 2020 to March 20, 2021, a total of 5217 St. Jude employees met the criteria to receive the two-dose regimen of the Pfizer-BioNTech vaccine (BNT162b2) through the institution's vaccination program. Of those eligible, 3052 (58.5%) employees received at least one dose; 2776 (53.2%) received two doses, and 2165 (41.5%) were not vaccinated.

When the investigators compared routine (at least weekly) COVID-19 screenings between the two groups, they found that the cumulative incidence of any COVID-19+ result, as determined by PCR testing of mid-turbinate samples, was substantially lower in the vaccinated group. Overall, only 51 (1.7%) vaccinated employees (receiving at least a single dose) tested COVID-19+. In the unvaccinated group, 185 (8.5%) employees tested COVID-19+, and among those, 79 (42.7%) cases were asymptomatic infections. For those fully vaccinated (i.e., 2 weeks after the last dose), vaccine protection was 97.6%.

Creation of the Pediatric COVID-19 U.S. Registry

During the early days of the pandemic, infectious diseases clinicians at St. Jude were overwhelmed by communications from colleagues wanting to learn how to treat SARS-CoV-2 infections in children. In April 2020, Gabriela M. Marón Alfaro, MD, clinical research scientist Ronald Dallas, PhD (both of Infectious Diseases), and their team worked with Information Sciences to launch the Pediatric COVID-19 U.S. Registry.

The purpose of the registry was to gather information about the virus in a centralized location for clinicians and researchers and then generate guidelines for treating infected patients. Inclusion criteria were age 21 years or younger and a COVID-19+ test result; outpatient cases and hospitalized cases were accepted. A key goal of the registry was to provide preliminary data to help advance research and educate and inform clinicians. As of April 30, 2021, the database contained 12,003 cases from 170 institutions across the U.S. The data gathered were central to recognizing conditions associated with infection, such as multisystem inflammatory syndrome in children (MIS-C) and long-haul COVID.

The Pediatric COVID-19 U.S. Registry was created in partnership with the Pediatric Infectious Diseases Transplant Network (PIDTRAN). The Pediatric Infectious Disease Society spread the word about the registry and encouraged members to contribute to it. St. Jude's REDCAP database survey system was used to generate the registry, and the data are housed on campus. However, the data are publicly available and registry contributors can use it to develop manuscripts, with the approval of the Registry team, and/or research protocols, with the approval of the St. Jude Institutional Review Board and PIDTRAN.

As a result of this registry, St. Jude has been recognized as a national leader in COVID-19 efforts, and Dr. Marón Alfaro was invited by the National Institutes of Health to join their founding group of pediatric experts to assimilate the common data elements required to obtain future NIH funding to study COVID-19 in pediatric patients.

Ronald Dallas, PhD; Hailey Skonhovd; Gabriela M. Marón Alfaro, MD; Jose Amadeo Ferrolino, MD

Sheena Mukkada, MD, MPH

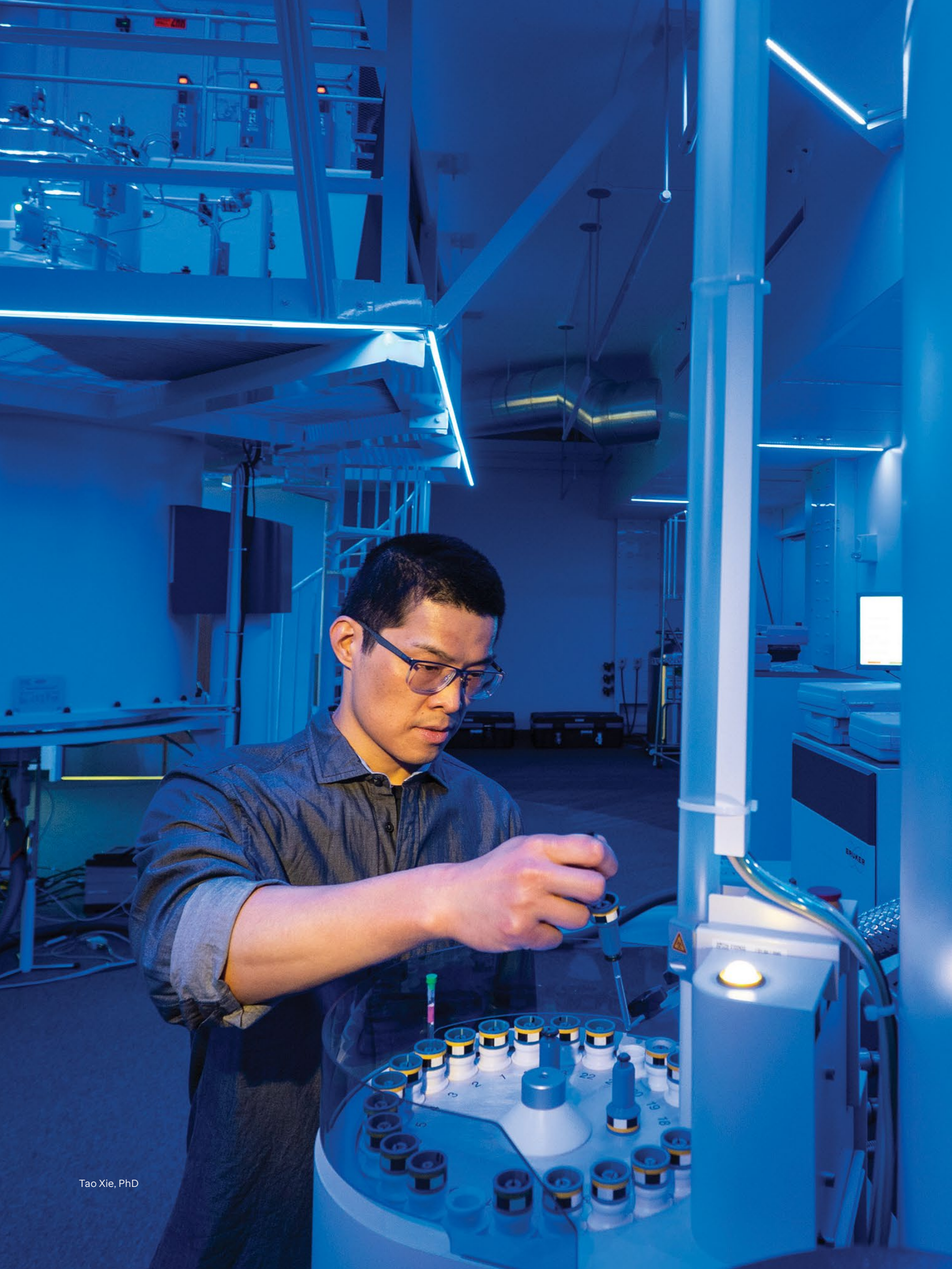
The Global Registry of COVID-19 in Childhood Cancer

The severity of disease caused by coronaviruses in immunocompromised children was well established; thus, when the novel SARS-CoV-2 virus was identified as the cause of the pandemic, pediatric oncologists worldwide knew that the effect on their patients could be devastating. Sheena Mukkada, MD, MPH (Global Pediatric Medicine), and her colleagues in St. Jude Global collaborated with the International Society of Pediatric Oncology to launch the Global Registry of COVID-19 in Childhood Cancer (GRCCC). The goal of the GRCCC is to quickly gather and share information about how the virus affects pediatric oncology patients and which treatments are effective in that population.

The inclusion criteria for the GRCCC are age younger than 19 years, oncology diagnosis or undergoing hematopoietic stem cell transplantation, and laboratory-confirmed COVID-19 infection. As of April 2021, the GRCCC included 1657 cases in 48 countries. The researchers found that SARS-CoV-2 infections occurred predominantly in boys (59%). The most common diagnosis was acute lymphoid leukemia/lymphoma (49%) or solid tumor (24%), and 83% of patients were currently receiving cancer-directed treatment. While infected, 44% of patients had cancer-directed treatment withheld or decreased. The most common approach to the infection was no treatment (70%) or steroids (14.6%). Dr. Mukkada and her colleagues determined that more than 80% of infections were cleared and that only 3% of pediatric oncology patients died of COVID-19. Thus, severe COVID-19 illness is not frequent in pediatric oncology patients, but it may have devastating consequences.

CONCLUSIONS

Despite the pandemic, St. Jude has continued to advance research and provide life-saving treatments while keeping staff, patients, and their families safe. Many investigators joined forces to end this global crisis by refocusing their efforts on understanding the novel SARS-CoV-2 virus and evaluating experimental approaches to prevent and treat COVID-19.



Tao Xie, PhD

Abl Kinase Regulation in the Development and Treatment of Cancer

Protein kinases form one of the largest protein families, with 518 members encoded in the human genome. Most share homology in their critical kinase domain, which catalyzes the transfer of a phosphate group to substrate proteins. Protein kinases influence a large variety of fundamental cellular processes, including signaling pathways involved in cell growth and development. Because of their central role in cellular physiology, kinase activity must be tightly regulated. This is typically achieved by a conformational switch between active and inactive protein states. In cancer, mutations in kinases are common. These can aberrantly increase kinase activity, thereby promoting tumor cell growth, proliferation, survival, and migration. As a consequence, protein kinases have been a key biological target for anticancer drug development. Indeed, more than 60 kinase inhibitors have been approved by the U.S. Food and Drug Administration in the past 2 decades.

Paulo Rossi, PhD; Tao Xie, PhD; Tamjeed Saleh, PhD

The initial success of imatinib, a kinase inhibitor targeting an oncogenic form of the protein kinase Abl that was developed to treat chronic myeloid leukemia (CML), sparked intense efforts to discover additional drugs of this class. Imatinib improves the survival of many patients with CML. Unfortunately, tumor cells can acquire drug resistance through additional mutations in Abl kinase, and this represents a major therapeutic challenge. Structural biologists at St. Jude are using the most advanced technologies available to study the structures and dynamics of protein kinases and thereby provide new windows into kinase function and regulation, understand how drug inhibitors alter kinases, and reveal the mechanisms underlying drug resistance to identify more effective therapeutics.

Abl Kinase Populates Distinct Conformational States

Protein kinases can exist in active or inactive states, and the conformational transitions between those states determine a kinase's activity. Despite extensive structural and biochemical studies, our understanding of how protein kinases switch between active and inactive states remains limited. One major challenge is in visualizing protein states that are functionally important but also highly transient. Such states are difficult to detect using conventional biophysical and structural approaches because those methods provide static "snapshots" of macromolecules. In contrast, solution nuclear magnetic resonance (NMR) is a powerful technology that can detect protein movements at atomic resolution over a wide range of timescales.

As reported in the journal *Science,* Charalampos Babis Kalodimos, PhD (Structural Biology), and his colleagues, Tao Xie, PhD, Tamjeed Saleh, PhD, and Paolo Rossi, PhD, used NMR spectroscopy to determine how conformational changes in Abl kinase regulate its function. The researchers found that the Abl kinase transitions between one active and two distinct inactive states (named I_1 and I_2), and they determined solution structures of all three states of Abl.

Both I_1 and I_2 inactive states are sparsely populated and short-lived; thus, they are difficult to capture using other techniques. In fact, the I_1 state differs from previously identified structures of Abl and may be used to design inhibitors that are more selective and have reduced off-target or side effects.

Figure. Structure of the dynamic Abl kinase domain determined by NMR spectroscopy.

Oncogenic and Drug-Resistant Mutations

Oncogenic mutations that dysregulate protein kinases occur frequently in specific regions of the protein, so-called hotspots, but the mechanisms underlying their effects remain unclear. Dr. Kalodimos and his team showed that many oncogenic mutations directly perturb the conformational equilibrium of Abl, releasing its intrinsic inhibitory mechanisms and constitutively activating the kinase.

Resistance to kinase inhibitors can arise from mutations in the drug-binding site that reduce the drug's affinity. However, in many kinases, only a few drug-resistant mutations directly affect the drug-binding site; most occur at remote sites and thus may exert their effects via an allosteric (indirect) mechanism. Elucidating such allosteric effects remains challenging. By using the recently developed NMR approach, chemical exchange saturation transfer (CEST), Dr. Kalodimos and his colleagues discovered that imatinib-resistance mutations weaken drug binding by reducing the amount of kinase molecules in the I_2 inactive conformation, which is required for imatinib binding. These findings show that by detecting and structurally characterizing the conformational state of a kinase to which a drug selectively binds, one can understand the mechanisms underpinning drug resistance. This knowledge may advance the design of inhibitors to overcome drug resistance and guide treatment choices for individual patients.

Allosteric Regulation and Phosphorylation of Abl Kinase

Like many other protein kinases, in addition to its kinase domain, Abl has a regulatory module that controls the kinase's activity. Furthermore, Abl activity can be regulated by small molecules, such as the allosteric inhibitor GNF5, and by phosphorylation. Using NMR spectroscopy, the researchers revealed that GNF5 and the regulatory module in Abl kinase exert their effects by selectively stabilizing the I_2 inactive state of the kinase domain. In contrast, phosphorylation of Abl at the tyrosine 412 residue in the A loop of the kinase domain destabilizes both the I_1 and I_2 inactive states to favor the active state. In fact, this modification can activate Abl mutants that exist predominantly in the I_2 inactive state. This study highlights the delicate balance between the different regulatory elements within the kinase and shows the complex modulation of this balance by protein modifications, drugs, and oncogenic mutations.

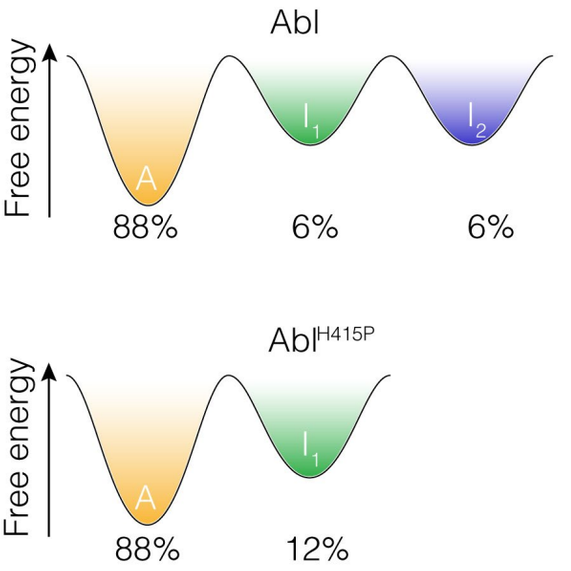


Figure. Comparison of the conformational distributions of wild-type (Abl) and mutant (Abl^{H415}) Abl kinase. In the wild-type Abl, most (88%) molecules exist in the active state (A; yellow), but some exist in the I_1 (6%; green) or I_2 (6%; purple) inactive states; the I_2 state is targeted by the drug imatinib. In contrast, the imatinib-resistant mutant Abl^{H415} occupies only the active state and I_1 inactive state, neither of which can bind imatinib. *Figure adapted from Xie T et al, Science 370(6513):eabc2754, 2020.*

Moving Forward

This groundbreaking work by Dr. Kalodimos and his colleagues has motivated the creation of a new St. Jude initiative in which the structures and binding properties of a large number of kinases will be analyzed using ultra-high-field NMR technologies. This approach will enable the researchers to gain insight into the differential activity and functional parameters of the kinases and learn how to better target this family of proteins to advance anticancer therapeutics.

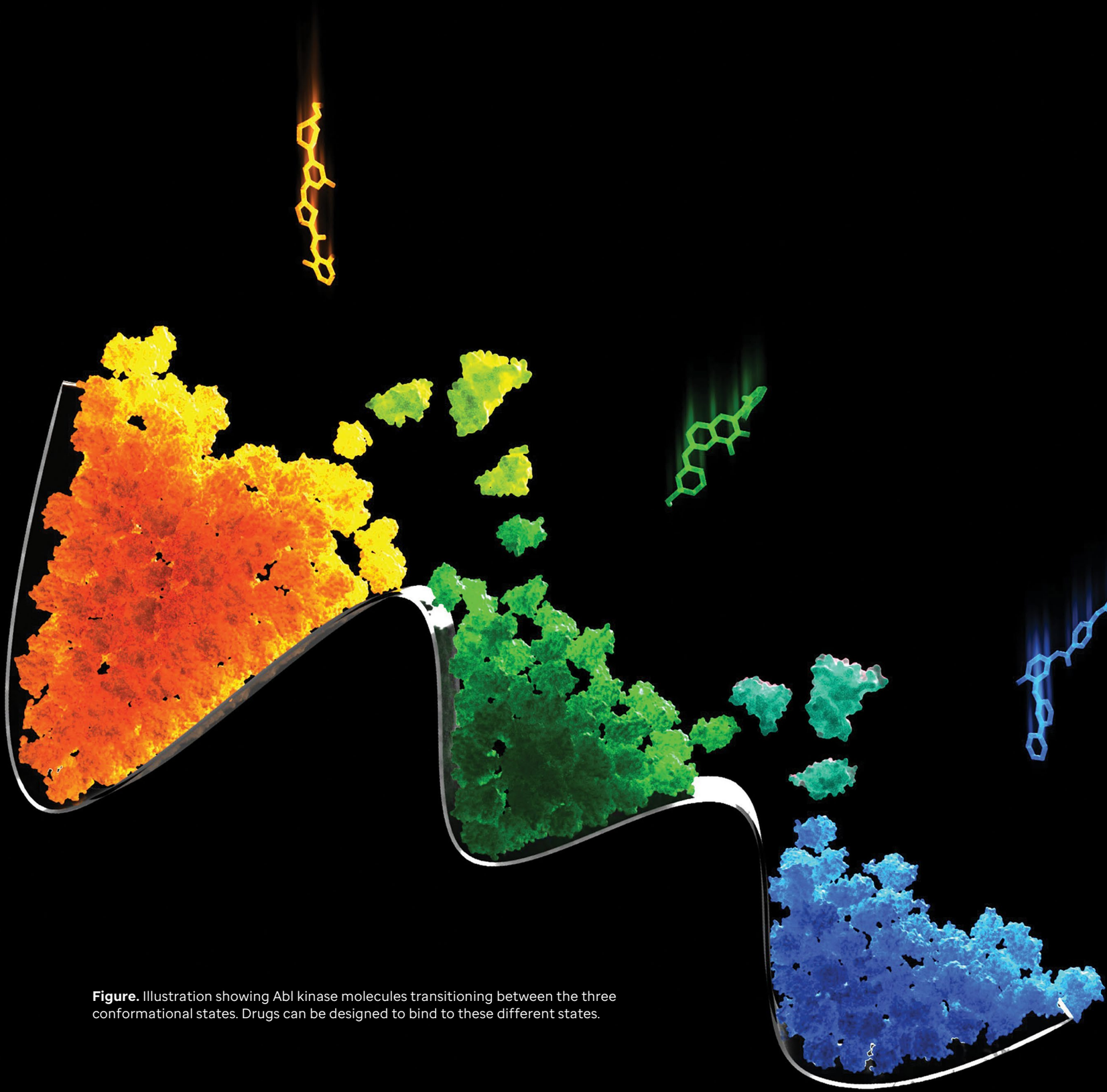


Figure. Illustration showing Abl kinase molecules transitioning between the three conformational states. Drugs can be designed to bind to these different states.

CONCLUSIONS

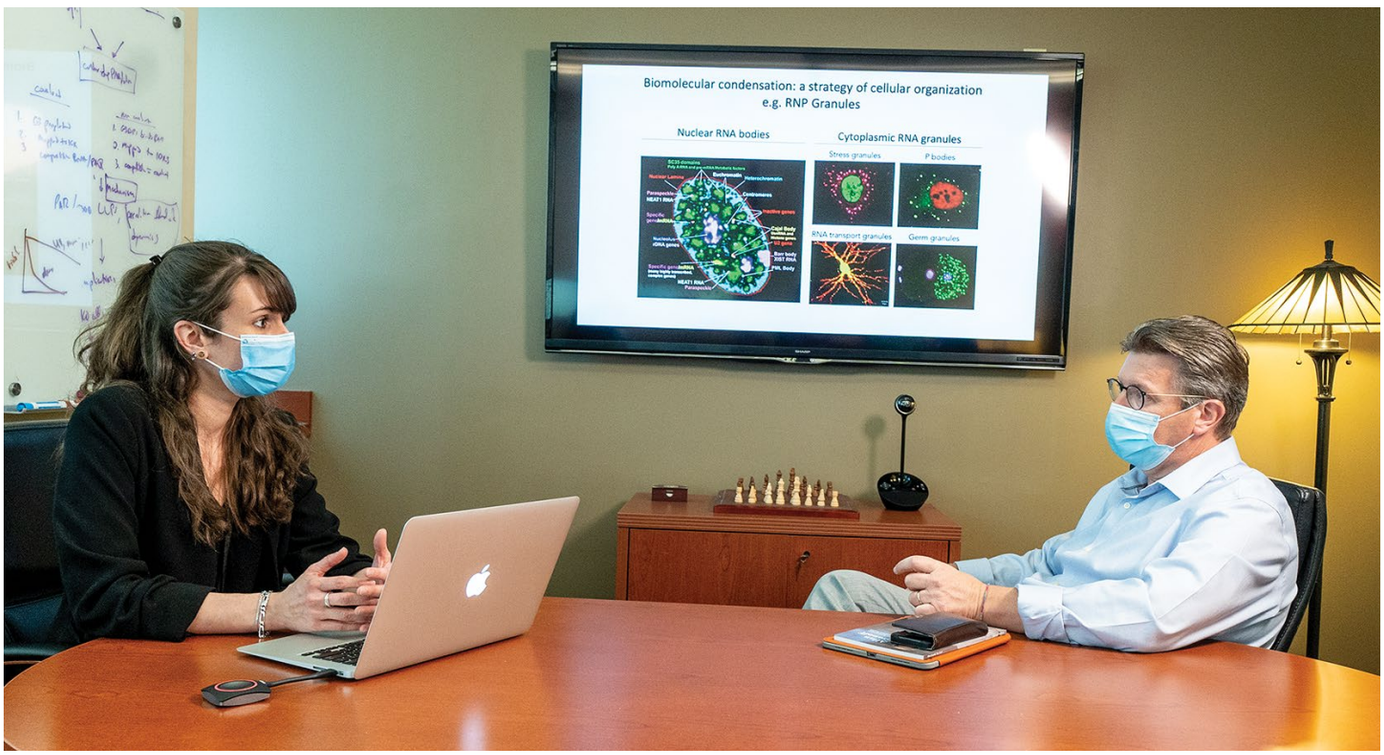
Structural biologists at St. Jude are using advanced NMR spectroscopy to characterize the conformational dynamics and regulation mechanisms of the protein kinase Abl. The molecular insights gained from these studies may enable the discovery of more potent, selective drugs for cancer treatment. These new NMR methods can also be applied to other kinases and medically relevant proteins.

Biomolecular Condensates Compartmentalize Cells

Cells are filled with organelles, which are distinct compartments that have specialized functions. Recent work has revealed that in addition to classic organelles, such as the nucleus, mitochondria, and endoplasmic reticulum, which are surrounded by their own lipid bilayer membranes, cells are extensively compartmentalized by a process called "liquid–liquid phase separation" (LLPS) that results in two coexisting liquid phases—a dilute phase and a dense phase. LLPS proceeds through the assembly of biomolecules into large three-dimensional networks, which then condense into liquid-like droplets called biomolecular condensates (or membrane-less organelles) that resemble oil droplets in water. Nucleoli and stress granules are two examples of biomolecular condensates that have been known for decades. However, other functional compartments are also formed via LLPS, including heterochromatin, super-enhancers, and membrane receptor clusters. Our rapidly increasing understanding that LLPS functions in many fundamental biological processes has not only reshaped our view of cellular organization but also resulted in the realization that the dysregulation of this process causes certain diseases, such as neurodegenerative diseases and some cancers.

Ivan Peran, PhD; Erik W. Martin, PhD; Tanja Mittag, PhD

St. Jude investigators made seminal contributions during the emergence of this new field investigating biomolecular condensation, and they remain at the forefront. Over the past year, they have advanced the conceptual understanding of LLPS and how it regulates fundamental and pathological processes in cells. They have revealed how the process is encoded in intrinsically disordered regions (IDRs) of cancer-related proteins, how multicomponent LLPS shapes the responsiveness of biomolecular condensates to cellular states, and how we can progress from a simplified view of phase separation of a few components to a network view that explains the emergent properties of one biomolecular condensate type, stress granules. The results of these studies and those of others showing how LLPS mediates the compartmentalization of biomolecules within the cell have fundamentally changed how scientists view cellular organization and are expected to generate new therapeutic opportunities.



Cecile Mathieu, PhD ; J. Paul Taylor, MD, PhD

Network Interactions Form Complex Condensates

Ribonucleoprotein (RNP) granules are an important class of biomolecular condensates that govern many aspects of RNA metabolism. RNP granules are composed of RNA and protein and are found throughout the cell in a wide variety of structures. Each RNP granule has a distinct composition and unique role in shepherding RNA molecules through their life cycle, from initial processing to eventual degradation. Over the last decade, studies of biomolecular condensation have yielded important advances in our understanding of how LLPS drives condensate formation. However, most of those studies used simplified in vitro systems that have only a few molecular components. Whether these concepts would apply to complex condensates, such as RNP granules, which contain hundreds or thousands of different proteins and RNAs, remained unknown. Indeed, the constituents of RNP granules are complex, dynamic, and often overlap with other RNP granules, yet the granules faithfully and consistently self-organize into various structures with distinct compositions and functions.

To address this enigma, J. Paul Taylor, MD, PhD (Cell & Molecular Biology), the organizer of the St. Jude Research Collaborative on Membrane-less Organelles in Health and Disease, and his team investigated the assembly of stress granules, which are prototypical cytoplasmic RNP granules that arise in response to various types of stress. By integrating data from an in-house genome-wide RNAi screen with published proteomic data sets, Dr. Taylor's group constructed a core stress granule network comprising 36 proteins that were constituents of stress granules and whose depletion hindered the formation thereof. The team found that the most central node within this network is G3BP1 and G3BP2 (G3BP1/2), which are RNA-binding proteins. When G3BP1/2 were depleted from cells, those cells could no longer form stress granules. Cells in which other nodes within the macromolecular network were knocked out retained the ability to form stress granules, albeit with reduced efficiency. This effect occurred in a consistent pattern: knocking out nodes with higher centrality had the greatest effect on the efficiency of stress granule formation, whereas knocking out nodes with lower centrality had relatively little effect. This observation led Dr. Taylor to propose a new concept to explain how complex condensates are formed; specifically, the forces governing the assembly of condensates are encoded by a condensate-specific network, and LLPS occurs through the collective contribution of individual nodes within that network. Thus, the forces driving LLPS are distributed unevenly across the network, such that nodes with higher centrality have greater influence than do nodes with lower centrality.

The prominent position of G3BP1 as the protein of highest centrality within the stress granule network predicted that it would play a major role in establishing the composition and, therefore, the identity of this RNP granule. Indeed, Dr. Taylor's group found that G3BP1 was required for cells to form stress granules; increasing the concentration of G3BP1 or forcing the protein to self-associate was sufficient to drive the assembly of stress granules, even in the absence of stress. Next, Dr. Taylor's group investigated the molecular mechanisms by which G3BP1 undergoes LLPS with RNA to initiate stress granule assembly. G3BP1 has three IDRs: IDR1, IDR2, and IDR3. Using a series of mutant forms of G3BP1, Dr. Taylor's team found that the IDRs contribute to a "molecular switch" that alternates between two conformations. The switch is dictated by the binding partner of IDR3, which binds either RNA (via an intermolecular interaction) or IDR1 (via an intramolecular interaction). In the open conformation, when IDR3 is available for RNA binding, LLPS occurs and stress granules are formed. In the closed conformation, IDR3 binds IDR1, thereby forming an autoinhibitory association that precludes LLPS and stress granule formation.

This study, which was published in *Cell,* defined the molecular mechanisms whereby G3BP1 initiates stress granule assembly. Moreover, it established a conceptual framework for understanding the formation of complex condensates, a process that is driven by condensate-specific networks of interactions in which the centrality of the protein determines its relative contributions to the network.

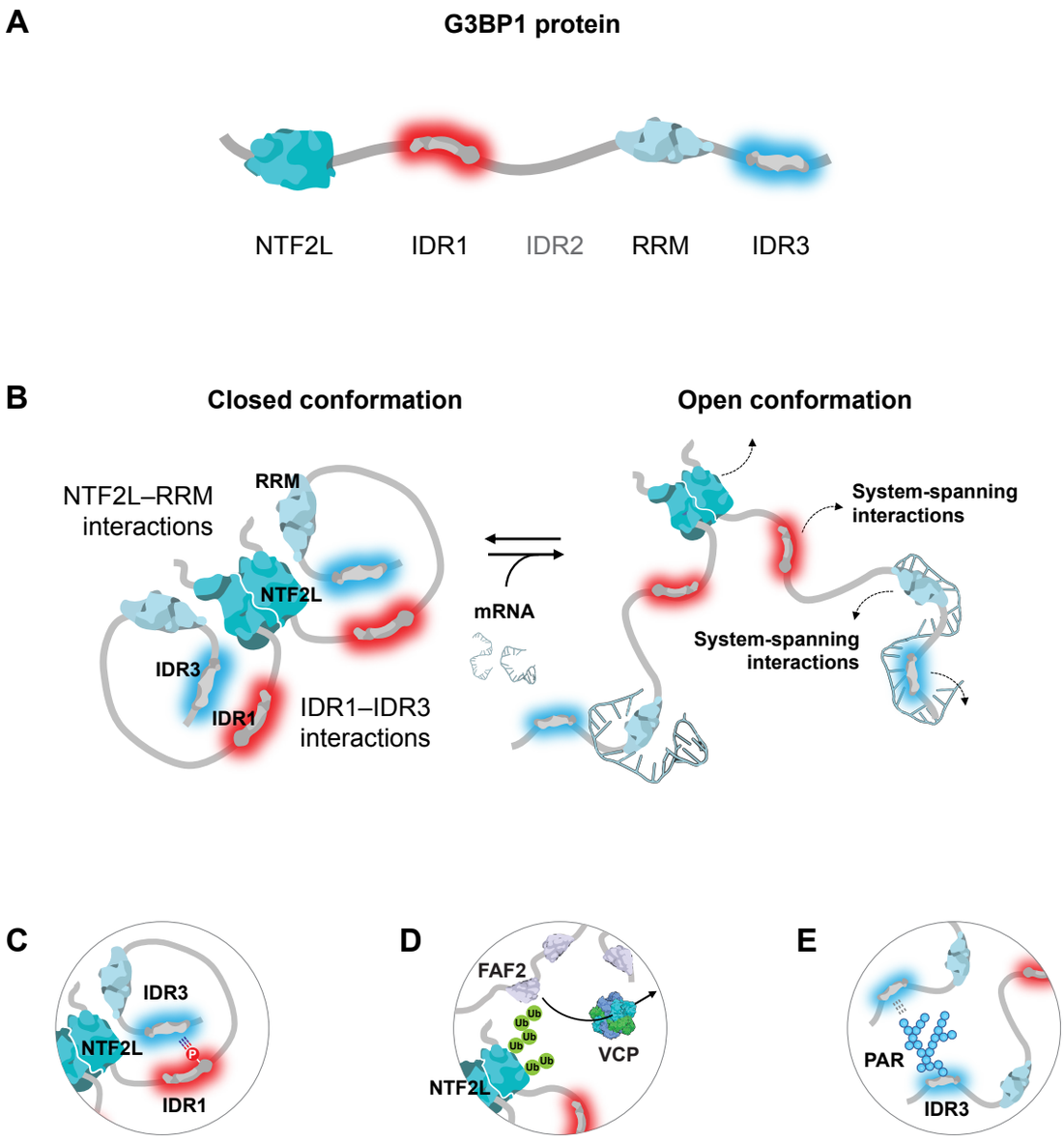


Figure. (**A**) G3BP1 exists as a homodimeric RNA-binding protein comprising folded NTF2-like (NTF2L) dimerization domains, folded RNA-recognition motifs (RRM), and three distinct intrinsically disordered regions (IDRs) (only IDR1 and IDR3 are shown). The RNA-binding activity of G3BP1 is mediated by RRM and IDR3. (**B**) G3BP1 establishes an equilibrium between closed and open conformations that controls stress granule assembly. When cytoplasmic mRNA concentrations are low, G3BP1 favors the closed conformation due to an electrostatic interaction between IDR1 and IDR3 and a domain–motif interaction between RRM and NTF2L. When the concentration of cytoplasmic mRNA rises, RNA competes to bind RRM and IDR3, driving the molecular switch to the open conformation. The open conformation of G3BP1 engages in multiple system-spanning interactions that underlie stress granule assembly. G3BP1 activity is further tuned by posttranslational modifications, including (**C**) phosphorylation, (**D**) ubiquitination, and (**E**) PARylation. **Abbreviations:** FAF2, Fas-associated factor family member 2; P, phosphorylation; PAR, poly(ADP-ribose); Ub, ubiquitin; VCP, vasolin-containing protein.

Erik W. Martin, PhD ; Tanja Mittag, PhD; Ivan Peran, PhD

Phase Separation of FET Family Proteins Is Determined by the Valence and Patterning of Aromatic Residues

LLPS is mediated by multivalent interactions and physical networking between macromolecules. LLPS of proteins with repeats of structured domains that bind to repeats of linear motifs in a binding partner is determined by the valence and strength of their interactions. However, some purely disordered proteins, which do not adopt unique well-folded structures, can also mediate LLPS in many biological processes. How is this ability encoded in their sequence? Do all IDRs mediate phase separation? These are key questions because LLPS mediated by IDRs is conceptually more difficult to understand than that mediated by multivalent domain/motif systems, given that the structures and interaction strengths of the underlying IDR-mediated interactions are unavailable.

Tanja Mittag, PhD (Structural Biology), and Rohit V. Pappu, PhD, at Washington University (St. Louis, MO), are both members of the St. Jude Research Collaborative on Membrane-less Organelles in Health and Disease. Together, their laboratories addressed these questions as they relate to intrinsically disordered, low-complexity domains (LCDs) of the FET family of proteins. This family is named for its most well-recognized members—Fused in sarcoma (FUS), Ewing sarcoma (EWS), and TATA-binding protein-associated factor 15 (TAF15)—whose roles in oncogenesis are thought to arise from their ability to undergo LLPS. Chromosomal translocations can give rise to fusions between the LCDs of FET family proteins and DNA-binding domains of transcription factors, like those in the ETS family. The resulting fusion proteins drive oncogenesis and are hypothesized to do so by forming aberrant biomolecular condensates that drive transforming transcriptional programs. Hence, it is essential that we understand how LLPS is encoded in the LCDs of FET family proteins.

Drs. Mittag and Pappu used the LCD of hnRNPA1, an RNA-binding protein from the FET family; its amino acid composition and sequence patterning are highly similar to those of FUS, EWS, and TAF15, but it phase separates less strongly, a feature that helped in fully quantifying its phase behavior. This work was based on the hypothesis that interactions between protein molecules that regulate LLPS should also exist within individual protein molecules. Therefore, the interactions should be identifiable in a dilute solution (i.e., in the absence of LLPS).

Erik W. Martin, PhD, and Ivan Peran, PhD (both of Structural Biology), two postdoctoral fellows working in Dr. Mittag's lab, used high-resolution nuclear magnetic resonance (NMR) spectroscopy to identify residues in the LCD sequence that interact with each other. This analysis identified a key role for the aromatic amino acids tyrosine and phenylalanine. Alex S. Holehouse, PhD, a postdoctoral fellow working with Dr. Pappu, performed a type of all-atom simulations developed in Dr. Pappu's laboratory. The simulations recapitulated the experimental properties of IDRs and thus provided insights into the atomic interactions. They revealed a network of cohesive interactions between aromatic amino acid residues uniformly distributed along the sequence. Dr. Mittag's team demonstrated that changing the number of aromatic residues altered the global dimensions of individual molecules: increasing the number led to more compact chains, and decreasing the number expanded the chains. Both laboratories then applied a framework in which each aromatic residue was treated as a so-called "sticker" (i.e., an adhesive element) and all other residues were treated as "spacers." This approach enabled the extraction of the strengths of pairwise sticker interactions, a previous bottleneck in gaining a thorough understanding of IDR phase separation. Indeed, simulations using the resulting stickers-and-spacers model recapitulated the experimental phase behavior of the hnRNPA1 LCD, its variants, and other FET protein LCDs.

This work, published in *Science*, revealed that the valence, interaction strength, and patterning of stickers (i.e., aromatic residues) in IDR sequences determine the phase behavior of FET proteins. It also clarified that not all IDRs mediate LLPS; this ability is encoded in the sequence of only some IDRs. This work expands our conceptual understanding of LLPS of FET family proteins and will enable the rational perturbation of LLPS to test whether it is the mechanism underlying oncogenesis.

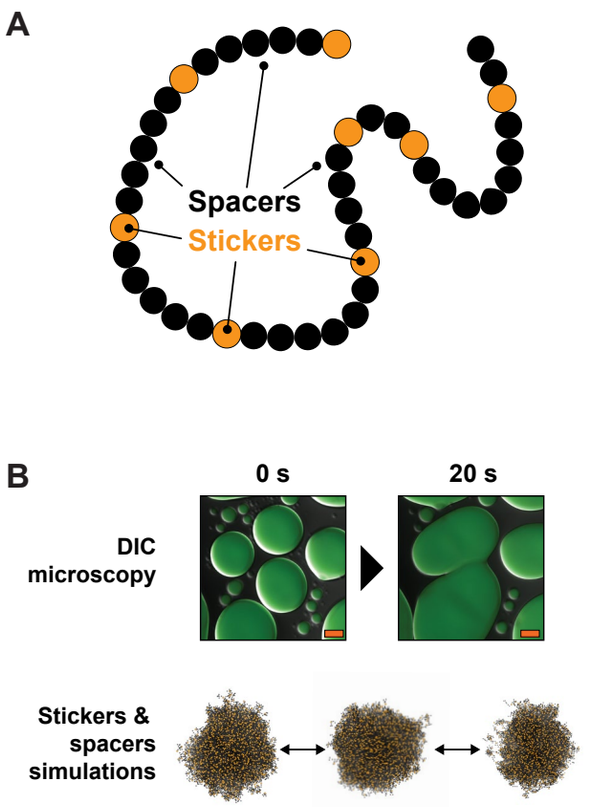


Figure. Stickers-and-spacers model of FET family protein liquid–liquid phase separation (LLPS). (**A**) LLPS of intrinsically disordered, low-complexity domains (LCDs) of FET family proteins can be conceptualized via the stickers-and-spacers framework, in which all adhesive elements (i.e., aromatic residues) are considered stickers (orange beads) and the nonaromatic residues are considered spacers (black beads). (**B**) The top panels show differential interference contrast (DIC) microscopy images of fluorescence-labeled dense-phase droplets of the LCD of hnRNPA1. The LCD droplets fuse and coalesce during a 20-second period, indicating their liquid-like behavior. Scale bar, 50 µm. The lower panel shows snapshot simulations of the stickers-and-spacers model that recapitulate the experimental phase behavior of the droplets and show internal rearrangements of the assemblies. *From Martin EW et al. Valence and patterning of aromatic residues determine the phase behavior of prion-like domains. Science 367: 694–9, 2020. Reprinted with permission from AAAS.*

The St. Jude Research Collaboratives Initiative

The St. Jude Research Collaboratives was launched in 2017. With oversight from the Comprehensive Cancer Center, this initiative funds multi-year collaborations conducted in multiple laboratories at St. Jude and at other institutions that have unique expertise and technologies not available on our campus. The advantage of these agreements, beyond basic collaborations, is that they bring together multiple experts and multidisciplinary approaches to address shared research questions. They also provide multiple experts with early access to unpublished data, thereby facilitating overall progress toward answering those questions.

To address the questions raised by their earliest discoveries in liquid–liquid phase separation (LLPS), Drs. Taylor and Mittag realized that they needed to collaborate with scientists who had expertise in multiple fields, including biophysics and theoretical physics, and an expansive understanding of intrinsically disordered proteins, cell biology, and disease biology. To that end, they formed a "dream team" of scientists at St. Jude, Princeton University (Princeton, NJ), and Washington University (St. Louis, MO) and were awarded funding for the first St. Jude Research Collaborative, Membrane-less Organelles in Health and Disease, which is featured in this story. St. Jude is also currently funding four other collaboratives.

CHROMATIN REGULATION IN PEDIATRIC CANCER

Organizer: Charles W.M. Roberts, MD, PhD (Oncology, Comprehensive Cancer Center)

Partner institutions: The Rockefeller University (New York, NY), Dana-Farber Cancer Institute (Boston, MA), and the University of Pennsylvania (Philadelphia, PA)

NOVEL GENE THERAPIES FOR SICKLE CELL DISEASE

Organizer: Mitchell J. Weiss, MD, PhD (Hematology)

Partner institutions: Harvard Medical School, Boston Children's Hospital, Massachusetts General Hospital, the Broad Institute (all of Boston, MA); Children's Hospital of Philadelphia (Philadelphia, PA); and the National Heart, Lung, and Blood Institute (Bethesda, MD)

3D GENOMICS OF PEDIATRIC CANCER

Organizer: Jinghui Zhang, PhD (Computational Biology)

Partner institutions: Whitehead Institute at the Massachusetts Institute of Technology (Cambridge, MA) and Dana-Farber Cancer Institute (Boston, MA)

IMPLEMENTATION SCIENCES

Organizer: Leslie L. Robison, PhD (Epidemiology & Cancer Control)

Partner institution: Washington University (St. Louis, MO)

Mylene Ferrolino, PhD; Michele Tolbert, PhD; Richard W. Kriwacki, PhD

Heterotypic Phase Separation Forms Nucleoli With Adaptable Composition

Another project from the St. Jude Research Collaborative on Membrane-less Organelles in Health and Disease was conducted by the member laboratories of Richard W. Kriwacki, PhD (Structural Biology), and Clifford P. Brangwynnne, PhD, at Princeton University (Princeton, NJ). Their studies have revealed how nucleoli, the biggest biomolecular condensates in a cell, respond to changes in the cell's state and how those changes affect the organelles' function. Nucleoli consist of three concentric layers that perform different aspects of assembling ribosomal subunits. Ribosomes are protein/RNA "machines" that synthesize proteins and constitute 70% of the mass of a cell. Ribosomal RNA (rRNA) is made in the innermost layer of a nucleolus and then moves to the middle layer, where it is processed. The processed rRNA then moves to the outer layer for final assembly with dozens of ribosomal proteins (rProteins) into mature ribosomal subunits. The outermost layer of a nucleolus, which is called the granular component (GC), is a liquid-like bath in which protein factors such as nucleophosmin (NPM1) help rRNA and rProtein molecules assemble into compact ribosomal subunits. NPM1 transiently binds rRNA and rProteins and undergoes LLPS with them to form liquid-like condensates that facilitate ribosome assembly.

Prior to this work by Drs. Kriwacki and Brangwynne, which was published in *Nature*, the view widely held by the LLPS field was that the concentrations of biomolecules within condensates are constant. This is the case for homotypic LLPS (i.e., phase separation driven by self-interactions of proteins). With respect to ribosome biogenesis, the composition of each nucleolus would be fixed, despite changes in the total cellular concentrations of ribosomal components in response to the cell's changing protein synthesis needs.

However, the researchers showed that nucleoli dynamically respond to changes in the level of NPM1. As more NPM1 is produced, more of it is found in the nucleoli, which in turn expand to produce more ribosomes for the cell. These surprising observations are rooted in the principles of heterotypic LLPS (i.e., phase separation driven by non-self interactions of proteins), which dictate the composition of a multicomponent biomolecular condensate. For example, the nucleoli change as the concentrations of individual components change within the cell. The realization that the principles of heterotypic LLPS dominate the behavior of nucleoli led to the discovery of how nascent rRNA is retained within nucleoli and how fully assembled ribosomal subunits escape from them. NPM1 has a dynamic three-dimensional structure that resembles a pentapus (a mythical five-legged octopus), and each "leg" of NPM1 transiently binds nascent rRNA and rProteins to drive LLPS. However, when rRNA and rProteins bind to each other within ribosomal subunits, the legs of NPM1 have nothing to bind to, thereby enabling the ribosome to move out of the nucleolus and into the cytoplasm, where protein synthesis occurs.

The importance of the interactions of NPM1 with other biomolecules versus its self-interactions discovered through this collaboration explains how the composition of nucleoli responds to the changing cellular needs and how ribosomal subunits at the end of their assembly exit the nucleoli to function in other parts of the cell. These discoveries apply to not only the behavior of nucleoli but also the many other phase-separated biomolecular condensates that perform diverse biological functions.

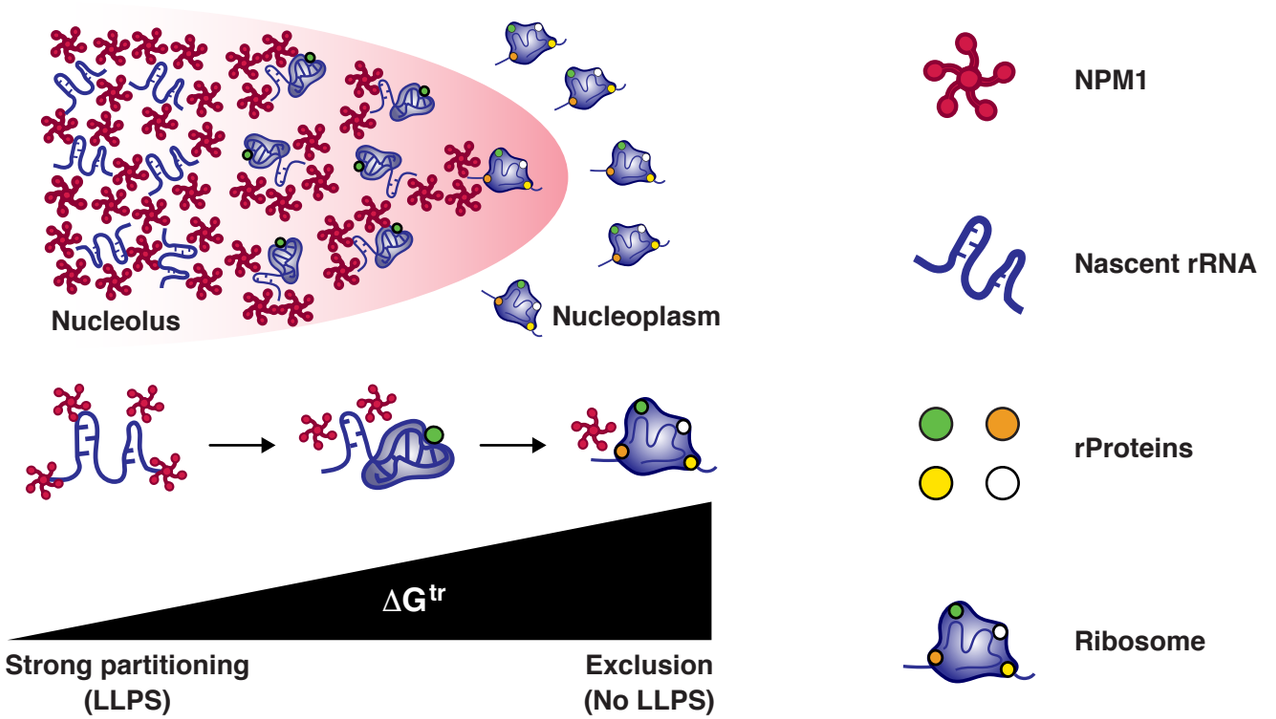


Figure. Proposed mechanism of the assembly and exit of ribosomes from the granular component of the nucleolus driven by the thermodynamics of nucleolar LLPS [i.e., noted as the gradient of the Gibbs free energy of transfer (ΔG^{tr})]. Nucleophosmin (NPM1) helps assemble nascent rRNA and rProteins into ribosomes in the granular component (GC), and then the mature ribosomes move into the nucleoplasm to mediate the production of new proteins. *Reprinted by permission from SNCSC GmbH: Springer Nature, Nature, 581:209–14. Composition-dependent thermodynamics of intracellular phase separation. Riback JA et al, © 2020*

CONCLUSIONS

Discoveries made in St. Jude laboratories and especially through the St. Jude Research Collaboratives Initiative are rapidly increasing our understanding of biomolecular condensates in fundamental biological processes. This work is not only rapidly reshaping our view of basic cell biology but also informing how aberrant phase behaviors of proteins give rise to neurological diseases and certain cancers.

Seth E. Karol, MD

Targeted Molecular Therapies to Improve Outcomes of Acute Leukemia

Leukemias comprise a set of diverse cancers that arise when blood cell progenitors called “blasts” are immortalized, growing while also failing to mature into healthy functioning blood cells. Acute leukemias are a subset of leukemias that progress quickly. They are categorized based on the type of blood cell involved. Acute lymphoblastic leukemia (ALL) develops when mutated lymphocyte progenitors, lymphoblasts, expand and fail to mature into lymphocytes, and acute myeloid leukemia (AML) occurs when blasts derived from progenitors of red blood cells, platelet-forming cells, and white blood cells proliferate uncontrolled. ALL is the most common cancer that arises in children. Cure rates exceed 90% for patients with ALL treated with current therapies. In contrast, AML represents only about 20% of pediatric acute leukemias. The likelihood of curing AML is much lower, especially in those with relapsed or refractory disease.

Jeffrey E. Rubnitz, MD, PhD

Molecularly targeted therapies selectively inhibit the molecular drivers of specific subtypes of acute leukemias and have the potential to dramatically alter treatment regimens. The specificity of molecular therapeutics can help circumvent the toxic effects of many classic chemotherapy agents caused by their deleterious effects on healthy cells. Molecularly targeted therapeutics, therefore, can provide a major treatment advancement by killing cancer cells while minimizing damage to healthy blood cells. Here we present recent studies by St. Jude researchers who are designing and testing new molecular therapies to improve survival and decrease treatment-related toxicities in children with acute leukemias.

New Therapies for Relapsed AML

AML is a hematopoietic malignancy that affects about 500 children in the U.S. each year. Treatment outcomes for AML have not significantly improved over the past 20 years and remain unacceptably poor; only about 70% of patients are cured. After AML relapse, the probability of survival is less than 40%. To address this, Jeffrey E. Rubnitz, MD, PhD, and Seth E. Karol, MD (both of Oncology), developed and led the St. Jude trial VENAML, the first Phase I clinical trial of venetoclax, a targeted inhibitor of BCL-2, in children with relapsed or refractory AML.

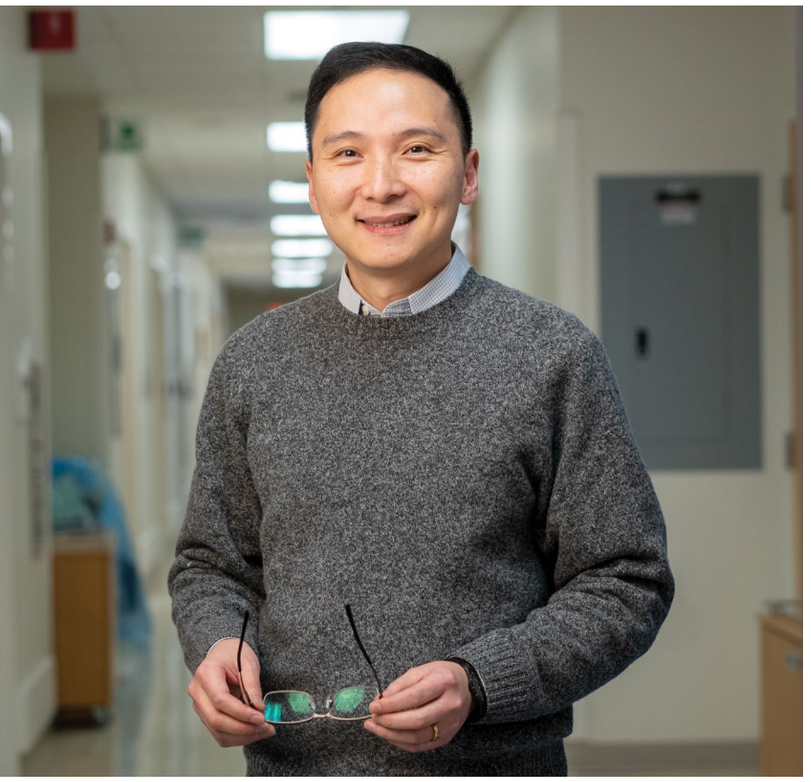
The main function of the BCL-2 protein is to prevent a programmed form of cell death called apoptosis; thus, it is an antiapoptotic protein. Cancer cells exploit antiapoptotic proteins to escape signals that would otherwise prompt cell death. The VENAML trial was based, in part, on preclinical studies performed in the laboratory of Joseph T. Opferman, PhD (Cell & Molecular Biology), whose group demonstrated that overexpression of the BCL-2 family of proteins is a mechanism of drug resistance in various malignancies and that BCL-2 inhibitors have activity against drug-resistant AML cell lines and patient samples.

As reported in *The Lancet Oncology* by Drs. Rubnitz and Karol and their colleagues, the VENAML trial showed for the first time that venetoclax holds promise in improving the survival of children with AML. The trial enrolled 38 patients with relapsed or refractory AML who were treated with venetoclax in combination with low- or high-dose cytarabine, with or without idarubicin. Although the patients were generally heavily pretreated (e.g., 18 patients had undergone prior hematopoietic cell transplantation), all dose levels of the inhibitor were well tolerated. None of the patients required dose reduction or discontinuation of therapy because of venetoclax-related toxicity. Overall responses (complete or partial response) were observed in 24 of 35 (69%) evaluable patients, and 13 of those patients became negative for minimal residual disease (MRD). Among the 20 patients treated at the recommended Phase II dose identified in the trial, the complete response rate was 70% and the overall response rate was 80%.

To explore the features that predict a favorable response to venetoclax, Drs. Rubnitz and Karol evaluated each patient's response to a 7-day prephase (or window) regimen in which venetoclax was given as a single agent. A better response to the venetoclax window was associated with a higher complete response to combination therapy.

BCL-2 is a member of the BCL-2 homology 3 (BH3) family of proteins that play critical roles in alternatively supporting or inhibiting apoptosis. Dr. Opferman's laboratory performed BH3-dependency profiling on blasts from each patient to determine whether those cells were dependent on BCL-2 or other BCL-2 family members, such as BCL-xL or MCL-1. BCL-2 dependency was associated with response to both window therapy and combination therapy.

Overall, the results of this work indicate that the specific BCL-2 inhibitor venetoclax is safe and highly active in combination with conventional chemotherapy in pediatric patients with relapsed AML. The favorable safety profile and outstanding response rate suggest that venetoclax should be further evaluated in children with newly diagnosed AML, and treatment regimens should be optimized to include this molecularly targeted therapeutic. To this end, Drs. Rubnitz and Karol are planning an international collaborative trial to evaluate the use and effectiveness of venetoclax in pediatric patients with AML. In addition, they are testing novel combinations of therapeutics with venetoclax. Dr. Rubnitz is leading the SELCLAX trial, which will test venetoclax plus selinexor in relapsed AML, and Dr. Karol is leading the RAVEN trial, which will test venetoclax plus navitoclax in relapsed ALL. Together, these trials may ultimately lead to a better definition of the optimal use of venetoclax and to improved outcomes for children with acute leukemias.



Jun J. Yang, PhD

Finding New Targets in ALL

T-cell acute lymphoblastic leukemia (T-ALL) comprises 10% to 15% of new cases of childhood ALL diagnosed annually. Due to differences in immunophenotypes (i.e., the markers or antigens expressed on cells) among individual patients, children with T-ALL have not benefited from immunotherapy or targeted therapies to the same extent as have those with B-cell ALL (B-ALL). Patients with T-ALL also experience higher rates of relapse and a greater degree of chemotherapy refractoriness at the time of relapse than do patients with B-ALL. As a result, novel treatments are needed for this population.

To identify new therapeutic targets for T-ALL, Jun J. Yang, PhD (Pharmaceutical Sciences, Oncology), led a group of researchers in testing the in vitro sensitivity of leukemic blasts from children and adults with T-ALL.

In *Nature Cancer,* the team reported that 44.4% of the pediatric samples and 16.7% of the adult samples were sensitive to the tyrosine kinase inhibitor dasatinib, despite lacking the *BCR–ABL1* fusion oncogene or other ABL-class fusions that dasatinib binds and that are associated with sensitivity to the agent. Further studies revealed that the T-ALL blasts were resistant to other ABL-specific inhibitors, including imatinib and nilotinib, but remained sensitive to ponatinib, which shares non-ABL inhibitory targets with dasatinib. These findings indicated that dasatinib sensitivity is mediated by targets other than ABL.

Dr. Yang's co-senior author, Jiyang Yu, PhD (Computational Biology), led the analysis of the RNA-sequencing–derived gene expression profiles. Using the systems biology algorithm NetBID, Dr. Yu and his team discovered an upregulation of pre–T-cell receptor signaling in T-ALL cells that were sensitive to dasatinib. When they compared the genes identified by this analysis with the kinases inhibited by dasatinib and ponatinib but not by imatinib or nilotinib, they identified the *LCK* gene as the most likely therapeutic target of dasatinib in T-ALL. Additional testing of LCK-target phosphorylation, global phosphoproteomics, and genome-wide CRISPR knockout screening confirmed that *LCK* drives dasatinib sensitivity in this acute leukemia subtype.

To identify the patients most likely to benefit from dasatinib therapy, Dr. Yang and his colleagues used RNA-sequencing data from dasatinib-sensitive and -resistant T-ALL to develop a 30-gene biomarker score that showed at least 93% sensitivity and 75% specificity in both a discovery cohort and a validation cohort. When this biomarker score was applied to additional T-ALL samples, it identified the patients whose leukemias were predicted to be dasatinib sensitive. Those patients had a lower probability of event-free survival than other patients with T-ALL treated with conventional chemotherapy. This finding provided a compelling rationale for adding dasatinib to the treatment regimens of this subset of patients to improve their survival. Because early T-cell precursor (ETP) ALL appeared to be dasatinib resistant, the investigators also studied the association between the T-cell developmental stage and dasatinib sensitivity.

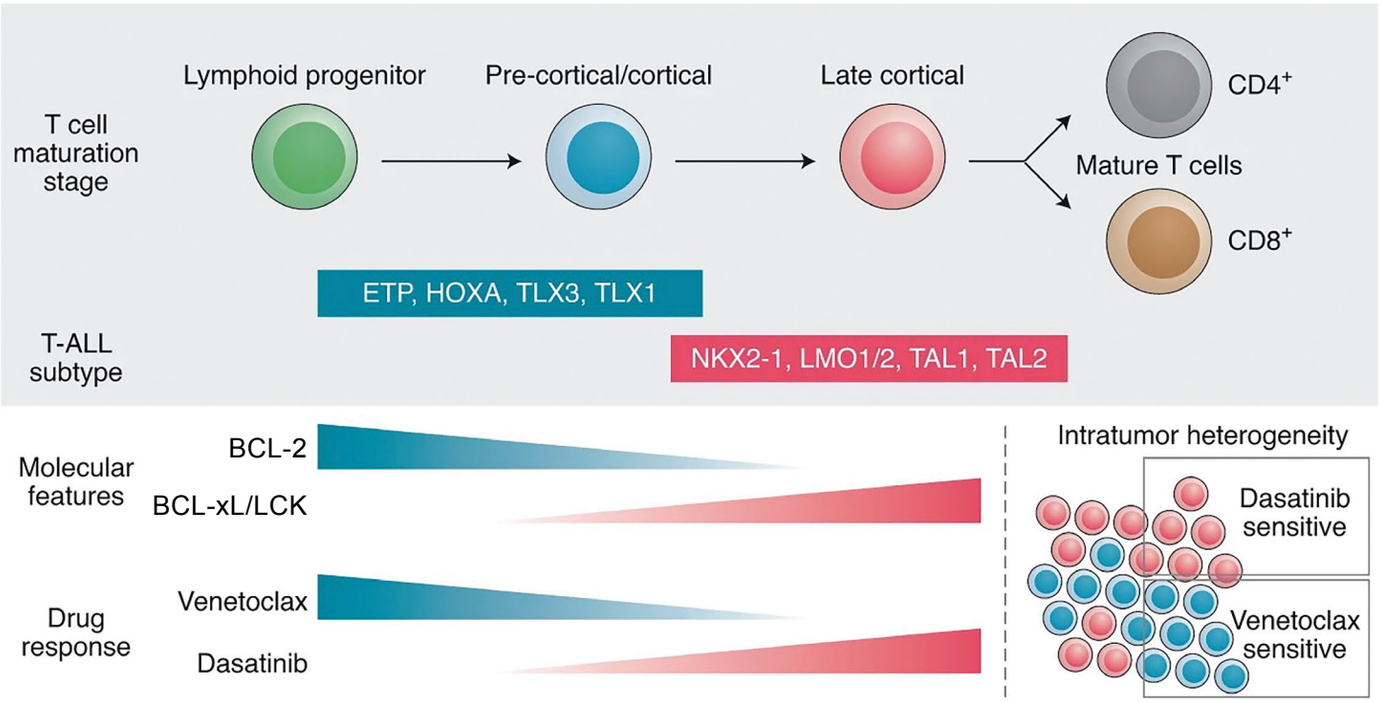


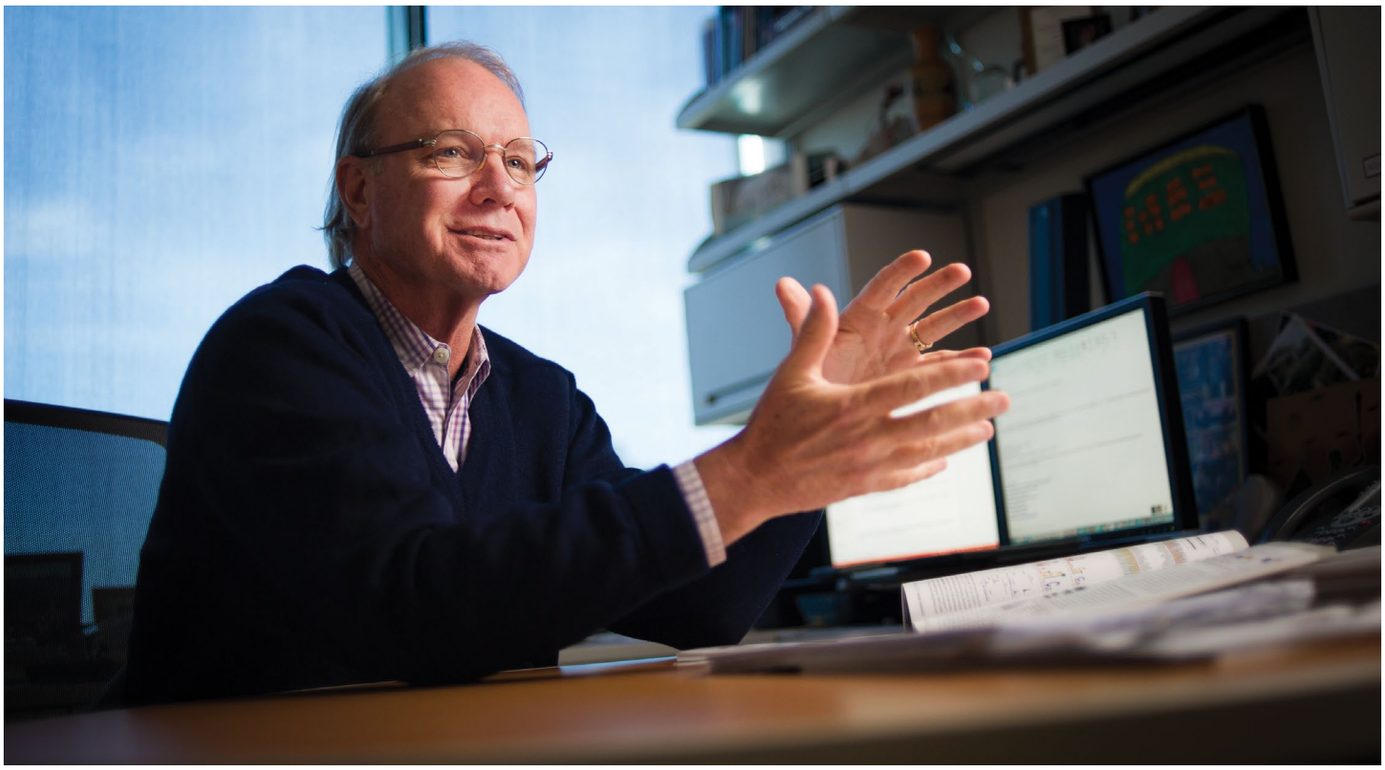
Figure. Illustration showing the developmental states of T-ALL associated with distinct drug responses. Developmental states of T cells and their associated T-ALL molecular subtypes are shown. Early developmental T-ALL states (especially the early T-cell precursor subtype) are associated with high BCL-2 activity and respond to venetoclax; more mature states (the TAL/LMO subtype) are associated with high activity of LCK and BCL-xL and respond to dasatinib. Intratumor heterogeneity of dasatinib- and venetoclax-sensitive T-ALL cells highlights the potential for combination therapy to combat drug resistance and disease relapse. *Reprinted by permission from SNCSC GmbH: Springer Nature, Nat Cancer, 2:256–7. Targeting the developmental origins of cancer. Skanderup AJ and DasGupta R, © 2021*

More mature T cells, such as those in the DN3-4 stage of maturation, appeared more sensitive to dasatinib than did immature cells, such as ETP cells, suggesting that differentiation arrest is a driver of *LCK* dependence and dasatinib sensitivity in T-ALL. This pattern was also associated with increased dependence on the antiapoptotic protein BCL-xL and decreased dependence on BCL-2. Consistent with these findings, dasatinib-sensitive T-ALL cells were more resistant to the BCL-2 inhibitor venetoclax, and dasatinib-resistant samples were more sensitive to the drug.

Together, these results suggest that dasatinib is beneficial for almost half of the pediatric patients with T-ALL, including those whose disease has responded poorly to conventional chemotherapy. Furthermore, dasatinib may act synergistically with venetoclax and/or navitoclax in a subset of patients with T-ALL. The therapeutic combination of venetoclax/navitoclax/dasatinib will be tested in the upcoming RAVEN trial led by Dr. Karol.

Elucidating the Mechanisms of Glucocorticoid Resistance in ALL

B-cell precursor ALL accounts for approximately 25% of new pediatric cancer diagnoses each year. Although contemporary treatments ultimately cure more than 94% of patients with ALL, relapse occurs in 6% to 20% of cases after initial remission. ALL blasts are more resistant to chemotherapy at the time of relapse than at the time of diagnosis. This resistance represents both an outgrowth of pre-existing resistant leukemic clones and the emergence of new treatment-resistant clones during initial therapy. Resistance to glucocorticoids, such as prednisone and dexamethasone, is particularly common at the time of relapse. Thoroughly understanding the mechanisms underlying resistance and ALL relapse will facilitate improvements in both upfront and relapse therapies.



William E. Evans, PharmD

In a recent *Nature Cancer* article, a group of researchers led by William E. Evans, PharmD (Pharmaceutical Sciences), reported their integrative genomic analyses of glucocorticoid resistance in ALL. They studied the sensitivity of leukemic blasts to prednisolone, the active metabolite of prednisone, and performed comprehensive genomic testing to understand the changes in gene expression that occur in leukemia cells and the somatic genetic variations associated with their glucocorticoid resistance. Using samples from 225 children with newly diagnosed B-ALL, Dr. Evans and his colleagues demonstrated that patients whose ALL cells are more resistant to prednisolone are more likely to have higher levels of leukemia in the bone marrow after 2 and 6 weeks of induction chemotherapy.

To understand how leukemic cells resist prednisolone, the investigators identified 192 distinct genes that are associated with either glucocorticoid sensitivity or resistance. Genes were affected by several mechanisms of resistance, including differential gene expression, copy number alterations, mutations in the exomes (i.e., the coding regions of the genes), differential methylation of the gene regulatory elements and/or gene bodies, and variations in microRNAs. By combining a genome-wide CRISPR knockout screen with a new genetic statistical analysis called TAP (truncated aggregation of *P*-values), which was developed by Cheng Cheng, PhD (Biostatistics), the researchers identified 15 candidate genes associated with glucocorticoid resistance; only one of those genes, *NLRP3,* was previously associated with glucocorticoid resistance.

Among the top candidate genes identified was *CELSR2,* a gene not previously associated with glucocorticoid resistance. In patient samples, decreased *CELSR2* expression was associated with increased prednisolone resistance. The association between *CELSR2* and resistance was validated in two separate ALL cohorts comprising 320 and 145 patients, respectively. The importance of this gene was also functionally validated using in vitro modulation in cancer cell lines. Downregulation of *CELSR2* resulted in the overexpression of the antiapoptotic protein BCL-2 in the presence of prednisolone, suggesting a potential mechanism of treatment resistance.

These findings suggested that decreased expression of *CELSR2* would sensitize leukemic blasts to treatment with the BCL-2 inhibitor venetoclax. Indeed, cell lines in which the expression of *CELSR2* was knocked down showed increased sensitivity to the drug and increased synergy between venetoclax and glucocorticoid in tumor killing in culture and xenograft models. Therefore, patients with drug-resistant leukemia may respond to combination therapy with venetoclax and glucocorticoids, a hypothesis that will be tested in the upcoming RAVEN clinical trial.

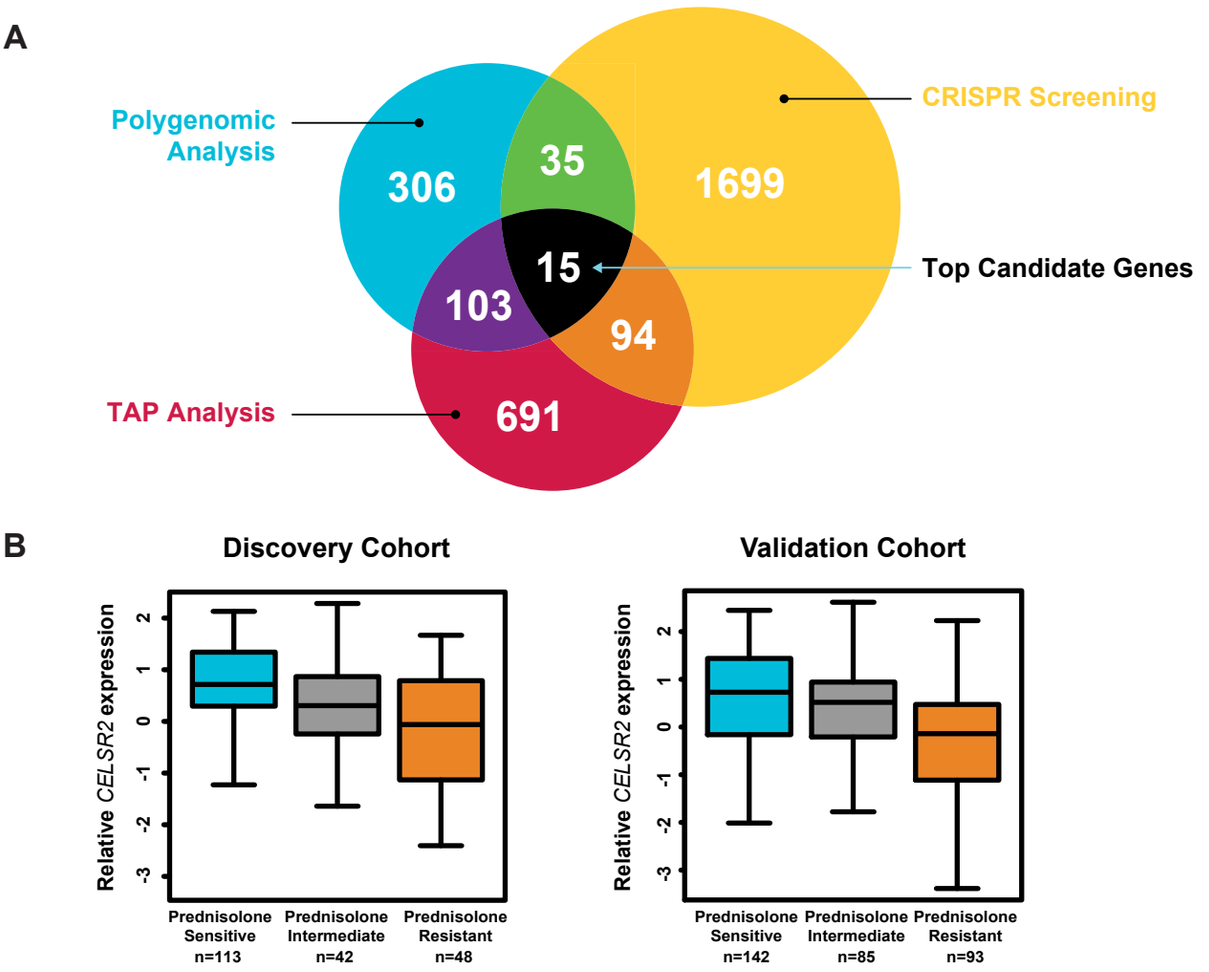


Figure. *CELSR2* is a key mediator of glucocorticoid resistance in ALL cells. (**A**) Venn diagram showing the overlap of genes significantly associated with glucocorticoid resistance in three different analyses of primary ALL cells: TAP (truncation of *P*-values), CRISPR knockout screen, and polygenomic analyses that included the genome-wide interrogations of six distinct genomic/epigenomic features. The 15 genes that were significant in all three analyses were considered the top candidates. (**B**) Lower *CELSR2* gene expression was associated with prednisolone resistance in both a discovery and a validation cohort of ALL cells from patients with newly diagnosed disease. *Reprinted by permission from SNCSC GmbH: Springer Nature, Nat Cancer, 1:329–44. Integrative genomic analyses reveal mechanisms of glucocorticoid resistance in acute lymphoblastic leukemia. Autry RJ et al, © 2020*

Improving Therapy for ALL by Improving Asparaginase Treatment

Asparaginase is a critical component of modern chemotherapy for ALL. Prior studies have shown that inadequate asparaginase therapy is associated with increased risk of leukemia relapse. Although prior studies indicated that 2500 IU/m^2 pegaspargase may be insufficient for the maximal effect, the recently completed St. Jude Total 16 study of children with newly diagnosed ALL did not find a benefit in increasing the asparaginase dose to 3500 IU/m^2, a dose predicted to provide adequate asparaginase activity.

To understand the inconsistency in these findings, Mary V. Relling, PharmD, bioinformatics research scientist Wenjian Yang, PhD (both of Pharmaceutical Sciences), and their colleagues assessed the pharmacokinetics of asparaginase therapy in patients enrolled in Total 16. Patients were randomized to receive either 2500 IU/m^2 or 3500 IU/m^2 pegaspargase during continuation and reinduction therapy. Patients with low-risk ALL received an intermittent schedule (four doses of pegaspargase after induction), whereas those with standard-risk ALL received asparaginase every 2 weeks for the first 30 weeks of continuation and reinduction. The investigators estimated the trough serum activity level (i.e., the lowest drug concentration before the next dose is given) of asparaginase 14 days after the dose, the drug clearance, and the threshold time (i.e., the time that asparaginase activity exceeded the therapeutically active threshold of 0.1 IU/mL). This work, which was reported in the journal *Blood*, demonstrated that asparaginase clearance varies based on its dose and schedule. At Week 7, trough serum asparaginase activity levels were higher in the group that received 3500 IU/m^2 than in the group that received 2500 IU/m^2 (1.3 vs. 0.9 IU/mL for patients with low-risk ALL and 1.8 vs. 1.3 IU/mL for those with standard-risk ALL). However, accelerated clearance in patients receiving 3500 IU/m^2 resulted in predicted threshold times similar to those of the 2500 IU/m^2 group (30.3 vs. 30.3 days for low-risk ALL and 29.2 vs. 28.6 days for standard-risk ALL). Accelerated clearance was also observed in patients with standard-risk ALL who received continuous asparaginase therapy, as compared to those with low-risk ALL who received intermittent postinduction therapy. Accelerated blood clearance, possibly due to immune system–mediated drug clearance, is a phenomenon that has been reported with other pegylated drugs in preclinical models, but this is the first time it has been reported for a pegylated drug in patients. Most courses achieved trough serum concentrations that were higher than 0.1 IU/mL with either dosage.

Wenjian Yang, PhD

Although patients receiving higher doses of asparaginase did not have a reduced relapse risk or improved survival compared to those receiving lower dosages, they also did not experience more severe toxicities. Patients receiving 3500 IU/m^2 asparaginase did not have higher rates of pancreatitis, thrombosis, serious liver injury, or osteonecrosis. The accelerated blood clearance data from the Total 16 study explain the clinical data: the lack of difference in efficacy and toxicity between dosages most likely reflects the unexpected similar durations of asparaginase exposure for patients receiving either dose of the drug. These data have informed the current Total 17 protocol for children with newly diagnosed ALL, in which all patients receive the lower (2500 IU/m^2) dose of pegaspargase.

Hope D. Swanson, PharmD; Seth E. Karol, MD

Although asparaginase therapy is generally not associated with significant long-term risks, acute complications are common and can impede the delivery of therapy. The most common side effect of asparaginase therapy is an allergic reaction, which occurs in 10% to 15% of patients. These reactions are associated with the development of anti-pegaspargase antibodies requiring the transition from pegaspargase to *Erwinia* asparaginase. Unfortunately, in recent years, chronic shortages of the *Erwinia*–derived drug have created challenges in completing asparaginase therapy for those with drug allergies.

To address these challenges, Dr. Karol and pharmacist–clinical specialist Hope D. Swanson, PharmD (Pharmaceutical Sciences), developed a protocol for desensitizing patients to pegaspargase. They combined pre-emptive use of antihistamines and other allergy-blunting medications with a slow, escalating infusion of pegaspargase for patients who experienced a prior allergic reaction. As reported in *Blood,* this protocol enabled the successful infusion of pegaspargase in seven of eight patients. Six of seven patients who were successfully infused maintained adequate serum asparaginase activity for 14 days, the period of activity expected in the absence of immune-mediated inactivation.

The study evaluated factors associated with asparaginase allergy to see if they were predictive of desensitization failure, which was defined as either a failure to complete the infusion or inactivation of asparaginase in fewer than 14 days. The combination of patients' symptoms at the time of their initial allergic reaction, including angioedema, emesis, or other gastrointestinal symptoms, and the persistence of anti-asparaginase antibodies at the time of desensitization was associated with an increased risk of desensitization failure. In contrast, desensitization succeeded in patients who either did not have emesis or angioedema during their initial asparaginase allergic reaction or who no longer had anti-asparaginase antibodies at the time of desensitization.

Overall, this study highlights the feasibility of desensitizing patients with prior allergic reactions to pegaspargase. Benefits include fewer visits to the hospital (one dose of pegaspargase after desensitization can replace as many as six doses of *Erwinia* asparaginase), lower costs, and the ability to continue to receive asparaginase therapy, despite shortages of *Erwinia*-derived medication. The study also identified patients who are more likely to be successfully desensitized, which can help oncologists select patients for potential desensitization or transition to *Erwinia* asparaginase. This work now informs the use of desensitization therapy after pegaspargase allergy at St. Jude and other institutions.

Raul C. Ribeiro, MD

Treating the Lowest-Risk ALL With Less Intensity

With cure rates for childhood ALL in the U.S. now exceeding 90%, a major focus of research has been the identification of patient populations with low-risk disease who can be cured with less-intensive therapy. Deintensification is expected to diminish toxicities and long-term sequelae of cancer treatment. However, this must be balanced against concerns that deintensification will compromise the excellent likelihood of a cure that currently exists. Unlike the U.S., countries with more limited supportive care resources for managing complications of therapy may already be using less-intensive therapeutic regimens that may be optimal for treatment outcome. Therefore, identifying the features of patients with excellent outcomes in settings that use less-intensive therapy may provide an opportunity to improve outcomes for patients with ALL around the world.

To that end, Raul C. Ribeiro, MD (Oncology), Gaston K. Rivera, MD (Global Pediatric Medicine), and their colleagues collaborated with oncologists in Recife, Brazil, to evaluate a less-intensive, risk-adapted therapy regimen for children with B-ALL in the RELLA05 study. As reported in *Blood*, the clinical trial assessed responses in children presenting with standard-risk B-ALL, as determined by bone marrow aspiration on Days 19 and 26 of remission induction and per the guidelines of the National Cancer Institute. Remission induction therapy included two doses of doxorubicin, 2 weeks of asparaginase, 4 weeks of prednisone, and four weekly doses of vincristine. Patients with MRD less than 0.01% at both time points were treated with very low-risk therapy. The postinduction therapy included four cycles of high-dose methotrexate followed by 104 weeks of continuation therapy consisting of mercaptopurine and weekly methotrexate, 1 year of dexamethasone and vincristine pulses, and a single reinduction course comprising dexamethasone, asparaginase, and vincristine, and one cycle of high-dose methotrexate.

Physicians at the Instituto de Medicina Integral Professor Fernando Figueira treated 454 patients on the RELLA05 protocol; the cohort included 101 patients with very low-risk B-ALL. Results in this patient cohort were excellent: overall survival was 96%, event-free survival was 92%, and the cumulative

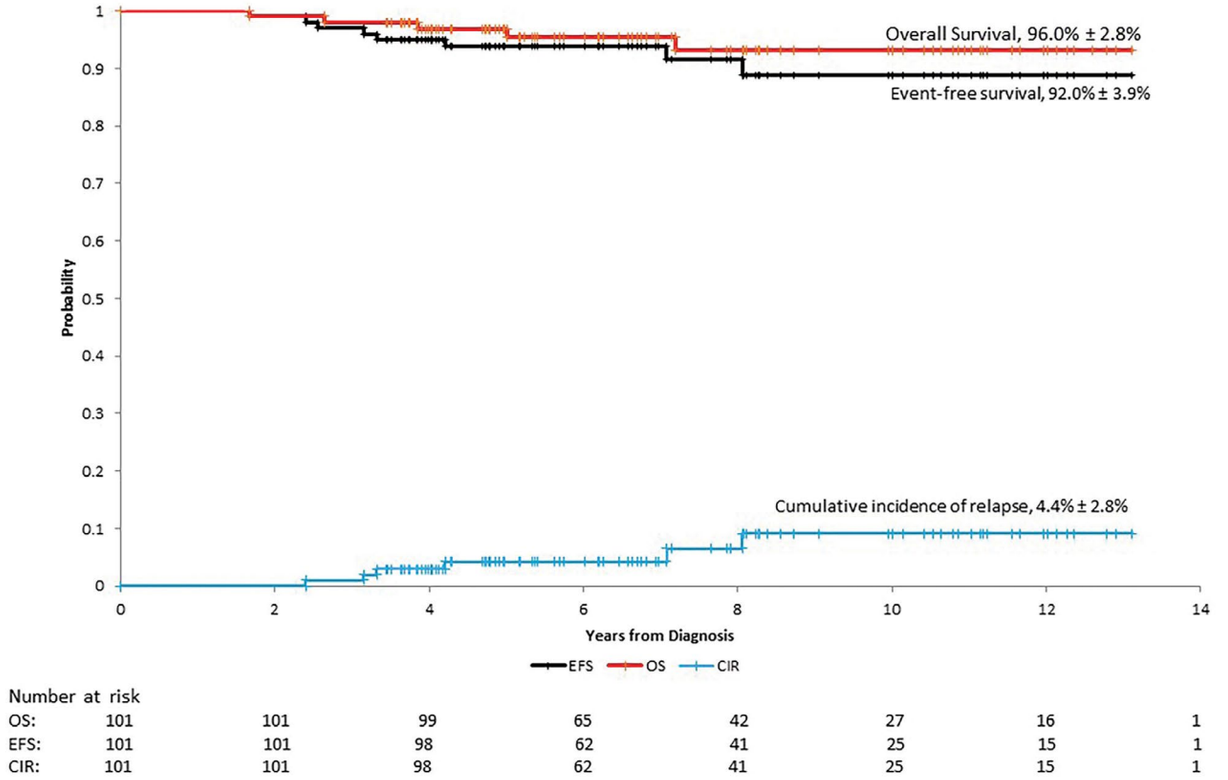


Figure. Kaplan-Meier analyses of outcomes in children with low-risk ALL who received deintensified treatment. The 5-year event-free survival, overall survival, and cumulative incidence of relapse are shown. *Republished with permission of Elsevier Science & Technology Journals, from Reduced-dose intensity therapy for pediatric lymphoblastic leukemia: long-term results of the Recife RELLA05 pilot study. Pedrosa F et al, Blood 135(17):1458-66, © 2020; permission conveyed through Copyright Clearance Center, Inc.*

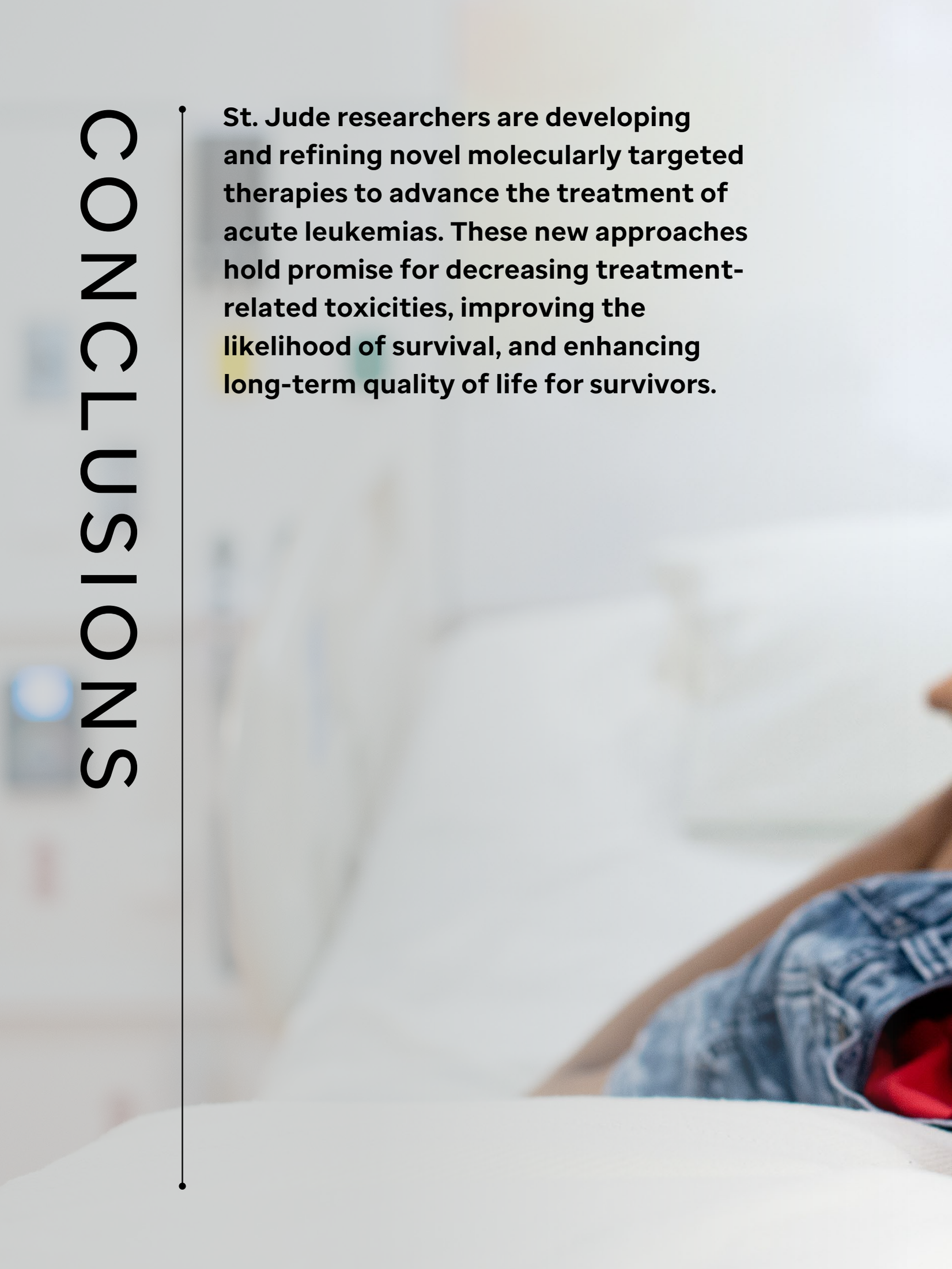
incidence of relapse was 4.4%. Treatment-related mortality occurred in only one patient during remission induction and in no patients during post-remission therapy. This stark reduction in treatment-related mortality was attributed to not only changes in therapy but also improvements in toxicity identification that were facilitated by weekly teleconference discussions between clinicians in Memphis and Brazil.

On the basis of the early success of the RELLA05 trial in Brazil, Drs. Ribeiro and Rivera then collaborated with oncologists at the Children's Cancer Hospital Egypt (Cairo, Egypt) to treat 200 children with very low-risk B-ALL following the same approach as evaluated in Recife. Again, patients' responses were excellent: the 5-year event-free survival was 89.5%, and the overall survival was 95.5%. To further clarify which patients responded best to this therapy, investigators evaluated the level of MRD in the bone marrow on Day 19 of induction. MRD between 0.001% and less than 0.01% was detected in 29 (14.5%) patients. Although these values are below the level traditionally considered MRD-positive, 17.2% of the patients experienced relapse, as compared to 5.3% of patients without detectable MRD. In this population with low-risk B-ALL, MRD detectable at less than 0.01% was a stronger prognostic factor for outcome than other common measures, such as the presence of favorable trisomies or the *ETV6-RUNX1* fusion oncogene. This work was also published in *Blood*.

Together, these studies confirm that presenting characteristics and flow cytometry results can be used to identify patients with B-ALL who can be cured with minimal therapy, and they highlight the importance of developing international collaborative research studies that optimize the adaptation of treatments to local resources. These findings have implications not only for maximizing cures and minimizing toxicity in low- and middle-income countries but also for providing insights into populations that may be eligible for therapy deintensification in the U.S. and other high-resource settings.

CONCLUSIONS

St. Jude researchers are developing and refining novel molecularly targeted therapies to advance the treatment of acute leukemias. These new approaches hold promise for decreasing treatment-related toxicities, improving the likelihood of survival, and enhancing long-term quality of life for survivors.

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Opening of a New Shared Resources Center at St. Jude

In what would be a huge undertaking in a year not affected by a global pandemic, St. Jude finished the construction of a new 30,000-ft^2 Shared Resources Center. The Center was designed and built with one purpose in mind—to create an ideal workspace for cutting-edge laboratory-based Shared Resources at St. Jude that allows synergy and coordination among disparate core laboratories. The work done in these facilities directly enhances the ability of St. Jude researchers to advance fundamental and translational research.

Sunita D'Souza, PhD

In July 2020, many of the Shared Resources laboratories began moving into the new Center, designed to meet their exacting specifications. The opening of the Center brings together some of the most technologically advanced equipment on campus and the talented staff scientists and technicians who have expertise in those technologies and approaches to help guide researchers in their application. The Center was built with added space to provide the flexibility to expand existing resources and add new laboratories as the need arises. This growth and improvement are already underway, as new Shared Resources are being planned and developed.

Design With a Purpose

The Shared Resources Center is staffed by nearly 60 highly skilled scientists and technologists. Rather than being squeezed into existing laboratory spaces, the new Center was designed and built to provide highly customizable spaces for the specific needs of the technology and staff.

The Hartwell Center for Biotechnology, one of the largest Shared Resources on campus, offers a large portfolio of services that relies on state-of-the-art technology and highly trained staff. Services provided by the Hartwell Center include next-generation sequencing, Sanger sequencing, and microarray analysis. The Macromolecular Synthesis group generates custom peptides that are tested by departments such as Chemical Biology & Therapeutics and Structural Biology. The design of the Hartwell Center's new space also includes the flexibility to spread out. In brief, the Hartwell Center's various services have been set up in areas designed specifically for them, and common equipment is now centrally located, so that it can be used efficiently and conveniently by everyone. The lack of physical walls and the staff's freedom to envision their ideal workspace resulted in laboratories such as the Macromolecular Synthesis Group designating a location for multiple vented hoods, a specialized area for protein synthesis and quality assessment, and another area for more traditional benchwork. Similarly, the Genomics Group designed a clean room for pre-PCR sample preparation in which nine people can work simultaneously (albeit after the pandemic ends), something that was not previously available on campus. The Proteomics and Metabolomics group uses liquid chromatography–mass spectrometry to sequence proteins and protein metabolites.

Many of the technologically advanced facilities require high-end equipment and instruments that need to be housed separately from the wet labs because the instruments produce heat and/or noise. Therefore, the new Center includes equipment zones that have controllable airflow and temperature that allow the instruments to operate more efficiently.

New Leadership and Laboratories in the Shared Resources Center

Christopher Calabrese, PhD (Administration), was recruited into the new role of Vice President of Laboratory Research Operations. In this capacity, Dr. Calabrese provides oversight of the functioning of most of the facilities within the Center and coordinates new laboratory research programs. To better align with the St. Jude Comprehensive Cancer Center's operations, Shondra M. Pruett-Miller, PhD (Cell & Molecular Biology), was named the Associate Director of Shared Resources in the Comprehensive Cancer Center. Dr. Pruett-Miller will extend her role as Director of the Center for Advanced Genomic Engineering within the Center and provide leadership for several additional facilities, including Cytogenetics, Flow Cytometry and Cell Sorting, Transgenic/Gene Knockout Core, and the Center for Modeling Pediatric Diseases.

The Center for Modeling Pediatric Diseases is the newest facility added to the Center. Born out of a Blue Sky initiative championed by Michael A. Dyer, PhD (Developmental Neurobiology), this laboratory expands patient fibroblasts, blood cells, and urine-derived cells and reprograms them to generate patient-derived induced pluripotent stem cells (iPSCs) for basic and translational research endeavors. It also provides a centralized source for iPSCs as a bank in conjunction with the Biorepository. The tissue samples and iPSCs will be used to develop new models to study the diseases affecting St. Jude patients. Under the direction of Sunita D'Souza, PhD, the new facility combines a highly skilled technical staff and advanced robotics to reproducibly reprogram somatic cells into stem cells, characterize these cells, and bank them for future differentiation into various lineages to aid with disease-modeling studies. Precision is key in this process, as error can introduce artifacts that hinder analysis.

Development and hiring are underway for the next addition to the Shared Resources Center, the Center for High Content Screening. This facility will enable researchers to simultaneously monitor multiple parameters in cells treated with drugs and/or other therapeutics. Such monitoring was once limited in scope; however, advanced technology and robotics now enable real-time imaging via multiple formats to determine the effect of treatments on various cellular parameters, including morphology, protein expression, and viability.

Shared Resources Center leadership worked with the Facilities Design team to ensure that the new Center meets the needs of the various groups. During the planning process, they also incorporated reserved space for future technologies as they are identified. The Center's leadership is always scanning the horizon for new technologies, so that those tools can be acquired and implemented swiftly upon approval.

Christopher Calabrese, PhD; Shondra M. Pruett-Miller, PhD

Growing a Shared Resource Center During the Pandemic

During the initial move, 13 laboratories relocated to the Shared Resources Center. The logistics of dismantling, moving, and re-establishing high-tech laboratories would be a challenge under normal circumstances. The complexity of the move was compounded by the COVID-19 pandemic. Faculty and staff had to navigate stay-at-home orders, remote work schedules, and COMPASS (COVID safety) requirements for social distancing and occupancy to move their workspaces into the new building. Vendors who visited campus to set up and recalibrate the equipment had to be trained and coordinated to comply with the new restrictions. Facilities Operations and Maintenance staff were instrumental in setting up new workspaces to exacting specifications before the highly choregraphed laboratory moves.

Mariana Santana Ponce

Although only a short walk from the main campus, the Shared Resource Center wanted to maintain the easy access to their services that researchers had previously enjoyed. To minimize disruption in the flow of thousands of specimens to and from the Center, the Shared Resources management team implemented a new sample-management system. Thanks to the development and deployment of this system by Yasmine Valentin-Vega, PhD (Administration), Information Services, and Materials Management, researchers can now access the Shared Resources services via kiosks that are strategically positioned across the campus. Samples are dropped off at a kiosk, where a QR code is assigned and scanned, and then the samples are stored safely until collected and delivered to the Center for processing.

Because of COVID safety guidelines, all visits to the Center must be prearranged, and nearly all meetings are conducted online. However, this has not impeded communication between the Shared Resources staff and researchers or among the various groups in the Center. Despite pandemic-related challenges, the Shared Resources staff members are increasingly united in their goal to provide the best technical services. The groups interact regularly through online platforms such as Microsoft Teams, an internal newsletter highlighting various groups and their services and capabilities, and other forms of engagement. In this manner, the Shared Resources Center provides not only essential services but also invaluable research partners and subject matter experts to scientists at St. Jude.

Suzanne McNeely

Richard Heath, PhD

Mishra Vibhor, PhD

Victoria Doyne, PhD

CONCLUSIONS

The new Shared Resources Center directly supports fundamental science, translational research, and preclinical trials at St. Jude. The Center also facilitates interactions among staff scientists and technologists with expertise in different fields to exchange ideas, improve best practices, and more effectively support St. Jude's mission.

SCIENTIFIC HIGHLIGHTS

Inhibiting the JAK/STAT Pathway Sensitizes CD8+ T Cells to Dexamethasone Treatment in Hyperinflammation

Cytokine storm syndromes (CSSs) are severe hyperinflammatory conditions that arise in patients with acquired or inherited immunodeficiency syndromes, autoimmune diseases, or cancer. They are often triggered by various infections. CSSs have also been described in patients receiving cancer-directed immunotherapies, such as chimeric antigen receptor–transduced T cells or bispecific T cell–engaging antibodies. CSSs are most commonly a consequence of ineffective lymphocyte cytolysis and/or excessive production of proinflammatory cytokines, which ultimately lead to tissue damage and multiorgan failure.

Hemophagocytic lymphohistiocytosis (HLH) is a CSS caused by mutations in the genes involved in immune cell cytotoxicity. The standard treatment for HLH consists of the glucocorticoid dexamethasone (DEX) and the chemotherapeutic agent etoposide. DEX induces apoptosis in CD8+ T cells, which have been implicated as drivers of HLH immunopathogenesis. In many patients, however, HLH is refractory to this treatment or relapses because the target cells are resistant to DEX. Kim E. Nichols, MD (Oncology), and Michelle L. Hermiston, MD, PhD (University of California, San Francisco), led a multi-institutional collaboration to investigate how the resistance of CD8+ T cells to DEX might be overcome. This work was published as a plenary article in the journal *Blood*.

Many cytokines that are elevated in HLH activate the JAK/STAT-signaling pathway in immune cells. Previously, Dr. Nichols and her research team reported that the JAK1/2 inhibitor ruxolitinib can lessen inflammation in mouse models of HLH. Nevertheless, ruxolitinib treatment did not eliminate all the manifestations of the disease. Concurrent with this work, Dr. Hermiston showed that cytokine-induced JAK/STAT signaling mediates DEX resistance in T-cell acute lymphoblastic leukemia cells and that this could be reversed by ruxolitinib. On the basis of these findings, Drs. Nichols and Hermiston teamed up to examine whether cytokine-mediated JAK/STAT signaling contributes similarly to DEX resistance in HLH and to assess whether ruxolitinib treatment would overcome this phenomenon. Together, they hypothesized that combined treatment would be superior to treatment with either agent alone.

The group first demonstrated that ex vivo exposure of activated mouse CD8+ T cells to the CSS-associated cytokines interleukin (IL)-2, IL-4, IL-7, and IL-15 facilitates the resistance of lymphocytes to DEX-induced apoptosis via the JAK/STAT pathway. Specifically, cytokine-activated JAK proteins phosphorylate STAT5, which activates pro-survival genes such as *BCL2*. Adding ruxolitinib to CD8+ T cells treated with IL-2 and DEX decreased STAT5 signaling in the cells and increased their sensitivity to DEX-induced cell death. The combination of ruxolitinib and DEX was then tested in a mouse model of HLH. The combination treatment decreased tissue immunopathology, as compared with that seen in mice treated with ruxolitinib or DEX alone, lowered the levels of soluble diagnostic markers for HLH, and substantially improved survival relative to that with DEX alone.

The researchers also analyzed plasma samples from humans with HLH and detected increased levels of cytokines that signal through STAT5. Of these, IL-2, IL-7, and IL-15 all conferred resistance to DEX-induced apoptosis of activated human CD8+ T cells in vitro, and this resistance was in proportion to the phosphorylation of STAT5. Together, these findings provide a rationale for administering ruxolitinib in combination with DEX to patients with HLH or other CSSs to reduce STAT5 signaling and thereby enhance the lymphotoxic effects of DEX to improve outcomes. *Meyer LK et al, Blood 136:657–68, 2020*

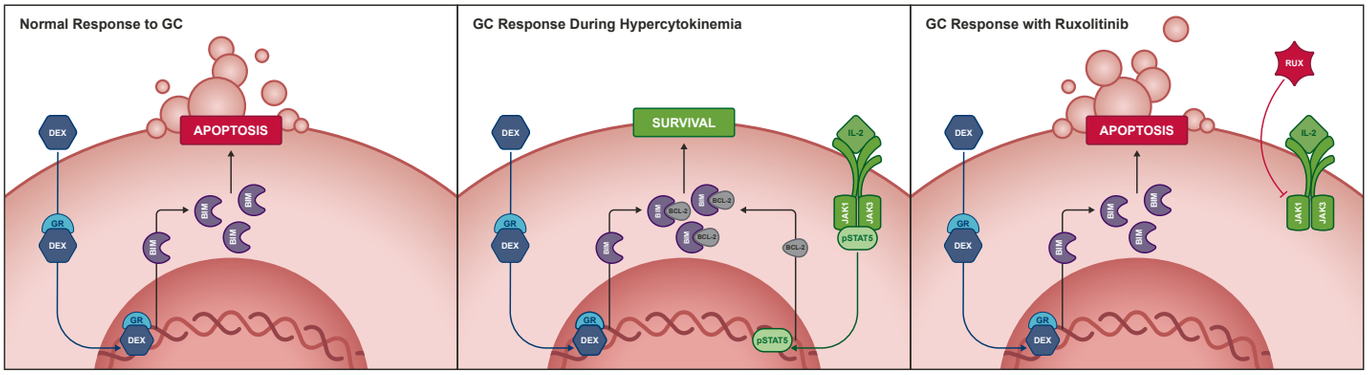


Figure. Under normal conditions, dexamethasone administration induces apoptosis of activated mouse T cells (left panel). Exposure of activated T cells to high levels of cytokines such as IL-2 upregulates pro-survival molecules such as BCL-2, which overrides dexamethasone-induced cell death (middle panel). Inhibition of JAK/STAT signaling through treatment with ruxolitinib sensitizes CD8+ T cells to dexamethasone-induced apoptosis during hyperinflammation (right panel). **Abbreviations:** BCL-2, B-cell lymphoma 2; BIM, BCL-2–like; DEX, dexamethasone; GC, glucocorticoid; GR, glucocorticoid receptor; IL-2, interleukin-2; pSTAT5 phosphorylated STAT5 protein; RUX, ruxolitinib. *Republished with permission of Elsevier Science & Technology Journals, from JAK/STAT pathway inhibition sensitizes CD8 T cells to dexamethasone-induced apoptosis in hyperinflammation, Meyer LK et al, Blood, 136:657–68. © 2020; permission conveyed through Copyright Clearance Center, Inc.*

A *Lancet Oncology* Commission Estimates the Disparities in Childhood Cancer Care and Outcomes in Low- And Middle-Income Countries and Provides Cost-Effective Solutions

Although remarkable strides in improving childhood cancer survival have been made over the last few decades, they have not been felt to the same extent in low- and middle-income countries (LMICs), as in high-income countries. Approximately 80% of the global cancer burden is borne by LMICs, yet only 5% of cancer care resources are allocated to these countries. How these considerable disparities in cancer burden and resources affect childhood cancer survival in LMICs, however, is unknown. To provide meaningful solutions that address these disparities, we must fully understand the incidence, outcomes, and care of childhood cancers in LMICs, as well as the cost-effective interventions and models for scale-up. Therefore, a *Lancet Oncology* Commission was tasked with evaluating current and projected childhood cancer incidence and outcomes in LMICs, the level of care and resources available for children with cancer in those countries, the services needed to correct the disparities in care and outcomes, and attainable and cost-effective ways by which these services can be provided. The Commission was co-led by Carlos Rodriguez-Galindo, MD (Global Pediatric Medicine, Oncology), and Prof. Rifat Atun (Harvard TH Chan School of Public Health) and included clinicians and researchers at St. Jude and other institutions around the world.

The Commission first estimated the global incidence of childhood cancers by creating a Global Childhood Cancer Microsimulation Model, which uses data extracted from cancer registries and national health system databases to estimate childhood cancer incidence in countries categorized according to their World Bank–designated income levels. The Commission estimated that by 2050, 13.7 million new cases of childhood cancer will occur worldwide, and 10.3 million of those cases will occur in LMICs. However, with the current level of cancer health care systems in place, 6.1 million childhood cancer cases will be undiagnosed by 2050.

In LMICs, more cases of childhood cancer will be undiagnosed than diagnosed, especially in south Asia and sub-Saharan Africa. Consequently, an estimated 9.3 million children in LMICs will die of cancer by 2050, accounting for 84.1% of all childhood cancer deaths in the world.

The Commission next assessed the current resources available for childhood cancer care and research. As expected, the availability of childhood cancer services greatly varies among LMICs, and public funding is not a priority in most of the countries. Foundations and philanthropic organizations generally provide what funding is available, and partnerships with hospitals in high-income countries, such as those facilitated by St. Jude Global, have improved childhood cancer research, education, clinical service quality, and outcomes.

The Commission identified three cost-effective and scalable interventions that, when implemented and scaled up simultaneously, would potentially prevent 6.2 million childhood cancer deaths worldwide by 2050: (1) increasing access to primary and specialty care, (2) establishing or improving social support services to lessen treatment abandonment rates, and (3) augmenting the availability of treatments and the quality of care. The lives saved and subsequent global productivity gained by simultaneously scaling up all of these interventions would be greatest in LMICs. The economic gains in global productivity would exceed the projected cumulative costs by four to one, thereby yielding a net global benefit in which every $1 spent would result in a $3 return in investment. Therefore, the Commission declared a global call to action to invest in the proposed interventions to ensure equitable childhood cancer care and outcomes that will benefit all countries, regardless of income level. *R Atun et al, Lancet Oncol, 21:e185–e224, 2020*

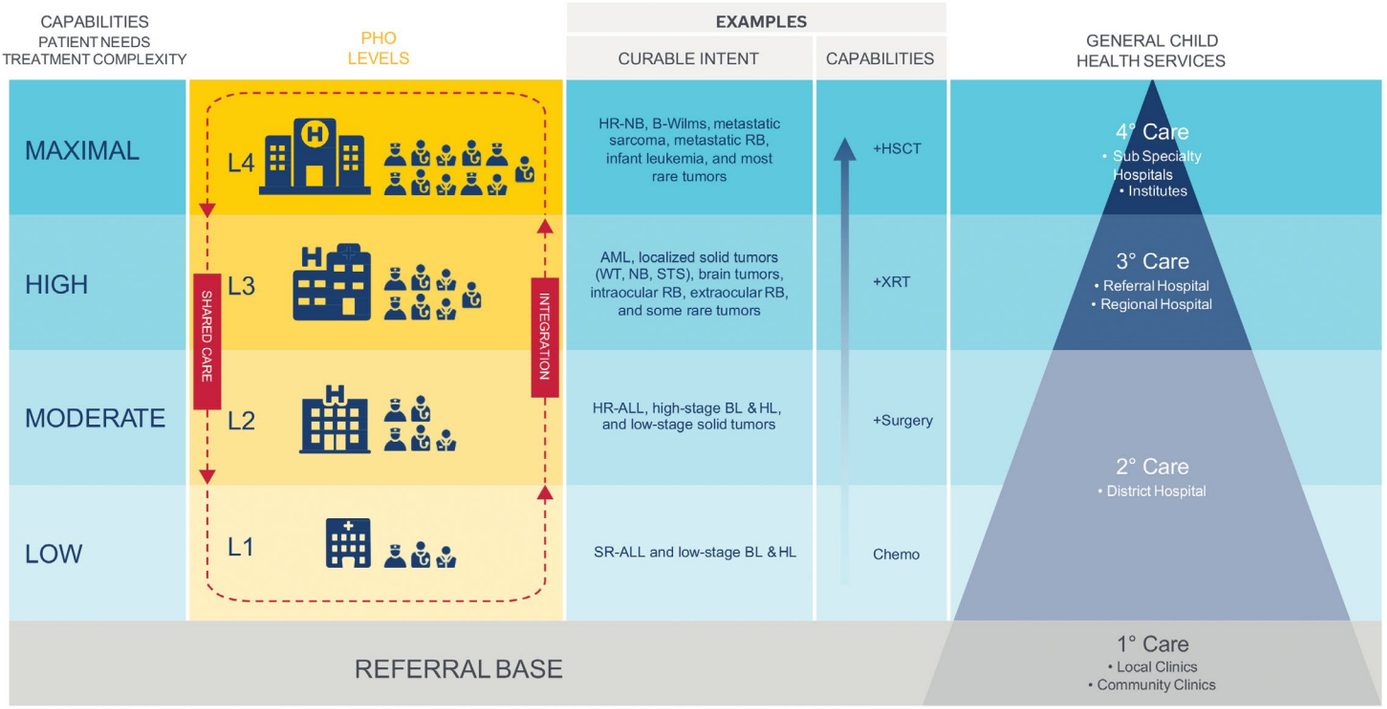


Figure. Illustration of the capabilities needed to provide interventions for childhood cancers. The correlation illustrated is not universal; many countries have only one or two levels (L), do not meet L3 capabilities, or do not have L4 capabilities. Childhood cancer treatment facilities coexist with general child health services. This framework proposes that facilities with greater capabilities benefit from the coexistence of greater general child health capabilities in their attempt to achieve favorable outcomes for children with cancer. It also proposes that improved capabilities for childhood cancer outcomes can help promote the development of increased general child health capabilities. Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; B-, bilateral; BL, Burkitt lymphoma; HL, Hodgkin lymphoma; HR, high-risk; NB, neuroblastoma; PHO, pediatric hematology-oncology; RB, retinoblastoma; SR, standard risk; STS, soft-tissue sarcoma; WT, Wilms tumor. *Reprinted from The Lancet Oncology, Atan R et al, Sustainable care for children with cancer: a Lancet Oncology Commission, e185–e224, © 2020, with permission from Elsevier.*

Lung Function Is Compromised by Exuberant Fibroblast Activity via the ADAMTS4 Protease

Severe respiratory infections can cause acute respiratory distress syndrome (ARDS), leading to respiratory failure and morbidity. No effective treatments for ARDS are available. To address this issue, Paul G. Thomas, PhD (Immunology), and his colleagues searched for a therapeutic target to improve the outcome of respiratory infections and avoid ARDS and reported their findings in the journal *Nature*.

The researchers started by closely examining the mechanisms by which the immune responses elicited by influenza infection to clear the pathogen transform to influence the development of ARDS. They determined the single-cell gene-expression profiles of murine lung cells at several timepoints after influenza infection and performed gene-set enrichment analysis to pinpoint the active pathways in the three main cell types in the lung: fibroblasts, epithelial cells, and endothelial cells. Fibroblasts expressing genes suggesting an inflammatory function were found in two activation states: damage-responsive fibroblasts, which were enriched for NF-kB–signaling genes, and interferon-responsive fibroblasts, which were enriched for type-1 interferon-responsive pathway genes. Similar expression patterns were verified in human lung biopsy samples.

Infecting healthy human bronchial epithelial cells with H3N2, H5N6, or H7N9 influenza induced fibroblasts to express genes that are enriched in inflammatory states, including the extracellular matrix protease genes *ADAMTS4, MMP*3, and *MMP13*. In studying the proteases' role in directing lung repair, Dr. Thomas and his colleagues found that ADAMTS4 was induced earliest and expressed throughout the repair stage. Furthermore, the researchers performed a meta-analysis of public gene-expression data sets from pulmonary fibrosis, interstitial lung disease, allergy and asthma, and viral infection with severe acute respiratory syndrome coronavirus (SARS-CoV-2), which revealed that *ADAMTS4* is overexpressed across a spectrum of inflammatory lung diseases. The researchers also performed a novel spatial transcriptomic analysis, integrating these results with their high-resolution single-cell transcriptomics, and found *Adamts4* was enriched in areas where damage-responsive fibroblasts were also present. When challenged with a lethal dose of influenza, *Adamts4*-knockout mice had less inflammation and damage to lung tissue than did wild-type mice, yielding better lung function results. In endotracheal aspirate samples from pediatric patients and adult patients hospitalized for influenza treatment, ADAMTS4 concentration was associated with disease severity, after controlling for demographic factors (e.g., age, sex, previous health status).

Maintaining a balanced immune response so that the pathogen can be cleared without inducing overwhelming lung tissue damage is key to patients' ability to survive a severe respiratory infection. This work suggests that such a balance depends on ADAMTS4 concentration, with high concentrations of the protease predicting a poorer outcome. The authors stress the need for additional studies of the role of ADAMTS4 in other respiratory infections, including SARS-CoV-2 infection, and propose the ADAMTS4 activity may be a therapeutic target through which ARDS can be controlled.
Boyd DF et al, Nature 587:466–71, 2020

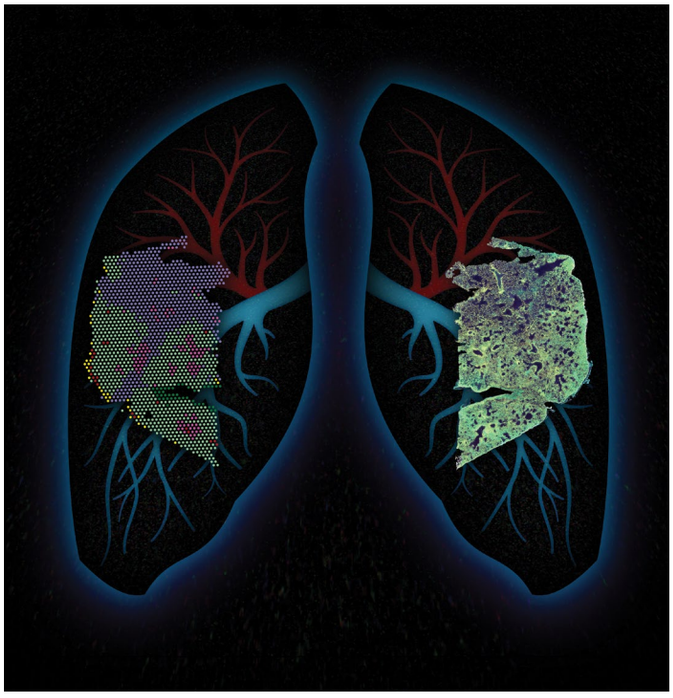


Figure. Illustration of mouse lungs with data images overlaid. Hematoxylin and eosin staining of a section of mouse lung (right) and spatial transcriptomics data (left) showing unsupervised clustering of transcriptional profiles across the lung. Purple areas show normal, relatively uninflamed gene signatures, and green and yellow show areas associated with extensive fibroblast activity, inflammation, and extracellular matrix remodeling. Magenta and red areas represent focal lymphocytic infiltration.

Mutations in DNA-Repair Genes Are Associated With Subsequent Neoplasms in Long-Term Survivors of Childhood Cancer

Survival of childhood cancer has considerably improved with advances in cancer-directed therapies. However, long-term survivors of childhood cancer experience increased risk of subsequent neoplasms later in life. As shown in a previously published study, these subsequent neoplasms may be partially driven by the pathogenic mutations in cancer-predisposition genes that presumably also caused the initial neoplasms. To further investigate the genetic factors in conjunction with genotoxic effects of the cancer-directed therapies and their roles in subsequent neoplasm development in long-term childhood cancer survivors, Zhaoming Wang, PhD (Epidemiology & Cancer Control, Computational Biology), and his colleagues expanded and analyzed mutations in DNA-repair genes with existing whole-genome sequencing data and reviewed the treatment regimens of 4402 childhood cancer survivors enrolled in the St. Jude Lifetime Cohort study.

Because many cancer-directed therapies induce DNA damage, the researchers specifically focused on pathogenic mutations in 127 genes involved in the following six major DNA-repair pathways: base-excision repair, Fanconi anemia, homologous recombination (HR), mismatch repair, nucleotide-excision repair, and nonhomologous end joining. An impaired ability to resolve the DNA damage induced by cancer-directed therapy in healthy cells because of mutations in DNA-repair genes may exacerbate genomic instability and drive future oncogenic events. In the *Journal of Clinical Oncology*, Dr. Wang and his team reported that 495 childhood cancer survivors experienced a total of 1269 subsequent neoplasms, including nonmelanoma skin cancer, meningioma, breast cancer, thyroid cancer, and sarcoma.

The researchers identified 538 pathogenic mutations in 98 DNA-repair genes from 508 survivors. The pathogenic mutations included 70 missense mutations, 175 nonsense mutations, 196 frameshift mutations, one in-frame protein deletion, 79 splicing mutations, and 18 copy-number variations. Most of the DNA-repair genes affected by these mutations are components of the HR pathway, which is important for repairing DNA double-strand breaks that result from ionizing radiation or anthracycline treatment. Indeed, female survivors with HR gene mutations who received treatment with high doses of chest-specific radiotherapy or anthracyclines had a four-fold increased risk of subsequent breast cancer. Furthermore, survivors with HR gene mutations who were treated with high doses of alkylating agents had a 15-fold increased risk of subsequent sarcoma. In addition, pathogenic mutations in genes involved in nucleotide-excision repair conferred a 13-fold increased risk of subsequent thyroid cancer in survivors who received high-dose, neck-specific radiotherapy.

Together, these findings demonstrate that understanding the genomic context and treatment history of long-term childhood cancer survivors is key to identifying those who are at the greatest risk of experiencing subsequent neoplasms. Survivors who are at high risk of subsequent neoplasms would greatly benefit from continuous cancer surveillance and enhanced prevention strategies to improve their long-term outcomes and quality of life. *Qin N et al, J Clin Oncol 38: 2728-40, 2020*

Zhaoming Wang, PhD

Chemotherapy Regimens That Include Thiopurine Can Cause Gene Mutations and Treatment Resistance in Children With Relapsed Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is the most common subtype of leukemia in children and affects blood cells and immune cells of patients. Although chemotherapeutic regimens have improved cure rates for childhood ALL in developed countries to almost 90%, relapse rates remain higher for children in developing countries that have a high incidence of ALL. Relapsed ALL is associated with a poor prognosis, as it frequently develops resistance to current chemotherapy regimens.

To better understand the genetic and mutational processes in relapsed ALL, an international collaboration between multiple medical centers and institutions in China and the U.S. was launched in 2016. The study included 103 children with relapsed ALL, most of whom were treated at the Shanghai Children's Medical Center, and was a collaboration with Jinghui Zhang, PhD (Computational Biology), and her group, Jun J. Yang, PhD (Pharmaceutical Sciences, Oncology), and Ching-Hon Pui, MD (Oncology, Pathology). This work was published in the journal *Blood*.

Studies have shown high rates of novel mutations in pediatric patients with relapsed ALL that were not detected at the time of initial diagnosis. Ultra-deep sequencing analysis performed in patients with relapsed ALL identified 12 genes that were frequently enriched for relapse-specific alterations. Functional analysis of these mutations showed that they were often related to increased resistance to common chemotherapy agents. Temporal modeling showed that the novel mutations may be present, yet undetectable, at the time of diagnosis in patients who experience ALL relapse very early (less than 9 months after diagnosis). In patients who experienced relapse after 9 months, detailed mutational analysis revealed that some of the mutations, specifically two novel relapse-specific mutational signatures, A and B, may be induced by the chemotherapeutic agents used to treat ALL. A subset of relapses that occur after 9 months can be attributed to "on-treatment" acquisition of drug-resistant ALL relapse.

Dr. Zhang and her colleagues also correlated specific mutations with chemotherapy regimens and found that signature B was definitively linked to thiopurines, a class of chemotherapy agents commonly used in ALL. Clonal analysis also revealed that clones with acquired resistance mutations are often undetectable at initial diagnosis and may appear during the course of treatment. The researchers showed that multiple resistance mutations can be acquired sequentially through chemotherapy-induced mutagenesis. Mutational signatures A and B were subsequently added to the Sanger Center's *Catalogue of Somatic Mutations in Cancer* (COSMIC), which includes approximately 60 validated mutational signatures that will enable other researchers to further study these therapy-induced mutations.

Results from this study suggest that chemotherapeutic agents can cause novel mutations and induce drug resistance. These data can guide precision medicine approaches and less toxic therapies to improve the treatment of relapsed ALL. Regular detailed genomic analysis of pediatric patients with high-risk ALL could enable early detection of mutations and guide effective therapy for relapsed ALL. *Li B et al, Blood 135:41–55, 2020*

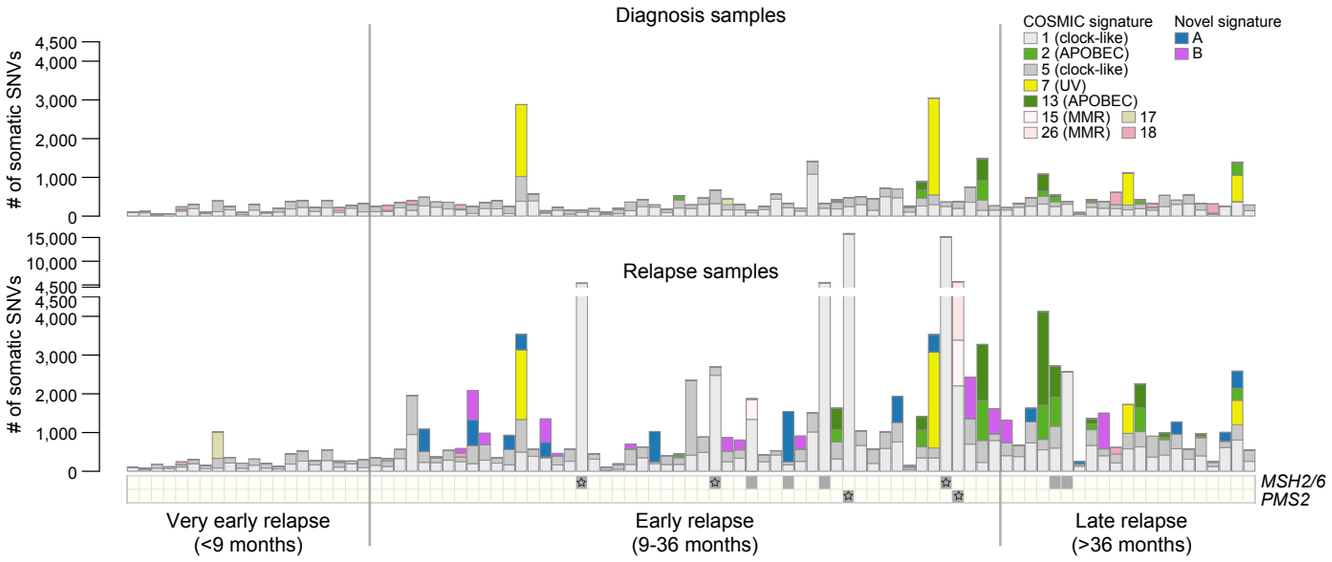


Figure. Evolution of mutational signatures. The two plots show the contributions of known *Catalogue of Somatic Mutations in Cancer* (COSMIC) signatures and two novel ALL relapse-specific signatures (A and B) to somatic single-nucleotide variants identified in the matched diagnostic (top) and relapse (bottom) samples from patients in the three time-to-relapse categories. Relapse-specific mutations in the DNA mismatch-repair genes *MSH2, MSH6*, and *PMS2* are indicated at the bottom. Samples with biallelic mutations are indicated by a star. APOBEC (apolipoprotein B mRNA-editing enzyme, catalytic polypeptide) is a prominent mutational signature in cancer. MMR indicates mismatch repair deficiency-associated signatures. UV indicates ultraviolet mutational signature. *Republished with permission of Elsevier Science & Technology Journals, from Therapy-induced mutations drive the genomic landscape of relapsed acute lymphoblastic leukemia, Li B et al, Blood, 135:41-55. © 2020; permission conveyed through Copyright Clearance Center, Inc.*

ELP1 Is a Novel Cancer-Predisposition Gene in Children With SHH Medulloblastoma

Despite advances in the field of genome analysis, the genetic and molecular bases of several rare cancers remain unclear. Only 5% to 10% of pediatric cancer diagnoses are linked to genetic predisposition, and the exact role of heritable genetic alterations in the development of cancer is not fully clear. One example is childhood medulloblastoma, which remains one of the most common malignant brain tumors.

An international collaborative study, including researchers from St. Jude, the European Molecular Biology Laboratory, the German Cancer Research Center, and other institutions, was undertaken to determine genetic predisposition to medulloblastoma. The team led by Paul A. Northcott, PhD (Developmental Neurobiology), conducted an in-depth genomic sequencing analysis to identify novel germline mutations in 713 pediatric patients with medulloblastoma. Analyses of loss-of-function (LOF) variation in autosomal protein-coding genes revealed germline mutations in the Elongator complex protein (ELP1) in 14% of children with Sonic hedgehog–subgroup medulloblastoma (MB_{SHH}). ELP1 is the largest subunit of the conserved Elongator protein complex, whose primary function is to modify the wobble position of transfer RNAs to drive translational elongation. In comparison, the low burden of these LOF germline mutations in cancer-free patients suggested that *ELP1* is an MB_{SHH}-specific predisposition gene. Germline *ELP1* LOF variants were also notably absent in 51 adult patients (older than 20 years) with MB_{SHH}, confirming the distinct association of these mutations with pediatric MB_{SHH}. The investigators also found that the pathogenic mutations were inherited across generations. These data strongly support the hypothesis that *ELP1* is a novel cancer-predisposition gene specifically associated with pediatric MB_{SHH}.

Transcriptome-level data from 208 patients in the study showed that expression of *ELP1* mRNA was significantly lower in MB_{SHH} than in other medulloblastoma subgroups. This result, along with associated changes in the expression of other key proteins involved in protein synthesis, suggests a potential association between *ELP1* deficiency and disruption of protein homeostasis. Proteome profiling of pediatric patients with MB_{SHH} and *ELP1* LOF mutations also showed disruption of the Elongator protein complex and presumed disruption of its function, resulting in aberrant protein synthesis, protein misfolding, and aggregation. Transcriptome analysis further showed that *ELP1* is primarily expressed in the cerebellum during development of the human brain, and mutations of *ELP1* are most likely associated with transcriptional changes in medulloblastoma.

This study emphasizes the need to expand genetic studies beyond known cancer-predisposition genes and extend surveillance in patients with cancer and their families. It also implicates a previously underappreciated role for translational deregulation in cancer cells, which could guide targeted molecular therapy of cancer in the future. *Wazak SM et al, Nature 580:396–401, 2020*

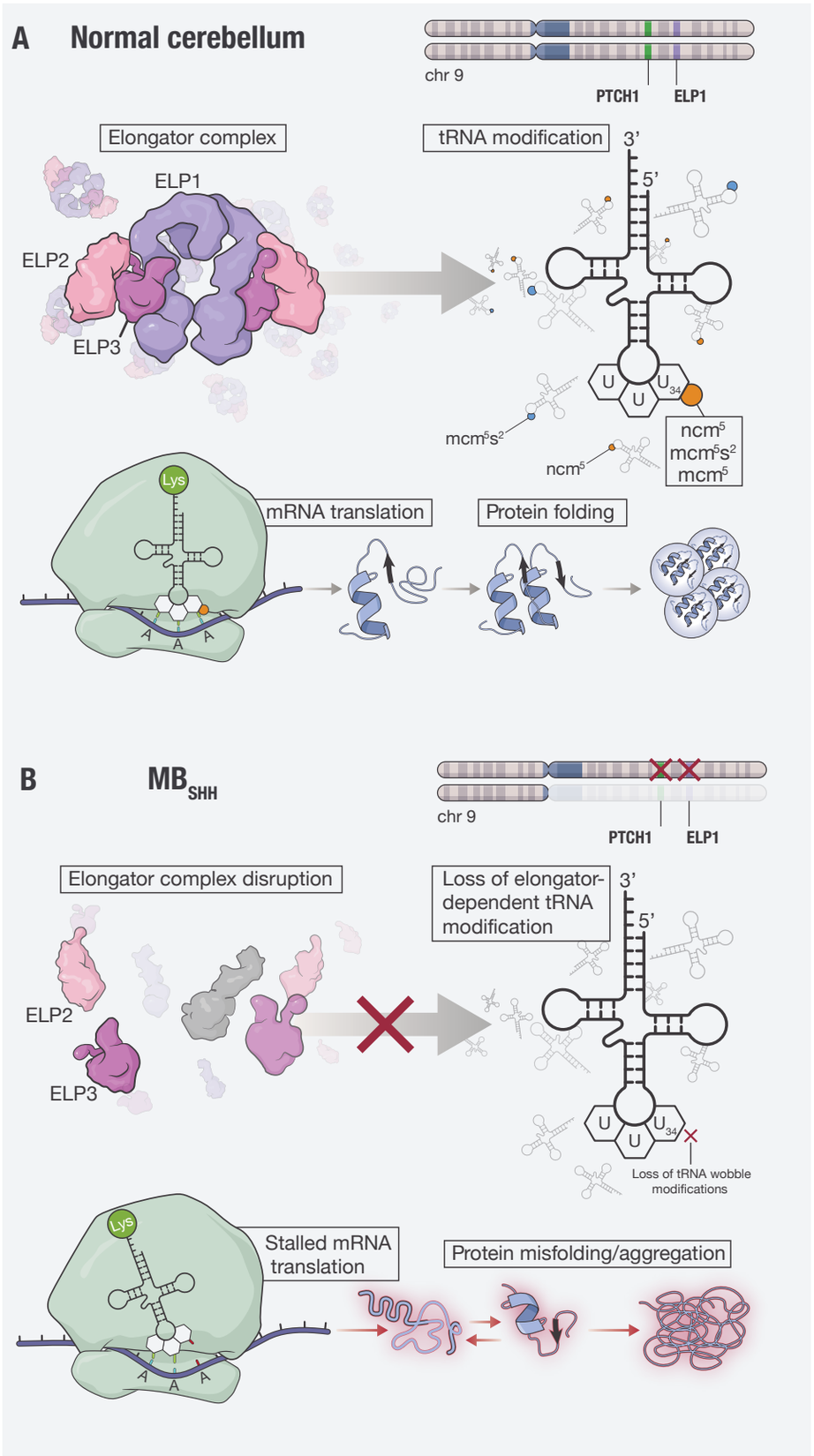


Figure. Diagram of (**A**) protein synthesis during normal cerebellum development and (**B**) the pathobiology that occurs in SHH-subgroup medulloblastoma (MB_{SHH}). Germline mutation of *ELP1*, followed by somatic inactivation of *PTCH1* and the second *ELP1* allele, both of which map to chromosome 9 (Chr. 9), destabilize the Elongator protein complex, which normally consists of six subunits (ELP1-ELP6). This destabilization causes the loss of Elongator-dependent tRNA modifications at the U34 wobble position (i.e., ncm^5, mcm^5s^2, mcm^5), stalled mRNA translation, protein misfolding, aggregation, and induction of the unfolded protein response. *Reprinted from Trends in Genetics, 37/3, Garcia-Lopez J et al, Deconstructing sonic hedgehog medulloblastoma: molecular subtypes, drivers, and beyond, 235-50, © 2021, with permission from Elsevier.*

Association of Hearing Impairment With Neurocognition in Survivors of Childhood Cancer

Although most patients with childhood cancer now survive more than 5 years beyond their initial diagnosis and are considered long-term survivors, they are still at risk for a number of morbidities stemming from the disease and/or its treatment. These chronic conditions may decrease childhood cancer survivors' quality of life. In healthy children, impaired hearing is associated with neurocognitive deficits, but the relation between these conditions in childhood cancer survivors has not been fully studied. To address this issue, Johnnie K. Bass, PhD (Rehabilitation Services), and other researchers involved in the St. Jude Lifetime Cohort study (SJLIFE) evaluated the association between hearing impairment and task-specific neurocognitive function in adult survivors of childhood cancer.

In a recent *JAMA Oncology* article, Dr. Bass and her colleagues reported their findings from a large cohort of 1520 childhood cancer survivors (median age, 29 years). Data were collected from 2007 to 2017 as part of SJLIFE, the hospital's ongoing follow-up study quantifying long-term health outcomes of childhood cancer survivors. A combination of standard, age-appropriate neurocognitive tests was performed to assess study participants' intelligence, attention, memory, executive function, processing speed, and academic function. Scores equivalent to the tenth percentile or lower were defined as indicating deficits. A battery of tests was used to assess hearing impairment, which was then graded by using the Chang Ototoxicity Grading Scale (grades 0-4), with 0 indicating normal hearing and 2b or higher indicating severe impairment.

As the researchers expected, the risk of hearing impairment was highest among childhood cancer survivors who had cochlear exposure to radiation or were treated with known ototoxins (i.e., drugs that can cause hearing loss). Those with severe hearing impairment also had impaired neurocognitive function in at least one of the specific areas tested, including executive functioning, processing speed, and other areas that do not rely on verbal abilities. The association of severe hearing impairment with neurocognitive deficits was independent of the type of cancer-directed treatment the survivor received. That is, the association held even for those whose treatment had not included cochlear irradiation or ototoxins.

On the strength of these results, the authors recommend that childhood cancer survivors receive early screening to detect hearing impairment and be offered additional interventions, such as hearing aids and educational accommodations, to help maintain neurocognitive skills. Further study is needed to determine whether correcting the severe hearing impairment already affecting some adult survivors can improve neurocognitive performance.
Bass JK et al, JAMA Oncol 6:1363-71, 2020

Johnnie K. Bass, PhD

Incompatibility of *ATRX* Mutations and *MYCN* Amplification in Neuroblastoma

Oncogenes enable tumors to grow unchecked, in direct opposition to tumor-suppressor genes, which confer a disadvantage to cancer cells. Many aggressive tumors have altered expression of both gene types, having not only mutations that activate oncogenes but also those that inactivate tumor-suppressor genes. In neuroblastoma, the most common extracranial solid tumor of childhood, activation of the *MYCN* oncogene and inactivation of the *ATRX* tumor-suppressor gene are both correlated with high-risk disease and poor prognosis. Recently, Michael A. Dyer, PhD (Developmental Neurobiology), and his colleagues initiated a study building on findings from both the Therapeutically Applicable Research to Generate Effective Treatment initiative and the Pediatric Cancer Genome Project aimed at uncovering patterns of gene expression in pediatric neuroblastoma that could aid our understanding of the disease and, ultimately, increase effective therapeutic options.

The researchers first examined DNA sequencing and copy number data from 828 germline and tumor samples from 473 patients with neuroblastoma to identify variations in the *ATRX* sequence and the *MYCN* copy number.

In a recent *Nature Communications* article, they reported that mutations of the *ATRX* tumor-suppressor gene and amplification of the *MYCN* oncogene are not found together. This result was further analyzed in genetically altered murine models of neuroblastoma with various combinations of modified *ATRX* and *MYCN* expression and followed up by a series of studies in human cell lines to determine the underlying molecular mechanisms at play.

The lethality of the combination of *ATRX* and *MYCN* alterations was due to the combination of replicative stress, metabolic reprogramming, and other detrimental effects induced by the individual mutations that the cells could not overcome. This result stands in contrast to the typical case of genetic alterations being incompatible because they affect the same pathway.

The researchers' long-term goal is to take advantage of the lethality of these genetic alterations in neuroblastoma cells by targeting *ATRX* in *MYCN*-amplified tumors and *MYCN* in *ATRX*-mutant tumors. However, the authors stress that much still needs to be learned about the proteins' targets before such a therapeutic strategy can be developed. *Zeineldin M et al, Nat Commun 11:913, 2020*

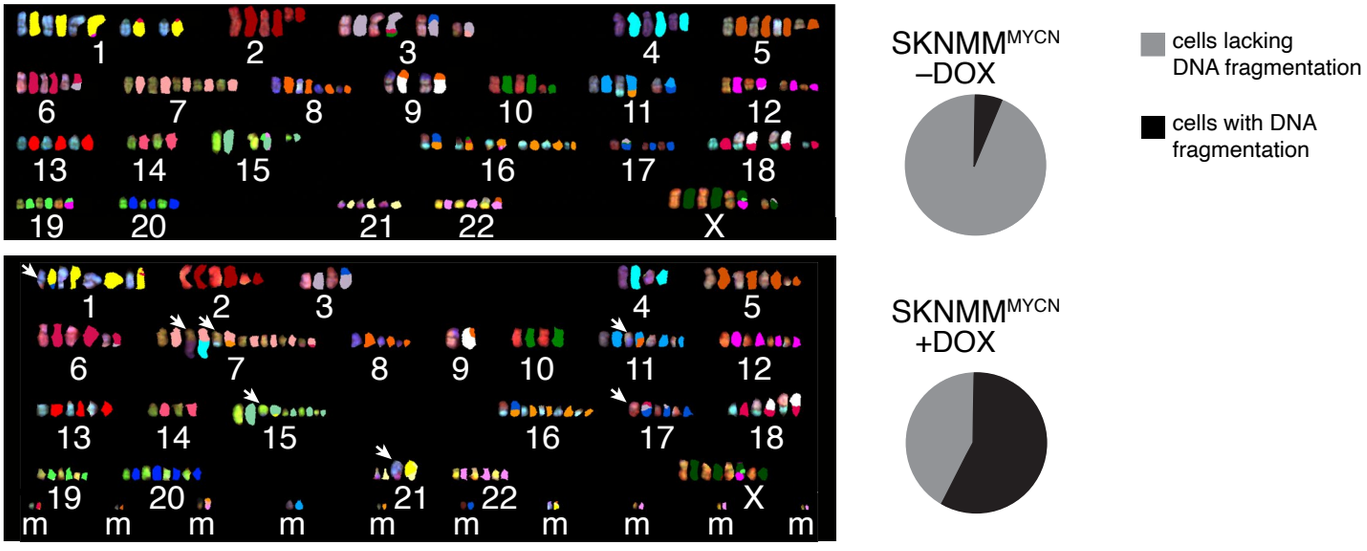


Figure. The expression of MYCN in *ATRX*-mutant neuroblastoma cells causes DNA damage. Spectral karyotype analysis of SKNMM^{MYCN} neuroblastoma cells shows a significant increase in DNA fragmentation and translocations in cells treated with doxycycline (DOX). Chromosomes are shown adjacent to the pseudo-colored representation. Arrows indicate translocations, and *m*s indicate marker chromosome fragments that could not be identified. Pie charts show the proportions of cells with or without DNA fragmentation (n=50). *Modified from Zeineldin M et al, MYCN amplification and ATRX mutations are incompatible in neuroblastoma. Nat Commun, 11:913, 2020. http://creativecommons.org/licenses/by/4.0/*

SJ733, a Novel Inhibitor of *Plasmodium Falciparum* ATP4, Has Favorable Pharmacokinetics, Tolerability, Safety, and Efficacy in Humans

Despite improvements in prevention and treatment, malaria remains a leading cause of morbidity and mortality in many countries, with most deaths being caused by *Plasmodium falciparum*. The rise of resistance to the standard combination therapies among *Plasmodium* species necessitates the development of new antimalarials. One such novel drug is SJ733, which was discovered and developed at St. Jude and is one of the first in a new class of antimalarial compounds to reach clinical trials.

The ATP4 protein helps maintain a low concentration of sodium ions in *P. falciparum*. By inhibiting ATP4 during the blood and sexual stages of *P. falciparum* development, SJ733 disrupts this sodium ion homeostasis, with lethal consequences for the parasite. To assess SJ733 in humans, Aditya H. Gaur, MD, MBBS (Infectious Diseases), and James S. McCarthy, MD (QIMR Berghofer Medical Research Institute, Brisbane, Australia), led a first-in-human Phase Ia/b trial of SJ733. Although hospital staff have led similar projects for vaccines and gene therapy initiatives, this is the first "soup-to-nuts" small-molecule project at St. Jude, in which a novel compound was created in the lab and brought to clinical trials. The results of the trial were published in *The Lancet Infectious Diseases*.

The Phase Ia study, which was conducted in Memphis, examined the tolerability, safety, and pharmacokinetics of SJ733 in 23 healthy participants without malaria who received the drug as one to three nonconsecutive doses (range, 75-1200 mg). In these patients, SJ733 was safe and well tolerated at all doses, with drug exposure being dose proportional up to 600 mg but reaching a plateau thereafter. With the 600-mg dose, the median time to peak plasma concentration was 1 hour. The researchers proceeded to test doses of 150 mg (predicted to be subtherapeutic) and 600 mg in volunteers with induced blood-stage malaria in a Phase Ib study conducted in Australia. In this study, 15 malaria-naïve, healthy volunteers were injected with *P. falciparum*–infected red blood cells and subsequently treated with a single dose of SJ733 (150 or 600 mg). The parasite clearance half-lives in these participants were 6.47 hours for the 150-mg dose and 3.56 hours for the 600-mg dose. In the 600-mg cohort, the median terminal half-life of the drug was 17.4 hours. Recrudescence (relapse after remission) of the parasite was predicted to occur 38 hours after dosing, at which time the plasma concentration of SJ733 would no longer be sufficient to clear the organism. No serious side effects were attributed to the SJ733 treatment, and all participants subsequently received a curative dose of conventional combination therapy.

Based on these findings, the effect of a single dose of SJ733 appears to be too short-lived to completely clear *P. falciparum* parasites from the blood; however, the favorable pharmacokinetic, tolerability, and safety profile of the drug and its rapid antiparasitic effect support its development as a fast-acting component of combination antimalarial therapy. The Phase Ia study team pursued two additional dosing strategies to increase drug exposure and time over threshold: a multidose approach, in which SJ733 was administered once a day for 3 days (NCT02661373), and a pharmaco-enhancement strategy using the CYP3A4 inhibitor cobicistat (because SJ733 is primarily metabolized by this enzyme). *Gaur AH et al, Lancet Infect Dis 20:964–75, 2020*

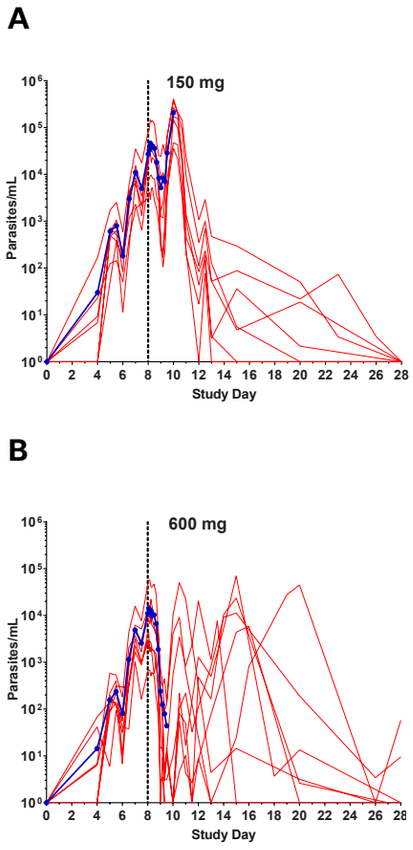


Figure. Parasite clearance profiles. Study participants received a single dose of SJ733 on Day 8 (vertical dashed line) after inoculation with *P. falciparum*–infected erythrocytes. Participants received either 150 mg (**A**) or 600 mg (**B**) SJ733. Parasitemia was measured by 18s ribosomal RNA quantitative PCR. Red lines indicate individual parasitemia, and blue lines indicate mean parasitemia until the earliest administration of artemether-lumefantrine. *Reprinted from The Lancet Infectious Diseases, 20, Gaur AH et al, Safety, tolerability, pharmacokinetics, and antimalarial efficacy of a novel Plasmodium falciparum ATP4 inhibitor SJ733: a first-in-human and induced blood-stage malaria phase 1a/b trial, 964–75, © 2020, with permission from Elsevier.*

Differential Expression of GPCR Isoforms Modulates Tissue-Specific Signaling and Drug Responses

G-protein–coupled receptors (GPCRs) comprise the largest family of membrane proteins in the human genome. GPCR-mediated signaling is an essential mechanism by which cells respond to extracellular signals. The binding of ligands to GPCRs on the cell membrane activates downstream signaling pathways that modulate the cell's physiological response to the environment. Predicting GPCR signaling is complicated by a phenomenon termed "signaling bias," whereby diverse ligands acting on the same receptor or the same ligand activate different receptors in different cells, tissues, or genetically diverse individuals, thereby triggering variable cellular responses.

Signaling bias in response to the same ligand can result from GPCR polymorphisms found in the population or in tissue-specific expression of GPCR isoforms in a single individual. In *Nature*, a team led by M. Madan Babu, PhD, FRSC (Structural Biology), reported a data science approach they pioneered to analyze how a single GPCR gene can generate different isoforms with distinct signaling properties in humans. Given that more than one-third of drugs target GPCRs, an in-depth understanding of GPCR isoform diversity and its influence on receptor function can help us understand receptor physiology and have a direct impact on future drug design to improve the response to GPCR-targeted drugs.

Dr. Babu's team used transcriptome analysis to identify 363 GPCRs with detectable expression that map to the wild-type "reference" genome and 262 alternate nonreference GPCR isoforms. Then, they performed structural analyses, which identified 55 distinct structural fingerprints capable of discriminating nonreference receptor isoforms. The observed diversity in key structural segments in GPCR isoforms represents an underappreciated source of functional variation in GPCRs; literature searches revealed that 12 of these isoform fingerprints have already been associated with functional variability in individual GPCRs. The observation that distinct structural changes are commonly associated with specific functional outcomes demonstrates how expression of uncharacterized alternate GPCR isoforms can contribute to GPCR functional diversification.

Combinatorial expression analysis revealed tissue-specific expression of distinct isoform combinations, potentially generating tissue-specific signaling outcomes in response to the same ligand. As illustrated for a set of newly characterized receptor isoforms, these isoform-mediated, system-specific signaling responses could be an important source of physiological signaling bias and influence the pharmacologic response to drugs. Thus, in-depth knowledge of the receptor isoforms expressed in a particular system can inform the selection of refined experimental models with increased translational value to understand receptor function and facilitate drug research and discovery.

Dr. Babu and his team's analysis of 111 GPCRs targeted by 474 drugs approved by the U.S. Food and Drug Administration showed that 42% of the GPCR drug targets exist in more than one isoform. This finding implies that the tissue-specific distribution of these isoforms can dictate the efficacy of existing drugs in different tissues. Furthermore, understanding the variations in structure and expression of different GPCR isoforms can facilitate future drug development and selection to improve pharmacologic specificity, therapeutic efficacy, and safety. Based on this work, future research can focus on developing drugs by considering context-specific GPCR signaling and isoform selectivity. *Marti-Solano M et al, Nature 587; 650–6, 2020*

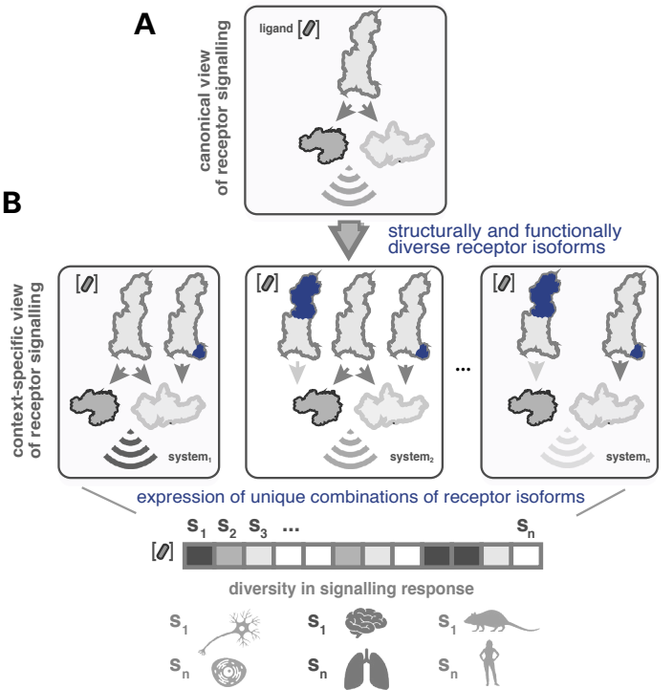


Figure. Canonical view vs. context-specific view of GPCR signaling. (**A**) Receptors that have a single isoform are activated by the binding of a specific ligand, resulting in one signaling response. (**B**) Receptors that have multiple isoforms in the same system can respond to the same ligand differently, thereby resulting in combinatorial expression of functionally distinct GPCR isoforms. This ability diversifies the signaling responses in different systems (s_1-s_n), which can correspond to different levels of complexity (e.g., single cell, tissue, or organism). *Reprinted by permission from SNCSC GmbH: Nature Springer, Nature, 587:650–6. Combinatorial expression of GPCR isoforms affects signalling and drug responses. Marti-Solano M et al, © 2020*

Bridging DNA Breaks Activates the PARP2–HPF1 Complex to Modify Chromatin

DNA-strand breaks recruit two poly(ADP-ribose) polymerase (PARP) enzymes, PARP1 and PARP2, to the chromatin to modify histone proteins and other substrates by adding mono- and poly(ADP-ribose). This ADP ribosylation is important for subsequent chromatin decompaction to facilitate damage repair, and it provides an anchor for recruiting downstream signaling and repair factors to the sites of the DNA breaks. ADP ribosylation occurs predominantly on serine residues and requires the participation of histone PARylation factor 1 (HPF1), which forms complexes with PARPs and switches their amino acid specificity.

Inhibitors of PARP catalytic sites are efficient anticancer agents. Used alone or in combination with chemotherapy or radiation therapy, PARP inhibitors prevent the repair of DNA damage in cancer cells, causing them to die. However, resistance to these inhibitors, which arises from mutations in the genes encoding PARPs, is a growing concern. To understand how PARPs interact with DNA breaks and gain insight into how mutations cause resistance to PARP inhibitors, Mario Halic, PhD (Structural Biology), and his colleagues used cryogenic electron microscopy to determine the molecular structure of human PARP2–HPF1 complexes bound to nucleosomes that mimick double-strand DNA breaks. They published their findings in the journal *Nature*.

The structural analysis revealed that the PARP2–HPF1 complex bridges two nucleosomes via the PARP2 WGR domain, with the broken DNA ends aligned for ligation. This binding and bridging of two nucleosomes by PARP2 induce structural changes in the enzyme that signal the recognition of a DNA break to the catalytic domain, which then licenses HPF1 binding and PARP2 activation. This in turn enables binding of the coenzyme NAD^+, which is required for ADP ribosylation to occur. The data suggest that active PARP2 cycles through conformational states to exchange NAD^+ and substrate, perform its catalytic function, and release the product. Such cycling would enable a PARP–HPF1 complex to bind and modify multiple substrate molecules while remaining bound to, and thereby protecting, the chromatin lesion.

Several mutations of PARP1 amino acid residues have been found in cancers resistant to PARP inhibitors. For one such mutation, which disrupts the signaling between the PARP WGR and catalytic domains, Dr. Halic and his group showed that mutating the corresponding residue in PARP2 abolished nucleosome binding and bridging, which might explain why the mutant PARP1 rapidly dissociates from chromatin, thereby avoiding the trapping that underlies PARP inhibitor cytotoxicity. Another mutation deregulates HPF1 binding and PARP activation, which may cause the PARP–HPF1 complex to be constitutively active in these cancer cells, counteracting the effect of the inhibitors.

These findings concerning PARP activation, the PARP catalytic cycle, and possible mechanisms of resistance to PARP inhibitors will aid in the development of more effective inhibitors for treating cancers. *Bilokapic S et al, Nature 585:609–13, 2020*

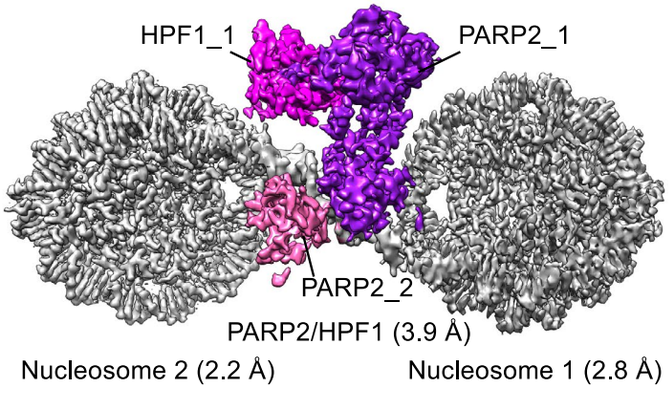


Figure. A composite cryogenic electron microscopy map of the PARP2–HPF1 complex bridging two mononucleosomes at a resolution of 2.2–3.9 Å. *Reprinted by permission from SNCSC GmbH: Springer Nature, Nature, 585:609–13. Bridging of DNA breaks activates PARP2–HPF1 to modify chromatin. Bilokapic S et al, © 2020*

Inflammasome Activation by Galactosaminogalactan Confers Host Protection Against Aspergillosis

Aspergillosis is a fungal infection caused by approximately 40 *Aspergillus* species, though infections with *Aspergillus fumigatus* are the most common in humans. In most people, exposure to *A. fumigatus* is not harmful, but it can be detrimental for immunocompromised patients. The fungal cell wall contains many polysaccharides that can trigger innate immune responses. Galactosaminogalactan (GAG), a polysaccharide-containing galactose and N-acetylgalactosamine, is required for *A. fumigatus* attachment to host tissues and is found in the lungs of patients with aspergillosis.

Innate immune responses and inflammatory cell death processes activated by many pathogens are mediated by proinflammatory multimeric protein structures known as inflammasomes; however, the specific molecules from *A. fumigatus* that activate the inflammasome have remained elusive. To explore the role GAG plays in inflammasome activation and subsequent immune responses, Thirumala-Devi Kanneganti, PhD (Immunology), and her team first identified GTC4 as the enzyme in *A. fumigatus* that is responsible for GAG synthesis. The researchers then generated a strain of *A. fumigatus* with the *GTC4* gene deleted (*Δgt4c*) and tested the strain's ability to initiate inflammasome activation and innate immune responses in bone marrow–derived macrophages (BMDMs) and mice. In *Nature*, Dr. Kanneganti and her colleagues reported that wild-type *A. fumigatus* infection of BMDMs results in GAG synthesis, in addition to caspase-1 cleavage and IL-1β release (markers of inflammasome activation), which is impaired in BMDMs infected with the *Δgt4c* strain of *A. fumigatus*. Priming the BMDMs with bacterial lipopolysaccharide before *Δgt4c A. fumigatus* infection did not rescue the impaired caspase-1 cleavage, indicating that this inflammasome activation is dependent on GAG.

Because GAG-induced inflammation is mitigated by its acetylation state, the researchers compared the ability of acetylated GAG (Ac-GAG) and deacetylated GAG (d-GAG) to induce inflammasome activation. Although d-GAG induced caspase-1 cleavage and cell death of BMDMs, Ac-GAG did not, indicating that the N-acetylgalactosamine component of GAG is required to activate inflammasomes. Stalled protein synthesis at ribosomes activates inflammasomes. BMDM ribosomal proteins interacted with d-GAG but not Ac-GAG, and GAG caused clumping of purified ribosomes. Furthermore, GAG, d-GAG, and *A. fumigatus* inhibited protein translation in BMDMs, suggesting that GAG induces inflammasome activation during aspergillosis by binding and immobilizing ribosomes, thereby inhibiting protein synthesis.

During aspergillosis, inflammasome activation is protective. The Δ*gt4c* strain, which does not produce GAG, was more virulent than wild-type *A. fumigatus* and led to reduced inflammasome-dependent cytokine release in the livers of the infected mice, suggesting that GAG-mediated inflammasome activation confers host protection during aspergillosis.

Inflammasome activation can also be beneficial in its functions beyond the control of pathogens. In the context of colitis, IL-18 production downstream of inflammasome activation protects against intestinal inflammation and damage. Indeed, GAG treatment in a mouse model of colitis mitigated body weight loss and inflammation, further demonstrating the protective role of inflammasome activation in the innate immune response to pathogenic insults. These findings contribute to the fundamental understanding of the regulation of the innate immune system and inflammatory responses and facilitate the continued search for therapeutic targets that can modulate innate immunity. *Briard B et al, Nature 588:688–92, 2020*

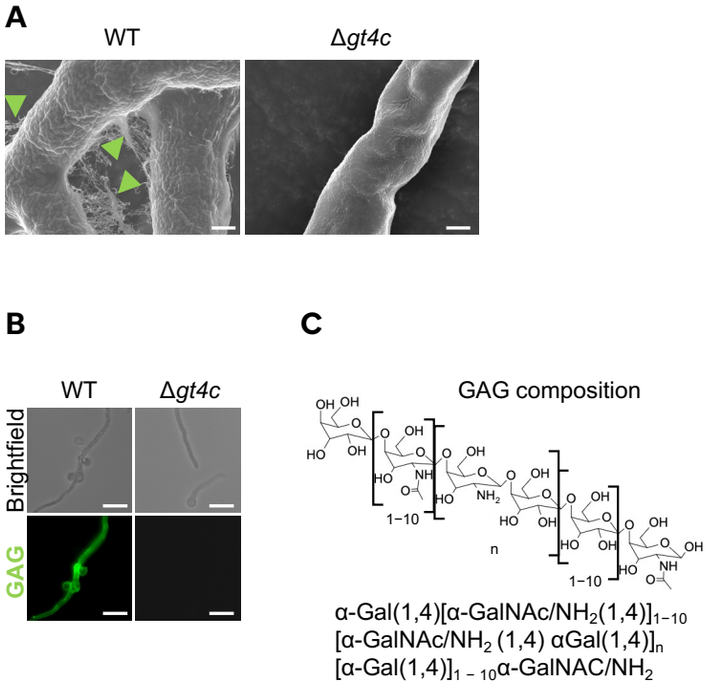
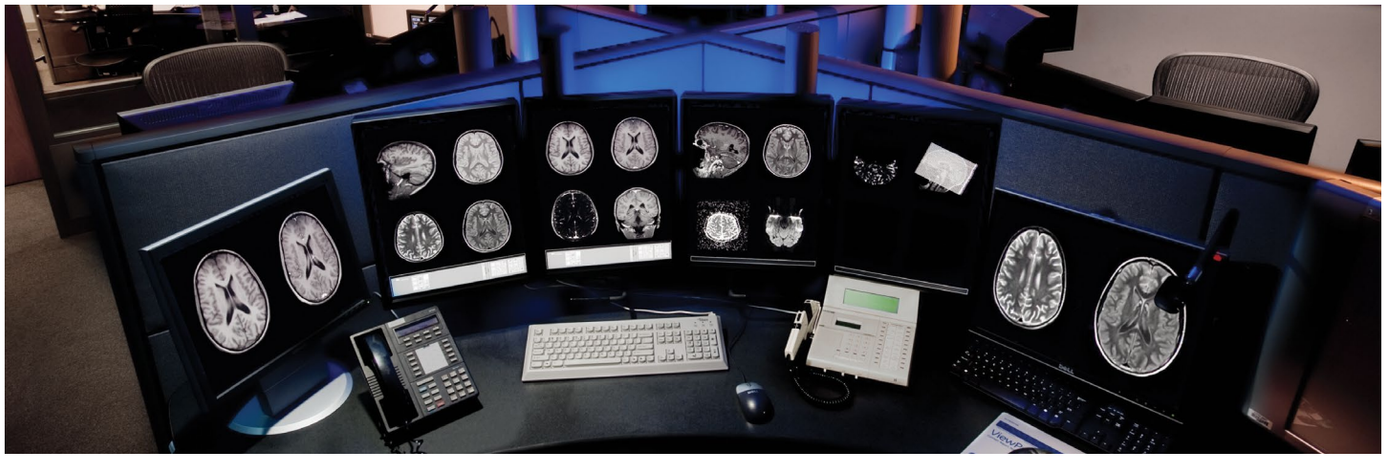


Figure. (**A**) Scanning electron microscopic images of the hyphae of wild-type (WT) and mutant (Δ*gt4c*) strains of *A. fumigatus*. Green arrowheads indicate extracellular matrix composed of galactosaminogalactan (GAG). (**B**) Immunofluorescence staining of GAG (green) on fungal mycelium. (**C**) Structure of *A. fumigatus* GAG. *Reprinted by permission from SNCSC GmbH: Springer Nature, Nature, 588:688–92. Galactosaminogalactan activates the inflammasome to provide host protection. Briard B et al, © 2020*

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. 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.



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 to 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 responses 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 allows 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

The mission of the Affiliate Program at St. Jude is to enable children to receive St. Jude pediatric oncology and hematology care close to home and to encourage their enrollment in clinical research trials. The eight affiliate clinics are located throughout the Southeast and Midwest regions of the United States. Together, these clinics contribute 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.

Over the past year, the Affiliate Program developed a patient navigator position to ease the transition for patients and families as they move from receiving care on the St. Jude campus to being treated at pediatric oncology clinics in or near their home communities. This intervention has improved communication and helped families feel more comfortable returning home. The patient navigator conveys messages from families to both care teams, thereby further facilitating collaborative care. Staff and families have found this unique intervention to be beneficial.

Kathy Cox Harris, Jennifer Morgan

ADMINISTRATION

Medical Director • Carolyn L. Russo, MD

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 Emeritus • Shelia Moore, MD

Medical Director • Jeffrey Deyo, MD, PhD

Kacie Sims, MD

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Peoria, IL

Children's Hospital of Illinois – OSF Healthcare System

University of Illinois College of Medicine at Peoria

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Beth Speckhart, NP

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Diana Simmons, NP

Shreveport, LA

Feist-Weiller Cancer Center – LSU Health Sciences Center – 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

Mohamed Elsaid, MD

Carolyn Sullivan, NP

Tulsa, OK

The Children's Hospital of Saint Francis

Medical Director • Greg Kirkpatrick, MD

Martina Hum, MD

Shilpa Shukla, MD

Samantha Zeller, NP

Alison Taylor, NP

St. Jude Global

The St. Jude Global initiative surpassed several milestones and achieved significant growth in all regions and programs during 2020. Our COVID-19 research showed that the pandemic disproportionately affected low- and middle-income countries. Therefore, the St. Jude Global Alliance adapted and continued to develop in the knowledge that the global health community is needed now more than ever.

ST. JUDE GLOBAL ALLIANCE

147 medical institutions in 57 countries applied for membership

93 finalized their membership agreements

17 virtual events

46 interactive sessions

The general session was attended by 831 participants in 71 countries

PROGRAM BUILDING

Despite the challenging year, the expansion of the St. Jude Global Alliance accelerated. By the end of December, 147 medical institutions in 57 countries had applied for membership, and 93 had finalized their membership agreements. Faculty and staff in the Department of Global Pediatric Medicine dedicated themselves to reimagining global engagement during the pandemic by developing new training materials and delivering virtual workshops. During the final quarter of 2020, they hosted 17 virtual events, including the Alliance convening in December, which showcased 46 interactive sessions. The general session was attended by 831 participants in 71 countries.

The St. Jude Global Childhood Cancer Analytics Resource and Epidemiological Surveillance System (SJCARES) suite of tools expanded its offerings in 2020. The SJCARES hospital-based registry tripled its engagement to 66 institutions. The team implementing the Pediatric Oncology Facility Integrated Local Evaluation (PrOFILE) tool conducted assessments and virtual national workshops in 20 countries. A suite of tools focused on health systems called Policies launched in October. These tools collaboratively address challenges in bridging evidence-to-policy and policy-to-action gaps. More than 900 national documents outlining government priorities, commitments, and joint actions to address cancer and other health needs have been collated and reviewed.

EDUCATION

The Global Scholars Program matriculated the second cohort of students into the Master's of Science in Global Child Health degree program. The students represent nine countries: Bolivia, Ethiopia, Ghana, Haiti, India, Nigeria, Pakistan, Peru, and Ukraine. The first graduating cohort dedicated the Fall of 2020 to developing their theses, which are the blueprints for their first interdisciplinary capstone projects. These projects aim to enhance treatment and care of childhood cancers and other catastrophic illnesses through systems-level change within the pediatric population, an organization, or a region.

RESEARCH

Faculty in the Department of Global Pediatric Medicine led *The Lancet Oncology Commission*, "Sustainable Care for Children with Cancer." This landmark study estimated that without additional investment, more than 11 million children aged 14 years or younger are expected to die from cancer over the next 30 years worldwide. The study demonstrated that with investment in expanding worldwide coverage of achievable cost-effective interventions and strengthening health systems, the lives of millions of children could be saved, resulting in huge economic benefits that far exceed the costs.

A trial conducted by the Chinese Children's Cancer Group showed that dasatinib is superior to imatinib in the treatment of Philadelphia chromosome–positive acute lymphoblastic leukemia, thereby generating a new paradigm and standard of care for children with this disease worldwide.

PANDEMIC RESPONSE

St. Jude Global partnered with the International Society of Paediatric Oncology to create the Global COVID-19 Observatory and Resource Center for Childhood Cancer, which includes a curated resource center for reliable information and guidelines, a collaboration space, and a global registry. By the end of 2020, 33,456 users in 164 countries had visited the Resource Center; the registry enrolled more than 1200 positive cases from 48 countries; and 11 COVID Conversations webinars were hosted with an aggregate of 3651 participants.

The COVIMPACT study assessed the impact of the COVID-19 pandemic on pediatric cancer care through a quantitative survey and qualitative focus groups. The study included 560 participants at 213 institutions in 79 countries and showed a significant decrease in the number of newly diagnosed cases and an increase in treatment abandonment and disruption of care, with a disproportionate impact in countries with limited resources. Nineteen focus groups at 16 institutions in 16 countries were formed to explore factors of resilient health care, as perceived by childhood cancer providers in settings of all resource levels.

WORLD HEALTH ORGANIZATION ACTIVITIES

St. Jude Global continued its work as the implementation partner for the World Health Organization (WHO) Global Initiative for Childhood Cancer, providing technical support to advance national cancer control programs in focus countries in all WHO regions. Additionally, St. Jude officially joined the WHO-hosted Global Accelerator for Paediatric Formulations platform.

Graduate School of Biomedical Sciences

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 and most recent is a Master's of Science in Clinical Investigations (MSc-CI) that trains clinicians and medical professionals in how to perform clinical research and conduct clinical trials. Approximately 170 faculty members 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, 50 PhD-BMS students and 20 MSc-GCH students have matriculated.

The COVID-19 pandemic made 2020 a challenging year. Classes and mentoring were disrupted, and the school was forced to adopt distance learning. Nevertheless, all classes and examinations were completed on schedule, student research continued with minimal disruption, and outstanding students were successfully recruited into the PhD-BMS and MSc-GCH programs. The MSc-GCH students were not allowed to visit the campus for their matriculation, orientation, and summer intersession. Instead, they have been working on the frontlines of the pandemic in their home countries. Despite these challenges, the MSc-GCH students are thriving in leadership roles in their fields and home countries, and many have published articles in prestigious journals.

Victoria Honnell

Most notably, in 2020 the new MSc-CI program was approved by the Tennessee Higher Education Commission. Logistically and operationally, this was a very challenging program to develop and deliver in such a short time, and much credit goes to the MSc-CI program leaders, the faculty, and the Graduate School administrative staff. Toward the end of the year, the MSc-CI program received several outstanding applications, which will shortly be reviewed, and the inaugural class will commence in Fall 2021. Lastly, the first two PhD-BMS degrees were awarded in 2020, and several PhD students received individual NIH predoctoral (F31) training grants.

Having awarded its first doctorate 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 extremely important process that confirms that a school maintains the highest educational standards as judged by peer institutions. The Graduate School administrative staff has completed SACSCOC training and begun preparing the accreditation application, which they plan to submit in Fall 2021. The Graduate School administration has also completed a detailed Strategic Plan in 2020 that charts the course and advancement of the school in the coming years and fully aligns with the *St. Jude Strategic Plan 2022–2027*.

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

GRADUATE SCHOOL BOARD OF TRUSTEES

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University of California San Diego
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James I. Morgan, PhD
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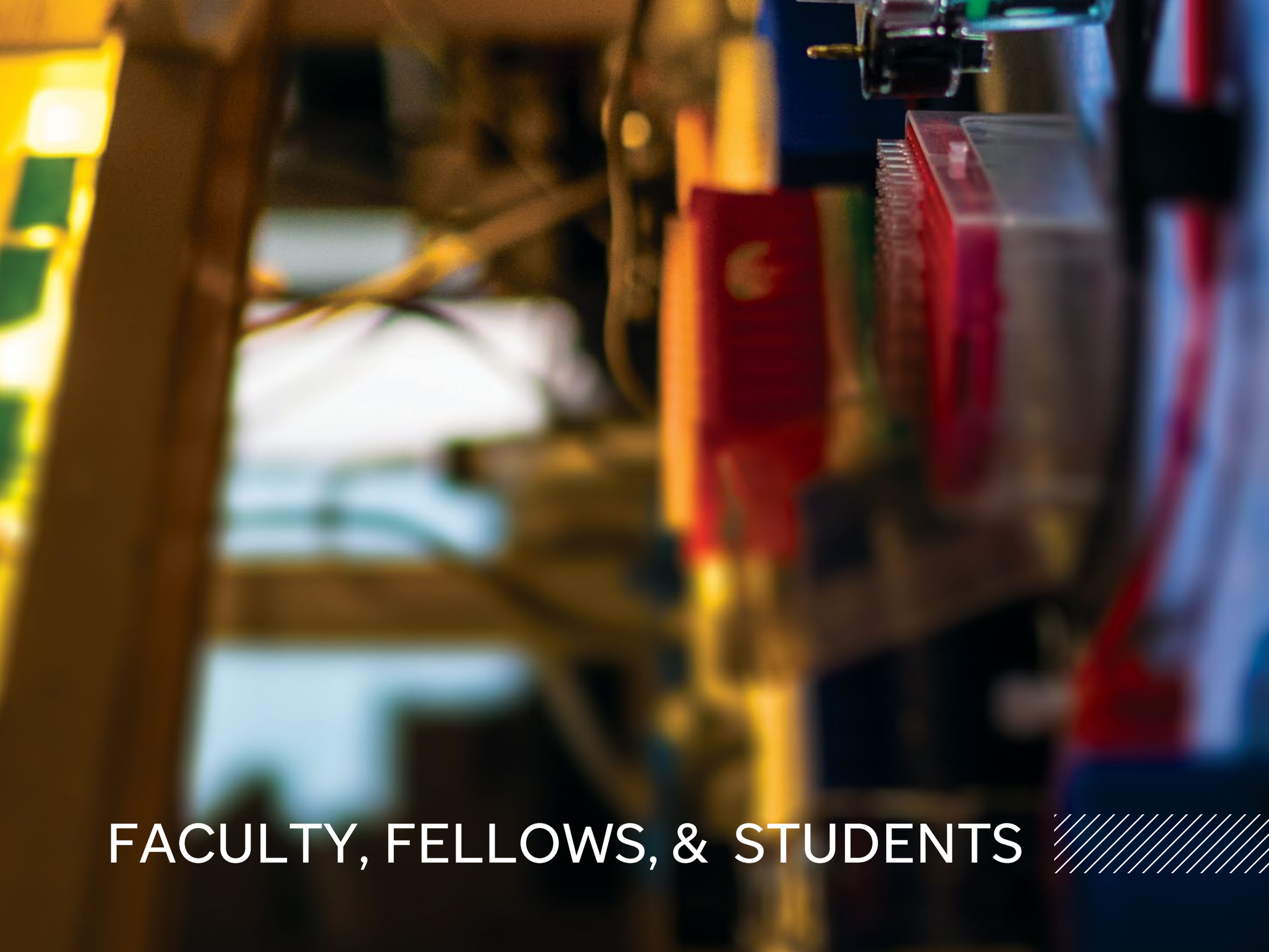
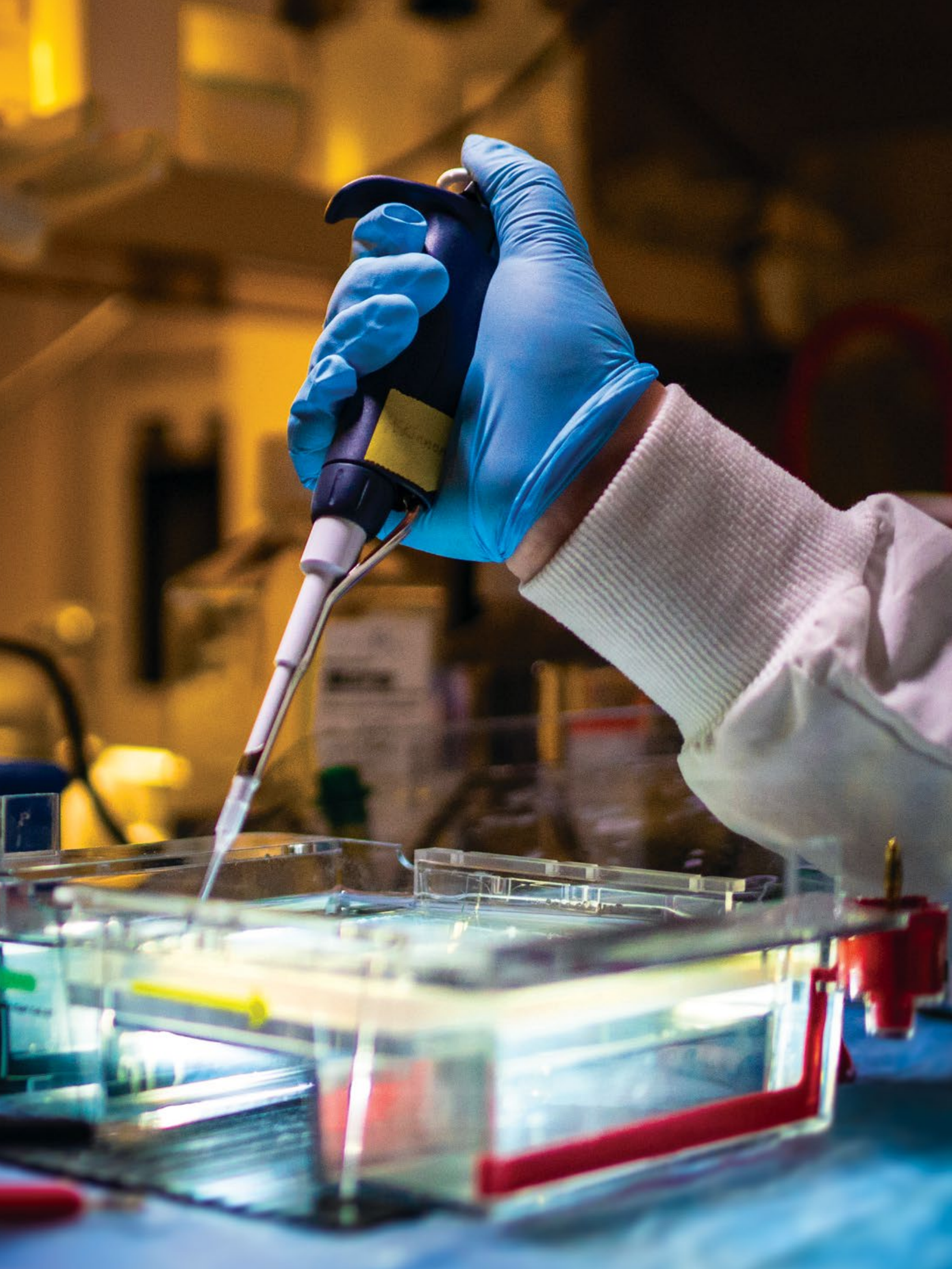
William E. Troutt, PhD
President Emeritus
Rhodes College

Stephen W. White, DPhil
President and Dean
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

Cheng Cheng, PhD • Statistical methods in cancer biology, clinical & translational studies

Meenakshi Devidas, PhD, MBA[1,2] • Biostatistics, pediatric hematology and oncology

Arzu Onar-Thomas, PhD[1] • Phase I/II designs, survival analysis, Bayesian statistics

Stanley B. Pounds, PhD[1] • Statistical methods for genomics studies

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

ASSOCIATE MEMBERS

Guolian Kang, PhD • Statistical genetics/genomics, modeling of complex data

Yimei Li, PhD • Statistical analysis of complex imaging data, survival data analysis & clinical trial design

Li Tang, PhD[1] • Prediction, validation, diagnostic testing, microbiome analysis

ASSISTANT MEMBERS

Qian Li, PhD • Analysis of microbiome data, integrative analysis of proteomics & metabolomics data

Zhaohua Lu, PhD • Statistical analysis of neuroimaging & genetic data, longitudinal & functional data analysis

Sedigheh Mirzaei Salehabadi, PhD[1] • Statistical methods for incomplete survival data, epidemiologic study designs

Haitao Pan, PhD • Bayesian adaptive designs for clinical trials, graphical modeling, microbiome data modeling

BONE MARROW TRANSPLANTATION & CELLULAR THERAPY

CHAIR

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

ASSOCIATE MEMBERS

Ashok Srinivasan, MD • Infections in the immune-compromised host

Brandon M. Triplett, MD[1] • Hematopoietic cell transplantation

ASSISTANT MEMBERS

Christopher DeRenzo, MD, MBA[1] • T-cell therapy for patients with solid tumors

Caitlin Hurley, MD[2] • Onco-critical care, HSCT/immunotherapy patients, long-term care

Giedre Krenciute, PhD[1] • CAR T-cell immunotherapy for pediatric brain tumors

Ewelina K. Mamcarz, MD • Transplantation in patients with nonmalignant diseases

Swati Naik, MBBS • Cellular therapy for hematological malignancies

Amr Qudeimat, MD • Transplant for bone marrow failure syndromes

Aimee C. Talleur, MD[1] • Cancer immunotherapy & cellular therapy

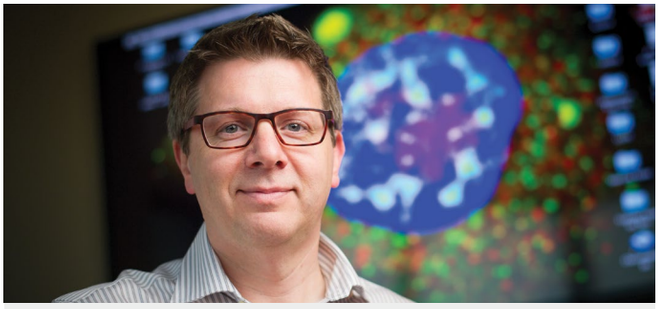
Paulina Velasquez, MD[1] • Immunotherapy of hematologic malignancies

INSTRUCTORS

Akshay Sharma, MBBS • Gene therapy & transplantation for nonmalignant hematological diseases

Ali Y. Suliman, MD, MSc • Immune reconstitution and T-cell function

Caitlin C. Zebley, MD, PhD • Cellular therapy and T-cell differentiation



CELL & MOLECULAR BIOLOGY

CHAIR

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

MEMBERS

Mondira Kundu, MD, PhD[1,2] • Autophagy-related proteins in health & human disease

Peter J. McKinnon, PhD[1] • DNA damage responses in the nervous system

ASSOCIATE MEMBERS

Stacey K. Ogden, PhD[1] • Mechanisms of Hedgehog signal transduction

Joseph T. Opferman, PhD[1] • Regulation of cell death & mitochondrial function

Ryan Potts, PhD[1,3]

ASSISTANT MEMBERS

Hans-Martin Herz, PhD[1] • Regulation of transcription & enhancer activity

Andrew T. Kodani, PhD[1] • Human genetics underlying neurodevelopmental disorders

Malia B. Potts, PhD[1,3]

Shondra M. Pruett-Miller, PhD • Genome-editing technologies

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

CHEMICAL BIOLOGY & THERAPEUTICS

CHAIR

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

MEMBERS

Scott C. Blanchard, PhD[1,2]; Endowed Chair in Molecular Imaging • Examining structure–function relations in macromolecular assemblies

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

ASSOCIATE MEMBERS

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

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

ASSISTANT MEMBERS

Tommaso Cupido, PhD[1] • Protein machines & chemical probe discovery

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

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

Fatima R. Rivas, PhD[1,3]

COMPUTATIONAL BIOLOGY

CHAIR

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

ASSOCIATE MEMBERS

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

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

ASSISTANT MEMBERS

Brian J. Abraham, PhD[1] • Transcriptional control of cell identity and disease

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

ADJUNCT MEMBER

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 Science • Control of neuronal death & differentiation

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

ASSOCIATE MEMBERS

Xinwei Cao, PhD[1] • Growth control during neural tube development

Fabio Demontis, PhD[1] • Protein homeostasis & stress sensing in skeletal muscle aging

Young-Goo Han, PhD[1] • Regulatory mechanisms of neural progenitors in brain development, diseases, & evolution

Khaled Khairy, PhD[1] • Biomechanics-based computational models as priors for biological image analysis

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

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

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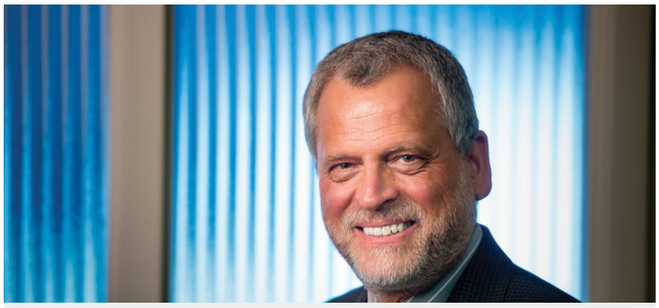
Myriam Labelle, PhD[1] • The role of the microenvironment in cancer metastasis

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

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

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

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



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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Wilburn E. Reddick, PhD • CNS structural changes during and after therapy

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Ranganatha Sitaram, PhD • Multimodal functional brain imaging & neurorehabilitation

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Asim K. Bag, MBBS, MD • Response to immunotherapy & radiation therapy; cancer therapy-induced neuroinflammation & brain damage; imaging low-grade gliomas

Julie H. Harreld, MD[1,3]

Noah D. Sabin, MD, JD • Imaging of brain tumors & side effects of therapy

ASSISTANT MEMBERS

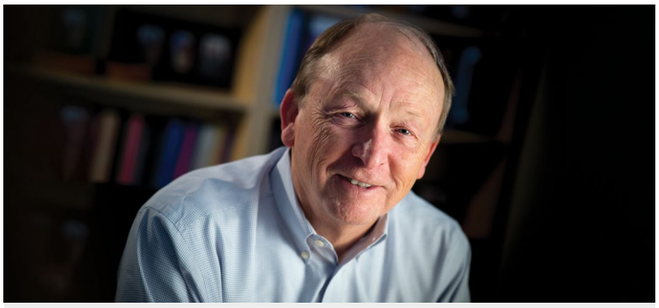
Puneet Bagga, PhD • Metabolic imaging, MR spectroscopy, molecular MRI, & cancer metabolism

Scott N. Hwang, MD, PhD • Quantitative imaging and computational modeling

INSTRUCTORS

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

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



EPIDEMIOLOGY & CANCER CONTROL

CHAIR

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MEMBERS

Gregory T. Armstrong, MD, MSCE[1] • Cancer survivorship & long-term follow-up

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

Tara M. Brinkman, PhD • Psychosocial outcomes of pediatric cancer

Wassim Chemaitilly, MD[2] • Endocrine sequelae in childhood cancer survivors

Daniel A. Mulrooney, MD, MS[1,2] • Cardiovascular outcomes of cancer therapy

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

ASSISTANT MEMBERS

Nickhill Bhakta, MD, MPH[1,2] • Global health, survivorship, epidemiology, childhood leukemias

Angela Delaney, MD[2] • Hypothalamic/pituitary dysfunction in childhood cancer survivors

Matthew J. Ehrhardt, MD, MS[2] • Late effects of childhood cancer therapy

Carmen L. Wilson, PhD[1] • Late effects of childhood cancer therapy

INSTRUCTOR

Yadav Sapkota, PhD • Genomic basis of pediatric cancer outcomes

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

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

GLOBAL PEDIATRIC MEDICINE

CHAIR

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

MEMBERS

Miguela A. Caniza, MD, MPH[1] • Global health, infection care and control

Meenakshi Devidas, PhD, MBA[1] • Biostatistics, pediatric hematology and oncology

Randall T. Hayden, MD[2] • Clinical microbiology of immunocompromised hosts

Sima Jeha, MD[1] • Global health, childhood leukemias, developmental therapeutics

Monika L. Metzger, MD[1] • Global health, Hodgkin & non-Hodgkin lymphomas

Ching-Hon Pui, MD[1,2]; Fahad Nassar Al-Rashid Endowed Chair in Leukemia Research • Biology & treatment of childhood leukemia

Bhaskar N. Rao, MD[2,4]

Victor M. Santana, MD[1]; Charles B. Pratt Chair in Solid Tumor Research • Global health, novel therapeutics, neuroblastoma, research ethics

ASSOCIATE MEMBERS

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Catherine G. Lam, MD, MPH[1] • Global health, health systems, pediatric solid tumors

Ibrahim A. Qaddoumi, MD, MS • Global health, brain tumors, telemedicine, retinoblastoma

ASSISTANT MEMBERS

Asya Agulnik, MD, MPH[1] • Global health, pediatric onco-critical care, quality improvement

Nickhill Bhakta, MD, MPH[1] • Global health, survivorship, epidemiology, childhood leukemias

Paola Friedrich, MD, MPH[1] • Global health, health disparities, health services, pediatric solid tumors

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

Teresa C. Santiago, MD[2] • Laboratory quality improvement & assessment

INSTRUCTORS

Abdelhafeez H. Abdelhafeez, MD[2] • Fluorescence-guided, minimally invasive, & subamputative pediatric surgical oncology

Daniel Moreira, 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

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John D. Crispino, PhD, MBA; The Wall Street Committee Endowed Chair • Mechanisms of leukemogenesis & benign and malignant blood disorders

Jane S. Hankins, MD, MS[1] • Sickle cell disease, transition to adult care & health outcomes during adolescence & young adulthood

Arthur W. Nienhuis, MD[4]

Ellis J. Neufeld, MD, PhD; Executive Vice President; Clinical Director; John & Lorine Thrasher Endowed Chair in Pediatric Medicine • Patient-oriented studies in nonmalignant hematology

Clifford M. Takemoto, MD; Lemuel Diggs Endowed Chair in Sickle Cell Disease • Hemostasis & thrombosis, vascular malformations, bone marrow failure

Winfred C. Wang, MD[4]

ASSOCIATE MEMBERS

Wilson K. Clements, PhD[1] • Hematopoietic development & leukemia

Jeremie H. Estepp, MD[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

Yong Cheng, PhD[1] • Cis-regulatory modules in normal & pathological gene expression

Rohith Jesudas, MBBS • Hemostasis, thrombosis, & immune cytopenias

Latika Puri, MD[3]

Shengdar Q. Tsai, PhD[1] • Genome engineering technologies for therapeutics

Marcin W. Wlodarski, MD, PhD • Inherited bone marrow failure & MDS predisposition syndromes

INSTRUCTORS

Nidhi Bhatt, MD • Health communication & implementation science

Marta Derecka, PhD • Hematopoiesis & the bone marrow microenvironment

Parul Rai, MD • Cardiac injury in sickle cell disease

Jason R. Schwartz, MD, PhD[3]

RESEARCH ASSOCIATE

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

ADJUNCT MEMBER

Kenneth Ataga, MD • Glomerulopathy, coagulation activation, & vasculopathy in sickle cell disease

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

IMMUNOLOGY

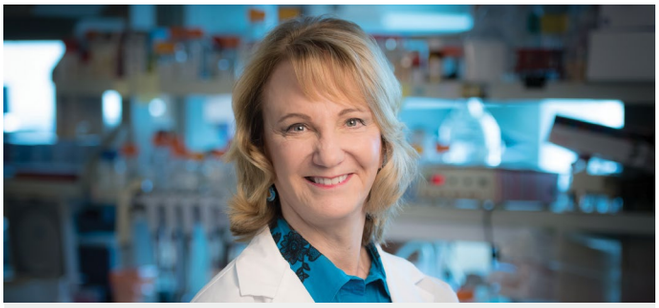
CHAIR
Douglas R. Green, PhD[1]; Peter C. Doherty Endowed Chair in Immunology • Cell death, autophagy, & immune function

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

MEMBERS
Hongbo Chi, PhD[1]; Robert G. Webster Endowed Chair in Immunology • Immune signaling and metabolism
Peter C. Doherty, PhD[4]; Nobel Laureate; Michael F. Tamer Endowed Chair in Immunology
Paul G. Thomas, PhD[1] • Mechanisms of antiviral and antitumor immunity

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

MEMBERS
Miguela A. Caniza, MD, MPH[1,2] • Global health, infection care, & control
Patricia M. Flynn, MD[1]; Deputy Clinical Director; Arthur Ashe Endowed Chair in Pediatric AIDS Research • HIV/AIDS in children & infections in children with cancer
Aditya H. Gaur, MD, MBBS[1] • Clinical research in HIV prevention & treatment
Walter T. Hughes, MD[4]
Julia L. Hurwitz, PhD[1] • Pathogen/vaccine-induced immunity, nuclear hormones
Suzanne Jackowski, PhD[1,3]
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]

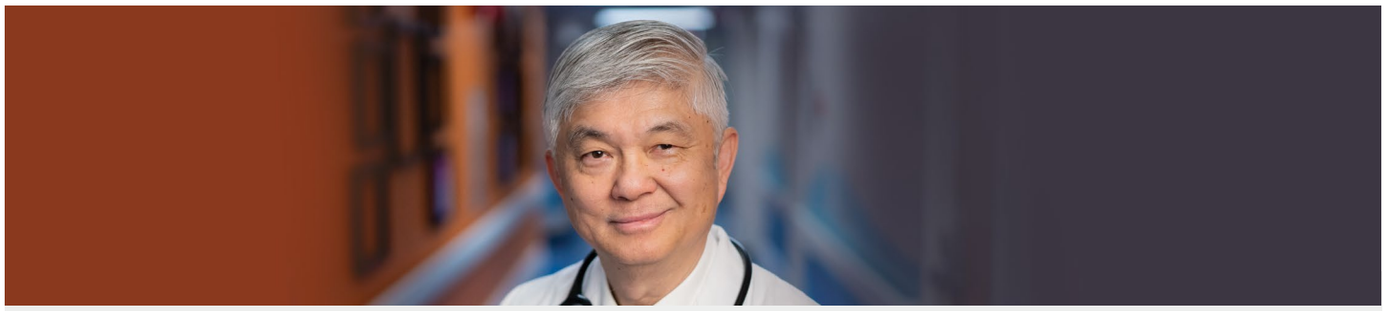
ASSOCIATE MEMBERS
Elisabeth E. Adderson, MD[1] • Epidemiology & treatment of infections
Hana Hakim, MD, MS • Infection prevention & control
Katherine Knapp, MD • Perinatal HIV exposure/HIV clinical trials
Gabriela M. Marón Alfaro, MD • Infectious complications in transplant patients
Nehali Patel, MD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



ONCOLOGY

CHAIR

Ching-Hon Pui, MD[1]; Fahad Nassar Al-Rashid Endowed Chair in Leukemia Research • Biology & treatment of childhood leukemia

CO-CHAIR

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

MEMBERS

Gregory T. Armstrong, MD, MSCE[1,2] • Pediatric neuro-oncology & cancer survivorship

Justin N. Baker, MD[1] • Quality of life/palliative care & ethics

Elizabeth Fox, MD, MS • Developmental therapeutics in pediatric oncology

Wayne L. Furman, MD • New drug development, neuroblastoma, liver tumors

Daniel M. Green, MD[1] • Adverse hepatic, renal, & reproductive effects of therapy

Melissa M. Hudson, MD; The Charles E. Williams Endowed Chair 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]; Executive Vice President, 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

John T. Sandlund, MD[1,3]

Victor M. Santana, MD[1,2]; Charles B. 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

Tanja A. Gruber, MD, PhD[3]

Mark E. Hatley, MD, PhD[1] • Origins of pediatric sarcomas

Catherine G. Lam, MD, MPH[1,2] • Global health, health systems, pediatric solid tumors

Daniel A. Mulrooney, MD, MS[1] • Cardiovascular outcomes of cancer therapy

Ibrahim A. Qaddoumi, MD, MS[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

Nickhill Bhakta, MD, MPH[1,2] • Global health, survivorship, epidemiology, childhood leukemias

Michael W. Bishop, MD[1] • Osteosarcoma, Ewing sarcoma, soft-tissue sarcomas

Adam 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

Kellie B. Haworth, MD • Immunotherapies for pediatric neurogenic tumors

Sara Helmig, MD • Sarcoma, thyroid carcinoma, & quality improvement

Lauren P. Jerkins, MD • Cellular therapy, quality improvement, and patient safety

Liza-Marie Johnson, MD, MPH, MSB • Ethical issues in pediatrics

Seth E. Karol, MD • Toxicity reduction during acute leukemia therapy

Erica C. Kaye, MD • Prognostic communication, early integration of palliative care in oncology

Deena R. Levine, MD • Pediatric palliative & end-of-life care

Esther A. Obeng, MD, PhD[1] • Myeloid malignancies & bone marrow failure syndromes

Kimberly E. Sawyer, MD, MA • Shared decision-making, ethics, pediatric palliative care

Jitsuda Sitthi-Amorn, MD • Quality improvement & patient safety

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 (ATRT) and ependymoma

Anna Vinitsky, MD, MS • Pediatric neuro-oncology & process improvement

Liqin Zhu, PhD[1,2] • Stem cells in normal & malignant development

INSTRUCTORS

Allison M. Ast, MD • Integrative therapies in pediatric hematology-oncology patients

Aditi Bagchi, MD, PhD • Molecular and genomic characteristics of pediatric brain tumors

Kari L. Bjornard, MD, MPH • Fertility and sexual health, cancer survivorship

Rachael Courtney, DO[3]

Andrea Cuviello, MD • Early palliative care integration in pediatric oncology

Stephanie Dixon, MD • Pediatric cancer survivorship

Jessica Gartrell, MD • Solid tumors

Jennifer L. Kamens, MD[3]

Daniel Moreira, MD[2] • Global pediatric oncology, evidence-based education, pediatric CNS tumors

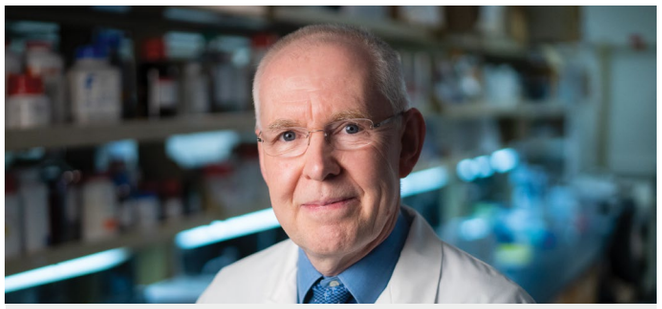
Anand G. Patel, MD, PhD • Recurrent pediatric sarcomas and intratumor heterogeneity

ADJUNCT MEMBERS

Francisca R. Fasipe, MD • Improving care for pediatric hematology & oncology patients

Marcela Popescu, MD • Pediatric hematology & oncology patients

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



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]; Senior Vice President and Deputy Director for Academic and Biomedical Operations; Endowed Chair in Pediatrics • T-cell regulation, adoptive immunotherapy

Randall T. Hayden, MD • Clinical microbiology of immunocompromised hosts

Mondira Kundu, MD, PhD[1] • Autophagy-related proteins in health & human disease

Michael M. Meagher, PhD[1]; Vice President, Therapeutics Production & Quality; 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

Armita Bahrami, MD[1,3]

John K. Choi, MD, PhD[1,3]

Larissa V. Furtado, MD • Clinical genomics and data management systems

Gabriela Gheorghe, MD • Pediatric leukemias and lymphomas, histiocytic lesions

Tanja A. Gruber, MD, PhD[2,3]

Laura Janke, DVM, PhD • Pathology of mouse models of disease

Jeffrey M. Klco, MD, PhD[1] • Genomic & functional characterization of pediatric myeloid neoplasms

Mihaela Onciu, MD • Pediatric lymphoma, leukemia, and bone marrow failure syndromes

Brent A. Orr, MD, PhD • Molecular classification of tumors of the nervous system

Janet F. Partridge, PhD[1] • Chromosome segregation, heterochromatin assembly

Harshan Pisharath, DVM, PhD • Animal models of human diseases, preclinical safety

Richard J. Rahija, DVM, PhD[3]

András Sablauer, MD, PhD; Chief Medical Information Officer • Imaging informatics & computerized tumor modeling

Lu Wang, MD, PhD • Genomic profiling & functional analysis of genetic alterations in pediatric tumors

ASSISTANT MEMBERS

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

Michael R. Clay, MD[3]

Heather L. Glasgow, PhD • Novel diagnostics for clinical microbiology

Teresa C. Santiago, MD • Laboratory quality improvement & assessment

Heather S. Tillman, DVM, PhD • Comparative pathology

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 Program • Novel treatments for children with brain tumors

ANESTHESIOLOGY

Michael J. Frett, MD; Division Director • Pediatric anesthesia

Doralina L. Anghelescu, MD[1] • Pain management, anesthesia risks, palliative care

Angela Camfield, MD, MS • Patient safety, malignant hyperthermia, multimodal analgesia

Wasif H. Dweik, DO • Patient safety, regional anesthesia, acute pain management

Kyle J. Morgan, MD • Pain management for pediatric cancer & sickle cell disease

Kavitha C. Raghavan, MBBS, FRCA • Patient safety & quality of care in pediatric anesthesia

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 • Pain management techniques, peripheral nerve blocks

CENTER FOR EXPERIMENTAL NEUROTHERAPEUTICS

Richard S. Finkel, MD; 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

Lama Elbahlawan, MD • Pediatric critical care, acute lung injury

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[1]; Division Director • Endocrine sequelae in childhood cancer survivors

Angela Delaney, MD • Hypothalamic/pituitary dysfunction in childhood cancer survivors

GASTROENTEROLOGY

Mark R. Corkins, MD • Pediatric gastroenterology

NEUROLOGY

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

James W. Wheless, MD • Epilepsy, tuberous sclerosis complex, & Dravet syndrome

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

PULMONOLOGY

Patricia J. Dubin, MD • Pediatric pulmonology and sleep medicine

RHEUMATOLOGY

Terri H. Finkel, MD, PhD • Pediatric rheumatology, autoimmune disease

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

PHARMACEUTICAL SCIENCES

CHAIR

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

VICE-CHAIR

John D. Schuetz, PhD[1] • Regulation & function of ABC transporters

MEMBERS

William E. Evans, PharmD[1,4]

William L. Greene, PharmD; Chief Pharmaceutical Officer • Optimizing pharmacotherapy

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

Clinton F. Stewart, PharmD[1] • Pharmacology of anticancer drugs in children

Jun J. Yang, PhD[1] • Pharmacogenomics of anticancer agents & drug resistance

ASSISTANT MEMBERS

Daniel D. Savic, PhD[1] • Pharmacogenomics & cis-regulatory architecture of pediatric leukemia

Liqin Zhu, PhD[1] • Stem cells in normal & malignant liver development

INSTRUCTOR

Jeffrey M. Rybak, PharmD, PhD • Antifungal pharmacotherapy

PSYCHOLOGY

CHAIR

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

MEMBERS

Heather M. Conklin, PhD[1] • Cognitive outcomes of childhood cancer treatment

Melissa M. Hudson, MD[2]; The Charles E. Williams Endowed Chair 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

Valerie M. Crabtree, PhD[1] • Sleep disruptions and fatigue in pediatric oncology

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

Nicole M. Alberts, PhD[3]

Jennifer M. Allen, PhD • Pain management, adolescent/young adults, health behavior

Kristin E. Canavera, PhD • Pediatric bioethics

Jennifer L. Harman, PhD • Psychosocial functioning of young children with cancer

Lisa M. Jacola, PhD • Neurobehavioral outcomes in children treated for cancer

Kendra R. Parris, PhD • Coping & adjustment in youth with cancer

Brian S. Potter, PhD • Neurocognitive outcomes in children with cancer

Darcy Raches, PhD • Acute neurological injury & cognitive outcomes associated with childhood cancer treatment

Victoria W. Willard, PhD • Social outcomes in children with cancer

INSTRUCTORS

R. Elyse Heidelberg, PsyD • Pain and symptom management in pediatric hematology/oncology

Andrew 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

Rachel N. Tillery, PhD • Promotion of healthy lifestyle behaviors in children with cancer & survivors of childhood cancer

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

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

MEMBER

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

ASSOCIATE MEMBER

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

ASSISTANT MEMBERS

Sahaja Acharya, MD • Brain tumors, proton therapy, image-guided radiation

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

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

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

INSTRUCTOR

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

STRUCTURAL BIOLOGY

CHAIR

Charalampos Babis 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

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

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

ASSOCIATE MEMBERS

Eric J. Enemark, PhD[1] • Molecular mechanisms of DNA replication

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

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

ASSISTANT MEMBERS

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

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

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

Andrew Jackson Murphy, MD • Renal tumors, neuroblastoma, Wilms tumorigenesis, cancer stem cells

Jun Yang, MD, PhD • Cancer epigenetics & targeted therapy

INSTRUCTORS

Abdelhafeez H. Abdelhafeez, MD • Fluorescence-guided, minimally invasive, & subamputative pediatric surgical oncology

Lindsay J. Talbot, MD • Sarcomas, immunotherapeutic strategies against sarcoma & solid tumor metastases

ADJUNCT MEMBERS

Frederick Boop, MD; St. Jude Chair in Neurosurgery • Pediatric neurosurgery

Jeremiah L. Deneve, DO • Surgical oncology

Joseph M. Gleason, MD • Pediatric urology, Wilms tumor, pelvic RMS

Mary Ellen Hoehn, MD • Pediatric ophthalmology

Paul D. Klimo Jr, MD • Pediatric neurosurgery

Michael Neel, MD • Pediatric orthopedic oncology

Anthony Sheyn, MD • Pediatric otolaryngology

Jerome Thompson, MD, MBA • Pediatric otolaryngology

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

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

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

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

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

William E. Evans, PharmD
Endowed Chair in Pharmacogenomics

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

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

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

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

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

Aditi, PhD, Genetics
Anup Aggarwal, PhD, Structural Biology
Sabrin Albeituni, PhD, Oncology[2]
Lisa Alcock, PhD, Pathology
Tyler Alexander, PhD, Epidemiology & Cancer Control
Kavya Annu, PhD, Cell Biology & Therapeutics
Shariq Ansari, PhD, Cell & Molecular Biology
Sasi Arunachalam, PhD, Computational Biology
Robert Autry, PhD, Pharmaceutical Sciences[1]
David Baggett, PhD, Structural Biology
Lu Bai, PhD, Immunology
Balaji Banoth, PhD, Immunology
Juan Martin Barajas, PhD, Oncology
Stefanie Baril, PhD, Pharmaceutical Sciences
Aditya Barve, PhD, Hematology
Justin Batte, PhD, Infectious Diseases[1]
Jordan Beard, PhD, Pharmaceutical Sciences[2]
Swarna Beesetti, PhD, Cell & Molecular Biology
Laure Bihannic, PhD, Developmental Neurobiology
Emilio Boada Romero, PhD, Immunology
Shannon Boi, PhD, Immunology
Nancy Bolous, MD, Global Pediatric Medicine
Wade Borcherds, PhD, Structural biology
Austin Boucher, PhD, Hematology
David Boyd, PhD, Immunology
Anne Bremer, PhD, Structural Biology
Benoit Briard, PhD, Immunology[1]
David Brice, PhD, Immunology
Mark Brimble, PhD, Surgery[1]
Cameron Buchman, PhD, Chemical Biology & Therapeutics
Monicah Bwayi, PhD, Chemical Biology & Therapeutics
Kirby Campbell, PhD, Developmental Neurobiology
Deviprasanna Chakka, PhD, Structural Biology
Bappaditya Chandra, PhD, Structural Biology
Phillip Chapman, PhD, Developmental Neurobiology
Kanokporn Chattrakun, PhD, Structural Biology
Deepti Chaturvedi, PhD, Structural Biology
Meixia Che, PhD, Oncology
Helen Chen, PhD, Cell & Molecular Biology[2]
Po-Ling Chen, PhD, Infectious Diseases
Xiaolong Chen, PhD, Computational Biology
Li Cheng, MD, PhD, Hematology[1]
Surendhar Reddy Chepyala, PhD, Structural Biology
Peter Chockley, PhD, Bone Marrow Transplantation & Cellular Therapy
Partha Sarathi Chowdhury, PhD, Immunology[1]
Shelbi Christgen, PhD, Immunology
Chia-Lung Chuang, PhD, Developmental Neurobiology
Elizabeth Cleverdon, PhD, Cell & Molecular Biology
Elizabeth Coffey, PhD, Hematology
Valerie Cortez, PhD, Infectious Diseases
Yixin Cui, PhD, Structural Biology
Preeti Dabas, PhD, Chemical Biology & Therapeutics
Mahmoud Dabbah, PhD, Hematology
Adithi Danda, PhD, Chemical Biology & Therapeutics
Emily Darrow, PhD, Developmental Neurobiology
Jitendra Das, PhD, Structural Biology
Christian DeJarnette, PhD, Pharmaceutical Sciences
Kaushik Dey, PhD, Structural Biology
Jonathan Diedrich, PhD, Pharmaceutical Sciences[1]
Karissa Dieseldorff Jones, PhD, Computational Biology
Phillip Doerfler, PhD, Hematology
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Asaf Elazar, PhD, Structural Biology
Rabeh Elshesheny, PhD, Infectious Diseases
Daniel Estevez Prado, PhD, Structural Biology
Leonardo Estrada, PhD, Infectious Diseases[1]
Myron Evans, PhD, Developmental Neurobiology
Li Fan, PhD, Pharmaceutical Sciences
Daniel Ferguson, PhD, Pharmaceutical Sciences
Carlos Fernandez Pena Acuna, PhD, Developmental Neurobiology
Dinesh Fernando, PhD, Chemical Biology & Therapeutics[1]
Martina Finetti, PhD, Collaborative Research Program[1]
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Elizabeth Foley, PhD, Epidemiology & Cancer Control
Adolfo Frias, PhD, Immunology
Guotong Fu, PhD, Immunology
Katherine Gadek, PhD, Oncology
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Debolina Ganguly, PhD, Chemical Biology & Therapeutics
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Clifford Gee, PhD, Chemical Biology & Therapeutics
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Chuansheng Guo, PhD, Immunology
Youngdae Gwon, PhD, Cell & Molecular Biology
Kohei Hagiwara, MD, Computational Biology
Priyanka Halder, PhD, Genetics
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Bradlee Heckmann, PhD, Immunology[1]
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Roketa Henry, PhD, Genetics
Carl Mikael Holm, PhD, Structural Biology
Rebekah Honce, PhD, Infectious Diseases
Seyed Mohammad Hosseini, PhD, Computational Biology
Laura Hover, PhD, Developmental Neurobiology
Meng Hu, PhD, Infectious Diseases
Hongling Huang, PhD, Immunology
Xin Huang, PhD, Computational Biology
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Liam Hunt, PhD, Developmental Neurobiology
Carolyn Jablonowski, PhD, Surgery[2]
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Yajun Jiang, PhD, Structural Biology
Yanbo Jiang, PhD, Developmental Neurobiology
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SangJoon Lee, PhD, Immunology
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William Letsou, PhD, Epidemiology & Cancer Control
Dongfang Li, PhD, Pathology
Jun Li, PhD, Immunology
Wei Li, PhD, Immunology
Yizhen Li, PhD, 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
Beiyun Liu, PhD, Immunology
Danting Liu, PhD, Structural Biology
Fengming Liu, PhD, Developmental Neurobiology
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Joelle Magne, PhD, Immunology
Yujiao Mai, PhD, Biostatistics[1]
Efran Maldonado, PhD, Chemical Biology & Therapeutics
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[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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Xiaoqing Wang, PhD, Biostatistics
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Zhen Wang, PhD, Structural Biology
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Xu Yang, PhD, Cell & Molecular Biology
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Shanshan Yu, PhD, Chemical Biology & Cellular Therapeutics[2]
Maged Helmy Abdalla Zeineldin, MD, PhD, Developmental Neurobiology[1]
Jingliao Zhang, PhD, Pharmaceutical Sciences[1]
Peipei Zhang, PhD, Cell & Molecular Biology
Min Zheng, PhD, Immunology
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

CLINICAL FELLOWS

Bone Marrow Transplantation & Cellular Therapy Fellows

Rebecca Epperly, MD
Jamie Truscott, MD[1]

Cancer Survivorship Fellow

Stephanie Dixon, MD, MPH[3]

Critical Care Fellow

Anita Arias Prado, MD

Global Pediatric Medicine Fellows

Zebin Al Zebin, MD[1]
Lisa Force, MD[2]
Dylan Graetz, MD, MPH

Infectious Diseases Pediatric HIV Fellow

Patricia Pichilingue-Reto, MD[1]

Ocular Oncology Fellows

Ilyse Kornblau, MD[2]
Jacqueline Laplant, MD

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

Fellows & Students

Neuropsychology Fellows

Jeanelle Ali, PhD[1]
Diana Cohen, PhD
Holly Hasler, PhD
Nicole Salman, PhD

Pediatric Hematology-Oncology Fellows

Taylor Aglio, MD
Senthil Bhoopalan, MBBS
Lindsay Blazin, MD, MPH[1]
Jessica Bodea, MD
Kenneth Caldwell, MD
Georgios Christakopoulos, MD
Caitlyn Duffy, MD
Kayla Foster, MD
Joshua A. Hess, MD[1]
Camille Keenan, MD
Justin Kirkham, MD, PhD
Harry Adrian Lesmana, MD[1]
Michael McNeil, MD
Jonathan J. Miller, MD, PhD[1]
Margaret Nagel, MD
Ayo Olanrewaju, MD
Matthew Rees, MD
Marta Salek, MD
Richa Sharma, MD
Aurora Tarun, MD
Michael A. Terao, MD[1]
Ruth Wang'ondu, MD, PhD
Caitlin C. Zebley, MD[3]

Pediatric Infectious Diseases Fellows

Ruba Barbar, MD[1]
Ghussai Abd El Gadir, MBBS[1]
Kathryn Goggin, MD[1]
Amanda Green, MD
Jennifer Hidinger, MD[1]
Melissa Shenep, MD
Ivan Tinoco, MD[1]

Pediatric Neuro-Oncology Fellows

Aditi Bagchi, MD
Richard Graham, MD
Trisha Larkin, MD
Pakyin Anthony Liu, MD[1]

Pediatric Surgical Oncology Fellows

Oswaldo Gomez Quevedo, MD
Sara Mansfield, MD
Pattamon Sutthatarn, MD

Pharmacogenetics Resident

Sarah Morris, PharmD

Pharmacy Fellows

Chelsea Drennan, PharmD
Alyssa Gaietto, PharmD[1]
Jaclyn Hopp, PharmD
Madeleine King, PharmD[1]
Katherine Robinson, PharmD
Deann Tims, PharmD

Pharmacy–Medication Safety Resident

Kelly Huston, PharmD[1]

Psychology Fellows

Vanessa Aguilera, PhD
Emily Crochet, PsyD[1]
Mallorie Gordon, PhD
Dana Kamara, PhD
Kayla LaRosa, PhD[1]
Melanie Morse, PhD
Megan Schafer, PhD

Solid Tumor Fellow

Jessica A. Gartrell, MD

GRADUATE STUDENTS

St. Jude Graduate Students

Alhassan Abdul-Mumin, MD, Global Child Health
Alia Ahmad, MD, Global Child Health
Ana Patricia Alcasabas, MD, Global Child Health
Ahmad Alokl-Moussa, Global Child Health
Alexandra Beckett, Bone Marrow Transplantation & Cellular Therapy
Matthew Bell, Bone Marrow Transplantation & Cellular Therapy
Brennan Bergeron, Pharmaceutical Sciences
Mackenzie Bloom, Oncology
Kaitlyn Budd, Developmental Neurobiology
Madeline Bush, Oncology
Terri L. Cain
Christina Daly, Cell & Molecular Biology
Yogesh Dhungana
Rosdali Diaz Coronado, MD, Global Child Health
Marygrace Duggar, Immunology
Jessica Gaevert, Immunology
Rebecca Gee, Cell & Molecular Biology
Anne C. Gilmore, Developmental Neurobiology
Jamuni Gunasekera, MD, Global Child Health
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
Yusuf Danasabe Jobbi, MD, Global Child Health
Christina Kackos, Infectious Diseases
Matthew B. Kieffer, Oncology
Allison Kirk, Immunology
Roman Kizyma, MD, Global Child Health
Rahul Kumar, Developmental Neurobiology
Christy LaFlamme
Randolph Larsen, Oncology
Andrea Lee, Hematology
Hayden Malone
Mora Mel, MD, Global Child Health
Ramon A. Misla David
Sarah E. Moore, Bone Marrow Transplantation & Cellular Therapy
Trevor S. Penix
Nicolas B. Peterson, Immunology
Gregory Phelps, Cell Biology & Therapeutics
Brittany Pioso, Structural Biology
Adriana M. Porras, MD, Global Child Health
Rehana Punjwani, Global Child Health
Venkatraman Radhakrishnan, MD, Global Child Health
Sandi Radko-Juettner, Oncology
Kirtikumar Rathod, Global Child Health
Isaiah Reeves, Surgery
Rawad Rihani, MD, Global Child Health
Jocelyn Rivera, MD, Global Child Health
Jordan T. Roach, Developmental Neurobiology
Juan Pablo Rodriguez Auad, MD, Global Child Health
Jaylan Sears
Sarah J. Sherman
Jamaica F. Siwak
Maria Smith, Infectious Diseases
Bradley T. Stevens
Morgan Sutton
Liliana Vasquez, MD, Global Child Health
Ana Vazquez-Pagan, Infectious Diseases
Thelma Velasquez Herrera, MD, Global Child Health
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Elizabeth Wickman, Bone Marrow Transplantation & Cellular Therapy
Kristin Wiggins, Infectious Disease
Benjamin Wilander, Immunology
McLean Williamson, Hematology
Stephen Winston, Surgery
Tristen D. Wright, Cell & Molecular Biology
Caitlin C. Zebley, MD, Immunology[3]

External Graduate Students

Ahmed Abuzaid, Surgery
Flora Achiko, Oncology[1]
Fabienne Adriaanse, Oncology
Hannah Allen, Oncology[1]

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

Alejandro Anido, Bone Marrow Transplantation & Cellular Therapy[2]
Kavya Annu, Pharmaceutical Sciences[4]
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Julie Bach, Structural Biology[1]
Donna Bartel, Social Work
Daniel Bastardo Blanco, Immunology[2]
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Meredith Bernhard, Surgery
Bryce Beyer, Surgery
Tharwa Bilbeisi, Oncoloy
Madison Boles, Radiation Oncology[1]
Lauren Brakefield, Cell & Molecular Biology
Mark Allen Brimble, Surgery[4]
Anthony Brown, Pharmaceutical Sciences
Michael Brunner, Diagnostic Imaging
Theresa Bub, Pathology
Elizabeth Byers, Oncology
Francesca Caputo, Radiation Oncology[1]
Jingjing Chen, Hematology[1]
Michael Chen, Global Pediatric Medicine
Weng Choy, Oncology[1]
Brandi Clark, Immunology
Kenneth Coca, Oncology[1]
Jane Craig, Cell & Molecular Biology[1]
Tina Hong Dao, Infectious Diseases
Nisha Das, Chemical Biology & Therapeutics
Amy Davis, Infectious Diseases
Kirsten Dickerson, Pathology
Laura Doorley, Pharmaceutical Sciences
Leigh Fremuth, Genetics
Elizabeth Garfinkle, Oncology[1]
Joacy Gerard Mathias, Hematology[1]
Ashley Gray, Pharmaceutical Sciences
Bursa Gungor, Surgery[1]
Kimberly Anna Lise Halford, Infectious Diseases
Trent Hall, Hematology[4]
Xian Han, Structural Biology
Virginia Hargest, Infectious Diseases[4]
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Jianzhong Hu, Pharmaceutical Sciences
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Mayuko Iijima, Oncology[1]
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Olivia Kan, Oncology
Ayub Karwandyar, Surgery
Fatemeh Keramatnia, Chemical Biology & Therapeutics
William Kuenzinger, Developmental Neurobiology
Xin Lan, Hematology
Anna Lee, Cell & Molecular Biology[1]
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Yu Li, Pharmaceutical Sciences
Chun-Yang Lin, Immunology
Lydia Makepeace, Diagnostic Imaging[1]
Reagan Mead, Surgery[1]
Kaitlynn Messler, Structural Biology
Joseph Miller, Cell & Molecular Biology
Ashley Millett, Epidemiology & Cancer Control[1]
Thomas Montoya, Social Work
James Morgan, Surgery[1]
Robert Neel, Surgery
Zelda Ode, Bone Marrow Transplant & Cellular Therapy[1]
Arushi Pandyam, Legal Services[1]
Vanisha Patel, Infectious Diseases
Christopher Patton, Infectious Diseases
Lee Pribyl, Genetics[1]
Brooke Prinzing, Bone Marrow Transplantation & Cellular Therapy[4]
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Aaron Ross, Surgery
Emily Rundlet, Structural Biology
Anjelica Saulsberry, Hematology
Claire Sentilles, Radiation Oncology
Dewan Shrestha, Hematology
Hailey Shwr, Social Work
Kaitlyn Smith, Cell & Molecular Biology
Aisha Hegab Souquette, Immunology[4]
Lucy Soyinka, Legal Services[1]
Rachel Speltz, Clinical Nutrition
Hannah Spiegl, Surgery
William Stafford, Surgery[1]
Gregory Starks, Legal Services[1]
Wei Su, Immunology
Brittany Campbell Thomas, Structural Biology[1]
Kylie Thompson, Legal Services
Jennifer Toth, Pharmaceutical Sciences
Erica Tsai, Diagnostic Imaging[1]
Patricia Umberger, Cell & Molecular Biology
Kelsey Van-Noy, Oncology[1]
Elena Varotto, Oncology[1]
Nicole Vita, Chemical Biology & Therapeutics
Xinyu von Buttlar, Oncology
Megan Walker, Hematology[1]
Amber Ward, Pathology
Jason A. Weesner, Genetics
Kendall Whitt, Infectious Diseases
Taylor Wilson, Immunology
Rachael Wood, Tumor Cell Biology
Kaitly Woodard, Hematology
William Charles Wright, Chemical Biology & Therapeutics[2]
Jinjun Wu, Cell & Molecular Biology
Zhen Xie, Computational Biology
Zemin Yang, Cell & Molecular Biology
David Yanishevski, Surgery[1]
Jay Yarbro, Structural Biology
Satoshi Yoshimura, Pharmaceutical Sciences
Ugur Yurtsever, Cell & Molecular Biology
Xujie Zhao, Pharmaceutical Sciences
Yumei Zheng, Structural Biology
Jingwen Zhu, Pharmaceutical Sciences
Chan Zou, Pharmaceutical Sciences[1]

[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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[1] July–December, 2020 [2] Ex officio voting member [3] January–June, 2020 [4] Nonelected member [5] Deceased

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This panel of physicians and scientists, serving during 2020, 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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Paul J. Finnegan Family Director, Center for Brain Science
Department of Molecular and Cellular Biology
Harvard University

OPERATIONS & STATISTICS

OPERATIONS	
Operating expenses[1]	$1.091 billion
Number of employees[2]	5122
RESEARCH STATISTICS	
Grant funding[1]	$119.4 million
Peer-reviewed publications	667
Faculty members[3]	339
Postdoctoral fellows	306
Clinical residents and fellows[4]	192
Graduate research scholars	187
CLINICAL STATISTICS	
Number of beds open[5]	73
Total outpatient visits	181,712
Inpatient admissions	3073
Total inpatient days	18,051
Total protocol enrollments in 2020	3529
Patients enrolled in therapeutic trials	677
Patients enrolled in nontherapeutic trials	2851 2090 in prospective trials 10 in retrospective trials 751 in tissue-banking protocols
Total number of protocols that were open to accrual in 2020	588
Number of active therapeutic trials	162
Number of active nontherapeutic trials	423 152 prospective trials 268 retrospective trials 3 tissue-banking protocols

[1] Data represent the period July 1, 2019 to June 30, 2020.

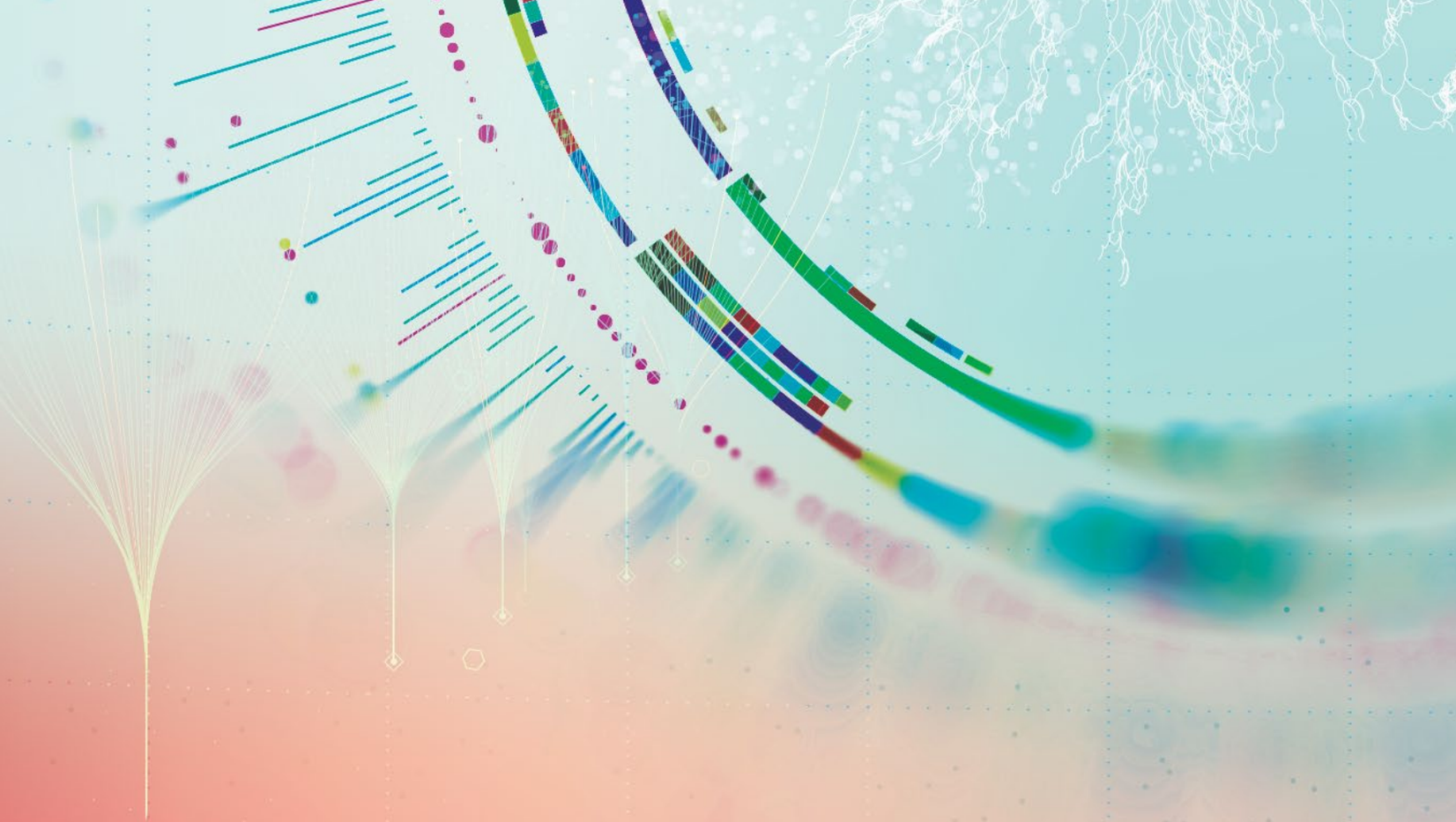
[2] Data are from July 1, 2020.

[3] Data include emeritus and adjunct faculty members.

[4] Data include 67 full-time St. Jude fellows and 125 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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stjude.org/scientificreport

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