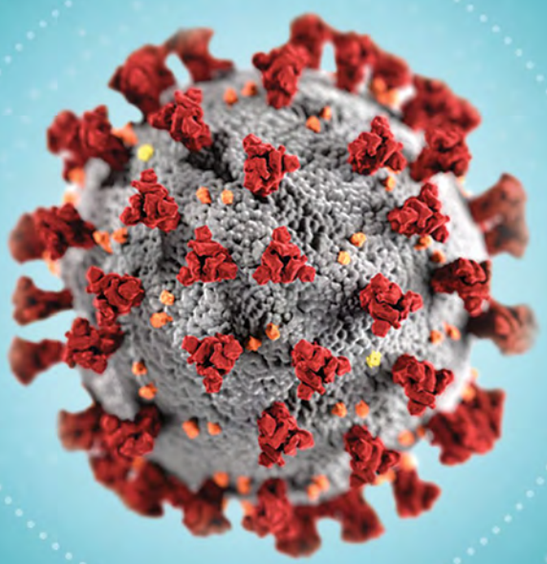
# Translating Science into Survival



## SCIENTIFIC REPORT

2020

## BEHIND THE COVER

The image on the cover is a schematic of the novel coronavirus SARS-CoV-2, the pathogen that caused the COVID-19 pandemic. We quickly learned that the virus is transmitted primarily by respiratory droplets and that the most severe infections occur in the elderly and those with underlying medical conditions. However, we did not fully know how the virus would affect pediatric oncology patients, many of whom are immunocompromised. In response to the World Health Organization's declaration of COVID-19 as a pandemic, executive leadership implemented the St. Jude Emergency Operations Plan and developed approaches to keep St. Jude operational and safe.

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

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

**PHOTOGRAPHY DISCLAIMER:**
All images herein that depict multiple people not wearing masks or physical distancing were obtained before the COVID-19 pandemic was declared.

## WE LIVE IN EXTRAORDINARY TIMES, AND SCIENCE AND MEDICINE PLAY EVERMORE IMPORTANT ROLES IN NAVIGATING THE FUTURE.

With the emergence of the COVID-19 pandemic, life across the country and around the world transformed nearly overnight. At St. Jude Children's Research Hospital, we moved quickly to protect the health and safety of employees, families, and the most vulnerable members of our community—patients. The steps taken, which are detailed in the first story, include a first-of-its-kind SARS-CoV-2 testing program for employees, patients, and their families; campus zoning; reduced personnel and visitor access; and heightened infection prevention and control procedures. Thanks to these precautions, the St. Jude campus is one of the safest harbors from COVID-19 in the nation.

Even in the midst of a pandemic, cancer and other catastrophic diseases do not stop, and St. Jude scientists have continued to travel their path of innovation, accelerating progress and sharing their findings with the world. The following pages of this Scientific Report showcase how our researchers are pushing boundaries in exploration and discovery.

Children with X-linked severe combined immunodeficiency, also known as “bubble boy” disease, lack the immune cells necessary to fight off harmful viruses, bacteria, and fungi. The second article illustrates how a decades-long journey to create a safer and more effective way to deliver gene therapy led to a groundbreaking approach with curative potential for the rare immune disorder.

For many patients, surviving childhood cancer comes at a cost. Treatment-related toxicities can have devastating long-term effects on the quality of life of adult survivors. The third story outlines research that seeks to maximize cures while minimizing lasting consequences for pediatric patients with cancer. St. Jude scientists are determining how cancer treatments can be modified to reduce toxicities without compromising cures. This initiative holds the promise of helping children not only survive cancer but also thrive once therapy ends.

Cells continuously synthesize new proteins and fold them into unique shapes. When a protein is misfolded, it does not function properly and can lead to cancer or other disorders. Molecular chaperones, such as heat-shock protein (Hsp) 40 and Hsp70, guide protein folding. The fourth feature describes how St. Jude structural biologists are using advanced spectroscopy techniques to elucidate the structure and mechanisms of the Hsp40/Hsp70 protein chaperone machinery and, ultimately, identify new targets for cancer treatment.

Immunotherapy can involve using a patient’s own immune cells to treat cancer. The fifth story explains how St. Jude immunologists are investigating approaches to optimize immunotherapy to target pediatric cancers. These researchers are examining intrinsic T-cell function, metabolism, and exhaustion to determine why pediatric immune systems do not control tumor growth and to identify novel targets and strategies that may improve immunotherapy.

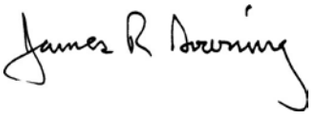
Medulloblastoma is one of the most common and deadly brain cancers in children. St. Jude researchers are using single-cell RNA sequencing to identify new molecular subtypes of medulloblastoma and the cells of origin from which these tumors arise. The sixth article chronicles the efforts to advance our overall understanding of the disease biology and to improve diagnosis and treatment, which will ultimately improve survival.

Skin cancer rarely arises in children or adolescents; thus, pediatric melanoma is one of the least understood childhood cancers. The final feature details the research of a multidisciplinary team that is using comprehensive genomics analyses to investigate pediatric melanoma subtypes and develop prognostic markers and new treatments. The investigators recently showed that MAP-kinase signaling has a central role in the development of a subset of melanomas. These scientists are now testing the efficacy of *MAP3K8* kinase inhibitors in treating pediatric and adult melanomas harboring *MAP3K8* gene mutations.

Beyond the activities described in this Report, St. Jude has reached new milestones during the past year. These include installing the world’s largest superconducting magnet for studying proteins, DNA, RNA, and other biomolecules; accepting the largest number of new oncology patients in the institution’s history; and uniting health care providers across countries in a global alliance to improve pediatric cancer survival rates.

The world may be experiencing unprecedented change, but the St. Jude mission—finding cures and saving children—remains the same. This year has shown unequivocally that ingenuity abounds across all levels of the organization. Whether meeting the challenges of a pandemic, uncovering scientific insights, or setting new standards for patient care, the institution continues to make advances in the laboratory, the clinic, and around the globe. During the days and months ahead, let us remember what the history of St. Jude has shown—when courage and compassion are applied to a shared purpose, the greatest of obstacles can be overcome.

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



# ST. JUDE RESPONDS TO THE COVID-19 PANDEMIC

**In December 2019, an outbreak of the novel coronavirus SARS-CoV-2 was reported in Wuhan, China. The virus rapidly spread around the world, and the first case of coronavirus disease 2019 (COVID-19) in the United States was reported on January 21, 2020, in Seattle, WA. On March 11, 2020, the World Health Organization officially declared COVID-19 a pandemic. On March 12, 2020, St. Jude Leadership implemented the St. Jude Emergency Operations Plan.**

SARS-CoV-2 is transmitted from person to person primarily by respiratory droplets; thus, maintaining physical distance, wearing face masks, and frequent handwashing can reduce the likelihood of infection. The elderly and those with underlying medical conditions, including immunocompromised individuals, can suffer from severe infections with increased morbidity and mortality. Although children generally do not experience severe illness, multisystem inflammatory syndrome, which can permanently scar internal organs, occurs in some pediatric cases. Infants and children aged 5 years or younger also appear to experience more severe disease than do older children.

The full spectrum of effects of SARS-CoV-2 infection on pediatric oncology patients is not understood; however, most children with severe COVID-19 disease have pre-existing conditions, such as respiratory diseases or immune disorders. Therefore, patients at St. Jude, many of whom are immunocompromised, are at increased risk of severe disease. Here we summarize how St. Jude responded to the COVID-19 pandemic to protect the health of our patients, their families, and staff.

## THE INCIDENT COMMAND CENTER IS ACTIVATED

Since 2006, the Joint Commission has mandated that all accredited hospitals have a Pandemic Emergency Operations Plan in place that is regularly updated and tested at least twice a year. The Plan specifies the teams and processes for activating an Incident Command Center (ICC) to ensure that the institution remains functional during an emergency. The St. Jude ICC was designed to ensure efficient, centralized decision-making and a comprehensive understanding of the activities occurring at St. Jude during the institution's response to an emerging catastrophic event. Because the COVID-19 pandemic is a clinical disaster, rather than a natural disaster, Clinical Director Ellis J. Neufeld, MD, PhD, was appointed commander of the ICC.

Deputy Clinical Director Patricia M. Flynn, MD, and Medical Director of the Infection Prevention and Control Program Hana Hakim, MD, created a pandemic playbook and defined the phases of the ICC's responses based on information provided by the Centers for Disease Control and Prevention and Memphis–Shelby County public health officials.

James R. Downing, MD

Ellis J. Neufeld, MD, PhD

Joshua Greer; Patricia M. Flynn, MD

Hana Hakim, MD

Because information about the virus was changing daily, campus processes had to be adjusted in response, and those changes needed to be communicated quickly. In the early days of the pandemic, the ICC and institutional leadership met three times each day to share new information; discuss and prioritize needs, activities, and challenges; and develop responses to new information, as needed. All St. Jude employees received daily emails from the President and CEO James R. Downing, MD. Because this pandemic is a prolonged emergency and its demands are continuously changing, establishing a “new normal” has been an ongoing, fluid process.

## THE COMPASS PROGRAM IS ESTABLISHED

St. Jude is unique because it is both a hospital and an academic research center. While the ICC managed all clinical decisions and activities, the COVID-19 Monitoring, Preparedness, Screening, and Surveillance (COMPASS) Program was created to address other campus-wide needs. Specifically, the COMPASS team identified processes that are essential to keep the facility operational, those that needed modifying during the pandemic, and those that could be suspended. Dr. Downing and the Deputy Director for Academic and Biomedical Operations, Terrence L. Geiger, MD, PhD, lead the COMPASS Program. Aligning a large panel of St. Jude leaders and experts, including Senior Vice President of Human Resources Dana Bottenfield and Director of Biomedical Communications Diane Roberts, COMPASS leadership acted swiftly to develop operational teams that worked to simultaneously protect the health of everyone on campus and maintain the ease of access and campus operations.

To minimize the risk of on-campus viral spread, in late March the institution implemented a shutdown that redirected approximately 2000 employees to off-campus remote work. With this shutdown, the ICC permitted only one family member per patient on campus, and the campus was closed to visitors and nonessential vendors. The campus was sectored into clinical and nonclinical zones for the employees who remain on campus. Staff ID badges were modified with a color-coded "badge buddy" to denote which zone(s) employees can access. This system minimizes interactions between nonclinical staff and patients/families, thereby reducing the potential for patient exposure to the virus.

Because information and processes have changed frequently during the pandemic, new tools were needed to communicate those changes efficiently. The *OurStJude* mobile app and *595-INFO* phone line were created for patients/families, and

Terrence L. Geiger, MD, PhD


Dana Bottenfield

the *595-NEWS* phone line and *COVID-19 Updates and Information* intranet site were created for employees to gain rapid access to the most up-to-date information, requirements, and processes. The executive communications team, including Summer Freeman, Virgil Holder, Diane Roberts (all of Administration), and Elizabeth Walker (Communications), worked with Dr. Downing to provide daily updates. Staff communication was supplemented with monthly virtual Town Hall Meetings. The goals of these communications were to provide accurate and consistent information about the pandemic, address employees' questions and concerns, and help remote employees remain connected to the campus.

Brandon Gregory

## INFECTION CONTROL PROCESSES

As the SARS-CoV-2 virus spread, health care facilities were inundated with infected patients, increasing the risk of spread to other patients and clinical staff. Health care facilities initially implemented screening/testing programs for symptomatic staff. However, early in the pandemic, it became clear that the virus can also be transmitted by asymptomatic carriers and presymptomatic individuals. To create the safest campus environment possible, St. Jude was one of the first workplaces to develop a comprehensive screening program that included laboratory testing of all employees on campus. All entrants to campus are screened using simple questions to identify individuals at risk of disease. All employees working on campus, initially in the clinical zone and later throughout the campus, are also tested for the SARS-CoV-2 virus every 4 days (clinical care providers) or 7 days (all other employees). Upon campus entry, employees are notified if they have been selected for testing. If so, they are directed to an on-site testing facility in the Marlo Thomas Center. The benefits of this program were evident early; affected employees were identified through both the questionnaire and laboratory testing. This enables rapid quarantine of individuals with new infections, thereby decreasing the risk of viral spread and allowing employees to rapidly seek medical care and take measures to protect their families and contacts outside of St. Jude.

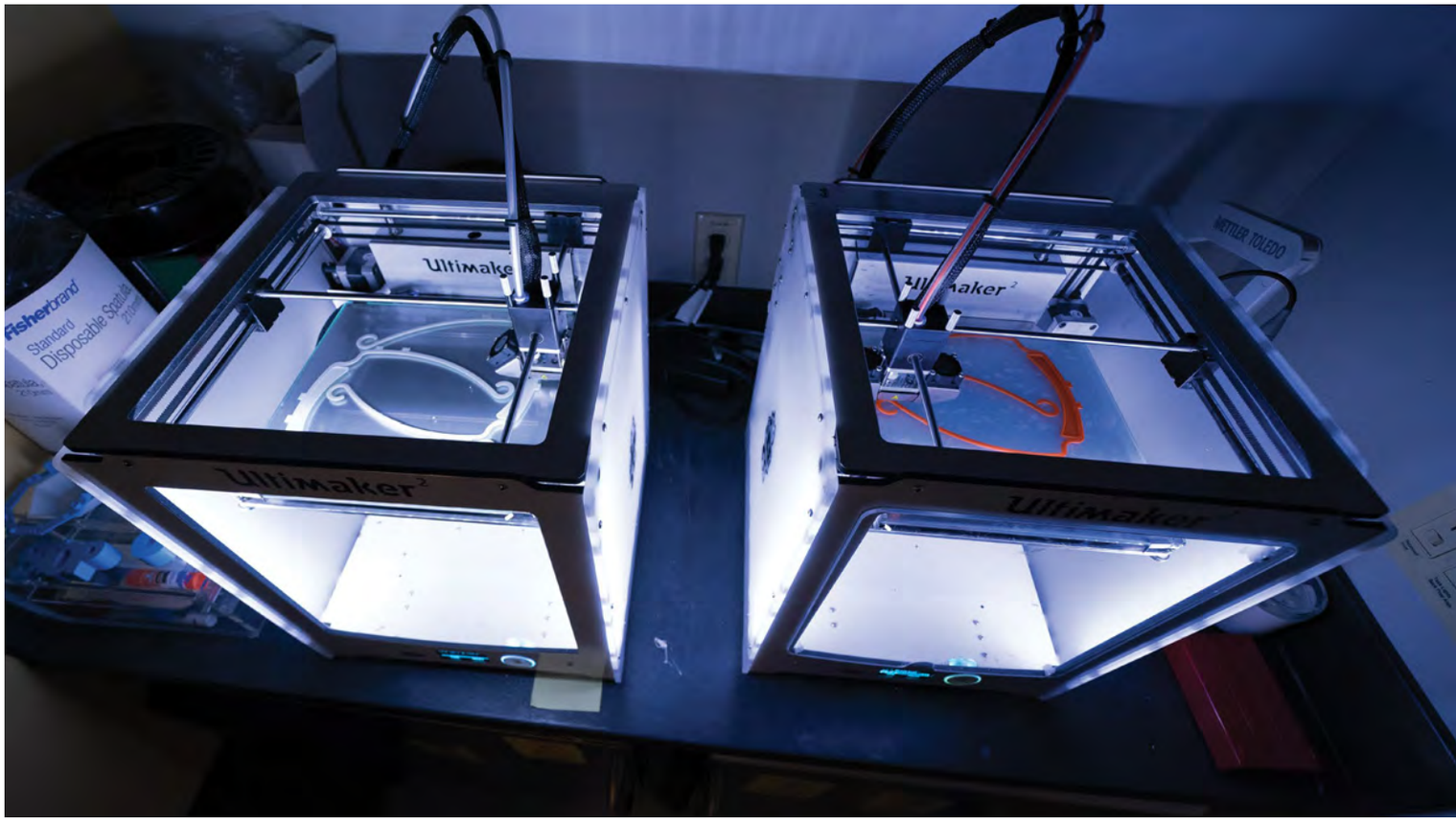
Medical Director of Occupational Health Aditya H. Gaur, MD, MBBS, and Chief Patient Safety Officer James M. Hoffman, PharmD, were instrumental in developing and administering the screening and surveillance program. Assistant Medical Director of Occupational Health Diego R. Hijano, MD, developed an on-site contact-tracing program. Contact tracing involves interviewing a person who has tested positive to identify all individuals with whom that person interacted during the 48-hour period preceding the COVID-19+ test result. Individuals who may have been exposed to the contagion are then contacted, quarantined, and receive testing. The St. Jude contact-tracing program is performed in coordination with that of the Memphis–Shelby County Department of Public Health.

Lisa Wallace; Jeffrey Rubnitz, MD, PhD

Due to the limited early capacity for SARS-CoV-2 testing in St. Jude clinical laboratories, the laboratory testing program was initially conducted as a collaboration between the clinical laboratories, led by Randall T. Hayden, MD, Medical Director of Clinical Pathology and Director of Clinical and Molecular Microbiology, and researchers Stacey L. Schultz-Cherry, PhD, Richard J. Webby, PhD (both of Infectious Diseases), and Paul G. Thomas, PhD (Immunology). These and many other individuals coordinated with Drs. Gaur and Hoffman to set up early methods for detecting SARS-CoV-2 RNA in nasal swab samples from St. Jude staff. During that time, Dr. Hayden established a new clinical laboratory dedicated exclusively to SARS-CoV-2 testing. With the inauguration of this new laboratory, all testing moved to that facility. The SARS-CoV-2 Testing Laboratory has a running capacity of 6000 nucleic acid tests per week and a surge capacity nearly double this.

A drive-thru COVID-19 testing center was also opened at the St. Jude Garden for symptomatic staff members or staff with potential virus exposure. Test results are available within hours of acquiring samples. Once an infection is confirmed, staff in the Occupational Health Program rapidly initiate contact tracing. These measures have been highly effective in keeping the virus off the St. Jude campus.

Because childhood catastrophic diseases do not pause for a pandemic, new pediatric patients continue to be referred to St. Jude for treatment. Clinical leaders in the ICC decide which patients should be seen on campus and which patients can be treated elsewhere. A new telehealth program was launched to support off-campus care. For those who need to come to campus, a facility for screening, testing, and isolation was established in the Kmart St. Jude LIFE Center. A program for regular testing of patient family members was also established to maintain the safety of everyone on campus and in St. Jude housing.




## BASIC RESEARCH IS SUSPENDED AS THE CAMPUS CLOSES

As the pandemic reached the Memphis area, research laboratories were closed for all but essential functions. On March 27, 2020, the campus was closed to approximately 1500 (90%) St. Jude researchers to prevent the spread of COVID-19. The remaining research staff ensured that essential resources and equipment were maintained. Some Shared Resources were enlisted to support COVID-19–related efforts. As national shortages of essential equipment (e.g., ventilators), personal protective equipment (PPE), and testing reagents for the virus occurred in many other health care facilities, the Children's GMP, LLC, began making clinical-grade reagents and packaging approximately 20,000 vials of viral transport medium per week for nasal swab samples. All 3D printers on campus were repurposed to make PPE head gear, and the Print Shop used lamination film to make clear face guards.

Under the direction of Chief Information Officer Keith Perry, the Information Services department scrambled to help St. Jude researchers and support staff work efficiently from home. Researchers used their time at home to write, analyze data, improve databases, and engage in electronic journal clubs and virtual meetings with colleagues. The increased demand for off-campus access to St. Jude's electronic resources led the Information Services department to create the *remote.stjude.org* and *myapps.stjude.org* websites. These tools enable staff to access digital resources without taxing the institution's virtual private network (VPN), which before the pandemic could accommodate 800 users at a time. Information Services also engineered and developed a new VPN portal for staff working from home who require VPN access; the VPN capacity is now 2800 users at a time.

Many researchers also needed more powerful computational abilities and faster access to large genomic data files; thus, Information Services increased the capacity of the SJ Cloud. Researchers can now move their large files on demand from the high-power computer server at St. Jude to the SJ Cloud for off-campus data analysis and storage.

## CLINICAL RESEARCH EFFORTS ARE RESTRUCTURED

During the pandemic, St. Jude has had to reorganize its clinical research efforts. Clinical Trials Operations involves 130 staff members who monitor 260 therapeutic clinical trials with more than 800 enrolled participants. Questions and concerns of the clinical teams are fielded by the COVID-19 Clinical Operations staff working in the ICC. Tracy Parks (Quality Management), Janice English (Patient Experience), and the ICC team support clinical staff and patients/families via a dedicated email address and phone lines.

Although studies have continued to accrue new participants during the pandemic, campus visits were cancelled, and travel was discouraged. Enrollment of international patients was either stopped or delayed. For participants in the Memphis area, routine clinical care is provided, when possible, at St. Jude Housing Facilities (i.e., Target House, Ronald McDonald House, or Tri Delta Place) to decrease patient travel and the number of people on campus.

The eight St. Jude Affiliate clinics (and other health care facilities) provide care to St. Jude patients living in their vicinity to ensure continuity of their treatment. As all St. Jude business-related travel was suspended, clinical research associates switched from in-person site visits to virtual site visits to review data, monitor safety, and establish new data-sharing methods.

Follow-up appointments were cancelled for the childhood cancer survivors who return to campus annually to be monitored in the After Completion of Treatment Clinic or to participate in the St. Jude Life (SJLIFE; NCT00760656) or Childhood Cancer Survivor Study (CCSS; NCT01120353) trials. However, Epidemiology & Cancer Control investigators provided updated Survivorship Care Plans to all study participants so that their medical histories will be in hand if a survivor contracts COVID-19 and is hospitalized. The CCSS investigators expanded their call center to provide information about COVID-19 and survey survivors about their pandemic-related anxiety and exposure. Within 1 week, the call center had provided information to more than 25,000 survivors, and nearly 3000 CCSS participants have completed the phone survey.

To determine how SARS-CoV-2 infection affects children, Gabriela M. Marón Alfaro, MD (Infectious Diseases), developed the Pediatric COVID-19 US Registry. The registry includes 133 participating institutions and contains more than 5000 cases in the United States. Because St. Jude partners with many countries to improve worldwide care for children with catastrophic diseases who may be severely affected by COVID-19, St. Jude Global developed the Global Registry of COVID19 in Childhood Cancer to follow the impact of COVID-19 on pediatric oncology patients around the world.

Nina Antoniotti; David White; Sarina Horn


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

## THE SJTRC TRIAL OPENS

Although the COVID-19 pandemic disrupted research on campus, it created the opportunity for new initiatives to improve our understanding of the pandemic and the SARS-CoV-2 virus. Multiple researchers adjusted their efforts to also address the core unknowns related to the pandemic. One on-campus study, Tracking of Viral Host Factors Associated with COVID-19 (SJTRC), is investigating such core unknowns. Led by Dr. Thomas and Joshua Wolf, MBBS, PhD (Infectious Diseases), a multidisciplinary group of scientists is conducting a 1-year prospective study of COVID-19–associated host factors in St. Jude employees. The SJTRC trial includes 1300 participants with no prior exposure to SARS-CoV-2 and up to 250 participants who have had prior exposure. Participants receive periodic blood tests, nasal swabs, and health surveys.

The researchers will track immune responses at the molecular level, develop a comprehensive profile of the participants' T-cell responses to the virus, map relevant viral epitopes and identify which ones are the most effective vaccine targets, and determine the host factors that affect the disease course. The SJTRC trial should advance our understanding of COVID-19 infections, help identify potential therapies or effective antiviral responses, and support the design and evaluation of vaccines to prevent future infections.


SCREENING
1
2
SWAB TESTING
HAND HYGIENE
3
4
FACE MASKS
5
CLEANING & DISINFECTING
6
PHYSICAL DISTANCING

## PHASING ST. JUDE STAFF BACK TO CAMPUS

Under the COMPASS Program, a team lead by Gregory T. Armstrong, MD, MSCE (Epidemiology & Cancer Control, Oncology), and Tomi Mori, PhD (Biostatistics), developed a program to monitor an array of data on the pandemic and its impact locally, regionally, nationally, and internationally. Furthermore, Drs. Armstrong and Mori represent St. Jude on the Memphis–Shelby County joint COVID task force, which includes local elected and medical leaders and regional public health officials engaged in decision-making during the public health crisis. Relevant local, regional, national, and world-wide data are provided by the COMPASS monitoring group through an electronic dashboard and are reviewed daily by the executive leadership team. Based on information from Memphis–Shelby County public health officials about the regional outbreak, a decision to bring St. Jude employees back to campus was made in May.

As the initial wave of COVID-19 cases in the Memphis area appeared to be subsiding, COMPASS Program leaders worked with the Office of the Deputy Director of Academic and Biomedical Operations and the Human Resources department to develop a plan for phasing staff back to campus in 2-week intervals. The Human Resources Learning and Organizational Development Office, under the direction of Dennis Reber, EdD, and staff in the Medical Content/Patient Outreach Office, under the direction of Diane Roberts, developed an orientation and communication program designed to inform employees about the processes necessary to return to campus safely (e.g., physical distancing, face masks, COVID-19 screening and testing, etc.). The orientation and communication program also informs employees about the changes resulting from campus zoning and altered operational processes. This on-site training is conducted by Human Resources staff. Between May and July, 2020, approximately 1000 employees returned to work on campus.

Under the direction of Dr. Hakim, the Biomedical Communications staff developed graphics to disseminate institutional safety guidelines. To ensure continued safety across campus, signage was expanded to indicate room occupancies and COVID-19 safety and physical distancing requirements. Les Steele and Mike Harber (both of Facilities Management) were responsible for installing thousands of signs around campus.

To monitor compliance with safety needs and provide education and information, Dana Bottenfield and John Leech (Human Resources) developed the COVID Captains Program. This group of volunteers provides a safety patrol for the entire campus. Now under the direction of the General Safety Officer Guy Joyner, nearly 60 employee volunteers dedicate part of their time to checking for proper mask usage, physical distancing, and room occupancy limits around campus, educating and correcting unsafe behaviors, and identifying areas that need improvement.

Early in the pandemic, all on-campus staff received symptom screening in the Marlo Thomas Center as they arrived to work each day. As employees were coming back to campus, Keith Perry and Trey Waring (Information Services) developed and launched the *SJPASS* mobile app. This app enables employees to self-screen on their cell phones each day and learn whether they have been randomly selected for nasal-swab testing. This has substantially decreased the number of people requiring in-person screening in the Marlo Thomas Center and allows employees to choose a convenient time during their workday to receive testing. Because not everyone has a smart phone or access to a computer at work, the COMPASS Program continues to develop new approaches to facilitate screening and testing and ensure a safe environment for all employees on campus.

# WHAT LIES AHEAD?

All pandemics eventually end. Until that time, St. Jude will continue to vigilantly protect the health of our staff and the patients/families who have entrusted us with their care. Childhood catastrophic diseases do not stop for a pandemic, and delaying treatment can impair survival. Therefore, St. Jude clinicians and investigators persevere, embodying the institution's mission and values, and persisting in the institution's life-saving activities in whatever form is needed and possible. As the pandemic continues to evolve, St. Jude will continue to adapt and make strides toward finding cures and saving children.

# GENE THERAPY EFFECTIVELY RECONSTITUTES THE IMMUNE SYSTEM OF INFANTS BORN WITH X-SCID

**X-linked severe combined immunodeficiency disease (X-SCID), also known as "bubble boy" disease, is a life-threatening disorder in which children are born without a functioning immune system. One of 100,000 boys are born with X-SCID, but girls can have this disease too. Without an immune system, children with X-SCID are at high risk of overwhelming infections. To cure X-SCID in infants, researchers at St. Jude have successfully developed and clinically tested a novel gene therapy approach. Their efforts provide a paradigm for the future treatment of monogenic hematopoietic disorders by gene therapy.**

## EARLY STUDIES OF X-SCID

X-SCID is caused by mutations in the interleukin 2 receptor subunit gamma (*IL2RG*) gene, which is also called the common gamma-chain receptor gene because it is a component of the receptors for several cytokines involved in immune cell development and function. Thus, patients with X-SCID do not produce important cells of the immune system, including T cells, B cells, and natural killer (NK) cells. Infants with X-SCID appear healthy at birth, but in the absence of treatment, they succumb to recurrent and opportunistic infections by 4 to 6 months of age, as the residual protection provided by maternal antibodies wanes.

The only treatment for X-SCID is to restore the patient's immune system. Hematopoietic stem cell transplantation is one approach to accomplish this. Matched-sibling donor transplants are the current standard of care for X-SCID. However, more than 80% of patients with X-SCID do not have a matched-sibling donor. Although other stem cell sources, including matched-unrelated donors, parental (haploidentical) donors, and cord blood, have been evaluated as life-saving therapies, they are associated with a significant risk of complications, including graft-versus-host disease.

Investigators started to explore gene therapy for X-SCID more than 2 decades ago. To correct X-SCID by gene therapy, a healthy copy of *IL2RG* is inserted into the hematopoietic stem cells of patients with defective versions of the gene. Early gene therapy efforts used gamma retroviral vectors containing *IL2RG*-restored T-cell but not B-cell or NK-cell function. More disturbing, the vectors used induced leukemia in 30% of patients by insertional mutagenesis. Although this severe complication brought clinical gene therapy studies on X-SCID to a paralyzing halt, investigators were not dissuaded from identifying the cause of these leukemia cases and developed novel vectors with decreased risk of insertional mutagenesis.

Ewelina K. Mamcarz, MD

The late Brian P. Sorrentino, MD (Hematology), led a team of investigators at St. Jude to develop a novel lentiviral vector for gene therapy of X-SCID. Specific safety features of the vector included a normal cellular promoter to drive the expression of *IL2RG* and "insulators" or "firewalls" (i.e., sections of DNA that prevent the unintended activation of genes close to lentivirus-integration sites) to prevent the inserted vector from modulating other genes in the genome. Once all safety testing was completed, a clinical-grade vector was developed in collaboration with Michael M. Meagher, PhD (Pathology), President of Children's GMP, LLC, on the St. Jude campus. Other key members of the team included Albert Zhou, PhD (Experimental Cellular Therapeutics Laboratory), and Timothy Lockey, PhD (Therapeutics Production & Quality).

The safety and efficacy of the novel lentiviral vector was first evaluated in older children with X-SCID who had not been cured by hematopoietic stem cell transplantation. This clinical trial was conducted at the National Institutes of Health and led by Dr. Sorrentino's long-term collaborator Dr. Harry Malech. Hematopoietic stem cells were collected from patients and genetically modified in the laboratory by using a gene therapy vector developed and manufactured at St. Jude. Patients received low-dose busulfan chemotherapy to create space in the bone marrow before the gene-corrected cells were infused. The gene therapy was well tolerated and restored a functional immune system in five older children with X-SCID. Leukemia was not seen in any of the patients. On the basis of these encouraging findings, Dr. Sorrentino then developed a gene therapy study for infants with X-SCID who had not received any other therapy.

Brian P. Sorrentino, MD
1958–2018

## CLINICAL TRIAL OF *IL2RG* GENE THERAPY IN INFANTS WITH X-SCID

For this trial, Dr. Sorrentino collaborated with Ewelina K. Mamcarz, MD, and Stephen Gottschalk, MD (both of Bone Marrow Transplantation & Cellular Therapy), and Drs. Morton Cowan and Jennifer Puck at the University of California–San Francisco Benioff Children's Hospital (San Francisco, CA). The study was designed as a safety and early efficacy study. The treatment involved collecting bone marrow hematopoietic stem cells from affected infants, a procedure performed under general anesthesia. In the St. Jude Children's GMP facility, scientists then selected stem cells from the extracted bone marrow, genetically modified those cells with the lentiviral vector carrying the healthy *IL2RG* gene, and cryopreserved the modified cells. The cell product was released by the Children's GMP for clinical use only after it passed extensive quality-control testing. The patients received two low doses of busulfan chemotherapy prior to the infusion of their own gene-corrected stem cells. Each busulfan dose was individually calculated based on the patient's weight and age, and the plasma levels of the drug were monitored to guide dosing and enhance the safety of the approach. The dose of busulfan administered was approximately one third of that received by infants who undergo a standard hematopoietic stem cell transplantation.

The outcomes of the first eight patients, who completed the trial with a median follow-up of 16.4 months (range, 6.7–24.9 months), were published in *The New England Journal of Medicine*. Since then, updated data have been presented at the 61st Annual Meeting of the American Society of Hematology (December 7–10, 2019, Orlando, FL). The data included three more patients (N=11), 8 months of additional follow-up (median, 23.6 months; range, 1.5–33.9 months), more extensive analysis of T- and B-cell functional recovery, and detailed studies of vector-integration sites.


Ewelina K. Mamcarz, MD; Stephen Gottschalk, MD

Both the initial and follow-up results have been outstanding for the patients thus far. All patients tolerated busulfan well, with no serious adverse events other than the expected hematologic effects (i.e., busulfan suppresses the production of blood cells). None of the patients required a blood product transfusion, and all had robust hematopoietic recovery within 3 to 4 weeks after infusions of the modified cells. Nine patients who were followed for more than 3 months had normal-for-age numbers of T cells and NK cells within 4 months of completing gene therapy. This finding exceeded the primary study objective. Furthermore, patients' T cells matured appropriately, as assessed by normal T-cell receptor (TCR) excision circles (a marker indicative of the recombination of TCR genes in developing T cells within the thymus) and TCR Vβ–repertoire analysis (an indicator of the diversity of the TCR repertoire). Unlike previous clinical gene therapy studies for X-SCID, five patients were able to discontinue intravenous immunoglobulin treatment because they had normal B-cell function. Impressively, three of the patients mounted normal immune responses to vaccinations. Leukemia was not evident in any of the study participants. In addition, integration-site analysis of the lentiviral vector did not reveal a premalignant state in any of the analyzed patients. Gene therapy delivered by lentiviral vectors to patients with X-SCID resulted in a normal, fully functioning immune system and excellent clinical benefits. All prior infections resolved, and the study participants showed normal growth. Foremost for the families, all protective isolation measures could be stopped, and the patients were able to join their families and other children in everyday activities.

## MOVING FORWARD

Drs. Mamcarz and Gottschalk and their colleagues at Benioff Children's Hospital continue to monitor the study participants to ensure that the gene therapy provides a sustainable cure without complications. More patients need to be treated to assess the efficacy and durability of this gene therapy approach for X-SCID and extend these promising initial results. St. Jude has partnered with the biotechnology company Mustang Bio (Worcester, MA) to develop a later phase clinical study, with the ultimate goal of approval of this X-SCID gene therapy by the U.S. Food and Drug Administration.

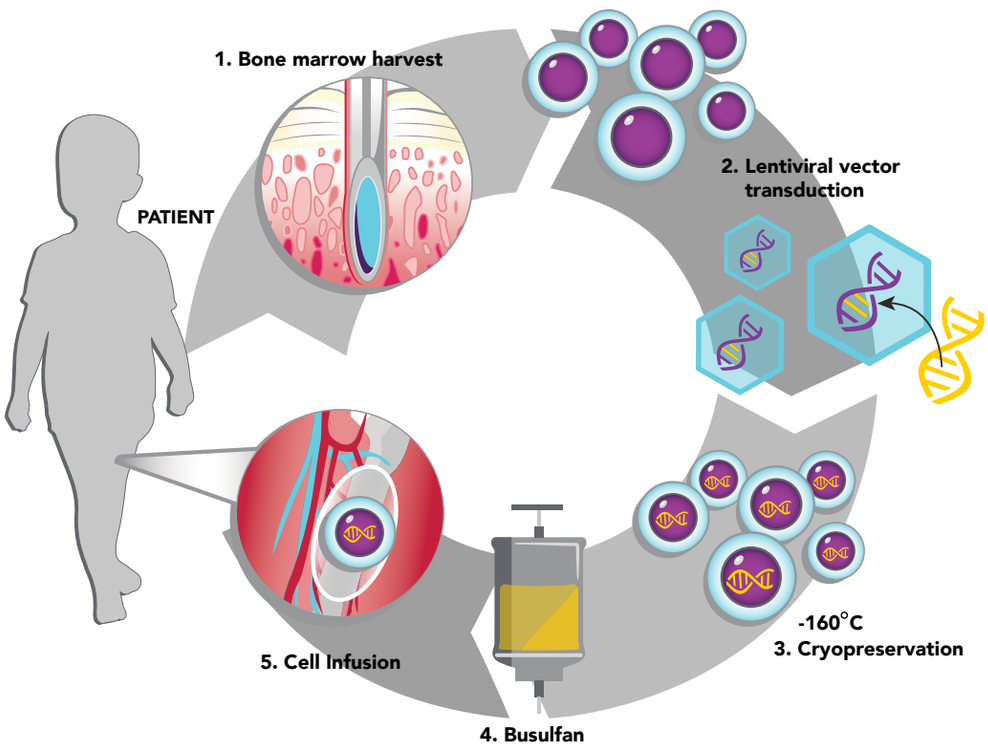



**Figure.** Schematic of *IL2RG* gene therapy for X-SCID.

# CONCLUSION

Translating lentiviral vector–mediated gene therapy to the clinic required more than a decade's effort and team science that brought together investigators with expertise in gene therapy, hematology, bone marrow transplantation and cellular therapy, and good manufacturing practice. By exploiting the latest insights in lentiviral biology and molecular biology, St. Jude researchers have generated a safe, effective treatment for children with X-SCID.

# MOVING BEYOND THE CURE: REDUCING THE NEUROTOXICITY OF CANCER TREATMENT TO IMPROVE QUALITY OF LIFE FOR CHILDHOOD CANCER SURVIVORS

**Survival rates for many childhood cancers have improved dramatically over the last few decades. However, for many patients, cure comes at a cost—cancer treatment is associated with toxicities, including neurologic and cognitive deficits. These toxicities impair social, academic, and vocational attainment, resulting in a reduced quality of life. As the population of childhood cancer survivors grows, efforts to prevent adverse effects of cancer treatment have become imperative. St. Jude researchers are determining how cancer therapies can be modified to reduce treatment-related neurologic and cognitive impairment without compromising survival.**

## THE TOTAL THERAPY 16 TRIAL SHOWS DECREASED RISK OF CENTRAL NERVOUS SYSTEM RELAPSE WITHOUT INCREASED TOXICITY IN PATIENTS WITH HIGH-RISK ACUTE LYMPHOBLASTIC LEUKEMIA

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, accounting for 29% of all childhood cancers. For the past 2 decades, St. Jude researchers have pioneered sequential Total Therapy studies for children with newly diagnosed ALL. This work, which has been led by Ching-Hon Pui, MD (Oncology, Pathology, Global Pediatric Medicine), has substantially contributed to the remarkable advances made in improving the outcome of this disease.

Currently, 94% of pediatric patients with ALL enrolled in a Total Therapy clinical trial are expected to be long-term survivors. Researchers at St. Jude are now focusing on not only further advancing cure rates for ALL but also reducing the long-term treatment-related adverse effects. The question is—can this be done without jeopardizing leukemia control and ultimately survival?

Cranial irradiation to prevent central nervous system (CNS) relapse has long been a standard treatment for ALL. Most national study groups still include it in their treatment regimens for patients with high-risk disease, especially for those with T-cell ALL or overt CNS leukemia at the time of diagnosis. However, cranial irradiation is associated with a wide range of late effects, including second cancers, stunted growth, hormone imbalances, and neurocognitive deficits.

Ching-Hon Pui, MD

St. Jude Total Therapy 15 (2000–2007) was the first study to omit prophylactic cranial irradiation in all enrolled patients, regardless of their clinical or biological features at diagnosis. The study achieved not only an outstanding 5-year survival of 94% but also a low isolated CNS relapse rate of 4%. However, the Total Therapy team continued to strive for better outcomes by further decreasing the CNS relapse rate to minimize the need for therapeutic cranial irradiation. St. Jude Total Therapy 16 (2007–2017) evaluated whether a higher dosage of the chemotherapy drug PEG-asparaginase and early intensification of triple intrathecal therapy (i.e., methotrexate, hydrocortisone, and cytarabine injected directly into the cerebrospinal fluid) would improve systemic and CNS control beyond that observed in patients at high risk for relapse who were enrolled in Total Therapy 15. In the *Journal of Clinical Oncology,* Sima Jeha, MD (Global Pediatric Medicine, Oncology), Dr. Pui, and their colleagues reported findings from the Total Therapy 16 trial. In brief, patients with T-cell ALL, the *TCF3–PBX1* fusion gene, or leukemic blasts in cerebrospinal fluid were treated with two additional doses of triple intrathecal therapy during the first 2 weeks of remission induction. All patients were given leucovorin rescue after intrathecal therapy to reduce the risk of neurotoxicity. Like Total Therapy 15, Total Therapy 16 did not include prophylactic cranial irradiation.

Total Therapy 16 enrolled 598 consecutive patients, including 12 infants and 359 children and adolescents with presenting features indicating an increased risk of CNS relapse. Infants with ALL are generally at higher risk of neurotoxicity, as their developing tissues are vulnerable to intensive chemotherapy and radiation. Although higher doses of PEG-asparaginase did not improve outcome, the additional intrathecal therapy significantly reduced the risk of CNS relapse for patients with high-risk ALL from 5.7% (observed in Total Therapy 15) to 1.8%, the lowest risk reported to date. Also, the additional intrathecal therapy was not associated with increased toxicity. No CNS relapses occurred in many patients with high-risk subtypes of ALL, including infantile ALL.

By combining data from 1096 patients treated on the two consecutive trials that omitted prophylactic cranial irradiation, the team found that 18 (1.6%) experienced isolated CNS relapse, with two succumbing to their disease. Thus, CNS relapse in patients who had not received prophylactic cranial irradiation is highly curable. With the recent advent of chimeric antigen receptor–modified T-cell therapy, even patients who experience CNS relapse might be cured without the use of therapeutic cranial irradiation. One patient in Total Therapy 16 had a combined CNS and ocular relapse and was treated with remission induction chemotherapy only, including intrathecal therapy followed by CD19+ chimeric antigen receptor T-cell therapy. That child has remained in remission for more than 2 years.

In the current Total Therapy 17 trial, a precision medicine approach is used to replace toxic chemotherapy with targeted therapy to further diminish toxicities and improve the cure rate and quality of life of patients, the vast majority of whom will become adult survivors of childhood cancer.


Ching-Hon Pui, MD; Sima Jeha, MD

## NEW RADIATION THERAPY APPROACHES IMPROVE SURVIVAL AND COGNITIVE OUTCOMES IN CHILDREN WITH BRAIN TUMORS

Since 1996, radiation oncologists at St. Jude have been developing conformal radiation therapy using photons (x-rays) for children with brain tumors. Conformal radiation therapy targets the tumor as accurately as possible. The overarching hypothesis is that reducing the irradiated volume of healthy tissue surrounding the postoperative tumor bed will decrease adverse neurocognitive effects without affecting the rate or pattern of treatment failure. Early studies relied on the use of computerized tomography and magnetic resonance imaging during the radiotherapy treatment-planning process and used a well-designed battery of neurocognitive tests administered at the start of treatment and during follow-up to assess patients for neurocognitive impacts.

The promise of conformal radiation therapy was realized early for children younger than 3 years with ependymoma treated on the St. Jude RT1 protocol (1997–2010). Cure rates were low and complication rates were high when radiotherapy was delayed or omitted in favor of chemotherapy for very young children with ependymoma; conventional methods of radiation therapy were used to treat those with progressive tumors.


Thomas E. Merchant, DO, PhD

Very young children treated with immediate postoperative conformal radiation therapy on the RT1 protocol had improved tumor control and decreased adverse cognitive effects over time, as indicated by follow-up cognitive results that were compared to initial assessments. The success of the RT1 protocol for children with ependymoma led to the development of the Children's Oncology Group (COG) protocol ACNS0121, which was led by Thomas E. Merchant, DO, PhD (Radiation Oncology), and supported by a cadre of St. Jude investigators in the Departments of Radiation Oncology, Diagnostic Imaging, and Pathology.

The ACNS0121 protocol for childhood ependymoma was the first national and international protocol to systematically use immediate postoperative radiation therapy for children as young as 12 months of age. Based on the excellent functional outcomes and the high rates of tumor control observed in these patients, the ACNS0121 trial completed enrollment in less than 4 years. In total, 356 children with newly diagnosed ependymoma were treated at 115 institutions and benefitted from knowledge shared by St. Jude investigators. Dr. Merchant and his colleagues published the results from the ACNS0121 trial in the *Journal of Clinical Oncology*. First, they dispelled the myth that very young children with ependymoma have a uniformly worse prognosis than older children; the 5-year overall survival was 87% in children aged 3 years or younger and 86% for those older than 3 years. Second, compared to the prior approach of treating children younger than 3 years with postoperative intensified chemotherapy to delay or avoid irradiation, the current protocol was associated with substantially better 5-year overall survival (87% vs. 43%).

These results pioneered by the St. Jude neurosurgery, neuro-oncology, and radiation oncology teams further enabled the novel assessment of important molecular markers in a prospectively treated cohort of patients. Dr. Merchant and his colleagues showed that gain of chromosome 1q in children with infratentorial (posterior fossa) ependymoma is an important prognostic factor and that fusion status of the *RELA* gene in supratentorial ependymoma is not prognostic. The St. Jude RT1 and COG ACNS0121 protocols deployed a 1-cm clinical target volume margin (i.e., the width of healthy tissue surrounding the postoperative tumor bed that is included in the irradiated volume). To improve upon the success of these protocols and further reduce the side effects associated with radiation therapy (e.g., neurotoxicity), Dr. Merchant and his colleagues adopted a 0.5-cm margin and used proton therapy for the subsequent St. Jude SJYC07 and COG ACNS0831 protocols, the latter succeeding ACNS0121 and supported by St. Jude investigators from multiple departments.

In another key publication from the RT1 protocol, appearing in *Neuro-Oncology* in 2019, Sahaja Acharya, MD (Radiation Oncology), and her colleagues showed that exposure of the hippocampus to high doses of radiation had a significant impact on multiple cognitive outcomes associated with memory. The RT1 study enrolled 80 pediatric patients (median age, 9.5 years; range, 6–20 years) with low-grade glioma. Although tumor control rates were excellent with the use of conformal radiation therapy, most tumors were located adjacent to the hippocampus, the region of the brain that encodes new memories. Neurocognitive assessments were completed at baseline, 6 months, annually for 5 years, and then at 7, 8, and 10 years after completion of therapy. Dr. Acharya and her colleagues determined that radiation doses to the hippocampus in excess of 40 Gy were associated with a decline in cognitive performance, and the higher dose was associated with a greater decline in memory.

These results provide clinicians with an important normal tissue dose parameter to monitor and an important brain structure to avoid when designing radiation treatments for children with this common tumor. Agents targeting the MAPK and other pathways provide an excellent option to delay or avoid irradiation, but many of those children still require radiation therapy. Highly conformal, intensity-modulated proton therapy is now used to spare crucial structures, such as the hippocampus, which in turn reduces memory loss and improves quality of life. The benefit of reducing radiation dose to the hippocampus is now being tested in the prospective St. Jude clinical trial HALGG.

Sahaja Acharya, MD


Anthony Liu, MBBS; Amar J. Gajjar, MD

## REDUCED-DOSE CRANIOSPINAL IRRADIATION CAN CURE NONMETASTATIC PINEOBLASTOMA IN CHILDREN

Pineoblastoma is a rare childhood malignancy that arises from the pineal gland in the brain. This embryonal tumor tends to metastasize within the CNS and has a long-term cure rate of approximately 60%. Because pineoblastoma accounts for less than 1% of all pediatric brain tumors, the literature on this disease is sparse, and the optimal strategy for treating it remains elusive.

Previous pineoblastoma studies have applied conventional approaches used to treat children with other CNS embryonal tumors that have high-risk features. Specifically, the patients underwent a regimen of surgical resection, high-dose craniospinal irradiation (36 Gy), and adjuvant chemotherapy. However, craniospinal irradiation can lead to dose-dependent, long-term neurocognitive impairment in children, and it is unclear whether all patients with pineoblastoma require such intense treatment.

Amar J. Gajjar, MD (Pediatric Medicine, Oncology), is leading clinical research efforts to improve the care of patients with pineoblastoma and expand our understanding of this disease. His team's goal is to maximize disease control while minimizing treatment-related toxicity. Two multi-institutional, risk-adapted pediatric brain tumor clinical trials, SJMB03 and SJYC07, enrolled patients with newly diagnosed pineoblastoma. The SJMB03 study included patients who were 3 years or older, and for the first time, treatment was stratified based on the extent of tumor resection and the patient's metastatic status at the time of diagnosis. Specifically, patients whose tumors were completely resected and had no evidence of metastasis were assigned to an average-risk group

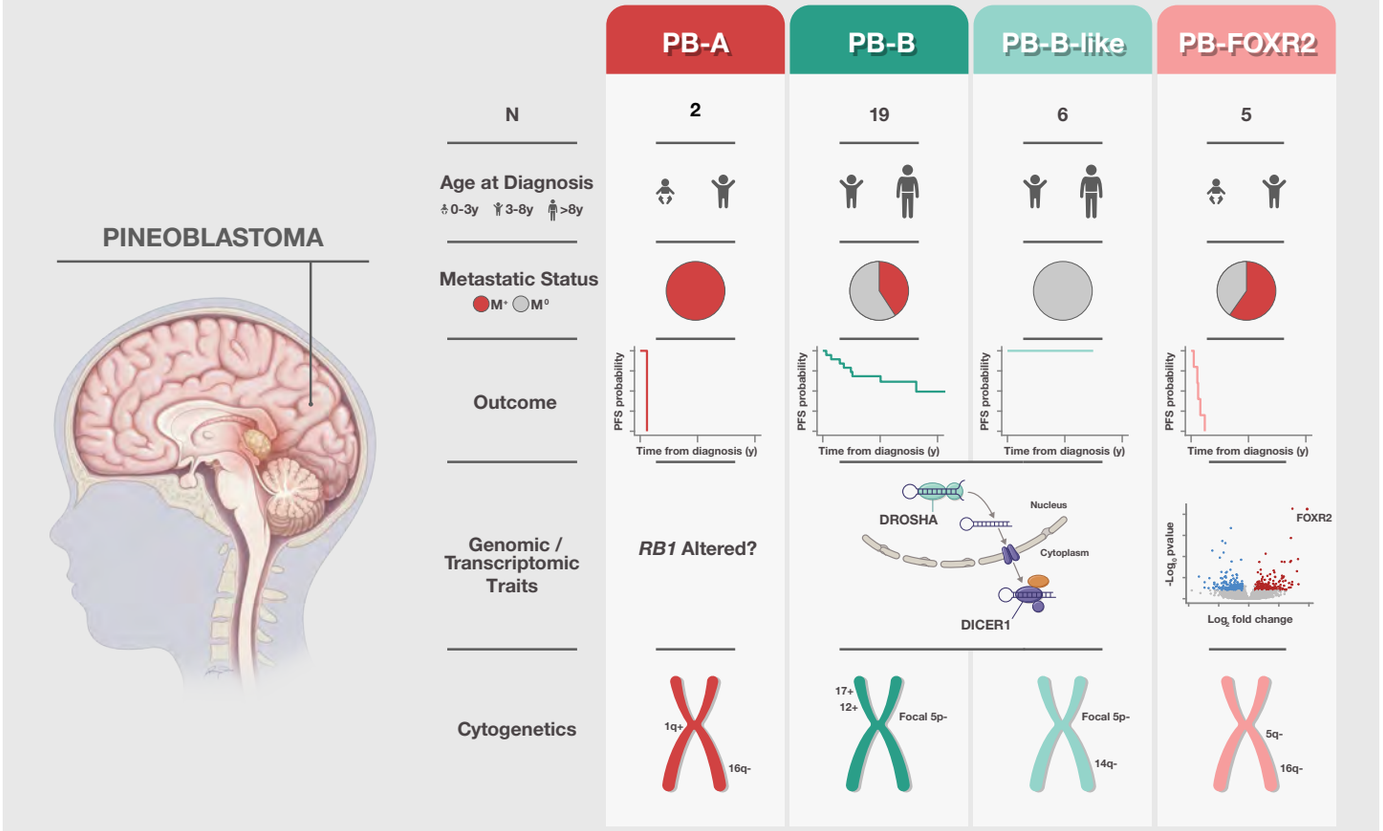



**Figure.** Summary of clinical, genomic, and cytogenetic traits that define the four molecular subgroups of pineoblastoma: PB-A, PB-B, PB-B-like, and PB-FOXR2. The propensity for metastasis and progression-free survival of each subgroup are shown. *RB1* alteration in the PB-A subgroup has been reported by other groups but was not detected in this study. The PB-B and PB-B–like subgroups showed alterations in the miRNA-processing pathway genes *DICER* and *DROSHA*, and the PB-FOXR2 subgroup overexpressed the *FOXR2* proto-oncogene. Abbreviations: $M^0$, nonmetastatic disease; $M^+$, metastatic disease; N, number of patients; PB, pineoblastoma; PFS, progression-free survival; y, years. *Reprinted by permission from SNCSC GmbH: Acta Neuropathol, 139:259–71, Liu APY et al, Risk-adapted therapy and biological heterogeneity in pineoblastoma: integrated clinico-pathological analysis from the prospective, multi-center SJMB03 and SJYC07 trials. © 2020 Springer*

and were treated with reduced-dose (24 Gy) craniospinal irradiation. Those who either had tumors that were not completely resected or had metastatic disease at diagnosis were assigned to a high-risk group and received standard-dose (36 Gy) craniospinal irradiation. All patients in the SJMB03 study also received a radiation boost to the primary disease site, followed by four cycles of chemotherapy. The SJYC07 trial enrolled patients younger than 3 years and treated them with chemotherapy, with or without focal irradiation.

Through these trials and using comprehensive genomic profiling of banked pineoblastoma samples, Dr. Gajjar and his colleagues have investigated the clinical and biological heterogeneity within pediatric pineoblastoma. Anthony Liu, MBBS (Oncology), a Pediatric Neuro-Oncology fellow working with Dr. Gajjar, led a team that included Paul A. Northcott, PhD (Developmental Neurobiology), and Brian Gudenas, PhD (Developmental Neurobiology), a postdoctoral fellow working in Dr. Northcott's laboratory. In *Acta Neuropathologica*, they reported findings in 58 children with pineoblastoma. Patients treated using the SJMB03 trial's approach had significantly better outcomes than did their younger counterparts who were treated in the SJYC07 trial. Specifically, patients with average-risk disease in the SJMB03 study had superior disease control; 17 of 18 (94.4%) patients survived without disease progression, despite receiving lower-dose craniospinal irradiation. Such promising results negate the notion that all patients with pineoblastoma experience an aggressive disease course and support the integration of risk-adapted treatment stratification based on the extent of surgical resection and metastatic status in children older than 3 years with pineoblastoma.

Using 43 tumor samples obtained during the clinical trials, Dr. Liu and his colleagues performed methylation profiling, whole-exome sequencing, and RNA sequencing to increase our understanding of the disease's biology. The researchers identified four relevant molecular subgroups: PB-A, PB-B, PB-B–like, and PB-FOXR2. Patients in these subgroups differed in age at diagnosis, likelihood of presenting with metastasis, tumor cytogenetics, putative oncogenic drivers, and survival. Older children with pineoblastoma were most likely to harbor PB-B or PB-B–like tumors, which were enriched for alterations in the microRNA-processing genes *DICER1, DROSHA,* and *DGCR8.* In contrast, the younger children harbored PB-A, which were characterized by *RB1* loss, or PB-FOXR2 tumors, which were characterized by over-expression of the *FOXR2* oncogene.

This comprehensive clinicomolecular study shed light on the optimal treatment strategy for and oncogenic mechanisms of an extremely rare pediatric brain tumor. Such insight will be invaluable in designing the next generation of treatment protocols for pediatric pineoblastoma and guiding preclinical research to discover novel therapeutics based on the implicated oncogenic drivers. Moving forward, the investigators have shown that a risk-stratified approach can mitigate potential long-term neurocognitive deficits in older patients with pineoblastoma.

## GENOME-WIDE DNA-METHYLATION PROFILING ADVANCES OUR UNDERSTANDING OF CNS TUMOR BIOLOGY

Central nervous system (CNS) tumors carry the highest mortality rate of all childhood cancers. Therefore, a better appreciation of the oncogenic mechanisms and molecular heterogeneity underlying those morphologically diverse disease entities is essential to developing risk-stratification and therapeutic strategies. Over the past decade, the study of genome-wide epigenetic patterns by DNA-methylation arrays have discerned intertumoral molecular heterogeneity within childhood brain tumors, including medulloblastoma, glioma, ependymoma, atypical rhabdoid/teratoid tumor, pineoblastoma, and other CNS embryonal tumors. These epigenetically defined subgroups harbor specific oncogenic drivers at the mutational and/or transcriptomic levels and unique clinical characteristics and outcome.

DNA-methylation arrays are tolerant of poor-quality nucleic acids, such as those extracted from formalin-fixed paraffin-embedded tumor tissue. Thus, such diagnostic assays can be integrated into routine histopathologic pipelines in the clinical setting. Multi-institutional efforts have led to a growing pediatric CNS tumor reference set, MolecularNeuropathology, in which thousands of samples have been profiled epigenetically. This database is a publicly available resource, where individual patient samples can be compared against the reference set. Furthermore, studies led by St. Jude researchers and others are underway to develop and validate molecular classifiers that enable the automated prediction of disease entities based on methylation patterns. DNA-methylation assays will, therefore, most likely complement radiographic and histopathologic features to enhance the accurate classification of pediatric CNS tumors in clinical practice. This will, in turn, facilitate the development of molecularly driven clinical trials and ultimately translate into improved patient survival and quality of life.

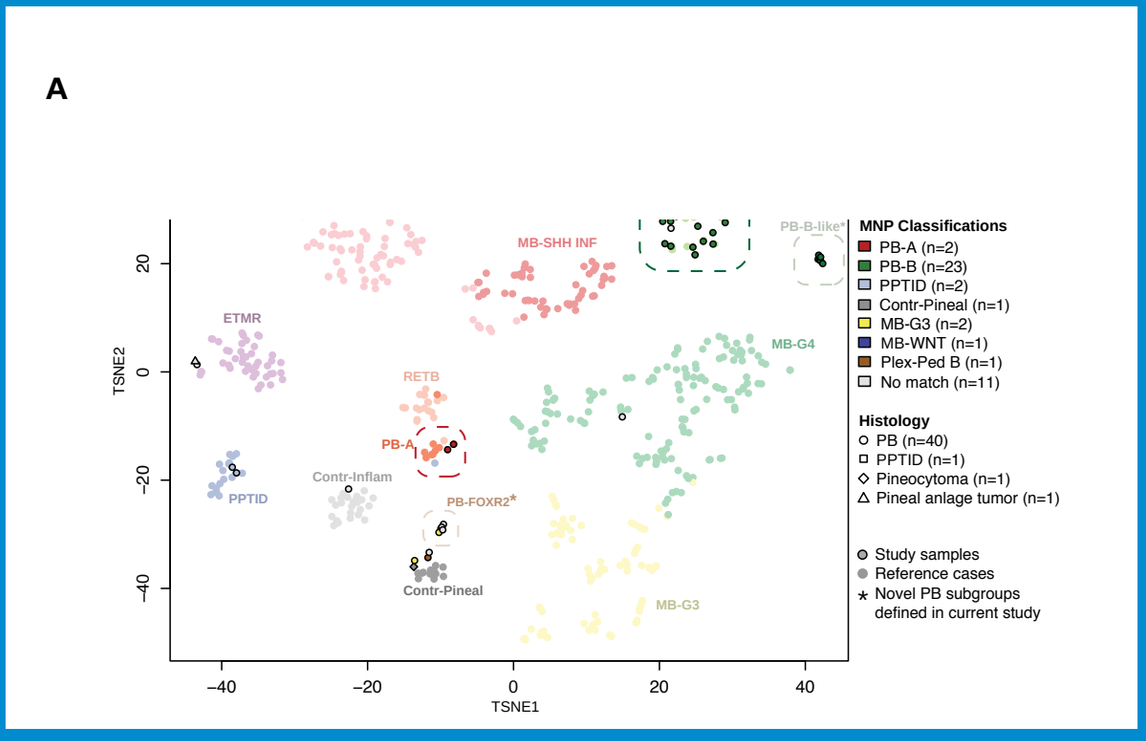




**Figure.** Novel molecular subgroups of pineoblastoma were defined by DNA-methylation analysis. The t-stochastic neighbor embedding (TSNE) analysis revealed four main subgroups (PB-A, PB-B, PB-B–like, and PB-FOXR2). Other subgroup outliers are also shown. Colors indicate methylation-class assignment by the MolecularNeuropathology (MNP) brain tumor classifier (www.molecularneuropathology.org). Abbreviations: Contr, control; MB-G3, group 3 medulloblastoma; MB-WNT, WNT-subgroup medulloblastoma; PB, pineoblastoma; PFS, progression-free survival; Plex-Ped B, plexus tumor subclass pediatric B; PPTID, pineal parenchymal tumor of intermediate differentiation; *y*, *years. Reprinted by permission from SNCSC GmbH: Acta Neuropathol, 139:259–71, Liu APY et al, Risk-adapted therapy and biological heterogeneity in pineoblastoma: integrated clinico-pathological analysis from the prospective, multi-center SJMB03 and SJYC07 trials. © 2020 Springer*

Heather M. Conklin, PhD; Traci W. Olivier, PsyD

## REDUCING OTOTOXICITY AND TREATING POSTTREATMENT HEARING LOSS MAY IMPROVE COGNITIVE OUTCOMES IN CHILDREN TREATED FOR MEDULLOBLASTOMA

After completing treatment for pediatric brain tumors, survivors are at risk of declines in cognitive and academic skills. These changes, often described as cognitive late effects, can manifest several years after diagnosis and persist throughout adulthood. Children who are younger than 3 years at the time of diagnosis of a CNS tumor and who receive higher-intensity treatment are often the most at risk for neurocognitive declines.

Hearing loss is a well-documented side effect of cancer treatment. Chemotherapy (i.e., platinum-containing agents) and craniospinal irradiation are associated with damage to the inner ear, cochlea (the sensory organ of the ear), and/or brain. Such changes can result in sensorineural hearing loss (SNHL). Previous studies have established the prevalence and course of SNHL after cancer treatment, as well as the effects of SNHL in children without a history of cancer. However, few studies have focused on the neurocognitive effects of SNHL in childhood cancer survivors.

Given the importance of reading for academic success and that learning to read can be more difficult for children with SNHL, Heather M. Conklin, PhD, (Psychology), Traci W. Olivier, PsyD (Psychology), a Neuropsychology fellow working with Dr. Conklin, and their international team of neuropsychologists investigated reading outcomes among childhood cancer survivors at risk for hearing loss. Because previous studies had demonstrated that pediatric SNHL is associated with declines in global measures of intellectual and academic functioning, Dr. Conklin's team sought to identify the specific neurocognitive skills that contribute to poor reading outcomes in children with SNHL as a result of cancer treatment.

Data were gathered from 260 participants enrolled in the SJMB03 trial, which was described in the previous section. Treatment in this protocol for medulloblastoma and other embryonal brain tumors included surgery, risk-adapted craniospinal irradiation, and chemotherapy. Participants were assessed using neurocognitive and audiological measures at baseline and then periodically up to 5 years after diagnosis and were grouped according to the severity of SNHL. Of the 260 participants, 196 had either intact hearing or mild-to-moderate SNHL and 64 had severe SNHL. The researchers analyzed performance on eight neurocognitive measures targeting reading outcomes (e.g., phonemics, fluency, and comprehension) and supportive cognitive processes (e.g., working memory and processing speed).

Dr. Conklin's team reported the results of this study, which was the first of its kind, in the *Journal of Clinical Oncology*. Children treated for embryonal brain tumors showed declines in several language-based abilities, including phonologic skills (i.e., the skill to manipulate sounds that constitute the primary components of language), the ability to phonetically decode (to recognize or sound out single words), and reading comprehension. In addition, they showed declines in neurocognitive abilities, such as working memory (i.e., the combination of attention and short-term memory that supports problem-solving skills) and speed of information processing. Survivors with severe SNHL showed a significantly greater decline in these skills than did those with intact hearing or mild-to-moderate SNHL. They also showed decreased reading fluency (i.e., the rate at which one can read). After controlling for the effects of age at diagnosis and CNS treatment intensity, the team found that performance in the following four areas remained significantly lower in those with severe SNHL: phonologic skills, phonetic decoding, reading comprehension, and processing speed.

Phonologic skills help children detect subtle differences in speech sounds; thus, these skills are considered one of the building blocks for successfully developing reading skills. Difficulties in these skills, combined with a slower rate at which the brain can process information, appear to lead to declines in more complex skills, such as the ability to comprehend written text. The early academic years focus on teaching a child the skills needed to become a successful reader; however, a fundamental shift occurs during third grade. At 8 to 9 years of age, children are expected to have mastered reading; thus, reading becomes a required skill for accessing and mastering other subjects, such as math (i.e., word problems), science, and social studies. Dr. Conklin's group showed that childhood cancer survivors with SNHL may, therefore, be at a significant academic disadvantage.

There is still work to be done to identify ways in which neurocognitive processes can be rehabilitated in children undergoing cancer treatment. Identifying potentially modifiable factors like hearing loss can inform future changes in anticancer therapy, such as using cochlea-sparing radiation therapy and/or otoprotectant medications. Furthermore, by identifying specific skills that are affected in children who have lost their hearing as a result of cancer treatment, intervention efforts can be tailored to specific cognitive and academic skills. Dr. Conklin and her team hypothesize that greater intervention and/or adherence to hearing loss treatment (e.g., acceptance of cochlear implantation or more consistent use of hearing aids) could further reduce the adverse effects of ototoxicity on the development of children's reading skills.

# CONCLUSION

St. Jude researchers are modifying and refining cancer treatments to maintain high survival rates and improving the quality of life for the increasing number of childhood cancer survivors. Their studies focused on developing interventions that prevent or lessen the impact of cognitive late effects demonstrate the importance of comprehensive evaluations of pediatric patients with cancer and the ability of therapeutic improvements to minimize long-term adverse effects of cancer treatment.


DIALYARD

# TOWARD DISRUPTING THE DYNAMIC PROTEIN-FOLDING MACHINERY THAT SUPPORTS TUMORIGENESIS

**For a protein to function, it must fold into a unique three-dimensional shape. Correctly folding a newly synthesized polypeptide into its final structure is a remarkably complex task because a single functional configuration must be formed among a myriad of possible shapes. Failure of proteins to correctly fold can have devastating consequences and serve as the molecular basis for cancer or other disorders. To prevent protein misfolding, cells use a network of molecular chaperones, which are proteins that create and maintain a functional proteome.**

When proteins are misfolded in the context of malignant transformation, the chaperone network is extensively remodeled and can foster transformation and support tumorigenesis. Molecular chaperones can also buffer critical elements of signaling pathways that empower tumor evolution and lead to chemoresistance of cancer cells. Because of these roles in malignancy, molecular chaperones, such as heat-shock protein (Hsp) 70 and Hsp40, hold potential as therapeutic targets against cancer.

As a molecular hub in the chaperone network, the tripartite chaperone machinery composed of Hsp70, Hsp40, and the nucleotide-exchange factor (NEF) functions in a wide range of cellular housekeeping activities, including folding newly synthesized proteins, translocating proteins to different cellular compartments, disassembling protein complexes, and regulating protein activity. Furthermore, the Hsp70/Hsp40 machinery safeguards cells from deleterious effects of a wide range of proteotoxic stresses by preventing the aggregation and refolding of misfolded proteins, solubilizing aggregated proteins, and cooperating with the protein degradation machinery to remove aberrant proteins.


Paolo Rossi; Yajun Jiang, PhD

## MECHANISMS UNDERLYING THE MOLECULAR CHAPERONE MACHINERY

Because of its central role in maintaining the proteome, the Hsp70/Hsp40 chaperone complex has been intensively studied for 3 decades. However, the molecular mechanisms underlying the function of this machinery have remained largely unknown. The main challenge in characterizing this system has been its inherently dynamic nature. Charalampos Babis Kalodimos, PhD (Structural Biology), and his team recently elucidated how the Hsp70/Hsp40 complex mediates its functions.

In the journal *Science,* the researchers reported results from solution nuclear magnetic resonance (NMR) spectroscopy studies of Hsp70/Hsp40. NMR is highly suited for studying dynamic protein machines, and St. Jude has an impressive lineup of NMR spectrometers, including a 1.1-GHz NMR that is the most advanced NMR spectrometer in the world.

Dr. Kalodimos and his colleagues found that Hsp70 uses ATP binding and hydrolysis, coupled to NEF-induced ADP release, to regulate its binding to and release from client proteins. Hsp40 chaperones (also referred to as DnaJ or J-domain proteins) serve various roles in the functioning of the chaperone machinery. The J domain is essential for stimulating the ATPase activity of Hsp70. Hsp40 recognizes and binds non-native proteins, which are then presented to Hsp70. Additionally, Hsp40s appear to diversify the function of Hsp70 by determining client specificity and possibly the fate of the client protein (e.g., refolding vs. degradation).

Most species express many more genes encoding Hsp40 proteins than Hsp70 proteins. The human genome encodes more than 50 Hsp40s but only 11 Hsp70s. Members of the Hsp40 family can synergize with each other and function independently of Hsp70 to suppress protein aggregation. Several key questions related to how Hsp40s function in physiological and pathological circumstances remain unanswered: How do Hsp40s recognize and engage non-native proteins? How do they modify the folding properties of their bound clients? How do they work with Hsp70 to give rise to functional chaperone machinery?

## HSP40 CHAPERONES BIND UNFOLDED CLIENT PROTEINS

There are three major classes of Hsp40s: A, B, and C. Classes A and B are the most ubiquitous Hsp40 chaperones. They are present in all four kingdoms and in most compartments of eukaryotic cells. To probe the interaction of class A and class B Hsp40s with unfolded proteins, Dr. Kalodimos and his team used two physiological substrates, alkaline phosphatase (PhoA, 471 amino acids) and maltose-binding protein (MBP, 396 amino acids), as client proteins and studied their Hsp40 interactions in cells from various species, including bacteria, yeast, and humans. Hsp40 chaperones in *Thermus thermophilus* bacteria engage their client proteins through four substrate-binding sites on the hydrophobic surfaces that can engage unfolded proteins. These four binding sites are present on two distinct surfaces, one in each of the Hsp40 β-barrel domains.

Using solution NMR spectroscopy, the researchers determined the structure of Hsp40 in complex with full-length, unfolded PhoA. In PhoA, seven sites interact relatively strongly with Hsp40, whereas another eight sites interact weakly. The four binding sites in Hsp40 span approximately 150 Å. The simultaneous engagement of several nonpolar sites, which typically cluster within the hydrophobic core of the PhoA client protein in its native state, prevents PhoA from forming a collapsed structure (native or molten globule) and stabilizes an extended, non-native state. Structural data suggest that by binding sites on the client protein, Hsp40 effectively melts the unfolded client protein's secondary structure and, in this manner, disrupts not only secondary but also tertiary structures.

Analysis of the NMR spectra of PhoA in the presence of Hsp40 showed that an Hsp40 molecule can interact with all the binding sites in PhoA, including, albeit transiently, the weak binding sites. Hsp40 has only four binding sites, whereas PhoA has many more locations that can engage Hsp40. This indicates a dynamic formation of the Hsp40–PhoA complex, a feature that is typical of chaperone complexes with proteins in their non-native state. This broad specificity for client protein–interaction regions may allow Hsp40 to alter the secondary and local higher-order structures of a large number of client regions by using a limited number of binding sites.

## COMPARING THE BINDING PROPERTIES OF HSP40 CHAPERONES

Using NMR spectroscopy to characterize the binding properties of Hsp40s across various species, Dr. Kalodimos and his colleagues found that the number of client-binding sites varies within this chaperone family. Class A Hsp40s can feature as many as six client-binding sites, whereas Class B Hsp40s have as few as two.

The researchers also used solution NMR spectroscopy to analyze how Hsp40 interacts with Hsp70 within the Hsp70/Hsp40 machinery. Their data showed that, in addition to the interaction mediated by the J domain of Hsp40 and the nucleotide-binding domain of Hsp70, there is a specific interaction between the C-terminal tail of Hsp70 and the second client-binding domain (CBD2) of Hsp40. Interestingly, the Hsp70 C-terminal tail and client proteins bind to overlapping sites on Hsp40. This suggests that Hsp70 competes with client proteins to bind to Hsp40. In the presence of both Hsp70 and PhoA, the first client-binding domain (CBD1) of Hsp40 is occupied by PhoA, and the CBD2 domain of Hsp40 is occupied by the Hsp70 C-terminal tail, giving rise to a ternary complex.

This work paves the way for the Hsp70/Hsp40-driven client-refolding cycle to be further refined. The data indicate that Hsp40 binds to several hydrophobic regions within the client and presents the client to Hsp70 in an unfolded state, a conformational state to which Hsp70s prefer to bind. The C-terminal tail of Hsp70 then either partially or completely displaces the client from Hsp40, depending on the number of client-binding sites that are on the Hsp40. Within the context of a ternary complex of Hsp40, Hsp70, and the client protein, Hsp40 has a lower affinity for the client and exhibits weaker holdase activity (i.e., less ability to bind intermediate proteins so they can re-fold) than in the absence of Hsp70 because two of the client-binding sites are occupied by the C-terminal tail of Hsp70. In this state with lower affinity for the client, the ternary chaperone complex is expected to readily release the client, so that it can either fold into its native state or be recaptured by Hsp70/Hsp40 for another chaperone-mediated cycle of protein folding.

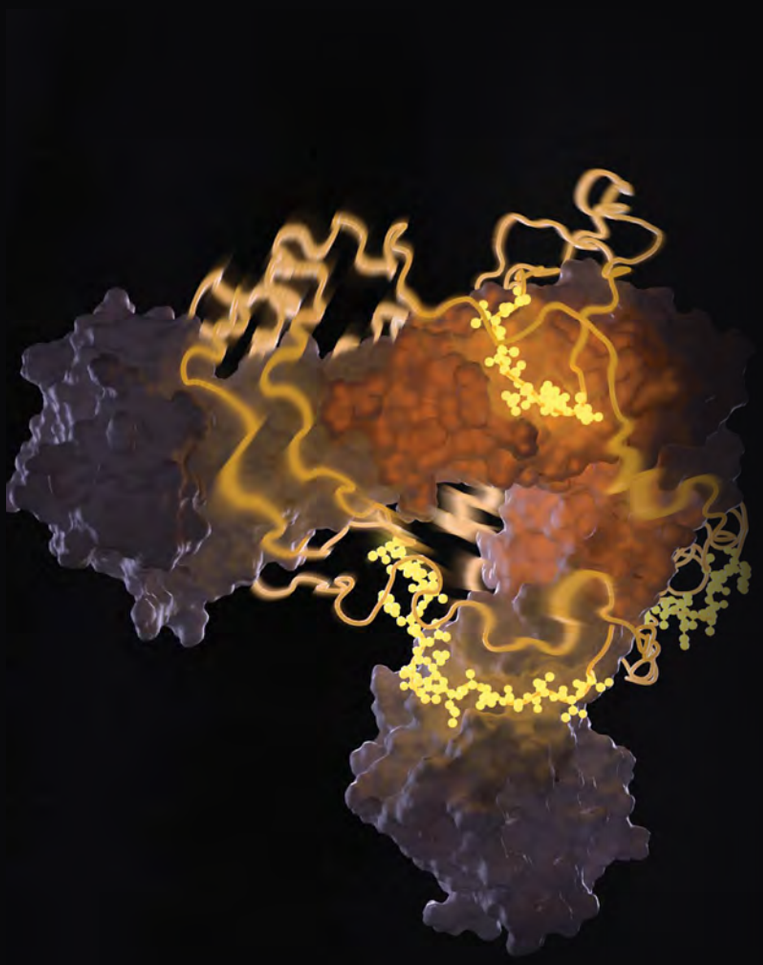


**Figure.** Illustration of the Hsp40 (purple) molecular chaperone in complex with its unfolded client protein alkaline phosphatase (yellow). Binding sites on the client protein are represented by the ball-and-stick model.

# CONCLUSION

Structural biologists at St. Jude are using advanced spectroscopy techniques to elucidate the structure and fundamental mechanisms of the Hsp40/Hsp70 protein chaperone machinery and, ultimately, identify new targets for cancer treatment. The molecular analysis approaches can also be used to study other dynamic, disease-related molecular machines.

# NEW DISCOVERIES IN IMMUNOTHERAPY TO FIGHT PEDIATRIC CANCER

**Immune cells can be manipulated to directly kill tumor cells and control cancer. Adoptive cell therapy (ACT) using T cells that specifically target tumors has produced unprecedented results in the clinic and provides a new paradigm for cancer immunotherapy. T cells can be isolated from a patient's blood, engineered to express T-cell receptors or chimeric antigen receptors (CARs) that specifically re-target the cells against a patient's tumor, and then be reintroduced into the patient's bloodstream to fight the disease. One major challenge of ACT is an often immunosuppressive tumor microenvironment (TME) that can blunt antitumor T-cell responses. This is evidenced by the poor activity of many endogenous, tumor-specific T cells and the limited accumulation and low potency of adoptively transferred T cells in human solid tumors and preclinical ACT models. Here we present recent advances at St. Jude to improve immunotherapy for pediatric patients with cancer.**

## PEDIATRIC PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA GENERATE NEOANTIGEN-SPECIFIC CD8$^+$ T-CELL RESPONSES

The adaptive immune system protects the body against illnesses such as cancer and invading pathogens (e.g., viruses) by recognizing "foreign" peptides that the body normally does not make. Within a cell, proteins are degraded by the proteasome, which breaks them down into smaller fragments (i.e., peptides). Those peptides bind human leukocyte antigen (HLA) system proteins, which present the peptides on the cell surface. T cells have special receptors that recognize peptides bound to HLA proteins. Through complex developmental programming, T cells that recognize self-peptides are eliminated or turned off. However, T cells can quickly identify a cell presenting neoantigens (i.e., unfamiliar peptide sequences on the cell surface), and this may lead them to attack it. When a mutation arises in the DNA of a tumor cell, it changes the protein's amino acid sequence. If mutated peptides are presented by HLA proteins, the body's T cells may recognize the resulting peptide as foreign. If those T cells are activated, they may be able to attack and kill the cells that express the mutant peptides. In some highly mutated adult cancers, the neoantigen burden is great enough and T cells recognizing the tumor are abundant enough that when the "safety brakes" are removed from the T cells via therapies called immune checkpoint blockade, those T cells can attack and destroy the tumor.

Paul G. Thomas, PhD; Anthony E. Zamora, PhD; Jeremy Chase Crawford, PhD

The substantial benefits of immune checkpoint blockade, the first form of immunotherapy developed, were reported for adult cancers a few years ago; however, immunotherapy was not considered a viable option for pediatric cancers. It was thought that fundamental differences between pediatric cancers and adult cancers would prevent children's immune systems from naturally detecting tumors, and most pediatric tumors were unlikely to respond to immune checkpoint blockade or other immunologic therapies. Work from the laboratory of Paul G. Thomas, PhD (Immunology), put that assumption to the test.

Anthony E. Zamora, PhD (Immunology), a postdoctoral fellow, and Jeremy Chase Crawford, PhD (Immunology), a staff computational biologist, both of whom were working with Dr. Thomas, analyzed B-cell acute lymphoblastic leukemia (ALL) tumor samples from patients by using a combination of flow cytometry, computational modelling, and single-cell transcriptomics. In every case, there was a small but obvious population of T cells that comprised 0.5% to 5% of the total cells. Although these were not large percentages, the discovery suggested that the patients had infiltrating T cells that could play a key role in fighting their tumors.

Pediatric and adult cancers differ in the number of mutations they harbor. In adults, most tumors develop from cells that have slowly acquired mutations throughout their lifetime, sometimes taking decades to build up enough mutations to transform into malignant cells. Adult melanoma, for example, can have hundreds to thousands of coding mutations. In contrast, many pediatric tumors have few mutations. B-cell ALL has, on average, 10 coding mutations; other tumors have as few as one or two.

The prevailing dogma was that the presence of many mutations increases the chances of T cells effectively detecting and targeting cancer cells. The screening of tumors harboring a high number of mutations has consistently found that only about 2% of the mutations are actively targeted by T cells. Scientists reasoned that if only 20 of 1000 mutations were immunogenic, then the immune system would probably never be able to mount an immune response against a tumor with very few mutations.

Dr. Thomas believed this logic was flawed. From years of experience studying viral infections in mice and humans, he knew that just because the immune system did not appear to target a certain peptide, did not mean that it could not target it. During influenza infections, immunodominance hierarchies (i.e., the different levels of immune responses mounted against a select few neoantigens when many are produced) emerge, and the immune system prefers to target certain peptide–HLA epitopes. However, when dominant epitopes are disrupted, the immune system always finds new epitopes with which to target the virus. Dr. Thomas reasoned that even when only a few mutations are present, as in pediatric cancers, the immune system should still be able to target them.

In *Science Translational Medicine,* the researchers reported that every pediatric ALL specimen that they tested contained T cells targeting multiple tumor mutations. In fact, rather than only 2% of the mutations being recognized, they found that 60% to 90% of the mutations in each tumor had recruited a responding T-cell population. This result was reminiscent of those seen with immune responses to viruses. When the immune system has fewer targets to attack, it will target a larger proportion of them, thereby maintaining an equivalent overall response magnitude.

One particularly exciting target that the team identified was the ETV6–RUNX1 fusion protein. Fusion proteins are produced when two genes move from their normal chromosomal locations, fuse together, and create a hybrid gene that has an aberrant and potentially harmful function. Many pediatric tumors harbor fusion genes, which are often tumor drivers (i.e., mutations that the cells must maintain to stay malignant). The most common form of pediatric ALL is driven by the *ETV6–RUNX1* fusion gene. The researchers found that the majority (77%) of patients had T cells that recognized this fusion. This result suggests that if this native response can be boosted, it might provide an Achilles' heel within the tumor and a way to attack and destroy cells expressing essential tumor drivers.

In addition to identifying tumor-targeting T cells in each patient, Dr. Thomas and his colleagues characterized the T cells' functional state to understand why they did not normally control the tumor's growth. The team identified various cell profiles, including ones that appeared functional, and subsets of antigen-specific cells that were overwhelmed by the cancer and had become exhausted or dysregulated. Ongoing work in Dr. Thomas' laboratory is developing strategies to improve the functional profile and magnitude of these T-cell responses so that, ultimately, the T cells can eradicate the tumor, thereby setting the foundation for advances in the treatment of pediatric cancers.

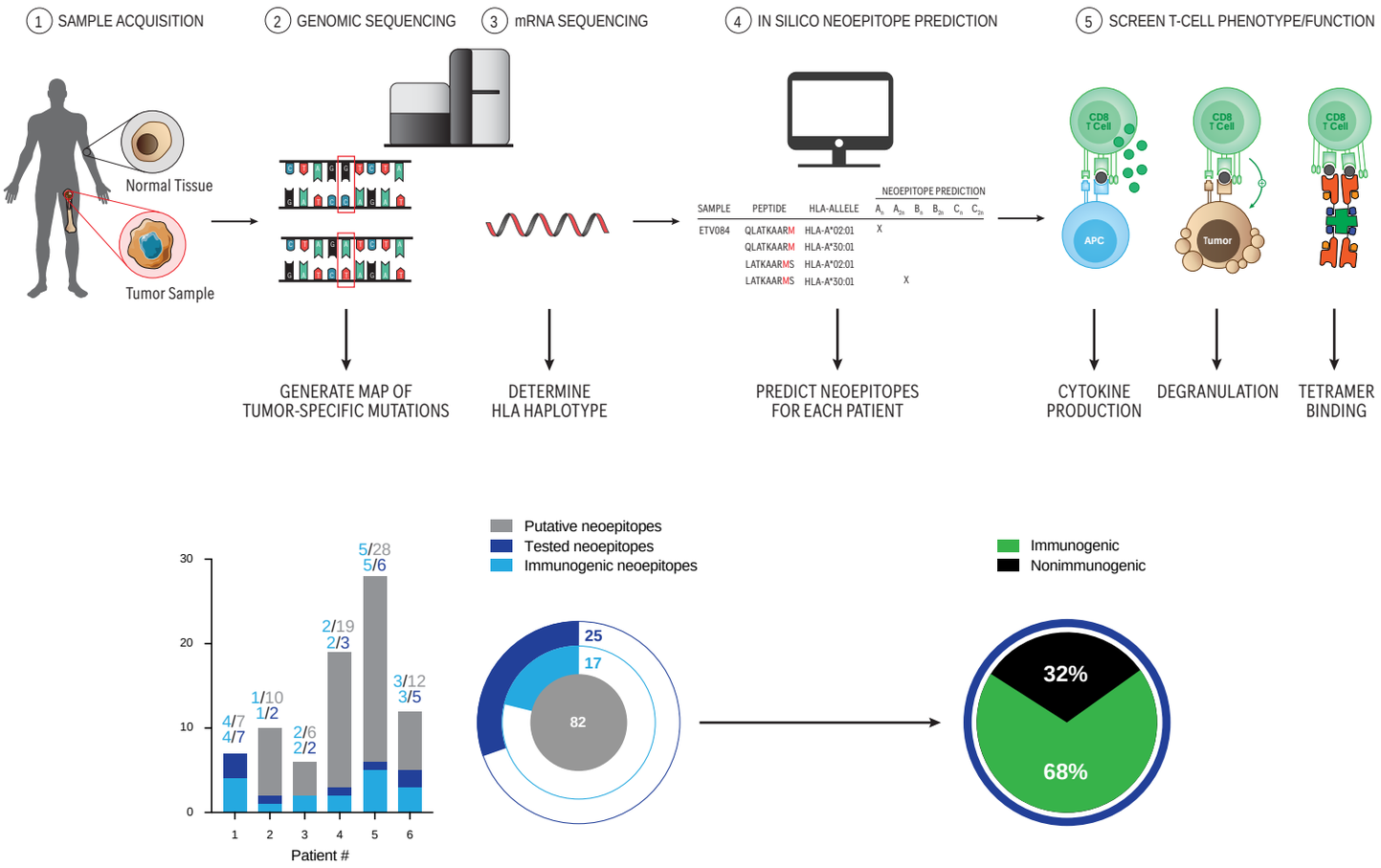



**Figure.** Antitumor CD8⁺ T-cell responses are neoepitope specific. (**A**) Scheme of experimental pipeline used to identify cancer neoepitopes, the mutant proteins expressed on cancer cells. (**B**) T-cell response statistics for all putative neoepitopes in individual pediatric patients with acute lymphoblastic leukemia (bar graph) and in the group of six patients (pie charts). Most (68%) of the neoepitopes elicited an endogenous antitumor CD8⁺ T-cell response. *Zamora AE et al, Pediatric patients with acute lymphoblastic leukemia generate abundant and functional neoantigen-specific CD8⁺ T cell responses. Sci Transl Med 11, eaat8549, 2019. Reprinted with permission from AAAS.*

## TARGETING REGNASE-1 PROGRAMS LONG-LIVED EFFECTOR T CELLS FOR CANCER TREATMENT

Emerging evidence suggests that cell metabolism has a crucial role in immune cell function and differentiation. T cells undergo extensive metabolic reprograming during differentiation and adaptation to their microenvironment. The longevity and function of T cells during cancer immunotherapy have been proposed to be closely associated with their metabolic fitness, though the underlying molecular mechanisms remain elusive. In the journal *Nature*, Hongbo Chi, PhD (Immunology), and his colleagues reported their development of a pooled, unbiased CRISPR–Cas9 mutagenesis screening approach to identify genes responsible for supporting antitumor responses. By targeting 3017 cell metabolism–related genes (i.e., genes that encode metabolic enzymes, small-molecule transporters, or metabolism-related transcriptional factors) in a mouse model of ACT for melanoma, the researchers systematically investigated metabolism-associated factors influencing T-cell accumulation within and activity against tumors. The study identified REGNASE-1 as a master negative regulator of T cell–mediated antitumor responses within the TME. REGNASE-1 binds and degrades mRNA and inhibits T-cell responses, but its function in immunotherapy had remained elusive. REGNASE-1 deficiency drastically improved $CD8^+$ T-cell accumulation (as much as 2000 fold) within tumors. Given the improved longevity of REGNASE-1–null $CD8^+$ T cells within tumors, Dr. Chi and his colleagues assessed the efficacy of REGNASE-1–null $CD8^+$ T cells in ACT in three preclinical models of tumors. REGNASE-1–null $CD8^+$ T cells profoundly improved therapeutic efficacy against solid tumors, including aggressive melanoma, and blood cancers such as ALL.

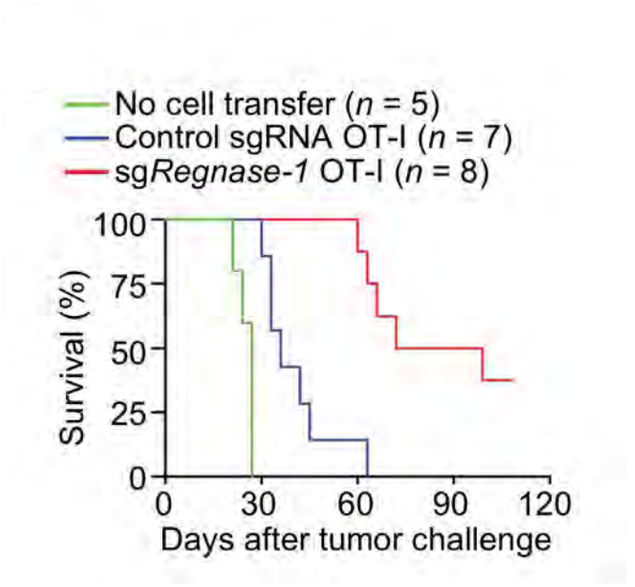



**Figure.** Deleting REGNASE-1 enhances the efficacy of adoptive cell therapy against solid tumors and blood cancers. OT-I cells transduced with nontargeting control sgRNA (blue plot) or sgRNA against *Regnase-1* (red plot) were transferred into mice 12 days after engraftment of B16 Ova melanoma cells and survival was assessed. Control mice received no T-cell transfer (green plot). *Reprinted by permission from SNCSC GmbH: Nature, 576:471–6, Wei J et al, Targeting REGNASE-1 programs long-lived effector T cells for cancer therapy. © 2019 Springer Nature*

## REGNASE-1 DEFICIENCY REPROGRAMS T CELLS INTO LONG-LIVED EFFECTOR CELLS

When naive CD8⁺ T cells recognize a tumor cell, they can proliferate and differentiate into effector cells that are tumor-killing but short-lived. In the TME, most of these effector cells progressively lose their function and become exhausted. A small population of tumor-infiltrating CD8⁺ T cells, however, can exhibit memory cell–like gene signatures. These cells are long-lived and can further differentiate into cytotoxic effector CD8⁺ T cells that promote tumor killing. The persistence of memory cell–like CD8⁺ T cells, even with impaired effector function, is associated with remission in clinical cases.

The ideal population of CD8⁺ T cells for ACT would include both robust cytotoxic function and the capacity for long-term persistence. Dr. Chi and his team, including the project's lead scientists, Jun Wei, PhD (Immunology), a staff scientist, and Lingyun Long, PhD (Immunology), a postdoctoral fellow, hypothesized that REGNASE-1 deficiency endows T cells with these traits. To better understand how REGNASE-1 deficiency improves the efficacy of ACT against tumors, the scientists analyzed the cellular and molecular phenotypes of tumor-infiltrating REGNASE-1–null T cells. Surprisingly, the cells are reprogrammed specifically in the TME to acquire memory cell–associated gene signatures promoting persistence and a survival advantage. However, they also retain robust effector function, as evidenced by high-level expression of effector molecules, such as IFN-γ and granzyme B. By selectively deleting REGNASE-1, the researchers could reprogram T cells [including CAR T cells via a collaboration with Terrence L. Geiger, MD, PhD (Pathology)] into long-lived effector cells; this result has great potential for improving cancer immunotherapies.

To learn more about the molecular mechanisms of long-lived effector cells, Dr. Chi and his colleagues performed a secondary genome-scale CRISPR–Cas9 mutagenesis screening. The screen identified key downstream pathways and genes that control REGNASE-1–mediated protective immunity in tumor-specific CD8⁺ T cells. It also uncovered enhanced oxidative metabolism in the mitochondria of REGNASE-1–null T cells that was linked with the increased accumulation of these cells in tumors. Moreover, the team identified the transcription factor BATF as a direct target of REGNASE-1 that is important in limiting antitumor responses. REGNASE-1–deficient CD8⁺ T cells showed enhanced BATF expression and associated chromatin accessibility, and deletion of BATF suppressed the elevated in vivo effector responses and metabolic fitness of REGNASE-1–null CD8⁺ T cells. Accordingly, BATF overexpression in wild-type T cells improved T-cell accumulation preferentially in tumors and was associated with increased expression of effector molecules, including IFN-γ, granzyme B, and TNF-α. These results highlight the role of BATF in mediating antitumor-effector responses and extend our understanding of the context-dependent roles of BATF in adaptive immunity.

To further explore the therapeutic potential of REGNASE-1–null CD8⁺ T cells, the researchers investigated the top-enriched genes in tumor infiltrating lymphocytes in the secondary genome-scale CRISPR–Cas9 mutagenesis screening. Dr. Chi and his colleagues found that the combined depletion of REGNASE-1 with either PTPN2 (a protein phosphatase) or SOCS1 (an inhibitor of JAK/STAT signaling) synergistically enhanced tumor-site accumulation and therapeutic efficacies of REGNASE-1–null CD8⁺ T cells. This study revealed that by targeting REGNASE-1, we can engineer long-lasting effector responses, thereby overriding the downregulation of immune responses that normally occurs in the TME.

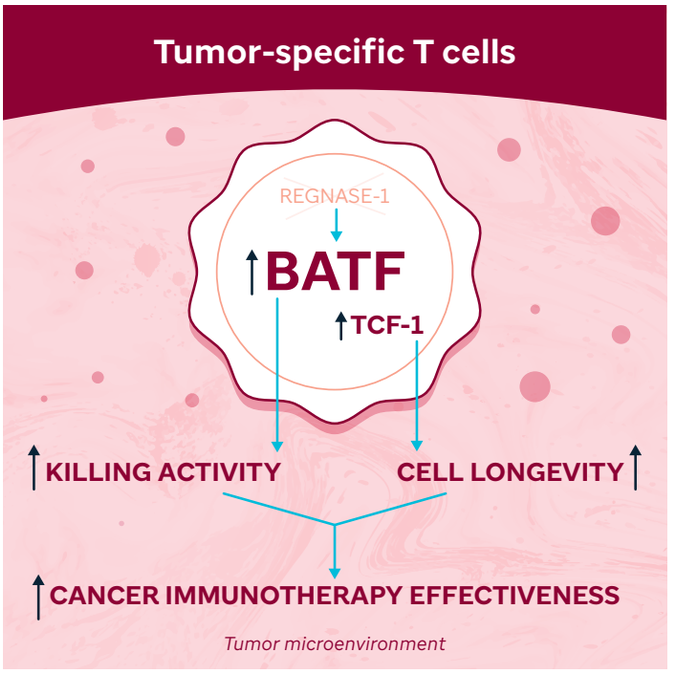
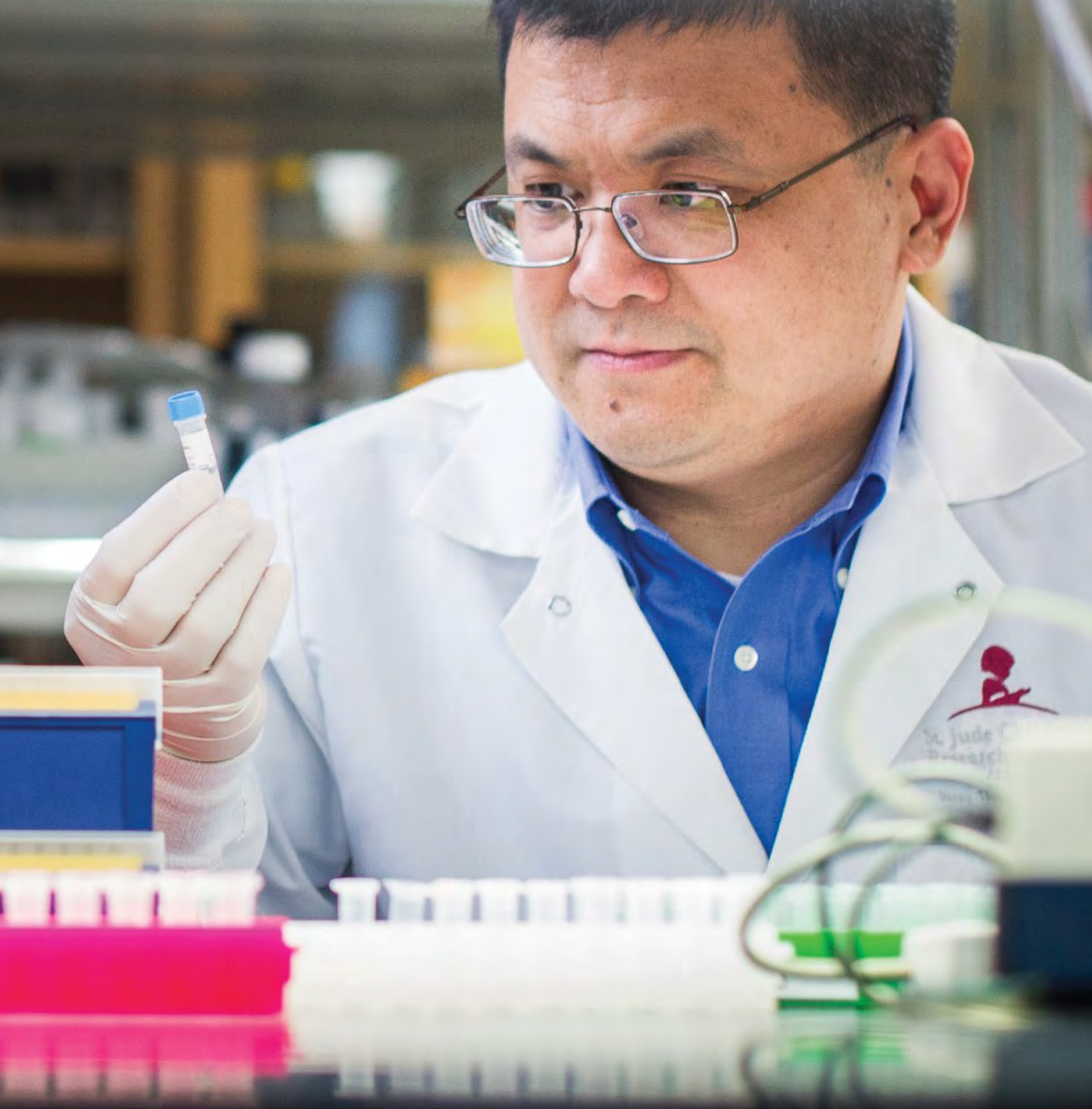



**Figure.** Scheme showing that REGNASE-1 deletion in tumor-specific T cells induces increased expression of the transcription factors BATF and TCF-1. REGNASE-1–deficient T cells exhibit markedly improved longevity and therapeutic efficacy.

## CLINICAL APPLICATION OF CRISPR–CAS9 SCREENING IN VIVO

From a therapeutic perspective, the findings from Dr. Chi's study establish novel targets for ACT against solid tumors and blood cancers. They also point to new avenues to reprogram the T-cell state in cancer immunity and immunotherapy. The impact of this study on the field is exemplified by its inclusion in the "News and Views" section of *Nature* and the "Research Highlights" sections of both *Nature* Reviews *in Drug Discovery* and *Nature Immunology*. Dr. Chi's laboratory is also exploring the therapeutic potential of combining REGNASE-1–null $CD8^+$ T cells with checkpoint blockade therapy (e.g., anti–PD-1 therapy), chemotherapy, and irradiation for treating many types of cancer.

There is a great urgency to identify novel targets and engineering strategies to mobilize antitumor immunity, develop robust preclinical models, and establish strong translational teams to rapidly move findings from the laboratory to the clinic. The development of CRISPR–Cas9 technology has revolutionized genome editing and precision medicine, and pooled CRISPR–Cas9 mutagenesis screening is being used in various cell culture systems to discover novel genes that regulate a particular cellular phenotype. However, applying CRISPR–Cas9 screening in vivo has been challenging. The novel tools developed by Dr. Chi's team facilitate the use of pooled CRISPR–Cas9 mutagenesis screening to directly modulate T cells in vivo, especially for cancer treatment. Through new collaborations with Dr. Geiger and Stephen Gottschalk, MD (Bone Marrow Transplantation & Cellular Therapy), they are extending this work to CAR T–cell therapy of pediatric leukemia, solid tumors, and brain tumors, which may accelerate the translation of these discovery research and preclinical studies to the clinic.



Hongbo Chi, PhD

## TOX REINFORCES THE PHENOTYPE AND LONGEVITY OF EXHAUSTED T CELLS IN CHRONIC VIRAL INFECTION

Using a patient's own immune cells, particularly cytotoxic T cells, as immunotherapy for cancer holds great promise. T-cell exhaustion is a cellular state that limits the efficacy of current treatments, as it reduces the cells' ability to attack cancer cells. As a result of T-cell exhaustion, patients are often nonresponsive or experience relapse after immunotherapy. Benjamin A. Youngblood, PhD (Immunology), and Dr. Dietmar Zehn (Technical University of Munich, Freising, Germany) led an international team of scientists to elucidate the mechanisms that initiate and maintain T-cell exhaustion.

In the journal *Nature*, the researchers reported that the *Tox* gene is a major activator of the transcriptional programs that promote T-cell exhaustion. Their experiments revealed that *Tox* has an unexpected dual function—it promotes exhaustion and supports the long-term survival of T cells. Dr. Youngblood and his collaborators also revealed that *Tox* acts to broadly regulate the epigenetic machinery that remodels T cells so as to produce exhaustion. This work represents a major advance in the field, because until now no transcription factor had been associated with or assigned to the exhausted fate of $CD8^+$ T cells. Furthermore, this finding extends earlier work, which showed that once acquired, the exhaustion programs are imprinted and persist for the life of the cell. Exhaustion plays an important protective role in the immune system by dampening prolonged effector T-cell responses that may be toxic to the host.

In the setting of cancer, T-cell therapies that do not become exhausted but continue to attack tumor cells are greatly needed. The question is: How can we design T cell–based cancer immunotherapies that maintain the ability to attack tumors? Building upon their published work showing that epigenetic programs causally reinforce T-cell exhaustion and limit therapeutic responses to immune checkpoint blockade, Dr. Youngblood and his collaborators have been defining the epigenetic landscape of functional human T cells and exhausted human T cells. His laboratory is now applying those signatures to predict whether patients will or will not respond to T cell–based therapies before treatment is initiated. They are also working with colleagues in the Department of Bone Marrow Transplantation & Cellular Therapy to test a predictive index by analyzing data from the ongoing St. Jude $CD19^+$ CAR T–cell protocol (SJCAR19). Additionally, now that Dr. Youngblood and his colleagues have identified regulators of the exhaustion program, the team plans to use gene-editing approaches to modify T cells for ACT, so that the cells resist exhaustion and can persist in targeting tumors. Such persistence is strongly correlated with the clinical outcome of existing T-cell immunotherapies; therefore, Dr. Youngblood and his colleagues believe that their findings have the potential to greatly improve the longevity of current CAR T–cell and other immune therapies for cancer.


Benjamin A. Youngblood, PhD; Hazem Ghoneim, PhD

# CONCLUSION

Immunologists at St. Jude originally advanced our understanding of immune recognition and immunodominance hierarchies by studying how the immune system responds to infection. They are now using comparable concepts to explain how it responds to cancer. Their long-term goal is to develop approaches to boost endogenous immune responses in children with various cancers and ultimately cure those diseases. These efforts show how discoveries at St. Jude are expeditiously translated from the laboratory to the clinic to advance the treatment of pediatric cancer.

# SINGLE-CELL RNA SEQUENCING OF MEDULLOBLASTOMA IDENTIFIES CELLS OF ORIGIN AND HASTENS THE DEVELOPMENT OF NEW TREATMENTS

**Medulloblastoma is among the most common and deadly brain cancers in children, being diagnosed in approximately 400 children annually in the United States. Despite improvements in overall survival attributed to advances in treatment, nearly one third of patients succumb to progressive or recurrent disease. Medulloblastoma survivors often experience debilitating treatment-related effects, including neurologic, endocrine, and psychosocial deficits that prevent them from leading a normal life. Better understanding medulloblastoma biology and identifying improved treatment options is an urgent priority.**

Due to discoveries made by Paul A. Northcott, PhD (Developmental Neurobiology), Amar J. Gajjar, MD (Pediatric Medicine, Oncology), and an international team of researchers, medulloblastoma is no longer considered a single disease entity. Genomic characterization of large cohorts of patient tumors during the past 15 years identified at least four biologically and clinically distinct disease subgroups: WNT, SHH, Group 3, and Group 4 medulloblastoma. These subgroups exhibit unique patterns of chromosomal alterations, gene mutations, RNA and protein expression, and DNA-methylation signatures. They are also associated with different patient demographics, sex ratios, and survival outcomes. Patients with WNT medulloblastoma comprise approximately 10% of cases and have a 5-year overall survival of about 95%; those in the SHH subgroup make up about 30% of cases and have a 5-year overall survival of 60% to 85%; together, patients in Group 3 and Group 4 account for about 60% of cases and have a 5-year overall survival that ranges from 40% to 80%.

Identifying a patient's molecular subgroup of medulloblastoma has become an integral part of diagnosis and treatment planning. To further understand the molecular underpinnings of medulloblastoma subgroup differences, Drs. Northcott and Gajjar are analyzing medulloblastoma tumors at the single-cell level by using cutting-edge genomic approaches.

Paul A. Northcott, PhD; Amar J. Gajjar, MD

## UNDERSTANDING THE BIOLOGICAL BASIS OF MOLECULAR SUBGROUPS OF MEDULLOBLASTOMA

The realization that medulloblastoma consists of distinct molecular subgroups has motivated basic scientists to investigate the biological origins of the disease. The dissimilar molecular nature and clinical behaviors of types of medulloblastoma suggest that they each arise from discrete neuronal populations in the developing cerebellum, the part of the brain responsible for balance and coordination and where these tumors are identified. Insights gained from genetically engineered preclinical models of medulloblastoma support this hypothesis, especially for the WNT and SHH subgroups, which are believed to originate from different anatomical regions in the developing hindbrain. In contrast, the origins of Group 3 and Group 4 tumors had until recently remained unknown.

To identify the cellular origins of these subgroups, Dr. Northcott's team used single-cell RNA sequencing (scRNA-seq), a genomic technology that quantifies gene expression in an individual cell. They took advantage of the current St. Jude–led clinical trial SJMB12 for newly diagnosed pediatric medulloblastoma that opened in June 2013. The SJMB12 study includes 17 participating sites that have enrolled a total of 510 participants as of July 17, 2020. Patients enrolled in SJMB12 are treated based on their tumor subgroup, whereby therapy is intensified or reduced depending on the patients' subgroup status.

Before scRNA-seq could be applied to patient samples, the researchers had to create a reference of gene expression in individual cells during normal cerebellar development. In collaboration with members of the Department of Computational Biology, Dr. Northcott's group created a single-cell atlas of normal cerebellar development in mice (*https://cellseek.stjude.org/cerebellum/*). The atlas includes more than 87,000 cells collected at 13 developmental stages. With this first-in-class reference in hand, researchers in Dr. Northcott's laboratory worked closely with Dr. Gajjar and collaborators at Massachusetts General Hospital (Boston, MA) and Vienna Medical University (Vienna, Austria) to collectively perform scRNA-seq studies in a series of 25 tumors from patients with medulloblastoma; the specimens, representing each of the four molecular subgroups, were obtained during surgical resection procedures. The results of this work were recently published in *Nature*.

Bioinformatics techniques were applied to analyze more than 8000 tumor cells and classify them according to their gene-expression profiles. In doing so, the team uncovered unique cellular programs within each medulloblastoma subgroup. All tumors, irrespective of molecular subgroup, had a proportion of cells that were actively undergoing cell division, an observation consistent with similar scRNA-seq studies performed in other cancers. WNT medulloblastoma emerged as the most cellularly complex subgroup. These tumors include three different cellular states: neuronal progenitors, mature neuronal cells, and poorly defined postmitotic undifferentiated cells. SHH medulloblastoma has a simpler cellular composition than the other subgroups, consisting of undifferentiated granule neuron progenitors and differentiated granule neurons, a prevalent cell type in the developing cerebellum. Consistently, studies in genetically engineered preclinical models of SHH tumors suggest that granule neuron progenitors are the cell of origin for this medulloblastoma subgroup.

Analyses of Group 3 and Group 4 medulloblastoma cells provided unprecedented insight into their cellular compositions and origins. Group 3 tumors consist mostly of undifferentiated progenitor cells that appear to be locked in a primitive, stem cell–like state and a smaller number of mature neuronal cells. In contrast, Group 4 tumors are almost exclusively composed of differentiated neuronal populations and exceedingly rare undifferentiated progenitors. Surprisingly, a small subset of Group 3 and Group 4 tumors consist of a balanced mixture of undifferentiated stem-like cells and differentiated neuron-like cells, giving them the appearance of "intermediate" Group 3/Group 4 medulloblastomas. This observation was further validated by bioinformatic interrogation of RNA-seq datasets from bulk medulloblastoma tumors whose gene-expression profiles could be decomposed into the cellular programs identified by scRNA-seq.

As a result of this enhanced cellular understanding of Group 3 and Group 4 tumors, the researchers provided a biological explanation for the ambiguity between them and the difficulty that pathologists sometimes encounter in rendering an accurate and consistent classification of tumors to these subgroups. The discovery made by Dr. Northcott, Dr. Gajjar, and their colleagues is expected to accelerate the development of improved methods for classifying these tumors, expand our understanding of the clinical significance of intermediate Group 3/Group 4 tumors, and provide insight into their treatment.

## CANONICAL CORRELATION ANALYSIS IMPLICATES TWO CEREBELLAR CELL POPULATIONS AS THE ORIGIN OF GROUP 4 TUMORS

To map the cellular correlates between the normal developing cerebellum and single medulloblastoma cells, the research team used a computational tool, canonical correlation analysis (CCA). CCA enabled the team to compare gene expression in normal cerebellar populations and malignant cells from individual medulloblastoma subgroups. WNT tumors were believed to originate outside the cerebellum in neuronal progenitor populations proximal to the brainstem. Consistent with this notion, significant cellular correlates of these tumors in the cerebellar reference atlas were lacking. In contrast, the researchers observed a high degree of similarity between granule neuron progenitors and SHH tumor cells, corroborating findings from prior biological studies and reaffirming this lineage as the probable developmental origin of SHH medulloblastoma.

When CCA was used to compare cerebellar cell populations with Group 3 and Group 4 tumor cells, the team found disparate results. Group 3 cells were poorly correlated with all cell populations in the cerebellar atlas, suggesting that, like WNT tumors, Group 3 tumors arise from a cell population(s) that is not represented in the atlas. Alternatively, Group 3 cells may lack a correlation with identified cerebellar populations because cellular reprogramming or aberrant differentiation programs in these cells distinguish them from their precursors and conceal their cellular origin. In contrast, CCA revealed a significant similarity between Group 4 tumor cells and two related glutamatergic populations of the developing cerebellum, unipolar brush cells (UBCs) and glutamatergic cerebellar nuclei (GluCN).

The UBC and GluCN lineages are both born out of an integral structure of the cerebellum known as the upper rhombic lip, which represents the primary germinal zone for various excitatory cerebellar cell types during development. Because UBCs and GluCN are similarly correlated with Group 4 cells, the researchers were unable to definitively determine whether some Group 4 tumors originate from UBCs and others from GluCN or whether these tumors consist of a mixture of malignant cells related to these two lineages. However, these populations (or their rhombic lip–derived progenitors) being implicated as potential cells of origin of Group 4 medulloblastoma creates new opportunities to engineer preclinical model systems needed to study this poorly understood subgroup. Such tools will be essential for gaining mechanistic insights into the aberrant biology driving Group 4 medulloblastoma and testing new approaches to treating the large proportion of children with this subgroup of disease.

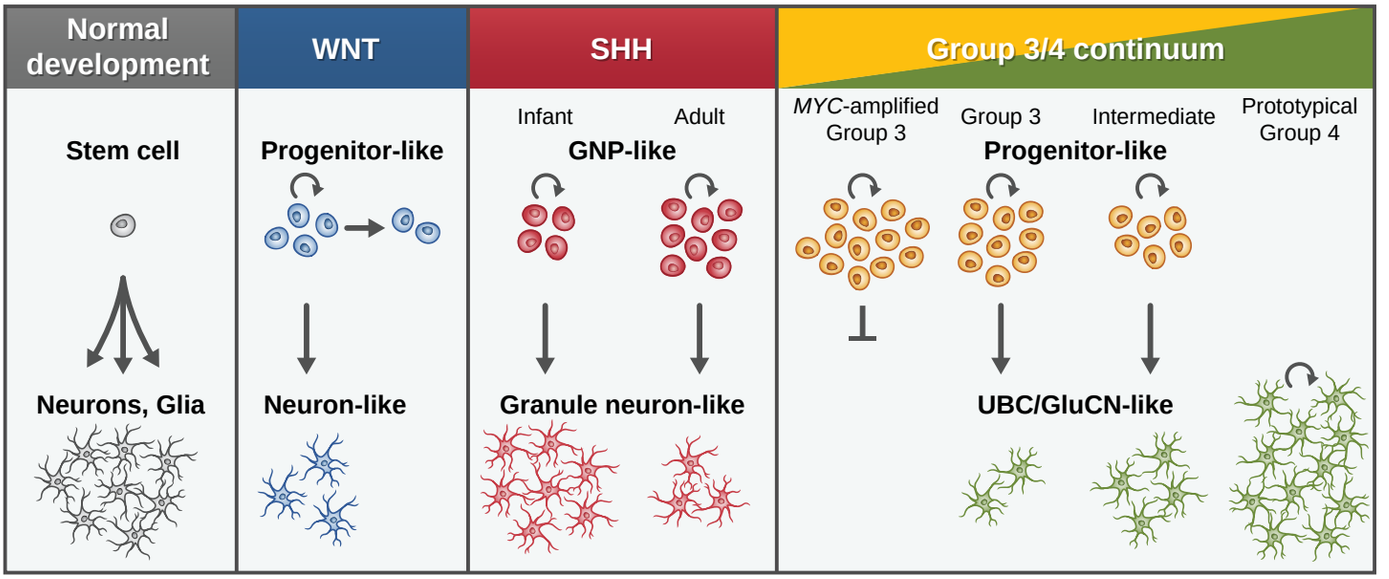



**Figure.** Illustration of the cellular hierarchies in medulloblastoma subgroups, as determined by single-cell RNA sequencing. Undifferentiated progenitor-like cells and differentiated neuron-like cells comprise WNT medulloblastoma. The undifferentiated, cycling cells in SHH medulloblastoma resemble granule neuron progenitor (GNP) cells, and the differentiated cells resemble granule neurons. The frequency of these cell populations varies with age: SHH medulloblastoma tumors in infants contain more differentiated cells, and those in adults contain more GNP-like cells. Group 3 and Group 4 medulloblastomas consist of undifferentiated progenitor-like cells and differentiated neurons that express the same markers as glutamatergic cerebellar nuclei (GluCN) and unipolar brush cells (UBCs). A continuum of frequencies of these cell types is observed: Group 3 tumors contain undifferentiated cells; Group 4 tumors contain predominately differentiated cells; and intermediate Group 3/4 tumors contain both. These transcriptional states are superimposed on genetic alterations that are associated with molecular subtypes. *Reprinted by permission from SNCSC GmbH: Springer Nature, Nat Rev Cancer, 20:42–56, 2020. Medulloblastomics revisited: biological and clinical insights from thousands of patients. Hovestadt V et al, © 2020*

# CONCLUSION

This study is the first to apply scRNA-seq to a sizable series of pediatric medulloblastoma samples. Additional single-cell studies are warranted to learn how the cellular composition of medulloblastoma changes in response to conventional treatment and better define the mechanisms underlying treatment resistance and relapse. Knowledge pertaining to the genetic and epigenetic composition of medulloblastoma will advance our overall understanding of the disease biology and help improve diagnosis and treatment options, which will ultimately improve survival and quality of life.

# MOLECULAR GENOMICS STUDIES REVEAL THE CENTRAL ROLE OF *MAP3K8* MUTATIONS IN SPITZ MELANOMA

**Melanoma, a form of skin cancer, is rare during childhood or adolescence. Pediatric melanoma accounts for less than 1% of all melanoma cases and approximately 5% of all malignancies in adolescents. Approximately 400 new cases of melanoma are diagnosed each year in children and adolescents in the United States. Pediatric melanoma includes three major subtypes: conventional (adult) melanoma, melanoma in giant congenital nevus, and Spitz melanoma, and each subtype has unique clinical and pathologic characteristics. Until recently, pediatric melanoma was one of the least understood childhood cancers. However, comprehensive genomic analyses of these tumors are enabling St. Jude researchers to learn more about this disease and develop prognostic markers and new treatments through research and clinical whole-genome sequencing efforts.**

## CHARACTERISTICS OF SPITZ MELANOMA

Spitz melanoma is the most common subtype of childhood melanoma. The tumors are composed of large malignant-appearing melanocytes (i.e., melanin-producing cells) with abundant eosinophilic cytoplasm and a distinct architectural growth pattern in which the cells grow in vertically oriented "nests." On dermatologic assessment, Spitz melanoma often has the appearance of a nonpigmented skin lesion, and is not suspected of being melanoma. Spitz melanoma affects all age groups but more commonly arises during the first 2 decades of life.

Most pediatric patients with Spitz melanoma have excellent outcomes, and despite a high probability of lymph node metastasis, distant disease rarely develops.

Spitz melanoma is distinct from other melanoma subtypes in its genetic composition. Unlike other melanomas, which are initiated by a single-nucleotide variation in an oncogene, most commonly the serine-threonine kinase gene *BRAF* or *NRAS,* Spitz tumors are driven by the fusion of *BRAF* or a receptor tyrosine kinase gene, such as *ALK, NTRK1/3, ROS1, RET,* or *MET,* with various partner genes. These kinase genes are found in about 50% of Spitz melanomas; for the remaining cases, the driver mutation was previously unknown.

Armita Bahrami, MD; Jinghui Zhang, PhD; Scott Newman, PhD

The first comprehensive genomic analysis of pediatric melanoma was conducted in 2014, as part of the St. Jude Children's Research Hospital–Washington University Pediatric Cancer Genome Project. The study, which was led by Jinghui Zhang, PhD (Computational Biology), Alberto S. Pappo, MD (Oncology), and Armita Bahrami, MD (Pathology), defined the landscape of the main somatic mutations that occur in the three subtypes of pediatric melanoma. Findings that emerged from that study laid the foundation for subsequent research and further advanced our knowledge of the molecular genomics of pediatric melanoma. St. Jude has since served as a center of excellence for the diagnosis and clinical management of challenging cases of pediatric melanocytic tumors. Drs. Pappo and Bahrami also helped establish the country's first Pediatric Melanoma Clinic at St. Jude.

## A SINGLE CASE UNCOVERS *MAP3K8* MUTATIONS IN SPITZ MELANOMA

In 2015, an 11-year-old boy was referred to Dr. Pappo for the evaluation of a skin lesion that had been removed from his ankle 7 months earlier. The involved area was re-excised, but multiple new skin papules had already developed, which was consistent with regional lymphatic spread and metastatic Spitz melanoma. Over the course of a year, the patient was treated, but his disease continued to progress.

The patient subsequently enrolled in the St. Jude protocol Genomes for Kids (G4K), which was designed to test the feasibility of a prospective three-platform integrative analysis of whole-genome sequencing (WGS), whole-exome sequencing, and whole-transcriptome sequencing (RNA-seq) for use in precision oncology. Precision oncology is a clinical strategy in which each patient's tumor is molecularly profiled at base-pair resolution to identify the genetic mutations harbored therein and enable the oncologist to design the optimal approach to treat that patient's disease.

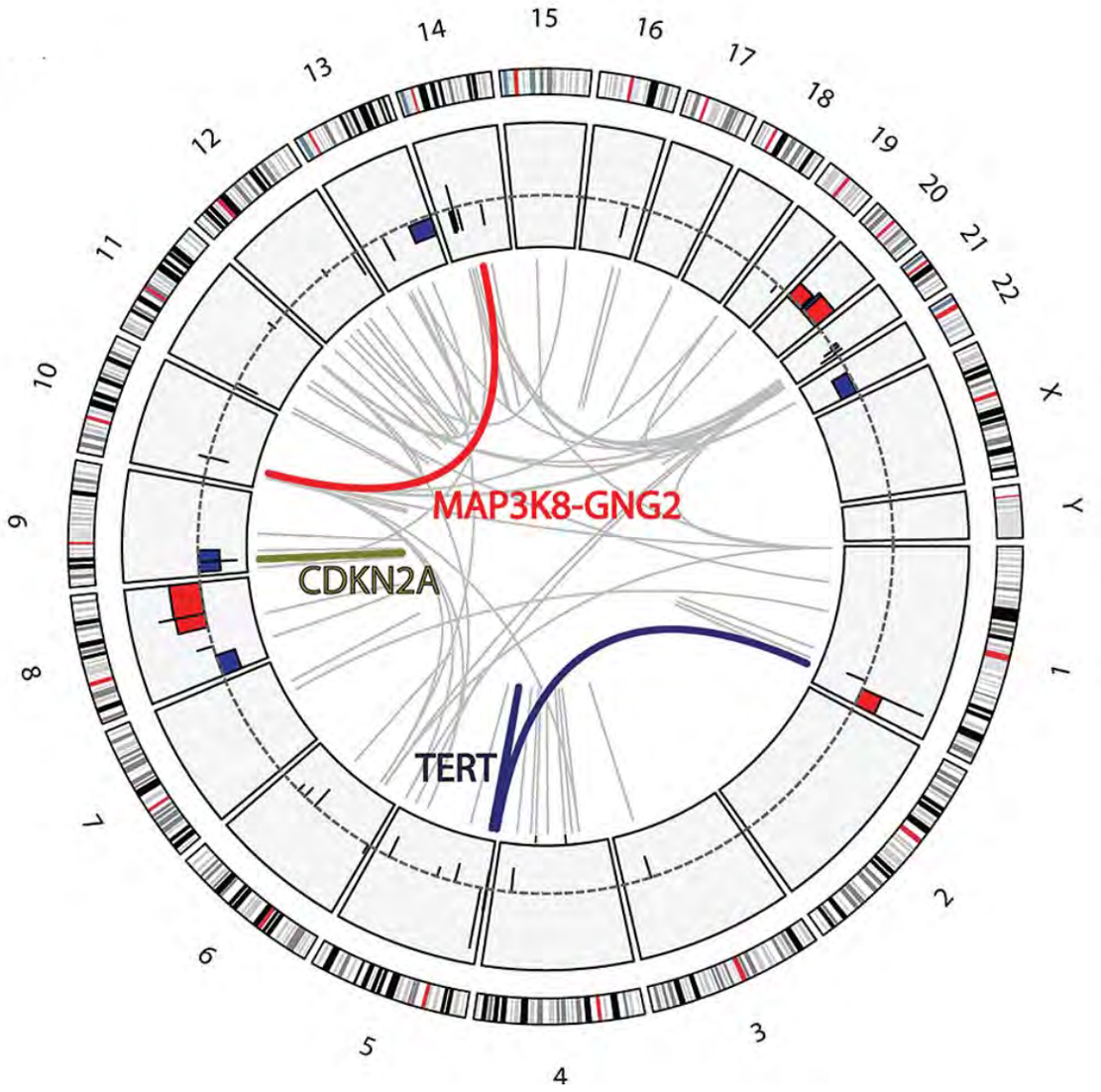
The G4K analysis of the boy's tumor identified the novel gene fusion *MAP3K8–GNG2* by WGS and RNA-seq. *MAP3K8* is a serine-threonine kinase gene that activates the MAP kinase–signaling pathway by phosphorylating MEK. High levels of *MAP3K8* expression have been implicated in resistance to BRAF inhibitors in melanoma. *MAP3K8* is downregulated by the autoinhibition of its carboxyl terminus, which is encoded by exon 9. The patient's *MAP3K8–GNG2* fusion was in-frame and produced a chimeric protein that retained the kinase domain of *MAP3K8* but removed its autoinhibitory carboxyl terminus. Immunohistochemical staining of the tumor showed that MEK, the downstream target of MAP3K8, was phosphorylated, indicating that the protein was active.

Because the patient had already received all standard treatment options, the decision was made to treat him with the MEK inhibitor trametinib. Within 12 months of therapy, all the patient's in-transit nodules and papules diminished in size or disappeared on clinical examination and radiologic imaging studies. The patient experienced a cardiac-related adverse reaction to the medication, prompting its temporary discontinuation. When the drug was reinstated, the patient was resistant to it. A tumor sample revealed a four-fold increase in the copy number of the fusion gene, suggesting that increased dosage of the fusion gene contributed to this resistance.

## IDENTIFYING NEW THERAPEUTIC TARGETS FOR PEDIATRIC PATIENTS WITH SPITZ MELANOMA

To determine the prevalence of *MAP3K8* fusions in Spitz melanoma, Drs. Bahrami and Zhang initiated a systematic study in which they analyzed 49 independent Spitz melanomas by RNA-seq. In *Nature Medicine,* the researchers reported that 16 (33%) of the tumors harbored alterations in *MAP3K8,* making it the most frequently mutated gene in Spitz melanoma. Notably, the alterations, which occurred by in-frame fusion or out-of-frame truncation, all led to the removal of the gene's ninth exon (the autoinhibitory region) and the constitutive activation of the MAP kinase–signaling pathway, as was observed in the index case study. Drs. Bahrami and Zhang noted that removal of the ninth exon of *MAP3K8,* whether by fusion or truncation, is an oncogenic event that drives the development of Spitz melanomas.

By further studying 472 adult melanomas from The Cancer Genome Atlas Program, which is led by the National Cancer Institute and the National Human Genome Research Institute, the investigators found gene fusions or truncations affecting *MAP3K8* in seven (1.5%) of the adult tumors. This finding shows that the *MAP3K8* abnormality is potentially oncogenic in both pediatric and adult melanomas. In vitro transformation of the truncated *MAP3K8*, performed by Philip M. Potter, PhD (Chemical Biology & Therapeutics), confirmed the oncogenicity of *MAP3K8* mutations. The researchers further performed a histopathologic assessment of the *MAP3K8*-altered melanomas and found them to be morphologically distinct from other Spitz melanomas. The distinct morphologic properties of *MAP3K8*-rearranged tumors will help distinguish this molecular subtype from other melanomas and facilitate the delivery of appropriate treatment that targets MEK activity.

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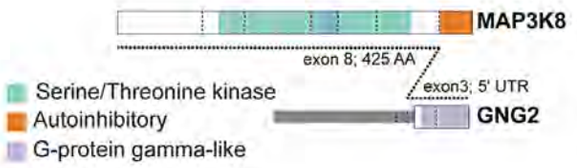


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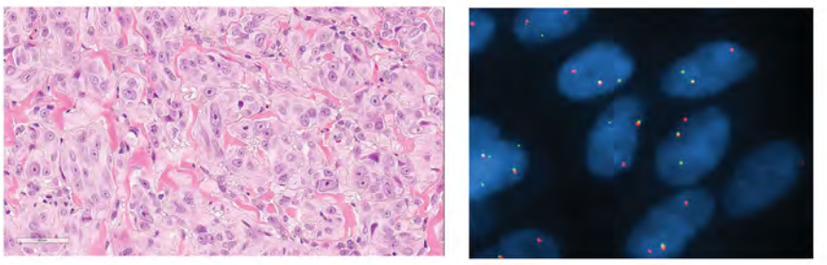

**Figure.** Genomics sequencing and pathologic assessment of Spitz melanoma. (**A**) Circos plot from an individual patient tumor. Chromosomes are plotted as ideograms around the outside perimeter. Moving inwards, copy number abnormalities are shown as histograms with gains in red and losses in blue relative to a normal diploid genome (dotted line). Structural variants are shown as inner gray links with the following notable variants highlighted: *CDKN2*A deletion in green, *TERT*-deregulating translocation in dark blue, and a complex translocation fusing *MP3K8* and *GNG2* in red. (**B**) Schematic of the *MAP3K8–GNG2* fusion gene. (**C**) Hematoxylin and eosin–stained section of Spitz melanoma. (**D**) Fluorescence in situ hybridization image of melanoma cells shows the *MAP3K8* gene rearrangement. The 5' end of *MAP3K8* is shown in green, and the 3' end is shown in red. Magnification, 100×. *Reprinted by permission from SNCSC GmbH: Springer Nature, Nat Med, 25:597–602, 2019. Clinical genome sequencing uncovers potentially targetable truncations and fusions of MAP3K8 in spitzoid and other melanomas. © 2019 Newman S et al*

# CONCLUSION

A multidisciplinary team of St. Jude researchers identified a new role for MAP-kinase signaling in the development of pediatric and adult melanomas. They are identifying inhibitors that selectively target MAP3K8 kinase to treat these tumors. Their goal is to find a more effective, less toxic treatment for pediatric Spitz melanoma and a subset of adult melanomas harboring *MAP3K8* mutations.

# SCIENTIFIC HIGHLIGHTS

# THE GLOBAL BURDEN OF PEDIATRIC CANCER DISPROPORTIONATELY AFFECTS POPULATIONS IN RESOURCE-LIMITED SETTINGS

In high-income countries, approximately 80% of children with cancer survive for at least 5 years after their diagnosis. However, more than 90% of children at risk of cancer live in low- or middle-income countries (LMICs), where resources for treating cancer and supporting patients may be limited. Thus, far fewer children in LMICs than in high-income countries survive their disease.

To increase the survival of children with cancer, LMICs must carefully plan to ensure adequate resources are provided. Such planning requires accurate data on the incidence and outcomes of childhood cancer, key information many LMICs lack due to weak or nonexistent cancer registries and vital registration systems. Additionally, countries often face competing health-financing priorities and must make difficult decisions regarding where to focus their efforts. To support governments and health policy stakeholders globally, researchers use a metric called the disability-adjusted life-year (DALY). The DALY is a metric that accounts for both the mortality and morbidity of a disease, thereby enabling policy makers to compare the lifelong impact of a diagnosis with other diseases affecting their community when making resource allocation decisions.

Lisa M. Force, MD (Oncology, Global Pediatric Medicine), a Pediatric Hematology-Oncology fellow, worked with Nickhill Bhakta, MD, MPH (Global Pediatric Medicine, Oncology, Epidemiology & Cancer Control), and Dr. Christina Fitzmaurice (University of Washington, Seattle, WA) to estimate, for the first time, the global burden of cancer in children (aged 0–19 years) in 2017, with respect to DALYs. The researchers used data from the Global Burden of Diseases, Injuries, and Risk Factor Study (GBD) 2017 and published their findings in *The Lancet Oncology*.

The study revealed that globally, childhood cancer was the cause of 11.5 million DALYs: 97.3% were attributable to years of life lost, and 2.7% were attributable to years lived with disability. The researchers found that childhood cancer was the sixth leading cause of total cancer burden globally and the ninth leading cause of childhood disease burden globally. The burden was disproportionately high in resource-limited settings (mainly in Asia, Africa, and Central and South America), which accounted for 82.2% of the global childhood cancer DALYs.

These DALY-based estimates demonstrate that the global childhood cancer burden is much greater than previously estimated, despite the relatively low absolute number of cases and deaths recorded. Childhood cancer should be a major concern for both the global cancer and child health communities. Therefore, childhood cancer merits a place in prioritization frameworks used by policy makers to plan resource allocation in LMICs. *GBD 2017 Childhood Cancer Collaborators, Lancet Oncol 20:1211–25, 2019*

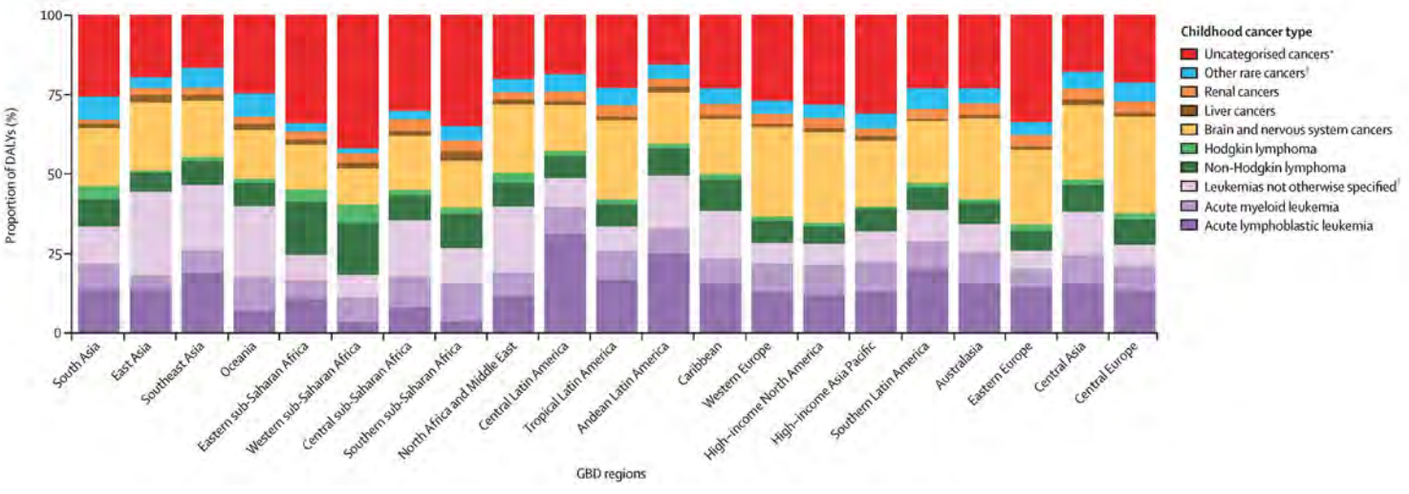


**Figure.** The proportional DALYs due to childhood cancer types by world regions in the GBD 2017 study. *Cancers without a detailed GBD cause. †Cancers with fewer than 1000 deaths globally in 2017. ‡Included leukemias not otherwise specified, chronic lymphocytic leukemias, and chronic myeloid leukemias. *© 2019 GBD 2017 Childhood Cancer Collaborators. Reprinted from Lancet Oncol 20:1211–25. The Creative Commons License is available at creativecommons.org/licenses/by/4.0/*

# WATER NETWORKS PLAY KEY ROLES IN LIGAND–PROTEIN BINDING AFFINITY

Water is a universal solvent and an indispensable component of all living organisms. In the cellular context, water is essential for protein functions, such as folding, enzyme catalysis, and ligand binding. Protein–ligand binding events are driven by the ability to either displace water molecules or rearrange them to participate in ligand binding.

Some studies find that the contribution of water in ligand binding is primarily entropic, whereas others suggest that it is also enthalpic, as it displaces poorly ordered water molecules or forms newly ordered water networks during binding. To better understand how water contributes to the thermodynamics of protein–ligand interactions, Marcus Fischer, PhD (Chemical Biology & Therapeutics, Structural Biology), and his team studied the *Haemophilus influenzae* substrate-binding protein SiaP, which uses a "Venus flytrap" mechanism to engulf the substrate and more than a dozen water molecules. They perturbed water in two ways. First, they analyzed the role of water networks in SiaP binding to three highly similar sialic acid ligands that cause systematic disturbance of the water network. Second, they crystallized wild-type (WT) SiaP and residue 11 (A11N)-mutant SiaP proteins to comprehensively study the impact of disturbing water networks via the protein. Ligand-binding studies included isothermal titration calorimetry (ITC) to measure the ligand-binding affinity of sialic acid and WT SiaP and a thermodynamic cycle to isolate the contribution of water to ligand binding. The thermodynamic impact of introducing the A11N mutation to the apo (i.e., not ligand bound) state of the protein was considered, and crystal structures of the SiaP–ligand complexes were generated.

The study results were reported in the *Journal of the American Chemical Society*. Crystallographic and thermodynamic analyses of WT and A11N SiaP revealed a key binding contribution of water molecules. Introducing a single alanine-to-asparagine mutation at residue 11, which does not directly interact with the ligand, led to a 1400-fold change in sialic acid binding affinity. To reduce the artifacts of cryogenic crystallography, Dr. Fischer's team generated high-resolution crystal structures of these proteins at room temperature. The investigators found that temperature changes binding-site residues and, consequently, the solvent network.

This study spotlights the crucial role of water in the thermodynamics of ligand binding. The significant decrease in binding affinity after introducing the mutation was largely due to perturbation of solvent networks and could be linked to changes in affinity for different ligands. The results indicate that solvent structure is an evolutionary constraint on protein sequence that contributes to ligand affinity and selectivity. Water networks play seminal roles in ligand discovery and protein engineering, and these networks can help us understand the impact of disease-causing mutations.
*Darby JF et al, J Am Chem Soc, 141:15818–26, 2019*

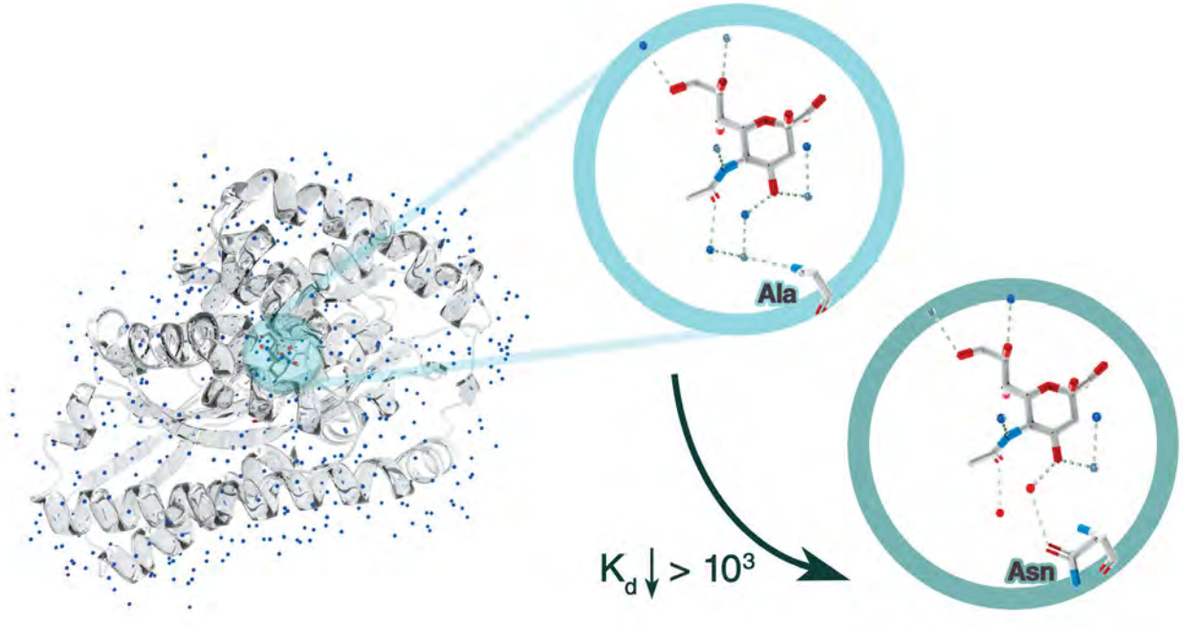


**Figure.** Crystal structures of SiaP in the presence of sialic acid reveal how the greater than 1000-fold decrease in binding affinity ($K_d$) is caused by the disruption of the water network, in otherwise indistinguishable sites, upon the mutation of alanine (Ala) to asparagine (Asn).

# TRANSIENT, NONSPECIFIC CHARGED INTERACTIONS FORM AND SHAPE THE IMP7:IMPβ:H1.Ø PROTEIN COMPLEX

Transport receptors mediate the import or export of proteins across the nuclear membrane by recognizing nuclear localization or export signals. These receptors facilitate transport through nuclear pore complexes (NPCs), which are composed of nucleoporins, and regulate the selective exchange of molecules between the nucleus and cytoplasm. Most proteins are transported by one receptor; however, highly charged proteins, such as histone H1 and ribosomal proteins, require two receptors for transport through the NPC. Histones are basic proteins that associate with DNA in the nucleus and condense it into chromatin. Nuclear import of linker histones requires a heterodimeric transport complex that includes importin β (Impβ) and importin 7 (Imp7). The Imp7:Impβ dimer also imports some ribosomal proteins and HIV integrase.

Mario Halic, PhD (Structural Biology), and his team, as part of an international collaboration, used cryoelectron microscopy (cryo-EM) to solve the structures of Imp7:Impβ:H1.0 and Impβ:H1.0 complexes; H1.0 is a linker histone. Their results, which were published in *Molecular Cell*, showed that the two importins form a cradle to bind and chaperone the linker histone. Cryo-EM maps showed that both importins had a curved solenoid structure, which is characteristic of the karyopherin-β family of proteins. Furthermore, the researchers found that a disordered region of the linker histone shapes the complex.

The H1 tail acts as a zipper that closes and stabilizes the Imp7:Impβ:H1.0 complex. Sequence alignment, pull-down experiments, and gel-shift assays showed that the FG motif in the C-terminal tail of Imp7 is required to interact with Impβ and transport cargo through the NPC. On the nuclear side, FG repeats promote RanGTP-dependent disassembly of the Impβ:Imp7:H1.0 complex. These findings reveal that fuzzy interactions (i.e., interactions involving intrinsically disordered proteins that have no defined structure) are key for the architecture and function of the Imp7:Impβ:H1.0 complex.

Dr. Halic and his colleagues revealed the structure of import receptors Imp7 and Impβ in complex with the linker histone H1.0 as cargo. The architecture and organization of this complex are mediated by charged interactions of disordered regions. The study's results show that small highly charged proteins (e.g., histones or ribosomal proteins) need transport receptors to pass through the NPC. Transient electrostatic interactions between the disordered H1.0 tail and importins stabilize the complex. The disordered Imp7 tail containing the FG motif is required for complex formation. Other complexes may also be structured by transient electrostatic interactions of disordered regions.
*Ivic N et al, Mol Cell 73:1191–203, 2019*

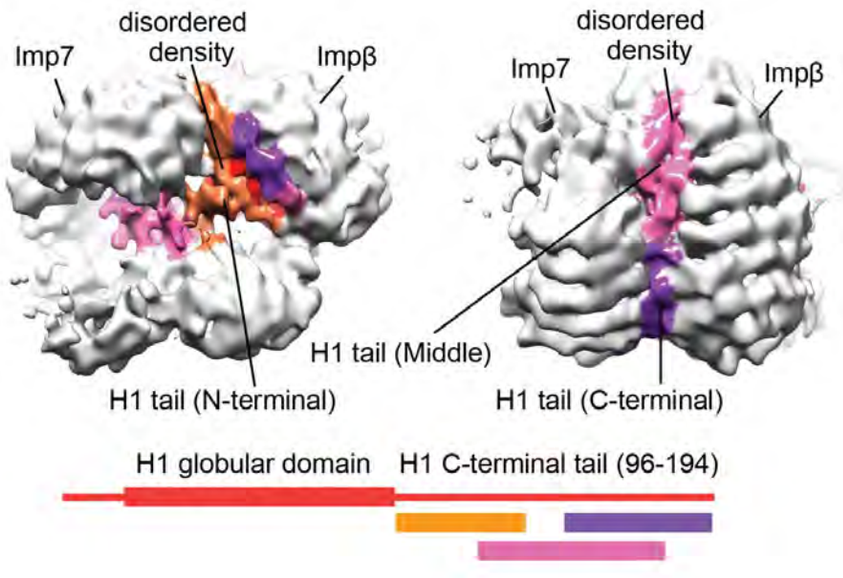


**Figure.** Two views of the structure showing the disordered density in the cradle between two importins, Imp7 and Impβ. The density in proximity to the importin residues that cross-link predominantly to the N-terminal part of the H1 tail is shown in orange, the middle part of the H1 tail is in pink, and the C-terminal part is in purple. Contour level, ~0.025. *© 2019 Ivic N et al, Reprinted from Mol Cell 73:1191–203.e6, https://doi.org/10.1016/j.molcel.2019.01.032.* The Creative Commons License is available at *https://creativecommons.org/licenses/by/4.0/*

# DDX3X ACTS AS A LIVE-OR-DIE CHECKPOINT IN STRESSED CELLS

Stress granules enable cells to survive during periods of stress, and defects in the assembly or disassembly of stress granules have been linked to multiple diseases, including cancer. Conversely, inflammasomes are protein complexes that assemble into structures known as ASC specks when they sense cellular damage or invading pathogens. When activated, inflammasomes drive cell fate towards pyroptosis, a type of cell death. Thus, although both stress granules and inflammasomes respond to cellular stress, their responses lead to opposite results.

A research team led by Thirumala-Devi Kanneganti, PhD (Immunology), recently examined the crosstalk between stress granules and inflammasomes containing NLRP3 and reported their findings in *Nature*. Dr. Kanneganti's group is a founding member of the inflammasome field and continues to make fundamental contributions to the understanding of inflammasome biology and inflammatory cell death. NLRP3 is a pyrin domain–containing member of the nucleotide-binding domain– and leucine-rich repeat–containing protein family. Dr. Kanneganti was the first to show the role of NLRP3 inflammasome activation in response to microbial laboratory components, and her laboratory has built on that discovery to establish the importance of inflammasomes in infection, inflammation, metabolic disease, and cancer.

To determine the effect of stress granules on NLRP3 inflammasome activation, Dr. Kanneganti's team triggered cells to assemble stress granules and observed defects in the subsequent assembly of ASC specks, suggesting that stress granules inhibit NLRP3 inflammasome activation. The presence of stress granules also inhibited the cell death normally driven by the NLRP3 inflammasome. Affinity-purification mass spectrometry revealed that DDX3X, a component of stress granules, interacts with NLRP3. This result indicated that DDX3X might be involved in the stress granule–mediated inhibition of NLRP3 inflammasomes.

Mutant mice lacking the *Ddx3x* gene in the myeloid compartment were generated at St. Jude and then used to further explore the function of DDX3X. NLRP3 inflammasome activation was reduced in the macrophages of the DDX3X-deficient mice, suggesting that DDX3X is required for inflammasome activation, in addition to its role in stress granule formation. Furthermore, the induction of stress granules and the loss of DDX3X in the myeloid compartment led to decreased production of inflammasome-dependent signaling molecules in vivo.

Together, these findings suggest that the mechanism for regulating cell-fate decisions in stressed cells is to use the availability of DDX3X to interpret stress signals, with the cell choosing to form either pro-survival stress granules or pro–cell death ASC specks. Thus, DDX3X, being crucial to stress granule assembly and NLRP3 inflammasome activation, functions as a live-or-die checkpoint in stressed cells, making it an attractive therapeutic target in the design of drugs for modulating stress responses and NLRP3 inflammasome activation. Additionally, DDX3X is mutated in several human cancers and in DDX3X syndrome, which causes intellectual disability and neurodevelopmental deficits in children. This study improved our understanding of the crucial functions of DDX3X, thereby making a fundamental contribution to both the stress granule and inflammasome fields and identifying the physiological importance of this live-or-die checkpoint. *Samir P et al, Nature 573:590–4, 2019*

Thirumala-Devi Kanneganti, PhD

# PROLONGED ANESTHESIA EXPOSURE INCREASES THE RISK OF NEUROCOGNITIVE IMPAIRMENTS IN LONG-TERM SURVIVORS OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

Pediatric patients with acute lymphoblastic leukemia (ALL) are frequently exposed to anesthetic agents during the course of their treatment, which includes lumbar punctures, bone marrow transplants, and magnetic resonance imaging. Repeated exposure to anesthetic agents is negatively associated with brain development in young children. Moreover, certain ALL treatments can impair long-term neurocognitive ability. Thus, repeated and prolonged exposure to anesthetic agents may exacerbate neurocognitive declines in long-term survivors of childhood ALL.

To determine the effects of repeated anesthesia exposure on long-term neurocognitive function in ALL survivors, Kevin R. Krull, PhD (Epidemiology & Cancer Control, Psychology), led a study examining the long-term consequences of repeated exposures to anesthetics, sedatives, analgesics, anxiolytics, and neuromuscular blockers on the neurocognitive and neuroimaging outcomes of ALL survivors. In *JAMA Oncology*, Dr. Krull and his colleagues reported that the 212 ALL survivors who participated in the study experienced a total of 5395 anesthesia exposures during their treatment course. The average number of exposures per survivor was 26.9, and the mean total duration of anesthesia exposure was 15.6 hours. The most commonly received anesthetic agents were propofol and fentanyl, which 100% of patients received at least once, and fluranes such as sevoflurane and isoflurane. Neurocognitive impairment—measured as reduced attention, processing speed, executive function, and intelligence—was present in 42.9% of the survivors.

Chemotherapy dose, age at diagnosis, and female sex substantially contribute to neurocognitive impairments in cancer survivors; thus, the researchers statistically adjusted their data to account for these factors. Despite these adjustments, the risk of neurocognitive impairment was increased 64% in survivors who received high cumulative doses of propofol, 24% in those who had flurane exposures, and 55% in those with long cumulative anesthesia exposures. Furthermore, exposure to high doses of propofol and long anesthesia duration were associated with changes in brain structures (i.e., increased white matter diffusivity in the corpus callosum), suggesting that prolonged anesthesia exposure affects interhemispheric connectivity and neuronal communication.

Based on these findings, the current Total Therapy 17 clinical trial for ALL (NCT03117751) at St. Jude was modified to remove research-only medical procedures that require anesthesia and reduce the duration of medically necessary procedures that require anesthesia. Dr. Krull's team calculated that these changes should decrease the overall propofol doses by 25% and the number of flurane exposures by 47%, which should abolish the anesthesia-associated risk of neurocognitive impairment in patients with ALL treated at St. Jude. *Banerjee P et al, JAMA Oncol 5:1456–63, 2019*

Pia Banerjee, PhD; Kevin R. Krull, PhD

# CLEANDEEPSEQ ANALYSIS DISCRIMINATES BETWEEN SOMATIC SINGLE-NUCLEOTIDE VARIANTS AND NEXT-GENERATION SEQUENCING ERRORS

Next-generation sequencing (NGS) is a multistep process used to identify disease-causing genetic mutations. Although advances in NGS methods have enabled the identification of single-nucleotide variants (SNVs) as oncogenic drivers, this technology also frequently produces sequencing errors that confound the detection of low-frequency genetic variants in the specimen. For the last decade, the limit of detection has lingered above 2% and prevented the development of NGS applications for early cancer detection and disease monitoring. To circumvent this challenge, Xiaotu Ma, PhD, and Jinghui Zhang, PhD (both of Computational Biology), and their research team created the computational tool CleanDeepSeq to identify and mitigate such errors.

Sequencing errors can be introduced at any step of the NGS workflow, including sample processing, PCR amplification, and sequencing. The researchers established an experimental model and analyzed substitution errors in datasets produced by St. Jude, the HudsonAlpha Institute of Biotechnology (Huntsville, AL), the Broad Institute (Cambridge, MA), and Baylor College of Medicine (Houston, TX). Their findings were published in *Genome Biology*.

The team first established a reference dataset containing 19 low-frequency somatic SNVs in samples generated from 1:1000 and 1:5000 dilutions of melanoma cells and matched healthy lymphoblastoid cells. They discovered that suboptimal mapping and problematic alignment distorted allele counting. They also found that the reliability of base calling was influenced by both the base of interest and its neighboring bases. CleanDeepSeq identifies and filters the sequencing errors, which reduces the error rate 10- to 100-fold lower than that of common approaches and enables detection of rare variants with a frequency of 0.1% to 0.01%.

CleanDeepSeq analysis also revealed error patterns that shed light to further improve sequencing accuracy. First, transitions have higher error rates than transversions, indicating a substrate effect. Second, although the error rate of C>T/G>A substitutions is approximately $10^{-4}$, it was elevated (~$10^{-3}$) in CG or GC contexts. The team also discovered that Q5 performs better than Kapa polymerase. These observations indicate that all three players—PCR polymerases, DNA templates, and nucleotide substrates—influence sequencing fidelity. By analyzing patient samples, the authors also detected 8-oxoG stress (i.e., oxidation of guanine bases) that is most likely induced during sample handling or high-energy sonication–based library preparation. Therefore, optimization of these steps in the workflow may further improve resolution.

Together, these findings provide insights into the sources of common sequencing errors produced by deep NGS technology. CleanDeepSeq reduces the prevalence of false positives, thereby greatly improving the reliability and precision of NGS to identify disease-causing SNVs.
*Ma X et al, Genome Biol 20:50, 2019*

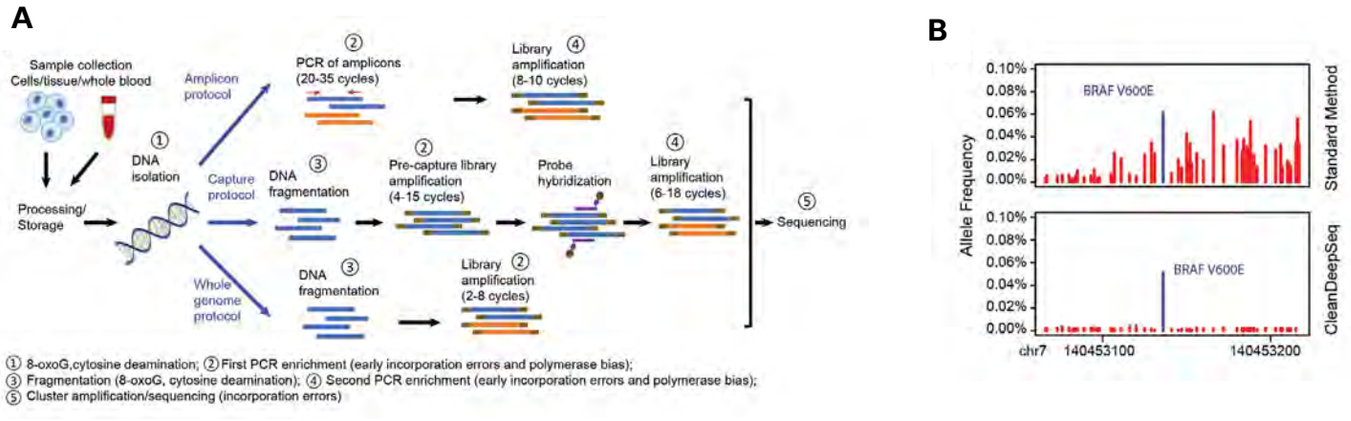


**Figure.** (**A**) Typical NGS workflow. Understanding the source of errors in each step will help develop more accurate sequencing approaches. (**B**) Compared to standard NGS methods (top panel), CleanDeepSeq (bottom panel) achieved a limit of detection of approximately 0.01% for BRAF V600E (purple) in chromosome 7 (chr7). Note the uniformly low error rate of A>T changes after CleanDeepSeq error suppression. These data were generated at a dilution of 1:5000 by the Computational Biology Genomics Laboratory. 

# INTEGRATIVE GENOMICS REVEALS NOVEL SUBTYPES OF B-PROGENITOR ACUTE LYMPHOBLASTIC LEUKEMIA

B-progenitor acute lymphoblastic leukemia (B-ALL) is the most common pediatric cancer, and the genetic basis of B-ALL has been extensively studied. Many B-ALL subtypes are classified according to the presence of specific genetic mutations or chromosomal rearrangements. However, the underlying genetic basis of a substantial minority of B-ALL cases has been unknown; these cases have been unclassified and termed "B-other." Defining the basis of such cases is important to understanding leukemogenesis and developing potential targeted therapeutic approaches.

To further refine the classification system of B-ALL, Charles G. Mullighan, MBBS, MD (Pathology), and his colleagues conducted a large, multi-institutional study of 1988 pediatric and adult patients with B-ALL. The researchers performed integrative genomic analyses, including RNA sequencing of the leukemic cells of patients to identify chromosomal rearrangements, gene expression profiles, and copy number variations. They utilized hierarchical clustering, stochastic neighbor embedding–based visualization, and predictive modeling of RNA-sequencing data, coupled with whole-genome and -exome sequencing and single-nucleotide polymorphism array analysis data to define 23 genetically distinct B-ALL subtypes. These findings were published in *Nature Genetics*.

In this revised taxonomy, 75.8% of the cases comprised 12 previously established subtypes. The remaining cases comprised 11 novel subtypes, which included eight with distinct expression profiles or mutations, one with an *IKZF1* mutation, and two with *PAX5* alterations. The newly defined PAX5-associated B-ALL subtypes included PAX5-altered (PAX5alt) and PAX5 P80R. The PAX5alt subtype was characterized by *PAX5* rearrangements, mutations, and intragenic amplifications. The average age of patients with PAX5alt B-ALL was 15.4 years, and these patients were more likely to have high-risk disease. All PAX5 P80R cases had a mutation causing a proline-to-arginine substitution at residue 80 (P80R) in the DNA-binding domain of PAX5. The average age of patients in this group was 22 years, and the mutation was homozygous in most cases. Both PAX5 subgroups demonstrated a loss of PAX5 transcriptional activity and secondary mutations in signaling pathway genes, which is consistent with the notion that loss of PAX5 transcriptional function drives leukemogenesis.

Expression of PAX5 P80R in Pax5-null lineage–depleted bone marrow cells failed to rescue B-cell maturation, consistent with the known role of PAX5 in that process. To further characterize the oncogenic potential of Pax5 P80R, the researchers generated heterozygous *Pax5*$^{P80R/+}$ and homozygous *Pax5*$^{P80R/P80R}$ knockin mice. Expression of *Pax5*$^{P80R/+}$ caused leukemia within 160 days with alteration of the wild-type *Pax5* allele in the tumors that developed. Leukemia developed more rapidly in *Pax5*$^{P80R/P80R}$ homozygous mice, and the tumors also acquired mutations in signaling pathway genes, recapitulating the genomic features of human PAX5 P80R B-ALL.

PAX5alt and PAX5 P80R accounted for 9.7% of previously classified B-other subtypes of B-ALL, providing a molecular basis for the pathogenesis of those diseases. Therefore, using integrative genomics to refine the B-ALL classification system elucidated novel subtypes that can be used to improve risk stratification and develop targeted therapies.
*Gu Z et al, Nat Genet 51:296–307, 2019*

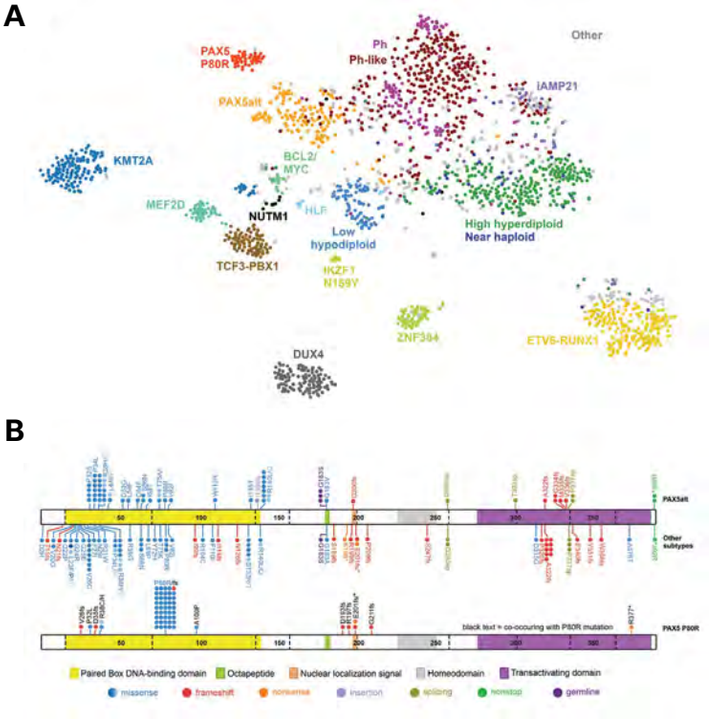


**Figure.** Identification of novel B-ALL subtypes. (**A**) Gene expression profiling of 1988 cases of B-ALL is shown in a two-dimensional t-distributed stochastic neighbor–embedding (tSNE) plot. Each dot represents a single sample. The 1000 most variable genes were processed by the tSNE algorithm. The major B-ALL subtypes are shown in different colors; the PAX5 P80R and PAX5alt subtypes are noted in red. (**B**) Protein domain plot of PAX5 showing the alterations detected in the PAX5 P80R subgroup (bottom), compared with those in PAX5alt and other B-ALL subtypes. *Reprinted by permission from SNCSC GmbH: Nature Springer, Nat Genet 51:296–307, 2019. PAX5-driven subtypes of B-progenitor acute lymphoblastic leukemia, Gu Z et al, © 2019*

# GLOBAL COLLABORATIONS IMPROVE THE SURVIVAL OF CHILDREN WITH PHILADELPHIA CHROMOSOME-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA

The Philadelphia chromosome (Ph) is an abnormal chromosome seen in leukemia blasts of 3% to 4% of pediatric patients with acute lymphoblastic leukemia (ALL). It was the first chromosomal aberration identified in patients with leukemia and results from a reciprocal translocation (i.e., mutual exchange of fragments between two broken chromosomes) involving the q arms of chromosomes 9 and 22. This translocation results in the fusion of genes *ABL* on chromosome 9 and *BCR* on chromosome 22 (*BCR–ABL*), and the fusion gene encodes a tyrosine kinase–signaling protein that leads to uncontrolled cell division.

Children with Ph-positive ALL have historically had a dismal prognosis [5-year event-free survival (EFS), 28%–32%] and required cranial irradiation and allogeneic hematopoietic stem cell transplantation (HSCT). Administration of the first-generation drug imatinib, an inhibitor of BCR–ABL tyrosine kinase, led to increased 5-year survival in this patient cohort; however, almost all patients were still treated with cranial irradiation, and many underwent HSCT.

To determine if the second generation of inhibitors would improve EFS without the use of cranial irradiation in children with Ph-positive ALL, researchers at St. Jude, led by Ching-Hon Pui, MD (Oncology, Pathology, Global Pediatric Medicine), and investigators in the Chinese Children's Cancer Group (including 20 hospitals in China), collaborated to initiate a Phase 3 randomized clinical trial in October 2018. This trial enrolled 189 patients (aged 0–10 years) and compared imatinib at 300 mg/m$^2$ per day (n=97) with the second-generation BCR–ABL inhibitor dasatinib at 80 mg/m$^2$ per day (n=92). Patients in both groups received chemotherapy but no cranial irradiation, and only four patients received HSCT (three in the imatinib group and one in the dasatinib group).

In *JAMA Oncology*, the team reported that a daily dosage of 80 mg/m$^2$ of dasatinib was significantly better than a daily dosage of 300 mg/m$^2$ of imatinib and improved the 4-year EFS (71.0% vs 48.9%) and 4-year overall survival (88.4% vs 69.2%). The 4-year cumulative risk of any relapse was lower in the dasatinib group than in the imatinib group. The frequency of severe toxicity did not differ between the two groups.

These results are more favorable than those from two previous Phase 2 studies by the Children's Oncology Group and the international collaborative study CA180-372, which used lower dosages of dasatinib (60 mg/m$^2$ per day). This study is also an exceptional example of how international scientific collaborations can save the lives of children worldwide and reduce the global cancer burden. *Shen S et al, JAMA Oncol, 6:358–66, 2020*

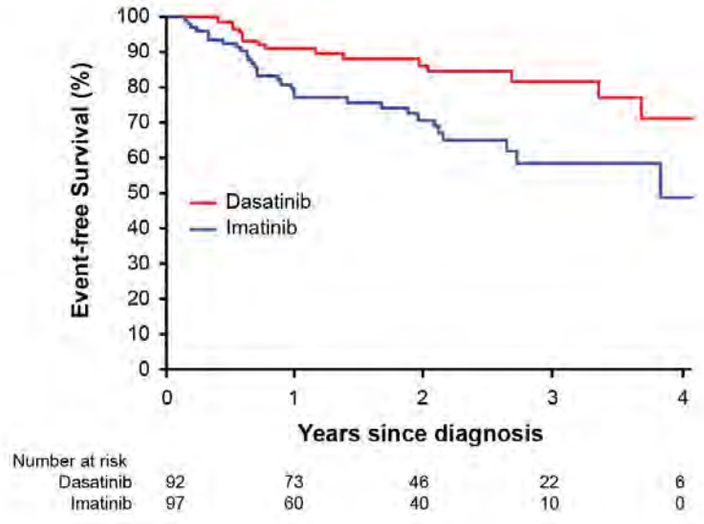


**Figure.** Kaplan–Meier plots showing event-free survival (EFS) by treatment group. *Reproduced with permission from JAMA Oncol, 2019, 6(3):358–66. © 2019 American Medical Association. All rights reserved.*

# CROSS-KINGDOM INTERACTIONS WITH INFLUENZA ENHANCE BACTERIAL ADHERENCE DURING RESPIRATORY INFECTIONS

Influenza infection increases the likelihood and severity of bacterial infections, particularly *Streptococcus pneumoniae*– or *Staphylococcus aureus*–related pneumonia. This relation has been observed in the clinic and in preclinical models of infections. Although such cross-kingdom interactions of enteric viruses have been well studied, the interactions and underlying mechanisms of respiratory tract pathogens are still being uncovered.

In a recent *Nature Microbiology* article, Jason Rosch, PhD (Infectious Diseases), and his colleagues showed that influenza directly binds various bacteria in the context of respiratory infections. Confocal and super-resolution microscopy of *S. pneumoniae* cultures that had been mixed with purified influenza virus for 30 minutes showed that influenza binds directly to the surface of *S. pneumoniae*. After mixing each of three strains of *S. pneumoniae* with an influenza strain known to adhere to human cells through different receptors than those used by the bacteria, the researchers found that adherence of influenza-bound bacteria to human lung and human nasopharyngeal cells in culture was significantly greater than that of non–influenza-bound bacteria.

Given that influenza virus attachment to the pneumococcal surface enhanced the bacteria's adherence to respiratory epithelial tissues, the team then tested for similar effects in other types of bacteria. Influenza virus bound to gram-positive *S. aureus* and *Staphylococcus epidermidis*, gram-negative *Moraxella catarrhalis*, and nontypeable *Haemophilus influenzae*, all of which frequently colonize the human respiratory tract. The adherence of these influenza-bound bacteria to isolated respiratory tract cells was variably enhanced across species. Following up on their data indicating enhanced bacterial adherence of influenza-bound *S. pneumoniae*, Dr. Rosch's team tested the effect of this enhancement on infections in mice. They found that influenza-bound *S. pneumoniae* caused a greater bacterial burden in nasal passages and the inner ear than did *S. pneumoniae* alone. Furthermore, the mortality rate of mice infected with influenza-bound bacteria was higher than that of mice infected with the bacteria alone or coinfected with bacteria and unbound virus.

This study supports the notion of an additional mechanism of bacteria–influenza virus synergy during early pathogenesis and highlights the importance of learning how such cross-kingdom interactions lead to disease. *Rowe HM et al, Nat Microbiol 4:1328–36, 2019*

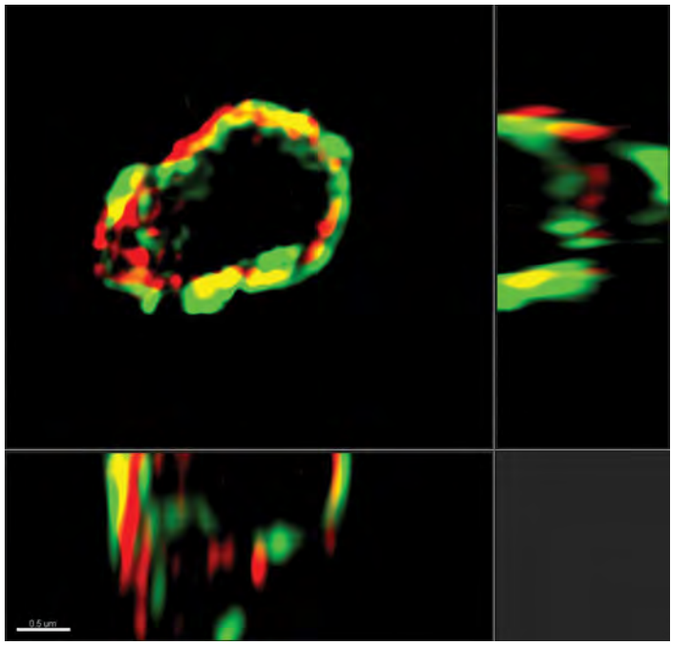


**Figure.** Structured illumination microscopy of influenza A virus (red) bound to pneumococcus bacteria (green). Scale bar, 0.5 µm. *Reprinted by permission from SNCSC GmbH: Nature Springer, Nat Microbiol, 4:1328–36, 2019. Direct interactions with influenza promote bacterial adherence during respiratory infections, Rowe HM et al, © 2019*

# ULK1 MEDIATES THE CLEARANCE OF FREE α-GLOBIN IN β-THALASSEMIA

Each molecule of adult human hemoglobin (HbA) consists of two α-globin subunits and two β-globin subunits. The β-globin protein is encoded by the *HBB* gene. *HBB* mutations that reduce or eliminate β-globin expression cause β-thalassemia, a common, often debilitating, inherited form of anemia. This leads to insufficient HbA being produced, which reduces the oxygen-carrying capacity of red blood cells (RBCs), causing tissue hypoxia. The shortage of β-globin also results in an excess of unstable free α-globin, which generates toxic reactive oxidant species and cellular precipitates that impair RBC maturation and viability.

Several groups, including that of Mitchell J. Weiss, MD, PhD (Hematology), have shown that protein quality control systems, including ubiquitin-mediated proteolysis and autophagy (a process in which unwanted proteins are enveloped in vesicles called autophagosomes and delivered to lysosomes for degradation), can mitigate the pathophysiology of β-thalassemia by degrading free α-globin. Both normal and β-thalassemic RBC precursors can detoxify excess α-globin, but pathology arises in the latter cells when the amount of free α-globin exceeds the capacity of the endogenous protective mechanisms.

Dr. Weiss, Mondira Kundu, MD, PhD (Pathology, Cell & Molecular Biology), Christophe Lechauve, PhD, (Hematology), and their colleagues examined the role of two core autophagy proteins in the progression of β-thalassemia in a mouse model in which the *Hbb* gene was disrupted. They published their findings in the journal *Science Translational Medicine*.

The proteins investigated were Unc-51–like kinase 1 (ULK1) (encoded by the *Ulk1* gene), which initiates autophagosome formation, and autophagy-related 5 (ATG5) (encoded by the *Atg5* gene), which is involved in autophagosome maturation. By introducing null alleles of *Ulk1* or *Atg5* into β-thalassemic mice to produce double mutants and measuring the resulting α-globin accumulation in the RBCs, the researchers showed that the loss of *Ulk1* reduced the autophagic clearance of α-globin in RBC precursors and exacerbated the disease, whereas *Atg5* inactivation had relatively minor effects on disease progression. Therefore, α-globin elimination by autophagy is mediated by ULK1 and is largely independent of ATG5.

The mammalian target of rapamycin complex 1 (mTORC1) inhibits autophagy by phosphorylating ULK1; thus, the team investigated the therapeutic potential of rapamycin, an mTORC1 inhibitor, in β-thalassemia. Treating β-thalassemic mice systemically with rapamycin reduced the α-globin precipitates and lessened the associated pathology via an ULK1-dependent pathway. Similarly, rapamycin reduced the accumulation of free α-globin in cultures of human RBC precursors derived from CD34+ cells of patients with β-thalassemia. Together, these findings define a pathway for ameliorating β-thalassemia by using mTORC1 inhibitors to promote α-globin clearance. *Lechauve C et al, Sci Transl Med 11:eaav4881, 2019*

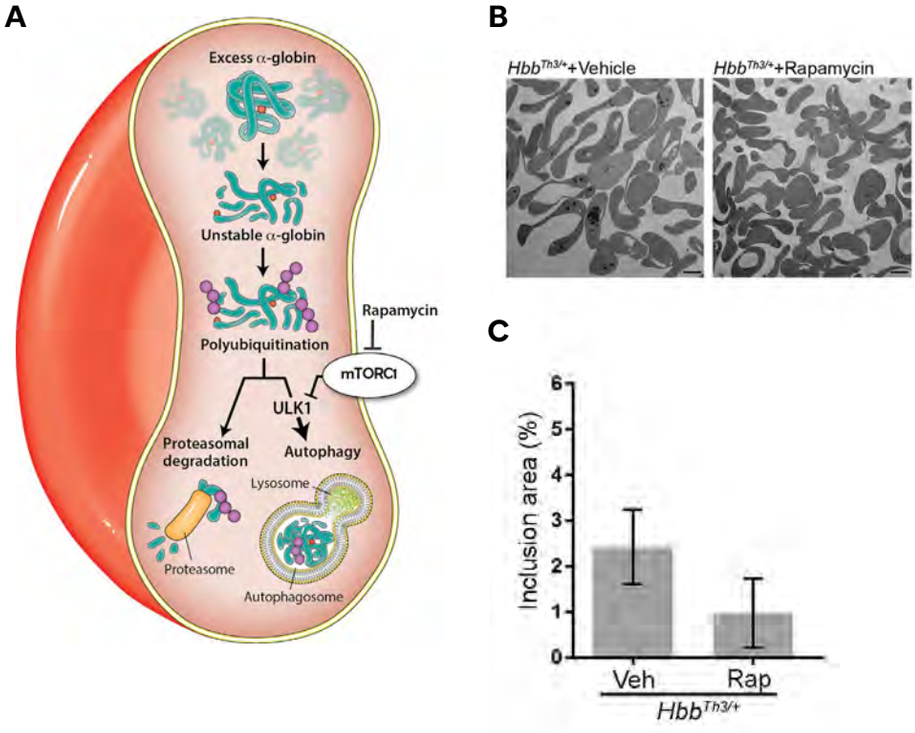


**Figure.** (**A**) Scheme of an RBC eliminating free α-globin. (**B**) Transmission electron micrographs of RBC precursors from β-thalassemic mice treated with either rapamycin (Rap) or vehicle (Veh). Free β-globulin appears as dark inclusions within the cells. Scale bars, 2 µm. (**C**) Quantification of the α-globulin inclusions in the cells shown in B, as determined by automated image analysis of the electron micrographs. *From Lechauve C et al. The autophagy-activating kinase ULK1 mediates clearance of free α-globin in β-thalassemia. Sci Transl Med 11:eaav4881, 2019. Reprinted with permission from AAAS.*

# 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: Melissa M. Hudson, MD; Leslie L. Robison, PhD**

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

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

## NEUROBIOLOGY & BRAIN TUMOR PROGRAM

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

Brain tumors are the leading cause of cancer-related death in children. The goal of the Neurobiology & Brain Tumor Program is to improve survival and reduce morbidity for children with brain tumors by developing effective, relatively nontoxic therapies through a better understanding of pathogenesis. By integrating the latest genomic and genetic technologies into studies of the developing nervous system, members of this program are efficiently translating laboratory findings into opportunities for new treatments. Key advances include the identification of the cells of origin of important pediatric brain tumors and the modeling of some of the most aggressive forms of these tumors, including high-grade gliomas. Close collaboration among the laboratory and clinical members of the program 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 Affiliate Program at St. Jude enables more children to access pediatric oncology and hematology care close to home. It also gives more children access to novel treatment strategies afforded by a large research hospital. Currently, eight clinics are affiliated with St. Jude. The 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. All eight clinics serve mainly rural and suburban communities with broad patient demographics. Approximately 350 new oncology patients each year receive care in the eight affiliate clinics.**

**During the past year, the physicians and staff in the Affiliate Program have completed three multisite quality improvement initiatives to improve communication, medication adherence, and coordination of care for shared patients receiving care in the clinical network.**

Carolyn L. Russo, MD

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Shilpa Shukla, MD

Samantha Zeller, NP

Alison Taylor, NP

# ST. JUDE GLOBAL

**The St. Jude Global initiative achieved several milestones and significant growth in all regions and programs in 2019. We formally launched the St. Jude Global Alliance, rapidly accelerated efforts in education and research, and developed new tools and resources. Following the success of the first St. Jude Global Alliance meeting in December 2018, the St. Jude Global Executive Committee approved the Medical Institution Membership Agreement, and the Alliance membership application was made available online in March. By the end of the year, 116 institutions from 44 countries had applied for membership, and 47 institutions had completed the process. In April, the Pediatric Cancer and Blood Disorders Center of Armenia became the first member of the St. Jude Global Alliance in a signing ceremony at St. Jude, which included a visit from Mrs. Anna Hakobyan, the wife of the Prime Minister of Armenia.**

**One of the first opportunities for Alliance members to contribute to a global project is by engaging with the St. Jude Global Childhood Cancer Analytics Resource and Epidemiological Surveillance System (SJCARES) suite of tools. SJCARES is a hospital-based registry that launched in July 2019. By the end of the year, 19 institutions were actively participating in SJCARES, and 26 individuals were training in data management and the implementation process. Over the course of the year, another SJCARES tool, the Pediatric Oncology Facility Integrated Local Evaluation (PrOFILE) tool, was tested in both full and abbreviated versions. PrOFILE provides a guide for institutions to self-evaluate their health service delivery and develop individual quality improvement plans. Beta tests of the full version of PrOFILE were conducted in Pakistan, Lebanon, Zimbabwe, Thailand, and the United States; the abbreviated version was tested in Morocco, Brazil, and Lebanon.**

In January 2019, the Tennessee Higher Education Commission approved our application to establish a Master's degree program in Global Child Health in collaboration with the St. Jude Graduate School of Biomedical Sciences. Upon receiving the Commission's approval, we started the student application process. The program received 47 applicants from 19 countries in all seven St. Jude Global regions, and 10 students from 10 countries were admitted. Orientation was delivered in July, and courses began in August.

The St. Jude Global Academy offerings expanded in 2019 with the launch of the first Pediatric Oncology Critical Care certificate-based seminar. Seventy-four participants were selected for the online portion of the course, which began in November. The Academy also hosted the residential component of the first Neuro-Oncology Training Seminar, which brought together 20 participants in multidisciplinary teams from seven countries. The Global Infectious Diseases team created two educational hubs, the Tata Medical Center (Kolkata, India) and the American University of Beirut (Beirut, Lebanon), to support residential training seminars for infection preventionists. Professional development seminars were also offered in the areas of infectious diseases, leadership, and palliative care.

New training programs were developed and offered via our distance-learning platform *Cure4Kids*. Recognizing the need to train data managers and coordinators in low- or middle-income countries, our Clinical Research Operations and Education teams delivered a foundational program consisting of two online courses: *Introduction to Pediatric Oncology* and *Introduction to Clinical Data Abstraction*. This program is a major milestone toward supporting nonclinical personnel at our partner sites. Additionally, the St. Jude Global Nursing Program launched the first modules of their online course titled *Essential Orientation to International Pediatric Hematology/Oncology Nursing* in September.

St. Jude Global continued its work as the implementation partner for the WHO Global Initiative in Childhood Cancer. Capitalizing on the momentum of the announcement of the initiative at a United Nations High-Level Meeting in September 2018, St. Jude Global Regional Programs assisted in coordinating workshops in several focus countries, including Myanmar, Peru, the Philippines, and Uzbekistan. In October 2019, St. Jude signed an agreement with the International Atomic Energy Agency. The goals of this collaboration are to raise awareness of childhood cancers, mobilize resources to support the establishment of nuclear and radiation medicine services, increase training for professionals in the field of radiotherapy, and support research in pediatric radiation oncology and related areas.

Carlos Rodriguez-Galindo, MD; Mrs. Anna Hakobyan; Gavorg Tamamyan, MD, PhD; Sima Jeha, MD

# GRADUATE SCHOOL OF BIOMEDICAL SCIENCES

**The St. Jude Children's Research Hospital Graduate School of Biomedical Sciences includes a premier Doctorate of Philosophy in Biomedical Sciences (PhD-BMS) program that trains outstanding young scientists to advance our understanding of the molecular basis of disease and therapy, and a Master's of Science in Global Child Health (MSc-GCH) program that is developing a global community of change agents and leaders dedicated to enhancing children's health worldwide. In 2019, the Graduate School also began a strategic initiative to establish a Master's of Science in Clinical Investigations (MSc-CI) program. Approximately 150 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.**

**During 2019, the inaugural class of 11 PhD-BMS students successfully completed their admission to candidacy examinations and applied for NIH funding. Most impressively, three students received fundable scores. On June 21, 2019, St. Jude held its first commencement ceremony, and all 11 students were awarded Master's of Science degrees. The 13 second-year PhD-BMS students completed the challenging first-year curriculum and began full-time research with their chosen mentors, and the 12 first-year PhD-BMS students arrived on campus and began the first-year curriculum.**

Andrea Lee

The Tennessee Higher Education Commission formally approved the MSc-GCH program in January 2019, and the inaugural class of 10 outstanding students from 10 different countries arrived on the St. Jude campus in July for their matriculation, orientation, and first summer intersession, which included training in the areas of leadership and communication. The students then returned to their home countries to pursue their curricular training via distance learning. The successful launch of this program exemplifies the impact and pre-eminence of St. Jude Global and the Department of Global Pediatric Medicine. 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-GCH program leaders, faculty, and the graduate school administrative staff. Toward the end of 2019, many outstanding applications to the MSc-GCH program were received and reviewed for the second class starting in Summer 2020.

With the success of both degree programs, the Graduate School is now qualified 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 staff completed SACSCOC training, identified essential consulting resources, and formally started preparing for the accreditation application process. Formal submission of the application is planned for Winter 2020. As part of the accreditation process, the Graduate School administration will develop a Strategic Plan in 2020 that aligns with the St. Jude Strategic Plan and charts the course of the school during the coming years.

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

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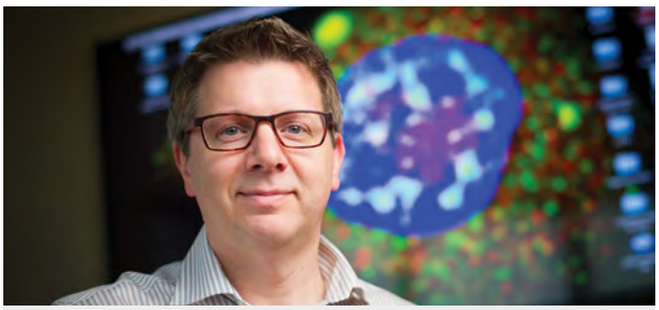

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[1] Graduate school faculty member / [2] Secondary appointment / [3] No longer at St. Jude / [4] Emeritus / [5] Deceased

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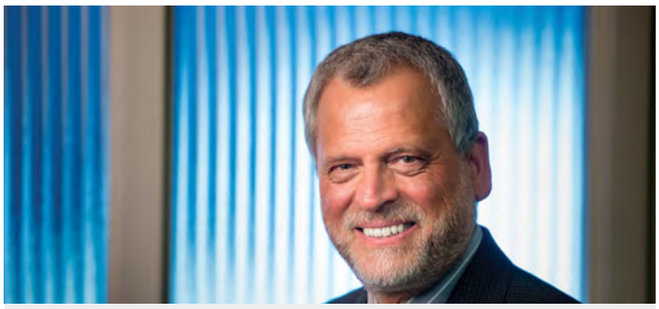
Jamy C. Peng, PhD[1] • Epigenetic regulation of stem cell functions

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 / [5] Deceased



## DIAGNOSTIC IMAGING

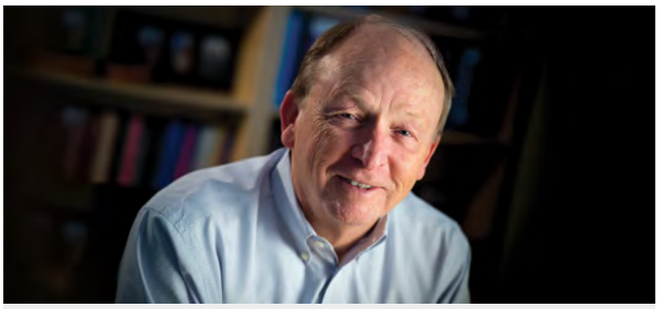
**CHAIR**
Zoltán Patay, MD, PhD;
Endowed Chair in Diagnostic Imaging • Imaging genomics & brain tumor characterization by quantitative MRI

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

**ASSOCIATE MEMBERS**
Asim K. Bag, MBBS, MD • Response assessment of immunotherapy & radiation therapy, assessment of cancer therapy–related brain damage
Julie H. Harreld, MD[1] • Magnetization transfer MR imaging & cerebral perfusion
Claudia M. Hillenbrand, PhD[3]
Robert J. Ogg, PhD[3]
Noah D. Sabin, MD, JD • Imaging of brain tumors & side effects of therapy
Scott E. Snyder, PhD[3]

**ASSISTANT MEMBER**
Scott N. Hwang, MD, PhD • Brain tumors, quantitative imaging, computational modeling

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



## EPIDEMIOLOGY & CANCER CONTROL

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

**MEMBERS**
Gregory T. Armstrong, MD, MSCE[1] • Cancer survivorship & long-term follow-up
Melissa M. Hudson, MD[2]; The Charles E. Williams Endowed Chair 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
I-Chan Huang, PhD • Patient-reported outcomes measurement after pediatric cancer
Daniel A. Mulrooney, MD, MS[1,2] • Cardiovascular outcomes of cancer therapy
Zhaoming Wang, PhD[1] • Genetic epidemiology of pediatric cancer & survivorship

**ASSISTANT MEMBERS**
Nickhill Bhakta, MD, MPH[1,2] • Global pediatric medicine
Angela Delaney, MD[2] • Hypothalamic/pituitary dysfunction in childhood cancer survivors
Matthew J. Ehrhardt, MD, MS[2] • Late effects of childhood cancer therapy
Todd M. Gibson, PhD[3]
Carmen L. Wilson, PhD[1] • Late effects of childhood cancer therapy

**ADJUNCT MEMBER**
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

**MEMBERS**
Alessandra d'Azzo, PhD[1]; Jewelers for Children Endowed Chair in Genetics and Gene Therapy • Lysosomal/proteasomal function in health & disease
Peter J. McKinnon, PhD[1] • DNA damage responses in the nervous system



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

## 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[1] • Global health, infection care and control
Meenakshi Devidas, PhD[1] • 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]
Gaston Rivera, MD[4]
Victor M. Santana, MD[1]; Charles B. Pratt Chair in Solid Tumor Research • Global health, novel therapeutics, neuroblastoma, research ethics

**ASSOCIATE MEMBERS**

Catherine G. Lam, MD, MPH[1] • Global health, health systems, pediatric solid tumors
Ibrahim A. Qaddoumi, MD, MS[1] • Global health, brain tumors, telemedicine, retinoblastoma

**ASSISTANT MEMBERS**

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

**INSTRUCTORS**

Daniel Moreira, MD • Global pediatric oncology, evidence-based education, pediatric CNS tumors
Sheena Mukkada, MD, MPH[1] • Global health, infection care & control

## HEMATOLOGY

**CHAIR**

Mitchell J. Weiss, MD, PhD[1]; Arthur Nienhuis Endowed Chair in Hematology • Blood development; genome editing for sickle cell disease

**MEMBERS**

Ellis J. Neufeld, MD, PhD; Executive Vice President; Clinical Director; John & Lorine Thrasher Endowed Chair in Pediatric Medicine • Patient-oriented studies in nonmalignant hematology
Arthur W. Nienhuis, MD[4]
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
Jane S. Hankins, MD, MS[1] • Sickle cell disease, transition to adult care & health outcomes during adolescence & young adulthood
Shannon L. McKinney-Freeman, PhD[1] • Mechanisms of hematopoietic stem cell development & transplantation
Ulrike M. Reiss, MD[1] • Bleeding disorders, gene therapy for hemophilia, bone marrow failure
Carolyn Russo, MD • Quality improvement in clinical networks
Byoung Ryu, PhD[3]

**ASSISTANT MEMBERS**

Yong Cheng, PhD[1] • Cis-regulatory modules in normal & pathological gene expression
Jeremie H. Estepp, MD[1] • Sickle cell disease, novel therapies, translational studies
Latika Puri, MD • Sickle cell disease, thrombocytopenias, chronic transfusion
Shengdar Q. Tsai, PhD[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
Parul Rai, MD • Cardiac injury in sickle cell disease
Jason R. Schwartz, MD, PhD • Pediatric MDS & bone marrow failure

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

## 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 MEMBERS**
Yongqiang Feng, PhD[1] • Epigenetic & transcriptional basis of T-cell immunity
Rhea M. Sumpter Jr, MD, PhD[5]

## INFECTIOUS DISEASES

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

**MEMBERS**
Miguela A. Caniza, MD[1,2] • Global health, infection care, and control
Patricia M. Flynn, MD; Deputy Clinical Director; Arthur Ashe Endowed Chair in Pediatric AIDS Research • HIV/AIDS in children & infections in children with cancer
Aditya H. Gaur, MD, MBBS[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] • Coenzyme A in health & disease, regulation of membrane phospholipids
Charles O. Rock, PhD • Membrane phospholipid metabolism
Stacey L. Schultz-Cherry, PhD[1] • Pathogenesis of influenza & enteric virus infections
Richard J. Webby, PhD[1] • Influenza virus pathogenicity
Robert G. Webster, PhD[4]

**ASSOCIATE MEMBERS**
Elisabeth E. Adderson, MD[1] • Epidemiology & treatment of infections
Hans Haecker, MD, PhD[3]
Hana Hakim, MD • Infection prevention & control
Katherine Knapp, MD • Perinatal HIV exposure/HIV clinical trials
Gabriela M. Marón Alfaro, MD • Infectious complications in transplant patients
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, MBBS, PhD[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

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

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



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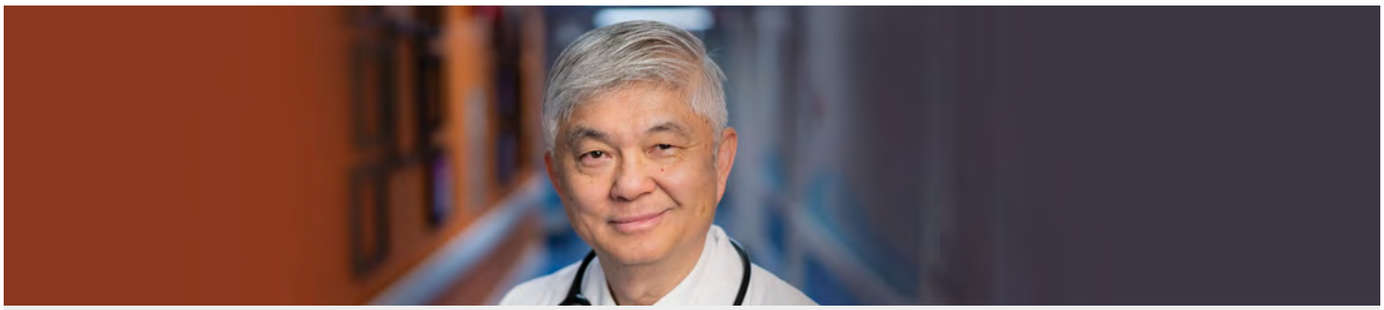


## ONCOLOGY

**CHAIR**

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

**CO-CHAIR**

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

**MEMBERS**

Gregory T. Armstrong, MD, MSCE[1,2] • Pediatric neuro-oncology & cancer survivorship
Justin N. Baker, MD[1] • Quality of life/palliative care & ethics
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] • Clinical & biologic investigation of NHL & ALL
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 • Pathogenesis of infantile ALL & pediatric AMKL
Mark E. Hatley, MD, PhD[1] • Origins of pediatric sarcomas
Catherine G. Lam, MD, MPH[1,2] • Global health, health systems, pediatric solid tumors
Daniel A. Mulrooney, MD, MS[1] • Cardiovascular outcomes of cancer therapy
Ibrahim A. Qaddoumi, MD, MS[1,2] • Global health, brain tumors, telemedicine, retinoblastoma
Giles W. Robinson, MD[1] • Origin & genomics of medulloblastoma, translational studies
Carolyn Russo, MD[2] • Quality improvement in clinical networks

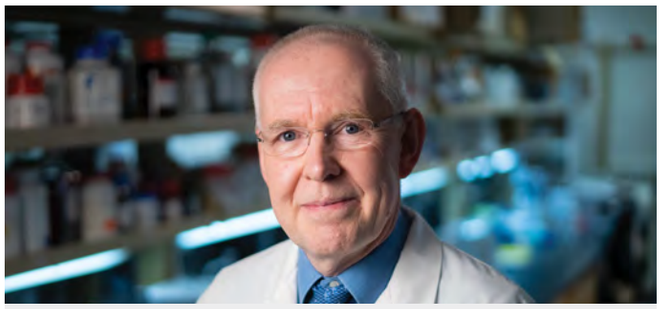
**ASSISTANT MEMBERS**

Allison M. Ast, MD • Integrative therapies in pediatric hematology-oncology patients
Nickhill Bhakta, MD, MPH[1,2] • Global health, survivorship, epidemiology, childhood leukemias
Michael W. Bishop, MD[1] • Osteosarcoma, Ewing sarcoma, soft-tissue sarcomas
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
Charles Gawad, MD, PhD[3]
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
Chimene Kesserwan, MD[3]
Deena R. Levine, MD • Pediatric palliative & end-of-life care
Esther A. Obeng, MD, PhD[1] • Myeloid malignancies & bone marrow failure syndromes
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**

Kari L. Bjornard, MD, MPH • Fertility and sexual health, cancer survivorship
Jennifer L. Kamens, MD • DNA damage repair in high-risk acute leukemias
Anand G. Patel, MD, PhD • Recurrent pediatric sarcomas and intratumor heterogeneity
Daniel Moreira, MD[2] • Global pediatric oncology, evidence-based education, pediatric CNS tumors

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



## PATHOLOGY

**CHAIR**

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

**MEMBERS**

James R. Downing, MD; President and Chief Executive Officer; Dr. Donald Pinkel Chair of Childhood Cancer Treatment • The molecular pathology of acute leukemia

Terrence L. Geiger, MD, PhD[1]; Senior Vice President and Deputy Directory for Academic and Biomedical Operations; Endowed Chair in Pediatrics • T-cell regulation, adoptive immunotherapy

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

Michael M. Meagher, PhD[1]; 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

Susana C. Raimondi, PhD[4]

Jerold E. Rehg, DVM • Preclinical models of infectious diseases & cancer

A. Peter Vogel, DVM, PhD • Pathology of animal models of human disease

Gerard P. Zambetti, PhD[1] • The function of p53 in tumor suppression & tumorigenesis

**ASSOCIATE MEMBERS**

Armita Bahrami, MD[1] • Molecular pathogenesis of sarcomas and melanoma

John K. Choi, MD, PhD[1] • Transcription factors in acute leukemias

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

Tanja A. Gruber, MD, PhD[2] • Pathogenesis of infantile ALL & pediatric AMKL

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

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

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

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 • Animal models of human disease

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**

Jason Cheng-Hsuan Chiang, MD, PhD • Diagnosis & classification of CNS tumors

Michael R. Clay, MD[3]

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 G. Rossi, DO, FAAP, FASA; Division Director • Patient safety and cognitive effects of 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

Michael J. Frett, MD • Pediatric anesthesia

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

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

Luis A. Trujillo Huaccho, MD • Regional anesthesia & anesthetic approach in high-risk cases

Becky B. Wright, MD • Pain management techniques, peripheral nerve blocks

**CRITICAL CARE MEDICINE**

R. Ray Morrison, MD[1]; Division Director • Pediatric critical care, myocardial protection

Asya Agulnik, MD, MPH[1,2] • Global pediatric health

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

Melissa R. Hines, MD • Diagnosis and treatment of hemophagocytic lymphohistiocytosis

Caitlin Hurley, MD • Onco-critical care, HSCT/immunotherapy patients, long-term outcomes of critical care illnesses

Jennifer A. McArthur, DO • Improving outcomes for oncology and transplant patients with critical illness

**ENDOCRINOLOGY**

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

Angela Delaney, MD • Endocrine disorders in childhood cancer survivors

**NEUROLOGY**

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

**NURSING RESEARCH**

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

**PSYCHIATRY**

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



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

## PHARMACEUTICAL SCIENCES

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

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

**MEMBERS**
William E. Evans, PharmD[1]; Endowed Chair in Pharmacogenomics • Pharmacogenomics of antileukemic agents in children
William L. Greene, PharmD; Chief Pharmaceutical Officer • Optimizing pharmacotherapy
Erin G. Schuetz, PhD[1] • Mechanisms of human variation in drug response
Clinton F. Stewart, PharmD[1] • Pharmacology of anticancer drugs in children
Jun J. Yang, PhD[1] • Pharmacogenomics of anticancer agents & drug resistance

**ASSOCIATE MEMBER**
James M. Hoffman, PharmD; Chief Patient Safety Officer • Medication safety & outcomes

**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

## 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
Megan L. Wilkins, PhD • Clinical & research psychological services for youth with HIV/AIDS

**ASSISTANT MEMBERS**
Nicole M. Alberts, PhD • Pain, psycho-social outcomes, & eHealth/mHealth in psycho-oncology & sickle cell disease
Kristin E. Canavera, PhD • Pediatric bioethics
Jennifer L. Harman, PhD • Psychosocial functioning of young children with cancer
Lisa M. Jacola, PhD • Neurobehavioral outcomes in children treated for cancer
Kendra R. Parris, PhD • Coping & adjustment in youth with cancer
Jerlym S. Porter, PhD, MPH • Transition from pediatric to adult care in SCD
Brian 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**
Jennifer M. Allen, PhD • Pain management, adolescent/young adults, health behavior
R. Elyse Heidelberg, PsyD • Pain and symptom management in pediatric hematology/oncology
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 / [5] Deceased

## RADIATION ONCOLOGY

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

**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

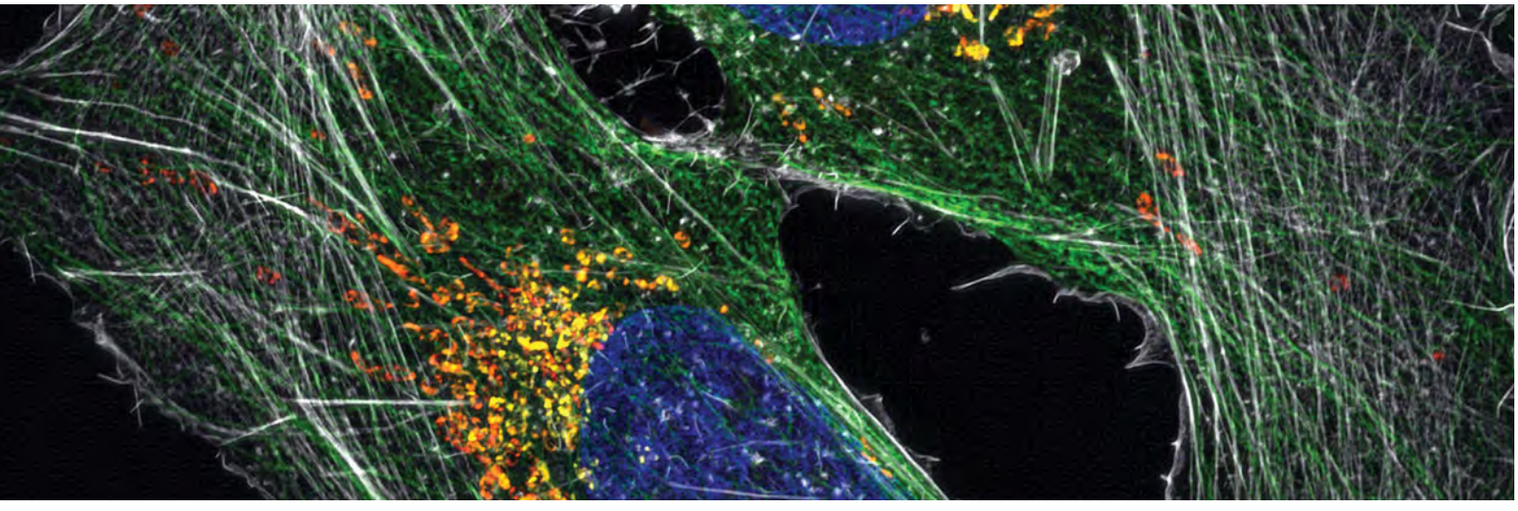
**CHAIR**
Charalampos Babis Kalodimos, PhD[1]; Joseph Simone Endowed Chair in Basic Research • Functional mechanisms of protein machineries

**MEMBERS**
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 White, DPhil[1]; Endowed Chair–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 / [5] Deceased

## SURGERY

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

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

**ASSISTANT MEMBERS**
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
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

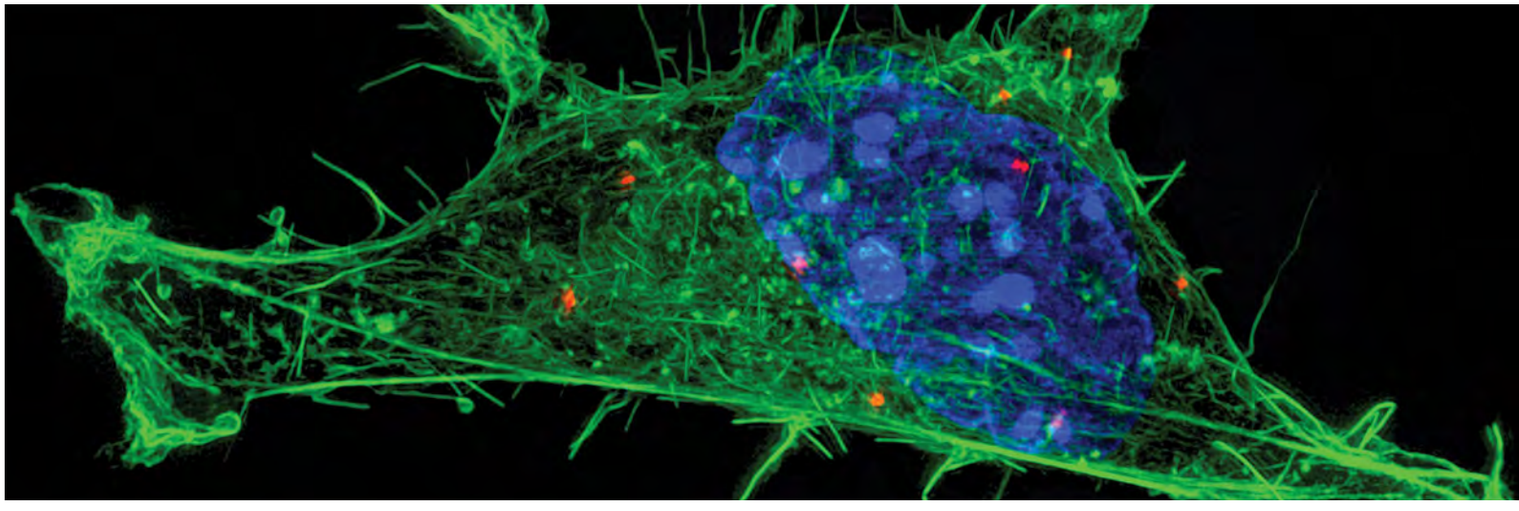
**CHAIR**
Charles J. Sherr, MD, PhD; Herrick Foundation Endowed Chair in Tumor Cell Biology • Tumor suppressor–dependent signaling networks

**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

**ASSOCIATE MEMBER**
Richard A. Ashmun, PhD[2] • Applications of flow cytometry & cell separation

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

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



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

# ENDOWED CHAIRS

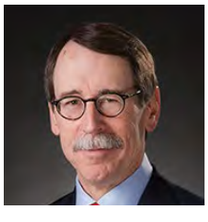
**Alessandra d'Azzo, PhD**
Jewelers Charity Fund Endowed Chair
in Genetics & Gene Therapy

**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

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

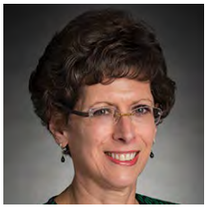


**James R. Downing, MD**
Dr. Donald Pinkel Endowed Chair in
Childhood Cancer Treatment

**William E. Evans, PharmD**
Endowed Chair in Pharmacogenomics

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

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



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

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

**Kevin R. Krull, PhD**
Endowed Chair in Cancer Survivorship

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**James I. Morgan, PhD**
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**Charles G. Mullighan, MBBS(Hons), MD**
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**Clifford M. Takemoto, MD**
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[1] No longer at St. Jude / [2] Promoted to staff position / [3] Promoted to faculty position

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Huan Sun, PhD, Structural Biology
Xiaojun Sun, PhD, Structural Biology
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Jessica Wagner, PhD, Bone Marrow Transplantation & Cellular Therapy
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Lydia Wilson, PhD, Radiation Oncology
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Wenting Zheng, PhD, Pathology[2]
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### BONE MARROW TRANSPLANTATION & CELLULAR THERAPY FELLOWS

Ali Suliman, MD, MSc[3]
Jamie Truscott, MD

### CANCER SURVIVORSHIP FELLOWS

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### GLOBAL PEDIATRIC MEDICINE FELLOWS

Zebin Al Zebin, MD
Lisa Force, MD

### INFECTIOUS DISEASES IN IMMUNOCOMPROMISED CHILDREN AND ADOLESCENTS FELLOW

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### PEDIATRIC HIV FELLOW

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### OCULAR ONCOLOGY FELLOW

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### NEUROPSYCHOLOGY FELLOWS

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

# FELLOWS & SCHOLARS

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### PEDIATRIC INFECTIOUS DISEASES FELLOWS

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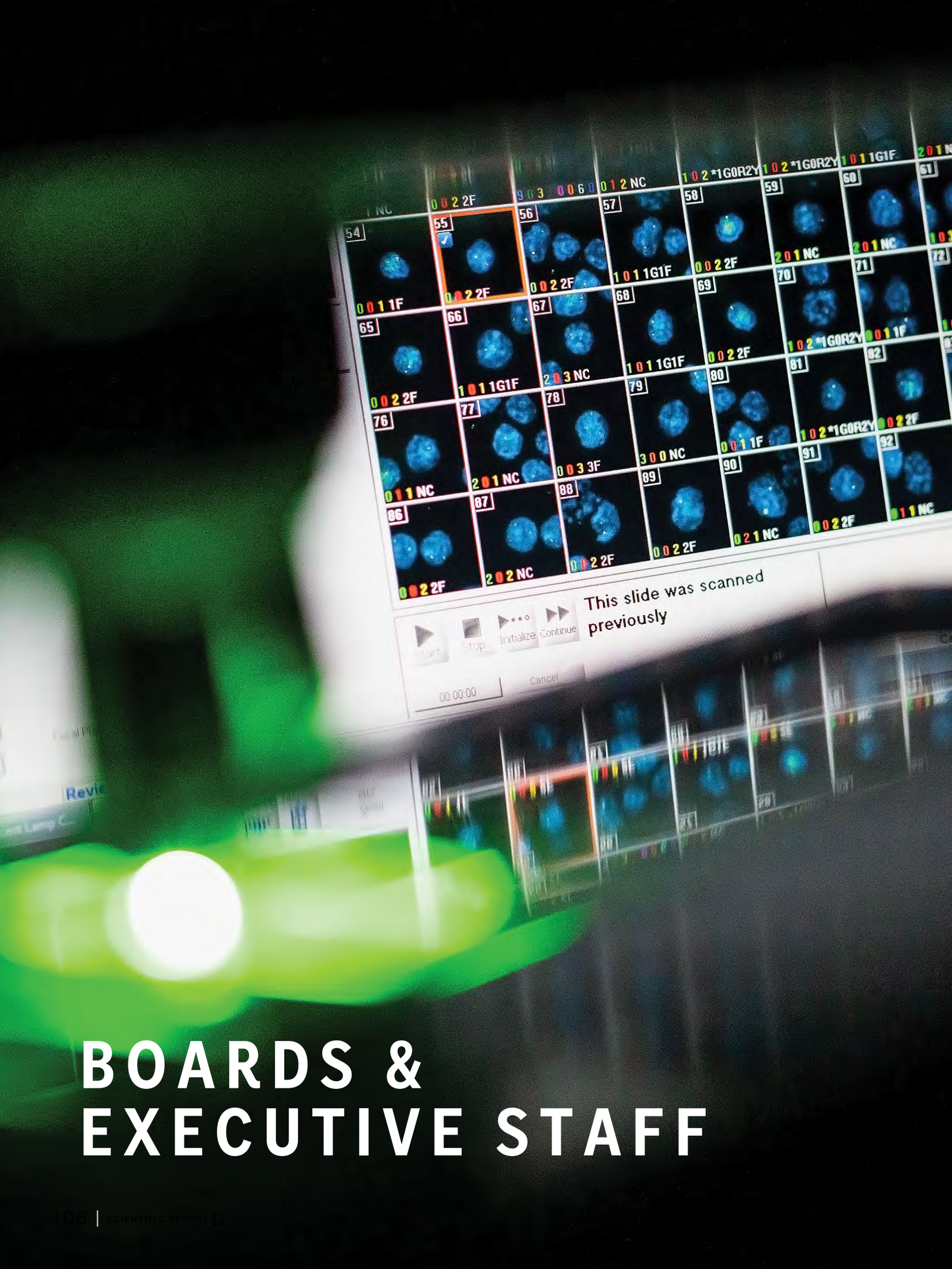
Brooke Prinzing, Bone Marrow Transplantation & Cellular Therapy
Alix Rice, Medical Content Outreach
Spencer Richardson, Immunology
Jordan Roach, Surgery[1]
Sarah Rockwell, Oncology
Aaron Ross, Surgery
Zachary Rubnitz, Infectious Diseases[1]
Emily Rundlet, Structural Biology
Sushree Sahoo, Hematology
Anjelica Saulsberry, Hematology
Hao Shi, Immunology[2]
Kenneth Shiao, Oncology[1]
Dewan Shrestha, Hematology
Geetika Singh, Structural Biology[2]
Kaitlyn Smith, Cell & Molecular Biology
Aisha Souquette, Immunology
Rachel Speltz, Clinical Nutrition
Hannah Spiegl, Surgery
William Stafford, Surgery
Wei Su, Immunology
Parker Tumlin, Radiation Oncology[1]
Erica Tsai, Diagnostic Imaging
Patricia Umberger, Cell & Molecular Biology
Elena Varotto, Oncology
Nicole Vita, Chemical Biology & Therapeutics
Xinyu von Buttlar, Oncology
Elena Varotto, Oncology
Megan Walker, Hematology
David Wallace, Oncology[1]
Miranda Wallace, Chemical Biology & Therapeutics[1]
Amber Ward, Pathology
Jason A. Weesner, Genetics
Rachael Wood, Tumor Cell Biology
Kaitly Woodard, Hematology
William Charles Wright, Chemical Biology & Therapeutics
Jinjun Wu, Cell & Molecular Biology
Zemin Yang, Cell & Molecular Biology
David Yanishevski, Surgery
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
Tony Zhuang, Oncology[1]
Chan Zou, Pharmaceutical Sciences

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




# BOARDS & EXECUTIVE STAFF

# 2019 BOARD OF GOVERNORS

**These volunteers served on the Board of Governors of St. Jude Children's Research Hospital during 2019. Officers are indicated by the titles under their names.**

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Hasan M. Elkhatib

Fred P. Gattas Jr

Sam F. Hamra

Frederick R. Harris

Theodore J. Hazer

Richard J. Karam

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Salli E. LeVan

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George M. Maloof

Paul J. Marcus

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David B. Nimer

Talat M. Othman

Manal B. Saab

Frederick W. Smith

Ronald A. Terry

Terre Thomas

Pat Kerr Tigrett

Thomas C. Wertz

Robert P. Younes, MD

Ramzi T. Younis, MD

[1] July–December, 2019 / [2] Ex officio voting member / [3] Nonelected member / [4] January–June, 2019

# 2019 EXECUTIVE COMMITTEE

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President and Chief Executive Officer

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Oncology

**SUZANNE J. BAKER, PHD**
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Co-Chair, Oncology

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Deputy Director for Academic and Biomedical Operations
Pathology

**STEPHEN M. GOTTSCHALK, MD**
Chair, Bone Marrow Transplantation & Cellular Therapy

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**GERARD C. GROSVELD, PHD**
Chair, Genetics

**MELISSA M. HUDSON, MD**
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Structural Biology

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Pediatrician-in-Chief, Le Bonheur Children's Hospital
Infectious Diseases

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Director, St. Jude Global

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Tumor Cell Biology

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Oncology

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Structural Biology

**KELVIN WOMACK**
Vice President, Diversity and Inclusion

**JINGHUI ZHANG, PHD**
Chair, Computational Biology

[1] January–October 2019 / [2] September–December 2019 / [3] No longer at St. Jude

# 2019 SCIENTIFIC ADVISORY BOARD

**This panel of physicians and scientists, serving during 2019, fostered the institution's development through discussion with faculty members, reports to the Board of Governors, and advice to the President and CEO on scientific and clinical research directions.**

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Professor and Division Chief, Hematology/Oncology
University of California Benioff Children's Hospital
University of California, San Francisco

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Perelman School of Medicine, University of Pennsylvania
Physician-in-Chief and Chair, Department of Pediatrics
The Children's Hospital of Philadelphia
Member, National Academy of Medicine

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The Skaggs Institute for Chemical Biology
The Scripps Research Institute
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UCLA Fielding School of Public Health
Professor of Medicine
UCLA David Geffen School of Medicine
Director, Cancer Prevention & Control Research
Jonsson Comprehensive Cancer Center
University of California, Los Angeles
Member, National Academy of Medicine

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Professor of Radiation Oncology
Medical Director, Princess Margaret Cancer Centre

**DAPHNE A. HAAS-KOGAN, MD**
Professor of Radiation Oncology
Harvard Medical School
Chair, Department of Radiation Oncology
Dana-Farber Cancer Institute
Member, National Academy of Medicine

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Harvard TH Chan School of Public Health
Professor, Department of Biostatistics and Computational Biology
Dana-Farber Cancer Institute

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Chancellor's Professor
Professor of Molecular Biology and Professor of Chemistry
University of California, Berkley
Member, National Academy of Medicine

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Kathleen Wellenreiter Klotz Chair in Cancer Research
James Cancer Hospital & Solove Research Institute
Professor of Surgery, Division of Surgical Oncology, College of Medicine
The Ohio State University Wexner Medical Center

**AVIV REGEV, PHD**
Investigator, Howard Hughes Medical Institute
Professor, Department of Biology
Massachusetts Institute of Technology
Core Member and Chair of the Faculty
Director, Cell Circuits Program and Klarman Cell Observatory Broad Institute

**MICHAEL K. ROSEN, PHD**
Investigator, Howard Hughes Medical Institute
Mar Nell and F. Andrew Bell Distinguished Chair in Biochemistry
University of Texas Southwestern Medical Center

**MICHEL W. SADELAIN, MD, PHD**
Stephen and Barbara Friedman Chair
Director, Center for Cell Engineering
Memorial Sloan-Kettering Cancer Center

**JOSHUA R. SANES, PHD**
Jeff C. Tarr Professor of Molecular and Cellular Biology
Paul J. Finnegan Family Director, Center for Brain Science Harvard University

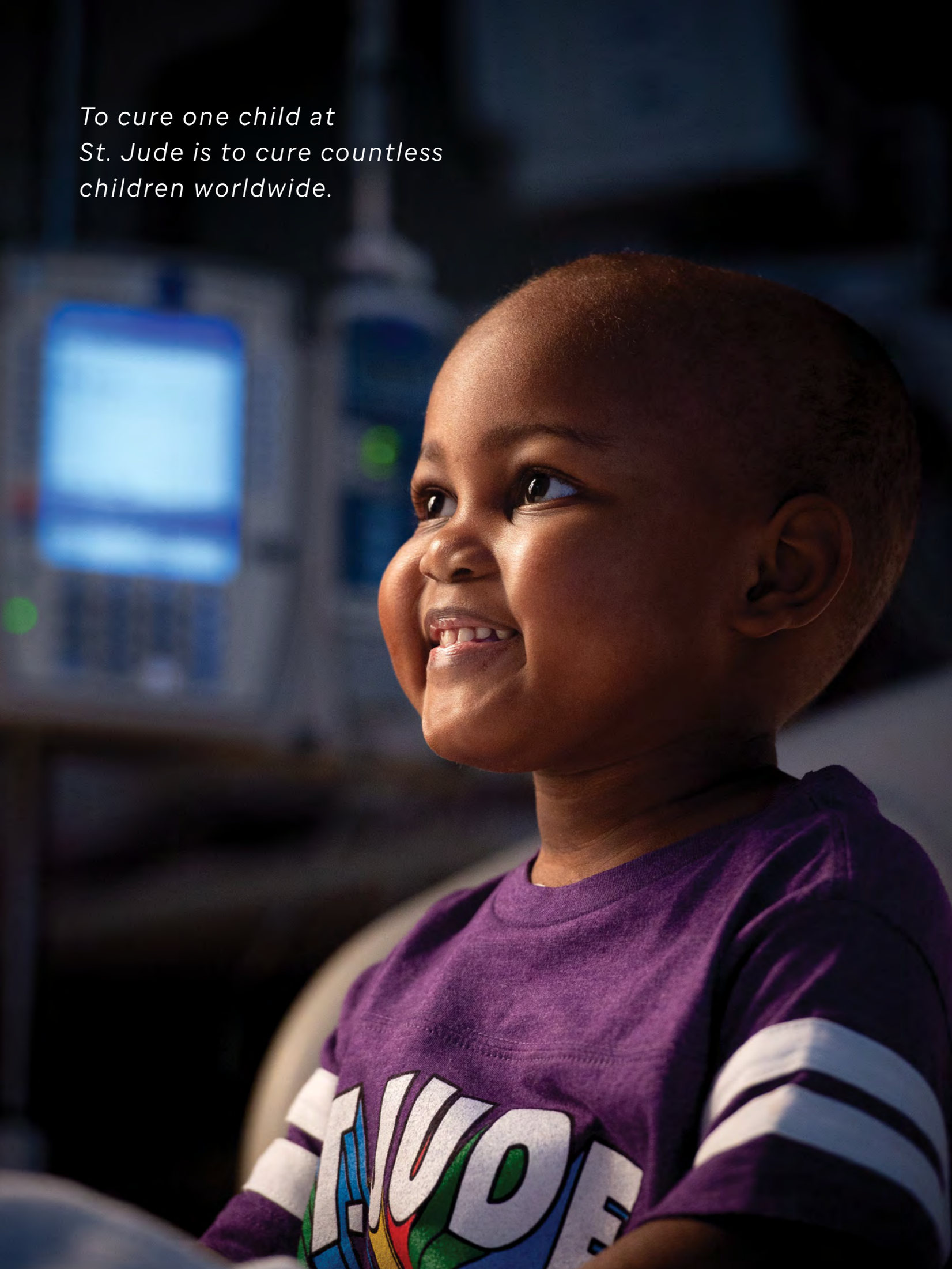
**AKIKO SHIMAMURA, MD, PHD**
Associate Professor of Pediatrics, Harvard Medical School
Samuel E. Lux IV Chair in Hematology/Oncology
Director, Bone Marrow Failure and Myelodysplastic Syndrome Programs
Dana-Farber/Boston Children's Cancer and Blood Disorders Center

**KIMBERLY STEGMAIER, MD**
Attending Physician, Pediatric Oncology, Boston Children's Hospital
Principal Investigator, Pediatric Oncology, Dana-Farber Cancer Institute
Co-Director, Pediatric Hematologic Malignancy Program
Boston Children's Hospital and Dana-Farber Cancer Institute
Ted Williams Chair, Pediatric Oncology, Dana-Farber Cancer Institute
Dana-Farber/Boston Children's Cancer and Blood Disorders Center

# OPERATIONS & STATISTICS

| | |
|---|---|
| **OPERATIONS** | |
| Operating expenses[1] | $1.014 billion |
| Number of employees[2] | 4956 |
| **RESEARCH STATISTICS** | |
| Grant funding[1] | $116.6 million |
| Peer-reviewed publications | 683 |
| Faculty members | 313 |
| Postdoctoral fellows | 318 |
| Clinical residents and fellows[3] | 224 |
| Graduate research scholars | 145 |
| **CLINICAL STATISTICS** | |
| Number of beds open[4] | 73 |
| Total outpatient visits | 262,094 |
| Inpatient admissions | 3488 |
| Total inpatient days | 19,559 |
| Total protocol enrollments in 2019 | 6376 |
| Patients enrolled in therapeutic trials | 770 |
| Patients enrolled in nontherapeutic trials | 5604<br>4371 in prospective trials<br>1233 in tissue-banking protocols |
| Total number of protocols that were open to accrual in 2019 | 588 |
| Number of active therapeutic trials | 150 |
| Number of active nontherapeutic trials | 404<br>136 prospective trials<br>265 retrospective trials<br>3 tissue-banking protocols |

[1] Data represent the period July 1, 2018 to June 30, 2019 / [2] Data are from July 1, 2019 / [3] Data include 68 full-time St. Jude fellows and 156 rotating fellows from the University of Tennessee Health Science Center or other medical schools / [4] 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.*

St. Jude Children's Research Hospital®

Finding cures. Saving children.

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Memphis, TN 38105

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