St. Jude Children's Research Hospital®

Finding cures. Saving children.

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Scientific Report 2018

St. Jude Children's Research Hospital

Translating Science into Survival

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Behind the Cover

The scientific image on the cover is a fluorescence image of pyramidal neurons in the auditory cortex. The brain can modify the structure and function of neuronal connections in response to sensory experiences. This ability is known as neuroplasticity. Stanislav S. Zakharenko, MD, PhD (Developmental Neurobiology), and his colleagues are investigating the role of neuroplasticity in the auditory cortex during learning and how dysfunction in that part of the brain can cause catastrophic neurologic or psychiatric diseases.

ST. JUDE INVESTIGATORS, BACKED BY EXTRAORDINARY RESOURCES AND SUPPORT TEAMS, HAVE THE FREEDOM TO FOCUS ON MAKING BIG DISCOVERIES. OUR CULTURE AND CAMPUS FOSTER THE FREE EXCHANGE OF IDEAS AMONG SCIENTISTS AND CLINICIANS TO PROMOTE CREATIVE, COLLABORATIVE SCIENCE.

TRANSLATING SCIENCE INTO SURVIVAL

James R. Downing, MD
President and Chief Executive Officer

In the early 1960s, the first medical director of St. Jude Children's Research Hospital employed a unique sales pitch to lure talent to the fledgling hospital. "Here, you have the opportunity to make your own center. It's unplowed ground. If you come here, you're an innovator," Donald Pinkel, MD, promised recruits. Within a decade, those words proved true as the hospital showed the world that childhood cancer—once deemed incurable—could, in fact, be successfully treated. In the years that followed, survival rates for childhood cancer have risen to more than 80%. St. Jude also has made a lifesaving difference for young people with other catastrophic illnesses, such as sickle cell disease or bleeding disorders.

In this *Scientific Report*, we detail some of our latest innovations. In the first feature, we celebrate the opening of the St. Jude Children's Research Hospital Graduate School of Biomedical Sciences, LLC. This historic event marks a new era of higher education at St. Jude. The second article describes the recent creation of the Childhood Solid Tumor Network, a resource that freely provides well-characterized solid tumor samples to researchers worldwide. This network holds the promise of expanding knowledge about these rare diseases and expediting the development of more effective treatments and cures.

The third story presents a new approach to calculating the cumulative burden of surviving childhood cancer. Using new statistical methods, epidemiology researchers are assessing the chronic medical conditions that arise in this vulnerable population. They are also applying this approach globally to determine the true cost of treating pediatric cancers in low- and middle-income countries, where officials often assume pediatric oncology care is economically out of reach. The fourth feature highlights exciting discoveries in neuroplasticity and neural circuit research. Stanislav Zakharenko, MD, PhD, Developmental Neurobiology, and his colleagues are studying the mechanisms underlying age-related changes in auditory learning and severe mental illness. This work is advancing our knowledge and identifying novel therapeutic targets for patients with brain injury such as stroke or diseases like schizophrenia.

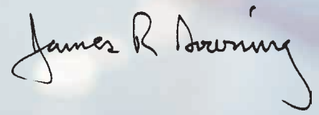
Beyond the work outlined herein, St. Jude established the Center for Advanced Genome Engineering, a shared resource for basic research, gene therapy, and cellular therapy programs. The hospital also welcomed two new department chairs: Stephen Gottschalk, MD, Bone Marrow Transplantation & Cellular Therapy; and Charalampos "Babis" Kalodimos, PhD, Structural Biology. These scientists are leading exciting initiatives in their respective areas and helping us to better understand life and disease.

Through the St. Jude Research Collaborative, the institution is funding two new projects—exploring gene therapy and gene editing to cure sickle cell disease and understanding the epigenetic regulation of pediatric cancer. These collaborations involve investigators at St. Jude, Harvard Medical School, Dana-Farber Cancer Institute, and Rockefeller University.

Last year, St. Jude also expanded its footprint on campus and around the globe. We opened a new data center to consolidate the hospital's advanced computing infrastructure and support resources, began planning a 625,000-square foot advanced research center, and took steps to broaden the institution's reach for children with cancer in low- and middle-income countries.

For its efforts, St. Jude was ranked the No. 1 pediatric cancer hospital in the nation by *U.S. News & World Report*. In addition, the hospital received several top workplace recognitions, including *Fortune* magazine's "100 Best Companies to Work For," Glassdoor's "Best Places to Work," and *People* magazine's "50 Companies That Care." Faculty and staff were recognized with scores of accolades, including the National Cancer Institute Outstanding Investigator Award and the Society of Memorial Sloan Kettering Prize. Fittingly, Dr. Pinkel was also inducted into the Tennessee Health Care Hall of Fame.

Although we have made great strides, we still have much ground to cover. There is an urgency to our work, as we seek to cultivate untapped potential and opportunities in science and medicine. We remain committed to pursuing the paths to discovery and innovation to ensure that children everywhere have the best hope for the future.



USHERING IN A NEW ERA OF EDUCATION AT ST. JUDE

Since its founding, the mission of St. Jude Children's Research Hospital has been to advance cures and means of prevention of pediatric catastrophic diseases. This cannot be achieved without the dedicated work of researchers who continuously push against the barriers of what we know and what we can do. St. Jude recognizes its obligation is not only to tackle these diseases now but also to train the next generation of scientists who will continue to fight to develop new cures for children with life-threatening illnesses.

Alex Hughes

In 2015, the state of Tennessee granted St. Jude a charter to establish the St. Jude Children's Research Hospital Graduate School of Biomedical Sciences, LLC, and become a PhD-granting academic institution. This created opportunities for some of the brightest and most motivated students in the country to come to St. Jude at the earliest stages of their scientific careers and join this fight. Here, we share the story of this historic achievement and what it means for the future of our institution.

James I. Morgan, PhD; James R. Downing, MD; Stephen W. White, DPhil

ST. JUDE BECOMES A DEGREE-GRANTING INSTITUTION

Since shortly after its inception, St. Jude began accepting graduate students and fellows from other institutions to perform or supplement the research portion of their training in St. Jude laboratories. The hospital quickly became a desired destination for many graduate students in the biological sciences.

Senior leaders recognized the unmet need for graduate educational opportunities and contemplated expanding our academic programs. The group studied many options and concluded that St. Jude would have the greatest impact on developing scientists by establishing its own independent, top-tier graduate school. Working with Camille F. Sarrouf Sr, a long-standing member of the St. Jude Board of Governors, they worked to realize this concept. A graduate program would increase the visibility of St. Jude's research programs and draw to St. Jude laboratories top students from the U.S. and, ultimately, around the world. Most importantly, a St. Jude graduate program could imprint on students at the earliest stage of their careers the integrated approach to discovery and clinical application that characterizes St. Jude science.

These new scientists could carry St. Jude's unique emphasis on translating basic knowledge into cures for childhood diseases to laboratories and institutions around the world. Once enrollment reaches its planned steady state, the graduate school will provide graduate education to approximately 60 Doctorate of Philosophy (PhD) students at any one time.

Stephen W. White, DPhil; Caitlin C. Zebley, MD

OBTAINING A CHARTER FROM THE TENNESSEE HIGHER EDUCATION COMMISSION

The Tennessee Higher Education Commission (THEC) develops, implements, and evaluates postsecondary education programs in the state. It reviews and approves new academic programs and authorizes institutional operations. Stephen W. White, DPhil (Structural Biology and future Dean of the graduate school), and McGehee Marsh, JD, PhD (Legal Services), were tasked with designing the graduate school and developing the THEC application, with support from Dayna Baker (Structural Biology and future Coordinator of Graduate School Operations).

Once the application was approved, intensive efforts were undertaken to ensure that the school would be ready to welcome its first class in Fall 2017. Brian Walton, MBA (Associate Dean), J. Racquel Collins, PhD, MBA (Assistant Dean), and Tiffany Young-Polk, MA (Registrar), joined the graduate school staff. The Board of Trustees and External Advisory Board were also formed.

J. Racquel Collins, PhD, MBA; Brian Walton, MBA; Dayna Baker; Stephen W. White, DPhil

WHAT MAKES THE ST. JUDE GRADUATE SCHOOL EXPERIENCE UNIQUE?

The St. Jude Children's Research Hospital Graduate School of Biomedical Sciences, LLC, is designed to provide independent, self-directed students with the tools they need to complete a PhD degree within 5 years. It is open to trainees at different stages of their careers, including medical students receiving MD/PhD training, St. Jude clinical fellows, and others with advanced degrees who choose to pursue additional PhD training. Because the program is internally funded, students can concentrate exclusively on their development as researchers, without extraneous obligations.

During their first year, students complete all required coursework, three 6-week laboratory rotations, and introductory training in 15 core facilities offering diverse instruction on research methods and instrumentation. At the end of Year 1, the students select a laboratory in which to conduct their thesis research. During Years 2 through 5, students may take elective courses, but their primary focus is on their thesis research. Although St. Jude is best recognized for its programs in pediatric cancer, graduate research is available in many fields within biomedicine, including cell and molecular biology, developmental biology, structural biology, neurosciences, chemical biology, immunology, infectious diseases, and new emerging fields such as RNA biology, genomics and epigenomics, computational biology, and genome engineering.

At the end of their second year, all students are required to pass an admission to candidacy examination, which involves writing a grant application that will be submitted to an appropriate funding agency. Successful candidates will be awarded transitional Masters in Science (MSc) degrees. To complete a PhD degree, students will be expected to write a dissertation, pass an oral defense examination, and publish at least two peer-reviewed manuscripts based on their thesis research.

The graduate school includes approximately 75 basic science faculty members and 35 clinical faculty members committed to teaching and mentoring students. Most of the basic science members also hold adjunct faculty positions at the University of Tennessee Health Science Center and are experienced in mentoring graduate students. Suzanne J. Baker, PhD (Developmental Neurobiology), led the design of the school's modern and innovative basic science curriculum. Fundamental concepts are taught through current research in various biomedical fields. This is complemented by in-depth analysis of current scientific literature and independent learning. The program is crafted to develop the skills required for a student to transition into an independent scientist capable of analyzing complex problems, developing approaches to resolve those problems, mastering the technical requirements of modern science, and engaging with scientific peers productively and collaboratively.

The program also has a unique translational research curriculum, which was developed by Michael A. Dyer, PhD (Developmental Neurobiology), Alberto S. Pappo, MD (Oncology), and Elizabeth A. Stewart, MD (Oncology). Translational research bridges the gap between laboratory discoveries and the application of those discoveries in the clinical setting. This curriculum provides students with an understanding of the integration of the key steps required to move basic science discoveries into clinical trials and, ultimately, new therapeutics. Each student completes six clinical/translational research segments. Each segment consists of an experiential component, in which the students interact with patients and their medical teams, and a conceptual component, in which they learn the scientific and clinical basis of therapeutic approaches. Students are included in the medical team's recurring discussions about patients' diseases, treatment regimens, complications, setbacks, and successes. The link between scientific research and its clinical applications is fundamental to the St. Jude training program. It provides students with an understanding of the perspectives of clinicians and the know-how to effectively engage them. By mastering the complete pathway of research translation from bench to bedside and bedside to bench, students will be able to design the most clinically effective research in their areas of specialization.

To prepare students to be successful, independent primary investigators, they will receive additional training in essential skills, including responsible conduct of research, scientific writing and publication, public speaking, grantsmanship, and scientific management. The graduate school works with the Life Science Tennessee Academic Alliance (Nashville, TN), a nonprofit organization that brings together graduate students and postdoctoral fellows with leaders from the state's top life sciences companies and organizations to promote networking and an understanding of the life sciences industry. This enables the students to learn how to optimally engage with the biopharmaceutical industry and better understand entrepreneurship, research in industry settings, and patents and technology licensing.

Madeline Bush; Elizabeth A. Stewart, MD

RECRUITING THE STUDENT BODY

Richard W. Kriwacki, PhD (Structural Biology), developed the student-recruitment plan and served as the first chair of the Admissions Committee. A national advertising campaign was developed, and Carole Weaver, PhD (Communications), and Leigh Tanner (Information Services) led efforts to develop the graduate school's website. To showcase opportunities at St. Jude, the graduate school staff also developed and hosted the first National Undergraduate Research Symposium. This annual symposium continues to bring more than 40 top undergraduate students interested in advanced biomedical science to the St. Jude campus for 2 days of oral presentations, poster sessions, and one-on-one meetings with faculty.

These and other outreach efforts resulted in the receipt of more than 100 applications, a remarkable number for a new PhD program. After a competitive selection process, 12 applicants matriculated from colleges and universities across the United States.

Matthew Bell, Alex Hughes, Brennan Bergeron, Allison Kirk

Steven J. Bares, PhD, MBA; James E. K. Hildreth, MD, PhD; James R. Downing, MD; James I. Morgan, PhD; David Mark Brown; Allison Kirk

DOORS OPEN IN AUGUST 2017

On August 4, 2017, the St. Jude Children's Research Hospital Graduate School of Biomedical Sciences, LLC, officially opened with a convocation, and the inaugural class was welcomed by Dr. James R. Downing (President & Chief Executive Officer of St. Jude), Dr. White, the faculty, the Graduate School Board of Trustees, and local dignitaries.

The faculty were charged with the mission of the graduate school—to educate and train future generations of scientists seeking to understand the molecular basis of human disease and develop novel therapies based on that understanding. The students were charged with embracing the graduate school's vision—to choose an individualized path to success and leadership in scientific discovery through pioneering translational research.

THE ROAD FORWARD

Although the graduate school is not eligible to receive accreditation by the Southern Association of Colleges and Schools Commission on Colleges until the first PhD degree has been awarded, the school is not on hold. It continues to develop and grow based on its experiences and the vision of its faculty and leadership. The graduate school is now expanding by developing an MSc Program in Global Pediatric Health. This program will be affiliated with the St. Jude Department of Global Pediatric Medicine and provide specialized training to medical scientists dedicated to advancing the care of children with catastrophic diseases throughout the world.

Evadnie Rampersaud, PhD

DEVELOPMENT OF A MASTERS OF SCIENCE PROGRAM IN GLOBAL PEDIATRIC HEALTH

The graduate school has begun preparatory work to offer an MSc Program in Global Pediatric Health. The curriculum is currently in development. A search is underway to hire a Director of Education and Assistant (or Associate) Dean for Global Education in the graduate school, an expert in education and distance learning who will also hold a faculty position in the Department of Global Pediatric Medicine.

We anticipate that this 2-year program will enroll 10 new students per year from the U.S. and overseas. Students will visit the St. Jude campus to observe operations and meet with faculty during a 4- to 6-week session each summer and a 2-week session each winter. Between campus visits, students will complete coursework and training via distance learning online during the fall and spring terms. Each student will be assigned a mentor from the Global Pediatric Health Program's faculty. The inaugural MSc in Global Pediatric Health class is anticipated to be recruited in early 2019, with classes beginning in Summer 2019.

GOVERNANCE OF THE GRADUATE SCHOOL

BOARD OF TRUSTEES

The Board of Trustees provides oversight to the graduate school and shapes the school's plans, policies, and budget priorities.

Camille F. Sarrouf Sr, Chair
Steven J. Bares, PhD, MBA
James E.K. Hildreth, MD, PhD
James I. Morgan, PhD
William E. Troutt, PhD
Stephen W. White, DPhil

EXTERNAL ADVISORY BOARD

Four distinguished scientists and experienced administrators of graduate education programs in the biomedical sciences constitute the External Advisory Board. These individuals support the strategic development of the graduate school through reports to the Board of Trustees and advice to the Dean, Graduate Council, faculty, and staff.

Mark S. Anderson, MD, PhD
Director, Medical Scientist Training Program
Professor of Medicine
Robert B. Friend and Michelle M. Friend Endowed Chair in Diabetes Research
University of California, San Francisco

Margaret H. Baron, MD, PhD
Senior Associate Dean for Education
Director, MD/PhD Program
Fishberg Professor of Medicine
Icahn School of Medicine at Mount Sinai

R. Scott Hawley, PhD
Dean, The Graduate School of the Stowers Institute
Professor of Molecular and Integrative Physiology
School of Medicine, University of Kansas

Leemor Joshua-Tor, PhD
Howard Hughes Medical Institute Investigator
Former Dean, Watson School of Biological Sciences
Cold Spring Harbor Laboratory

GRADUATE COUNCIL

The Graduate Council approves changes to policies, programs, and curriculum and assists with applications, enrollment, academic progress, and decisions related to the awarding of degrees.

Stephen W. White, DPhil, Chair
Dean of the Graduate School
Structural Biology

Dayna Baker[1]
Coordinator of Graduate School Operations

Suzanne J. Baker, PhD
Chair, Basic Science Curriculum Development Committee
Developmental Neurobiology

James R. Downing, MD
President & Chief Executive Officer of St. Jude

Michael A. Dyer, PhD
Chair, Translational Curriculum Development Committee
Chair, Developmental Neurobiology

Stephen M. Gottschalk, MD
Chair, Bone Marrow Transplantation & Cellular Therapy

Richard W. Kriwacki, PhD
Member, Admissions Committee
Structural Biology

McGehee Marsh, JD, PhD[1]
Senior Counsel, Legal Services

James I. Morgan, PhD
Executive Vice President of St. Jude
Scientific Director of St. Jude

P. Ryan Potts, PhD
Cell & Molecular Biology

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

Paul G. Thomas, PhD
Chair, Admissions Committee
Immunology

Brian Walton, MBA[1]
Senior Vice President of the Graduate School
Associate Dean of the Graduate School

[1]Nonvoting member

CONCLUSION

The opening of the St. Jude Children's Research Hospital Graduate School of Biomedical Sciences, LLC, has ushered in a new era of higher education and increased focus on collaborative, translational research. By educating and training future generations of scientists devoted to discovery in human disease, the graduate school will ensure the continuity and spread of St. Jude's mission—to advance cures, and means of prevention, for pediatric catastrophic diseases through research and treatment—via the many scientists who distinguish themselves through their training here.

Mackenzie Bloom

ST. JUDE CREATES AN INTERNATIONAL RESOURCE FOR PEDIATRIC SOLID TUMOR RESEARCH AND TREATMENT

Solid tumors encompass several types of cancers that arise in the bone, muscle, kidney, or any number of organs. As solid tumors arise during development, they are more common in children and adolescents than in adults. Treatment is multimodal, including chemotherapy, radiation therapy, and surgery. Overall survival for children with newly diagnosed solid tumors is about 75%, but for those with recurrent disease, it is less than 30%. There has been little improvement in outcome for patients with recurrent solid tumors over the past 20 years.

Alberto S. Pappo, MD

At St. Jude, researchers are focused on gaining a deeper understanding of the pathobiology of recurrent solid tumors to find new ways to prevent or more effectively treat relapsed or refractory disease. To achieve this goal, they are studying the clonal evolution of tumors (i.e., the genetic and epigenetic changes that occur in an individual cell and enhance its ability to survive and proliferate) and other biologic changes that occur during relapse to identify vulnerabilities that can be exploited through new therapeutic approaches. To support its goal of understanding and eradicating solid tumors, St. Jude established the Childhood Solid Tumor Network (CSTN), a publicly available resource to accelerate biomedical research on childhood solid malignancies.

FORESEEING A GROWING NEED FOR PRECLINICAL MODELS OF CHILDHOOD SOLID TUMORS

In 2010, at the the start of the St. Jude Children's Research Hospital–Washington University Pediatric Cancer Genome Project (PCGP), Michael A. Dyer, PhD (Developmental Neurobiology), and Alberto S. Pappo, MD (Oncology), launched an effort to systematically develop orthotopic patient-derived xenografts (O-PDXs) of pediatric solid tumors. An orthotopic xenograft is generated by transplanting donor tissue from one species (e.g., human cancer) into comparable tissues of another species (e.g., an immunocompromised mouse). Drs. Dyer and Pappo realized that as new cancer-related genetic lesions were discovered through the efforts of the PCGP, researchers would need laboratory models, including O-PDXs, to study the functions of those mutations.

Sara M. Federico, MD (Oncology), led the development of a biologic, nontherapeutic clinical protocol to obtain primary human solid tumor samples to create O-PDX models. Her *Molecular Analysis of Solid Tumors* (MAST) protocol (NCT01050296) was approved by the St. Jude Institutional Review Board in 2010 and remains open to accrual. The MAST protocol offers patients and their families the opportunity to donate to this effort surplus solid tumor tissue obtained during medically warranted surgical procedures. More than 400 patients have consented to participate in the MAST protocol to date, and more than 100 tumors, representing a dozen types of childhood solid tumors, have been grown, characterized, and banked for research.

As the pool of solid tumor O-PDX specimens expanded, Drs. Dyer and Pappo established the CSTN. In a 2016 article in *Developmental Biology*, Elizabeth A. Stewart, MD (Oncology), Drs. Dyer and Pappo, and colleagues publicized this new resource. In addition to the O-PDXs, the CSTN offers comprehensive genomic and molecular data, cell lines, and genetically engineered mouse models of the diseases represented. These materials are shared freely with the developmental biology and oncology research communities, with no obligation to collaborate.

In addition to providing essential laboratory models to study the genetic and epigenetic landscapes of pediatric solid tumors, the CSTN has been central to the rapid translation of basic science discoveries to the clinic. Some of the first scientific achievements at St. Jude made possible by the CSTN are described here.

Sara M. Federico, MD

Sara M. Federico, MD; Elizabeth A. Stewart, MD

HASTENING ADVANCES IN THE CLINICAL TREATMENT OF SOLID TUMORS THROUGH A PRECLINICAL TRIAL PARADIGM

In 2014, Dr. Stewart and colleagues described in *Cell Reports* a preclinical Phase I, II, III paradigm that closely mimics comparable trials in the clinic. In preclinical Phase I trials, clinically relevant chemotherapy doses and scheduling are administered to a small number of mice carrying O-PDXs to test the animals' ability to tolerate the treatment. In preclinical Phase II trials, small groups of mice are randomized and receive different treatment combinations to identify the combination(s) with the greatest potential for benefit. In preclinical Phase III trials, mice with O-PDXs are treated in a blinded, randomized, placebo-controlled manner designed to yield a definitive determination of effectiveness.

The investigators tested new treatments for Ewing sarcoma, a bone cancer that arises in approximately 250 pediatric patients per year in the United States. Ewing sarcoma cells have defective DNA damage–repair mechanisms. Therefore, chemotherapies that break DNA strands, such as irinotecan and temozolomide, are useful for treating this disease. Ewing sarcoma cell lines are also selectively sensitive to poly-ADP ribose polymerase inhibitors ($PARP_i$s), which cause cytotoxicity and cell death. Dr. Stewart and colleagues showed that the combination of these three drugs enhances cytotoxicity and the killing of Ewing sarcoma cells.

This treatment paradigm is now the standard in the field. Dr. Stewart's preclinical studies have led to three new clinical trials for patients with solid tumors (NCT02095132, NCT02392793, and NCT01858168), including recent efforts to translate the successful use of $PARP_i$s in O-PDX models into treatment protocols for patients with recurrent Ewing sarcoma. Dr. Federico is the principal investigator of the *Talazoparib plus Irinotecan with or without Temozolomide in Children with Refractory or Recurrent Solid Malignancies* (BMNIRN) clinical trial (NCT02392793), which has shown early promise in this patient population and has increased our understanding of the underlying biology of these recurrent tumors.

The CSTN shares drug sensitivity data, pharmacokinetic data, and preclinical testing data with pediatric solid tumor investigators around the world. This is consistent with its underlying philosophy that essential assets and information that can be used to develop new lifesaving treatments should be made as easily accessible to researchers as possible. As of February 2018, the CSTN has handled 424 requests for 957 samples from 172 investigators at 82 institutions located in 14 different countries. Every 6 months, 10 to 20 new solid tumors are added to the CSTN, with associated characterization data, including whole-genome sequencing, clonal analysis, histologic analysis, RNA sequencing, and for some tumors, drug sensitivity data.

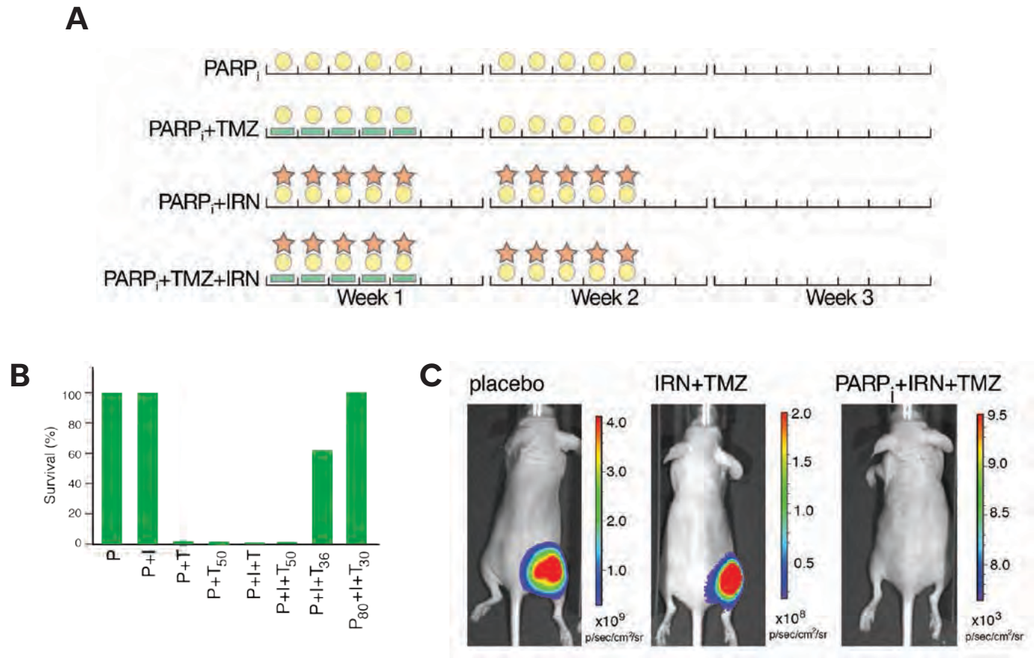


Figure. (**A**) Drug-combination schedules for mice in a Phase I/II preclinical trial. Yellow circles indicate $PARP_i$ treatment; green bars indicate temozolomide (TMZ); and red stars indicate irinotecan (IRN). (**B**) Survival of mice that received the $PARP_i$ BMN-673 (P) alone or in combination with irinotecan (I) and/or a high- or low-dose temozolomide (T) in a Phase I preclinical trial. In some groups, the TMZ dose (0.125 mg/kg) was reduced by 50% (T_{50}), 64%(T_{36}), or 70% (T_{30}). In one group, the dose of BMN-673 was reduced by 20% (P_{80}). (**C**) Xenogen imaging of mice from the three treatment groups in (**B**). *Reprinted from Cell Reports, 9, Stewart E et al, Targeting the DNA repair pathway in Ewing sarcoma, 829–40, © 2017, with permission from Elsevier.*

Matthew Lear

ST. JUDE BIOREPOSITORY BECOMES THE SECOND CAP-ACCREDITED PEDIATRIC FACILITY IN THE UNITED STATES

The St. Jude Biorepository provides sample processing, biobanking, and distribution services for all St. Jude patients and more than 100 clinical trials. This facility is responsible for collecting and distributing fresh tumor samples for xenografting by the MAST protocol. Under the direction of Charles G. Mullighan, MBBS(Hons), MSc, MD (Pathology), and Matthew Lear, technical director, nine staff members manage this core facility. The College of American Pathologists (CAP) granted accreditation to the St. Jude Biorepository in 2012.

The Biorepository staff collects, stores, and distributes human tissue samples for use in research aimed at increasing our knowledge of disease pathobiology and developing novel therapies for catastrophic childhood diseases. The Biorepository has been a highly used resource at St. Jude for over 30 years. With more than 300,000 tissue samples in its inventory and approximately 23,000 samples released in the past 5 years, the Biorepository has helped researchers substantially expand their understanding of the biologic basis of catastrophic childhood diseases and find more effective treatments for them.

Rosa Nguyen, MD; Michael A. Dyer, PhD

IMPROVING IMMUNOTHERAPY FOR PATIENTS WITH NEUROBLASTOMA

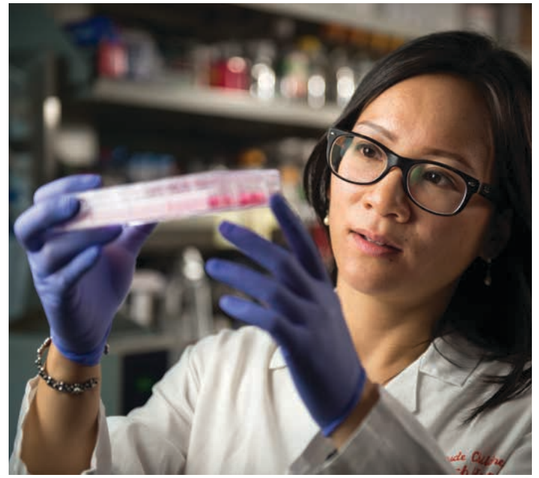
Neuroblastoma arises from primitive peripheral nerve cells (or neuroblasts) during development, accounts for up to 10% of all childhood tumors, and is the most common cancer in infants. Nearly 800 new cases of neuroblastoma are diagnosed annually in the United States. About 70% of children with neuroblastoma have metastatic disease at diagnosis, and despite the use of contemporary multimodal therapy (i.e., chemotherapy, immunotherapy, and differentiation therapy), only about half of those patients are cured.

The addition of immunotherapy to the pediatric neuroblastoma treatment regimen in 2010 increased the 2-year event-free survival by 20% and has since become the standard of care. Immunotherapy involves using immune cells, immune cell products such as cytokines, or a combination thereof to selectively kill tumor cells. Unlike most normal cells, neuroblastoma cells overexpress the disialoganglioside GD2 on their cell surface. At St. Jude, immunotherapy for neuroblastoma incorporates a monoclonal anti-GD2 antibody, hu14.18K322A, manufactured in the St. Jude Children's GMP, LLC; the cytokine interleukin 2 (IL-2), which enhances natural killer (NK) cell activity against tumor cells; and granulocyte-macrophage colony-stimulating factor. Although immunotherapy shows significant clinical benefit, a major drawback of this approach is its toxicity.

Various strategies have been used in the clinic to improve antibody-dependent cell-mediated cytotoxicity (ADCC), but the cellular mechanisms of intervention-augmented ADCC in neuroblastoma are not fully understood. Rosa Nguyen, MD, a clinical fellow in the St. Jude Physician–Scientist Training Program, is working on this problem in Dr. Dyer's laboratory. She and her colleagues reported in *Cancer Immunology, Immunotherapy* the development of a new ex vivo assay to test ADCC by using nine neuroblastoma cell lines and two O-PDXs from the CSTN. The researchers delineated the roles of IL-2, NK-cell receptors, and retinoid-induced differentiation of tumor cells during ADCC. They found that IL-2 is a key component of immunotherapy; it enhances the cytolytic function of NK cells against neuroblastoma targets. Subpopulations of NK cells may also have different levels of antitumor activity that depend on properties such as their activation status, killer cell immunoglobulin–like receptor (KIR) expression, and KIR–KIR ligand interaction. Optimizing the use of NK-cell therapy in association with an anti-GD2 antibody is important for improving outcomes for patients with high-risk neuroblastoma and for reducing the side effects of treatment.

Personalized medicine can also help optimize immunotherapy and minimize its adverse effects. The team used their new ex vivo assay to test ADCC in two neuroblastoma O-PDXs from the CSTN, which were maintained in culture with NK cells from the respective donors. In both cases, ADCC was induced by the anti-GD2 antibody. In the absence of the antibody, with or without IL-2 stimulation of NK-cell activity, the neuroblastoma O-PDX cells showed less NK cell–mediated cytotoxicity.

Dr. Nguyen and colleagues further observed that differentiation therapy with all-*trans* retinoic acid stabilized GD2 expression on neuroblastoma cells, thereby enhancing ADCC. Cancer cells are primitive cells in which the maturation process has been halted and growth is uncontrolled. Differentiation therapy with agents such as all-*trans* retinoic acid stimulates those cells to resume their differentiation into mature cells. Although this approach does not kill tumor cells, it slows their growth, which increases their susceptibility to conventional chemotherapy. All-*trans* retinoic acid has a favorable toxicity profile compared with those of many other agents used for anticancer treatment modalities and is well tolerated by most patients. Collectively, these preclinical results shed light on the mechanisms of ADCC and point to several potential strategies that warrant further preclinical validation in vivo before translation into clinical trials to improve immunotherapy for high-risk neuroblastoma.



Rosa Nguyen, MD

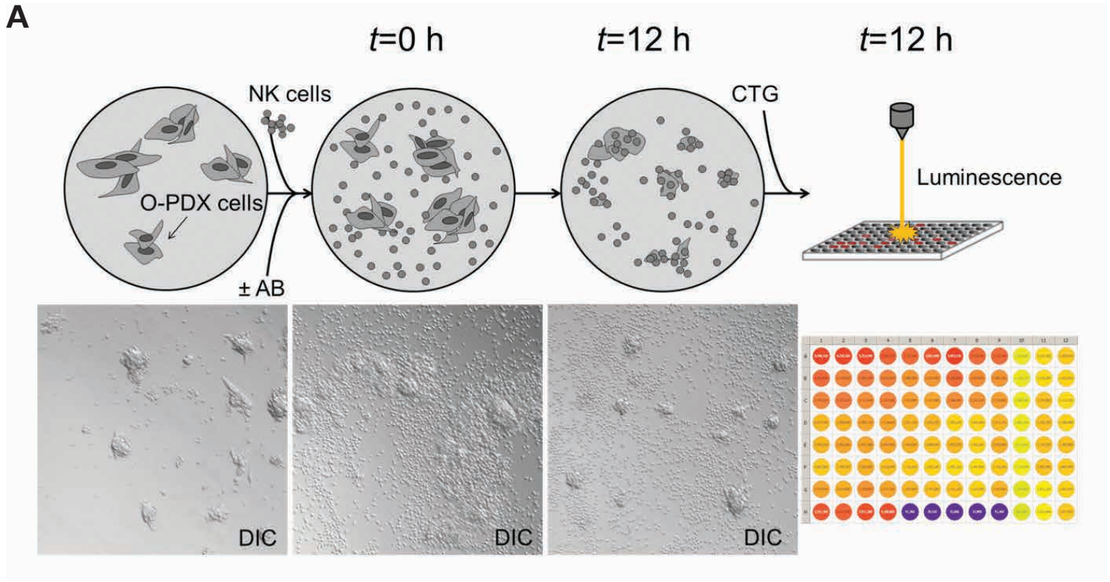


Figure. (**A**) Scheme of a newly developed assay to measure natural killer (NK) cell–mediated cytotoxicity and antibody-dependent cell-mediated cytotoxity (ADCC) in O-PDXs. Dissociated tumor cells from the O-PDXs are maintained in culture. NK cells are then added with or without antibody (±AB), and the cells are incubated for 12 h. The CellTiter-Glo (CTG) luminescent cell viability assay is then used to quantify ADCC. (**B**) Representative ADCC assay results from two PDXs, SJNBL108_X and SJNBL013761_X1, maintained in culture with matched NK cells (NK) and treated with or without antibody (AB) and interleukin-2 (IL-2). ADCC assay results are plotted as relative light units (RLU). *Reprinted by permission from Springer, Cancer Immunology, Immunotherapy, 67, Nguyen R et al, The role of interleukin-2, all-*trans *retinoic acid, and natural killer cells: surveillance mechanisms in anti-GD2 antibody therapy in neuroblastoma. © 2018*

Wayne L. Furman, MD

PILOTING ANTI-GD2 CLINICAL TREATMENT FOR NEUROBLASTOMA

Despite dose-intensive treatment, fewer than half of the patients with high-risk neuroblastoma survive, and those who experience disease recurrence or progression during therapy often die of the disease. In recent years, the introduction of an anti-GD2 monoclonal antibody in the setting of minimal residual disease (i.e., when a small number of neuroblastoma cells remain in the patient during or after treatment) to induce ADCC has improved the 2-year event-free survival of children with high-risk neuroblastoma from 46% to 66%. Preclinical studies in neuroblastoma cell lines and clinical studies of adult cancers have demonstrated an enhanced effect when chemotherapy is combined with monoclonal antibodies.

On the basis of this information, Dr. Federico and colleagues conducted a first-of-its-kind pilot trial, *Combination Chemotherapy, Monoclonal Antibody, and Natural Killer Cells in Treating Young Patients with Recurrent or Refractory Neuroblastoma* (GD2NK), that combined a fixed dose of the humanized anti-GD2 antibody hu14.18K322A with chemotherapy, cytokines (i.e., IL-2), and haploidentical (partial genetic match) NK cells from parent donors to treat recurrent or refractory neuroblastoma.

In *Clinical Cancer Research*, the team reported results from 13 patients (median age at diagnosis, 6.4 years; range, 1.9–13.4 years) who received as many as six courses of immunotherapy. The overall response rate in this cohort was 61.5%, and five (38.5%) patients showed a complete response. Historically, patients with recurrent neuroblastoma have shown no more than a 50% overall response to the chemotherapy regimen used in this study. Adding concurrent immunotherapy resulted in a clinically significant improvement.

Dr. Federico and colleagues demonstrated that combination therapy comprising hu14.18K322A, chemotherapy, cytokines, and NK cells is feasible; has promising antitumor activity; and should be further studied in patients with newly diagnosed or relapsed neuroblastoma. Furthermore, this study provided the rationale for including hu14.18K322A and cytokines in the induction chemotherapy phase of treatment for patients with newly diagnosed high-risk neuroblastoma enrolled in the *Therapy for Children with Advanced Stage High-Risk Neuroblastoma* (NB2012) protocol.

Wayne L. Furman, MD (Oncology), is the principal investigator of the NB2012 study, which has enrolled 42 patients to date. Preliminary results from that trial, evaluating an early response time point, demonstrated a near doubling of the tumor response from 40% in historic controls who received chemotherapy alone to 76.2% in those receiving the combination of chemotherapy, hu14.18K322A, and cytokines.

Alberto S. Pappo, MD; Elizabeth A. Stewart, MD; Michael A. Dyer, PhD

USING O-PDX MODELS TO CAPTURE THE COMPLEXITY AND DIVERSITY OF SOLID TUMOR RECURRENCE

As mentioned earlier, when a solid tumor recurs, the patient's probability of survival drastically falls from 75% to less than 30%. This fact led solid tumor researchers at St. Jude to realize the importance of expanding the MAST protocol and adding a rebiopsy protocol to access tumor samples taken from each patient at multiple points during the course of the disease. Samples are now available for some tumors at diagnosis, recurrence, and autopsy.

Last year, Dr. Stewart and her colleagues reported in *Nature* their extensive characterizations of the O-PDXs held by the CSTN. Tumor specimens donated by 168 patients were used to generate 67 O-PDXs of 12 types of cancer, including neuroblastoma, osteosarcoma, rhabdomyosarcoma, retinoblastoma, Wilms tumor, desmoplastic small round-cell tumors, Ewing sarcoma, high-grade sarcoma, adrenocortical carcinoma, and other rare tumors. Genetic and epigenetic analyses of the O-PDXs revealed their developmental origins. Comparisons of the genetic profile and the molecular, cellular, and histologic profiles of each O-PDX with those from the corresponding primary tumor from the patient showed that the O-PDXs faithfully recapitulate the original tumor cells. Furthermore, these major features remained stable in the O-PDXs after multiple passages in vivo.

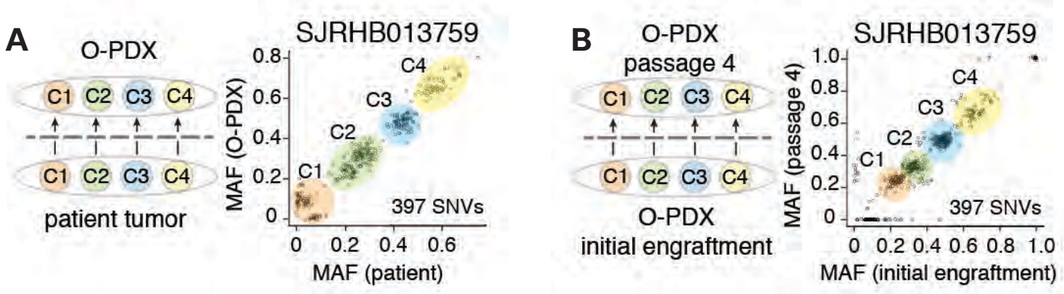


Figure. (**A**) Scatterplot of mutant allele frequencies (MAFs) for the single-nucleotide variants (SNVs) in an O-PDX that preserved clonal diversity. Individual clones are color-coded and labeled C1 through C4. (**B**) Comparison of clonal composition at the initial engraftment and after the fourth passage. *© 2017, Stewart E et al*

High-throughput screening of the O-PDX cells in primary culture identified several drug vulnerabilities, suggesting new targets for clinical therapies and informing in vivo testing. Many drugs showed broad activity across various types of solid tumors, but some were selective. Of note, multiple rhabdomyosarcoma O-PDXs (derived from diagnostic or recurrent tumors) responded to the WEE1 inhibitor AZD1775 when it was administered with irinotecan and vincristine in vivo. This finding was particularly interesting because irinotecan and vincristine are the standard treatment for patients with recurrent rhabdomyosarcoma. Thus, Dr. Stewart and colleagues added AZD1775 to that combination chemotherapy regimen in a preclinical Phase III trial.

In their randomized, blinded, and placebo-controlled trial, 140 mice with O-PDXs were treated in one of the following four treatment groups: placebo, AZD1775 only, irinotecan + vincristine, or irinotecan + vincristine + AZD1775. All mice that received the triple-agent regimen had better outcomes than did those that received the standard of care or AZD1775 alone. This study not only provides proof of principle that O-PDX models are an invaluable approach to accelerating advances in the research and treatment of pediatric solid tumors but also validates O-PDXs as a new and instructive platform for studying clonal selection in disease recurrence.

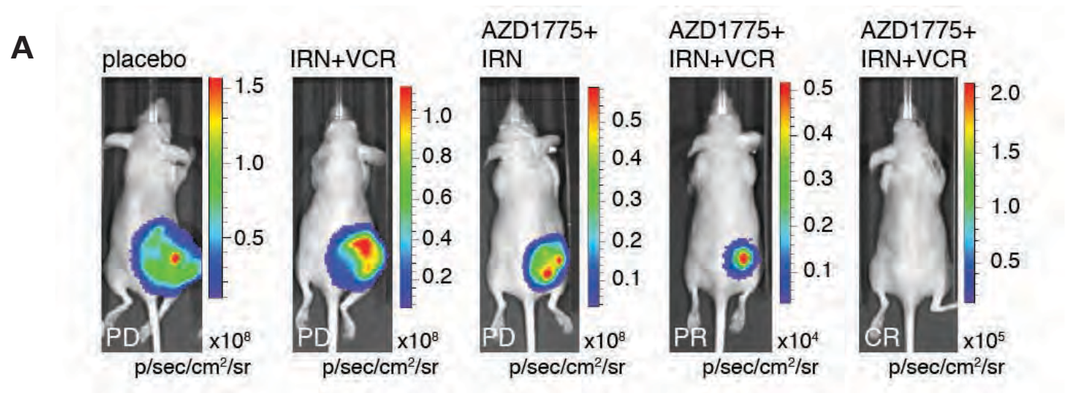


Figure. (**A**) Representative Xenogen imaging of progressive disease (PD), partial response (PR), and complete response (CR) of rhabdomyoscarcoma O-PDXs in a Phase III preclinical trial. Mice were treated with placebo or combinations of irinotecan (IRN), vincristine (VCR), and AZD1775. (**B**) Tumor response of mice bearing a representative rhabdomyoscarcoma O-PDX (SJRHB000026_X1) in the Phase III trial. (**C**) Survival curves for the mice shown in (**B**). *© 2017, Stewart E et al*

Michael R. Clay, MD; Armita Bahrami, MD

HISTOPATHOLOGIC CHARACTERIZATION OF SOLID TUMORS AT AUTOPSY

The molecular and histologic analyses of solid tumors are essential for advancing the treatment of those diseases. However, in many cases of high-risk disease, the tumors are inoperable, and tissues are available for analysis only after the patient's demise. Armita Bahrami, MD, and Michael R. Clay, MD (both of Pathology), are experts in the histopathologic analysis of solid tumors. The MAST protocol gives patients and families the opportunity to donate solid tumor samples at the time of autopsy. Although this study does not directly benefit the patients and families who enroll in it, it enables them to help advance the research and treatment of their child's disease for the benefit of future patients.

RARE TUMOR CLINICS OPEN AT ST. JUDE

Adrenocortical carcinoma is so rare that only about 25 cases are seen annually in the United States. Thus, it is extremely difficult to elucidate the molecular properties of these tumor cells, let alone develop effective targeted therapies. Such rare cancers, which also include melanoma and thyroid carcinoma, account for only about 10% of all cancer in patients younger than 20 years. Approximately 75% of these tumors arise in 15- to 19-year-olds; in this population, rare cancers account for about 24% of all cancers, and this population has long been underrepresented in National Cancer Institute–sponsored clinical trials. Furthermore, improvements in the survival of adolescents have lagged behind those seen in younger pediatric age groups.

Catherine G. Lam, MD, MPH

To facilitate the study of rare childhood cancers, St. Jude has developed specialized rare tumor clinics in which patients are recruited to participate in natural history (noninterventional studies) and genomic analyses of their tumor samples. The goal is to better understand the biology of these cancers to improve treatments and patient outcomes. Examples include St. Jude's Pediatric Melanoma Clinic, which is led by Drs. Pappo and Bahrami, and the Pediatric Rare Endocrine Tumor Clinic, which is led by Catherine G. Lam, MD, MPH (Global Pediatric Medicine, Oncology). Patients come for expert consultation, medical examinations, educational seminars, and introduction to disease-related resources. Some patients may qualify for clinical trials at St. Jude and stay to receive multimodal therapy, including surgery, radiation therapy, immunotherapy, and targeted therapies. Other patients return home for treatment but with the additional support of a St. Jude multidisciplinary team that is familiar with their cases and available for consultation.

Since its inception in April 2016, the Pediatric Melanoma Clinic has provided expert consultation to more than 20 patients from 11 different states and Puerto Rico, and the Pediatric Rare Endocrine Tumor Clinic, which opened in June 2017, has evaluated four patients from three different states.

THE DEVELOPMENTAL BIOLOGY & SOLID TUMOR PROGRAM IN THE ST. JUDE COMPREHENSIVE CANCER CENTER

The goal of the Developmental Biology and Solid Tumor Program (DBSTP) is to improve the survival and quality of life for children with solid tumors by integrating basic, translational, and clinical research. Investigators in the DBSTP incorporate cutting-edge technologies to identify therapeutically relevant tumor vulnerabilities that are unique to pediatric solid tumors because of their developmental origins.

Under the co-leadership of Drs. Dyer and Pappo, the DBSTP is currently focusing research efforts in the following four thematic areas: (1) elucidation of the molecular and cellular mechanisms of clonal evolution in recurrent solid tumors; (2) development of more effective, less toxic immunotherapy for solid tumors; (3) discovery of vulnerabilities in rare pediatric tumor that can be clinically exploited; and (4) design of precision medicine approaches to improve the survival and quality of life of patients with solid tumors. The CSTN provides essential support to research in each of these thematic areas.

CONCLUSION

By freely providing researchers around the world with well-characterized solid tumor samples, the Childhood Solid Tumor Network is hastening discoveries of more effective treatments and cures for catastrophic childhood cancers. St. Jude solid tumor physicians are also conducting specialized clinics to further advance treatments and improve the survival of children with the rarest of rare diseases.

A NEW APPROACH TO CALCULATING THE COST OF SURVIVING CHILDHOOD CANCER

As treatments for pediatric cancers continue to improve, the number of childhood cancer survivors in the United States is rapidly approaching 500,000. Thus, St. Jude researchers and clinicians have focused on and are leaders in the study of pediatric cancer survivorship. By investigating the long-term health of survivors, we are gaining invaluable information about the adverse effects of childhood cancer and anticancer treatment and using that information to inform future pediatric oncology clinical trials. St. Jude studies are also advancing our understanding of good health practices that enable long-term survivors of childhood cancer to enjoy the best-possible quality of life.

Nickhill Bhakta, MD, MPH

Past methods of examining the long-term effects of childhood cancer have been limited to determining the prevalence and incidence of certain chronic health conditions that tend to arise with age in this population. We describe a new approach to determining the cumulative burden of childhood cancer. This comprehensive analysis holds promise for improving future clinical guidelines, clinical trials, and health services planning for this vulnerable population. Efforts are also underway to perform a global assessment of childhood cancer burden via the new St. Jude Global initiative. Determining the cumulative burden of treating childhood cancers in low- and middle-income countries (LMICs) will facilitate efforts to accurately determine the incidence and survival of children with cancer worldwide and define the long-term impact of childhood cancer and its treatment. Such data will enable policymakers, particularly those in LMICs, to guide the funding and implementation of national health services for pediatric oncology patients based on comparative and cost-effectiveness data, rather than assumptions about the expense and outcome of anticancer treatment.

DELINEATING THE LANDSCAPE OF HEALTH OUTCOMES IN CHILDHOOD CANCER SURVIVORS

Much of the childhood cancer survivorship research conducted at St. Jude centers around two major survivor cohorts: the St. Jude Lifetime Cohort Study (SJLIFE) and the Childhood Cancer Survivor Study (CCSS). Together, these studies include more than 40,000 five-year survivors whose childhood cancers where diagnosed and treated during the last 50 years. These cohorts are enabling St. Jude investigators to define the landscape of pediatric cancer survivorship through the conduct of innovative research that addresses a broad spectrum of health, social, and quality-of-life outcomes.

In 1984, St. Jude established the After Completion of Therapy (ACT) Clinic. The overarching mission of the ACT Clinic continues to be to improve the quality of life of long-term survivors through clinical initiatives focusing on physical and emotional health, social functioning, and educational and vocational achievement. Most survivors are evaluated annually in the ACT Clinic until they are either 18 years old or 10 years post-diagnosis. At that point, survivors are discharged to the care of their community physicians. In 2007, St. Jude established the SJLIFE study. After completing treatment in the ACT Clinic, survivors are invited to participate in this unique research resource that provides lifelong, comprehensive, and organ system–based clinical assessments on the St. Jude campus for all survivors whose pediatric cancer was treated at the institution since its inception in 1962. Under the leadership of Melissa M. Hudson, MD (Oncology, Epidemiology & Cancer Control, Psychology), and Leslie L. Robison, PhD (Epidemiology & Cancer Control), this bold initiative is facilitating earlier characterization of treatment-related morbidity and identifying survivors who may benefit from early interventions to preserve their health.

The CCSS, which was established in 1994, is the single-largest cohort of pediatric cancer survivors in the world. This St. Jude–led multi-institutional, multidisciplinary collaborative research project, directed by Gregory T. Armstrong, MD, MSCE (Epidemiology & Cancer Control, Oncology), includes more than 35,000 childhood cancer survivors who received their diagnoses and treatments at 29 centers across the United States and Canada. This unique resource includes banked biospecimens and detailed information on the cancer diagnoses, treatment-related exposures, and self-reported health outcomes of more than 24,000 actively participating survivors.

Survivorship research conducted at St. Jude through SJLIFE and the CCSS is not only identifying survivors at high risk for adverse late effects of therapy but also translating those findings into clinical care recommendations designed to systematically deliver optimized care to this medically complex population, clinically validated models for individualized prediction of the level of risk for adverse outcomes, and the development and testing of intervention strategies to prevent or ameliorate the adverse consequences of successful anticancer therapy.

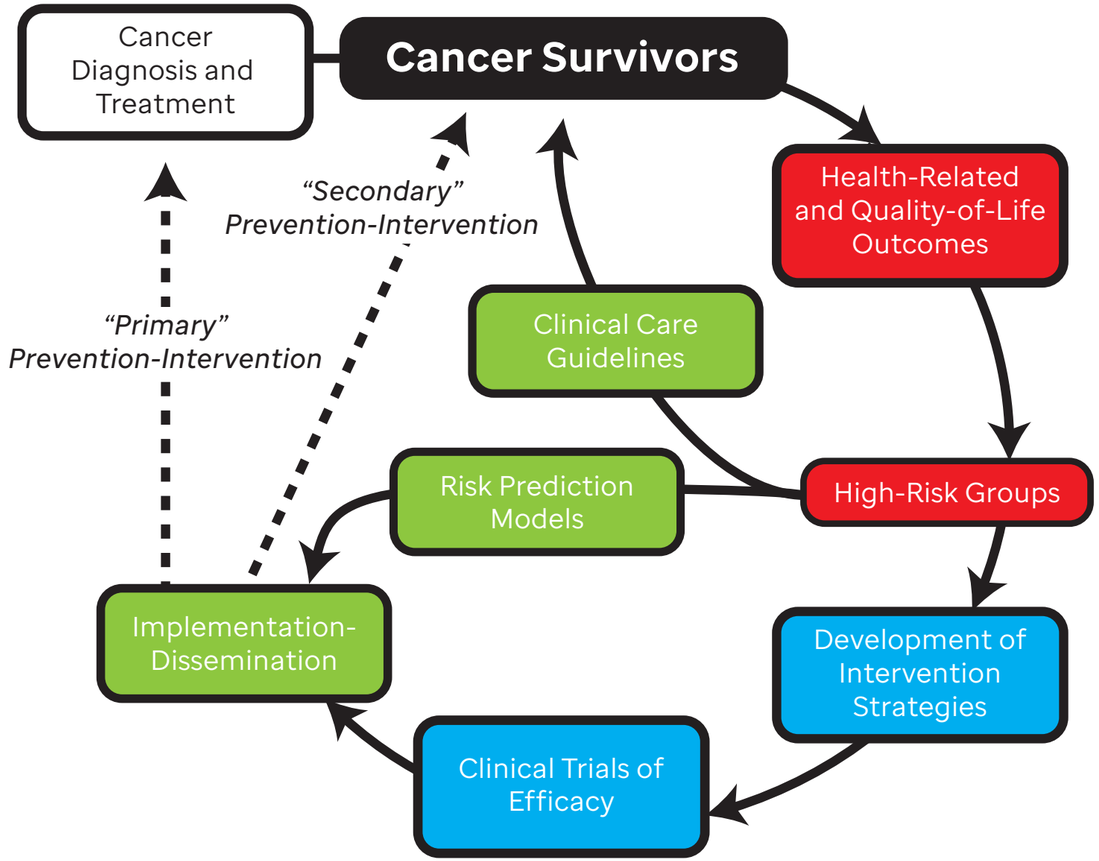
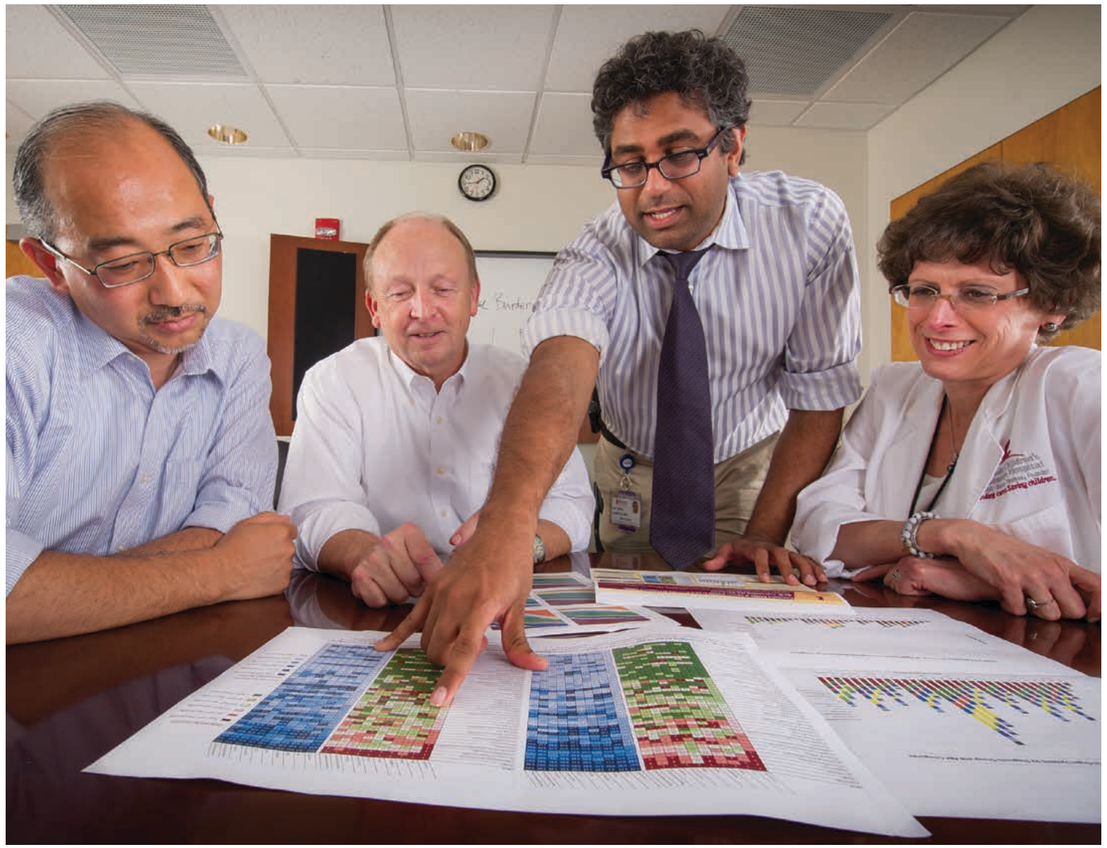


Figure. Diagram of cancer survivorship issues and future direction. © *2008 Bhatia S and Robison LL*

Gregory T. Armstrong, MD, MSCE; Leslie L. Robison, PhD



Yutaka Yasui, PhD; Leslie L. Robinson, PhD, Nickhill Bhakta, MD, MPH; Melissa M. Hudson, MD

REDEFINING THE LANDSCAPE OF CHRONIC HEALTH CONDITIONS IN CHILDHOOD CANCER SURVIVORS THROUGH CUMULATIVE BURDEN

The probability of surviving for at least 10 years after childhood cancer is now greater than 80% in high-income countries such as the United States. Surviving cancer comes at a cost, however, as the curative therapies used to achieve this level of success are associated with long-term chronic health conditions. Previous research, much of it led by epidemiology researchers at St. Jude, has shown that survivors face higher risks of multiorgan morbidity, poor health status, and premature death than do their siblings and the general population. Thus, a comprehensive evaluation of the long-term morbidities that survivors may encounter as they age is crucial for health services planning and future clinical research activities.

Over the past 20 years, survivorship researchers have detailed the many long-term associations between specific chemotherapeutic agents or radiation exposure and a single or small number of chronic diseases. However, a comprehensive assessment of long-term morbidity, in which all chronic health conditions are quantified using a common standard that compares patterns of illness, has not been possible due to methodologic constraints. Until recently, traditional statistics (i.e., the types of statistical tests commonly used in most survivorship studies) allowed researchers to examine only the time it takes for the first chronic health condition to develop in survivors. The difficulty when studying populations such as childhood cancer survivors is that these individuals do not develop just one chronic disease. Rather, they are at high risk of multiple and recurrent morbidities. For example, a Hodgkin lymphoma survivor who received chest irradiation is not just at high risk of a single myocardial infarction but also at high risk of having multiple myocardial infarctions. In addition, depending on the types of treatment received, the same Hodgkin lymphoma survivor is susceptible to heart valve disease, arrhythmias, and several other severe or life-threatening chronic health conditions.

To measure multimorbidity in large populations, such as the SJLIFE cohort, a team led by Nickhill Bhakta, MD, MPH (Global Pediatric Medicine, Epidemiology & Cancer Control, Oncology), Yutaka Yasui, PhD (Epidemiology & Cancer Control), and Drs. Hudson and Robison developed a new analytic approach termed, “the cumulative burden.” The cumulative burden is a statistical measure that researchers can now use to estimate the average number of chronic health conditions per survivor, according to a specific time scale (i.e., age), taking into consideration multiple and recurrent events and accounting for competing risks. Simply stated, investigators can use this metric to determine the number of events of a condition of interest that are observed, on average per subject, within a population over a given period. The metric was written using R and SAS software, and it is freely available.

As described in *The Lancet*, the team applied the cumulative burden approach to data from the SJLIFE study to generate the most comprehensive medical account to date of the landscape of chronic diseases affecting childhood cancer survivors. Their analysis included 5522 childhood cancer survivors from whom detailed chemotherapy, radiation therapy, and surgical treatment data were abstracted from medical records from the 1960s to the early 2000s. More than half of the participants were clinically assessed using a robust prospective protocol. Additionally, a comparison cohort of general population community controls was included to help contextualize the impact of surviving childhood cancer.

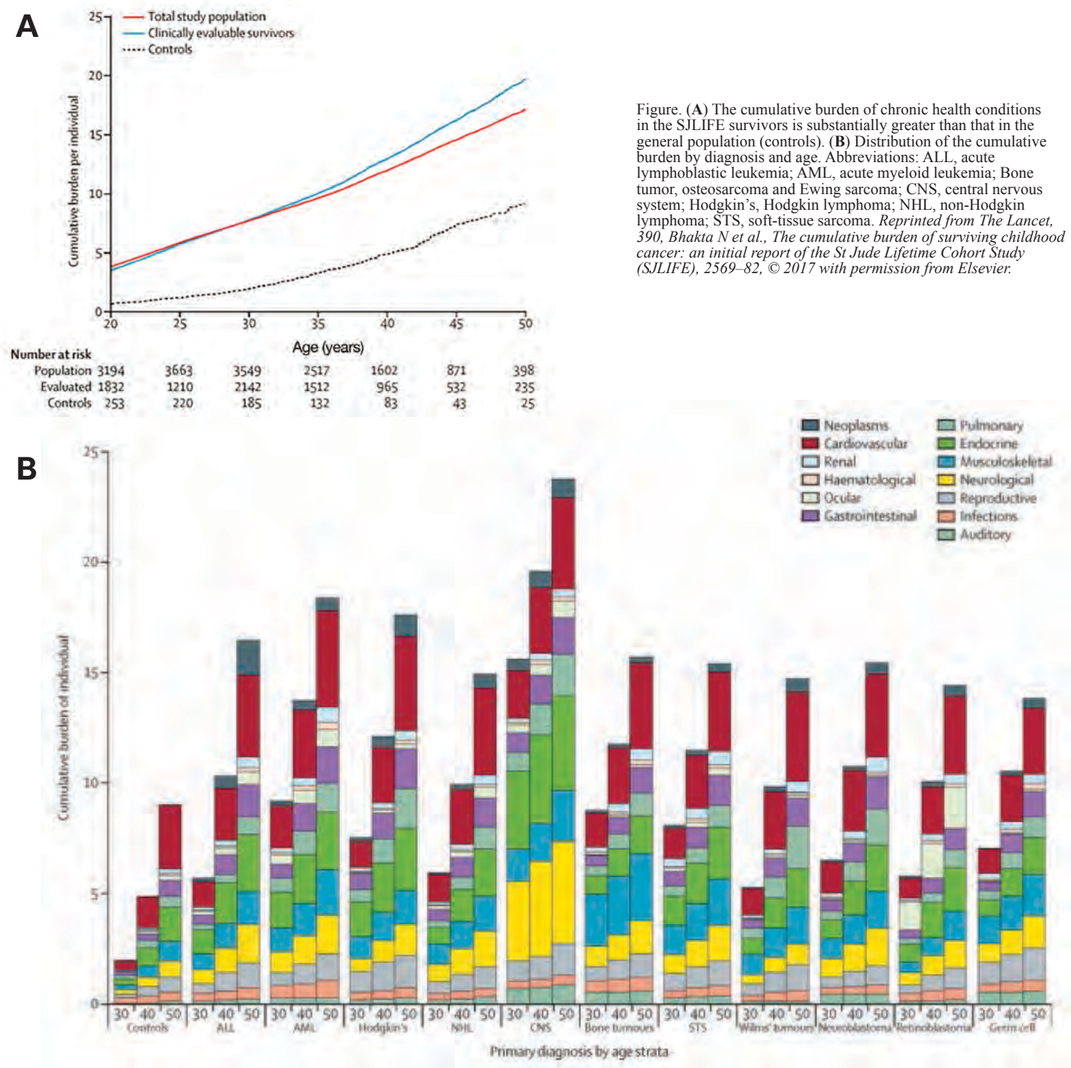


Figure. (**A**) The cumulative burden of chronic health conditions in the SJLIFE survivors is substantially greater than that in the general population (controls). (**B**) Distribution of the cumulative burden by diagnosis and age. Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; Bone tumor, osteosarcoma and Ewing sarcoma; CNS, central nervous system; Hodgkin’s, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; STS, soft-tissue sarcoma. *Reprinted from The Lancet, 390, Bhakta N et al., The cumulative burden of surviving childhood cancer: an initial report of the St Jude Lifetime Cohort Study (SJLIFE), 2569–82, © 2017 with permission from Elsevier.*

Yutaka Yasui, PhD

Using this new cumulative burden method, Dr. Bhakta and his colleagues showed that by 50 years of age, the average childhood cancer survivor experiences 4.7 severe, life-threatening, or fatal chronic health conditions. This is in marked contrast to the community controls, who experience 50% fewer chronic health conditions. When individual causes of chronic health conditions were analyzed, second neoplasms, spinal disorders, and pulmonary disease were identified as major contributors to the excess cumulative burden. In multivariable analyses, older age at diagnosis, treatment era, and higher doses of brain and chest irradiation were all significantly associated with a greater cumulative burden and severity of chronic health conditions. Finally, in addition to describing the landscape of chronic disease burden among survivors, the study found notable heterogeneity in the distribution of chronic health conditions among survivors with different primary cancer diagnoses.

The findings reported by Dr. Bhakta and his colleagues affect multiple facets of survivorship care, ranging from clinical research to health policy. In clinical and research settings, general health practitioners and clinical investigators can now use these data to educate patients about risks as part of their anticancer treatment, assess trade-offs between exposures and different chronic health conditions to aid the design of future clinical trials, and inform the development of follow-up guidelines. In addition, for survivors, the patterns of disease found in this study raise the question of whether new or additional health service delivery mechanisms are needed. Based on the changes in cumulative burden over time that the researchers identified, childhood cancer survivors appear to have two classes of morbidities: late-occurring morbidities, which increase as the cohort ages and at a faster rate than in community controls, and early-onset conditions, which are associated with the acute effects of anticancer therapy. For example, among survivors of hematologic malignancies, the contribution of cardiovascular disease and secondary and recurrent neoplasms to overall cumulative burden increases at a relatively faster rate over time than do the other contributors to overall burden. Alternatively, the cumulative burden of neurologic and auditory outcomes among survivors of central nervous system cancers was initially large but remained mostly static over the follow-up period due to early irreversible toxicities, such as hearing loss and neuropathies. From a clinical care perspective, these static conditions might be either well controlled or inadequately managed at any time. Thus, this study highlights the extra effort primary care physicians must expend to surveil potential early signs of treatment-associated late effects and vigilantly monitor the pre-existing long-term sequelae associated with anticancer treatment. However, this effort may not be feasible in many primary care practices.

Finally, beyond the clinical and policy implications of this study, the cumulative burden approach represents a new method of estimating disease burden that is highly relevant to clinical research being conducted in other fields. Traditional statistics (e.g., incidence and prevalence) and health-adjusted life-year methods currently dominate disease burden estimation across all disciplines. None of these methods, however, can describe or infer outcomes from the multiple chronic and recurrent diseases that are typically encountered in clinical and population research. For clinical cohorts with an aging population and high rates of both early mortality and chronic, recurrent morbidity (e.g., HIV-infected individuals, diabetics, or hematology patients with sickle cell disease or hemophilia), the methods that Dr. Bhakta and his colleagues have developed provide a novel and highly relevant statistical opportunity to better illustrate disease burden in easily comprehendible clinical terms that are useful for both the lay audience and medical professionals.

TRANSLATING SURVIVORSHIP CONCEPTS TO THE GLOBAL BURDEN OF CHILDHOOD CANCER

Fifty years ago, pediatric cancer was essentially a fatal diagnosis. Today, more than 80% of children with cancer who have access to contemporary treatments and robust supportive care are cured. Often hailed as a modern medical success story, translating outcomes to improve care among the more than 90% of children who live in LMICs has proven difficult. Many children in LMICs do not have access to any modern anticancer treatment. Although multiple clinical, policy, and financial obstacles contribute to the disparity between outcomes in high-income countries and LMICs, using epidemiologic data to inform cancer control planning is a requisite first step to improving outcomes globally. Unfortunately, we still do not know with reasonable certainty the number of children in whom cancer develops, is diagnosed, and treated, or the number who survive cancer around the world each year.

In March 2017, the St. Jude Board of Governors approved a new initiative proposed and led by Carlos Rodriguez-Galindo, MD (Global Pediatric Medicine, Oncology), to address disparities in global childhood cancer survival. The new program, St. Jude Global, builds on our institution's rich history in international health. Almost 25 years ago, the International

Nickhill Bhakta, MD, MPH; Carlos Rodriguez-Galindo, MD

Outreach Program was founded as a humanitarian effort for children with cancer in LMICs. The program established 24 partner programs in 17 countries that worked with St. Jude to improve local cancer care. However, a path toward further scaling this effort was lacking. St. Jude Global is a new institution-wide program coordinated by the Department of Global Pediatric Medicine that will support regional cooperative groups, as opposed to single-institution partnerships, engage government agencies (e.g., the National Cancer Institute) and nongovernment global health organizations (e.g., the World Health Organization), and coordinate these efforts with academic departments at St. Jude to meet the challenge of improving the care of children with cancer worldwide. Using this cooperative, integrative approach, St. Jude's efforts will be scaled to reach many more children globally than is currently feasible.

With the goal of engaging all expertise at St. Jude, one of the initial projects supported by Dr. Rodriguez-Galindo and led by Dr. Bhakta uses the cumulative burden approach to inform global priority setting. The absence of statistics on global disease burden is often wrongly interpreted by health policymakers, funders, and other stakeholders in LMICs as indicating a lack of disease burden attributable to pediatric cancer. One early priority that Dr. Rodriguez-Galindo has set for St. Jude Global is to improve our understanding of global pediatric cancer epidemiology. To address this challenge, Dr. Bhakta and colleagues at the Institute for Health Metrics and Evaluation (IHME; Seattle, WA) are working to improve the current estimates of global childhood cancer disease burden.

The team is studying not only how many children experience cancer but also the cost effectiveness of treating childhood cancers and how long-term chronic health conditions affect health based on where a patient resides. To label an intervention cost effective, the costs of treatment need to be tabulated, and the long-term effects need to be estimated. The first data detailing the costs involved in treating children with cancer at a pediatric cancer unit in El Salvador were recently reported in the journal *Cancer* by Dr. Soad Fuentes-Alabi (National Children's Hospital Benjamin Bloom, San Salvador, El Salvador), Dr. Bhakta, and their colleagues. Over the past 5 years, Dr. Fuentes-Alabi has worked with Dr. Rodriguez-Galindo and has become a regional leader in the epidemiology of childhood cancer in Central America. The study, representing the first comprehensive costing analysis for pediatric cancer in an LMIC, calculated the average cost of treating a child with newly diagnosed cancer at $30,000 (USD). Replication studies using the method developed by the team are now ongoing at several other pediatric cancer centers to generate more data on how costs vary around the world.

The effectiveness component in cost-effectiveness analyses is more complex. Although 5-year survival is the "gold standard" for measuring the success of clinical trials, a more holistic approach that incorporates the consequences of survivorship is required to accurately estimate lifelong effectiveness. By adapting the cumulative burden approach, Drs. Bhakta and Yasui are working with colleagues at IHME to ensure that the late effects of cancer are incorporated into their disease burden analyses and reflect the true outcomes associated with curing cancer globally. The team anticipates that researchers using these data will be able to optimize treatment decisions and balance the short-term goal of cure with the long-term benefits of a healthy life when designing clinical treatment guidelines. This will provide justification for the effective use of resources to treat pediatric cancer and improve advocacy efforts globally through relevant, actionable data.

CONCLUSION

Epidemiology researchers at St. Jude have developed a novel, highly relevant approach to assessing the cost effectiveness of treating childhood cancer and the cumulative burden of surviving the disease. This work holds promise for improving health care for this vulnerable population and accurately determining the actual cost and benefits of treating pediatric cancer in low- and middle-income countries around the world.

DECIPHERING THE MECHANISMS OF NEUROPLASTICITY IN LEARNING AND ANIMAL MODELS OF PSYCHIATRIC DISEASES

The brain is constantly bombarded by sensory information in the forms of sight, smell, touch, and sound. These modalities make up our environment and help us perceive the outside world. The cerebral cortex contains multiple sensory cortices, including the auditory cortex for sound, that store specific sensory information and are capable of reorganizing in response to new sensory stimuli, a trait known as neuroplasticity.

Ildar T. Bayazitov, PhD

Neuroplasticity is defined as the brain's ability to modify the structure and function of connections between neurons (i.e., synapses) in response to changes in sensory experience. These changes in neuronal circuits are thought to underlie our ability to learn and memorize sensory information. The auditory system enables us to remember streams of sounds that comprise music or language, for example, and to associate that information with other important events. In individuals with catastrophic psychiatric or neurologic diseases such as schizophrenia or stroke, the auditory cortex (ACx) and other parts of the cerebral cortex become dysfunctional. This results in auditory hallucinations, learning disabilities, and other debilitating symptoms.

In 2017, the laboratory of Stanislav S. Zakharenko, MD, PhD (Developmental Neurobiology), made three key discoveries that have altered our understanding of the role of ACx neuroplasticity in learning and how ACx dysfunction influences the onset and symptoms of schizophrenia. The researchers used state-of-the-art imaging approaches, including two-photon laser-scanning microscopy, which makes it possible to observe the activity of neurons at the cellular and subcellular levels in living animals exhibiting specific behaviors, and optogenetics and chemogenetics, which reversibly activate or disrupt specific neuronal circuits in the brain.

A CHILD'S BRAIN IS MORE PLASTIC THAN AN ADULT'S BRAIN

Neuroplasticity is a fundamental phenomenon that occurs in developing and adult brains. It allows the brain to adapt to an organism's unique experiential history; sensory history is effectively incorporated into the brain's neuronal circuits (i.e., the network of neuronal connections). This ensures that information processing and behavioral responses are appropriate for and concordant with sensory inputs. Neuronal circuits further serve as a scaffold for subsequent reorganization that underlies learning and memory.

The processing of auditory information is a crucial function of the ACx, but this region is also a substrate for auditory learning and memory. Acquisition and retention of auditory memory occurs throughout life and is crucial to determining the level of importance of a particular sound. The ACx is organized into groups of neurons that are tuned to different sounds. The organization of these groups of neurons is referred to as a cortical map. Like individual neuronal connections, cortical maps change in response to external stimuli or events. ACx cortical map plasticity is thought to underlie auditory learning and can be induced throughout life, but the mechanisms appear to differ in children and adults.

In the ACx of young mice, cortical map plasticity can be induced by enriching the environment with a single acoustic stimulus (i.e., a tone continually played at a constant volume and frequency). This phenomenon is most likely essential for constructing stable, adapted cortical representations of the auditory world and, in humans, for acquiring language early in life. In mature animals, this passive plasticity does not occur. Cortical map plasticity is induced in the ACx only when the acoustic stimulus is behaviorally relevant. Behavioral relevance is generally associated with the activation of modulatory synaptic inputs (i.e., cholinergic, dopaminergic, or noradrenergic synapses). This suggests that cortical map plasticity in mature animals is regulated or gated. The gating mechanism must be released by activation of modulatory neuronal inputs before cortical maps can be modified (i.e., before new auditory information can be learned), potentially explaining why auditory learning is easier for children than for adults.

RESTORING PLASTICITY IN THE AUDITORY CORTEX OF MATURE MICE

The thalamus is a central hub that routes sensory information to sensory cortices. Auditory information is conveyed by thalamic neurons that connect to ACx neurons via thalamocortical (TC) inputs. Long-term potentiation (LTP) and long-term depression (LTD) are two forms of synaptic plasticity. LTP is defined as the long-lasting strengthening of synaptic connections between a pair of neurons after stimuli, and LTD is defined as the long-lasting dampening of strength of those connections after stimuli. Both LTP and LTD can be induced at TC synapses in rodents but only during the first several days after birth. Attempts to directly induce LTP/LTD at TC synapses after postnatal day 15 in brain slices from rodents usually fail. This indicates that there is an "early critical period" of TC synaptic plasticity and supports the idea that plasticity is lost upon maturation, making auditory learning difficult for adults.

Over the last several years, Dr. Zakharenko's group has shown that long-term plasticity at TC synapses is actually not lost upon maturation. Long-term plasticity remains possible in adults; however, with maturation gating mechanisms are acquired that restrict this plasticity. Such gating depends on the production and signaling of the neuromodulator adenosine. Adenosine production is mediated by the presynaptic enzyme ecto-5′-nucleotidase (Nt5e). Adenosine then signals through presynaptic adenosine A1 receptors (A_1Rs). The A_1R response curbs the glutamate release from presynaptic thalamic terminals that is required to induce LTP or LTD during sustained neuronal activity. Dr. Zakharenko's work was initially performed on brain slices, and the researchers posited that this adenosine-dependent gating mechanism is released by activating cholinergic receptors on thalamic presynaptic terminals. Cholinergic activation downregulates the presynaptic adenosine machinery, which, in turn, sustains glutamate release from the thalamic neurons.

Jay A. Blundon, PhD

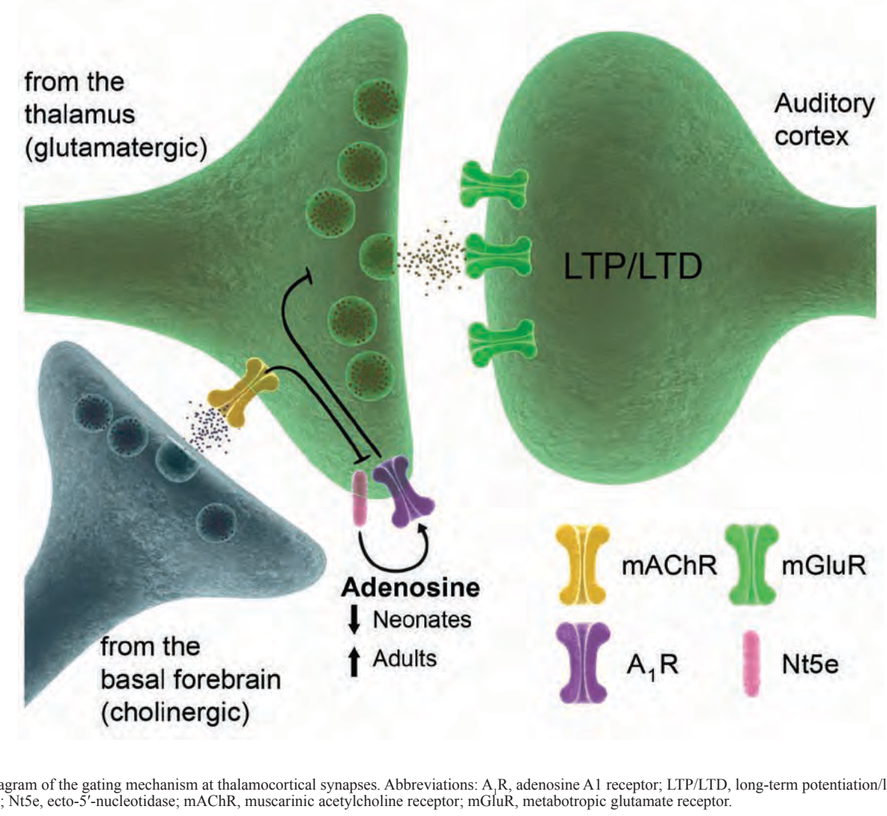


Figure. Diagram of the gating mechanism at thalamocortical synapses. Abbreviations: A_1R, adenosine A1 receptor; LTP/LTD, long-term potentiation/long-term depression; Nt5e, ecto-5′-nucleotidase; mAChR, muscarinic acetylcholine receptor; mGluR, metabotropic glutamate receptor.

The molecular mediators connecting acetylcholine receptors with the adenosine machinery are as yet unknown, as are the molecular mechanisms of Nt5e regulation. The release of presynaptic gating allows mature TC synapses to undergo LTP/LTD. During the early critical period, Nt5e expression and adenosine levels are low in the thalamus. However, the levels of both molecules dramatically increase later in development, thereby terminating the early critical period for LTP/LTD at TC synapses.

In a recent article in *Science*, Jay A. Blundon, PhD, an associate scientist working in Dr. Zakharenko's laboratory, and colleagues showed that the same mechanisms that regulate LTP/LTD at TC synapses in brain slices also regulate the early critical period for cortical map plasticity in vivo. When the researchers either deleted or knocked down the expression of A_1Rs or Nt5e in the thalamus of mature mice, they extended the early critical period into late adulthood. The same effect was achieved when the scientists treated animals with the A_1R-specific antagonist FR194921. The genetic or pharmacologic treatments that extended the critical period also improved auditory perception. Animals with deleted A_1Rs or Nt5e and those treated with FR194921 performed tone-discrimination tasks better than untreated animals did. Cortical map plasticity was eliminated in adult mice when the authors blocked glutamate receptors and in pups when they administered an A_1R agonist. Thus, the mechanisms of TC synaptic plasticity match those of cortical map plasticity in the ACx and may provide new insights into the molecular mechanism of auditory learning and memory.

These results show that juvenile neuroplasticity can be rejuvenated in the adult ACx at the level of cortical maps and individual neurons. Thus, targeting adenosine signaling holds promise as a new strategy to improve auditory perception, which is required for auditory learning in adults. Targeting adenosine signaling could also restore neural activity in patients with neurologic diseases such as stroke. This work also has broad implications for expanding our understanding of fundamental mechanisms and disease processes that affect sensory processing and memory.

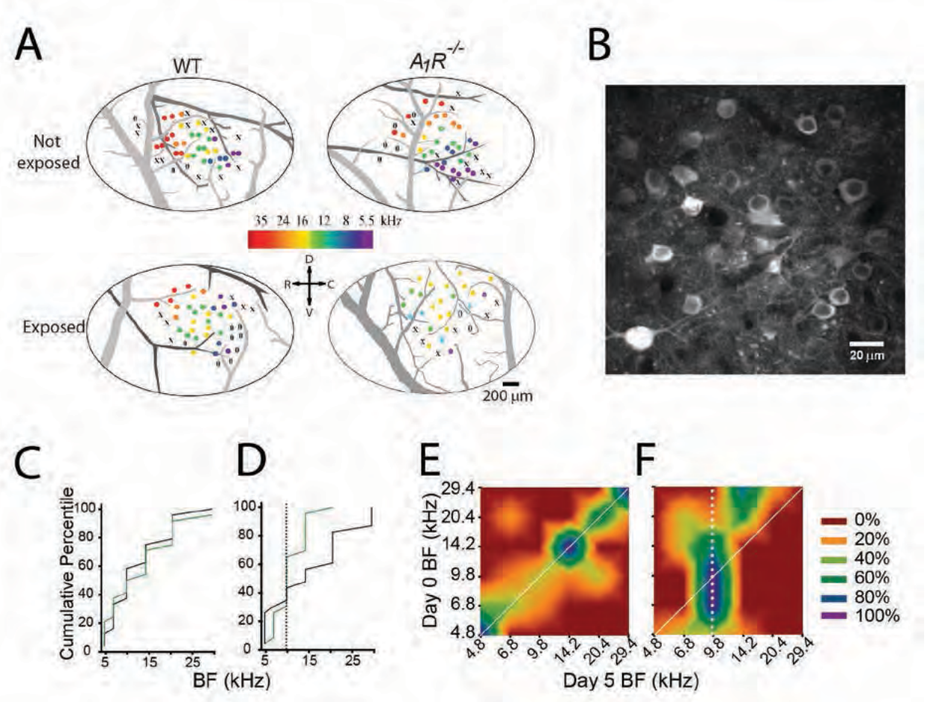


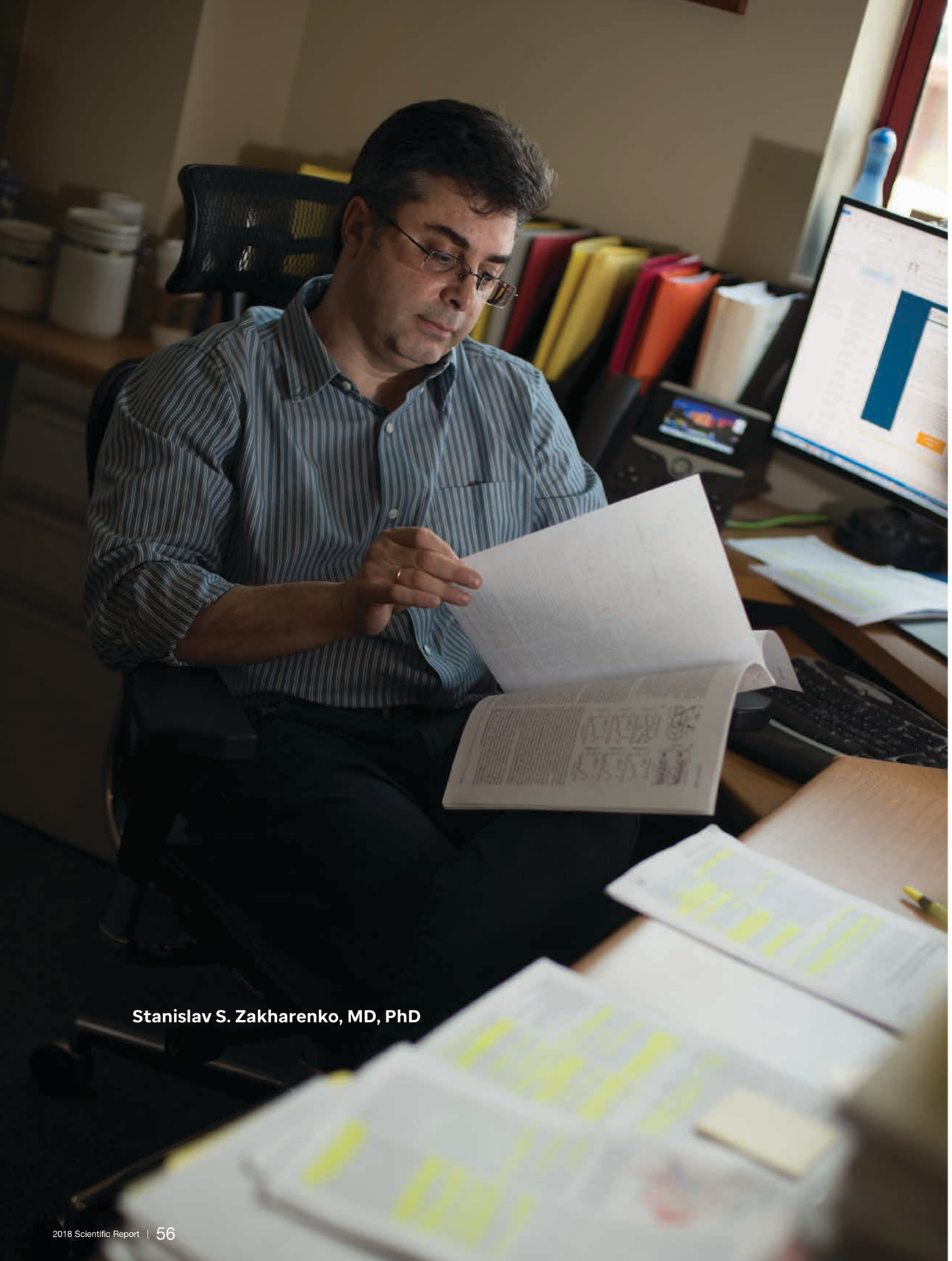
Figure. (**A**) Representative ACx cortical maps in wild-type (WT) or adenosine receptor–null ($A_1R^{-/-}$) mice that were either unexposed or exposed to a 16.4-kHz tone. (**B**) Image of fluorescence-labeled excitatory neurons in the ACx in vivo. (**C-D**) Cumulative histograms of best frequencies (BFs) and (**E-F**) receptive field heat maps recorded from ACx neurons in which adenosine production was blocked by *Nt5e* siRNA1. Day 0 (black) and Day 5 (green) BFs in unexposed mice (**C** and **E**) or mice exposed to a 9.8-kHz tone (vertical dotted line; **D** and **F**). *From Blundon JA et al. Restoring auditory cortex plasticity in adult mice by restricting thalamic adenosine signaling. Science 356:1352–6, 2017. Reprinted with permission from AAAS.*

IMPLICATIONS OF THALAMOCORTICAL PROJECTIONS IN SCHIZOPHRENIA

TC projections, which are important for auditory learning and memory, become dysfunctional in schizophrenia, a disease in which most patients experience auditory hallucinations (hearing voices). Schizophrenia is a devastating mental illness that affects approximately 1% of people and imposes a huge toll on patients and their families. The symptoms of schizophrenia are grouped into three main categories: positive symptoms (i.e., hallucinations and delusions), negative symptoms (i.e., anhedonia and amotivation), and cognitive symptoms (i.e., disorganized thoughts, impaired working memory, and impaired emotional memory). The disease generally arises during adolescence or early adulthood and is lifelong in most cases. The current treatment for schizophrenia is primarily antipsychotics, mostly dopamine receptor (DRD2) antagonists, such as haloperidol. Although such drugs effectively treat the positive symptoms of the disease, they are not as effective for treating the negative and cognitive symptoms. Furthermore, systemic inhibition of DRD2s causes severe side effects that impede treatment compliance.

Hallucinations are sensory perceptions in the absence of external stimuli. Patients with schizophrenia mostly experience auditory hallucinations, though hallucinations also occur in other sensory modalities. Because hallucinations are self-reported, studying this symptom in animals is challenging, and determining the underlying mechanism is even more difficult. Also, because schizophrenia is a polygenic disease (i.e., a disease that results from the combined action or interaction of multiple genes), generating a bona fide mouse model is problematic. Thus, Dr. Zakharenko's laboratory studies schizophrenia-relevant pathogenesis in models of 22q11.2 deletion syndrome (22q11DS), the most common microdeletion syndrome in humans, which is also strongly linked to schizophrenia.

The 22q11DS occurs in approximately one of 4000 births, and in about 30% of patients with 22q11DS, schizophrenia arises during adolescence or early adulthood. The risk of schizophrenia for patients



Stanislav S. Zakharenko, MD, PhD

with 22q11DS is about 30 times greater than that for the general population, making 22q11DS one of the strongest genetic predictors of schizophrenia. The symptoms of 22q11DS-related schizophrenia are indistinguishable from those of idiopathic schizophrenia, suggesting that the molecular mechanisms affected by 22q11DS are similar to those affected by schizophrenia. Furthermore, 22q11DS is caused by a well-defined genetic lesion that can be reliably reproduced in mice (i.e., 22q11DS mice).

One well-established theory of conscious perception is that it is encoded by TC circuits, and the connectivity in those circuits generates intrinsic activity in the presence or absence of sensory input. This hypothesis predicts that hallucinations are caused by impaired TC projections to sensory cortices. Indeed, multiple groups have reported TC abnormalities in patients with schizophrenia. Schizophrenia-like syndromes also emerge when illnesses such as stroke selectively damage the thalamus. Hallucinations and impaired reality monitoring (i.e., the ability to distinguish between memories of actual events and imagined events) also occur in patients with thalamic lesions. Moreover, local ischemic infarction (i.e., loss of blood flow) that disrupts TC projections to the ACx in nonpsychotic patients can cause auditory hallucinations. These clinical data point to deficits in the function of TC projections as a cellular correlate of positive symptoms. Furthermore, the evidence of TC connection deficits in schizophrenia is overwhelming, leading some to suggest that it is a disease caused by disrupted TC neuronal networks.

DISRUPTION OF THALAMOCORTICAL PROJECTIONS TO THE AUDITORY CORTEX UNDERLIES THE LATE ONSET OF SCHIZOPHRENIA

Auditory hallucinations and other psychotic symptoms occur in 60% to 90% of patients with schizophrenia, arising at a median age of 21 years. Mice aged 3 to 6 months are thought to developmentally correspond to human adults aged 20 to 30 years. Dr. Zakharenko's group identified a specific, robust deficit in synaptic transmission at TC projections to the ACx of 22q11DS mice that was age dependent, occurring only in mice older than 3.5 months. Thus, the onset of the TC deficits in 22q11DS mice appears to correspond with that of positive symptoms in patients with 22q11DS and/or schizophrenia. Because of the strong association between 22q11DS and psychosis, the authors hypothesized that 22q11DS mice could be used to identify the gene responsible for abnormal auditory processing and elucidate the underlying molecular mechanisms.

The 22q11DS mice have a synaptic deficit in their TC projections that is specific (only auditory TC projections are affected) and robust (resulting in a greater than 50% decrease in synaptic transmission). This TC disruption is rescued by antipsychotic drugs, suggesting that the phenotype is relevant to positive symptoms. To identify the culprit gene, Dr. Zakharenko's group screened TC synaptic transmission in mutant mouse lines encompassing the entire 22q11DS genomic region and used their respective wild-type littermates as controls. Only *Dgcr8*$^{+/-}$ mice were deficient in TC synaptic transmission, and this deficit was similar to that seen in 22q11DS mice, suggesting that *Dgcr8* haploinsufficiency in 22q11DS mice disrupts synaptic transmission at TC projections.

The Dgcr8 protein supports the biosynthesis of microRNAs (miRs), which are small, noncoding RNAs that fine-tune gene expression. Thus, when one of two copies of the *Dgcr8* gene is deleted, less Dgcr8 protein is produced, resulting in the reduced biosynthesis of miRs. In a recent *Nature Medicine* article, Dr. Zakharenko's group identified miR-338-3p as the culprit miR that disrupts TC projections in 22q11DS mice. Normally, miR-338-3p targets Drd2s, decreasing the expression of these dopamine receptors, and is enriched in the thalamus of mice and humans. Its level of expression also decreases with age in both species. As the level of miR-338-3p expression decreased in the thalamic neurons of older 22q11DS mice, Drd2 expression became abnormally high. However, when researchers deleted only miR-338-3p in mice, TC disruption occurred at all ages tested. Replenishing the level of miR-338-3p in mature 22q11DS mice rescued the TC deficits in the ACx.

This work revealed that in 22q11DS mouse models the newly discovered Dgcr8–miR-338-3p–Drd2 pathway underlies the deficits in TC synaptic transmission in the ACx. This pathway may also control the delayed onset and pathogenic mechanism of psychosis and positive symptoms of schizophrenia and/or 22q11DS. This work also puts forward a new target that has the potential to advance the treatment of these diseases.

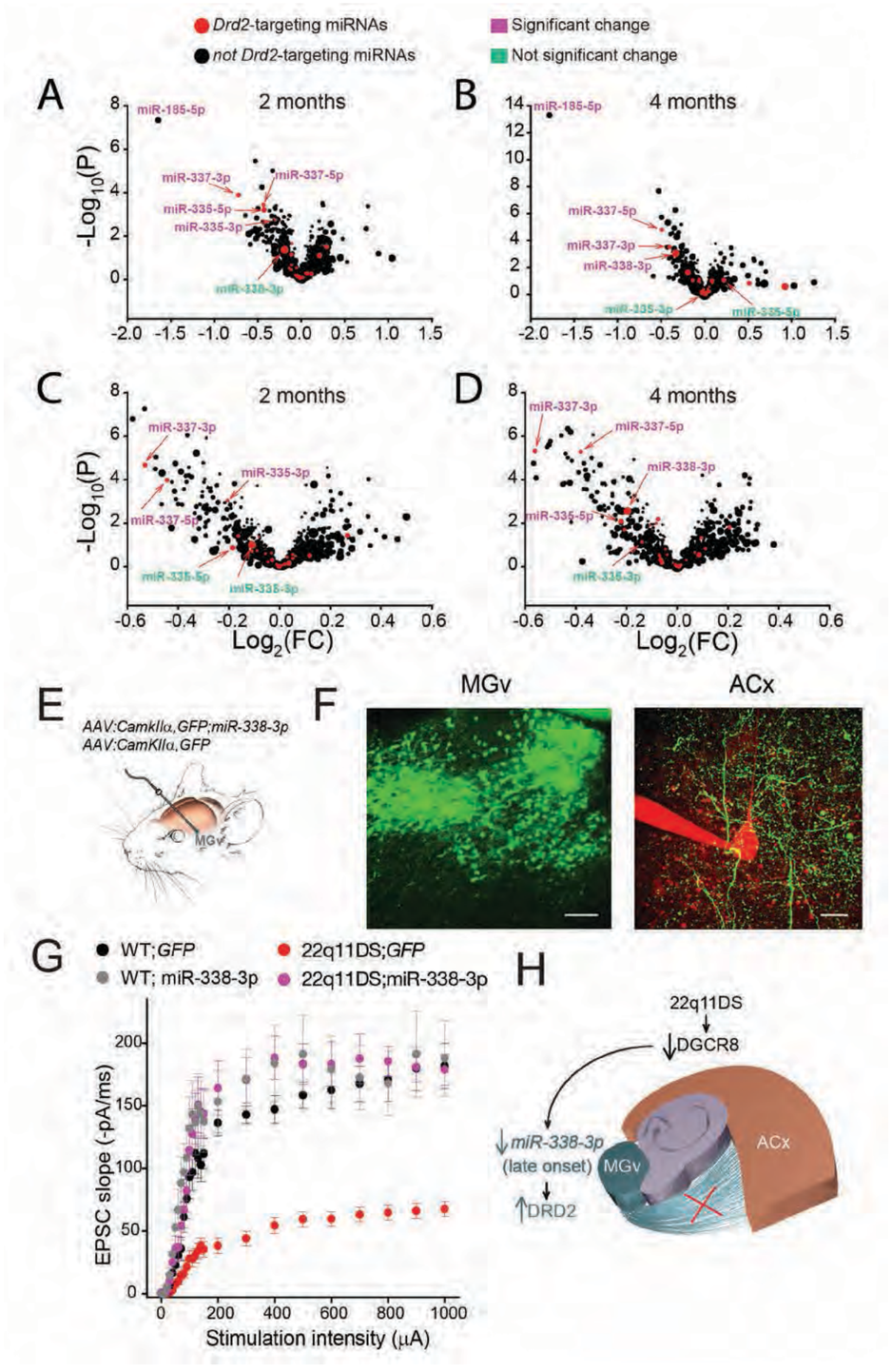


Figure. (**A-D**) Volcano plots of microRNA (miRNA) data from 22q11DS mice (**B**), *Dgcr8*$^{+/-}$ mice (**D**), and wild-type littermates (**A** and **C**) at 2 or 4 months of age. The thalamus-enriched mir-338-3p was identified in these experiments. (**E**) Diagram of experimental replenishment of mir-338-3p via adeno-associated virus injection into the auditory thalamus (medial geniculate nuclei; MGv) of a mouse. (**F**) Representative images of green fluorescent protein (GFP)-labeled mir-338-3p in MGv cell bodies (left) and projections to the excitatory neurons in the ACx (right). A patch pipette and a pyramidal neuron filled with Alexa 594 (red) are also shown. Scale bar, 100 μm. (**G**) Input–output relations between stimulation intensity and excitatory postsynaptic current (EPSC) in 22q11DS mice and wild-type (WT) littermates. (**H**) Model of TC disruption (red X) in individuals with 22q11DS. *© 2017 Chun S et al*

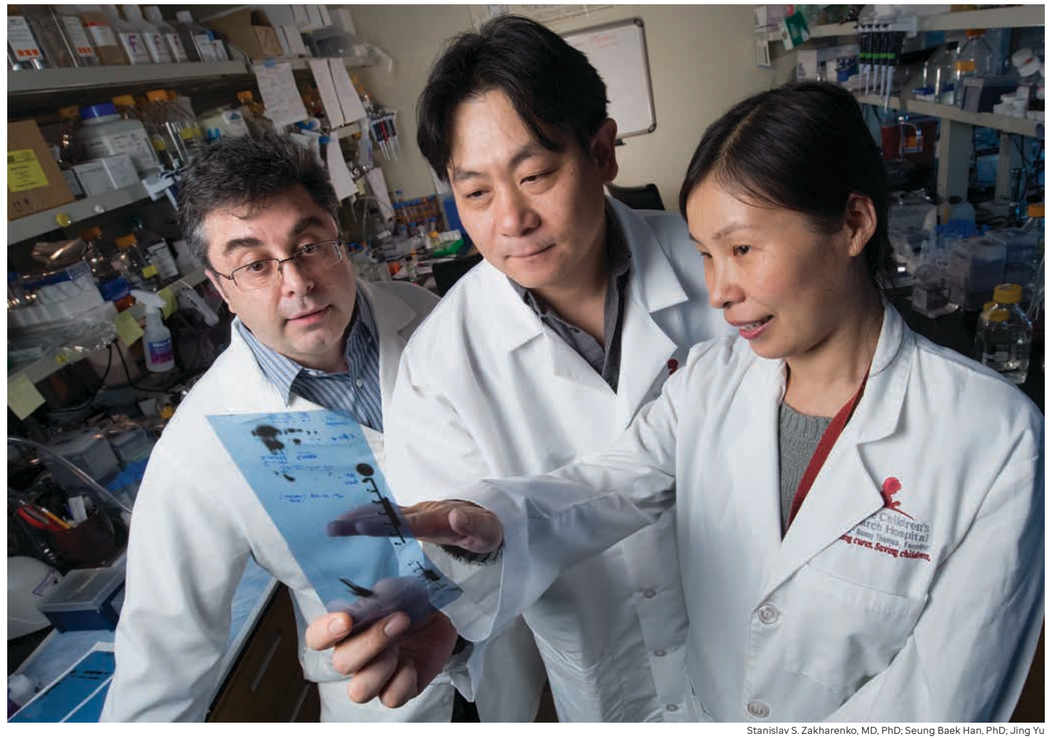
EMOTIONAL MEMORY DEFICITS IN SCHIZOPHRENIA

Decisions made by healthy individuals are thought to be based, in part, on the anticipation or recall of emotional experiences. Specifically, memories of positive or negative emotional experiences guide one's decision on whether to repeat a past action.

The cognitive symptoms of 22q11DS and schizophrenia include emotional memory deficits (e.g., impaired facial memory, difficulty in recognizing emotions, and inability to anticipate or recall emotions). These deficits can be caused by abnormal memory consolidation processes in response to emotional stimuli. Also, they may contribute to the negative symptoms of schizophrenia, including anhedonia (the inability to experience pleasure) and amotivation (lacking motivation to engage in an activity). A relation between emotional memory deficits and the negative symptoms of schizophrenia has been identified, but the neuronal circuits underpinning those deficits remain elusive.

The amygdala is the region of the brain that is responsible for emotional learning and memory. Thalamic neurons project to the lateral amygdala (LA) region of the basolateral amygdala, which assigns emotional significance to environmental cues and acquires and stores emotional memories. In rodents, this ability is generally studied using Pavlovian fear conditioning or active-avoidance training. Rodents may be trained to associate a conditioned stimulus (CS) such as a sound with a negative unconditioned stimulus (US). A US is a stimulus that naturally triggers an automatic response in an individual. Thalamo–lateral amygdala (thalamo-LA) projections from the thalamus and cortico–lateral amygdala (cortico-LA) projections from the ACx converge on LA neurons to convey CS information to the amygdala. Synaptic plasticity at thalamo-LA projections mediates emotional memory.

Pavlovian fear conditioning causes rodents to freeze upon the delivery of an associated CS. An active-avoidance behavior depends on Pavlovian information but also requires instrumental learning for the rodent to suppress the urge to freeze when the CS is presented, so that the animal can perform an avoidance response (i.e., escape the US). Although the behavioral outputs of this form of Pavlovian conditioning and the learning of an avoidance behavior differ, both depend on the delivery of the CS to the LA.

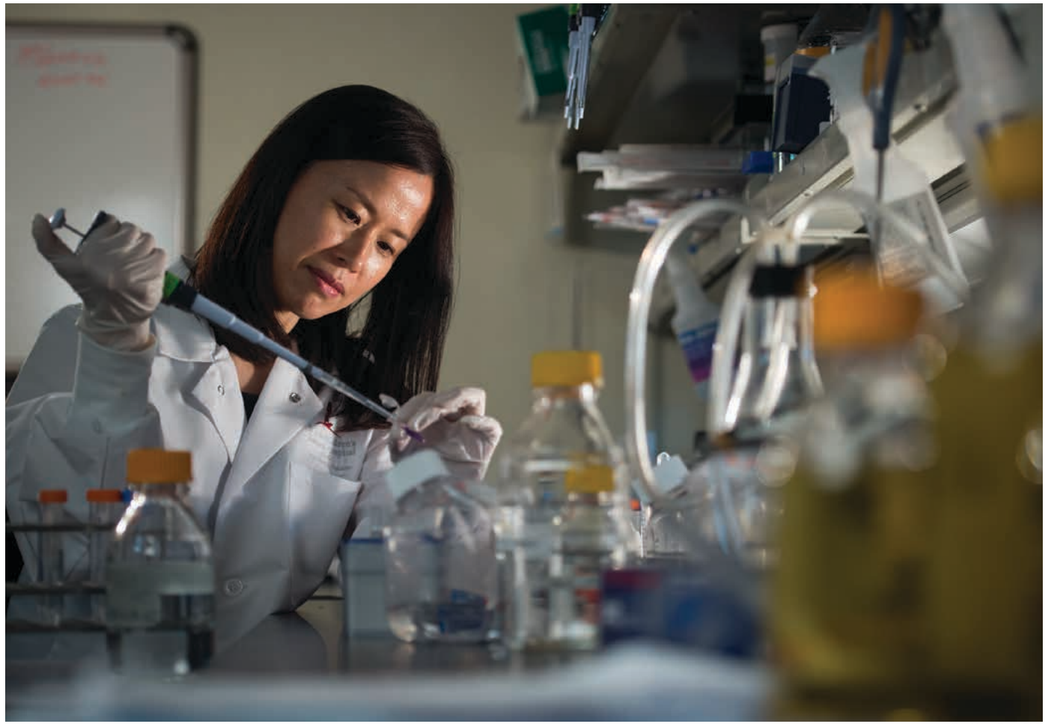


Stanislav S. Zakharenko, MD, PhD; Seung Baek Han, PhD; Jing Yu

Donnie Eddins, PhD; Lauren Beloate, PhD

THE NEUROBEHAVIORAL CORE PROVIDES ESSENTIAL SUPPORT TO NEUROPLASTICITY STUDIES

The Neurobehavioral Core Laboratory in the Department of Developmental Neurobiology assists St. Jude investigators with behavioral testing of preclinical models of neurologic or psychiatric diseases, such as schizophrenia, Alzheimer disease, and Parkinson disease. Under the management of Donnie Eddins, PhD, the core provides test batteries of behavioral paradigms that comprehensively assess cognition (learning and memory), neurologic functioning (e.g., motor coordination), emotional responses (e.g., depression/anxiety), and sensorimotor gating (psychiatric disorders). Equipment available in the core includes a Morris water maze, multicamera video-acquisition systems, standard operant-conditioning and shuttle chambers, radial arm and Y mazes, three-chamber social-interaction arenas, startle sensitivity/prepulse inhibition chambers, open-field activity chambers, rotor-rod systems, a treadmill, a horizontal ladder, elevated plus and zero mazes, a grip-strength meter, and a hot plate box. For most behavioral tests, data acquisition is automated, and data are collected via specialized software or video-tracking systems.



Tae-Yeon Eom, PhD

DISRUPTION OF THALAMO–LATERAL AMYGDALA INPUTS MEDIATES EMOTIONAL MEMORY DEFICITS IN 22q11DS MICE

Dr. Zakharenko's group previously showed that the microdeletion of 22q11DS genes increases Drd2 levels in the thalamus and that the thalamus is central to communicating a CS to the amygdala; thus, the thalamus is essential for emotional memory. In a recent *Cell Reports* paper, Tae-Yeon Eom, PhD, a postdoctoral fellow working in Dr. Zakharenko's laboratory, and colleagues tested two hypotheses: first, that 22q11DS mice have impaired emotional (fear) memory due to a Dgcr8–Drd2-dependent deficit in synaptic transmission at thalamo-LA projections; second, that inhibition of Drd2 activity or reduction in Drd2 expression in the thalamus of 22q11DS mice would rescue this deficit in emotional memory.

The researchers observed that 22q11DS mice are deficient in emotional (fear) memory. Compared to responses in wild-type littermates, 22q11DS mice exhibited less fear memory of a CS–US pairing 24 hours after training. In the active-avoidance test, the 22q11DS mice were also less successful at escaping the US than were their wild-type littermates. Consistent with this finding, 22q11DS mice have deficient synaptic transmission in thalamo-LA projections. Further testing found no differences between 22q11DS mice and controls, in terms of sensitivity to pain or locomotor abilities. Similar testing of *Dcgr8*$^{+/-}$ mice revealed deficits in freezing, avoidance, and synaptic transmission. Knocking down *Drd2* expression in the thalamus rescued the deficits. These results indicate that the Dcgr8–Drd2 molecular axis has a key role in emotional memory and suggest that antipsychotics could alleviate not only positive symptoms but also emotional memory deficits in patients with 22q11DS.

The finding that thalamo-LA projections and TC projections are impaired in 22q11DS mice suggests that synaptic transmission is compromised at all thalamic projections in 22q11DS and schizophrenia. This notion may have substantial ramifications, because thalamic neurons project to multiple brain areas that control different behaviors. Synaptic malfunction at thalamic projections, therefore, may give rise to a constellation of positive, negative, and cognitive symptoms. Furthermore, catastrophic psychiatric diseases, such as schizophrenia and 22q11DS, might be caused by presynaptic deficiency in a single brain region (e.g., the thalamus) or in a certain thalamic subdivision (e.g., the auditory thalamus).

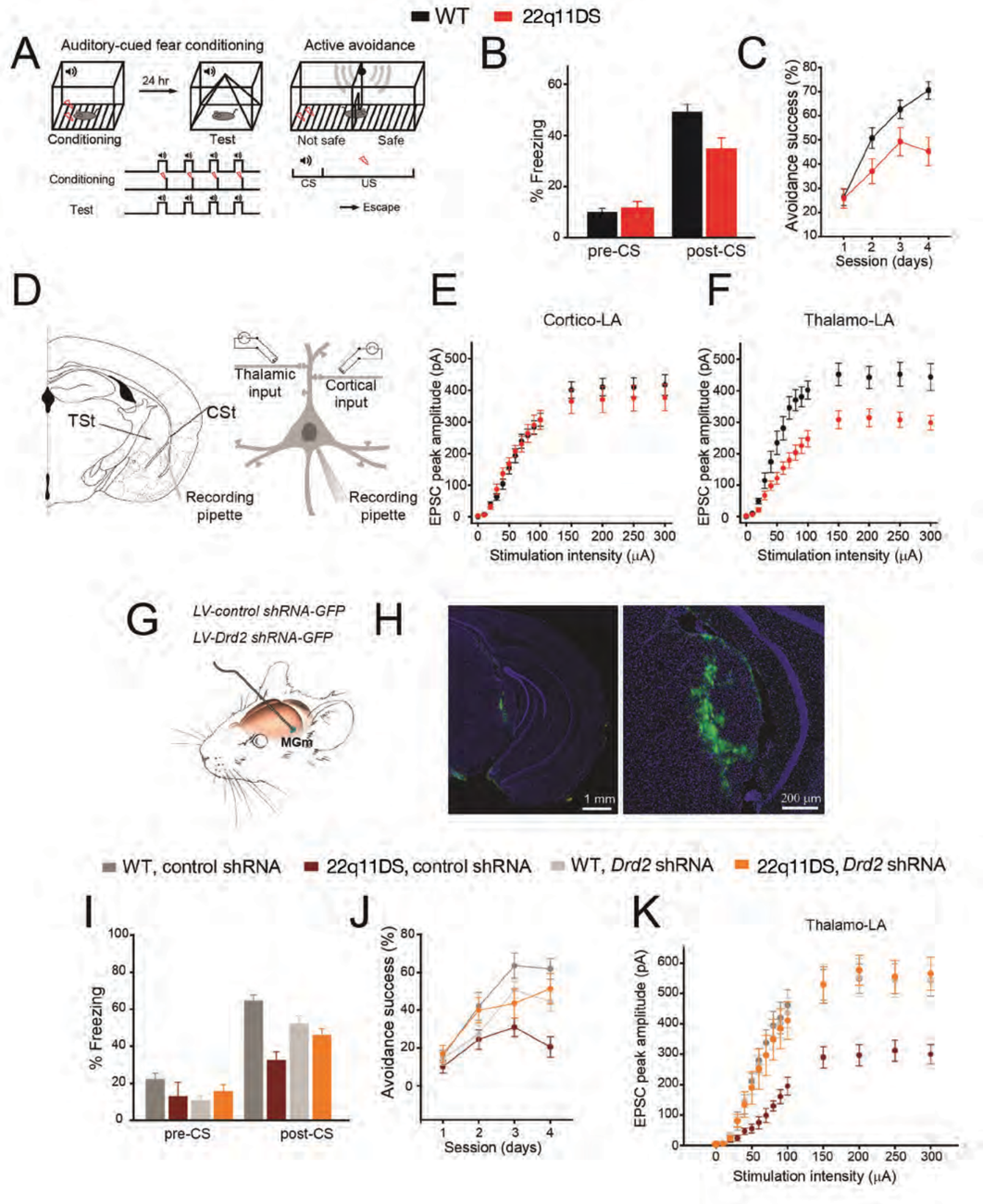


Figure. (**A**) Schematics for auditory fear conditioning and active avoidance tests. (**B**) Twenty-four hours after fear conditioning of wild-type (WT) and 22q11 mice, freezing behavior was compared between the two groups. Freezing before the presentation of the conditioned stimuli (pre-CS) did not differ, but freezing during the presentation of the tone (post-CS) was diminished in 22q11 mice. (**C**) Active-avoidance success rates in wild-type and 22q11DS mice as a function of the number of training days. (**D**) Diagram of electrode positions to stimulate thalamic (TSt) and cortical (CSt) projections and the recording pipette in the lateral amygdala. (**E-F**) Excitatory postsynaptic current (EPSC) data from those recordings show a difference between wild-type and 22q11DS neurons in the thalamo-LA projections only. (**G**) Diagram of Drd2 knockdown via lentivirus injection in the mouse auditory thalamus. (**H**) Representative low- and high-magnification images of neurons in the auditory thalamus (green). (**I-K**) Same as in **B**, **C**, and **F**, respectively. *Reprinted from Cell Rep, 19, 1532–44, © 2017 Eom T-Y et al. The Creative Common License is available at https://creativecommons.org/licenses/by/4.0/.*

CONCLUSION

By studying animal models of psychiatric disease, researchers at St. Jude are deciphering mechanisms of neuroplasticity that can be exploited to rejuvenate auditory learning in older individuals or patients with brain injury or neurologic disease. In addition, this work is expanding our understanding of the pathogenic mechanisms of these diseases, which holds promise for much-needed advances in the treatment of catastrophic mental illnesses such as schizophrenia.

LEADERSHIP PROFILE: Ellis J. Neufeld, MD, PhD

What was your career path that led you to St. Jude?

I'm a pediatric hematologist. I attended medical school at Washington University, in St. Louis, and then spent 32 years at Boston Children's Hospital as a resident and a fellow and then as a faculty member. I worked on nonmalignant blood diseases and ran the hemophilia program there, and I had been a clinic director, which was a middle-management job.

I was recruited to St. Jude by Dr. Jim Downing (Chief Executive Officer), with former Boston colleagues Drs. Charlie Roberts (Director of the Comprehensive Cancer Center) and Carlos Rodriguez-Galindo (Chair, Department of Global Pediatric Medicine) assisting. At first, I wasn't sure how the Clinical Director position could be a good role for me, but Dr. Downing was very persuasive! I already knew about the amazing people and resources at St. Jude, because several years ago I served on St. Jude's Data Safety and Monitoring Board, and for a couple of years before I became the Clinical Director, I served on the Scientific Advisory Board. Thinking about how things turned out, I realize that this position is a great fit. Although I didn't come from either an administrative or an oncology background, I am from a large hematology/oncology program at Dana-Farber/Boston Children's, and I really enjoy thinking about how to run clinical programs efficiently.

What are the primary responsibilities of a clinical director?

I am in charge of the clinical operations. The inpatient and outpatient clinical services, the doctors and nurses, and the ancillary programs, like the labs, pathology, and diagnostic imaging, report to me. St. Jude is quite a small hospital with a very large research component, and that research touches the clinical operations in so many ways. A very large portion of our inpatients and outpatients are on clinical protocols, and we need to get the research done to speed discoveries and cures for children. At the same time, we also need to ensure that we are running a safe hospital. The interface between these two areas is a key part of my role.

The second main part of my job is that I'm the Academic Chief for the clinical departments, for example, Oncology, Hematology, Infectious Diseases, Radiation Oncology, and Bone Marrow Transplantation & Cellular Therapy. In addition, Biostatistics and Epidemiology & Cancer Control report to me. Thus, I am responsible for the oversight or leadership of the faculty in these clinical departments.

What was the biggest surprise you had once you started working here?

I have been at St. Jude for just over a year now, and I'm still learning something surprising and new almost every day. One particularly eye-opening experience I had this first year was the budget process. I arrived at the end of the Fiscal Year 2018 budget process, so I attended only the very last meeting before the Board of Governors approved the budget. That seemed easy! This year, I was involved in the entire process for the first time. It was unique compared to my prior experience, because there is a generous budget to start and some growth built into the strategic plan process. Nevertheless, requests outpace the planned growth, and I learned how to help design that kind of budget and how the different parts of St Jude, the clinical and research domains and all the support functions, work together to make the final budget.

In the clinical domain, there are surprises all the time. I came from a very large children's hospital that had an emergency room, and all the specialists were on staff right there. Here, we share our consultants with Le Bonheur Children's Hospital, so strengthening that relationship is a very important part of what I do. Learning about that relationship has been thought provoking. Learning about the unique St. Jude patient-acceptance process and financial-support policies has also been very interesting.

What's your top priority for improving clinical care and research at St. Jude?

My main priority is to work on improving the hospital's operational efficiency. We're proud of being ranked the #1 Top Children's Cancer Hospital, and we have unparalleled research; yet in some ways, we're not necessarily efficient. If we can run the clinical programs more efficiently, then we can get patients in and out faster. This may help with increased patient satisfaction and lead to safer treatment, because, for example, we will be able to start to treat more patients on the day shift, when staffing is most ample, than in the evenings or nights.

This idea of operational efficiency is really about improving throughput. We don't have to cut anything, or even necessarily make people work harder, for things to be more efficient. What we need is for our processes to support a better flow of patients. This has been and still will be my #1 priority this coming fiscal year.

At the same time, my other main priority is to foster the spirits of teamwork and togetherness among the clinical staff. To accomplish this at the same time we are striving for better efficiency is going to take a degree of culture change. That is a key challenge. I need to be sure to bring everyone along together and to be sure we can reach consensus about the goals and move forward together.

Who inspires you in what you do?

Dr. David Nathan, from Boston Children's Hospital and Dana Farber, is one of the fathers of modern pediatric hematology/oncology as we now know it. He was a key inspiration to me.

At St. Jude, I think we get inspirational leadership from Dr. Downing. He has really captured, for me, both what is special about this place and what we need to do better. In addition to Dr. Downing, I love the people I work with here. The executive leadership team is terrific. I enjoy working with Pat Keel, the Chief Financial Officer, because she really "gets it." I also enjoy working with Dr. Pat Flynn, the Deputy Clinical Director. She also runs the Quality and Patient Care Program, which is extraordinarily important to the hospital. I really appreciate what she does.

My mom, Dr. Elizabeth Neufeld, is a scientist, and she has been a big influence on my whole career, in terms of trying to do the best science. She is a bit bewildered by my decision to take up hospital administration, though she was ultimately a department chair and then a dean. Although I don't mind it, I admit that nobody really likes going to meetings all day. Of course, the important part is to see past the meetings to the goals and working with the teams and faculty to make a difference.

Ellis J. Neufeld, MD, PhD
Clinical Director
Physician-in-Chief
John and Lorine Thrasher Endowed Chair in Pediatric Medicine

LEADERSHIP PROFILE: Stephen M. Gottschalk, MD

What drives you scientifically?
The biggest driver of my research is the insight that the immune system can destroy cancer cells. Cell-based immunotherapies hold the promise to improve outcomes for children with cancer who currently cannot be cured. Because cell therapies are also highly cancer specific, they might ultimately reduce the incidence of long-term treatment-related complications endured by all pediatric cancer survivors.

What was your career path that led you to St. Jude?
I am originally from Germany and attended medical school at Georg August University in Göttingen. During medical school, I did laboratory-based research on lysosomal storage diseases, under the mentorship of Dr. Kurt von Figura. In the early 1990s, we all believed that gene therapy for storage diseases was "just around the corner." Therefore, I joined the laboratory of Dr. Savio Woo at Baylor College of Medicine. His lab was actively conducting preclinical gene therapy studies, and I focused on developing nonviral gene-delivery complexes.

Initially, I had planned to stay at Baylor for 2 years and then go back to Germany. However, Dr. Ralph Feigin, the former chair of Baylor's Department of Pediatrics, offered me a pediatric residency position at Texas Children's Hospital, and I decided to stay. Based on my research interest, I initially wanted to become a medical geneticist, but this changed during my intern rotation on the general pediatric oncology ward. Taking care of patients with cancer was very rewarding, and I realized that pediatric oncology offered ample research opportunities.

Dr. David Poplack, the director of Texas Children's Cancer Center, encouraged me to do a pediatric hematology-oncology fellowship, which I started in 1998. Research-wise, I immediately gravitated to hematopoietic stem cell transplantation and cell therapy. This was mainly driven by Dr. Malcolm Brenner and his team, Drs. Helen Heslop, Cliona Rooney, and Robert Krance, who had just arrived at Baylor from St. Jude. I joined Clio's laboratory and focused on immunotherapy of Epstein-Barr virus (EBV)-associated diseases with EBV-specific T cells.

In 2001, I became a faculty member and developed a research program focused on immunotherapies with genetically modified T cells for sarcomas and brain tumors. A major focus of my lab's work remains to explore genetic approaches to improve the antitumor activity of T cells. I stayed at Texas Children's Cancer Center and Baylor's Center for Cell and Gene Therapy for my entire professional career, until I became Chair of the Department of Bone Marrow Transplantation & Cellular Therapy at St. Jude in August 2017.

What qualities are required to lead a department of translational and clinical researchers?
First, you must have a clear vision of what you want to accomplish. Since translational and clinical research is team science, you also must be able to build and lead research teams and enable physician-scientists to be leaders. For example, Dr. Brandon Triplett is Chief of our Bone Marrow Transplant Clinical Service. Without him, I could not do my job.

Another key quality, for me, is that I still see patients. Patients are great motivators, and their stories and diseases should drive our research. They are also a good reality check when you have been in the lab, in meetings, or in your office for a while, and you are upset about something that has not worked out.

Finally, you have to be able to interact with other departments and centers at St. Jude. I believe that the ability to develop and maintain collaborations not only with St. Jude investigators but also with investigators at other institutions will be critical for the success of our department.

What are your long-term goals for bone marrow transplantation and cellular therapy research and treatment at St. Jude?
First, we want to build on our excellence in hematopoietic stem cell transplantation and develop the next generation of transplant protocols. This will include the transplantation of genetically modified hematopoietic stem cells for diseases such as sickle cell disease. Second, we want to build an exemplary experimental cell-based immunotherapy program focused on pediatric cancers that are difficult to treat, including acute myeloid leukemia, metastatic sarcoma, and brain tumors.

Who inspires you in what you do?
At each step of my career, my mentors have inspired me. Kurt von Figura inspired me to become a physician-scientist; David Poplack inspired me to be a pediatric oncologist; and Malcolm Brenner and Robert Krance inspired me to become a pediatric transplanter. Then there was Clio Rooney. Without her, it would have taken me much longer to figure out that one particular type of immune cell, a so-called T cell, can cure cancer. As Clio likes to say, "T stands for terrific!"

Stephen M. Gottschalk, MD
Chair, Department of Bone Marrow Transplantation & Cellular Therapy
Endowed Chair in Bone Marrow Transplantation & Cellular Therapy

LEADERSHIP PROFILE: Charalampos Kalodimos, PhD

What drives you scientifically?
I feel that this has changed over time. I became a scientist because I was driven by curiosity. I wanted to be able to make discoveries or find out how something works. Structural Biology is especially gratifying in this regard, because we determine atomic-resolution structures of proteins and other biological molecules. As a structural biologist, you actually see what a molecule looks like in exquisite detail, and in many cases, you are the very first person to ever see that molecule, which is very exciting.

As my career advanced, I felt the need for my scientific discoveries to have an impact on society and the community in general. That has become a very important motivation for what I do. Since coming to St. Jude, it has been impossible for me to not be inspired by the mission of the hospital and the kids themselves. I see the kids every day and, as a parent, I admire their courage and strength despite what they are going through. I reflect every day on how to steer my research program, and that of the Structural Biology department, to more directly address questions about these catastrophic diseases.

What was your career path that led you to St. Jude?
I earned my undergraduate degree in chemistry and physics in Greece. Then, I moved to Paris, France, to the Institut Curie, where I did my PhD in biophysics. After that, I moved to The Netherlands, where I completed a postdoctoral fellowship in structural biology at Utrecht University. In 2004, I moved to the United States. First, I was at Rutgers University in New Jersey, as an assistant professor, and then in 2015, I went to the University of Minnesota Medical School. Last summer, I came to St. Jude to assume the Chair of the Department of Structural Biology. Although I had turned down previous offers to become a chair at other institutions, it was an easy decision to accept St. Jude's offer. I am very excited that I have been given the opportunity to implement my vision for establishing a world-class Structural Biology department here.

What are the most important scientific questions that you hope to address at St. Jude?
We are working on a lot of questions that relate to a variety of biological systems. One of the most important areas is protein kinases. When these molecules malfunction, they can cause leukemia. We don't really understand how most protein kinases function. How and why do they malfunction? Why do they give rise to leukemia? How can we generate therapeutic molecules as drugs? Another very important question that only structural biology can answer is about the molecular basis for drug resistance. Why do some patients become resistant to certain drugs? How do we get around that problem? Can we develop new drugs to prevent resistance? My lab also works on a number of other biological systems that are involved in bacterial infections and neurologic diseases.

How does structural biology research support the mission of St. Jude?
There is absolutely no way to understand the molecular basis of any disease, or life for that matter, unless you understand the underlying basic mechanisms of the function of the biological systems under investigation. To gain that understanding, the atomic-resolution structure of these biological systems, which shows you their exact shape and how it changes as a function of the environment or mutations, is required. Structural biology provides such information in amazing detail and thus is key to understanding diseases and discovering new therapies. For example, the process of developing drugs by leveraging the information provided by structural biology approaches has been tremendously successful.

St. Jude is investing in multiple advanced technologies that will enable us to determine high-resolution structures of proteins that have been, until recently, very challenging to get. One approach is nuclear magnetic resonance (NMR) spectroscopy. We are bringing the most powerful (1.1-GHz) magnet in the world to campus later this year. We are also in the process of installing two cryoelectron microscopes (cryo-EM), among other new high-resolution systems. St. Jude will be one of the very few institutions in the United States that houses all of these high-resolution technologies under one roof.

My vision is to make structural biology more accessible to all researchers on campus. We plan to create five centers based on high-resolution technologies: NMR spectroscopy, cryo-EM, x-ray crystallography, mass spectrometry, and single-molecule spectroscopy. These centers are staffed by directors and specialized scientists. Our department will double in size over the next few years, in terms of the number of faculty and staff, and all centers will be running at full capacity with the highest standards.

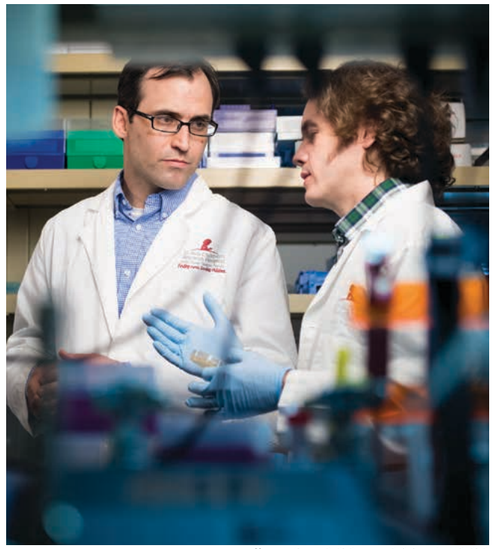
Who inspires you in what you do?
As I said earlier, you go through different phases in your scientific life. Before I came to St. Jude, my work was rarely inspired by outside influences, other than important biological issues. I was curious. I have a passion for science, and I like discovering new things. Coming to St. Jude has been a life-altering experience for me.

At St. Jude, the ones who are most inspiring, by far, are the kids. Here the kids are not isolated from the researchers. You see them every day. I have never experienced this kind of proximity to patients or clinical departments before. When I was working in my lab at my previous academic institutions, I did not think about how my work related to the reality of what patients are going through, but here, you see it and can't help but think about it.

I have two daughters, and as a father, I never thought about calamities happening or what the experience of a catastrophic disease would be like as a parent. Working at St. Jude has changed that for me. When you are here, you realize that the projects you are working on in the lab can really have an impact on people's lives.

Charalampos Babis Kalodimos, PhD
Chair, Department of Structural Biology
Joseph Simone Endowed Chair in Basic Research

SCIENTIFIC HIGHLIGHTS



Jeffery M. Klco, MD, PhD; Jason R. Schwartz, MD, PhD

Mutations in the Ras/MAPK Pathway or *SAMD9/SAMD9L* Genes Can Lead to Pediatric Myelodysplastic Syndrome

Myelodysplastic syndromes (MDS) are a heterogeneous group of disorders that affect hematopoiesis (the production of blood cells). MDS account for less than 5% of pediatric hematologic cancers and typically has a poor prognosis. Most genomic studies of pediatric MDS have focused on genes implicated in adult MDS, despite the fact that pediatric MDS and adult MDS have different clinical and pathologic features. Thus, a comprehensive sequencing study was needed to gain a more complete understanding of MDS in children.

Working in the laboratory of Jeffery M. Klco, MD, PhD (Pathology), Jason R. Schwartz, MD, PhD, a clinical fellow in the Physician-Scientist Training Program, and colleagues used a range of next-generation sequencing approaches to elucidate the somatic and germline genetic changes in pediatric MDS. In *Nature Communications*, Dr. Klco's team published their results from 77 pediatric patients, including 46 patients with primary MDS, 23 patients with overlapping features of MDS and a myeloproliferative neoplasm [including 19 with juvenile myelomonocytic leukemia (JMML)], and eight patients with acute myeloid leukemia (AML) with myelodysplasia-related changes. Whole-exome sequencing was performed on paired samples of tumor and normal cells from 54 (70%) patients; tumor material from the remaining 23 patients was analyzed using a targeted-sequencing strategy.

The most common mutations (germline or somatic) in pediatric MDS involved genes in the Ras/MAPK-signaling pathway and chromosomal deletions involving chromosome 7. Ras/MAPK mutations were detected in 42 (55%) patients and up to 65% of patients with high-grade MDS. In contrast, they reportedly occur in only 10% of adult MDS cases. Likewise, deletions involving chromosome 7 were present in 41% of children with MDS. Germline variants in *SAMD9* or *SAMD9L* were found in nearly 20% of the patients with primary MDS, and all of those patients also had monosomy 7. In a separate study, Dr. Klco's group discovered a germline *SAMD9* mutation in three siblings with monosomy 7 and MDS but no family history suggestive of a predisposition to MDS or AML. This finding, published in *Leukemia*, represents the first report of *SAMD9* mutations in isolated familial MDS.

The *SAMD9* and *SAMD9L* genes are both located on chromosome 7, and their expression is induced by interferons, such as during a viral infection. Surprisingly, the tumor cells with monosomy 7 do not contain the germline mutation. Furthermore, other cells will remove or inactivate the germline mutation through loss of heterozygosity or acquisition of additional somatic alterations that counteract the germline variant (so-called revertant mutations). Thus, there is strong selective pressure to not express the germline mutation in hematopoietic cells. Considering that monosomy 7 contributes to MDS, it appears that the MDS in children with germline *SAMD9/SAMD9L* mutations most likely is not caused by the germline mutations per se but is a consequence of the cells' adaptation to the mutation.

Collectively, these data reveal distinct mutation patterns in pediatric MDS and confirm that adult MDS and pediatric MDS are separate diseases with different underlying mechanisms. Furthermore, the researchers consider *SAMD9/SAMD9L* mutations a new class of pediatric MDS-predisposition genes that warrant further investigation. *Schwartz JR et al, Nat Commun 8:1557, 2017; Schwartz JR et al, Leukemia 31: 1827–30, 2017*

Selective Inhibition of a Novel Protein Interaction Mitigates Drug Resistance in Acute Myeloid Leukemia Cells

The prognosis for survival of acute myeloid leukemia (AML) is poor; more than 70% of patients with AML die within 5 years of diagnosis. Amplification or overexpression of the ATP-binding cassette (ABC) transporter *ABCC4* on AML cells facilitates drug resistance and, therefore, further reduces patient survival. The ABCC4 protein contains a common structural domain, termed the PDZ domain, which is found in many signaling proteins. PDZ domain–containing proteins are frequently regulated by interactions with proteins that harbor PDZ-binding domains. However, whether ABCC4 is regulated by such interacting partners is unknown. To identify potential new molecular targets for the treatment of AML, John D. Schuetz, PhD (Pharmaceutical Sciences), and his colleagues performed an unbiased screen of proteins containing a single PDZ-binding domain that are overexpressed in the leukemic cells of patients with AML.

As reported in *Nature Communications*, the team identified membrane palmitoylated protein 1 (MPP1) as the protein containing a PDZ-binding domain that had the highest level of expression in conjunction with ABCC4 in AML cells. Accordingly, high levels of MPP1 were also associated with a low probability of survival in patients with AML. The researchers observed that MPP1 interacts with ABCC4 via its PDZ domain to promote ABCC4 translocation to the plasma membrane. This interaction is also required for the drug-resistance activity of ABCC4. CRISPR/Cas9-mediated deletion of the *MPP1* gene from human AML cell lines reduced the plasma membrane localization of ABCC4 and increased the cells' sensitivity to 6-mercaptopurine, a chemotherapeutic substrate of ABCC4. Moreover, murine hematopoietic progenitor cells transduced with *MPP1* exhibited increased colony formation when serially replated in methylcellulose. This activity depended on the presence of endogenous ABCC4, suggesting that the MPP1–ABCC4 interaction contributes to leukemogenesis.

To elucidate a potential chemical inhibitor of the PDZ domain–dependent interaction between MPP1 and ABCC4, Dr. Schuetz's group performed an in vitro screen of 11,297 small-molecule compounds. Of the 219 compounds that inhibited the PDZ domain–mediated MPP1–ABCC4 interaction, 17 were dose responsive in a time-resolved fluorescence resonance energy transfer (TR-FRET) assay, and antimycin A was the most potent of these. Antimycin A treatment sensitized human AML cells expressing high levels of MPP1 and ABCC4 to 6-mercaptopurine–induced cytotoxicity. It also blocked the translocation of ABCC4 to the plasma membrane of human AML cells and inhibited the colony formation of murine hematopoietic progenitor cells transduced with *MPP1*. Therefore, compounds like antimycin A may improve chemotherapeutic efficacy for AML and other cancers prone to drug resistance by inhibiting the unexpected MPP1–ABCC4 interaction that is essential for ABCC4 activity. *Pitre A et al, Nat Commun 8:1547, 2017*

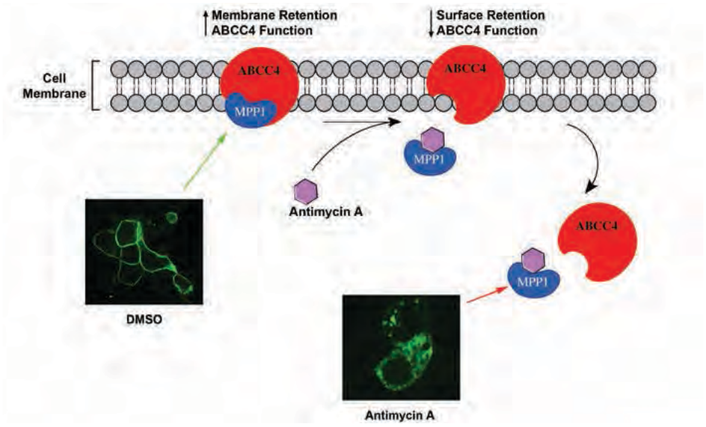


Figure. Model of antimycin A treatment blocking the MPP1 interaction with ABCC4 (green stain in confocal microscopy images) in AML cells. The MPP1–ABCC4 interaction is essential for ABCC4 to translocate to the plasma membrane. It is also required for the drug-resistance activity of ABCC4. Treatment with antimycin A prevents ABCC4 translocation to the plasma membrane; therefore, compounds like antimycin A may improve outcomes for patients with AML by impeding drug resistance. *© 2017 Pitre A et al. The Creative Commons License is available at https://creativecommons.org/licenses/by/4.0/.*

Liver Kinase B1 Programs the Metabolic and Functional Fitness of Regulatory T Cells to Modulate Inflammatory Responses

Regulatory T cells (T_{regs}) constitute a subpopulation of immunosuppressive T cells that dampen aberrant inflammatory responses and prevent autoimmune diseases. The metabolic programs and functions of T_{regs} are distinct from those of other T-cell subpopulations, but the underlying mechanisms and molecular regulators remain poorly understood. To investigate metabolic control of T_{regs} and how this regulation affects T_{reg}-modulated inflammatory responses, Hongbo Chi, PhD (Immunology), and his colleagues specifically deleted the *Stk11* gene, which encodes the tumor suppressor and metabolic sensor liver kinase B1 (LKB1), from the T_{regs} of mice.

In *Nature*, the researchers reported that the targeted loss of *Stk11* in mouse T_{regs} resulted in a fatal inflammatory disease characterized by reduced body weight and size, skin ulcerations, splenomegaly, lymphadenopathy, and immune cell infiltration of numerous organs. This phenotype was also associated with a marked depletion of the T_{reg} population, indicating that LKB1 is important for T_{reg} survival. *Stk11* depletion impaired T_{reg} mitochondrial function, leading to decreased mitochondrial mass and membrane potential, diminished intracellular ATP levels, and aberrantly accumulated lipids.

The AMP-activated protein kinase AMPK is a well-known downstream effector of LKB1 that acts as an energy sensor and metabolic switch in many cell types. When Dr. Chi's team deleted the genes encoding the two catalytic subunits of AMPK in mouse T_{regs}, the survival and anti-inflammatory functions of T_{regs} were preserved. Furthermore, when constituents of the mTORC1–HIF-1α axis (i.e., downstream effector pathways associated with tumorigenesis in LKB1-deficient cancer cells) were deleted in LKB1-deficient T_{regs}, mitochondrial dysfunction and cell survival were not rescued. These findings indicate that LKB1 regulates T_{reg} metabolic and functional fitness independently of these conventional pathways.

Stk11-depleted T_{regs} expressed elevated levels of the programmed cell death 1 (PD-1) receptor and TNFR superfamily proteins glucocorticoid-induced TNFR-related protein (GITR) and OX40, which are negative regulators of T_{reg} function and generation. In addition, protein levels of β-catenin, a transcription factor ectopically activated in many cancers, were reduced in *Stk11*-depleted T_{regs}. To determine the role of β-catenin in T_{reg} function, Dr. Chi's team introduced constitutively active β-catenin in *Stk11*-depleted T_{regs}. This attenuated PD-1, TNFR, and GITR levels and restored immunosuppressive functions to LKB1-deficient T_{regs}, indicating that LKB1 mediates T_{reg} function through a novel mechanism in which the LKB1–β-catenin axis dampens PD-1, GITR, and OX40 expression to permit proper control of inflammatory responses. *Yang K et al, Nature 548:602–6, 2017*

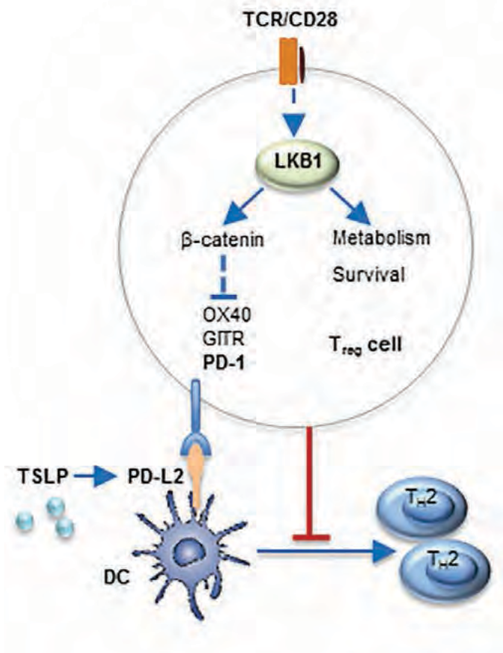


Figure. Illustration of LKB1 coordinating the metabolic and functional fitness of T_{regs} to prevent undesired immune responses. Abbreviations: DC, dendritic cell; GITR, glucocorticoid-induced TNFR-related protein; PD-1, programmed cell death 1; PD-L2, programmed death ligand 2; TCR, T-cell receptor; T_H2, T helper 2 cell; TSLP, thymic stromal lymphopoietin. *© 2017 Yang K et al*

Asya Agulnik, MD, MPH

Accurately Predicting Critical Illness in Hospitalized Pediatric Oncology Patients in Resource-Limited Settings

Cardiopulmonary arrests in hospitalized children are rare; they occur in fewer than 1% of hospital admissions and fewer than 1.5% of pediatric intensive care unit (PICU) admissions. Unfortunately, survival of these children to hospital discharge is low (less than 40%), particularly for those with cancer. Outcomes are worse still in hospitals in low- and middle-income countries because of limited resources and personnel shortages. To determine whether using a low-cost Pediatric Early Warning System (PEWS) could accurately identify hospitalized children with cancer who are experiencing clinical deterioration in resource-limited settings, Asya Agulnik, MD, MPH (Global Pediatric Medicine, Critical Care), and her colleagues retrospectively analyzed data of children treated at the Unidad Nacional de Oncologia Pediatrica (Guatemala City, Guatemala) who required unplanned PICU transfer. Medical records from January 1 to December 31, 2015, were reviewed.

The PEWS system has two arms—a scoring tool and a response algorithm. The PEWS score has five components (i.e., behavior/neurologic, cardiovascular, respiratory, staff concern, and family concern) and is calculated by the bedside nurse with every set of vital signs for hospitalized patients. The PEWS escalation algorithm interprets the PEWS result and guides the clinical team in how to respond to a patient with clinical deterioration.

In the journal *Cancer*, Dr. Agulnik and her collaborators reported that the PEWS tool accurately predicted the need for unplanned transfer to the PICU as early as 24 hours before the PICU admission in hospitalized pediatric oncology patients. Patients requiring unplanned transfer to the PICU who had higher PEWS results had more organ dysfunction, a higher severity of illness, required more critical care interventions, and had higher mortality.

The investigators noted that not only was the PEWS score strongly associated with the subsequent need for transfer to the PICU, but also the performance of the system was similar to that found when the tool is used in high-resource hospitals. This finding supports the potential use of PEWS in a host of settings caring for children with cancer. The PEWS result increased, indicating possible deterioration, as early as 24 hours before PICU admission, suggesting that PEWS may identify deterioration before the clinical team does. Moreover, higher scores were predictive of critical illness and mortality risk. Thus, Dr. Agulnik's group concluded that the PEWS accurately identified clinical deterioration in hospitalized pediatric oncology patients and should be used to facilitate improved monitoring and earlier interventions for these patients at high risk, regardless of a hospital's resource level. They also propose that early PICU transfer for critically ill children with cancer may improve survival. *Agulnik A et al, Cancer 123:4903–13, 2017*

Identification of Seven Molecular Subgroups of Pediatric non–Down Syndrome Acute Megakaryoblastic Leukemia

Acute megakaryoblastic leukemia (AMKL) is a subtype of acute myeloid leukemia (AML) that is rare in adults but accounts for as many as 15% of new pediatric AML cases annually. AMKL is associated with a poor outcome when it occurs in patients who do not have Down syndrome (non–DS-AMKL). Gene rearrangements specific to non–DS-AMKL have been identified, but at least 30% of cases of the disease lack any known mutations. To more comprehensively understand the genetic basis of non–DS-AMKL, Tanja A. Gruber, MD, PhD (Oncology, Pathology), and a global network of collaborators used RNA- and/or exome-sequencing approaches to examine alterations in the genetic codes of samples from 75 pediatric patients and 24 adult patients with non–DS-AMKL. They then combined their data with that from a previous report of 14 pediatric cases, resulting in the genomic analysis of the largest pediatric non–DS-AMKL cohort to date.

In a recent *Nature Genetics* article, Dr. Gruber's group reported that pediatric and adult non–DS-AMKL are genomically distinct: 72.4% of the pediatric cases harbored genetic changes predicted to result in a fusion protein, whereas only 5.5% of adult cases did. Furthermore, they identified seven distinct subtypes of the disease: *GATA1*, *HOXr*, *RBM15-MKL1*, *NUP98-KDM5A*, *KMT2Ar*, *CBFA2T3-GLIS2*, and none/other, indicating that pediatric non–DS-AMLK is a heterogeneous disease. Some genetic changes seen in the pediatric samples were previously unreported. Clustering analysis indicated that these fusion events affected gene expression, with nearly half involving upregulation of the homeobox (HOX) genes, whose dysregulation results in leukemic transformation. Dr. Gruber's group also found substantial differences in overall survival, event-free survival, and disease relapse/recurrence across the molecular subgroups, with patients in the *GATA1* and *HOXr* groups having significantly better outcomes than those patients carrying *KMT2Ar*, *NUP98–KDM5A*, or *CBFA2T3–GLIS2* fusion events. On the basis of these data, the authors recommend stem cell transplantation during first remission for only a subset of patients with non–DS-AMKL.

This work highlights the benefit of using genetic classification in non–DS-AMKL to yield information about prognosis and best treatments. *de Rooij JDE et al, Nat Genet 49:451–6, 2017*

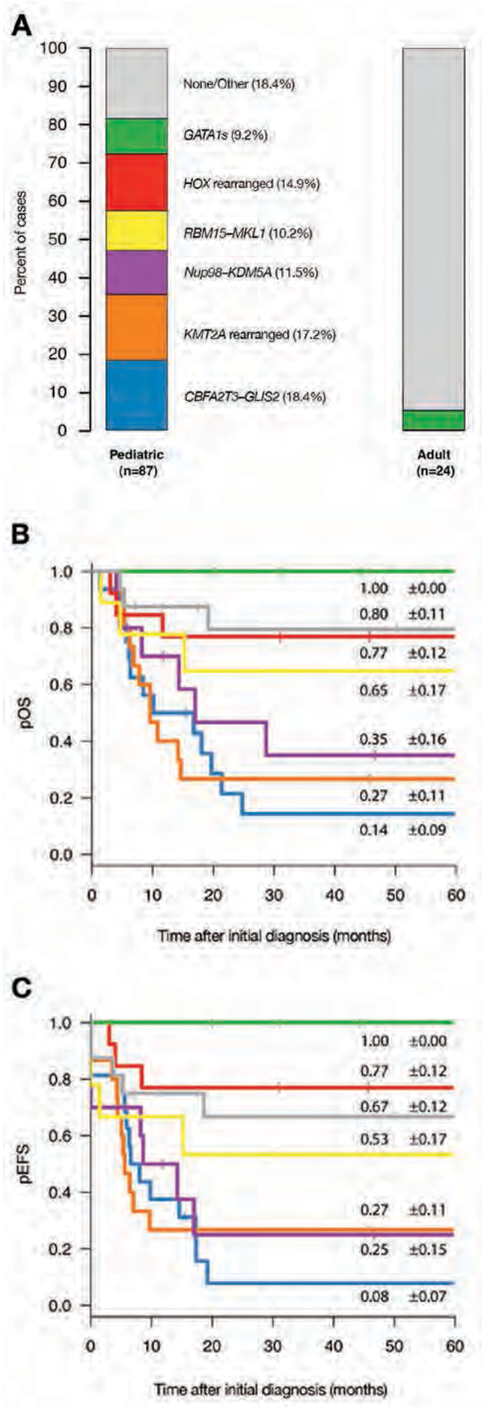


Figure. (**A**) The distribution of recurrent chromosomal translocations and *GATA1* mutations in pediatric and adult non–DS-AMKL indicate that these diseases are genomically distinct. (**B**) The probability of overall survival (pOS) and (**C**) event-free survival (pEFS) of pediatric patients with non–DS-AMKL grouped according to molecular subgroup. *© 2017 de Rooij JDE et al*

Defining the Features of Epitope-Specific T-Cell Receptor Repertoires and Adaptive Immune Recognition

The immune system is a complex network of cells, tissues, and organs working in conjunction to protect the body from pathogenic infections. Among the multitude of cells that make up the immune system, T cells are the most important for generating adaptive immune responses against pathogens. T-cell receptors (TCRs) on the T-cell surface recognize and respond to pathogen-associated epitopes (i.e., the portions of the molecules targeted by the immune system) on antigens through interactions with peptide and major histocompatibility complexes (pMHCs). Genomic rearrangements in the germline *TCR* locus can generate millions of different TCRs, which are collectively termed the T-cell repertoire.

The tremendous diversity among TCRs can make it difficult to categorize the ones that recognize the same epitope. However, TCRs that recognize the same epitope often share conserved sequence features, which may help predictively model epitope specificity. Paul G. Thomas, PhD (Immunology), and his colleagues developed an algorithm using analytical tools to characterize the determinants of epitope specificity. In a study reported in *Nature*, the researchers characterized 10 epitope-specific TCR repertoires of $CD8^+$ T cells from 78 mice infected with influenza or cytomegalovirus and 32 humans infected with influenza, cytomegalovirus, or Epstein-Barr virus, representing 4635 paired in-frame TCR sequences.

The tool TCRdist, which measures the distance between TCRs, was used to map epitope-specific TCR landscapes at high resolution and calculate the similarities and differences among TCRs. TCRdist-based clustering of epitope-specific receptors was performed, and hierarchical distance trees were constructed. This analysis revealed that in addition to core clusters of related receptors, each repertoire has divergent regions of receptors that are distinct. The diversity metric TCRdiv was used to capture not only the exact identities of receptors but also the similarities across receptors. To test the predictive power of TCRdist, the researchers defined a TCR classifier that assigns a given receptor to the repertoire with the greatest density of nearby receptors. The classifier correctly assigned 78% of mouse receptors and 81% of human receptors to one of 10 viral epitopes.

This algorithm represents a major advance in understanding the T-cell repertoire against a particular antigen and may be the Rosetta Stone needed to decode immune recognition. In future studies, Dr. Thomas and his collaborators plan to analyze mixed-repertoire data generated in clinical settings, wherein the identities of antigen-specific targets are unknown. The authors foresee the development of a model for TCR:pMHC recognition that could have important applications in cancer immunotherapy and the diagnosis of infectious diseases. *Dash P et al, Nature 547:89–93, 2017*

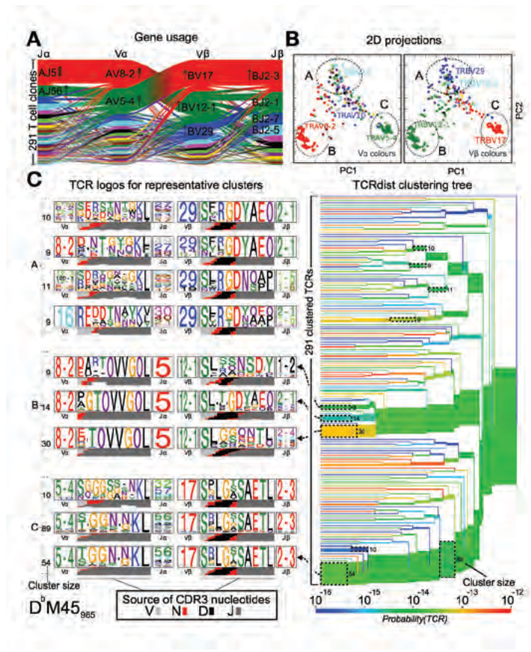


Figure. TCRdist analysis identifies clusters of antigen-specific receptors in a diverse T-cell repertoire. (**A**) Gene-segment usage and gene–gene pairing landscape are illustrated via four vertical stacks. Genes are colored by frequency within the repertoire (i.e., red, most frequent; black, least frequent). (**B**) Two-dimensional kernel principal component analysis of the TCRdist landscape colored by Vα (left) and Vβ (right) gene usage. Three TCR clusters are indicated within the dashed ellipses. (**C**) Average-linked dendrogram of TCRdist receptor clusters colored by generation probability. Dashed boxes indicate the TCR logos for selected receptor subsets. © *2017 Dash P et al*

Deena R. Levine, MD

Pediatric Oncology Patients and Their Parents Desire Integration of Palliative Care Early in Treatment

The symptoms associated with cancer and its treatment can considerably impair a patient's quality of life, especially in children. Early integration of palliative care for adult oncology patients leads to enhanced quality of life, reduced depressive symptoms, and improved outcomes. The benefits of palliative care for pediatric oncology patients at the end of life are also well known, and the American Academy of Pediatrics recommends that palliative care be offered at diagnosis and continued throughout cancer treatment. However, most children do not receive palliative care early in their treatment regimen. It is commonly assumed that such patients and their parents are more focused on pursuing a cure rather than quality of life at the time of diagnosis, but the evidence to support this assumption is lacking. To identify potential barriers to the early integration of palliative care in cancer treatment for children, Deena R. Levine, MD (Oncology), led a multicenter study in which a survey was administered to 129 pediatric patients (aged 10-17 years) with a recent diagnosis of cancer and one parent of each patient over a 4-year period at three pediatric oncology hospitals.

Patients and parents completed different surveys, in separate rooms, that ascertained the patient's symptoms within the first month of therapy, the degree of symptom-related suffering experienced, knowledge of palliative care, willingness to receive palliative care, and reasons for negative opinions about palliative care. Dr. Levine and her collaborators reported the survey findings in *JAMA Oncology*. The most prevalent symptoms experienced by patients during the first month of cancer therapy were nausea, loss of appetite, pain, anxiety, constipation, depression, and diarrhea, all of which affect quality of life. The majority of patients (98.4%) and their parents (69.8%) were unfamiliar with the term "palliative care." However, after a brief definition of a palliative care team was provided (i.e., a group of clinicians with expertise in symptom management and a goal of improving quality of life), very few patients (1.6%) or parents (6.2%) expressed opposition to early palliative care integration. Indeed, most patients (58.9%) and parents (50.4%) believed that palliative care teams should be involved at the beginning of treatment. This was particularly evident for patients who rated their current quality of life as poor.

Although both patients and parents expressed willingness to receive early palliative care, patients were more likely than their parents (40.3% vs 17.8%) to state that including a palliative care team around the time of diagnosis would have been helpful for symptom management. This is especially noteworthy due to the high burden of patient-reported symptom suffering [nausea (84.5%), loss of appetite (75.2%), pain (74.4%), anxiety (59.7%), constipation (53.5%), depression (49.6%), and diarrhea (40.3%)] and overall poor concordance between patients and parents in perceived symptom suffering (26%-29%). This finding suggests that oncology care providers should ascertain pain and symptom severity directly from patients, when possible, because their perceptions may not be accurately represented by their parents. *Levine DR et al, JAMA Oncol 3:1214–20, 2017*

Hundreds of Blood Progenitors Contribute to Lifelong Hematopoiesis in Mammals

Hematopoietic stem cells (HSCs) self-renew and differentiate into various blood lineages, thereby ensuring a continuous supply of new blood cells throughout the lifetime of an organism. The current view suggests that lifelong blood production in mammals is established by a small number of HSCs. However, the studies resulting in that view involved the disruption, transplantation, or growth in culture of embryonic tissues, which might not faithfully reflect HSC formation in vivo or identify the entire repertoire of cells that sustain lifelong hematopoiesis.

To accurately quantify the number of independently specified precursors contributing to lifelong blood production at specific stages of mouse ontogenesis, Shannon L. McKinney-Freeman, PhD (Hematology), and her research team measured sample-to-sample variance (SSV) of *Confetti*, a multicolored lineage trace reporter. Their novel method avoids disrupting the developing embryo. The *Confetti* allele recombined by Cre recombinase was used to label and analyze cellular progeny in the blood of adult mice from the following strains: *ROSA26*$^{+/Confetti}$, *Flk1*$^{+/Cre}$ (mesodermal precursors); *ROSA26*$^{+/Confetti}$, *VE cadherin*$^{+/Cre}$ (endothelial precursors); and *ROSA26*$^{+/Confetti}$, *Vav1*$^{+/Cre}$ (newly created blood progenitors).

In each case, SSV in the distribution of *Confetti* colors in the blood of mice was inversely correlated with the number of initially labeled cells. A formula derived to estimate starting cell numbers based on SSV accurately predicted the number of cell precursors in a reconstituting hematopoietic system. The formula also performed satisfactorily in a non–transplant-based biologic context. The authors measured the number of independently specified precursors contributing to lifelong hematopoiesis at distinct stages of development by flow cytometry analysis. SSV in the blood of mouse cohorts revealed that 719 mesodermal precursors, 633 endothelial precursors, and 545 fetal liver hematopoietic precursors establish the emerging hematopoietic system on embryonic days (E) 7–E8.5, E8.5–E11.5, and E11.5–E14.5, respectively. Furthermore, many intra-aortic hematopoietic cell clusters were polyclonal in origin.

This study, which was published in *Nature Cell Biology*, shows that the origin of blood cells is much more complex than previously thought. Contrary to the current dogma that lifelong hematopoiesis in mammals is established by a few progenitors, Dr. McKinney-Freeman's team showed that hundreds of mesodermal and endodermal precursors establish hematopoiesis at different stages of ontogeny. These findings suggest that a developmental bottleneck in or downstream of the fetal liver stage of hematopoietic ontogeny restricts the number of precursors ultimately contributing to lifelong hematopoiesis. This study has important clinical implications for unraveling the origins of blood disorders and identifying cells susceptible to disease-causing mutations. *Ganuza M et al, Nat Cell Biol 19:1153–63, 2017*

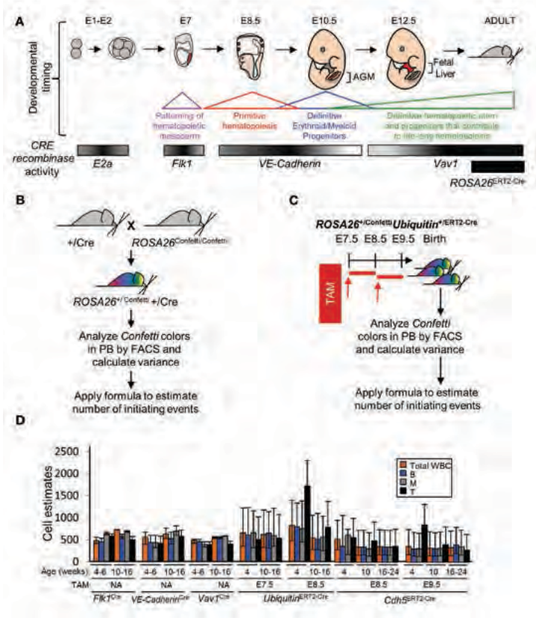


Figure. Hematopoietic cell development in mice. (**A**) Schematic of the timing and site of CRE recombinase activity during various stages of the development of hematopoiesis in different mouse strains. (**B**) Mating strategy to produce *ROSA26*$^{+/Confetti}$, +/Cre mice. (**C**) *ROSA26*$^{+/Confetti}$, *Ubiquitin*$^{+/ERT2-Cre}$ embryos were exposed to a single dose of tamoxifen at E7.5 or E8.5 to activate the *Confetti* label. At 10 weeks of age, peripheral blood was drawn from those mice; *Confetti* colors were analyzed; and sample-to-sample variance was calculated. (**D**) The numbers of hematopoietic precursor cells generating myeloid cells, B cells, and T cells are shown for different strains of mice exposed to tamoxifen at various embryonic stages. Abbreviations: FACS, fluorescence-activated cell sorting; NA, not applied; PB, peripheral blood; TAM, tamoxifen. *© 2017 Ganuza M et al*

Rejuvenating Exhausted T Cells to Control Chronic Viral Infections and Tumor Growth

Cytotoxic T cells are a major executor of adaptive immunity; they directly target and kill virus-infected or tumor cells. However, after prolonged stimulation, T-cell effector functions are gradually suppressed, until they develop a state of terminal T-cell exhaustion. Patients with conditions such as cancer or chronic infections can benefit from rejuvenation of the effector functions of exhausted T cells. To determine how T-cell exhaustion is regulated so that approaches to rejuvenate those cells and overcome their exhausted state can be designed, Benjamin A. Youngblood, PhD (Immunology), and his colleagues performed a series of sophisticated experiments in preclinical models of tumors or viral infection to map T cell–intrinsic DNA-methylation programs and determine their regulatory role in T-cell function.

Cells use DNA methylation to epigenetically silence the expression of certain genes under various conditions. In a study reported in *Cell*, Dr. Youngblood's team examined DNA methylation in the genomes of T cells collected from mice during two stages of chronic viral infection: the effector stage, when T cells interact to eliminate the antigen, and the exhaustion stage, when T-cell activity is suppressed. They also performed whole-genome bisulfite sequencing of CD8 T cells at both stages.

The researchers found that as the infection progressed, exhausted T cells methylated specific sets of genes, giving them epigenetic profiles similar to those of naïve T cells (i.e., inactive T cells that have not yet been exposed to antigen). These DNA-methylation programs mediated the development of T-cell exhaustion. During proliferation, exhausted T cells pass on their epigenetic program to their daughter cells, thereby perpetuating an inactive, exhausted state in the new cells, even in the absence of the original stimulating antigen.

Programmed cell death (PD-1) blockade therapy rejuvenates partially exhausted T cells but is unable to rejuvenate effector functions from terminally exhausted T cells. The researchers found that exhaustion-associated DNA-methylation programs were highly stable and could not be erased by PD-1 blockade treatment. In tumor-bearing mice, treatment with the chemotherapy drug decitabine, which turns off the DNA-methylation programming that causes T-cell exhaustion, enabled T-cell proliferation that ultimately helped reduce tumor growth. This work establishes the epigenetic programs that maintain T cells in the exhausted state and proposes a method by which this epigenetic programming can be overcome to maintain T-cell function needed for T cell–based immunotherapy. *Ghoneim HE et al, Cell 170:142–57, 2017*

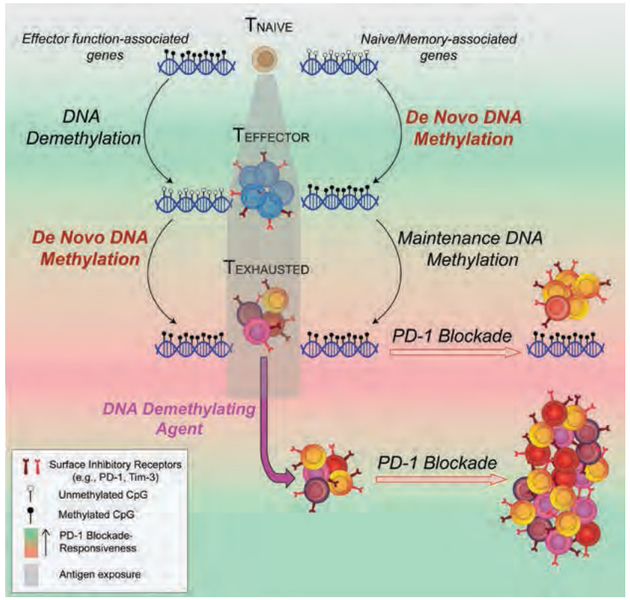


Figure. Illustration of de novo DNA-methylation programs that promote T-cell exhaustion. Inhibiting these programs can enhance T-cell rejuvenation and facilitate the control of chronic infections or tumor growth. *Reprinted from Cell, 170, Ghoneim HE et al, De novo epigenetic programs inhibit PD-1 blockade-mediated T cell rejuvenation, 142–57, © 2017, with permission from Elsevier.*

Rachel C. Brennan, MD

Topotecan Combination Therapy Helps Preserve Vision in Children with Advanced Retinoblastoma

Retinoblastoma is an aggressive intraocular cancer that usually occurs in very young children. When confined to the eye, it is very curable. Over the last 20 years, therapy has increasingly focused on ocular salvage and vision preservation. To avoid etoposide-related secondary leukemia associated with the current standard vincristine, carboplatin, and etoposide regimen, etoposide was replaced with topotecan in preclinical models and found to be effective in treating retinoblastoma. These encouraging findings led to the St. Jude prospective clinical trial RET5, which was open to accrual from February 2005 to November 2010. RET5 tested the vincristine and topotecan (VT) combination in children with advanced intraocular retinoblastoma. Treatment was stratified into three groups based on disease laterality and how advanced the disease was in each affected eye.

In the *Journal of Clinical Oncology*, Rachel C. Brennan MD (Oncology), Matthew W. Wilson, MD (Surgery), and colleagues reported a follow-up study conducted 10 years after the RET5 trial was initiated. This lengthy follow-up period ensured that the investigators could report ocular salvage and vision preservation in the patients enrolled in RET5 who received pharmacokinetically guided topotecan in combination with vincristine and carboplatin (Stratum B). This group included patients with bilateral disease whose eyes were classified as "unfavorable" or "very unfavorable," in terms of their likelihood for salvage. In previous studies, standard chemotherapy was able to save only 30% to 60% of eyes with advanced disease like this, often requiring radiation, which can lead to late effects such as second cancers in survivors. Patients on Stratum B of RET5 received neoadjuvant chemotherapy with two courses of VT, followed by vincristine and carboplatin, alternating with VT, for a total of 11 cycles of chemotherapy. Aggressive focal therapy (e.g., laser photocoagulation or cryotherapy administered directly to the eye) was also used, as was external-beam radiotherapy for evidence of tumor outside of the globe. Ocular survival (i.e., the interval between study entry and date of enucleation or last follow-up), event-free survival (EFS; the time between study entry and either enucleation or radiation), and adverse events were monitored.

Of the 27 patients (51 eyes) on Stratum B (median age at diagnosis, 8.4 months), 24 completed all chemotherapy courses (three were removed from protocol for disease progression or inability to tolerate therapy). Ten eyes were enucleated. The 10-year EFS and ocular survival per eye were 74%. The cumulative incidence of external-beam radiotherapy was 5.9% (two patients). Vision testing revealed 20/70 vision or better in one eye of 23 (83%) patients (median age, 7 years); 18 patients reported 20/40 vision in one eye (sufficient to obtain a driver's license). Adverse events included bone marrow suppression, fever, diarrhea, and one episode of allergic reaction to carboplatin. All patients were alive at a median follow-up of 7.4 years.

This study confirms the efficacy of incorporating topotecan into the treatment regimen of children with advanced bilateral intraocular retinoblastoma while avoiding etoposide exposure. Because the combination of topotecan, carboplatin, vincristine, and focal therapy significantly improves ocular survival with measurable vision, it should be considered as first-line therapy for advanced retinoblastoma. *Brennan RC et al, J Clin Oncol 35:72–7, 2017*

An N-Terminal Motif Positions the Active Site of Lysophosphatidic Acid Acyltransferase within the Cell Membrane

Phosphatidic acid is the central intermediate in membrane phospholipid synthesis and is generated via a two-step acylation pathway that is conserved in all organisms. In the first step, *sn*-glycerol-3-phosphate (G3P) is converted to 1-acyl-*sn*-glycerol-3-phosphate (LPA). This step is catalyzed by the enzyme G3P acyltransferase, which is called PlsB in bacteria. In the second step, LPA is converted to phosphatidic acid. This step is catalyzed by the enzyme 1-acyl-*sn*-glycerol-3-phosphate acyltransferase (LPAAT), which is called PlsC in bacteria. LPAAT enzymes are members of the evolutionarily conserved lysophosphatidic acid acyltransferase [or acylglycerolphosphate acyltransferase (AGPAT)] family of intrinsic membrane proteins.

Studies of the crystal structure of plant G3P acyltransferase had revealed an acyltransferase HX_4D active site within a single αβ-domain. G3P acyltransferase is a soluble enzyme, but LPAAT is an integral membrane enzyme that must gain access to its substrate within the phospholipid bilayer. The protein design that enables this access was unclear. The active sites of AGPAT enzymes were assumed to be positioned along the transmembrane helices at appropriate depths to enable the catalysis of membrane-embedded substrates. However, the various proposed models of the transmembrane helices of AGPATs were all unsatisfactory: the predicted structures were incompatible with the presence of a single acyltransferase αβ-domain and could not explain how AGPAT enzymes simultaneously access both membrane-bound and soluble substrates and bring them together at the active site for catalysis.

Stephen W. White, DPhil (Structural Biology), Charles O. Rock, PhD (Infectious Diseases), and their colleagues used x-ray crystallography and biochemical analyses to determine the structure and catalytic mechanism of PlsC from the bacterium *Thermotoga maritima*. Their findings were reported in *Nature Structural & Molecular Biology*. The structure–function analyses revealed that PlsC does contain the expected αβ-acyltransferase domain and the canonical HX_4D active site. However, this domain is linked to an unusual N-terminal two-helix motif that contains many hydrophobic and aromatic residues. Molecular dynamics simulations confirmed that the two-helix motif anchors PlsC to just one leaflet of the bilayer membrane, thereby allowing the enzyme to diffuse within the plane of the membrane in search of substrate. This arrangement enables the PlsC molecule to simultaneously bind membrane-associated LPA and the soluble acyl donor, position them in the active site for catalysis, and release the phosphatidic acid product directly into the phospholipid bilayer.

In humans, mutations in members of the AGPAT family are associated with diseases such as lipodystrophies, in which the body is unable to produce fat. Elucidating the structure of PlsC provides a model for understanding the structure and function of all AGPAT family members, including human AGPATs and their mutational defects. *Robertson RM et al, Nat Struct Mol Biol 24:666–71, 2017*

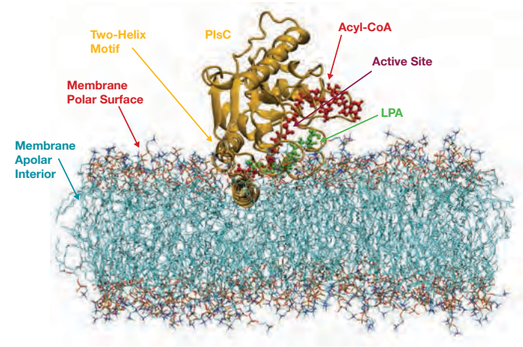


Figure. Ship-like model of how PlsC engages the membrane lipid bilayer. The model was obtained from a molecular dynamics simulation and shows the final equilibrium position. Note how the apolar two-helix motif acts like a "keel" that floats in the lipid interior "sea" of the membrane, which places the active site just above the polar membrane surface. This allows PlsC to simultaneously access and process the soluble acyl-CoA and the membrane-bound LPA.

COMPREHENSIVE CANCER CENTER

The National Cancer Institute (NCI) supports 69 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 10 shared resources, the Comprehensive Cancer Center emphasizes interdisciplinary laboratory-based and clinical research applicable to the understanding and treatment of childhood cancer.

CANCER BIOLOGY PROGRAM

Co-leaders: Martine F. Roussel, PhD; Douglas R. Green, 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 leads for therapeutic targeting, and explore and exploit anticancer mechanisms as routes to translation into clinical trials.

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, St. Jude Lifetime Cohort Study and the Childhood Cancer Survivor Study, program members are conducting research on a wide range of health-related and quality-of-life outcomes.

DEVELOPMENTAL BIOLOGY & SOLID TUMOR PROGRAM

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

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

HEMATOLOGICAL MALIGNANCIES PROGRAM

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

The overall goal of this program is to improve the cure rates for childhood leukemias and lymphomas, while minimizing treatment-related adverse effects. This established, highly interactive, transdisciplinary program has a long track record of major discoveries in cancer biology. Translation of these findings into new diagnostic and treatment approaches has changed the standard of care of pediatric 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, therapies through a better understanding of pathogenesis. By integrating genomic and genetic technologies into studies of the developing nervous system, members of this program are translating laboratory findings into new treatments. Recent efforts include the identification of the cells of origin of pediatric brain tumors and the modeling of some of the most aggressive tumors, including high-grade gliomas. Close collaboration among the laboratory and clinical members allows the rapid translation of candidate drugs identified in high-throughput drug screens.

SHARED RESOURCES

Animal Resource Center

Bioinformatics and Biotechnology

Biostatistics

Cell and Tissue Imaging

Cytogenetics

Flow Cytometry and Cell Sorting

Diagnostic Biomarkers

Pharmacokinetics

Protein Production

Transgenic/Gene Knockout

ST. JUDE AFFILIATE PROGRAM

The eight clinics that comprise the St. Jude Affiliate Program contribute to the institution's mission by enrolling patients on St. Jude protocols and participating in St. Jude treatment and research programs. The clinics provide patients the opportunity to receive part of their care at a facility near their home community.

Affiliate physicians and staff work together with comprehensive structured programs to achieve quality improvement for pediatric hematology-oncology patients in a clinical network of institutions. The Affiliate Program approaches quality improvement with a broad yet methodical system of monitoring, which is an effective strategy for consistently and uniformly affecting changes that improve patient outcomes across multiple institutions.

ADMINISTRATION
Medical Director • Carolyn L. Russo, MD

ST. JUDE AFFILIATE SITES

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Our Lady of the Lake Children's Hospital – Our Lady of the Lake Regional Medical Center
Medical Director Emeritis • Shelia Moore, MD
Medical Director • Jeffrey Deyo, MD, PhD
Kacie Sims, MD
Katherine Montgomery, NP
Jessica Templet, PA-C
Joseph Kent, PA

CHARLOTTE, NC
Novant Health Hemby Children's Hospital
Medical Director • Christine Bolen, MD
Randy Hock, MD, PhD
Jessica Bell, MD
Paulette Bryant, MD
Jenny McDaniel, MD

HUNTSVILLE, AL
Huntsville Hospital for Women & Children – Huntsville Hospital
Medical Director • Jennifer Cox, MD
Natalia Colorado, MD
Melanie Chipman, CRNP
Christine Thomas, CRNP
Ashley Duvall, CRNP

JOHNSON CITY, TN
Niswonger Children's Hospital – Johnson City Medical Center
East Tennessee State University
Medical Director • Marcela Popescu, MD
Abigail Cruz, MD
Angela Willocks, RN, MSN, CFNP

PEORIA, IL
Children's Hospital of Illinois – OSF Healthcare System
University of Illinois College of Medicine at Peoria
Pedro de Alarcon, MD, Chair of Pediatrics
Medical Director • Kay Saving, MD, Medical Director of CHOI
Mary Beth Ross, MD, PhD
Jaime Libes, MD
Brinda Mehta, MD
Beth Speckhart, NP
Sue Gaitros, NP
Diana Simmons, NP

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Feist-Weiller Cancer Center – LSU Health Sciences Center – Shreveport
Medical Director • Majed Jeroudi, MD
Diana Townsend, NP

SPRINGFIELD, MO
Mercy Children's Hospital – Springfield – Mercy Health System
Medical Director • Francisca Fasipe, MD
Mohamed Elsaid, MD
Carolyn Sullivan, NP

TULSA, OK
The Children's Hospital at Saint Francis
Medical Director • Greg Kirkpatrick, MD
Ashraf Mohamed, MD
Martina Hum, MD
Samantha Zeller, NP
Alison Taylor, NP

ST. JUDE GLOBAL

Approximately 90% of children live in low- or middle-income counties (LMICs), where access to quality pediatric oncology care is suboptimal to non-existent. Thus, most children with cancer or hematologic disorders, particularly β-hemaglobinopathies (e.g., sickle cell disease, thalassemia, or severe hemophilia) will have dismal outcomes in LMICs. The St. Jude Global initiative integrates multiple departments and programs to focus on capacity-building and developing an educational and clinical research infrastructure for LMICs. St. Jude Global is working closely with the St. Jude Children's Research Hospital Graduate School of Biomedical Sciences, LLC, to develop education programs and with the Comprehensive Cancer Center to develop a clinical and translational research infrastructure that facilitates and supports global research programs and international collaborations initiated by St. Jude faculty.

In March 2017, St. Jude Global's Strategic Plan was approved by the St. Jude Board of Governors. Our vision is that all children with cancer or catastrophic hematologic disorders in the world will have access to quality care and that we will create opportunities, advance human capacity, and provide innovative methods for programs around the world to attain maximum cure rates. Here we briefly describe the three overarching goals of St. Jude Global.

Goal 1: To develop and strengthen patient- and health systems–centered initiatives that encompass the continuum of care required for children with cancer or hematologic disorders. We will implement initiatives to strengthen health systems, policymaking, and quality patient care programs. Transversal frameworks have been created to develop regional, national, and program-specific initiatives and execute uniform programs. To integrate a health systems approach, we have established strong ties with the World Health Organization (WHO); St. Jude is the first WHO Collaborating Center for Childhood Cancer, and we plan to expand this relationship by developing the WHO–St. Jude Childhood Cancer Global Access Priority initiative. This 5-year collaboration will synergize the technical and operational expertise of St. Jude Global (working bottom-up with pediatric oncology care providers globally) with the authority of the WHO (working top-down with governments, nongovernment societies, and leaders of healthcare systems at the national, regional, and global levels). Through this initiative, we will integrate the diagnosis and treatment of childhood cancers into national policies and translate those policies into actions, while complementing the strategic priorities of St. Jude Global.

Goal 2: To train a global workforce to conduct the clinical and research initiatives needed to advance care and improve survival for children with cancer or hematologic disorders worldwide. Five new educational programs will help build clinical, research, health systems, and policymaking leadership.

1. Global health track has been added to the Pediatric Hematology-Oncology Fellowship Program.
2. St. Jude Global Fellowships will build regional pediatric hematology-oncology capacities.
3. St. Jude Global Academy will deliver certificate-based specialized training.
4. St. Jude Global Scholars Program will grant Masters of Science degrees in global pediatric health.
5. Advanced distance-learning curricula will be developed to support all of these initiatives.

Goal 3: Advance knowledge in global pediatric oncology and hematology through research. We can achieve this goal only through the judicious integration of research principles. Research will be integrated gradually at all LMIC sites, under the leadership and mentorship of St. Jude faculty. Local and regional research capacity will be built through the St. Jude Global Scholars Program and the St. Jude Global Academy. These networks will adopt consortium-like models to support research efforts. They will also be provided a solid clinical research infrastructure, including a global research database (integrated within the St. Jude clinical research database), support personnel, and training to implement science and develop regional clinical trials. We have prioritized the creation of a Global Clinical Research Support Unit and defined the standard operating procedures to regulate and oversee the research operations and scientific quality of the initiatives proposed by members of the Department of Global Pediatric Medicine and St. Jude Global. Several ongoing initiatives are related to developing framework and investment analyses, quality and implementation sciences, cumulative burden of cancer estimation, molecular epidemiology, and clinical research networks.

ACADEMIC DEPARTMENTS

BIOSTATISTICS

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

Members
Cheng Cheng, PhD • Statistical methods in cancer genomics and genetics
Arzu Onar-Thomas, PhD[1] • Phase I-II designs, survival analysis, Bayesian statistics
Stanley B. Pounds, PhD[1] • Developing statistical methods for genomics studies
Jianrong Wu, PhD[2]

Associate Members
Guolian Kang, PhD • Statistical genetics/genomics, modeling of complex data
Yimei Li, PhD • Statistical analysis of complex imaging data
Hui Zhang, PhD • Statistical methods for psychological research

Assistant Members
Zhaohua Lu, PhD • Statistical analysis of neuroimaging and genetic data
Haitao Pan, PhD • Bayesian adaptive designs for Phase I-II clinical trials
Li Tang, PhD • Measurement error & classification, longitudinal modeling

CELL & MOLECULAR BIOLOGY

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Stacey K. Ogden, PhD[1] • Mechanisms of Hedgehog signal transduction
Joseph T. Opferman, PhD[1] • Regulation of cell death and mitochondrial function
P. Ryan Potts, PhD[1] • Biochemical and molecular characterization of MAGE proteins

Assistant Members
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Malia B. Potts, PhD[1] • Higher-order regulation of autophagy
Shondra M. Pruett-Miller, PhD • Genome-editing technologies

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Ewelina K. Mamcarz, MD • Transplantation in patients with nonmalignant diseases
M. Paulina Velasquez, MD[1] • Immunotherapy of hematologic malignancies

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Aimee C. Talleur, MD • Immunotherapy and cellular therapy for solid tumors

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Member
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Philip M. Potter, PhD • Anticancer drug hydrolysis by carboxylesterases
Anang A. Shelat, PhD[1] • Multiscale modeling of biological and chemical data
Scott E. Snyder, PhD[3] • Design of radioactive diagnostic agents for molecular imaging

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Tudor Moldoveanu, PhD[1] • Programmed cell death in health and disease
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Yong Cheng, PhD[1,3] • Cis-regulatory modules in hematopoiesis and its disorders
Charles Gawad, MD, PhD[3] • Cellular and genetic origins of childhood cancers
Jiyang Yu, PhD • Systems biology, functional genomics, and immuno-oncology

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Jamy C. Peng, PhD[1] • Epigenetic regulation of stem cell functions
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Elizabeth A. Stewart, MD[1,3] • Translational research of pediatric solid tumors

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Robert A. Kaufman, MD • Optimization of diagnostic CT dose in children with cancer
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Mikhail Doubrovin, MD, PhD • Radiotracer imaging–based techniques of pediatric solid tumors
Julie H. Harreld, MD[1] • Magnetization transfer MR imaging and cerebral perfusion
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Robert J. Ogg, PhD • Imaging assessments of brain function in CNS and ocular tumors
Noah D. Sabin, MD, JD • Imaging of brain tumors and side effects of therapy
Scott E. Snyder, PhD[1] • Design of radioactive diagnostic agents for molecular imaging

Assistant Members
Samuel L. Brady, PhD[2]
Scott N. Hwang, MD, PhD • Brain tumors, quantitative imaging, computational modeling

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

ACADEMIC DEPARTMENTS

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I-Chan Huang, PhD • Patient-reported outcomes measurement after pediatric cancer
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Tara M. Brinkman, PhD • Psychosocial outcomes of pediatric cancer
Matthew J. Ehrhardt, MD, MS[2] • Late effects of childhood cancer therapy
Todd M. Gibson, PhD • Risk factors for late effects after pediatric cancer
Carmen L. Wilson, PhD • Late effects of childhood cancer therapy

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Catherine G. Lam, MD, MPH • Global health, health systems, pediatric solid tumors
Ibrahim A. Qaddoumi, MD, MS[2] • Global health, telemedicine, brain tumors, retinoblastoma

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Nickhill Bhakta, MD, MPH • Global health, survivorship, epidemiology, childhood leukemias
Paola Friedrich, MD, MPH • Global health, health disparities, health services, pediatric solid tumors

Research Associate
Sheena Mukkada, MD, MPH • Global health, infection care and control

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

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Mitchell J. Weiss, MD, PhD[1]; Arthur Nienhuis Endowed Chair in Hematology • Blood development and associated diseases

Members
Ellis J. Neufeld, MD, PhD; Clinical Director; John & Lorine Thrasher Endowed Chair in Pediatric Medicine • Patient-oriented studies in nonmalignant hematology
Arthur W. Nienhuis, MD[3]
Brian P. Sorrentino, MD[1]; Wall Street Committee Endowed Chair in Bone Marrow Transplant Research • Gene therapy and hematopoiesis
Winfred C. Wang, MD • Sickle cell disease, bone marrow failure

Associate Members
Jane S. Hankins, MD, MS[1] • Sickle cell disease, transfusional iron overload, transition to adult care
Shannon L. McKinney-Freeman, PhD[1] • Mechanisms of hematopoietic stem cell development and transplantation
Ulrike M. Reiss, MD[1] • Bleeding disorders, gene therapy for hemophilia, bone marrow failure
Byoung Ryu, PhD • Stem cell gene therapy for blood disorders

Assistant Members
Yong Cheng, PhD[1] • Cis-regulatory modules in hematopoiesis and its disorders
Wilson K. Clements, PhD[1] • Hematopoietic development & leukemia
Jeremie H. Estepp, MD[1] • Sickle cell disease, thrombosis, and anticoagulation
Shengdar Q. Tsai, PhD[1] • Genome engineering technologies for therapeutics

IMMUNOLOGY

Chair
Douglas R. Green, PhD[1]; Peter Doherty Endowed Chair in Immunology • Apoptosis, autophagy, and mitochondria

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

Members
Hongbo Chi, PhD[1] • Cellular signaling in innate and adaptive immunity
Peter C. Doherty, PhD[3]; Nobel Laureate; Michael F. Tamer Endowed Chair in Immunology
Peter J. Murray, PhD[4]

Associate Members
Maureen A. McGargill, PhD[1] • T-cell regulation to treat autoimmune diseases
Paul G. Thomas, PhD[1] • Innate and adaptive immunity to influenza

Assistant Members
Yongqiang Feng, PhD • Novel strategies to better manipulate immune cell behaviors
Rhea M. Sumpter Jr, MD, PhD • Selective autophagy, innate immunity, inflammation
Benjamin A. Youngblood, PhD[1] • T-cell memory differentiation and exhaustion

INFECTIOUS DISEASES

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

Members
Patricia M. Flynn, MD; Deputy Clinical Director; Arthur Ashe Endowed Chair in Pediatric AIDS Research • HIV/AIDS and infections in children with cancer
Aditya H. Gaur, MD, MBBS[1] • Clinical research in pediatric HIV infection
Walter T. Hughes, MD[3]
Julia L. Hurwitz, PhD[1] • Vaccine-induced immunity
Suzanne Jackowski, PhD • Phospholipids and coenzyme A in health and disease
Peter J. Murray, PhD[4]
Charles O. Rock, PhD • Membrane phospholipid metabolism
Stacey L. Schultz-Cherry, PhD[1] • Pathogenesis of influenza and astrovirus infection
Richard J. Webby, PhD[1] • Influenza virus pathogenicity
Robert G. Webster, PhD[5]

Associate Members
Elisabeth E. Adderson, MD • Clinical trials management
Miguela A. Caniza, MD[1,2] • Global health, infection care & control
Hans Haecker, MD, PhD[1] • Signal transduction of Toll-like and TNF receptors
Charles J. Russell, PhD[1] • Respiratory viruses: disease, cures, & prevention

Assistant Members
Hana Hakim, MD • Infection care and control
Ellie Margolis, MD, PhD • Microbiome dynamics in immunocompromised patients
Gabriela M. Marón Alfaro, MD • Infectious complications in transplant patients
Jason W. Rosch, PhD[1] • Bacterial genomics and pathogenesis
Joshua Wolf, MBBS[1] • Infections associated with implantable devices and immunosuppressed hosts

Research Associates
Diego R. Hijano, MD • Host–pathogen interactions of respiratory virus
Akinobu Kamei, MD[4]
Sheena Mukkada, MD, MPH[2] • Immunocompromised children in resource-limited settings
Amber M. Smith, PhD[4]

Adjunct Member
Jonathan A. McCullers, MD • Interactions between viruses and bacteria

ONCOLOGY

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

Co-Chair
Amar J. Gajjar, MD[1,2]; 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 and cancer survivorship
Wayne L. Furman, MD • New drug development, neuroblastoma, liver tumors
Daniel M. Green, MD[1,2,4] • Adverse cardiac & reproductive effects of therapy
Melissa M. Hudson, MD; The Charles E. Williams Endowed Chair of Oncology–Cancer Survivorship • Health outcomes after childhood cancer
Sima Jeha, MD • Global health, childhood leukemias, developmental therapeutics
Sue C. Kaste, DO[2] • Skeletal toxicities in childhood cancer
Monika L. Metzger, MD, MSc[1] • Global health, Hodgkin & non-Hodgkin lymphomas, leukemias
Kim E. Nichols, MD[1] • Heritable cancers and primary immunodeficiency syndromes
Alberto S. Pappo, MD[1]; Alvin Mauer Endowed Chair • New therapies for sarcomas and rare pediatric cancers
Raul C. Ribeiro, MD[1] • Hematological malignancies
Charles W. M. Roberts, MD, PhD[1]; Lillian R. Cannon Comprehensive Cancer Center Director Endowed Chair • SWI/SNF (BAF) chromatin remodeling/tumor suppressor complex
Carlos Rodriguez-Galindo, MD[1,2]; Four Stars of Chicago Endowed Chair in International Pediatric Outreach • Global medicine, pediatric solid tumors
Jeffrey E. Rubnitz, MD, PhD • Treatment of acute myeloid leukemia
John T. Sandlund, MD[1] • Clinical and biologic investigation of NHL and ALL
Victor M. Santana, MD; Charles B. Pratt Endowed Chair in Solid Tumor Research • Novel therapeutics, neuroblastoma, research ethics

Associate Members
Richard A. Ashmun, PhD[2] • Applications of flow cytometry & cell separation
Armita Bahrami, MD[2] • Pathology of bone and soft-tissue tumors
Justin N. Baker, MD[1] • Pediatric palliative and end-of-life care
Rachel C. Brennan, MD[1] • Retinoblastoma, novel therapeutics, renal tumors
Alberto Broniscer, MD[4]
Sara M. Federico, MD[1] • Drug development, pediatric soft-tissue sarcomas
Tanja A. Gruber, MD, PhD • Pathogenesis of infantile leukemia
Hiroto Inaba, MD, PhD[2] • New therapeutic strategies for leukemia
Catherine G. Lam, MD, MPH[2] • Global health, health systems, pediatric solid tumors
Daniel A. Mulrooney, MD, MS[2] • Cardiovascular outcomes of cancer therapy
Ibrahim A. Qaddoumi, MD, MS • Global health, telemedicine, brain tumors, retinoblastoma
Carolyn Russo, MD • Palliative and supportive care
Jun J Yang, PhD[2] • Pharmacogenomics of anticancer agents and drug resistance

Assistant Members
Nickhill Bhakta, MD, MPH[2] • Global health, survivorship, epidemiology, childhood leukemias
Michael W. Bishop, MD[1] • Osteosarcoma, bone and soft-tissue sarcomas, rhabdoid tumors
Patrick K. Campbell, MD, PhD • Histiocytic disorders; chronic myeloid leukemia
Matthew J. Ehrhardt, MD, MS • Late effects of childhood cancer therapy
Jamie E. Flerlage, MD, MS • Hodgkin lymphoma
Paola Friedrich, MD, MPH[2] • Global health, health disparities, health services, pediatric solid tumors
Charles Gawad, MD, PhD • Cellular and genetic origins of childhood cancers
Mark E. Hatley, MD, PhD[1] • Origins of pediatric sarcomas
Kellie B. Haworth, MD • Immunotherapies for pediatric neurogenic tumors
Liza-Marie Johnson, MD, MPH, MSB • Ethical issues in pediatrics
Erica C. Kaye, MD • Early integration of palliative care in oncology
Chimene Kesserwan, MD • Cancer predisposition
Deena R. Levine, MD • Pediatric palliative and end-of-life care
Esther A. Obeng, MD, PhD • Myeloid malignancies and bone marrow failure syndromes
Giles W. Robinson, MD[2] • Origin and genomics of medulloblastoma, translational studies
Holly Spraker-Perlman, MD • pediatric palliative care, symptom-management strategies
Elizabeth A. Stewart, MD[1] • Translational research of pediatric solid tumors
Anna Vinitsky, MD, MS • Pediatric neuro-oncology and process improvement
Liqin Zhu, PhD[2] • Stem cells in normal and malignant development

Research Associates
Seth E. Karol, MD[2] • Prevention of toxicity during acute leukemia therapy
Santhosh Upadhyaya, MD • Infant medulloblastoma, high-grade glioma in young children

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

ACADEMIC DEPARTMENTS

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]; Deputy Directory for Academic and Biomedical Operations; Endowed Chair in Pediatrics • T-cell regulation, autoimmunity
Randall T. Hayden, MD • Clinical microbiology of immunocompromised hosts
Michael M. Meagher, PhD[1]; Vice President, Therapeutics Production and Quality; President, Children's GMP, LLC • Cell culture, fermentation, protein purification, process scale-up, and GMP manufacturing
Charles G. Mullighan, MBBS(Hons), MSc, MD[1]; William E. Evans Endowed Chair • Genomic profiling of acute leukemia
Ching-Hon Pui, MD[2]; Fahad Nassar Al-Rashid Endowed Chair in Leukemia Research • Biology and treatment of childhood leukemia
Susana C. Raimondi, PhD • Cytogenetics of the leukemias and lymphomas
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] • p53 function in tumor suppression & tumorigenesis

Associate Members
Armita Bahrami, MD[1] • Pathology of bone and soft-tissue tumors
John K. Choi, MD, PhD[1] • Transcription factors in acute leukemias
Tanja A. Gruber, MD, PhD[2] • Pathogenesis of infantile leukemia
Laura Janke, DVM, PhD • Pathology of mouse models of disease
Mondira Kundu, MD, PhD[1] • Autophagy in health and human disease
Janet F. Partridge, PhD[1] • Chromosome segregation, heterochromatin assembly
Richard J. Rahija, DVM, PhD • Animal models of human disease
András Sablauer, MD, PhD; Chief Medical Information Officer • Imaging informatics and computerized tumor modeling
Lu Wang, MD, PhD • Functional analysis of genetic alterations in pediatric tumors

Assistant Members
Elizabeth M. Azzato, MD, PhD • Molecular pathology and clinical genomics
Jason Cheng-Hsuan Chiang, MD, PhD • Diagnosis and classification of CNS tumors
Michael R. Clay, MD • Molecular and histologic classification of bone and soft-tissue tumors
Jeffrey M. Klco, MD, PhD[1] • Genomic and functional characterization of acute myeloid leukemia
Vasiliki Leventaki, MD • Mechanisms of pathogenesis in pediatric lymphomas
Leta K. Nutt, PhD[3]
Brent A. Orr, MD, PhD • Molecular classification of tumors of the nervous system
Teresa C. Santiago, MD • Laboratory quality improvement and assessment
Heather S. Tillman, DVM, PhD • Investigative pathology of human cancers
Yan Zheng, MD, PhD • Red blood cell alloimmunization, cancer immunotherapy

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; Director • Patient safety and cognitive effects of anesthesia
Doralina L. Anghelescu, MD[1] • Pain management, anesthesia risks, palliative care
Wasif H. Dweik, DO • Patient safety, regional anesthesia, acute pain management
Michael J. Frett, MD • Pediatric anesthesia
Kyle J. Morgan, MD • Palliative care, NSAIDS after bone marrow transplantation
Kavitha Raghavan, MBBS, FRCA • Regional anesthesia, patient safety, and quality of care
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]; Chief • Pediatric critical care, myocardial protection
Asya Agulnik, MD, MPH[2] • Global pediatric health
Lama Elbahlawan, MD • Pediatric critical care, acute lung injury
Melissa R. Hines, MD • Pediatric critical care, hemophagocytic lymphohistiocytosis
Jennifer A. McArthur, DO • Improving outcomes in critically ill pediatric patients

Endocrinology
Wassim Chemaitilly, MD[1]; Director • Endocrine sequelae in childhood cancer survivors

Neurology
Raja B. Khan, MD; Chief • Effect of cancer on central and peripheral nervous systems
Zsila Sadighi, MD • Neurological outcomes in childhood cancer survivors

Nursing Research
Belinda N. Mandrell, PhD, RN, PNP[1]; Director • Biological mechanism of symptoms associated with cancer and cancer therapy

PHARMACEUTICAL SCIENCES

Chair
Mary V. Relling, PharmD[1]; Endowed Chair in Pharmaceutical Sciences • Pharmacokinetics and genetics of leukemia therapy

Members
William E. Evans, PharmD; Endowed Chair in Pharmacogenomics • Pharmacogenomics of antileukemic agents in children
William L. Greene, PharmD; Chief Pharmaceutical Officer • Optimizing pharmacotherapy
Erin G. Schuetz, PhD[3] • Mechanisms of human variation in drug response
John D. Schuetz, PhD[3] • Regulation & function of ABC transporters
Clinton F. Stewart, PharmD[3] • Pharmacology of anticancer drugs in children

Associate Members
James M. Hoffman, PharmD; Chief Patient Safety Officer • Medication safety and outcomes
Jun J. Yang, PhD[1] • Pharmacogenomics of anticancer agents & drug resistance

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

PSYCHOLOGY

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

Members
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] • Neurocognitive outcomes of pediatric cancer

Associate Members
Heather M. Conklin, PhD[1] • Cognitive outcomes of childhood cancer treatment
Valerie M. Crabtree, PhD[1] • Sleep disruptions in children with cancer
James L. Klosky, PhD[3]

Assistant Members
Tara M. Brinkman, PhD[2] • Psychosocial outcomes of pediatric cancer
Lisa M. Jacola, PhD • Neurobehavioral outcomes in children treated for cancer
Jerlym S. Porter, PhD, MPH • Transition from pediatric to adult care in sickle cell disease
Jane E. Schreiber, PhD[3]
Victoria W. Willard, PhD • Social outcomes in children with cancer

Research Associate
Nicole M. Alberts, PhD • eHealth and mHealth applications in psycho-oncology

RADIATION ONCOLOGY

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

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

Associate Members
Jonathan B. Farr, PhD[3]
Chia-Ho Hua, PhD • Image-guided radiation therapy and normal tissue effects

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] • Brain tumors and sarcomas
Weiguang Yao, PhD • Proton therapy and cone beam computed tomography

STRUCTURAL BIOLOGY

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

Members
Richard W. Kriwacki, PhD[1] • Structural basis of tumor suppressor function
Junmin Peng, PhD[1] • Application of proteomics to ubiquitin biology and human disease
Stephen W. White, DPhil[1]; Endowed Chair–Dean of St. Jude Children's Research Hospital Graduate School of Biomedical Sciences • DNA repair, catalysis and structure-based drug discovery

Associate Members
Eric J. Enemark, PhD[1] • Molecular mechanisms of DNA replication
Tanja Mittag, PhD[1] • Dynamic protein complexes in signal transduction

Assistant Members
Marcus Fischer, PhD[1] • Protein conformational ensembles
Tudor Moldoveanu, PhD[1] • Programmed cell death in health and disease

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

SURGERY

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

Members
Bhaskar N. Rao, MD • Surgical management of sarcomas and rare tumors
Stephen J. Shochat, MD[4]

Assistant Members
Israel Fernandez-Pineda, MD[3]
Kevin W. Freeman, PhD[1] • Genetic interactions that give rise to neuroblastoma
Andrew J. Murphy, MD • Renal tumors, neuroblastoma, Wilms tumorigenesis, cancer stem cells

Research Associate
Jun Yang, MD, PhD • Cancer epigenetics and targeted therapy

Adjunct Members
Frederick A. Boop, MD; St. Jude Chair in Neurosurgery
Joseph Gleason, MD • Pediatric urology
Mary Ellen Hoehn, MD • Pediatric ophthalmology
Paul D. Klimo Jr, MD • Pediatric neurosurgery
Michael D. Neel, MD • Orthopedics
Anthony Sheyn, MD • Pediatric otolaryngology
Jerome W. Thompson, MD, MBA • Pediatric otolaryngology
Robert D. Wallace, MD • Plastic surgery
Matthew W. Wilson, MD • St. Jude Chair in Ophthalmology

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

ACADEMIC DEPARTMENTS

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 and disease
Martine F. Roussel, PhD[1]; Endowed Chair in Molecular Oncogenesis • Genes and microRNAs in brain tumors

Assistant Member
Chunliang Li, PhD[1] • Genome editing in cancer development

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

[1]Graduate school faculty member

ENDOWED CHAIRS

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

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

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

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

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

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

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

Alberto S. Pappo, MD
Alvin Mauer Endowed Chair

William E. Evans, PharmD
Endowed Chair in Pharmacogenomics

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

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

Martine F. Roussel, PhD
Endowed Chair in Molecular Oncogenesis

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

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

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

Brian P. Sorrentino, MD
Wall Street Committee Endowed Chair in Bone Marrow Transplant Research

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

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

FELLOWS & SCHOLARS

POSTDOCTORAL FELLOWS
Hossam Abdelsamed, PhD, Immunology
Aditi, PhD, Genetics
Issam Al Diri, PhD, Developmental Neurobiology
Sabrin Albeituni, PhD, Oncology
Angela Arensdorf, PhD, Cell & Molecular Biology[1]
David Arroyo, PhD, Developmental Neurobiology
Bing Bai, PhD, Structural Biology[1]
Jesse Bakke, PhD, Chemical Biology & Therapeutics
Arjun Balakrishnan, PhD, Immunology
Diana Balasubramanian, PhD, Cell & Molecular Biology[1]
Katherine Baran, PhD, Immunology[1]
Pradyuamna Baviskar, DVM, PhD, Infectious Diseases[1]
Jordan Beard, PhD, Pharmaceutical Sciences
Veronika Bernhauerova, PhD, Infectious Diseases[1]
Anannya Bhattacharya, PhD, Immunology
Anusarka Bhaumik, PhD, Structural Biology
Wenjian Bi, PhD, Biostatistics
Laure Bihannic, PhD, Developmental Neurobiology
Randall Binder, PhD, Chemical Biology & Therapeutics
Emilio Boada Romero, PhD, Immunology
Andre Bortolini Silveira, PhD, Developmental Neurobiology
Rebba Boswell-Casteel, PhD, Pharmaceutical Sciences[1]
Jill Bouchard, PhD, Structural Biology
John Bowling, PhD, Chemical Biology & Therapeutics[2]
David Boyd, PhD, Immunology
Nicolas Bravo Vasquez, DVM, PhD, Infectious Diseases
Anne Bremer, PhD, Structural Biology
Benoit Briard, PhD, Immunology
R. John Brooke, PhD, Epidemiology & Cancer Control
Nicholas G. Brown, PhD, Structural Biology[1]
Victoria Bryant, PhD, Pathology
Cameron Buchman, PhD, Chemical Biology & Therapeutics
Amit Budhraja, PhD, Cell & Molecular Biology
Laura Buttrum, PhD, Infectious Diseases
Cristel V. Camacho, PhD, Genetics[1]
Kirby Campbell, PhD, Developmental Neurobiology
Nicole Chapman, PhD, Immunology
Helen Chen, PhD, Cell & Molecular Biology
Ping-Chung Chen, PhD, Structural Biology
Pei-Hsin Cheng, PhD, Surgery[2]
Jude Chenge, PhD, Chemical Biology & Therapeutics
Milu T. Cherian, PhD, Chemical Biology & Therapeutics[1]
Yin Ting Celyna Cheung, PhD, Epidemiology & Cancer Control[1]
Claiborne Christian, PhD, Hematology[1]
Christopher Coke, PhD, Pharmaceutical Sciences
Evan Comeaux, PhD, Pathology
Valerie Cortez, PhD, Infectious Diseases
Rebecca Crawford, PhD, Pharmaceutical Sciences
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Maxime Cuypers, PhD, Structural Biology
Erich Damm, PhD, Hematology
Neha Das Gupta, PhD, Developmental Neurobiology[2]
Soumyasri Das Gupta, PhD, Cell & Molecular Biology
Prakash Devaraju, PhD, Developmental Neurobiology
Kaushik Dey, PhD, Structural Biology
Suresh Dharuman, PhD, Chemical Biology & Therapeutics
Larissa Dias da Cunha, PhD, Immunology
Jonathan Diedrich, PhD, Pharmaceutical Sciences
Binbin Ding, PhD, Immunology[1]
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Pranay Dogra, PhD, Immunology[2]
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Thomas Fabrizio, PhD, Infectious Diseases
Slim Fellah, PhD, Diagnostic Imaging[1]
Ruopeng Feng, PhD, Hematology
Daniel Ferguson, PhD, Pharmaceutical Sciences
Dinesh Fernando, PhD, Chemical Biology & Therapeutics
Mylene H. Ferrolino, PhD, Structural Biology
Emily Finch, PhD, Pharmaceutical Sciences
Diane Flasch, PhD, Computational Biology
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Ruchika Gangwar, PhD, Developmental Neurobiology
Miguel Ganuza Fernandez, PhD, Hematology
Jesús García López, PhD, Developmental Neurobiology
Clifford Gee, PhD, Chemical Biology & Therapeutics
Jamie K. Genthe, PhD, Hematology
Hazem Ghoneim, PhD, Immunology
Eric Gibbs, PhD, Structural Biology
Nicole Glenn, PhD, Hematology
Yoshihiro Gocho, MD, PhD, Pharmaceutical Sciences
Yinan Gong, PhD, Immunology
Charnise Goodings Harris, PhD, Pharmaceutical Sciences
Tomoka Gose, PhD, Pharmaceutical Sciences
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Prajwal Gurung, PhD, Immunology[1]
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Eric Hall, PhD, Cell & Molecular Biology
Laura Hamel, PhD, Developmental Neurobiology
Seung Baek Han, PhD, Developmental Neurobiology
Jason A. Hanna, PhD, Oncology
Rhodri Harfoot, PhD, Infectious Diseases
Tarsha Harris, PhD, Immunology[1]
Samah Hayek, DPH, Epidemiology & Cancer Control
Robert Hazlitt, PhD, Chemical Biology & Therapeutics
Yanghua He, PhD, Hematology
Nikhil Hebbar, PhD, Bone Marrow Transplantation & Cellular Therapy
Bradlee Heckmann, PhD, Immunology
Andres A. Herrada Hidalgo, PhD, Immunology[1]
Wan-Ling Ho, MD, PhD, Developmental Neurobiology[1]
Joseph Holtrop, PhD, Diagnostic Imaging[2]
Laura Hover, PhD, Developmental Neurobiology
Meng Hu, PhD, Infectious Diseases
Hongling Huang, PhD, Immunology
Xin Huang, PhD, Cell & Molecular Biology
Liam Hunt, PhD, Developmental Neurobiology
Jung Won Hyun, PhD, Biostatistics[1]
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Jianqin Jiao, PhD, Developmental Neurobiology
Pedro Jimenez Bluhm, DVM, PhD, Infectious Diseases[1]
Jenny Johnson, PhD, Immunology
Barbara M. Jonchere, MD, PhD, Tumor Cell Biology
Zachary Jones, PhD, Pharmaceutical Sciences
Bhaskar Kahali, PhD, Bone Marrow Transplantation & Cellular Therapy[2]
Maduka Kalaurachchi, PhD, Radiation Oncology
Halime Kalkavan, MD, Immunology
Marcin Kaminski, PhD, Immunology[2]
Rajendra Karki, PhD, Immunology[2]
Peer Karmaus, PhD, Immunology
Nandish Khanra, PhD, Structural Biology
Colin C. Kietzman, PhD, Infectious Diseases[2]
Hyunsuh Kim, PhD, Infectious Diseases
Nam Chul Kim, PhD, Cell & Molecular Biology[1]
Sajjan Koirala, PhD, Cell & Molecular Biology
Regina M. Kolaitis, PhD, Cell & Molecular Biology[2]
David Krist, PhD, Structural Biology
Amit Kumar, PhD, Cell & Molecular Biology[1]
Lalit Kumar Sharma, PhD, Infectious Diseases[1]
Jeeba Kuriakose, PhD, Infectious Diseases[2]
Teneema Kuriakose, PhD, Immunology
Casey Langdon, PhD, Oncology
Jon D. Larson, PhD, Developmental Neurobiology
Christophe Laumonnerie, PhD, Developmental Neurobiology
Wanda S. Layman, PhD, Developmental Neurobiology[1]
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Natalie Lee, PhD, Infectious Diseases
Bofeng Li, PhD, Pathology[1]
Jun Li, PhD, Immunology
Yanfeng Li, PhD, Chemical Biology & Therapeutics[1]
Yizhen Li, PhD, Pharmaceutical Sciences
Swantje Liedmann, PhD, Immunology
Chengcheng Liu, PhD, Pharmaceutical Sciences[1]
Jingjing Liu, PhD, Computational Biology
Xueyan Liu, PhD, Biostatistics
Yanling Liu, PhD, Computational Biology
Yiwei Liu, PhD, Pharmaceutical Sciences
Yu Liu, PhD, Computational Biology
Lip Nam Loh, PhD, Infectious Diseases[1]
Ogheneochukome Lolodi, PhD, Chemical Biology & Therapeutics
Lingyun Long, PhD, Immunology
Allister Loughran, PhD, Infectious Diseases
Marybeth Lupo, PhD, Developmental Neurobiology
Heba Hamdy Mabrouk Mostafa, MD, PhD, Infectious Diseases[1]
Eda Rita Machado De Seixas, PhD, Genetics
Jamie Maciaszek, PhD, Hematology[2]
Joelle Magne, PhD, Immunology
Anil Maharaj, PhD, Pharmaceutical Sciences[1]
Ousman Mahmud, PhD, Oncology
Ankit Malik, PhD, Immunology
Eric W. Martin, PhD, Structural Biology
Nancy Martinez, PhD, Chemical Biology & Therapeutics
Cecile Mathieu, PhD, Cell & Molecular Biology
Jayadev Mavuluri, PhD, Immunology
Brian Maxwell, PhD, Cell & Molecular Biology
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J. Robert McCorkle, PhD, Pharmaceutical Sciences[1]
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Lisa Force, MD
Jessica A. Gartrell, MD
Dylan E. Graetz, MD
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Jennifer L. Kamens, MD
Harry Lesmana, MD
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Anand G. Patel, MD
Allison Pribnow, MD[1]
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Maria Garcia-Fernandez, MD
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Jacob Basham, Pathology
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Jane Craig, Cell & Molecular Biology
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[1]No longer at St. Jude
[2]Promoted to staff position

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[1]Nonelected member
[2]Ex officio voting member
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[1]No longer at St. Jude
[2]June–December, 2017

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The Children's Hospital of Philadelphia
Member, Institute of Medicine of the National Academies

OPERATIONS & STATISTICS

OPERATIONS	
Operating expenses[1]	$869.9 million
Number of employees[2]	4569
RESEARCH STATISTICS	
Grant funding[1]	$99.8 million
Peer-reviewed publications	804
Faculty members	275
Postdoctoral fellows	313
Clinical residents and fellows[3]	240
Graduate research scholars	113
CLINICAL STATISTICS	
Number of beds open[4]	69
Outpatient encounters[5]	308,074
Inpatient admissions	3418
Total inpatient days	19,561
Total protocol enrollments in 2017	6797
Patients enrolled on therapeutic trials	898
Patients enrolled on nontherapeutic trials	5899
	4516 on prospective trials
	1383 on tissue-banking protocols
Number of protocols open to accrual in 2017	402
Number of active therapeutic trials	205
Number of active nontherapeutic trials	197
	192 prospective trials
	5 tissue-banking protocols

[1]Data represents the period July 1, 2016 to June 30, 2017.
[2]Data is from July 1, 2017.
[3]Data includes 78 full-time St. Jude fellows and 162 rotating fellows from the University of Tennessee Health Science Center or other medical schools.
[4]Data represents the number of beds in use. St. Jude is licensed for 80 beds.
[5]Data represents the total number of ambulatory or ancillary encounters, not daily visits.

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