St. Jude Children's Research Hospital

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Scientific Report 2016

Translating Science into Survival

Behind the Cover

The scientific image on the cover shows neurons in the developing mouse cortex. Peter J. McKinnon, PhD (Genetics), and his colleagues are studying the role of DNA-repair pathways in neurogenesis and how mutations in the genes of those pathways can cause heritable neuro-degenerative diseases.

ST. JUDE IS THE ONLY NCI-DESIGNATED COMPREHENSIVE CANCER CENTER DEVOTED SOLELY TO CHILDREN. OUR SCIENTISTS ARE PIONEERING NEW WAYS TO TREAT AND ULTIMATELY CURE CATASTROPHIC PEDIATRIC DISEASES.

TRANSLATING SCIENCE INTO SURVIVAL

James R. Downing, MD
President and Chief Executive Officer

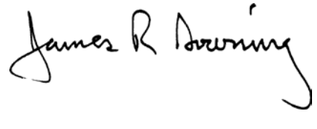
At St. Jude Children's Research Hospital, doctors, nurses, scientists, and many others work together every day to help children fight cancer and other life-threatening diseases. Through our unique model, families never receive a bill, and scientific progress is never halted due to a lack of resources. This freedom allows us to keep our focus exactly where it needs to be—finding cures and saving children.

In this *Scientific Report*, we detail the medical and scientific advances published in 2015 that are helping to fulfill the St. Jude mission. The report's four features represent work that spans diverse areas of study and serves as a testament to the collaborative culture at St. Jude. In our first article, we outline a fundamental discovery that elucidates the inner working of cells. The second and third features illustrate how advanced genomics are used to best treat patients. In the last article, we explain the promise of the new St. Jude Red Frog Events Proton Therapy Center for improving the treatment of pediatric brain tumors and solid tumors. These advances are built on the hospital's commitment to enhancing the basic and clinical research environment and the legacy of the Pediatric Cancer Genome Project, with the hope of providing patients with the most sophisticated and progressive therapy available.

Beyond the activities detailed in the features, the past year was marked by other milestones and achievements, including the addition of a seventh St. Jude affiliate, the Clinic at Novant Health Hemby Children's Hospital, located in Charlotte, North Carolina, and the establishment of the Department of Global Pediatric Medicine. Through the latter effort, our goal is to extend quality care to the more than 80% of children with cancer who live in low- or middle-income countries. A new educational endeavor, the St. Jude Graduate School of Biomedical Sciences, also began to take shape. The school, which welcomes its inaugural class in 2017, will train the next generation of academic researchers.

We also celebrated several leadership appointments, including those of Charles W. M. Roberts, MD, PhD, as Comprehensive Cancer Center director; Carlos Rodriguez-Galindo, MD, as International Outreach Program director and Department of Global Pediatric Medicine chair; Thomas E. Merchant, DO, PhD, as Radiation Oncology chair; Jinghui Zhang, PhD, as Computational Biology chair; and Carolyn Russo, MD, as Affiliate Program medical director. The hospital also received the designation of Magnet status from the American Nurses Credentialing Center and again was ranked one of Fortune magazine's "100 Best Companies to Work For."

This report is only a snapshot of the dynamic work underway at St. Jude. It shows what can be achieved when a collaborative and compassionate culture is united by a focused vision. Our future will be guided by this compass. As we move forward, our success will be determined by the things that matter most: a test result that brings relief to a worried family, a celebration to mark the end of a patient's chemotherapy, or a discovery that points to the day when no child will die in the dawn of life.



LIQUID ASSEMBLIES AND MOLECULAR MACHINES IN HEALTH AND DISEASE

Proteins and other biomacromolecules exist in a continuum of states that have different biological properties. Although macromolecules in these various states are required for diverse physiological functions, state changes can cause disease. In 2015, St. Jude scientists elucidated determinants underlying the physical state of macromolecules. Studies from five laboratories in the Departments of Structural Biology, Immunology, and Cell & Molecular Biology analyzing the role of liquid protein/RNA assemblies in the formation of ribonucleoprotein (RNP) granules, the molecular mechanisms of cell cycle regulation and apoptosis (or programmed cell death), and nucleocytoplasmic transport in neurodegenerative diseases have produced new insights into the molecular basis of normal protein function and how this is dysregulated in disease.

Brian Freibaum, PhD

CONTINUUM OF ORDER AND ASSEMBLY SIZE AMONG BIOMACROMOLECULES

Biomacromolecules exist on a continuum from order to disorder. Some proteins are fully structured, whereas others are intrinsically disordered. Proteins in the latter category do not adopt a unique folded structure; instead, they transition through countless rapidly interconverting conformations. Many proteins either contain both ordered and disordered domains or have domains that can interconvert between the two states, putting them somewhere on the spectrum between folded and disordered.

Proteins can also adopt different oligomeric states. Some proteins are monomers, meaning they consist of a single protein chain. However, others form oligomers, which are molecular complexes that consist of multiple monomers. These oligomers are termed homo-oligomers if formed of several copies of the same protein or hetero-oligomers if formed by different protein types coming together. Such protein complexes, when able to convert energy input into an output, such as transport or chemical modification of substrates, may be referred to as “molecular machines.” Self-association and hetero-association can lead to higher-order assemblies. The sizes of these assemblies are undetermined and usually vary widely. In extreme cases, such assemblies can become very large—termed mesoscale assemblies—and can be visualized by light microscopy. Assemblies of this size have material properties: they can be liquids, gels, or solids, depending on how ordered they are over their length and how mobile the individual molecules are in the assembly. These assemblies exist in a matrix of different protein states, with increasing disorder from top to bottom and increasing assembly size from left to right.

In 2015, St. Jude researchers made significant advances in elucidating the role of protein disorder in function, demonstrating how disorder in the p53 protein activates apoptosis, how a large molecular machine is harnessed to ubiquitinate a disordered substrate, how a channel filled with disordered protein regions contributes to the pathogenesis of neurodegenerative diseases, and how proteins with a certain type of disordered “tail” can self-associate into liquid droplets and underlie the formation of liquid, membrane-less organelles in cells. These examples represent distinct protein assembly types in the matrix of protein states.

Tanja Mittag, PhD

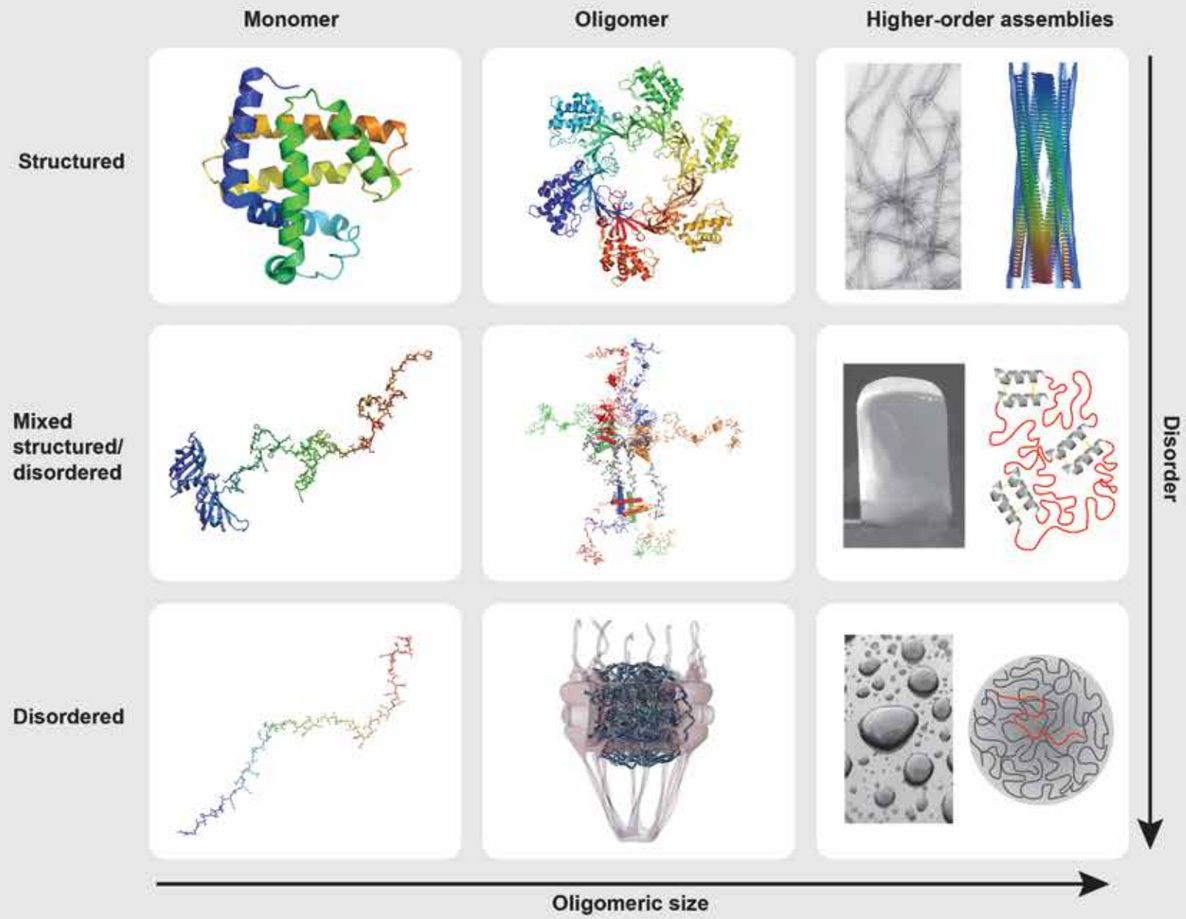


Figure. The continuum of protein states illustrated across nine categories of biomacromolecules. First column (top to bottom): myoglobin (5azq),[1] hnRNPA1 [modeled with Ensemble Optimization Method (EOM) software], and the disordered region of transcriptional regulator Ash1 (modeled with EOM); second column (top to bottom): a hexamer of the N-terminal domain of the MCM helicase (4pof),[1] a p53 tetramer,[2] and a model of the nuclear pore complex with disordered selectivity filter[3]; third column (top to bottom): a cryo–electron microscopic image of the structure of an SH3 amyloid fibril (left) and a model of its molecular packing (right),[4] vector graphic of a hydrogel (left) and a schematic of possible underlying interactions between folded regions connected by disordered linkers (right), and a schematic of liquid droplets (left) and a model of the proposed underlying disorder (right).

[1]Protein Data Bank identifier
[2]Joerger AC, Fersht AR, *Cold Spring Harb Perspect Biol*, 2:a000919, 2010
[3]Image credit: Samir S. Patel
[4]Jimenez JL et al, *EMBO J*, 18:15–21,1999

Amandine Molliex, PhD

THE DISORDERED TAIL SEGMENT OF hnRNPA1 PROMOTES STRESS-GRANULE ASSEMBLY THROUGH LIQUID–LIQUID PHASE SEPARATION

Research spearheaded by Tanja Mittag, PhD (Structural Biology), and J. Paul Taylor, MD, PhD (Cell & Molecular Biology), has revealed evidence of a mechanism at the heart of amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig disease) and related degenerative diseases. The study focused on usually short-lived cellular compartments called stress granules. Stress granules are one of the many membrane-less organelles that assemble within a cell, as needed. They perform various functions and then rapidly disperse. Until now, the mechanism underlying stress-granule formation was poorly understood.

Stress granules are associated with degenerative disorders, including ALS, frontotemporal dementia, and inclusion body myopathy. Genes encoding the protein components of stress granules are often mutated in patients with these diseases. The mutant proteins accumulate in amyloid fibrils, which are thread-like deposits that form in nerve and muscle cells, disrupt normal cell functioning, and eventually result in cell death. Mounting genetic evidence suggested that amyloid fibrils form in persistent stress granules, but how this occurred was unclear.

In the journal *Cell*, the team reported that the disordered segment or "tail" of heterogenous nuclear ribonuclear protein A1 (hnRNPA1), a protein that is sometimes mutated in ALS and related disorders, was the key to unlocking the connection. HnRNPA1 is an RNA-binding protein involved in stress-granule formation. Under certain conditions, the disordered tail of hnRNPA1 prompts the protein to condense into liquid droplets through a process called liquid–liquid phase separation (LLPS). The droplets have similar properties to stress granules, including the ability to fuse and grow. The formation of such droplets in the cell, through the combined action of many proteins with similarly disordered tails, leads to the formation of membrane-less compartments that provide functionally specialized spaces.

LLPS is at work in a wide range of settings, including when oil and water separate in solution. In fact, many proteins can undergo LLPS, and protein droplets are often observed during crystallization studies. However, those droplets usually form under nonphysiological conditions that include high concentrations of protein and salt. HnRNPA1 undergoes LLPS under physiological conditions, and its disordered tail appears to mediate its self-association and, therefore, this change in state. It is now being recognized that other proteins with similar tails also undergo LLPS. Amandine Molliex (Cell & Molecular Biology), a graduate student in Dr. Taylor's lab who worked closely with Dr. Mittag, showed how mutations in the disordered tail of hnRNPA1 most likely contribute to disease. When mutant hnRNPA1 underwent LLPS and concentrated into droplets, the protein rapidly formed amyloid-like fibrils. If the mutant protein did not concentrate into droplets, then fibrils did not form. These findings also suggested how mutations in other genes involved in dismantling stress granules can contribute to disease. By allowing stress granules to persist, the mutations increase the likelihood that amyloid-like fibrils will form. Rather than attempting to target each disease-causing mutation, the investigators are now interested in developing drugs that target the stress-granule assembly process itself.

This study was the first to link LLPS to stress-granule assembly. It not only elucidated the mechanism that links stress granules, toxic fibrils, and degenerative disease but also revealed how membrane-less organelles assemble. It is becoming increasingly clear that LLPS is most likely crucial for many additional cellular processes. These include ribosome assembly, gene transcription, centriole assembly, selective transport through the nuclear pore complex, responses to DNA damage, and membrane receptor clustering and signaling. Insights from the laboratories of Drs. Mittag and Taylor about how monomeric, partially disordered proteins transform to liquid droplets or amyloid fibrils have, therefore, provided a new understanding of the fundamental mechanisms underlying multiple cellular processes.

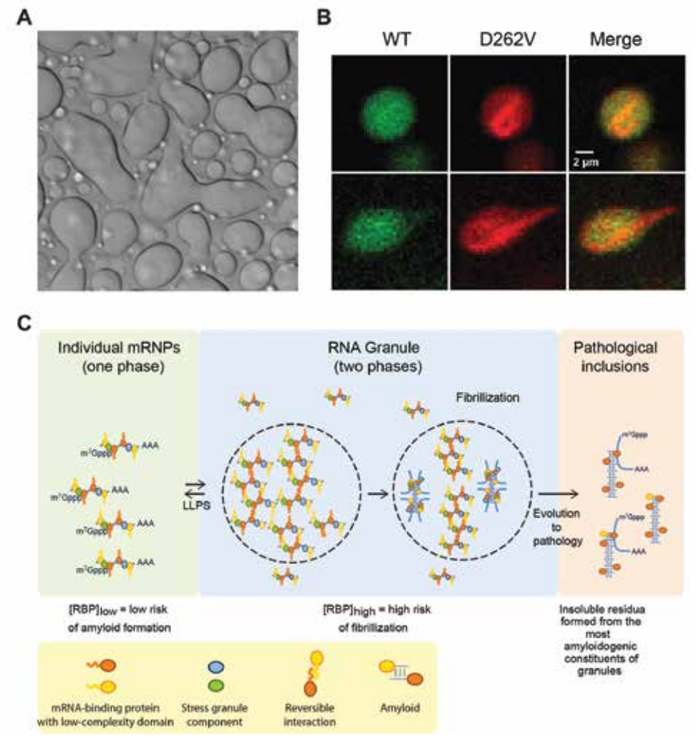


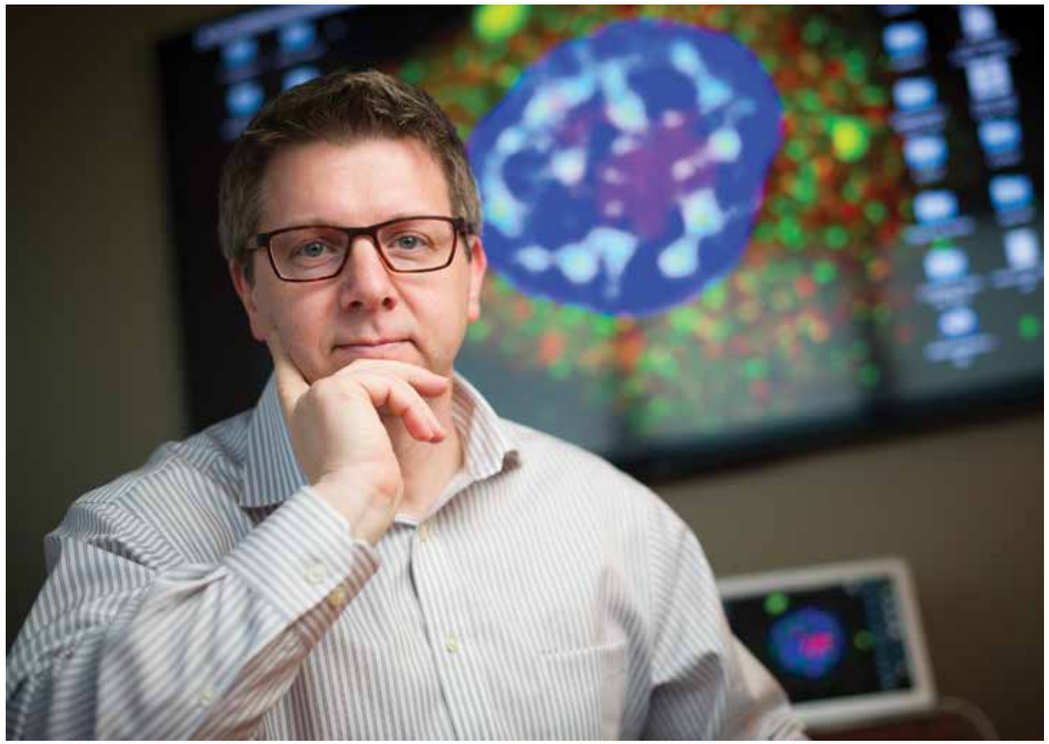
Figure. HnRNPA1 condenses into liquid droplets that drive fibrillization. (**A**) Differential interference contrast microscopic image of hnRNPA1 undergoing LLPS and generating protein-dense liquid droplets in a solution with a lower protein concentration than that of the droplets. The droplets wet the surface of a coverslip, as expected for a classic liquid. (**B**) Fluorescence images of two liquid droplets containing a mixture of Oregon green–labeled wild-type (WT) hnRNPA1 and rhodamine–Texas red–labeled disease mutant D262V hnRNPA1 (D262V). The mutant protein forms amyloid fibrils in the dense droplets. (**C**) Model depicting the relations among phase separation, fibrillization, and pathologic inclusions in neurodegenerative diseases. When stress granules are composed of RNA-binding proteins that contain fibrillization-promoting mutations or they persist because of disturbances in the disassembly machinery, pathologic fibrils can assemble and escape quality-control surveillance. *Reprinted from Cell, 163, Phase separation by low complexity domains promotes stress granule assembly and drives pathological fibrillization, Molliex A et al, 123–33, © 2015, with permission from Elsevier.*

DIPEPTIDE REPEAT–INDUCED TOXICITY HINDERS NUCLEOCYTOPLASMIC TRANSPORT

In another project, Dr. Taylor and his group shed light on how the expansion of a guanine (G) and cytosine (C) G_4C_2-repeat sequence in the *C9orf72* gene, the most common cause of ALS and frontotemporal dementia, leads to disease. Genetic interaction analysis showed that a key cellular structure affected in these neurodegenerative diseases is the nuclear pore complex (NPC), one of the largest and most disordered molecular machines, and the machinery that mediates nucleocytoplasmic transport, which includes the export of RNA and import of nuclear proteins.

Brian Freibaum, PhD (Cell & Molecular Biology), a staff scientist in Dr. Taylor's lab, introduced the human G_4C_2-repeat expansion into the fruit fly *Drosophila* to engineer a tractable genetic system. In the journal *Nature*, the investigators showed that the degenerative phenotype seen in the neuronal tissues of the flies was dosage dependent. Specifically, the longer the G_4C_2 repeats, the more severe the degenerative phenotype. The team identified locomotor defects and abnormalities in neuromuscular junctions. They used the mutant flies in an unbiased genetic screen of the *Drosophila* genome to learn about the consequences of the repeat expansion. The interacting genes identified function in nucleocytoplasmic transport and, in most cases, encode components of the NPC or the RNA/protein transport machinery. Using *Drosophila* as a screening tool thus permitted the discovery of NPC defects in ALS.

As mentioned above, the NPC is one of the largest molecular machines in the cell. It spans the nuclear envelope, consists of multiple copies of approximately 30 proteins, and has a molecular weight of 124 MDa. The channel within the pore has a diameter of 5.2 nm and is filled with a selectivity filter that facilitates the transport of specific biomolecules (i.e., carrier proteins) into and out of the nucleus. It can transport particles as large as ribosomal subunits but excludes all non-nuclear proteins larger than 40 kDa. FG-nucleoporins, which are components of the NPC, are anchored in the nuclear envelope and extend into the channel. Their disordered FG domains (so-called because they are rich in phenylalanine–glycine motifs) form the selectivity filter. The FG domains manage these demanding and seemingly disparate functions while remaining fully disordered.



J. Paul Taylor, MD, PhD

The genetic interactions identified in this work indicated that transport between the nucleus and cytoplasm through the NPC is impaired in the presence of G_4C_2-repeat expansions. Indeed, the nuclear envelope in cells expressing G_4C_2-repeat expansions had a wrinkled appearance, and the NPC component Nup107 formed nucleoplasmic inclusions (i.e., aggregates of protein in the protoplasm of the nucleus), indicating that Nup107 was not able to function properly. As a result, mRNA export from the nucleus was impaired. The researchers verified this discovery in motor neurons derived from patients with ALS, and it has now been independently verified in three different laboratories.

Two mechanisms of repeat expansion–related toxicity have been proposed: RNA transcribed from the repeat expansion directly mediates toxicity, or this repetitive RNA undergoes translation, leading to toxic dipeptide-repeat proteins via repeat-associated non-ATG translation (i.e., RAN translation without a start codon). Dr. Taylor's group detected the production of dipeptide-repeat proteins, but whether these proteins cause toxicity in the NPC by interacting with the FG domains remains to be studied. This work links ALS to the impaired function within the molecular NPC machine and raises the question of whether the NPC also plays a role in other neurodegenerative diseases.

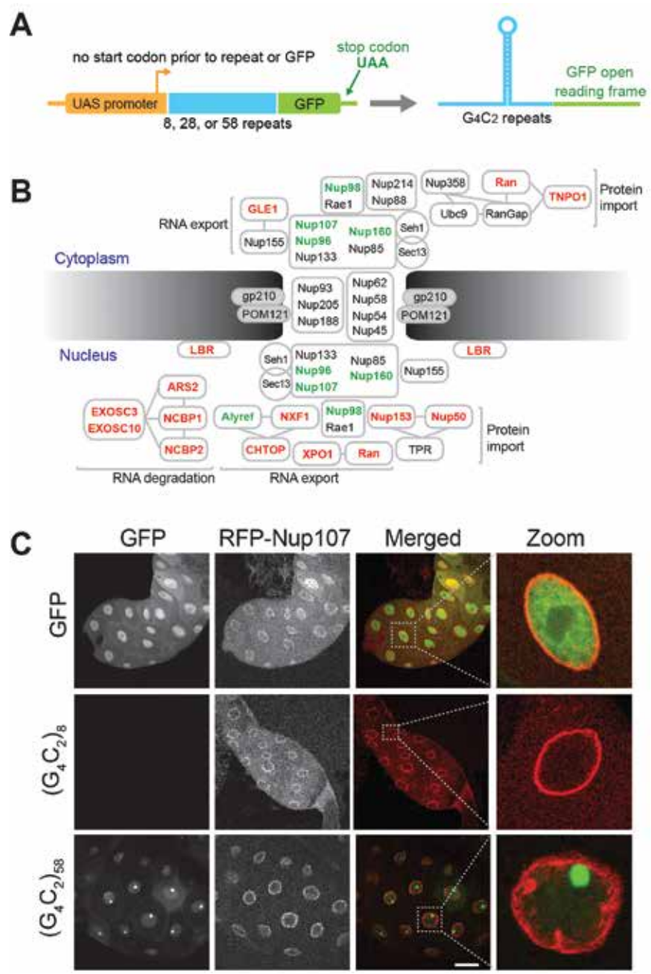
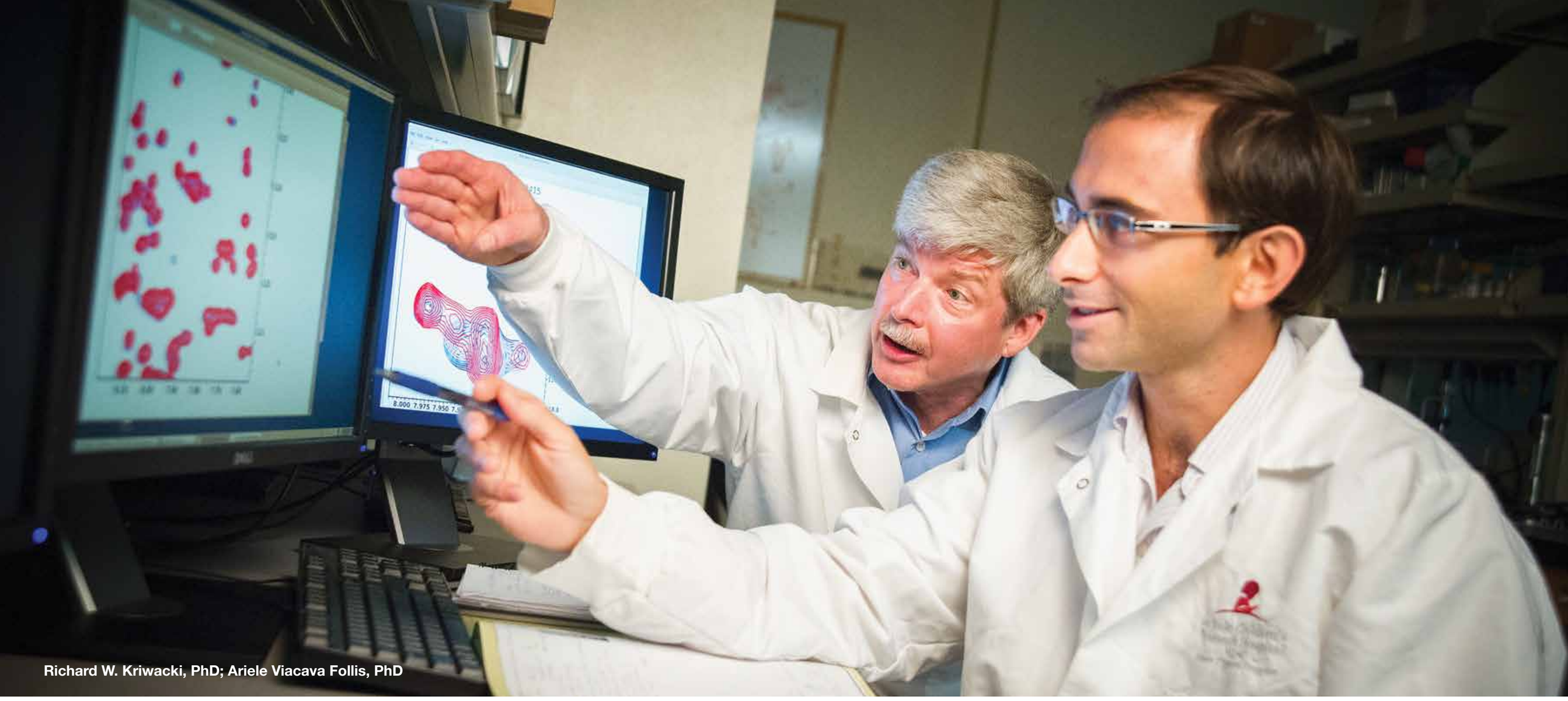


Figure. The G_4C_2-repeat expansion compromises nucleocytoplasmic transport through the NPC. (**A**) Constructs expressing 8, 28, or 58 copies of G_4C_2 repeats. (**B**) Suppressors (green) and enhancers (red) of $(G_4C_2)_{58}$-induced toxicity in the nucleocytoplasmic-trafficking pathway. (**C**) The expression of $(G_4C_2)_{58}$ causes the nuclear envelope to appear wrinkled and Nup107 to localize near the nuclear envelope and form inclusions. Scale bar, 50 µm. *© 2015 Freibaum BD et al*



Richard W. Kriwacki, PhD; Ariele Viacava Follis, PhD

PIN1-CATALYZED ISOMERIZATION OF A PROLINE IN p53 ACTIVATES BAX

The p53 tumor suppressor has crucial protective functions that are highlighted by the fact that more than 50% of cancer genomes contain p53-inactivating mutations. Cytotoxic stress leads to the induction of a p53-mediated transcriptional program, but p53 also has nontranscriptional cytosolic functions, which were first described by the laboratory of Douglas R. Green, PhD (Immunology). Cytosolic p53 activates the apoptotic-effector protein BAX, which triggers the permeabilization of the mitochondrial outer membrane and subsequent apoptosis. Work led by Dr. Green and Richard W. Kriwacki, PhD (Structural Biology), has now revealed the molecular mechanism of BAX activation, which is closely related to the intrinsically disordered nature of regions of p53.

Ariele Viacava Follis, PhD (Structural Biology), a postdoctoral fellow working in Dr. Kriwacki's laboratory, discovered that a serine–proline motif in the disordered transcriptional activation domain of p53 mediates binding of the tumor suppressor to BAX. Prolines are the only amino acids that undergo *cis*/*trans* isomerization, a slow structural change that introduces a kink in the protein backbone. Such interconversions are usually not possible in folded proteins but typically occur in disordered proteins. Using high-resolution nuclear magnetic resonance spectroscopy, a method that allows the structural characterization of dynamic biomolecules not amenable to crystallization, Dr. Follis realized that the *cis*-proline isomer in p53 was stabilized when bound to BAX.

In *Molecular Cell*, the investigators reported that the serine–proline motif is a substrate for the proline isomerase Pin1, which catalyzes the interconversion between *cis*- and *trans*-prolines. The presence of Pin1 enhanced p53-mediated activation of BAX. Dr. Follis then showed that it was not the *cis*-proline isomer, but the dynamic interconversion between the *cis* and *trans* states, that led to the activation. The interconversion dislodges a helix in BAX, which causes BAX oligomerization in the mitochondrial outer membrane and subsequent permeabilization. BAX activation through BH3-containing activator proteins takes a different pathway to structural destabilization but also causes BAX oligomerization. Structural characterization showed that the serine–proline motif in p53 remains exposed to solvent, even when bound to BAX; therefore, it most likely remains accessible to Pin1. Pin1 and p53 might cooperate to activate BAX in a ternary complex. The binding of the serine–proline motif to two proteins at the same time and the dynamic interconversion between *cis* and *trans* states are processes enabled specifically by disordered regions.

This study highlights the importance of completely disordered protein regions in the continuum of protein states and expands our understanding of the structural biology of molecular signaling mediated by proline isomerization in critical cellular processes.

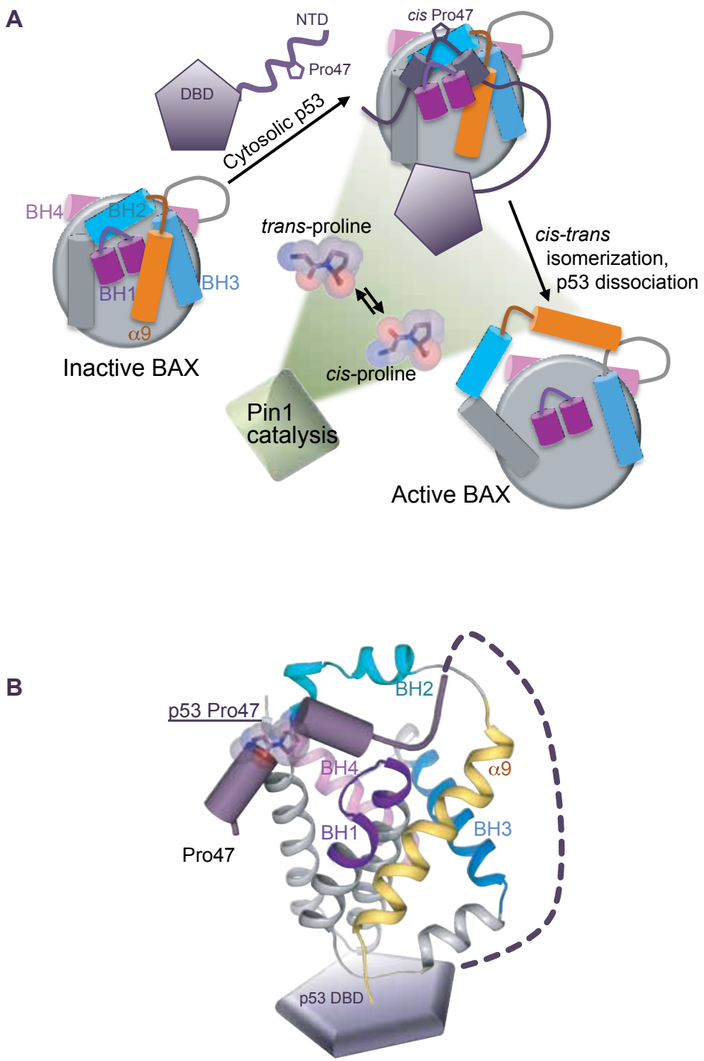
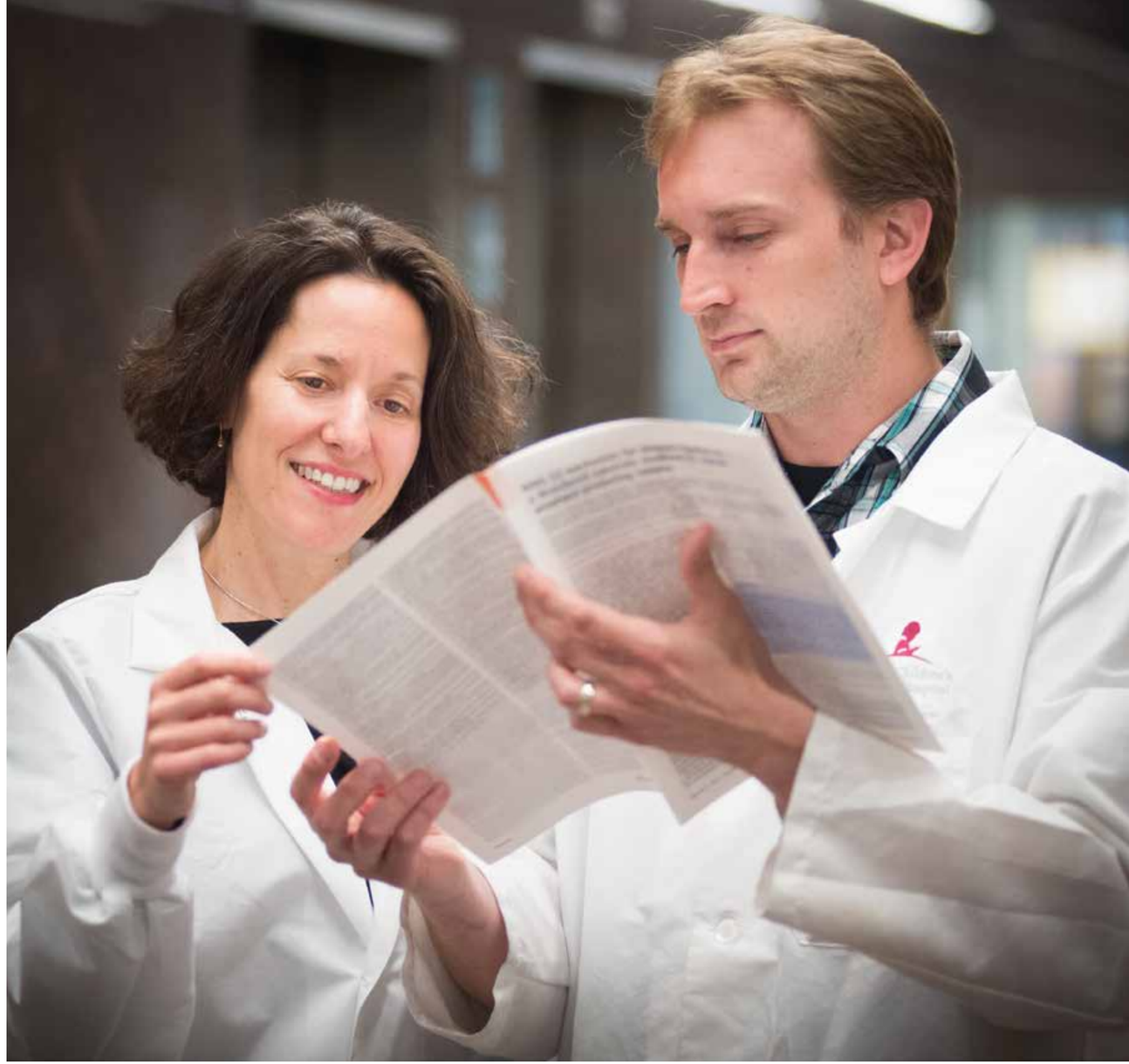


Figure. Cytosolic p53 mediates a conformational switch in activation of the apoptotic effector BAX. The structure of BAX is shown in a schematic (**A**) and as a ribbon diagram (**B**). Interaction of cytosolic p53 stabilizes the *cis* conformation of proline 47 (Pro47). *Cis*/*trans* isomerization, which can be catalyzed by Pin1, triggers conformational rearrangements in BAX that lead to its activation and result in apoptosis.



Brenda A. Schulman, PhD; Nicholas G. Brown, PhD

MECHANISMS OF SUBSTRATE UBIQUITINATION BY THE ANAPHASE-PROMOTING COMPLEX

Recent work led by Brenda A. Schulman, PhD (Structural Biology, Tumor Cell Biology), revealed molecular mechanisms of substrate ubiquitination by the anaphase-promoting complex (APC). The APC is a large multisubunit ubiquitin ligase, a molecular machine with a defined composition that ubiquitinates key substrates that coordinate eukaryotic cell division. Although the sequence of enzymatic steps involved in modifying substrates with ubiquitin is well known and numerous structures of participating proteins have been determined, the mechanism by which the APC coordinates the transfer of several ubiquitin molecules onto a disordered substrate, resulting in a polyubiquitin chain, was not understood.

In a report published in *The Proceedings of the National Academy of Sciences, U.S.A.*, Dr. Schulman and her colleagues showed that the transfer of a first ubiquitin onto substrates involves a series of enzymatic steps catalyzed by E1, E2, and E3 enzymes. Ubiquitin is activated by an E1 and then transferred onto an E2. The E3 enzyme coordinates binding of the substrate and the ubiquitin-charged E2 and stimulates the transfer of ubiquitin onto the substrate. The E3 APC, bound to the activator CDH1, binds the E2 UBCH10 for transfer of the first ubiquitin molecule. For polyubiquitination (i.e., the process by which polyubiquitin chains are built), the APC often switches to a second E2, UBE2S.

Many substrates are disordered, and this property is most likely beneficial for two reasons. First, the recruitment of substrates to the APC and the order of their turnover are encoded by several linear motifs in a disordered sequence. Second, the flexibility of disordered substrates appears to accommodate polyubiquitination and its associated dynamic ubiquitin-attachment sites. Furthermore, parts of the APC move relative to the other components of the complex, and these dynamics are most likely crucial for enzymatic activity. This raises a question: If both partners are flexible, then how are the modification sites on the substrate brought in close proximity to the catalytic cysteine residue of the E2?

Dr. Schulman's team collaborated with Naoaki Fujii, PhD (Chemical Biology & Therapeutics), to develop an innovative chemical approach to answer this question. The team covalently linked the substrate, UBCH10, and ubiquitin before binding it to the APC, thereby trapping the E2–E3–substrate complex in an active conformation that was poised for ubiquitin transfer. In an international collaboration that also involved the laboratories of Jan-Michael Peters (Institute of Molecular Pathology, Vienna, Austria) and Holger Stark (Max Planck Institute for Biophysical Chemistry, Göttigen, Germany), structural determination by crystallography and cryo–electron microscopy allowed Nicholas G. Brown, PhD (Structural Biology), a postdoctoral fellow working in Dr. Schulman's laboratory, to visualize this conformation. The structural determination revealed surprisingly intricate, multisite E2–E3–substrate interactions that allow the correct positioning of the substrate-modification site close to the ubiquitin-charged catalytic cysteine. The multisite interactions help harness the enzymatic activity of the APC molecular machine toward the moving, disordered substrate. These interactions increase the likelihood that the conformationally fluctuating substrate will collide with the catalytic site, thereby enabling the regulation of the cell cycle. Such multisite interactions may be important in many of the 600 RING E3 enzymes in humans, and their disruption through mutations can wreak havoc on the cell and cause cancer or other diseases.

Daniel Scott, PhD; Brenda A. Schulman, PhD; Nicholas G. Brown, PhD

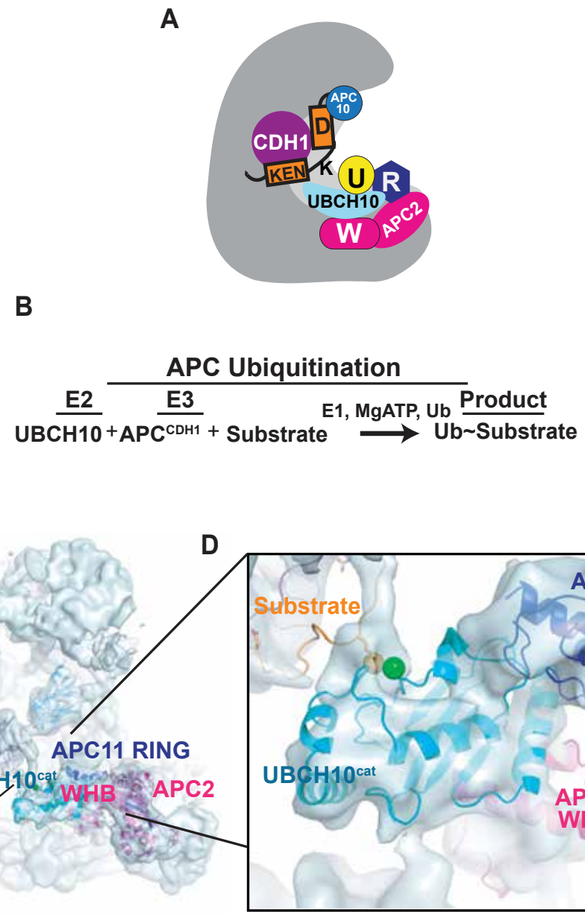


Figure. The APC is a molecular machine that harnesses multisite interactions to ubiquitinate disordered substrates. (**A**) Model of the APC with the activator CDH1 and the E2 UBCH10. Substrate is recruited at a distance via the binding of two linear motifs (KEN-box and D-box) to CDH1 and the APC core. Multisite E2 and substrate interactions establish specificity and reduce the degrees of freedom for flexibly tethered reactants to promote catalysis. (**B**) APC ubiquitination mechanism. The APC and the E2 UBCH10 ligate ubiquitin (Ub) directly to substrates. (**C**) Substrate complex showing the cullin (APC2) and RING mechanism for juxtaposing the UBCH10 catalytic site ($UBCH10^{cat}$) with substrate. (**D**) The crystal structure of $APC2^{WHB}$–$UBCH10^{cat}$ docked with the APC11 RING domain was fitted into the cryo–electron microscopy map. UBCH10–Ub is recruited via multisite interactions with the APC2–APC11 catalytic core.

CONCLUSION

Proteins function in a continuum of states. St. Jude investigators are characterizing the molecular mechanisms engendered via these different states to advance the discovery of novel therapies for cancer and other catastrophic diseases.

ELUCIDATING GENETIC PREDISPOSITION TO PEDIATRIC CANCER

Cancer is caused by one or more genetic abnormalities that result in the uncontrolled proliferation of malignant cells. In 1971, Alfred G. Knudson published his study of familial retinoblastoma, a childhood cancer of the eye. Dr. Knudson proposed a “two-hit” model of tumor development in which both alleles of a tumor-suppressor gene must be inactivated for cancer to develop. In familial retinoblastoma, the first hit is an inherited mutation, and the second hit occurs somatically. The Pediatric Cancer Genome Project (PCGP), which launched in 2010 as a collaboration between St. Jude Children’s Research Hospital and Washington University School of Medicine (St. Louis, MO), has generated whole-genome and whole-exome sequencing data of tumor and matching nontumor tissue samples from more than 1200 pediatric patients with cancer. Through the PCGP, we have gained unprecedented insight into the somatic mutations in pediatric cancer and the biological pathways and molecular processes that are altered in cancer cells, which has provided some novel targets for treatment. This effort continues with the characterization of the somatic genomic landscape of infant acute lymphoblastic leukemia (ALL) and has expanded our understanding of the molecular basis of relapsed ALL.

Jinghui Zhang, PhD; Xiang Chen, PhD

The analysis of nontumor tissue provides genetic data for exploring germline mutations that cause cancer predisposition. Such an investigation will shed light on one of medicine's most perplexing questions—Why do children get cancer? To answer this question, PCGP investigators have begun to evaluate the pathogenicity of germline variations in cancer-predisposition genes, first in patients enrolled in the PCGP and later in each new patient who comes to St. Jude for treatment. This is a daunting task that requires collecting and harmonizing 15 genetic-mutation databases, reviewing each patient's family history, evaluating evidence from the literature, and analyzing second hits in the tumor genome.

In 2013, James R. Downing, MD (Pathology), led a team of computational biologists, licensed pathologists and technologists, pediatric oncologists, geneticists, bioethicists, and genetic counselors in defining the prevalence of germline mutations in pediatric patients with cancer who were enrolled in the PCGP. This work is increasing our understanding of childhood cancers, improving our ability to diagnose and treat those diseases, and providing the opportunity to inform and counsel patients' families about the potential for other members to experience the same or similar diseases and help guide their healthcare choices. The study has also laid the foundation for discovering and reporting pathogenic mutations in the clinical setting.

Michael Rusch; Gang Wu, PhD; Jinghui Zhang, PhD

IDENTIFYING GERMLINE MUTATIONS THAT PREDISPOSE CHILDREN TO CANCER

In children with cancer, the prevalence of germline mutations in cancer-predisposition genes has been mostly unknown. Such information would increase our understanding of how tumors arise, help guide the optimal treatment for those diseases, and provide genetic counseling for patients and families with underlying cancer-predisposition syndromes. Therefore, Dr. Downing and Jinghui Zhang, PhD (Computational Biology), led a multidisciplinary team of investigators to identify those mutations and determine their contribution to childhood cancers.

In *The New England Journal of Medicine*, the authors reported finding germline susceptibility in 1120 children with cancer who are participating in the PCGP. Their analyses included whole-genome sequencing (WGS; the sequence of all DNA contained within the 23 chromosomes) of 595 patients, whole-exome sequencing (WES; the sequence of the 3% of DNA that encodes the proteins that make up the body) of 456 patients, or both approaches for 69 patients. As control cohorts, WES data from 966 participants in the 1000 Genomes Project and 723 participants in an autism study were analyzed in the same manner. A computational algorithm was developed to assign a preliminary score to each variant based on its population frequency, its match to curated variation databases, second hits in the tumor DNA, mutant allele expression in tumor RNA, and computational predictions of the mutation's effect on protein function. A panel of medical experts then used multiple resources (e.g., evidence in variation databases and scientific literature) to determine whether the identified mutations were pathogenic, probably pathogenic, variants of unknown significance, probably benign, or benign.

The study examined 565 cancer-related genes, with a focus on 60 that have been associated with autosomal-dominant cancer-predisposition syndromes. This approach identified 95 (8.5%) pediatric patients with cancer who carried either pathogenic or probably pathogenic mutations. The most commonly affected genes were *TP53*, *APC*, *BRCA2*, *NF1*, *PMS2*, *RB1*, and *RUNX1*. The prevalence of pathogenic germline mutations was highest (16.7%) in pediatric patients with solid tumors outside of the central nervous system (e.g., adrenocortical tumor, osteosarcoma, and retinoblastoma) and lowest (4.4%) in those with leukemia.

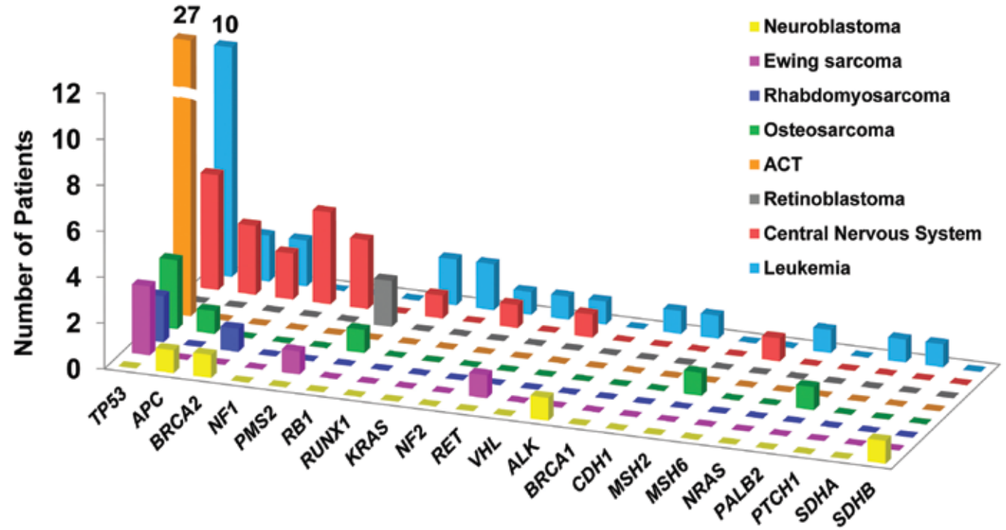
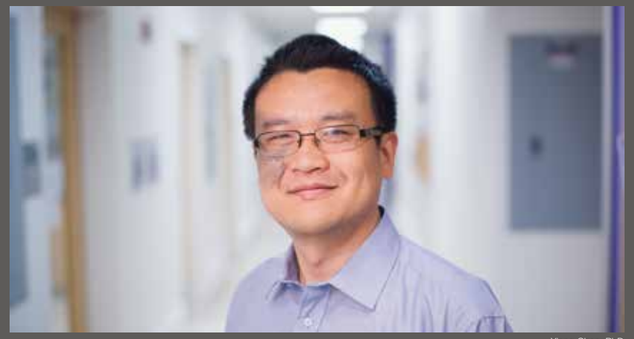


Figure. Distribution of pathogenic or probably pathogenic mutations within the 21 mutated autosomal-dominant genes across patients with various cancers who were included in the PCGP cohort.

Kim E. Nichols, MD (Oncology), led the review of family histories. Medical records were available for 75 pediatric patients who harbored a cancer-predisposition mutation; 58 of those records included information about family history. Of those, only 23 (40%) had a history of cancer, and only 13 had a family history that was consistent with the cancer-predisposition syndrome identified in the patient. An examination of the family histories of pediatric patients who did not have a germline mutation revealed that the prevalence was comparable (42%). Thus, the team concluded that a family history of cancer is not the sole predictor of the presence of cancer-predisposition syndromes in pediatric patients, and genetic testing should not be guided solely by family history.

These findings provide a strong argument that every child with newly diagnosed cancer should have samples of normal tissue and tumor tissue sequenced to identify mutations in genes associated with cancer risk. This represents a major change in standard of care—for practicing oncologists to incorporate an assessment of germline cancer predisposition into clinical care for pediatric patients. These findings also suggest that cancer surveillance will be important for survivors of childhood cancer and their own children. The data generated from this study will provide a means to address several pressing questions: Are children who are born with a single mutant allele of a classic adult-onset cancer-predisposition gene (e.g., *BRCA1*, *BRCA2*, or *PALB2*) at greater risk than the general population for childhood cancers? How does germline mosaicism (i.e., when the sperm or ovum contains more than one set of genetic information) influence the likelihood that disease will develop? What percentage of these mutations arises de novo, and what percentage was inherited from a parent in whom the disease never developed? How do mutations in the genes studied here interact with common and rare DNA variations elsewhere in the genome to influence malignant transformation?



Xiang Chen, PhD

A NEW ANALYTICAL METHOD INCREASES THE POWER OF GENOMIC STUDIES

Next-generation sequencing (NGS) technologies extract genetic information by simultaneously examining nucleotides or bases in DNA and running thousands of individual sequencing reactions in a highly parallel manner. In 2015, Dr. Zhang and her team of computational biologists reported a new method of data analysis that increases our ability to accurately evaluate NGS data and identify the germline mutations that predispose children to cancer.

In a study published in *Nature Methods*, Xiang Chen, PhD (Computational Biology), in collaboration with Dr. Zhang, reported the development of a new algorithm called CONSERTING, which stands for Copy Number Segmentation by Regression Tree in Next-Generation Sequencing. CONSERTING is a highly accurate and sensitive approach to detecting somatic copy-number alterations (CNAs; gains or losses of DNA segments) in WGS analysis. CNAs are a key category of genetic mutations that contribute to cancer initiation, progression, and relapse. Previously developed algorithms have been used to accurately identify large CNAs, but smaller genetic alterations are often missed and a large number of false-positive CNAs have been mistakenly identified by those approaches.

CONSERTING identifies copy-number variations through an iterative process of read-depth segmentation, segment merging, and structural-variant detection. This approach enables the discovery of complex CNAs caused by chromosome shattering and rejoining, a phenomenon known as “chromothripsis.” To test this new algorithm, Dr. Chen performed WGS analysis of 43 paired (cancer vs noncancer) DNA samples from patients with adult or pediatric forms of six different subtypes of cancer. He then compared the performance of CONSERTING with that of four established methods for analyzing CNAs (i.e., SegSeq, CNV-seq, FREEC, and BIC-seq). CONSERTING consistently identified CNAs that were missed by the established approaches.

CONSERTING has been applied to all PCGP studies. The most prominent discoveries included *ATRX* focal lesions in neuroblastoma, chromothripsis-driven *C11orf95–RELA* fusion in ependymoma, and complex rearrangements in osteosarcoma and adrenocortical tumor. As an important component of the Clinical Genomics Program’s pipeline, results generated by CONSERTING include copy-neutral loss-of-heterozygosity, percentage of tumor-in-normal contamination, and digital karyotyping, in addition to the standard copy-number and structural-variation profiles. To share CONSERTING with the research community, the authors developed a preconfigured version of CONSERTING that can be launched from Amazon Web Services’ cloud (*http://www.stjuderesearch.org/site/docs/conserting/conserting-ami-steps.pdf*).

Regina Nucci; Kim E. Nichols, MD; Rose McGee; Emily Quinn

CLINICAL GENOMICS BECOMES A REALITY AT ST. JUDE WITH THE OPENING OF THE GENOMES FOR KIDS PROTOCOL

To translate the findings of the PCGP into the clinic, Dr. Downing established the St. Jude Clinical Genomics Program. This program incorporates genomic sequencing into the molecular diagnosis and clinical care of every pediatric patient with cancer at St. Jude. The initial goal is to identify pathologic somatic mutations that alter biological functions in tumors and pathogenic germline mutations associated with increased risk of cancer. Each patient will be analyzed by WGS, WES, and RNA sequencing (RNAseq; the sequence of various RNA species that are expressed in cells) of tumor and/or normal tissue samples. Analysis of the massive amount of raw sequencing data needs to be accomplished in a clinically relevant time frame, so that genomic findings can be reported to doctors and patients and their families, as appropriate. An estimated 350 to 400 patients per year are expected to be analyzed using this approach.

A multidisciplinary team has been assembled to achieve these goals. Dr. Zhang led the development of analysis and reporting infrastructure for detecting and interpreting genetic lesions. Working with Sheila Shurtleff, PhD, and Joy Nakitandwe, PhD (both of Pathology), the team has solved the major challenges of clinical data processing (i.e., sample tracking, data quality control, pipeline optimization, variant integration, report generation, and results visualization). Using 78 tumors that have gone through molecular diagnostic analysis as a benchmark, the clinical pipeline is able to achieve more than 99% accuracy in identifying pathogenic somatic and germline mutations that are crucial for determining cancer-risk stratification, treatment options, and genetic predisposition.

In August 2015, Drs. Downing, Zhang, and Nichols collaborated to open the Genomes for Kids (G4K) protocol to perform genomic studies using the clinical genomics infrastructure. Pediatric patients with newly diagnosed, relapsed, or refractory tumors (i.e., tumors that have not responded to previous treatment), or noncancerous tumors may be eligible to participate in the G4K trial. As patients arrive at St. Jude for treatment, they are informed about the study and assessed for eligibility. The overall goals of the G4K protocol are to increase our knowledge about childhood tumors, determine whether NGS studies in the clinical setting will guide treatment and advance precision medicine, and learn the best ways of sharing genomic information with patients and their families, who may also benefit from genetic testing and counseling.

To achieve this last goal, Dr. Nichols and her colleagues in the Hereditary Cancer Predisposition Clinic are assessing the perceptions of patients and parents about genomic studies and research. The team is using mixed-measures approaches to examine the ability of patients and parents to understand and accept genomic-testing results. They are also investigating the impact of those results on patients and families. How do parents react to learning that their child has an inherited cancer-predisposition syndrome? What is the likelihood that the patients' siblings will also experience the disease?

The Hereditary Cancer Predisposition Clinic is one of only a few such programs in the world that is focused on evaluating and treating children and their families who have a known (or suspected) predisposition to cancer. Any St. Jude patient who harbors a germline mutation in a cancer-predisposition gene is referred to the clinic, which is staffed by two doctors, three genetic counselors, nurses, and clinical research associates. The team determines whether the patient's disease might have been inherited and collaborates with other St. Jude physicians and researchers to help families who have an elevated risk of cancer. If a germline mutation is found, genetic testing for first-degree relatives will be offered via the St. Jude Molecular Pathology/Clinical Genomics Laboratory, which is directed by Elizabeth M. Azzato, MD, PhD (Pathology).

Sheila Shurtleff, PhD; Elizabeth M. Azzato, MD, PhD

MOLECULAR PATHOLOGY/CLINICAL GENOMICS LABORATORY PROVIDES INFRASTRUCTURE TO THE GENOMES FOR KIDS PROTOCOL

Led by Drs. Azzato and Shurtleff, the medical and technical directors of Molecular Diagnostics, the CLIA (Clinical Laboratory Improvement Amendments)-certified Molecular Pathology/Clinical Genomics Laboratory uses cutting-edge NGS technologies to process DNA samples from tumor and nontumor tissues and tumor RNA samples for 350 to 400 patients per year. Tennessee-licensed clinical laboratory technologists analyze molecular biomarkers expressed in tumors and elucidate cancer genomic, transcriptomic, and epigenomic profiles for each patient to provide treating physicians with accurate cancer diagnosis and prognosis. Somatic mutations and germline mutations of pathologic importance are identified using multiple assays, and results are reported in clinically relevant time. The laboratory houses five HiSeq DNA-sequencing instruments, one NextSeq, and two MiSeQ DNA sequencers that allow staff to analyze as many as 20 cases per week.

In addition to the new germline mutation studies that comprise the Clinical Genomics Project of the PCGP Phase II initiative, there is still much to be learned by investigating the plethora of somatic mutations that were identified during Phase I. Here we briefly describe two acute lymphoblastic leukemia (ALL) studies that examined the somatic mutations associated with severe forms of the disease—infant leukemia with *MLL*-gene rearrangements (*MLL*-R ALL) and relapsed pediatric B-progenitor ALL (B-ALL).

Tanja A. Gruber, MD, PhD

SOMATIC MUTATIONS IN *MLL*-REARRANGED ACUTE LYMPHOBLASTIC LEUKEMIA IN INFANTS

Infants (i.e., persons younger than 1 year) make up no more than 5% of all pediatric patients with ALL, and nearly 80% of those cases include rearrangement of the *MLL* gene. Infants with ALL also tend to have a much poorer prognosis than older pediatric patients with the disease. Advances in ALL treatment have increased the survival of childhood ALL to nearly 90%; however, event-free survival of infants with ALL is only 28% to 36%.

An international team led by Dr. Downing, Anna K. Andersson, PhD (Pathology), and Tanja A. Gruber, MD, PhD (Oncology, Pathology), exploited NGS approaches (i.e., WGS, WES, RNAseq, and targeted DNA sequencing) to analyze the genetic landscape of somatic mutations in 65 infants with *MLL*-R ALL and compared it with the genetic landscape in 20 older pediatric patients (aged 7-19 years) with *MLL*-R leukemia (nine had *MLL*-R ALL; 10 had acute myeloid leukemia; and one had undifferentiated leukemia).

In *Nature Genetics*, the authors reported that infant *MLL*-R ALL has one of the lowest frequencies of somatic mutations (mean, 1.3 mutations/patient) of any sequenced human cancer. Thirty-one (48%) infants carried activating mutations in components of the kinase–PI3K–RAS–signaling pathway (e.g., *KRAS*, *NRAS*, *FLT3*, and *PIK3R1*); however, those mutations were often subclonal and some were lost at relapse. Thus, the activating mutations may not be essential for maintaining leukemic cells. In contrast, older children with MLL-R ALL carried significantly more somatic mutations (mean, 6.5 mutations/patient) and showed frequent somatic mutations in 11 epigenetic regulatory genes that were not mutated in infant *MLL*-R ALL.

The investigators concluded that the highly aggressive nature and brief latency to development of clinically overt infant *MLL*-R ALL, which often arises at birth, are consistent with the highly oncogenic properties of the MLL-fusion protein. Their results also suggested that therapy targeted to the MLL-fusion protein or proteins required for its function might be an effective treatment for *MLL*-R ALL in infants.

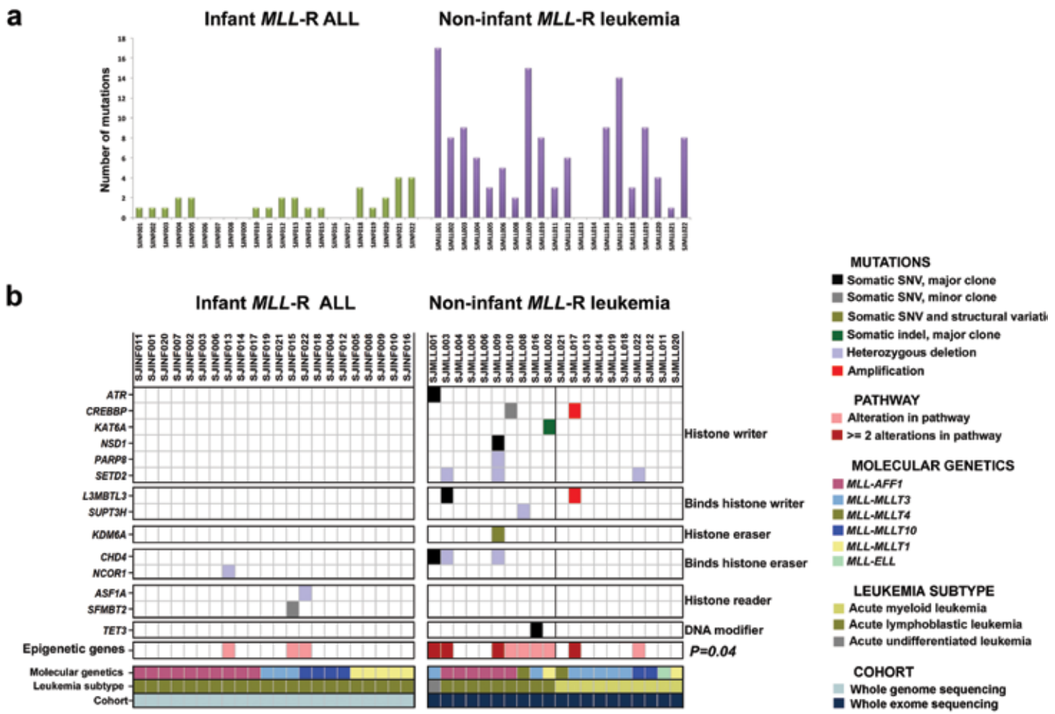


Figure. Mutational profiles of infant vs non-infant *MLL*-R ALL mutations. (**a**) The number of somatic mutations [i.e., nonsilent single-nucleotide variations (SNVs) and insertions/deletions (indels)] in the dominant leukemic clone that affects protein-coding genes in infant *MLL*-R ALL and non-infant *MLL*-R leukemia. (**b**) Distributions of somatic SNVs, indels, and copy-number alterations (CNAs) in epigenetic regulatory genes demonstrate that these genes are mutated more often in non-infant *MLL*-R leukemia. *© 2015 Andersson AK et al*

Xiaotu Ma, PhD; Xin Zhou, PhD; Jinghui Zhang, PhD

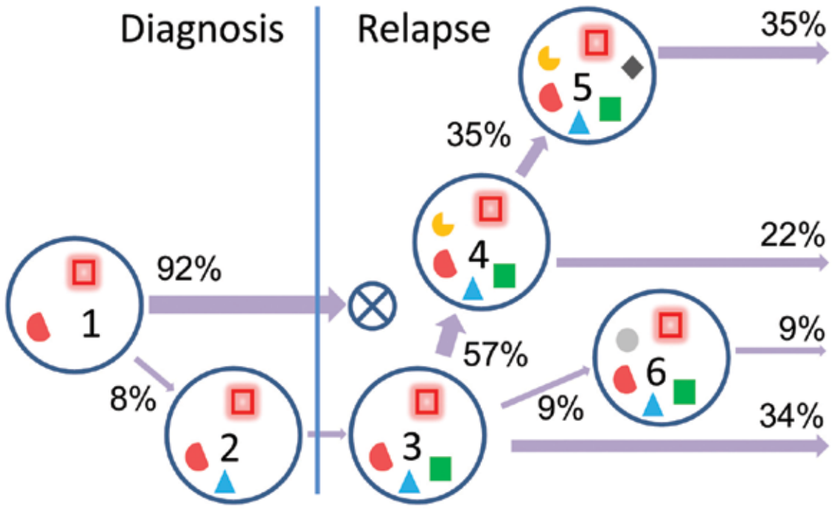
THE GENETIC BASIS OF TREATMENT FAILURE IN PEDIATRIC B-PROGENITOR ACUTE LYMPHOBLASTIC LEUKEMIA

Relapsed ALL continues to be a leading cause of cancer-related death among children. The probability of event-free survival of childhood ALL is approximately 85% when the disease is treated with contemporary therapies. However, approximately 15% of patients with pediatric ALL experience disease relapse, and most die of their disease. Multiple groups have reported relapse-specific mutations in pediatric ALL that have increased our knowledge about the genetic basis of cancer relapse.

To investigate the genetic heterogeneity (i.e., the property of a tumor having distinct cell types with different mutation profiles) and clonal evolution (i.e., the accumulation of genetic mutations over time within individual leukemia cells) during the course of cancer progression, Dr. Zhang and her colleagues used deep WES to analyze somatic mutations in DNA samples obtained from 20 pediatric patients (aged 2-19 years) with B-ALL. Cases were selected based on B-ALL relapse detected in bone marrow less than 36 months after initial diagnosis, an event that is associated with very poor prognosis. For each patient, NGS analyses were performed at the times of diagnosis, complete remission, and disease relapse to assess and compare the somatic mutations present in the leukemic cells at those stages of the disease. Mathematical models were developed by Xiaotu Ma, PhD (Computational Biology), a senior scientist in Dr. Zhang's lab, to map the tumor clonal lineages and the dynamic changes of the subclonal population from diagnosis to relapse.

As reported in *Nature Communications*, the investigators evaluated how clonal diversity, origin, mutation burden, and population frequency contributed to clonal evolution from diagnosis to relapse. They found that there was no significant difference between the number of subclones identified at diagnosis and relapse and that clonal survival does not depend on mutation burden. In 15 of 20 cases (75%), the tumor cells that survived therapy were a minor subclone at diagnosis (median population frequency, 7%; range, 2%-20%). Importantly, relapse-specific mutations present in the founder clone at relapse were observed in seven genes (*NT5C2*, *USH2A*, *WHSC1*, *TP53*, *NRAS*, *IKZF1*, and *CREBBP*).

The team concluded that the predominant clone present at diagnosis is eradicated by chemotherapy in the majority of patients with relapsed ALL. Minor subclones present at diagnosis survive treatment and serve as relapse-founder clones, which subsequently acquire additional mutations that lead to ALL relapse. This study provides new insight about the genetic basis of treatment failure and holds promise for advancing our ability to detect somatic mutations that drive B-ALL relapse.



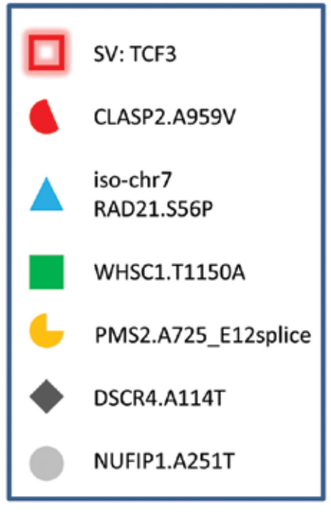


Figure. Clonal evolution of B-ALL in a single patient from diagnosis to relapse. Genomic lesions mapped to each clone are shown as colored symbols. The dominant clone at diagnosis (clone 1) constituted 92% of the tumor cells and was eliminated by therapy. The minor subclone (clone 2), which harbored an isochromosome 7 lesion, persisted to relapse. The founder clone (clone 3) acquired a WHSC1 T1150A mutation. One branch descended to acquire an additional PMS2 mutation (clone 4) and became the predominant clone in relapse (clone 5). *Reprinted from Ma X et al, Nat Commun, 6, 6604, © 2015 Macmillan Publishers Limited. The Creative Commons Attribution 4.0 International Public License is available at http://creativecommons.org/licenses/by/4.0.*

Figure. Global geographic locations of some research institutes that have been granted access to PCGP data sets. Colors indicate the number of data requests made by an institute: red indicates five requests; orange, four; yellow, 3; blue, one to two.

DEVELOPMENT OF THE MOST COMPREHENSIVE GENOMIC DATA RESOURCE FOR PEDIATRIC CANCER

The unprecedented amount of genomic data generated by the PCGP has not only provided major insights into the genomic and genetic landscape of pediatric cancer but also become an important resource for the research community. Raw data, which consist of approximately 6000 WGS, WES, and RNAseq datasets, have been presented in 25 published studies and uploaded to the public data archive, including the database of Genotypes and Phenotypes (dbGAP) and the European Bioinformatics Institute data portal (The European Genome-Phenome Archive, EGA). To date, 119 laboratories at 86 institutes across the world have accessed the PCGP data.

In addition to making the primary data accessible, Dr. Zhang's laboratory has developed a pediatric cancer genome portal, the PeCan data portal (*https://pecan.stjude.org*), to provide rich visual features for PCGP and pediatric genomic data generated by other major studies. The pediatric dataset includes more than 27,188 validated somatic mutations identified in 17 different subtypes of pediatric cancer, 252 pathogenic or loss-of-function germline mutations identified in 21 pediatric cancers, and RNAseq data from 36 pediatric cancers.

Jing Ma, PhD; James R. Downing, MD

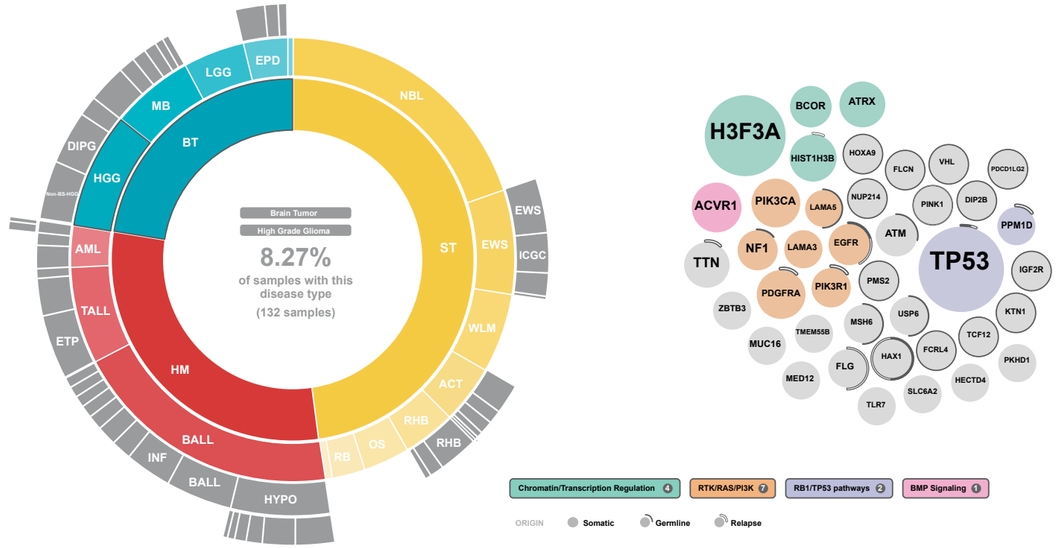


Figure. PeCan portal. The patient cohort is shown on the left, and the recurrently mutated genes in a user-selected cohort (i.e., high-grade glioma) are shown on the right. Mutated genes are colored based on the pathways to which they belong. The size of each gene is proportional to its mutation frequency in the selected cohort.

A key application of the PeCan data portal, called ProteinPaint, provides a visual-based navigation process that is intuitive to scientists. The tool, which was published in *Nature Genetics*, was developed by Xin Zhou, PhD (Computational Biology), a senior scientist working in Dr. Zhang's lab. ProteinPaint enables simultaneous review of somatic and germline lesions (including sequence mutations and gene fusions) and RNA expression. In addition, it allows a parallel review of the curated database COSMIC (Catalogue of Somatic Mutations in Cancer), which contains 1.6 million verified somatic mutations that were discovered mostly in adult cancers. Custom data can be uploaded for comparison with the published pediatric and adult cancer data sets, a feature that has been used frequently to determine the significance of mutations detected in patients in the St. Jude Clinical Genomics Program. Within the first month of its release to the public, ProteinPaint was accessed by researchers in 50 countries across five continents.

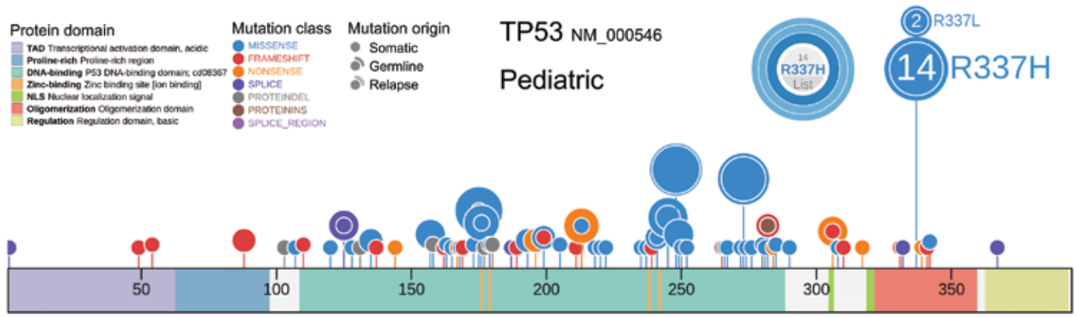


Figure. ProteinPaint view of *TP53* mutations identified in the pediatric patients with cancer. This included a total of 112 somatic mutations, 48 germline mutations, and six relapse-specific mutations.

CONCLUSION

Investigators at St. Jude are working to identify the germline mutations that predispose children to hereditary forms of cancer. Their goals are to determine the best approach to incorporating NGS data into the pediatric oncology setting, optimize pediatric cancer treatment, and inform and counsel families about the risk of cancer developing in other family members. The resulting data have been made publicly available because they are a valuable resource to the international pediatric cancer research community. Investigators around the world will use information gained at St. Jude to explore the causes of, improve treatments for, and potentially cure these catastrophic childhood diseases.

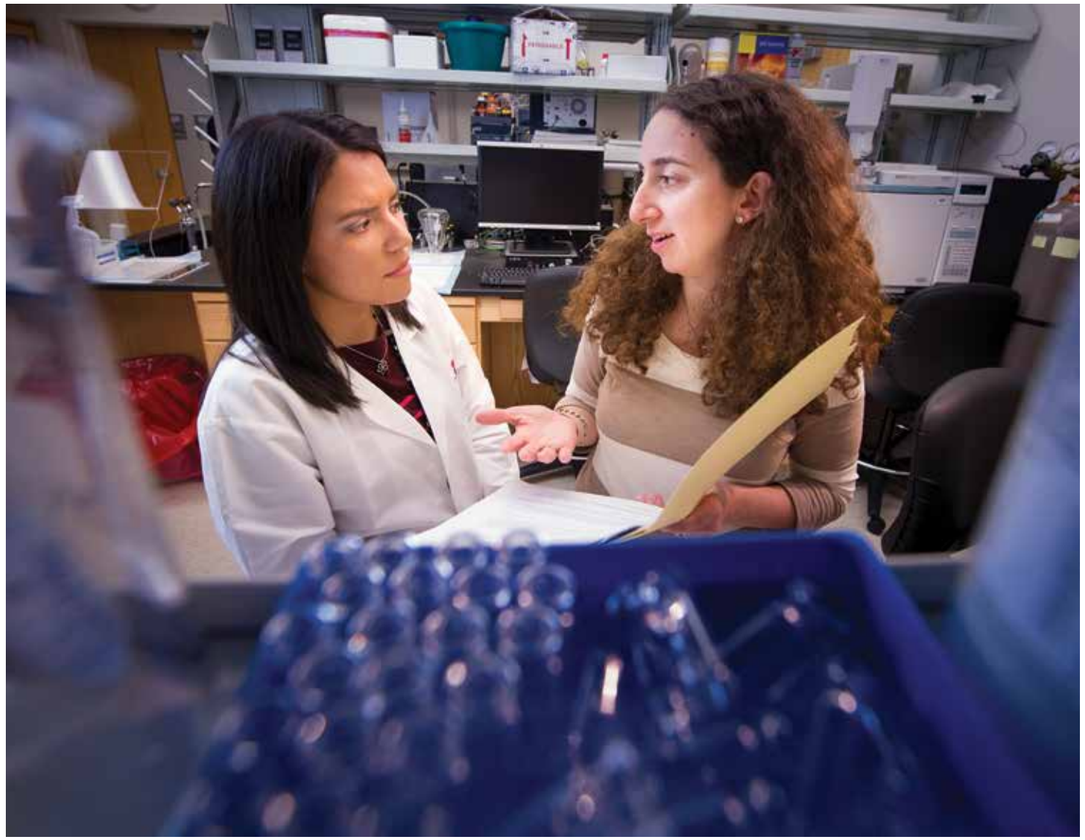
PHARMACOGENOMICS: A POWERFUL TOOL TO DESIGN INDIVIDUALIZED CHEMOTHERAPY

Medications do not work the same for everyone. Although most people benefit from a particular drug, others experience no effect, and some patients are seriously harmed by the treatment that was intended to improve their health or cure their disease. Although this interindividual variability in treatment response has been recognized for centuries, only in the past few decades have scientists begun to elucidate how differences across our genome influence the way patients respond to specific medications.

Jun J. Yang, PhD

Scientists at St. Jude working in the relatively young field of pharmacogenomics are investigating the genomes of patients to determine how genetic differences across patients influence how they respond to medications. By identifying the genetic variations associated with treatment-induced toxicity, investigators can then screen patients for those variants before initiating treatment. This allows clinicians to identify those patients who will require a different dose or drug regimen to successfully treat their disease, thereby preventing toxicity that can compromise quality of life during and after treatment.

The probability of cure for children with acute lymphoblastic leukemia (ALL) is now approximately 90%. This has been achieved largely by optimizing chemotherapy, in some cases based on genetic insights. Scientists are now designing personalized medication regimens in which the doses of essential life-saving medications are adjusted based on each individual patient's genome to improve treatment response, prevent adverse effects, and optimize the long-term quality of life for adult survivors of childhood cancer. St. Jude researchers are collaborating with scientists around the world to identify new genetic variants that influence how patients respond to medications and translate those findings into precision medicine strategies that improve the effectiveness and reduce the side effects of medications.



Laura Howell; Cyrine Haidar, PharmD

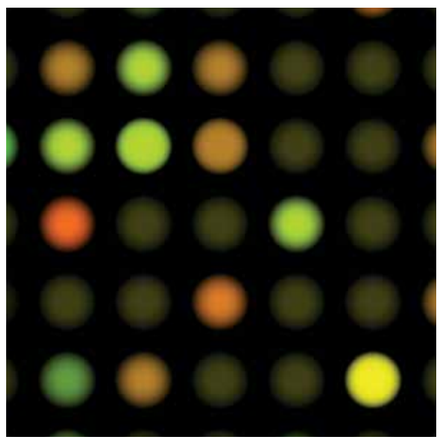
THE EMERGING ROLE OF PHARMACOGENOMICS IN PERSONALIZED MEDICINE

Pharmacogenetics research generally focuses on how single genes influence a person's response to a particular drug. Pharmacogenomics takes a broader approach by interrogating genes across a person's entire genome to more comprehensively elucidate the complex genetic determinants and interactions that mediate drug effects. St. Jude has played a pioneering role in pharmacogenetics and pharmacogenomics and is leading an NIH-funded international consortium (*www.cpicpgx.org*) that is developing guidelines for implementing pharmacogenetic tests in routine patient care. St. Jude is one of the few institutions that has implemented a comprehensive clinical program that uses pharmacogenomics with clinical decision support in the electronic health record to optimize the use of medications for children with cancer or other catastrophic diseases. The PG4KDS protocol, which opened in 2011, uses an array-based approach to preemptively identify inherited genetic variants important for pharmacologic responses to guide prescribing practices for St. Jude patients.

The human genome consists of approximately 20,000 genes, and each gene can differ somewhat in its sequence, resulting in genetic variants across a population. Inherited differences in genetic variants that influence the ability to metabolize, transport, or respond to a specific drug can determine whether that drug has a therapeutic or detrimental effect. Malignant transformation can also alter genetic content specific to tumor cells. This is called somatic mutation. Both inherited germline variants and somatic tumor mutations can influence a person's response to a particular anticancer drug. The most common type of gene variant is the single-nucleotide polymorphism (SNP). More than one million SNPs can be simultaneously interrogated to assess genetic variants across a patient's genome. Associating these differences with drug responses is the first step in genome-wide association studies (GWAS) to discover gene variants that alter drug effects.

The overall goal of pharmacogenomics is to make medications safer and more effective based on an individual patient's genetic makeup. As recently reviewed by Mary V. Relling, PharmD, and William E. Evans, PharmD (both of Pharmaceutical Sciences), in the journal *Nature*, the benefits of pharmacogenomics testing have now been repeatedly demonstrated for multiple drugs, and the role of this type of testing continues to grow. Indeed, the U.S. Food and Drug Administration now requires genetic testing of patients before the administration of some medications and has highlighted the potential importance of such tests for many other drugs.

Recent pharmacogenomics studies by St. Jude researchers have demonstrated the roles of genetic variants in influencing the toxicity of four essential curative agents used to treat pediatric cancer: vincristine, cisplatin, mercaptopurine, and glucocorticoids. Each of these can cause debilitating toxicities, such as peripheral neuropathy, permanent hearing loss, life-threatening infections, or osteonecrosis, and understanding the genetic influences modulating these toxicities is a first step to preventing their adverse effects. Additional pharmacogenomic studies have directly examined tumor cells to reveal new mechanisms by which somatic gene differences in leukemia cells can cause resistance to antileukemic agents.



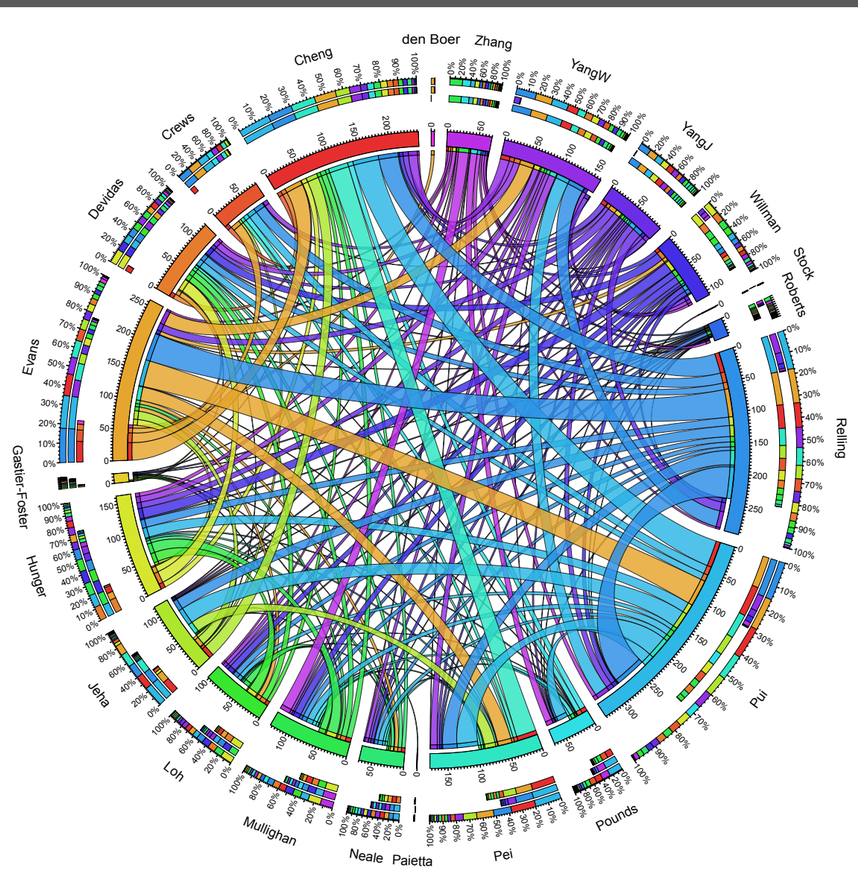


Figure. CIRCOS plot showing the various collaborations among investigators in the CPML based on joint authorship of research publications.

CENTER FOR PRECISION MEDICINE IN LEUKEMIA (CLPM) OPENS AT ST. JUDE

In 2015, the National Institutes of Health named St. Jude as one of three new Centers for Precision Medicine. These constitute the core of NIH's Pharmacogenomics Research Network (*www.pgrn.org*); the other two centers are located at the University of California, Berkeley, and Vanderbilt University (Nashville, TN). The mandate of these centers is to identify the genetic basis of individual differences in medication response and use that information to develop precision medicine strategies.

Under the leadership of Dr. Relling and Mignon L. Loh, MD (University of California, San Francisco), the CPML engages 10 academic centers and will compare adult and pediatric forms of ALL in its efforts to improve the likelihood of cure, minimize treatment-related toxicity and long-term adverse effects, and improve the quality of life of leukemia survivors. The CPML consists of three major projects: defining how the genomic landscape of ALL affects response to therapy in children and adults, identifying the genomic factors that mediate drug resistance in patients with ALL, and investigating the pharmacogenomics of drug-related toxicity.

Barthelemy Diouf, PhD; Kristine Crews, PharmD

VINCRISTINE-INDUCED NEUROPATHY IS ASSOCIATED WITH A GENETIC VARIANT IN THE *CEP72* GENE

The vinca alkaloid vincristine is a microtubule inhibitor that exerts cytotoxic effects by blocking chromosome separation during the metaphase of cell division. The drug effectively inhibits normal cell division in rapidly dividing cells, including cancer cells and bone marrow cells. This leads to apoptosis, a form of programmed cell death. Vincristine is widely used to treat leukemia and solid tumors in adults and children.

As many as 30% of children who receive vincristine as part of combination chemotherapy for ALL experience peripheral neuropathy, a side effect characterized by nerve damage and neurologic disease. This can impair movement, sensation, and gland or organ function, depending on the nerves that are affected. When a patient experiences severe peripheral neuropathy, antileukemic therapy needs to be modified or temporarily stopped, potentially compromising the likelihood of cure. Understanding how inherited genome variation influences the incidence or severity of vincristine neuropathy is an important step toward mitigating this side effect.

A team led by Dr. Evans examined the DNA from 321 pediatric patients with ALL who received as many as 39 doses of vincristine (1.5-2 mg/m^2) in two prospective clinical trials [St. Jude TOTAL XIIIB or Children's Oncology Group (COG) AALL0443]. The investigators performed a GWAS to identify inherited genetic variants that can increase the risk and/or severity of vincristine-induced peripheral neuropathy. As described in the *Journal of the American Medical Association*, Dr. Evans and his colleagues demonstrated that a SNP (rs924607) in the promoter region of the *CEP72* gene is associated with increased risk and severity of vincristine-induced peripheral neuropathy in pediatric patients with ALL. *CEP72* encodes a protein that supports microtubule formation. The SNP lies in the gene's promoter and decreases expression of the *CEP72* gene. Of the 321 patients in the study, 50 (16%) were homozygous for the high-risk allele (TT) and 28 (56%) of them suffered moderate to severe peripheral neuropathy. The cumulative incidence of peripheral neuropathy was 60.8% for patients who had the *CEP72* TT genotype. In contrast, patients whose *CEP72* gene carried the CC or CT allele experienced fewer, less severe episodes of vincristine-induced peripheral neuropathy; their cumulative incidence was 23.4%. Genetic ancestry–related differences were also detected: the high-risk genotype was less common in patients of African ancestry, which is consistent with the known lower incidence of vincristine neuropathy among African American children.

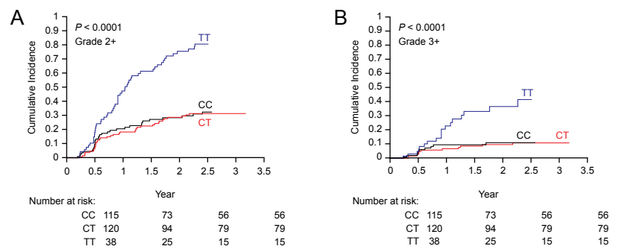
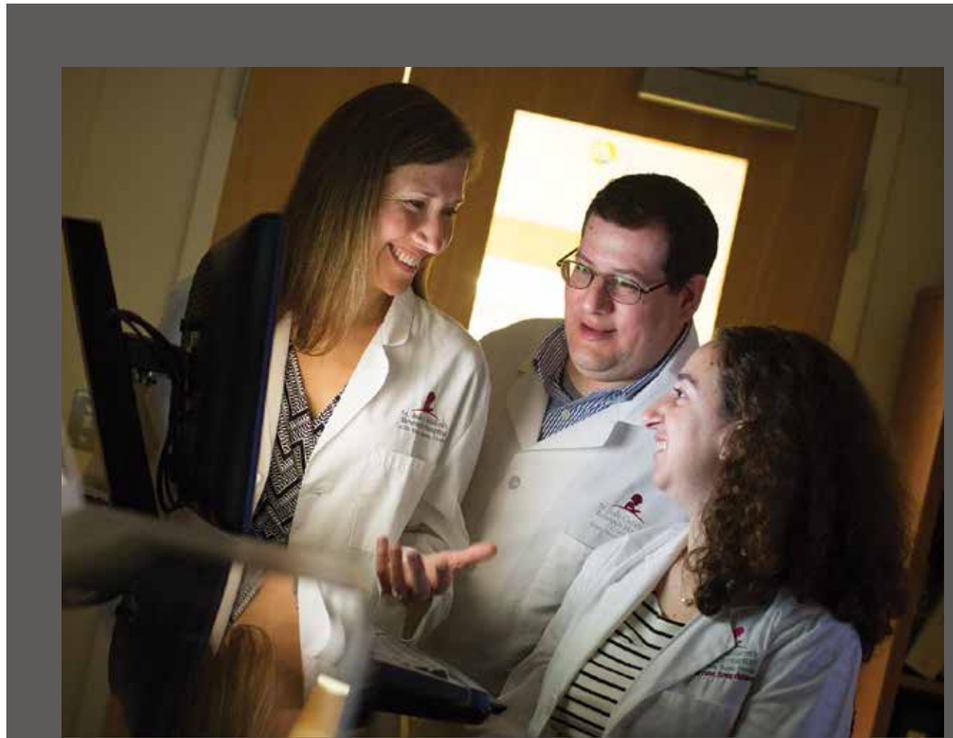


Figure. Cumulative incidence of moderate (**A**) or severe (**B**) vincristine-induced neuropathy in patients with different *CEP72* genotypes (CC, CT, or TT). The cumulative incidence of neuropathy was significantly higher in patients who were homozygous for the *CEP72* risk allele TT. *Reproduced with permission from JAMA. 2015. 313(8):815–23. Copyright © 2015 American Medical Association. All rights reserved.*

The leukemia cells of pediatric patients with ALL who inherit the *CEP72* TT genetic risk factor are more sensitive to vincristine than are those of patients with lower-risk alleles. Future studies will examine whether vincristine dosing can be reduced in these patients and determine whether this diminishes the incidence of significant toxicity and improves quality of life without compromising cure rates. Ongoing research is also focused on verifying this finding in other patient populations, including adults, and determining whether the *CEP72* variant influences the risk of persistent neuropathy in adults who were cured of childhood ALL.



Kristine Crews, PharmD; Alejandro Molinelli, PhD; Cyrine Haidar, PharmD

CLINICAL PREEMPTIVE PHARMACOGENETICS

In 2011, St. Jude initiated PG4KDS, a clinical protocol that uses preemptive array-based pharmacogenetic tests for inherited genetic variations (*www.stjude.org/pg4kds*). The protocol has enrolled more than 3000 St. Jude patients. Testing is coordinated by the Clinical Pharmacokinetics (CPK) Laboratory directed by Alejandro Molinelli, PhD. The CPK laboratory is a CLIA-certified facility that performs high-complexity testing.

The CPK laboratory provides state-of-the-art therapeutic drug monitoring and pharmacogenetic testing, with results interpreted by clinical pharmacists to assure optimal drug prescribing. Currently, genetic test results for seven genes (*CYP2C19*, *CYP2D6*, *CYP3A5*, *DPYD*, *SLCO1B1*, *TPMT*, and *UGT1A1*) are being used for patient care. Passive and active clinical decision support tools accompany the genetic test results to guide prescribing practice. St. Jude will continue to expand the reporting of actionable pharmacogenes, per the Clinical Pharmacogenetics Implementation Consortium's gene classification guidelines, to assist in the care of St. Jude patients.

Jun J. Yang, PhD; Clinton F. Stewart, PharmD

ACYP2 VARIANTS PROMOTE SUSCEPTIBILITY TO CISPLATIN-INDUCED OTOTOXICITY

Cisplatin is a platinum-containing chemotherapeutic agent that is widely used to treat various types of solid tumors in children and adults. Cisplatin binds DNA and causes crosslinking of the DNA strands, thereby preventing mitosis and ultimately inducing apoptosis. Platinum-containing agents are associated with severely debilitating side effects. As many as 70% of children who receive cisplatin dosages of 400 mg/m^2 or higher suffer ototoxicity (permanent hearing loss). Younger age and concurrent craniospinal irradiation increase the risk of this adverse side effect.

Jun J. Yang, PhD, and Clinton F. Stewart, PharmD (both of Pharmaceutical Sciences), and their colleagues conducted a GWAS of DNA from 238 pediatric patients with newly diagnosed brain tumors who were enrolled in two St. Jude medulloblastoma protocols (SJMB96 and SJMB03). Their goal was to identify inherited genetic variants that affect the susceptibility to cisplatin-induced ototoxicity. In *Nature Genetics*, the team reported that its assessment of approximately 1.7 million SNPs identified one locus in the *ACYP2* gene (rs1872328) that influences the risk of cisplatin-induced hearing loss. The authors found that 145 (61%) children experienced some degree of hearing impairment, independent of biologic sex, genetic ancestry, cumulative cisplatin dose, or tumor location.

The *ACYP2* A allele showed the strongest association with cisplatin-induced hearing loss: all 20 patients with the *ACYP2* AA genotype experienced ototoxicity. Three other SNPs in *ACYP2* that were located near rs1872328 showed various degrees of association.

Results from earlier studies demonstrated associations between the *ACPY2* genotype and severe neuropathy induced by oxaliplatin, another platinum-containing chemotherapeutic agent. Taking into consideration those findings and the results from the current study, Drs. Yang and Stewart concluded that the *ACPY2* gene might have a broad role in mediating platinum-based toxicity and represent a novel biologic pathway that underlies toxicities associated with platinum-containing drugs. Future studies will focus on understanding the molecular mechanisms and pathways by which *ACPY2* mediates these effects.

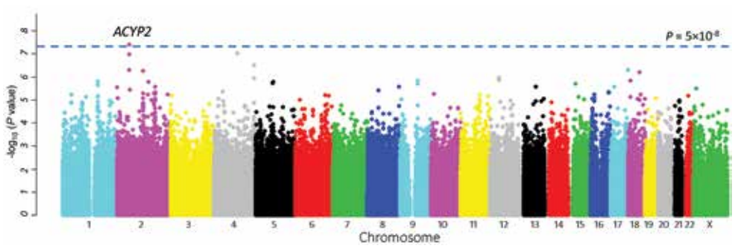


Figure. Association of SNP genotype and cisplatin-induced ototoxicity based on chromosome position. A Cox-regression model was used to evaluate more than 1.5 million SNPs in 238 children with brain tumors who received cisplatin therapy. *P*-values were plotted against the chromosomal position of each SNP, and only *ACYP2* exceeded the threshold for genome-wide significance (dashed line). *© 2015 Xu H et al*

Jun J. Yang, PhD; Mary V. Relling, PharmD

MERCAPTOPURINE INTOLERANCE IN CHILDREN WITH ALL IS DETERMINED BY INHERITED *NUDT15* AND *TPMT* VARIANTS

Mercaptopurine has been a cornerstone of most pediatric ALL treatment regimens since the 1950s. Prolonged daily exposure to this drug during the maintenance portion of chemotherapy regimens for pediatric ALL is essential to cure the disease. However, some children cannot effectively metabolize mercaptopurine and experience severe adverse reactions to it, including nausea, vomiting, diarrhea, and sometimes life-threatening infections. Mercaptopurine intolerance can disrupt curative therapy and compromise the survival of pediatric patients with ALL.

The laboratories of Drs. Evans and Relling were the first to discover inherited genetic variants in the *TPMT* gene that are associated with mercaptopurine intolerance and document the influence of those variants on the metabolism of mercaptopurine and its toxicity in children with ALL. Certain patients lacking risk-associated *TPMT* variants also experience mercaptopurine intolerance, and Drs. Yang and Relling hypothesized that additional genetic variants play a role in this.

The two investigators led a team that conducted a GWAS of DNA from 1028 pediatric patients with ALL to identify any genetic determinants that influence mercaptopurine intolerance. The patients were enrolled on one of two independent prospective clinical trials (COG AALL03N1 or St. Jude TOTAL XV). Drs. Yang, Relling, and their colleagues reported in the *Journal of Clinical Oncology* that mercaptopurine intolerance is correlated with East Asian ancestry and with two genetic loci: one SNP (rs1142345) in the *TPMT* gene and the other (rs116855232) in the *NUDT15* gene. NUDT15 removes altered nucleotides (including the active metabolites of mercaptopurine) from cells to minimize DNA damage and prevent apoptosis. On average, patients with the *NUDT15* TT genotype were extremely sensitive to mercaptopurine; they tolerated only 8.3% of the planned dose. Patients who carried the lower-risk alleles, TC or CC, tolerated nearly 63% or 83.5% of the planned dose, respectively. None of the children who were homozygous for the risk allele in either *TPMT* or *NUDT15* could tolerate more than 10% of the planned mercaptopurine dose.

The investigators found that the frequency of the *NUDT15* SNP differed across racial/ethnic groups. None of the patients of African ancestry carried the variant, and it was rare in those of European descent (0.2%); however, Hispanics (3.9%) and East Asians (9.8%) frequently carried it. The team concluded that the *NUDT15* variant contributes to racial differences seen in mercaptopurine intolerance. Regardless of racial/ethnic background, all patients who carried the genetic variant experienced similar mercaptopurine intolerance.

By identifying the relations between germline variants in the *TPMT* and *NUDT15* genes and mercaptopurine intolerance, this work has enabled St. Jude investigators to develop approaches for assessing mercaptopurine intolerance before initiating chemotherapy, thereby individualizing therapy for pediatric patients with ALL. This will minimize toxicity and long-term adverse effects due to ALL therapy. Some patients, nevertheless, experienced mercaptopurine intolerance in the absence of these genetic variants, indicating that additional factors play a role.

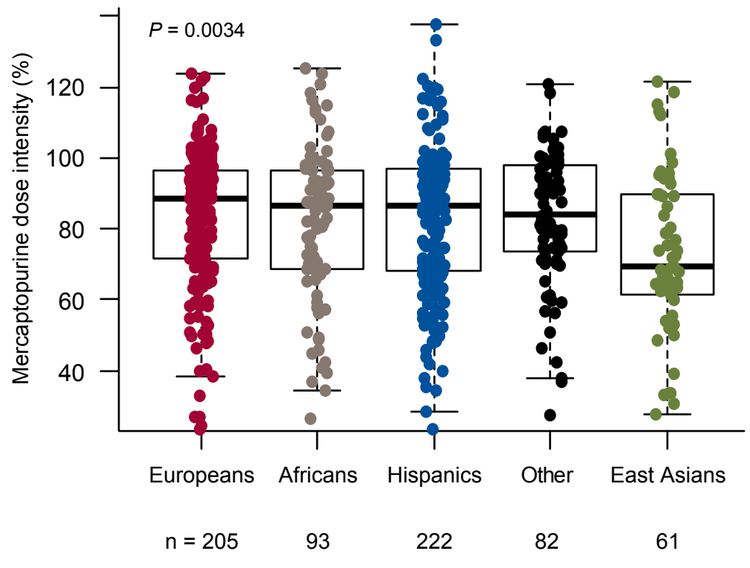


Figure. Genetic ancestry influences mercaptopurine intolerance. Patients were grouped into five genetic racial/ethnic categories. During the 6-month study, each patient's mercaptopurine dose was adjusted when he/she experienced toxicity. Mercaptopurine dose intensity was then calculated as the percentage of the protocol-planned dose that was actually prescribed. Cumulative values of dose intensity are shown. Genetically defined East Asians had the lowest median mercaptopurine dose intensity and were most likely intolerant of the drug. *Yang JJ et al, Inherited NUDT15 is a genetic determinant of mercaptopurine intolerance in children with acute lymphoblastic leukemia. J Clin Oncol, 33, 11, 1235–42. Reprinted with permission. © 2015 American Society of Clinical Oncology. All rights reserved.*

Chengcheng Liu, PhD; Seth E. Karol, MD; Mary V. Relling, PharmD; Wenjian Yang

IDENTIFYING THE RISK FACTORS FOR GLUCOCORTICOID THERAPY–ASSOCIATED OSTEONECROSIS IN PEDIATRIC ALL

Glucocorticoids are a class of steroid hormones that bind glucocorticoid receptors and are critically involved in different biologic processes, including immune function and inflammation. Thus, these agents are commonly used to treat immune diseases. Glucocorticoids can also cause the lysis of lymphocytes and are therefore a key component of chemotherapy for ALL. However, side effects such as glucocorticoid-associated osteonecrosis (i.e., cell death of bone components) are common. Nearly 10% to 40% of children who are older than 10 years at the time of glucocorticoid therapy suffer from osteonecrosis. The condition is caused by reduced blood flow to the bones that form joints, such as the hips, knees, shoulders, and ankles. Osteonecrosis can be extremely debilitating. Patients experience severe pain and restricted movement in the joint and often require surgical intervention. It is often necessary to stop glucocorticoid therapy early in such patients with ALL.

In two articles published in the journal *Blood*, Dr. Relling and her group performed two GWASs of SNPs to investigate the genetic variants that predispose pediatric patients with ALL to glucocorticoid-induced osteonecrosis. The first article reported results from the largest GWAS of osteonecrosis induced by glucocorticoid therapy. In that study, the discovery cohort included 2285 patients with ALL who were enrolled on the COG AALL0232 trial, and two replication cohorts that included 361 children with ALL on the St. Jude TOTAL XV trial and 309 adults and children who did not have cancer but received glucocorticoids at Vanderbilt University (Nashville, TN) to treat other conditions.

The team found that the SNP rs10989692 was associated with glucocorticoid-induced osteonecrosis in all three cohorts; the incidence of the condition was higher in patients who carried the rarer A allele at the locus. This SNP is located near the *GRIN3A* gene, which encodes a glutamate receptor. Meta-analysis of the GWAS data further revealed another SNP (rs2154490) associated with osteonecrosis that was located near the *GRIK1* gene, which encodes a different glutamate receptor.

In the discovery cohort, 249 (10.9%) patients experienced osteonecrosis. An age of 10 years or more and female sex were associated with a higher risk of the condition. African ancestry was associated with lower risk than was European descent. This report was the first to link genetic variations in glutamate receptors with the development of osteonecrosis in adults and children who received glucocorticoid therapy. These results indicate that the glutamate-signaling pathway is most likely involved in the pathogenesis of osteonecrosis.

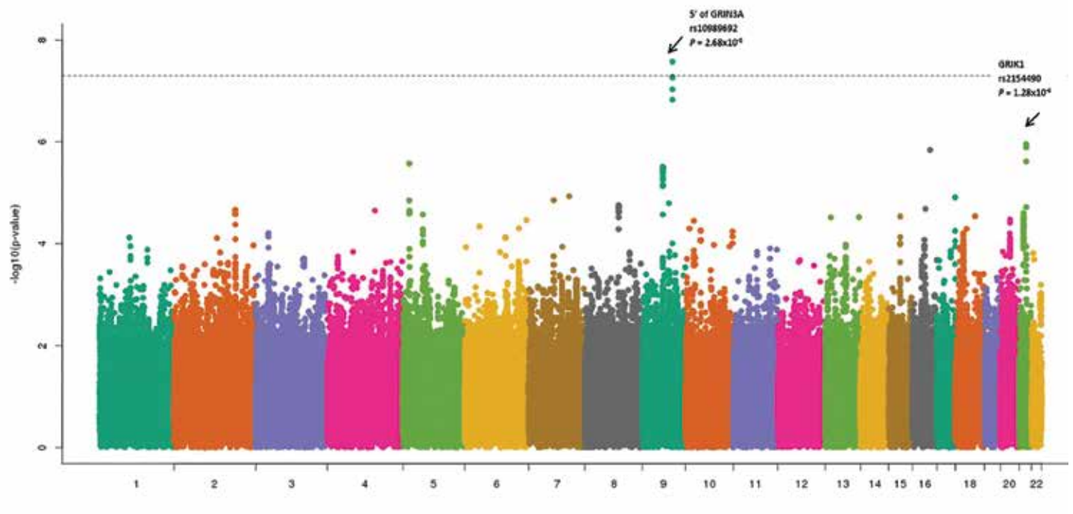


Figure. Association of SNPs with glucocorticoid-induced osteonecrosis based on chromosome position. SNPs were assessed in nearly 3000 patients who received glucocorticoid therapy for childhood ALL or other conditions. Inverse log *P*-values were plotted against the chromosomal position of each SNP, and SNPs near GRIN3A and GRIK1 had the strongest association. *Republished with permission of the American Society of Hematology, from Genetics of glucocorticoid-associated osteonecrosis in children with acute lymphoblastic leukemia, Karol SE et al, Blood, 126, 15, 1770–6, 2015; permission conveyed through Copyright Clearance Center, Inc.*

In the second report, Dr. Relling's team examined the genetic risk factors that mediate the development of glucocorticoid-induced osteonecrosis in pediatric patients with ALL who are younger than 10 years. Although age 10 years or older is the strongest risk factor for glucocorticoid-induced osteonecrosis, because children younger than 10 years account for more than 75% of all pediatric ALL cases, as many as 40% of cases of osteonecrosis occur in younger children. The goal of this study was to determine whether younger patients with ALL carry distinct genetic variants that contribute to osteonecrosis.

The investigators conducted a GWAS of DNA from 82 children with ALL enrolled on the COG AALL0331 trial who were younger than 10 years and had experienced glucocorticoid-induced osteonecrosis and 287 controls who were enrolled on the same trial. They then validated the findings in 817 children younger than 10 years treated on the COG AALL0232 trial. Their analysis revealed two unique SNPs in the younger patients: rs75161997 located near the *BMP7* gene, which encodes bone morphogenic protein 7, and rs1891059 located near *PROX1-AS1*, which encodes PROX1-antisense RNA1. BMP7 levels increase in response to mechanical stress or damage to bone, and PROX1-antisense RNA1 may alter the levels of lipids in the bone marrow or blood. A previous GWAS showed that genetic variants of genes involved in fat or cholesterol metabolism are associated with osteonecrosis.

The fact that earlier GWAS studies of older patients did not identify any association between *BMP7* and osteonecrosis suggests that genetic variants in this gene may be specific to younger children. The mechanisms by which BMP7 may play a role in osteonecrosis in younger patients are being studied in preclinical models by Seth E. Karol, MD (Physician-Scientist Training Program). Of note, the top-ranked coding genetic variant associated with osteonecrosis in younger patients was in a glutamate receptor gene. Thus, the glutamate receptor pathway appears to be important in osteonecrosis risk, regardless of age.

By increasing our understanding of the relations among patient age, dose intensity, and genetic variants with glucocorticoid-induced osteonecrosis, St. Jude investigators hope to design new treatment regimens that will prevent or minimize this debilitating condition in patients of all ages, while maintaining the desired antileukemic effects of glucocorticoids.

Sue C. Kaste, DO

EARLY SCREENING FOR GLUCOCORTICOID-INDUCED OSTEONECROSIS IN CHILDREN MAY IMPROVE LONG-TERM QUALITY OF LIFE

Glucocorticoid-induced osteonecrosis is a debilitating condition characterized by the death of bone. Osteonecrosis primarily affects major joints (e.g., hips, knees, shoulders, and ankles), and the condition can be asymptomatic for a period. With extensive hip osteonecrosis, defined as involving 30% or more of the epiphyseal surface (the end of the long bone) of the femur, the joint may collapse and require surgical intervention.

Sue C. Kaste, DO (Diagnostic Imaging), and her team conducted magnetic resonance imaging (MRI) examinations of the hips of 462 pediatric patients with ALL enrolled on the St. Jude TOTAL XV trial to determine whether early screening for osteonecrosis could identify patients in need of therapeutic intervention. The study included two early-screening MRI examinations at approximately 6.5 and 9 months after diagnosis, respectively, and one off-therapy MRI screening after completion of chemotherapy.

In the *Journal of Clinical Oncology*, Dr. Kaste and colleagues reported that 346 patients completed all three MRI screens. The authors identified extensive osteonecrotic lesions in 48 hips of 30 patients: 41 lesions were identified on early screens. Forty (83%) extensive osteonecrotic lesions were identified among patients older than 10 years: 19 lesions resulted in joint collapse, which required joint reconstruction or replacement surgery. Of the eight lesions identified in younger patients, none required surgical intervention and four showed improvement in off-therapy imaging.

Dr. Kaste and colleagues concluded that MRI screening may be unnecessary in children aged 10 years or younger who receive extended glucocorticoid therapy, because their risk of osteonecrosis is low and their asymptomatic necrotic lesions tend to heal. However, pediatric patients older than 10 years would benefit from screening for osteonecrosis, particularly if interventions can be devised to decrease the risk of progression while maintaining effective antileukemic therapy.

Erik Bonten, PhD; William E. Evans, PharmD

GENOMIC CHANGES IN LEUKEMIA CELLS CAN CAUSE RESISTANCE TO GLUCOCORTICOIDS

Combination chemotherapy now cures more than 90% of children with ALL, and as mentioned earlier, glucocorticoids are an essential component of that treatment. A team led by Dr. Evans has identified a new epigenetic mechanism (i.e., a mechanism that influences changes in gene function without altering the underlying DNA sequence) that causes glucocorticoid resistance in some patients with leukemia. This finding provides a path for developing more effective treatments for ALL and possibly other diseases for which glucocorticoids are widely prescribed.

Searching across the genome of ALL cells of more than 400 children, the investigators found differences in the expression of certain genes in leukemia cells that were either sensitive or resistant to glucocorticoids. The genes encoding caspase 1 (CASP1) and its activator NLRP3 were among those showing increased activity in glucocorticoid-resistant cells. The study included leukemia cells extracted from the bone marrow of children with newly diagnosed ALL who were treated at St. Jude or enrolled in clinical trials sponsored by the Dutch Childhood Oncology Group or the German Cooperative Study Group for Childhood ALL. Cells were extracted and studied at the time of diagnosis from all children and again at the time of disease relapse from 49 pediatric patients with ALL who were enrolled in COG clinical trials.

This research, which was published in *Nature Genetics*, revealed that epigenetic changes in ALL cells caused the genes encoding *CASP1* and its activator *NLRP3* to be overexpressed. Cells can lock genes in the "off" position by adding methyl groups to DNA at specific sites in the genome. Leukemia cells that overexpressed *CASP1* and *NLRP3* had lower methylation levels of the two genes than did leukemia cells that were sensitive to glucocorticoids. Dr. Evans and his colleagues also discovered that CASP1 cleaves the glucocorticoid receptor, leading to lower levels of those receptors in cells overexpressing *CASP1*. Because glucocorticoid receptors are required for glucocorticoids to exert pharmacologic effects, including their antileukemic effects, these epigenetic changes lead to glucocorticoid resistance.

Steroid resistance is more common in ALL cells at the time of disease relapse than at initial diagnosis. This study found that *CASP1* and *NLRP3* are also expressed at higher levels in ALL cells at the time of disease relapse than at initial diagnosis, suggesting that this is a new mechanism of acquired drug resistance, as well as de novo resistance at the time of initial diagnosis.

To confirm that CASP1 cleavage of the steroid receptor is pivotal to glucocorticoid resistance, Dr. Evans' team engineered a glucocorticoid receptor to remove the CASP1 cleavage sites and prevent glucocorticoid resistance in cells overexpressing CASP1. Furthermore, when a caspase 1 inhibitor was added to CASP1–overexpressing leukemia cells, it restored glucocorticoid sensitivity. These findings indicate that coadministration of a caspase 1 inhibitor with glucocorticoids may represent a new strategy to overcome glucocorticoid resistance caused by *CASP1* overexpression, and this possibility is being actively pursued by St. Jude investigators.

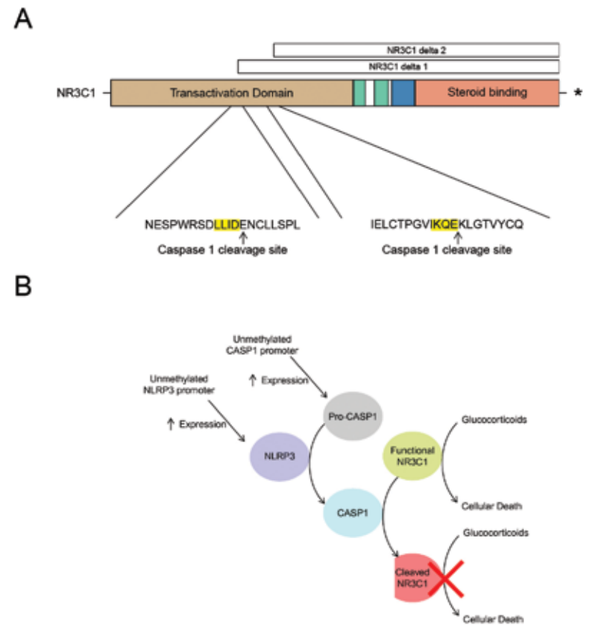


Figure. CASP1 cleaves the glucocorticoid receptor and increases resistance to glucocorticoids. (**A**) Diagram of the glucocorticoid receptor and the two amino acid sequence motifs identified as CASP1 cleavage sites. (**B**) Model of CASP1 regulation of glucocorticoid resistance. *© 2015 Paugh SW et al*

CONCLUSION

Using cutting-edge genomic-profiling technologies, St. Jude investigators are identifying genetic differences that influence the sensitivity of leukemia cells to chemotherapy and predisposition to drug-related toxicity in pediatric patients with cancer. By personalizing medication regimens, researchers in the Department of Pharmaceutical Sciences and across St. Jude are optimizing chemotherapy for each patient, minimizing toxicity and adverse long-term effects, and ultimately working to ensure the best quality of life for childhood cancer survivors.

PIONEERING THE FIELD OF PEDIATRIC PROTON THERAPY

Radiation therapy is effective in treating many cancers but is associated with significant adverse effects. In addition to cancer cells, healthy cells surrounding tumors may be damaged by radiation therapy. Resulting damage may have lasting effects on a patient's quality of life. This is especially true for young children who are still developing and growing.

Investigators in the Department of Radiation Oncology are working to improve radiation therapy for pediatric patients. After more than 15 years of planning and 5 years of construction, St. Jude has opened the world's first proton therapy center designed specifically for treating pediatric cancers. In November 2015, pediatric patients enrolled in cutting-edge clinical trials began receiving treatment at this unique facility. The St. Jude Red Frog Events Proton Therapy Center is a one-of-a-kind facility where radiation oncologists, radiation physicists, and radiation therapists are working together to advance therapy for children with cancer.

Chia-Ho Hua, PhD

Devon Barry, BSRS, RT; Matthew J. Krasin, MD; Heena Patel; Ariel White, MD

THE EVOLUTION OF RADIATION THERAPY

Radiation therapy is an essential component for treating leukemia, solid tumors, and brain tumors. During the past 20 years, the technologies and approaches in radiation oncology have evolved, driven by the linked goals of improving treatment while minimizing adverse side effects. Advances have been made possible by groundbreaking clinical research that has applied new developments in computer science and engineering. As radiation therapy methods have advanced, St. Jude protocols have been modified to incorporate the most cutting-edge treatments available. However, possessing the latest technology is not sufficient. The St. Jude radiation oncology staff studies how to apply the newest technologies to treat pediatric patients in the safest, most effective manner possible.

Early radiation therapy for children with cancer involved the delivery of x-ray radiation to an entire body part. With the development of photon-based three-dimensional conformal radiation therapy, technology and treatment planning advanced. The radiation dose was prescribed to a specific volume defined by three-dimensional imaging to ensure delivery of the intended treatment and minimize the exposure of normal tissues to collateral irradiation. Instead of irradiating an entire organ, investigators characterized the shape and exact location of the tumor and targeted the treatment to the area at risk. As a result, the treatment margin (i.e., the volume of healthy tissue surrounding the tumor that is unavoidably irradiated with the tumor) has progressively decreased. Early conformal photon therapy at St. Jude included standard margins that were measured in centimeters; after careful protocol-based investigation, these margins were reduced over time to millimeters, depending on the tumor type. Although this small amount of tissue damage may seem like an acceptable trade-off for the prospect of saving a child's life, the tumor location and a child's age can strongly influence the detrimental effects of radiation-induced damage on even small volumes of healthy tissue.

Proton therapy is the latest development in radiation oncology. Although proton technology is not new, the early systems used to accelerate protons for therapeutic applications were large and impractical, and its use was limited to physics research centers. Technologic advances leading to the potential application of proton therapies in hospitals or outpatient medical centers were realized in the 1990s. A key difference between photon and proton radiation therapy is that photon therapy involves a wave-form of energy that passes through the patient and interacts with all tissues in its path, whereas proton therapy involves a positively charged particle, the nucleus of a hydrogen atom. Protons traverse normal tissue on their way to a tumor, where the proton deposits most of its energy, thereby killing tumor cells. Because little of the protons' energy is deposited outside of a tumor, damage to normal tissues is substantially reduced.

Since its earliest applications in cancer treatment, proton therapy has continued to improve. Scientists have learned to make a smaller and more focused proton beam that can be magnetically scanned to deliver spots of radiation within the confines of the tumor. St. Jude has the most advanced form of proton therapy available, called “pencil-beam scanning.” Pencil-beam scanning is performed using the discrete-spot scanning method. Within a given layer of the tumor, the beam is turned on and off as it moves from position to position, layer by layer. The duration that the beam treats a particular spot is measured in fractions of a second and determined by the required radiation dose. Treatment of a given tumor may require irradiation of thousands of spots in dozens of layers over the course of a few minutes. Pencil-beam scanning has the potential to greatly improve the chances of sparing healthy tissues surrounding a tumor.

Because the Proton Therapy Center is the first one designed specifically to treat pediatric cancers, all radiation therapists working in the Center have received their training at St. Jude. As other proton therapy centers for children open around the world, we anticipate that investigators from those institutions will visit and receive training at our campus.

THE PROMISE OF PROTON THERAPY FOR IMPROVING THE CURE RATES OF PEDIATRIC PATIENTS WITH CANCER

Under the leadership of Thomas E. Merchant, DO, PhD, chairman of the Department of Radiation Oncology, St. Jude is positioned to test the limits of radiation therapy for pediatric cancer. Questions related to the optimal use of radiation therapy are incorporated into nearly all national cooperative and St. Jude pediatric oncology protocols. There remain several well-known gaps in our knowledge of this field: What is the lowest dose of radiation that will effectively kill cancer cells? Can we eliminate radiation therapy and still cure the disease? What is the largest radiation dose that can be administered before harm outweighs benefit? What is the relation between the extent of radiation exposure to normal tissues and the incidence and time to onset of clinically significant side effects?

With the opening of the Proton Therapy Center, Dr. Merchant and his team will test new hypotheses on improved approaches to radiation therapy in children in cutting-edge pediatric oncology trials. Because childhood cancers are rare, most hospitals do not treat enough patients to conduct such trials. However, St. Jude treats more pediatric patients with cancer than any other center in the United States. Therefore, Dr. Merchant and his team are in a strong position to develop standardized guidelines for safely and optimally administering proton therapy to children. Indeed, results from St. Jude clinical trials were previously used to establish the guidelines for the use of advanced methods of photon-based radiation therapy in children.

Whether proton therapy represents an improvement over photon therapy remains unproven. However, with the development of pencil-beam scanning, models by investigators in radiation oncology suggest that damage to healthy tissues surrounding the tumor can be substantially reduced. Proton therapy is thought to cause fewer, less severe side effects than photon therapy, but this needs to be substantiated with rigorous clinical investigation. Additionally, the long-term effects of proton therapy on quality of life will need to be assessed in survivors who received this treatment during childhood.

Three key features of proton therapy appear to provide an advantage over photon therapy and may apply to all tumor types: (1) Proton therapy may cause fewer adverse side effects than photon therapy. (2) Proton therapy will allow the concurrent administration of chemotherapy, targeted therapy, immunotherapy, and other forms of anticancer treatment with irradiation, which is not always possible with photon therapy because of combined-modality toxicity. (3) By developing new methods, investigators will be able to use proton therapy to increase the radiation dose administered to portions of a tumor, which may not be possible with photon therapy. To explore these and other questions, all St. Jude patients treated in the Proton Therapy Center will be enrolled in clinical trials.

Devon Barry, BSRS, RT; Thomas E. Merchant, DO, PhD

Weiguang Yao, PhD

DESIGNING A PROTON THERAPY CENTER FOR PEDIATRIC PATIENTS

St. Jude has the most advanced proton therapy center in the world, with some of the best imaging equipment available today. While a patient is lying on the treatment couch waiting for therapy to begin, radiation technologists image the tumor and use the computational treatment-planning system to compare real-time images with the patient's predetermined treatment plan. This novel design increases patient safety and ensures the accuracy of the plan at every stage of treatment.

During the first 4 months of the opening of the Proton Therapy Center, it has become the busiest proton therapy center for children in the United States. The administration of proton therapy to children, especially young children who require sedation to remain immobilized for such precise treatment, increases the complexity of treatment and the number of staff involved. As many as seven adults (three radiation technologists, a radiation physicist, a sedation nurse, a certified registered nurse anesthetist, and an engineer) might be in the room with an anesthetized child, but generally only two radiation technologists are required to treat an adult.

The Proton Therapy Center houses three treatment rooms, large anesthesia-administration/recovery areas, and spacious hallways. The design of the 190° gantries installed in two treatment rooms is more open than that of the standard 360° gantry used in photon therapy centers for adults. This modification allows the staff access to freely move around the patient on the treatment couch and increases patient comfort.

Some equipment in the center is still in development and will require 1 to 2 years to come online. Currently, the synchrotron requires time to generate and deliver particles of equal energy to each layer of the tumor. However, modifications to the accelerator hardware and software control systems will enable the machine to extract and deliver protons of different energies at the same time. This approach will enable each patient's treatment session to be shortened. The third treatment room has a horizontal fixed-beam system with a very small beam called a "microbeam." This will enable the treatment team to irradiate very small targets in close proximity to sensitive normal tissues. A camera-based alignment system will be used to augment the accuracy of the patient-positioning couch. It will monitor the position of the couch and make last-minute adjustments to increase the precision of the patient's position. These added features will soon be made available for use. Finally, the experience being gained by St. Jude investigators and clinicians is enabling them to make proton therapy safer and more effective for St. Jude patients.

John T. Lucas Jr, MS, MD

PROTOCOL-DRIVEN PRACTICE TO GUIDE THE DEVELOPMENT OF PROTON THERAPY STANDARDS FOR CHILDREN

In the United States, as many as 4000 children every year receive a diagnosis of cancer and will benefit from radiation therapy. Some patients require immediate radiation treatment, whereas others need it later during the therapeutic course. The Proton Therapy Center was designed with the capacity to accommodate as many as one of every 10 children with newly diagnosed cancer requiring proton therapy.

The large number of pediatric patients treated at St. Jude each year provides Dr. Merchant and his group with a large patient pool to advance radiation therapy for various childhood cancers at a remarkable pace. Because few children have been treated with pencil-beam proton therapy to date, the team's goal is to determine the feasibility, safety, and benefit of this recent advancement. This includes understanding the balance between tumor control and treatment-induced toxicity. Therefore, Dr. Merchant's team will develop protocols to distribute discrete spots of radiation, ensure treatment of the tumor, and minimize the dose to normal tissues.

In all forms of radiation therapy, energy is deposited in tissues and the beam is controlled to minimize harm. Pencil-beam scanning is the only form of proton therapy used at St. Jude. The accelerator and beam-transport of the proton therapy system (i.e., the synchrotron that accelerates the protons generated from ionized hydrogen gas and releases them into a vacuum tube that ends with the scanning nozzle) was approved by the Food and Drug Administration (FDA) in June 2015. The patient side of the proton therapy system, including robotic patient-positioning, cone-beam computed tomography (CT) robot, and all of the associated hardware and software used to align and verify the position of the patient and targeted tumor site, was approved by the FDA in November 2015. St. Jude is the only proton therapy center in the world that has this high-quality and accurate positioning and imaging equipment in a single system. With relative ease, fluid work flow, and the patient on the treatment couch, the radiation therapists image the tumor immediately preceding treatment and compare those images with the images used to create the treatment plan. This novel design increases patient safety and ensures the accuracy of the treatment plan at every stage.

HARNESSING THE PHYSICAL PROPERTIES OF PROTON THERAPY

Prior to initiating therapy, radiation oncologists, radiation physicists, and radiation therapists work together to develop individualized treatment plans. The radiation oncologist reviews CT images and magnetic resonance (MR) images of the tumor to fully characterize its shape, volume, location, and surrounding tissues. He draws the contours of the tumor and margins, decides where the dose needs to be administered, and determines the healthy tissues that need to be avoided. A team of radiation physicists then designs a plan that is in line with the overall goals of therapy. They calculate and visualize the best angles or routes of delivery that will distribute the protons strategically throughout the tumor. Heterogeneity in tissue that the beam may traverse increases the uncertainty of the range of the proton and must be understood, if not reduced or avoided. Whereas photons interact less efficiently with tissues and may view bone and soft tissues similarly, protons are more susceptible to differences in tissue composition and interfaces between bone, soft tissue, air, and foreign bodies, such as catheters and surgical clips, which are common in children treated for brain tumors or solid tumors.

To thoroughly understand proton therapy and design treatment plans that most effectively employ the many novel aspects of the proton therapy system, faculty radiation physicists Jonathan B. Farr, PhD, Chia-Ho Hua, PhD, and Weiguang Yao, PhD (all of Radiation Oncology), work closely with their clinical counterparts. Under their leadership, clinical radiation physicists, medical dosimetrists, and support personnel develop treatment plans and conduct quality-assurance testing before any patient receives proton therapy. Treatment planning takes approximately 2 weeks.

Each proton therapy session typically includes treatment using two to four beams, the number being determined by the size and location of the tumor. During each treatment, the gantry-based scanning nozzle is rotated into position and delivers pencil-point doses of protons in an array at a particular depth, advancing throughout the tumor volume until the entire mass is treated. The patient is then repositioned, and the next beam is administered using a different series of planes. Repositioning the patient between scans increases the likelihood of evenly distributing radiation throughout the tumor and avoiding healthy tissues.

The radiation physicists select the directions of the beams to optimize the dose and match the target volume of the tumor. Using state-of-the-art treatment-planning software and imaging systems that accurately determine the electron density of tissues and size, shape, and location of the target, they tailor each plan and then verify its accuracy using calibrated detectors in a simulation of the actual treatment. The detectors determine whether the beam shape is good, examine the homogeneity or smoothness of the radiation dose at depth in tissue, and assess whether the radiation dose is delivered properly. If the simulation is successful, the patient's therapy is initiated. If not, the treatment plan is re-evaluated and a new one is designed and tested.

Some tumors are dynamic entities that can grow or shrink and spread or retract. Patient shapes also may change during their treatment course due to weight loss or gain, reduction in swelling after surgery, or normal tissue reactions. As mentioned above, proton treatment plans are very sensitive to changes in tissue, including tumor shape and location. Therefore, each tumor must be continuously monitored by cone-beam CT and frequent MR imaging to ensure that all changes are detected and the treatment plan is modified accordingly.

Christopher L. Tinkle, MD, PhD

COLLABORATIVE PRECLINICAL STUDIES ON THE BIOLOGY OF PROTON THERAPY AND PEDIATRIC CANCERS

Protons interact with tissues in a completely different manner than do photons, and the biologic processes that mediate the effects of proton and photon therapy differ as well. Cancers that have not yet been targeted in great numbers by proton therapy, such as neuroblastoma, rhabdomyosarcoma, Ewing sarcoma, and head and neck sarcomas, appear to be good candidates for this approach. However, preclinical investigations are needed in parallel with clinical trials to determine the effect of protons on the biology of these tumors. Elucidating the biologic factors underlying the potential susceptibility of these cancers to proton therapy will guide the direction of treatment for pediatric patients with these diseases.

Preclinical models are an invaluable tool for increasing our knowledge about the pathogenesis and biology of human diseases and for designing and testing novel treatments. Model systems include isolated cells, patient-derived xenografts (i.e., human tumors or immortalized cancer cells implanted into animals), and genetically engineered animals that are designed to recapitulate a specific disease. The Proton Therapy Center is configured to allow for preclinical studies. Christopher L. Tinkle, MD, PhD (Radiation Oncology), is leading efforts in collaborating with laboratory researchers at St. Jude and other institutions to assess preclinical trials that include the use of proton therapy in disease models.

Collaborations with laboratory researchers will also enable radiation oncologists to exploit preclinical models to refine and troubleshoot their ideas for new clinical trials before opening enrollment to patients. The center has the potential to advance our understanding of the biology of various diseases, develop new approaches to treating those diseases, and expand St. Jude's network of invaluable collaborations with scientists around the world.

Laura Alexander Dodds, RN, LADAC

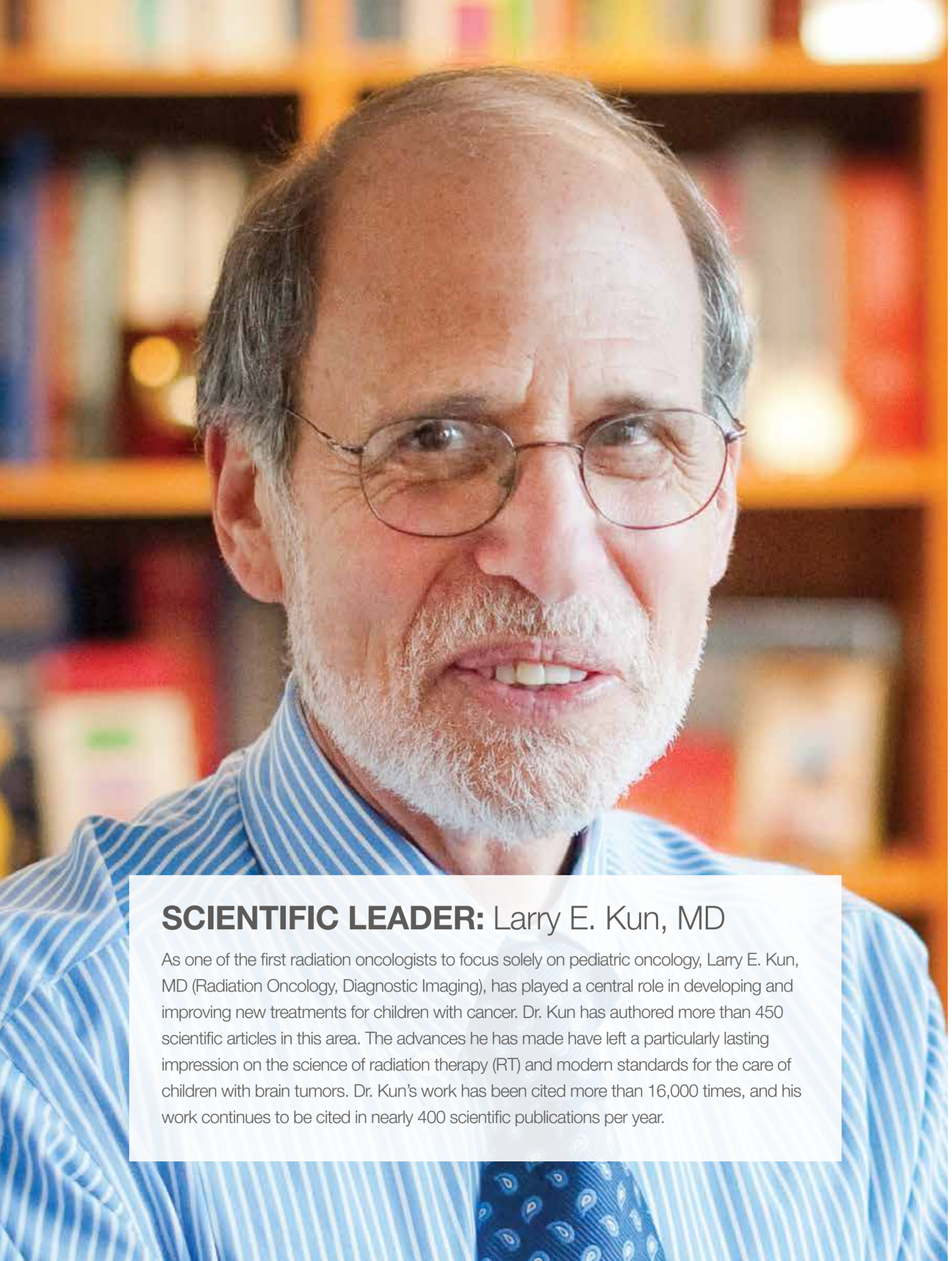
ESTABLISHING A NATIONAL RESOURCE FOR PEDIATRIC CANCER TREATMENT

The Proton Therapy Center has the potential to become a national resource for conducting proton therapy research. Medical specialists, radiation physicists, and computational researchers from other institutions have already started requesting permission to visit the St. Jude campus to learn more about the use of proton therapy in children and potentially use the center for their own research during periods when it is not engaged in clinical use. Such projects will facilitate collaborations with researchers from other institutions whose work will inform and advance our own.

The radiation oncology staff also plans to participate in national cooperative groups, such as the Children's Oncology Group and Pediatric Brain Tumor Consortium, and develop clinical trials. It is envisioned that patients may be enrolled and treated at other institutions on St. Jude clinical trials, come to St. Jude for proton therapy only, and then return to their home institution for the remainder of their care. We anticipate that approximately 100 pediatric patients will be treated during the first year of operation of the Proton Therapy Center, and this number is expected to more than double within 3 years. Within the next few years, more than 50% of all new patients at St. Jude will receive proton therapy.

CONCLUSION

With the opening of the world's first proton therapy center specifically designed to treat childhood cancers, St. Jude will continue to be the world's leader in radiation therapy for pediatric patients. Investigators working in the center are treating patients in cutting-edge clinical trials and designing new protocols that will increase our knowledge and improve radiation therapy and outcomes for pediatric patients with cancer.



SCIENTIFIC LEADER: Larry E. Kun, MD

As one of the first radiation oncologists to focus solely on pediatric oncology, Larry E. Kun, MD (Radiation Oncology, Diagnostic Imaging), has played a central role in developing and improving new treatments for children with cancer. Dr. Kun has authored more than 450 scientific articles in this area. The advances he has made have left a particularly lasting impression on the science of radiation therapy (RT) and modern standards for the care of children with brain tumors. Dr. Kun's work has been cited more than 16,000 times, and his work continues to be cited in nearly 400 scientific publications per year.

Dr. Kun came to St. Jude in 1984 as a member and chair of Radiation Oncology. Amongst his priorities was to establish the St. Jude Brain Tumor Program, now among the premier programs for pediatric brain tumor research and treatment in the world. At the same time, he was selected as Leader of the Brain Tumor Committee of the Pediatric Oncology Group (POG) and worked with R. Alex Sanford, MD (Neurosurgery), and Marc E. Horowitz, MD (Hematology-Oncology), to advance clinical trial research throughout the nation. Early on, Dr. Kun and colleagues spearheaded clinical trials for pediatric tumors in which chemotherapy was introduced in conjunction with RT for primary treatment and disease recurrence. The success of trials at St. Jude led to adopting this approach in POG international trials. In 2000, Dr. Kun was one of the founders of the Pediatric Brain Tumor Consortium created by the National Cancer Institute to improve treatment through novel clinical trials.
Dr. Kun served as the Consortium's leader from 2001 to 2012, a position now held by Maryam Fouladi, MD (Cincinnati Children's Hospital Medical Center), a former St. Jude trainee and faculty member.

Dr. Kun had particular interest in advancing therapies for infants with brain tumors, which are some of the most challenging cases in pediatric oncology. Infants are particularly vulnerable to the effects of RT, chemotherapy, and surgery. Indeed, few members of the POG Brain Tumor Committee had significant experience treating infants with brain tumors. In an early collaborative study with Texas Children's Hospital, Houston, Dr. Kun and colleagues explored treating infants with brain tumors who had undergone surgical intervention with prolonged chemotherapy. If residual tumor remained after 1 to 2 years of chemotherapy, gross total resection was again attempted; risk-adapted RT was then administered. Infants tolerated the treatment regimen and appeared to demonstrate improved outcomes. The study was expanded by POG as the first large multicenter trial conducted by the cooperative group. In 1993, POG investigators reported in T*he New England Journal of Medicine* that patients with medulloblastoma, malignant gliomas, or ependymomas responded well to the new therapeutic approaches, but those with primitive neuroectodermal tumors did not. The results indicated that very young children and infants with brain tumors benefited from delaying RT.

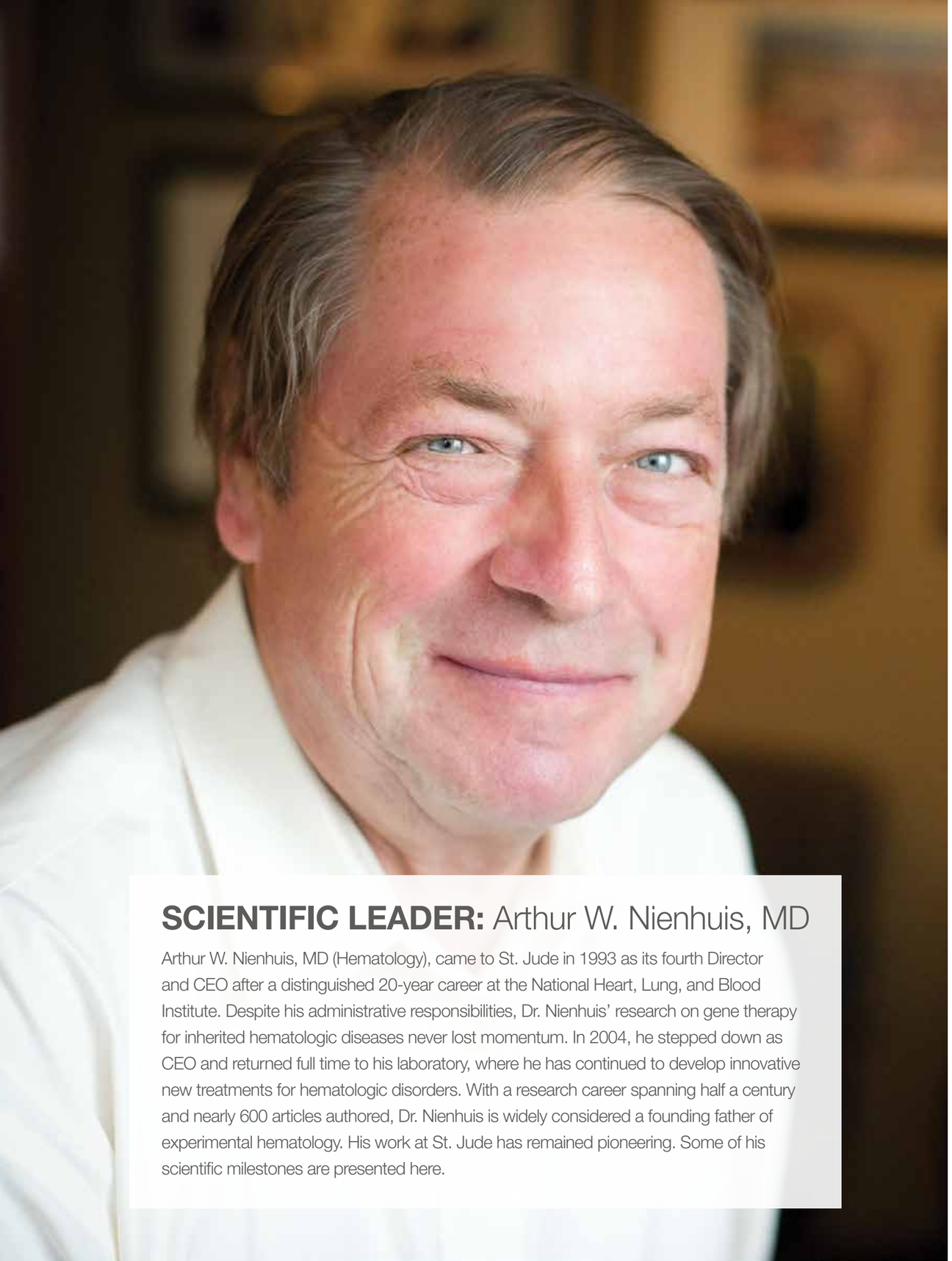
Dr. Kun's research has also focused on brainstem gliomas, a severe form of brain tumor with a particularly poor prognosis. Dr. Kun conducted a pilot study at St. Jude on the effects of hyperfractionated RT on these cancers, which used a smaller dose of irradiation delivered more frequently, allowing the total dose to be increased. Early findings led to a series of POG trials conducted over nearly 8 years. Overall survival was not improved, though the trials coalesced research interest in this devastating disease. Combining POG data with Children's Cancer Group data, Dr. Kun and colleagues were able to identify neuroimaging characteristics that distinguished patients with poor prognoses from the small cohort with better prognoses, allowing improved risk stratification and appropriate moderation or intensification of therapy.

Dr. Kun and colleagues, working with POG, also reported the clinical features associated with more favorable outcome in medulloblastoma, the most common childhood brain cancer. They demonstrated that reduced RT when given alone is not as effective for these children; subsequent trials showed the efficacy of reduced-dose RT given with chemotherapy for favorable cases, with survival actually surpassing that with higher-dose RT alone. The landmark study was reported in *Journal of Clinical Oncology* in 2004.

Dr. Kun transferred leadership of medulloblastoma trials at St. Jude to Amar J. Gajjar, MD (Oncology, Pediatric Medicine), in 1996. The SJMB96 trial, as published in *Lancet Oncology* in 2006, examined the effects of decreased RT, chemotherapy intensification, and inclusion of a second, post-RT surgical procedure to attempt gross total resection. Improved survival was observed, regardless of whether favorable or unfavorable disease was present. The study also showed that the use of amifostine could reduce cisplatin-induced hearing loss. This study was among the first in which St. Jude directly engaged a team of national and international collaborators to address therapy in pediatric neuro-oncology. Drs. Kun, Gajjar, and colleagues fine-tuned RT for pediatric medulloblastoma in the SJMB03 trial. Collaborators at multiple institutions provided tumor samples, enabling the team to identify biologic subtypes of medulloblastoma now well recognized as requiring more specific treatments.

In 1996, Dr. Kun recruited Thomas E. Merchant, DO, PhD (Radiation Oncology), to St. Jude, to lead efforts in refining RT, including three-dimensional conformal radiation therapy (3D-CRT), for pediatric brain tumors. Drs. Merchant and Kun optimized the use of 3D-CRT following surgical resection in patients with ependymomas. They were able to increase RT dose by 10% in older pediatric patients and more safely administer RT in 1 to 3 year olds. This was the first pediatric brain tumor study to integrate data from multiple subspecialists analyzing various outcome measures (e.g., cognitive function, hearing, and endocrine function) to evaluate treatment regimens.

Throughout his 32 years of leadership at St. Jude, Dr. Kun has tried to optimize how cures for pediatric cancer can be advanced through research and treatment. His efforts have reduced late effects in pediatric cancer survivors and delineated new approaches in treating pediatric cancer. In the process, Dr. Kun has influenced countless clinicians and scientists and helped create intense interest in pediatric radiation oncology. His greatest legacy is the thousands of children whose lives have been improved by his insights and life-saving research.



SCIENTIFIC LEADER: Arthur W. Nienhuis, MD

Arthur W. Nienhuis, MD (Hematology), came to St. Jude in 1993 as its fourth Director and CEO after a distinguished 20-year career at the National Heart, Lung, and Blood Institute. Despite his administrative responsibilities, Dr. Nienhuis' research on gene therapy for inherited hematologic diseases never lost momentum. In 2004, he stepped down as CEO and returned full time to his laboratory, where he has continued to develop innovative new treatments for hematologic disorders. With a research career spanning half a century and nearly 600 articles authored, Dr. Nienhuis is widely considered a founding father of experimental hematology. His work at St. Jude has remained pioneering. Some of his scientific milestones are presented here.

X-linked severe combined immunodeficiency (SCID) is an inherited disorder in which certain immune cells are not produced, increasing susceptibility to infection. Early trials of gene therapy for SCID were slowed by the discovery that the vector used to deliver the transgene could activate the proto-oncogene *LMO2*, thereby causing leukemia in some recipients. In 2008, Dr. Nienhuis and colleagues reported in the journal *Blood* a novel system for testing the safety of integrating vectors designed to deliver the therapeutic transgenes to hematopoietic stem cells (HSCs). They used this to validate the safety of a self-inactivating vector with an internal promoter flanked by insulator elements, a design currently used in clinical trials.

Hemoglobin (Hb) disorders, such β-thalassemia and sickle cell disease, reduce the ability of erythrocytes to deliver oxygen to tissues. This causes severe complications. Erythrocytes produce various forms of Hb at different developmental stages. In a 2010 article in *Blood*, Dr. Nienhuis and colleagues reported a novel approach for treating Hb disorders with gene therapy. They showed that adult $CD34^+$ HSCs could be genetically manipulated to switch production from adult Hb back to fetal Hb (HbF). HbF prevents the sickling of adult hemoglobin, thereby reducing the clinical complications of the disease. Cells were transduced with a lentivirus vector that enforced the expression of a zinc-finger transcription factor designed to interact with the γ-globin gene, an essential component of HbF. As a result, HbF levels were significantly increased without altering the erythrocytes' ability to mature. This effort influenced others to develop similar approaches that are widely used to treat Hb disorders.

Dr. Nienhuis and colleagues reported in M*olecular Therapy* in 2010 that lentiviral vectors are well suited for the lineage-specific transfer of therapeutic genes into HSCs. The HSCs not only permanently expressed the genetic modification but also passed it on to progeny cells. The team further identified VSV-G as the optimal envelope protein for incorporation into pseudotyped vector particles for this purpose. The use of lentiviral vectors minimized ex vivo manipulation and time requirements for transducing HSCs when compared with γ-retroviral vector transduction techniques previously used. This lentiviral-vector approach is now in use in multiple clinical trials, including the current St. Jude XSCID trial.

In 2011, Dr. Nienhuis, Derek A. Persons, MD, PhD (Hematology), and colleagues demonstrated that a lentiviral vector could enforce the expression of an HbF gene in human $CD34^+$ HSCs. Cells obtained from healthy adult volunteers and patients with β-thalassemia major were maintained in culture, and a lentiviral vector was used to transfer one of the following three genes: 1) human γ-globulin gene, 2) zinc-finger transcription factor, or 3) short-hairpin RNA targeting the γ-globulin gene repressor BCL11A. In the transduced $CD34^+$ cells from patients with β-thalassemia, HbF production was increased as much as 60%. The investigators concluded that all three vectors stimulated the production of therapeutic levels of HbF in β-thalassemic cells and had the potential as a treatment for patients with β-globin deficiencies. Administration of combined vectors also further augmented HbF production. This study, which was published in *Blood*, set the stage for other studies of multifunctional vectors and successful gene therapy trials using this approach.

Hemophilia B is an inherited hematologic disorder characterized by episodes of spontaneous bleeding, which result from the inadequate production of clotting factors, such as factor IX (FIX). Dr. Nienhuis, Amit Nathwani, PhD (University College of London Medical School, United Kingdom), Andrew M. Davidoff, MD (Surgery), and colleagues published two landmark papers in *The New England Journal of Medicine* describing clinical trials of an adeno-associated viral vector encoding human FIX transgene to treat hemophilia B. In the first study, which was reported in 2011, six adults with severe hemophilia B received low-, intermediate-, or high-dose vector as a single intravenous infusion and were followed for up to 16 months. All of the patients showed a dose-dependent, clinically significant increase in circulating FIX levels without any sign of substantial toxicity; four patients were able to discontinue prophylactic FIX-concentrate therapy and did not experience spontaneous bleeding; the remaining two were able to substantially increase the period between treatments. The team concluded that the FIX gene therapy provided therapeutic benefit and a potential cure.

In the second article, published in 2014, the team reported nearly 3 years of follow-up of the original six patients and four additional patients, all of whom received high-dose vector. Long-term benefits, risks, and late effects were assessed, and the optimal dose of the FIX transgene was determined. All 10 patients experienced therapeutic benefit, including the cessation of bleeding episodes; none showed significant toxicity. The investigators concluded that FIX gene therapy is a safe, durable, and effective treatment for hemophilia B.

Throughout his remarkable career as a physician-scientist, Dr. Nienhuis has pushed the envelopes of existing technologies to advance treatments and develop cures for the most severe inherited hematologic disorders. His dedication to improving human health via laboratory science and clinical trials and to educate young researchers has resulted in generations of experimental hematologists who will continue to advance upon his work and countless patients whose lives have been improved by his discoveries.

Regulatory T cells Require the Phosphatase PTEN to Control Effector T-Cell Responses

The interplay between immune regulatory mechanisms and effector T cells is a crucial determinant of adaptive immunity. Regulatory T cells (T_{reg} cells) play a central role in maintaining self-tolerance and preventing autoimmune diseases by employing distinct transcriptional programs to control the responses of effector cells, such as the T_H1, T_H2, and T_H17 subsets of $CD4^+$ helper T cells. The follicular helper T cells (T_{FH} cells) are another specialized subset of $CD4^+$ T cells. These cells help B cells form germinal center responses and develop humoral immunity. However, excessive T_{FH}-cell responses lead to autoimmune diseases, such as systemic lupus erythematosus.

The mTOR (mechanistic target of rapamycin) signaling pathway is central to T cell–mediated immune responses. The structurally distinct kinase complexes mTORC1 and mTORC2 contribute to effector T-cell responses and the functional fitness of T cells in general. Because of the potent effects of mTOR signaling, multiple mechanisms have evolved to actively suppress it. One such suppressive mechanism involves the protein phosphatase and tensin homolog (PTEN), a negative regulator of lipid kinase PI(3)K signaling and thus an inhibitor of mTORC1 and mTORC2 activity.

Hongbo Chi, PhD (Immunology), and his colleagues investigated the in vivo functions and mechanisms of PTEN in T_{reg} cells and published their findings in the journal *Nature Immunology*. They developed a mouse model in which PTEN was selectively deleted in the T_{reg} cells but not in the naive T cells, resulting in the mice developing a systemic lupus-like autoimmune and lymphoproliferative disease. The PTEN deletion was associated with excessive T_{FH}-cell and germinal center B-cell responses, along with exuberant interferon-γ (IFN-γ) production and T_H1-cell reactions, because the T cells of PTEN-deficient mice had a propensity to differentiate into cells with the IFN-γ–secreting T_H1-cell phenotype. The subsequent germline deletion of IFN-γ in these mice substantially rectified their T_{FH}-cell and autoimmune responses. These results indicate that PTEN plays an essential role in the process by which T_{reg} cells suppress the autoimmune responses mediated by T_H1 and T_{FH} cells.

Dr. Chi's team found that PTEN deficiency destabilized the function of T_{reg} cells and dysregulated the transcriptional and metabolic programs of those cells. Furthermore, PTEN deficiency upregulated the activity of the mTORC2 complex and the serine–threonine kinase Akt, whereas the loss of this activity restored the functioning of PTEN-deficient T_{reg} cells. Together, these results reveal the existence of a PTEN–mTORC2 axis that maintains T_{reg}-cell stability and coordinates the T_{reg} cell–mediated control of T_H1- and T_{FH}-cell responses. Given its apparent importance in immune regulation by T_{reg} cells, the PTEN–mTORC2 signaling axis represents a new therapeutic target for autoimmune and lymphoproliferative diseases. *Shrestha S et al, Nat Immunol 16:178–87, 2015*

Rod Photoreceptor–Derived Induced Pluripotent Stem Cells Are a Superior Source for Generating Differentiated Retinal Cells to Treat Retinal Degeneration

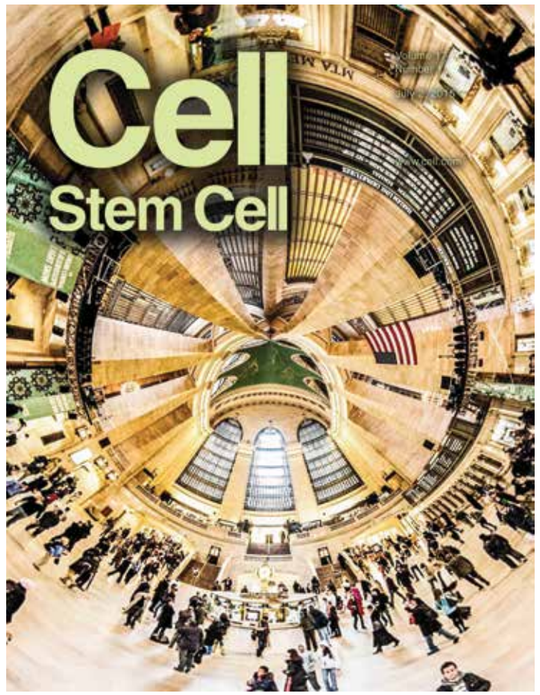
Retinal degenerative diseases are the leading cause of age-related visual impairment and blindness in millions of people worldwide. The dysfunction or death of rod photoreceptors leads to retinal degeneration. Therefore, by developing the technology to generate differentiated retinal photoreceptors for transplantation, we may be able to restore visual function in patients with retinal degenerative diseases, such as macular degeneration, retinitis pigmentosa, and Stargardt disease.

Stem cells have the potential to develop into many different cell types. In recent years, stem cell–based therapies have received considerable attention because of the promise they hold in preventing vision loss in patients with retinal degenerative diseases. Clinical trials have tested the feasibility of differentiating stem cells into cells that can replace retinal pigmented epithelial cells that are defective and lead to vision loss. However, whether the source of those stem cells is important for retinal cell differentiation, integration, and survival after transplantation was not known.

In a study reported in *Cell Stem Cell*, Michael A. Dyer, PhD (Developmental Neurobiology), and his team compared the ability of induced pluripotent stem cells (iPSCs) derived from two sources—murine fibroblasts (f-iPSCs) and rod photoreceptors (r-iPSCs)—to produce retinal cells. They devised a three-dimensional organ culture system to grow human and mouse embryonic stem cells (ESCs); this system closely mimics the key steps of normal retinogenesis (i.e., retinal development). To monitor and quantify retinogenesis in the f-iPSC and r-iPSC lines, the team developed the standardized quantitative protocol STEM-RET, into which molecular, cellular, and morphologic scoring were incorporated. The STEM-RET analysis revealed that the r-iPSCs more efficiently produced differentiated retinae than did f-iPSCs or ESCs. Retinae derived from f-iPSCs showed defects in the generation of amacrine and other inner nuclear layer cells.

Next, the researchers studied whether epigenetic mechanisms affected the ability of different iPSC populations to generate differentiated retinal cells. A stem cell's epigenetic memory of its previous differentiated cell type can affect its ability to differentiate into a new cell type. Dr. Dyer's team analyzed the correlation between DNA methylation (a common epigenetic mechanism) in r-iPSCs and f-iPSCs and gene expression in differentiated retinae derived from these lines. They found that DNA hypermethylation correlated with reduced expression of genes important for the formation of inner nuclear layer cells in retinae derived from the f-iPSCs. Furthermore, the rod-specific insulator protein CTCF may contribute to the epigenetic memory of r-iPSCs, which might explain why those cells are a superior source of retinal cells.

This study confirms that the source of stem cells plays a key role in their differentiation. Rod photoreceptor–derived iPSCs are a very efficient source of producing retinae in culture and can be pharmacologically manipulated to modulate retinal differentiation. The three-dimensional organ culture system and the STEM-RET protocol mark a significant advance in retinal biology. These approaches also provide an avenue to compare different stem cell lines across laboratories and genetically manipulate stem cells to develop novel therapies for retinal degenerative diseases. *Hiler D et al, Cell Stem Cell 17:101–15, 2015*



Richard J. Webby, PhD

The Ability of Avian Influenza A (H7N9) Virus to Adapt to Mammals Is Limited

The H7N9 subtype of avian influenza A virus crossed the species barrier to infect humans for the first time in China in February 2013. Since then, the virus has caused hundreds of human infections, and approximately 30% of those cases have resulted in fatalities. Influenza A (H7N9) infection in humans has typically been linked to exposure to infected birds, mainly chickens, via live-bird markets. However, because only a few amino acid changes in genes of interest (i.e., HA, NA, NP, and PB1) would enable this traditionally avian-adapted virus to be transmitted in an airborne manner among mammals, Richard J. Webby, PhD (Infectious Diseases), and fellow researchers initiated a study aimed at determining the transmission dynamics of avian influenza A (H7N9) virus.

The study compared the replication and transmission fitness of avian influenza A (H7N9) in chickens with that in ferrets. In a recent *Nature Communications* article, Dr. Webby and his collaborators reported that the virus replicated well in chickens, causing no illness in the birds but giving rise to several genetically diverse viruses with many mutations. Although the virus could initially infect ferrets via direct contact or aerosol droplet transmission, it was unable to mutate in ferrets into a form that allowed sustained airborne transmission among mammals. Further analysis of viruses from infected chickens and ferrets showed that replication in ferrets did not enhance the virulence or transmissibility of the virus further, and in contrast, actually led to a lack of genetic diversity and an attenuated phenotype in mammals. Furthermore, the low mammalian transmissibility of influenza A (H7N9) was not sustained over time, nor did a mutation conferring a preference for binding to human α2,6–linked sialic acid receptors fully displace the virus' affinity for avian α2,3–linked receptors.

These results indicate that although influenza A (H7N9) can generate and sustain a diverse genetic pool in chickens, a genetic "bottleneck" limits the virus from further mutating into a form that would allow direct mammal-to-mammal transmission after it replicates in ferrets. However, the authors caution that vigilant monitoring and surveillance are still needed because humans continue to be infected with these avian viruses. Therefore, influenza A (H7N9) remains a plausible pandemic threat and should remain a focus of preparedness efforts. *Zaraket H et al, Nat Commun 6: 6553–63, 2015*

Rubicon, NOX2, and Autophagy Proteins Have Distinct Roles in LC3-associated Phagocytosis

During periods of nutrient scarcity, cells activate a survival mechanism called macroautophagy, in which nonessential or dysfunctional cellular components are degraded and recycled. In contrast, phagocytosis is a routine process by which immune cells engulf and eliminate pathogens and dead cells. LC3-associated phagocytosis (LAP), which was first discovered at St. Jude and reported in *Nature* in 2007, is triggered by the phagocytosis of extracellular particles that engage certain cell-surface receptors. In LAP, some of the components involved in macroautophagy cooperate with the phagocytosis process by conjugating the protein LC3 to a subset of phagosomes (i.e., cytoplasmic vacuoles that form around particles that have been absorbed by phagocytosis), thereby facilitating the rapid maturation of the phagosomes, the degradation of the engulfed pathogens, and the modulation of immune responses.

Douglas R. Green, PhD (Immunology), and his colleagues characterized the molecular requirements for LAP and reported their findings in *Nature Cell Biology*. They first obtained a profile of the proteome of LAP-associated phagosomes, which they termed "LAPosomes," and identified the protein called Rubicon (RUN domain protein as Beclin-1 interacting and cysteine-rich containing) as being required for LAP but not for autophagy by conventional phagosomes. Rubicon is a negative regulator of the Class III phosphoinositide 3–kinase [PI(3)K] complex in macroautophagy. The researchers confirmed that silencing Rubicon in vitro increased the number of autophagosomes. Also, when they deleted Rubicon in mice, the animals failed to mount a LAP response, because their macrophages were unable to translocate LC3 to LAPosomes.

Macroautophagy proceeds through the sequential recruitment of a series of protein complexes, including the Class III PI(3)K lipid kinase complex (containing the Class III PI(3)K VPS34, VPS15, Beclin-1, and ATG14L). However, Dr. Green's group found that LAP requires the activity of a Class III PI(3)K complex containing UVRAG (ultraviolet radiation resistance–associated gene) but not ATG14 or Ambra 1, and they showed that Rubicon is essential for this activity. The UVRAG-containing Class III PI(3)K complex allows for the sustained localization of phosphatidylinositol 3-phosphate [PtdIns(3)P], which is crucial for recruiting downstream autophagic proteins and stabilizing the NOX2 complex. PtdIns(3)P and the reactive oxygen species produced by the NOX2 complex are required for the conjugation of LC3 to LAPosomes.

Having identified the molecules that differentiate LAP from canonical autophagy, the researchers investigated whether LAP was induced by the fungal pathogen *Aspergillus fumigatus*, which commonly infects immunocompromised patients, notably those with chronic granulomatous disease who have defective components of the NOX2 complex. In a series of experiments in genetically modified mouse strains, some of which lacked Rubicon or other requisites for LAP, Dr. Green's team showed that LAP was required for the optimal clearance of *A. fumigatus* in vivo and that LAP-deficient animals exhibited increased pathologic inflammation, proinflammatory cytokine levels, and fungal burden. Consequently, the inflammation, granulomas, and infectious susceptibility that are associated with chronic granulomatous disease in humans may be partly attributable to a defect in LAP. *Martinez J et al, Nat Cell Biol 17:893–906, 2015*

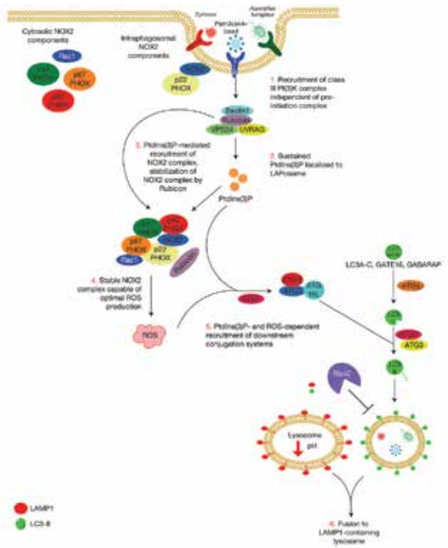


Figure. Proposed model of LAP. © *2015 Martinez J et al*

A Novel Three-Drug Combination for Specifically Targeting Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia

Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph^+ ALL) is an aggressive disease with a poor prognosis. Patients with Ph^+ ALL express the fusion oncogene *BCR–ABL*, which results from the translocation of chromosomes 9 and 22 (the Philadelphia chromosome) and encodes a constitutively active tyrosine kinase. Although treatment with potent BCR–ABL kinase inhibitors such as dasatinib is effective in patients with Ph^+ ALL, high rates of eventual relapse are due to persistent minimal residual disease. Therefore, there is a pressing need to identify other molecular targets that can be used in conjunction with BCR–ABL inhibition to improve the survival of patients with Ph^+ ALL.

Cytokine signaling within the hematopoietic microenvironment may help maintain minimal residual disease. Janus kinases (JAKs), which are key components of the cytokine-signaling pathway, therefore represent potential targets for Ph^+ ALL therapy. The JAK kinase inhibitor ruxolitinib has been previously approved for the treatment of some types of myelofibrosis.

Charles J. Sherr, MD, PhD (Tumor Cell Biology), and his colleagues developed a mouse model of Ph^+ ALL to study whether the coadministration of dasatinib and ruxolitinib effectively reduces minimal residual disease. The mouse model closely recapitulated the genetics, clinical behavior, and therapeutic response of the human disease. Mice were injected with leukemia-initiating cells (LICs), and leukemic infiltration was monitored following treatment with different drug concentrations and combinations. In a study reported in the journal *Blood*, the researchers found that even though ruxolitinib did not have an antileukemic activity by itself, its combination with dasatinib significantly extended the survival of mice by targeting parallel signaling pathways. Although the BCR–ABL kinase bypassed the cytokine requirement for LICs, the inhibition of the BCR–ABL kinase resensitized LICs to ruxolitinib.

Given the established efficacy of dexamethasone during induction therapy in crossing the blood-brain barrier and reducing the risk of Ph^+ ALL relapse in the central nervous system, this corticosteroid was added to the combination regimen of dasatinib and ruxolitinib. Disease remission after therapy and time to treatment failure were evaluated by bioluminescence imaging. Both dexamethasone and ruxolitinib offered additive benefits in reducing the leukemic burden, prolonging remission, preventing relapse of disease in the central nervous system, and extending survival in dasatinib-treated mice.

Because the results obtained from this mouse model of Ph^+ ALL showed great potential to be successfully translated to clinical practice, Dr. Sherr's colleagues at Memorial Sloan Kettering Cancer Center (New York, NY) have initiated a Phase I/II trial in which patients aged 40 years or older with Ph^+ ALL are receiving the combination of dasatinib, ruxolitinib, dexamethasone, and intrathecal methotrexate as first-line remission-induction therapy. *Appelmann I et al, Blood 125: 1444–51, 2015*

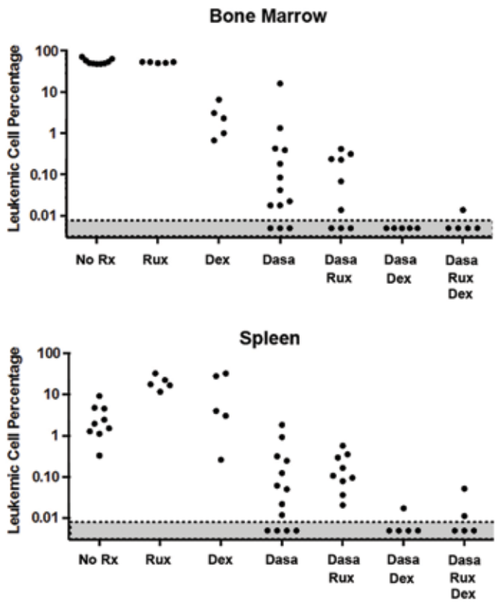


Figure. Mice were injected intravenously with LICs and allowed to develop disease (visualized by whole-body bioluminescence imaging). Animals were then randomized, and groups of mice were treated for 7 days with ruxolitinib (Rux), dexamethasone (Dex), dasatinib (Dasa), or combinations of dasatinib with other drugs. Quantitative polymerase chain reactions were used to quantify the residual levels of $BCR–ABL^+$ leukemic cells in bone marrow and spleens after short-term remission-induction therapy. *Republished with permission of the American Society of Hematology, from Janus kinase inhibition of ruxolitinib extends dasatinib- and dexamethasone-induced remission in a mouse model of Ph^+ ALL, Appelmann I et al, Blood 125, 1444, © 2015; permission conveyed through the Copyright Clearance Center, Inc.*

A Gene Attributed to the Microcephaly with Seizures Syndrome Is Essential for Multiple DNA-Repair Pathways during Neurogenesis

The developing central nervous system is highly susceptible to genotoxic stress (i.e., any destructive force on DNA or RNA that compromises the integrity of the cell). Consequently, mutations in DNA-repair genes are often associated with heritable neurodegenerative disease. Microcephaly with seizures (MCSZ) syndrome is an autosomal-recessive disorder characterized by profound microcephaly with preserved brain structure and the apparent absence of defects in any other tissues or organs. MCSZ is specifically caused by mutations within the polynucleotide kinase–phosphatase (*PNKP*) gene. PNKP is a dual-function kinase and phosphatase that promotes the repair of damaged DNA by removing 3′-phosphate groups and phosphorylating 5′-hydroxyl groups of cleaved DNA strands prior to ligation in single- or double-strand break repair. To elucidate the specific DNA-repair pathways regulated by PNKP and the role these pathways play in neurogenesis, Peter J. McKinnon, PhD (Genetics) and colleagues generated and extensively characterized several mouse models of PNKP-mediated microcephaly.

In *The EMBO Journal*, the researchers reported that targeted deletion of *Pnkp* during embryonic development of the central nervous system in mice results in early postnatal lethality and microcephaly. Microcephaly was associated with reduced numbers of cortical and cerebellar neurons and concomitantly increased programmed cell death. Although cortex size and neuronal viability were attenuated in the absence of *Pnkp* expression, the structural order of the cortical layers remained intact, similar to that observed in patients with MCSZ. Remarkably, the effects of reduced *Pnkp* expression in developing mouse brains were exquisitely sensitive to neurogenesis stage. Microcephaly and neuron loss were exacerbated when PNKP levels were reduced during earlier stages of neurogenesis. Moreover, cell type–specific loss of proliferating populations of differentiated neural cells, including oligodendrocytes and astrocytes, in postneurogenic brains revealed a role of PNKP in the homeostatic maintenance of adult neurogenesis.

To determine the function of PNKP in specific DNA-repair pathways during neurogenesis, Dr. McKinnon's team treated primary cultures of cortical neurons or embryonic fibroblasts from mice with deleted or attenuated *Pnkp* expression with a variety of genotoxins (i.e., ionizing radiation, hydrogen peroxide, camptothecin, bleomycin, mitomycin C, or cisplatin) to induce DNA damage. The researchers analyzed the specific cellular response to the genotoxins and compared it with that of other cell types that are deficient in single- or double-strand break repair. Dr. McKinnon and his team found that reduced *Pnkp* expression specifically impaired base-excision repair (a specific type of single-strand-break repair) and nonhomologous end joining (a specific type of double-strand break repair) and did not affect other DNA-repair pathways. These results suggest that PNKP function in the repair of single- and double-strand DNA breaks is essential for normal neurogenesis in the developing brain and adult brain. *Shimada M et al, EMBO J 34:2465–80, 2015*

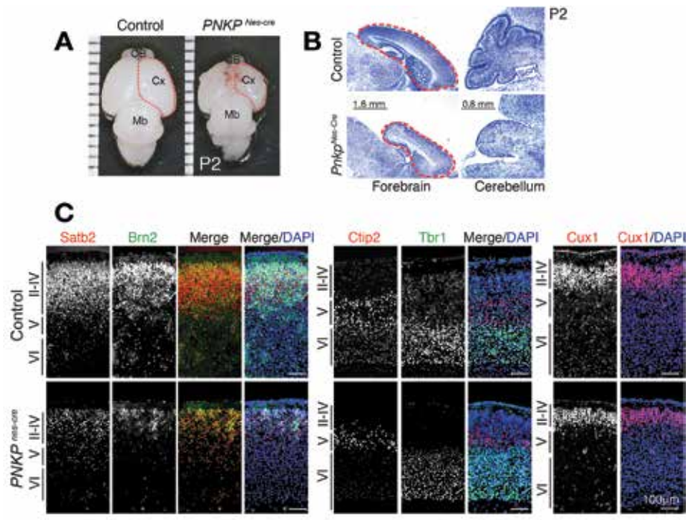


Figure. PNKP is essential for neurogenesis. (**A**) Photograph of mouse brains at postnatal day 2 shows that mice in which *Pnkp* was deleted ($PNKP^{Nes\text{-}cre}$) had a smaller cortex (red dashed line), cerebellum/midbrain (Mb), and olfactory bulb (OB) than did control mice. (**B**) Nissl staining of sagittal sections of the brains confirms the reduced cell number in the PNKP-deficient brain. (**C**) Although the number or neurons was reduced, the loss of PNKP did not markedly affect the six-layered structure of the mouse cortex (indicated by Roman numerals). *© 2015 Shimada M et al*

Gregory T. Armstrong, MD, MDSCE

A Comprehensive Approach to the Early Detection of Adult-Onset Cardiac Dysfunction in Survivors of Childhood Cancer

Anthracycline chemotherapy and chest-directed radiation therapy are among the most effective anticancer treatments; however, these interventions also greatly increase the risk of cardiac failure in long-term cancer survivors. Treatment-related cardiotoxicity is the most common noncancer cause of death among cancer survivors. Although more than 83% of children with cancer will survive into adulthood, approximately 12% of those survivors exposed to anthracycline chemotherapy or chest irradiation will experience congestive heart failure by 45 years of age. Decline in the left ventricular ejection fraction (LVEF), as detected by echocardiography, is the current standard for determining the presence of cardiotoxicity. Unfortunately, once a decline in LVEF is identified, survivors are on a progressive, irreversible path toward clinical heart failure. Therefore, early detection of cardiac dysfunction with novel echocardiographic measures may provide opportunities for early treatment of heart failure. To establish key parameters for accurate, early detection of adult-onset cardiac dysfunction in childhood cancer survivors, Gregory T. Armstrong, MD, MSCE (Epidemiology & Cancer Control, Oncology), and his colleagues used comprehensive echocardiographic approaches, including measuring myocardial strain, to assess the largest cohort of adult survivors of childhood cancer to date. The participants in this study were from the St. Jude Lifetime Cohort Study.

In the *Journal of the American College of Cardiology*, Dr. Armstrong and his team reported the key aspects of cardiac dysfunction in adults who had been exposed to anthracyclines, received chest-directed radiotherapy, or both. Comprehensive echocardiography was performed in 1820 adults who had survived 10 or more years since their cancer diagnosis, and the following measures were obtained: three-dimensional LVEF, global longitudinal strain, global circumferential strain, peak mitral flow velocity, mitral septal and lateral early diastolic velocity, and left atrial volume. The research team found that only 5.8% of the survivors had impaired LVEF. However, 31.8% showed abnormal global longitudinal strain, and most of those participants had a normal LVEF. Furthermore, global longitudinal strain abnormalities were strongly associated with anthracycline exposure and chest-directed radiation therapy in a dose-dependent manner.

The link between metabolic syndrome and increased risk for heart failure has been well characterized in the general adult population. Metabolic syndrome is defined as the presence of three or more of the following conditions: 1) abdominal obesity, 2) elevated concentration of plasma triglycerides, 3) decreased high-density lipoprotein levels, 4) hypertension, and 5) high blood glucose, and was recently established to multiplicatively increase the risk of heart failure among survivors treated with cardiotoxic therapies during childhood. Abnormal measurements of global longitudinal strain and diastolic dysfunction were nearly twice as likely to occur in survivors with metabolic syndrome, which further validated myocardial strain as an important marker. Dr. Armstrong and his colleagues concluded that abnormal global longitudinal strain and diastolic dysfunction may serve as useful prognostic tools for early detection of treatment-related cardiotoxicity, thereby facilitating early intervention in adult survivors of childhood cancer. *Armstrong GT et al, J Am Coll Cardiol 65:2511–22, 2015*

Ching-Hon Pui, MD

Minimal Residual Disease Measurements of Acute Lymphoblastic Leukemia Are Clinically Relevant even for Patients on Risk-based Therapy

In childhood acute lymphoblastic leukemia (ALL), the level of minimal residual disease during treatment is the key prognostic indicator of treatment outcome. However, the clinical significance of this measure in patients receiving therapy in which minimal residual disease level at sequential time points is use to guide treatment decisions is unclear. For the first time, Ching-Hon Pui, MD (Oncology, Pathology), and colleagues involved in the St. Jude Total Therapy Study XV have prospectively evaluated the association between event-free survival and minimal residual disease measured during and after remission-induction therapy in patients who received such risk-based treatment.

The study used a combination of flow cytometry and polymerase chain reaction analysis to measure residual disease in bone marrow specimens of 498 study participants (aged 1-18 years) with newly diagnosed ALL. After 4 days of methotrexate chemotherapy, patients were treated with prednisone, vincristine, daunorubicin, and asparaginase according to a conventional regimen to induce remission. Three additional doses of asparaginase were given to patients who had minimal residual disease measurements of 1% or more leukemic cells among the nucleated cells in their bone marrow on Day 19 of remission induction. After Day 46, whether intensive chemotherapy or hematopoietic cell transplantation was given was based on the patient's low, standard, or high risk of relapse, as determined by minimal residual disease measurements.

In a recent *Lancet Oncology* article, Dr. Pui and his colleagues reported that minimal residual disease levels on Days 19 and 46 of remission induction were most useful for selecting risk-directed treatment, especially for patients with low-risk ALL. In contrast, sequential minimal residual disease monitoring after remission induction had little clinical value among patients who attained negative minimal residual disease status after remission induction: residual disease reemerged in the bone marrow in only four of 382 patients tested on Week 7, one of 448 patients tested on Week 48, and none of the 430 patients tested on Week 120. Moreover, early treatment intervention failed to improve outcomes for patients who had re-emergent leukemia. Among patients with positive residual disease after remission induction, nine of 13 with decreasing residual disease (as compared to only one of three with an increasing level) were alive and in long-term continuous complete remission.

The authors concluded that minimal residual disease measurements during remission induction are prognostically relevant in ALL, and they recommend that sequential measurements be continued after remission induction only in patients who have detectable residual disease after remission induction. Whether a more sensitive method based on next-generation sequencing approaches to detect minimal residual disease is useful for monitoring requires further study. *Pui C-H et al, Lancet Oncol 16:465–74, 2015*

Re-Engineering Spectinomycin to Treat Drug-Resistant Bacterial Infections

Antibiotic resistance among bacterial pathogens is a major threat to public health. The increasing drug resistance of respiratory and sexually transmitted bacterial infections, such as pneumococcal pneumonia and gonorrhea, highlights the urgent need to develop new antibiotics with novel mechanisms of action.

The antibiotic spectinomycin, which is a strong inhibitor of bacterial protein synthesis, was originally used to treat gonorrhea in the 1960s. However, it is only weakly active and does not have adequate antibacterial activity against most other clinically important pathogens. In a study in 2014, Richard E. Lee, PhD (Chemical Biology & Therapeutics), and his colleagues used a structure-based design to develop a new class of spectinomycins called spectinamides to treat drug-resistant tuberculosis. Given the success of that study, the team decided to use a similar structure-based approach to generate other more potent spectinomycin analogs that are effective against a broad spectrum of drug-resistant bacterial pathogens.

In *Science Translational Medicine*, Dr. Lee and his team, including key contributions from Jason W. Rosch, PhD (Infectious Diseases), reported using computational modeling and structure-guided synthesis to generate a chemically distinct series of *N*-benzyl–substituted aminomethyl spectinomycins (amSPCs) that bind to ribosomes and inhibit protein synthesis across an expansive range of bacterial pathogens. On the basis of results from in silico modeling, the investigators designed and synthesized four targeted 3′ *R*-isomer amSPCs (compounds 1-4) and two corresponding 3′ *S*-isomer controls (compounds 5 and 6) from spectinomycin. From the 20 *N*-benzyl amSPCs initially synthesized in the series, these six compounds were selected for further testing because of their favorable clinical potential. Compounds 1 through 4 strongly inhibited bacterial protein synthesis but not mammalian protein synthesis, and they were more effective than spectinomycin at inhibiting the ribosomes of gram-positive bacteria. Furthermore, these compounds were not toxic to mammalian cells in vitro and were not cross-resistant with existing classes of antibiotics. Importantly, the compounds had increased potency against common respiratory bacterial pathogens (e.g., *Streptococcus pneumoniae, Haemophilus influenzae*) and sexually transmitted bacterial pathogens (e.g., *Neisseria gonorrhoeae, Chlamydia trachomatis*). The antibacterial spectrum of activity of these amSPC compounds was unique and not seen in previously reported spectinamides or alkyl amSPCs.

Compounds 1, 3, and 4 were selected for pharmacokinetic profiling and found to have pharmacokinetic properties that are recommended for antibacterial drugs. In mouse models of pneumonia and bacteremia, Compound 1 increased survival and effectively cleared infection. Further testing revealed that Compound 1 was as effective as ampicillin in protecting mice from pneumonia and bacteremia; it also had higher efficacy than spectinomycin in preventing the progression of fatal pneumococcal pneumonia, meningitis, and sepsis.

This study provides a clinically important example of how an old antibiotic with low potency can be redesigned and tested as a therapeutic for drug-resistant bacterial diseases. Dr. Lee and his team concluded that *N*-benzyl amSPCs are ideal candidates to be developed as treatment for drug-resistant respiratory tract or sexually transmitted diseases. *Bruhn DF et al, Sci Transl Med 7: 288ra75, 2015*

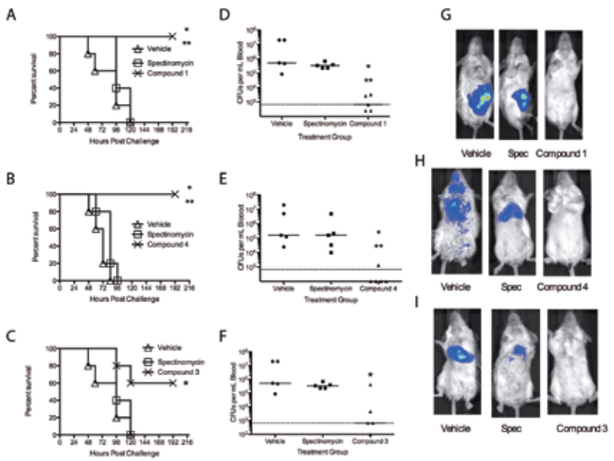


Figure. The amSPCs provide better protection than spectinomycin against invasive pneumococcal infection. Antibiotics (5 mg/kg) were administered twice daily starting 18 h after the challenge with *S. pneumoniae*. (**A-C**) Overall survival of mice that received vehicle, spectinomycin (Spec), or the indicated amSPC compound. (**D-F**) Bacterial burden in the blood of mice 48 h after the challenge. (**G-I**) Bioluminescent imaging of mice shows the extent of pneumococcal infection 72 h after the challenge. *From Bruhn DF et al, Aminomethyl spectinomycins as therapeutics for drug-resistant respiratory tract and sexually transmitted bacterial infections, Science Translational Medicine, 7:288ra75, © 2015. Reprinted with permission from AAAS.*

AIM2 Protein Protects against Colorectal Cancer by Attenuating Stem Cell Proliferation and Modulating the Microbiota of the Gut

Every year, approximately 160,000 people in the United States receive a diagnosis of colon cancer. Altered gut microbiota are found in many patients with colon cancer, and colorectal tumorigenesis (tumor development) and disease progression are regulated by the gut microbiota constitution. The absent in melanoma-2 (AIM2) protein is a double-stranded DNA sensor that protects against bacterial and viral pathogens by detecting the presence of cytoplasmic double-stranded DNA. Conventionally, AIM2 induces an inflammatory response and programmed cell death of infected cells by initiating the assembly of an inflammasome complex. Approximately half of all patients with colon cancer possess mutations in the *AIM2* gene, and the absence of *AIM2* expression in colorectal tumors greatly increases the risk of patient mortality. However, the specific mechanism through which AIM2 protects against colorectal tumorigenesis is unknown.

Thirumala-Devi Kanneganti, PhD (Immunology), and her colleagues used *Aim2*-deficient mice to determine the role AIM2 plays in modulating gut microbiota and colorectal cancer. In a study reported in *Cell*, the researchers induced colitis-associated colorectal tumorigenesis in normal and *Aim2*-null mice by treating them with azoxymethane (AOM) and dextran sulfate sodium (DSS). Loss of *Aim2* expression resulted in increased hyperplasia (i.e., enlargement of an organ due to the increased proliferation of cells) and tumor burden in the colon after AOM and DSS exposure. Furthermore, *AIM2* expression was reduced in tumors isolated from patients with colorectal cancer and in tumors from AOM- and DSS-treated wild-type (WT) mice. To elucidate the role of the AIM2-mediated inflammatory response in tumorigenesis, the researchers investigated many markers of inflammation, including inflammasome mediators, proinflammatory cytokines, and circulating white blood cell populations, in WT and *Aim2*-deficient mice. However, no discernible differences in any inflammatory hallmarks were observed, suggesting that the protective effect of AIM2 occurs through an inflammation-independent mechanism.

Dr. Kanneganti's team next assessed the proliferation of intestinal stem cells in AOM- and DDS-treated normal mice and *Aim2*-deficient mice. Loss of *Aim2* expression promoted proliferation and reduced programmed cell death in the intestinal crypts (i.e., structures that contain stem cells that will differentiate into the cells that form the intestinal inner lining), which was associated with upregulated mRNA expression of many oncogenes and activation of the phosphatidylinositol 3-kinase–Akt signaling pathway. Furthermore, intestinal stem cell activity was increased in AOM-treated *Aim2*-deficient mice. Bone marrow transplantation from WT donor mice into *Aim2*-null recipients increased tumor burden, and bone marrow transplantation from *Aim2*-null donor mice into WT recipients also increased tumor burden, indicating that AIM2 regulates tumorigenesis in the gut and bone marrow compartments.

To assess the role of the gut microbiota in AIM2-regulated tumorigenesis, the researchers determined the composition of microbiota from AOM-treated normal mice and *Aim2*-null mice. *Aim2* deficiency increased the prevalence of *Akkermansia muciniphila* and *Anaeroplasma* and reduced the levels of *Anaerostipes*, *Bifidobacterium*, *Flexispira*, *Prevotella*, and *Paraprevotella* species compared to that in WT mice. Colonic tumorigenesis has been previously linked to augmented *Akkermansia* levels and concomitantly reduced *Prevotella* levels in the gut. In addition, reciprocal exchange of microbiota between normal and *Aim2*-null mice altered tumor burden in both genotypes, indicating that AIM2 regulates colorectal cancer via genetic and environmental mechanisms. *Man SM et al, Cell 162:45–58, 2015*

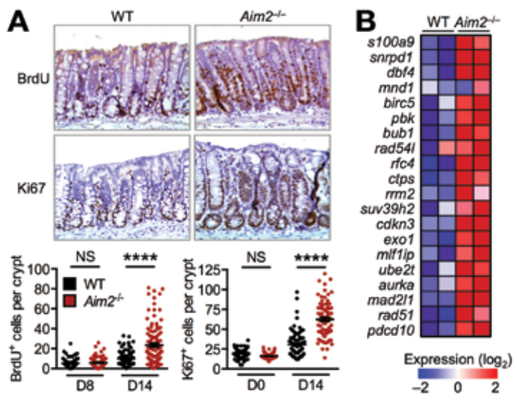


Figure. AIM2 suppresses the overt proliferation of cells in intestinal crypts. (**A**) Imaging of $BrdU^+$ cells and $Ki67^+$ cells in the crypts of wild-type (WT) or $Aim2^{-/-}$ mice at Days 0, 8, or 14 after AOM and DSS treatment. Quantification of the cells shown in **A**. (**B**) Microarray analysis of genes involved in cell proliferation in WT and $Aim2^{-/-}$ mice. *Reprinted from Cell, 162, Man SM et al, Critical role for the DNA sensor AIM2 in stem cell proliferation and cancer, 45–58, © 2015, with permission from Elsevier.*

The Glucose-Sensing Transcription Factor MLX Promotes Muscle Cell Differentiation via Myokine Signaling

Insulin resistance and diminished intracellular glucose uptake are components of both aging and diabetes, but it is largely unknown whether they are causally associated with the decline in tissue regeneration that is observed in these conditions. One possibility is that limited glucose uptake leads to lower ATP production and thus indirectly compromises regeneration by affecting cellular resources available for this process. Alternatively, glucose may act as a signaling molecule that directly modulates pathways responsible for regeneration. Skeletal muscle is one of the tissues most profoundly remodeled in response to changes in glucose levels, but the mechanisms and signaling pathways involved in that process have not been elucidated.

By examining muscle differentiation and regeneration, Fabio Demontis, PhD (Developmental Neurobiology), and his team demonstrated a previously unanticipated role for the glucose-sensing transcription factor Max-like protein X (MLX) in regulating myogenesis and muscle regeneration. In the journal *Genes and Development*, the researchers reported that MLX is necessary for myoblast fusion in response to glucose and promotes it not by adjusting glucose metabolism but rather by inducing the expression of several myokines (i.e., growth factors and cytokines secreted by skeletal muscle), including insulin-like growth factor 2 (IGF2). Conversely, MLX RNA interference and dominant-negative MLX reduced IGF2 expression and blocked myogenesis. This phenotype was rescued by conditioned media from control muscle cells and recombinant IGF2, which activates the myogenic kinase Akt. Importantly, MLX-null mice displayed decreased induction of IGF2 and diminished muscle regeneration in response to injury, indicating that the myogenic function of MLX is manifested in vivo. These results indicate that glucose is a signaling molecule that regulates myogenesis and muscle regeneration via MLX–IGF2–Akt signaling.

Considering that intracellular glucose levels change during aging and diseases characterized by metabolic dyshomeostasis, the findings from Dr. Demontis' group provide a mechanistic basis for understanding how glucose acts as a signaling molecule to control muscle cell fate and regeneration in different physiologic and pathologic contexts. *Hunt LC et al, Genes Dev 29:2475–89, 2015*

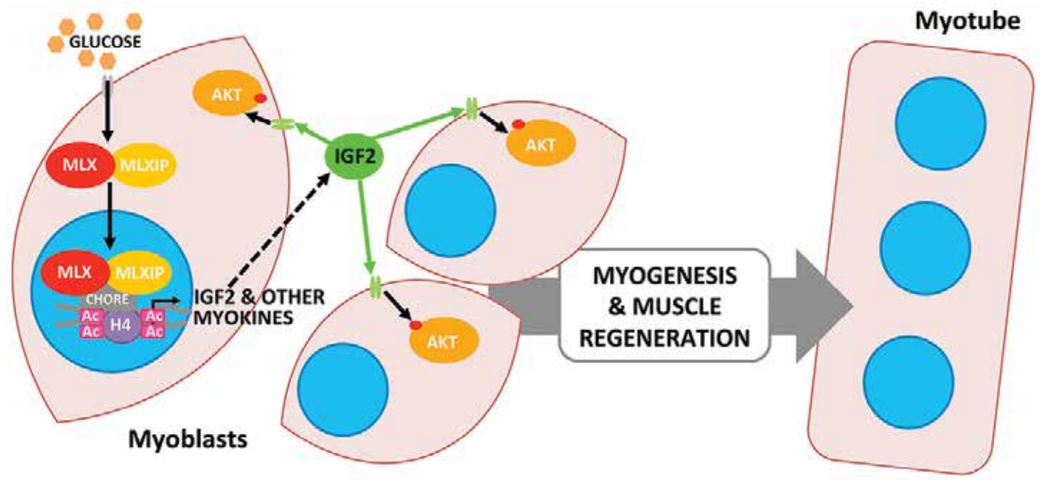


Figure. Model showing how MLX promotes myogenesis and muscle regeneration via myokine signaling. In response to glucose, MLX is activated in myoblasts. MLX transcriptionally activates myokines such as IGF2. Once IGF2 is secreted, it activates the Akt kinase, which in turn promotes myoblast fusion and differentiation. *Reprinted from Genes Dev 29, 2475–89, © 2015 Hunt LC et al. The Creative Commons License [Attribution-Noncommercial 4.0 International] is available at http://creativecommons.org/licenses/by-nc/4.0/.*

Giles W. Robinson, MD

Vismodegib Has Efficacy against Adult Recurrent SHH-Subgroup Medulloblastoma

The sonic hedgehog subtype of medulloblastoma (SHH-MB) accounts for approximately 30% of all medulloblastomas. SHH-MBs occur most frequently in children younger than 5 years, adolescents older than 16 years, and adults. For patients with recurrent disease, the prognosis is dismal; therefore, new treatments are needed to improve survival and prevent tumor recurrence, as well as to decrease the morbidity associated with current therapy.

The smoothened (SMO) protein is a key component of the SHH pathway. Inhibitors of SMO have demonstrated efficacy in treating basal cell carcinoma and shown some activity against recurrent medulloblastoma. As reported in the *Journal of Clinical Oncology*, Giles W. Robinson, MD (Oncology), and his colleagues conducted two prospective Phase II Pediatric Brain Tumor Consortium (PBTC) trials to assess the efficacy of the SMO inhibitor vismodegib in treating patients with recurrent medulloblastoma. They also investigated the genomic basis for the responsiveness or resistance of the tumors to vismodegib treatment.

The researchers enrolled 31 adult patients in trial PBTC-025B and 12 patients (aged 3.9-20 years) in trial PBTC-032. All patients received daily oral vismodegib (150 mg). In three adult patients and one pediatric patient, all of whom had SHH-MB, the treatment reduced the tumor size by at least 30% and sustained that reduction for at least 8 weeks, but no response was observed in patients with other subtypes of medulloblastoma (non-SHH–MBs). Progression-free survival was better in patients with SHH-MB than in those with non-SHH–MBs, and 41% of patients with SHH-MBs experienced prolonged disease stabilization. In patients with SHH-MB, aberrations of the *PTCH1* gene, which encodes a sonic hedgehog receptor, were associated with prolonged progression-free survival, whereas immunofluorescent staining patterns indicative of mutations in the *TP53* tumor-suppressor gene were associated with reduced survival. The researchers performed whole-exome sequencing of eight SHH-MBs and identified mutations in SHH-pathway genes downstream from the *SMO* gene in all four cases that did not respond to vismodegib and in genes upstream from *SMO* in two of four tumors that responded favorably to the drug.

These results indicate that, in adults, vismodegib is active against a subset of recurrent SHH-MB but not against recurrent non-SHH–MBs. Because SHH-MB is rare in children aged 5 to 16 years, too few patients were accrued to trial PBTC-032 to permit conclusions about the efficacy of vismodegib treatment in the pediatric population. However, the results of the molecular analyses support the hypothesis that the activity of SMO inhibitors depends on genomic aberrations within the tumor. Therefore, Dr. Robinson and his team concluded that molecular profiling of all SHH-MBs is essential to identify patients who will benefit from vismodegib treatment. *Robinson GW et al, J Clin Oncol 33:2646–54, 2015*

Charles W. M. Roberts, MD, PhD

COMPREHENSIVE CANCER CENTER

The National Cancer Institute (NCI) supports 69 Cancer Centers in the United States. Currently under the direction of Charles W. M. Roberts, MD, PhD, the St. Jude Comprehensive Cancer Center is the first and only NCI-designated Comprehensive Cancer Center solely focused on pediatric cancer. Comprising five programs and 10 Shared Resources, the Comprehensive Cancer Center emphasizes interdisciplinary laboratory-based and clinical research applicable to the understanding, prevention, and treatment of childhood cancer.

CANCER GENETICS, BIOCHEMISTRY, & CELL BIOLOGY PROGRAM

Co-leaders: Martine F. Roussel, PhD; Brenda A. Schulman, PhD

The goals of this program are to define the critical cellular pathways involved in normal cellular regulation and the pathways that are altered in transformed cells. It is organized into three highly interactive focus groups that provide thematic, complementary, basic science expertise to the other center programs, enhancing the translation of laboratory discoveries to the clinic. The three focus groups are as follows: Cell Stress & Metabolism, Genome Structure & Function, and Signaling Networks & Therapeutics.

CANCER PREVENTION & CONTROL 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 observational, clinical, and interventional research. With the establishment of large national and institutional cohorts of cancer survivors, 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 of childhood leukemias and lymphomas, while minimizing treatment-related adverse effects. This program has a distinguished track record in improving the 5-year survival rate of acute leukemias and reducing the use of harmful therapeutic modalities such as cranial irradiation. Most recently, the members of this program have used advanced genetics to identify novel subgroups of leukemias and the mutations that drive these diseases. 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

By integrating the latest genomic and genetic technologies with studies of the developing nervous system, members of this program are efficiently translating laboratory findings into opportunities for new treatments. Recent efforts include the identification of the cells of origin of important pediatric brain tumors and the modeling of some of the most aggressive forms of these tumors, including high-grade gliomas. Close collaboration among the laboratory and clinical members of the program allows the rapid translation of high-throughput drug screens in mouse models to clinical trials.

SHARED RESOURCES

Animal Resource Center

Bioinformatics and Biotechnology

Biostatistics

Cell and Tissue Imaging

Cytogenetics

Flow Cytometry and Cell Sorting

Diagnostic Biomarkers

Pharmacokinetics

Protein Production Facility

Transgenic/Gene Knockout

INTERNATIONAL OUTREACH PROGRAM

Approximately 175,000 children younger than 14 years of age receive a diagnosis of cancer each year. More than 80% of those children live in low- or middle-income countries. Despite dramatic improvements in the survival of children with cancer, approximately 60% lack access to adequate healthcare. More than 50% of children who receive a cancer diagnosis die, and most of those deaths occur in resource-poor settings.

Carlos Rodriguez-Galindo, MD

To address this gap, the St. Jude International Outreach Program (IOP) is working to improve the survival of children around the world who have cancer or other life-threatening diseases. The IOP accomplishes this by sharing knowledge, technology, and organizational skills; implementing new approaches to treat pediatric cancer globally; and generating international networks committed to eradicating cancer in children.

Currently, St. Jude partners with more than 20 medical institutions in 17 countries to promote sustainable improvements in pediatric cancer care. Faculty and staff at St. Jude work with those partners to advance clinical care by directly engaging with colleagues at partner sites and strengthening or developing new models for advancing care for that region through a networked approach. Centers within the networks share their expertise, thereby fostering growth in many centers in the region.

The Asociación de Hemato-Oncología Pediátrica de Centro América (AHOPCA) was one of the first organizations formed to address the disparity in pediatric cancer care in Central America and the Caribbean. A major achievement of AHOPCA, under St. Jude leadership, has been the implementation of standardized treatment regimens across institutions to improve therapy for children with cancer. For the past 20 years, AHOPCA hematologist-oncologists have implemented therapeutic regimens for more than 10 different childhood cancers.

The Pediatric Oncology East and Mediterranean Group (POEM) is a cooperative network of pediatric oncology healthcare professionals from more than 50 pediatric cancer centers across the Middle East and Mediterranean. The goal of POEM is to improve pediatric oncology research, training, patient care, and advocacy by working in multidisciplinary teams across political and territorial boundaries. Ultimately, POEM will serve as a platform for launching cooperative clinical trials and optimizing care for children with cancer. St. Jude's partner site in Lebanon serves as the administrative center for POEM, and St. Jude faculty and staff serve as expert consultants and sit on the POEM Board of Directors.

The National Childhood Acute Lymphoblastic Leukemia Study Group was created in 2014, after a demonstration project with St. Jude's partner sites in Beijing and Shanghai established that children with acute lymphoblastic leukemia treated on a standard therapeutic regimen could be cured at a relatively low cost. St. Jude's partner site in Shanghai serves as the coordinating center for the group, which consists of 20 major participating centers and will treat as many as 1500 children per year on the national protocol.

The Consorcio Latinoamericano de Enfermedades Hematooncológicas Pediátricas (CLEHOP) was created in 2015 as a result of the success of AHOPCA's program for children with Hodgkin disease. CLEHOP has integrated collaborative groups from Argentina, Peru, Ecuador, Mexico, Venezuela, and Brazil to become a true Latin American Pediatric Hematology-Oncology Cooperative Group.

The Prevencionistas e Infectólogos para Cáncer Infantil en América Latina (PRINCIPAL) is a consortium of infectious diseases experts who support the pediatric cancer programs in Latin America. The consortium includes experts from Mexico, Honduras, Nicaragua, El Salvador, Ecuador, Bolivia, Paraguay, and Argentina.

In addition to existing initiatives, new consortia will be created in the near future. For instance, plans are to create and strengthen groups similar to AHOPCA in Mexico and Southeast Asia. In the next 5 to 10 years, St. Jude will expand its reach to more than a third of children with cancer or hematologic disorders through these consortia, which will integrate regional capacity-building strategies, innovative training, educational programs, and global research initiatives.

Additional initiatives aimed at strengthening existing capacity-building strategies include dedicated educational programs in infection prevention, control, and care; nursing; data management; clinical microbiology; and anatomic pathology. As the regional networks grow, additional initiatives that will build regional capacity are planned.

An important component of St. Jude's approach to global capacity building is Cure4Kids (*www.Cure4Kids.org*), the IOP's education and collaboration website. Cure4Kids has more than 33,000 users in more than 160 countries. More than 2500 new users joined Cure4Kids in 2015. The website offers a variety of multilingual online educational content, including more than 3300 disease- and treatment-specific seminars, written articles, image challenges, and live and virtual instructor–led courses. Cure4Kids also promotes knowledge-sharing and collaboration by providing online meeting spaces and working groups for pediatric hematology-oncology professionals around the world. In 2015, more than 1800 online meetings were scheduled via Cure4Kids. As St. Jude's global program grows, the Cure4Kids platform will also evolve to meet targeted capacity-building and global research needs.

The St. Jude Cancer Education for Children Program (CECP) aims to educate school children about cancer, promote healthy lifestyle choices that can reduce their risk of cancer in adulthood, and inspire an interest in science and scientific careers. During the 2014–2015 school year, the CECP team delivered the program to more than 1600 students at 16 schools in the Memphis area. The CECP also partnered with Guam Cancer Care to deliver the curriculum to more than 2000 fourth graders in Guam. To date, the CECP has involved 1629 teachers in teacher-training seminars and 12,860 students (kindergarten to 12th grade) in cancer education. The CECP also maintains an interactive children's website and corresponding teachers' website with lesson plans related to cancer. More than 6500 users visited the website in 2015, bringing the total to just over 34,500 users since its inception. In addition, the CECP launched a Cancer Education Newsletter for K-12 educators that keeps them apprised of the latest research topics and new materials available on the website. The newsletter is emailed to 187 educators around the world.

The IOP strives to ensure that children everywhere benefit from new knowledge gained and clinical advances made at St. Jude. Through a combination of regional network development, engagement with partner centers, and direct support for educational and patient-care initiatives, the IOP makes a difference in the lives of children with cancer all over the globe. During the next year, the IOP will undergo major changes in its structure and function as the result of renewed initiatives in global medicine at St. Jude, including a new Department of Global Pediatric Medicine. The department will focus on global health science and gaining the knowledge necessary to build more effective, efficient, and sustainable models for pediatric cancer care and control worldwide. In addition, the IOP's educational initiatives will be reconfigured to maximize the training models for all healthcare professionals involved in the care of children with cancer, including new distance-learning systems and advanced education tracks through the St. Jude Graduate School of Biomedical Sciences, which will open in the fall of 2017. New global initiatives in capacity building, education, and research will also be integrated into the new St. Jude Global Cancer and Blood Disorders Center.

ST. JUDE AFFILIATE PROGRAM

The seven 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 also provide patients the opportunity to receive part of their care at a facility near their home community.

ADMINISTRATION
Medical Director • Carolyn L. Russo, MD
Administrative Director • Cindy Burleson, RN, MSN, CPON

ST. JUDE AFFILIATE SITES

BATON ROUGE, LA
Our Lady of the Lake Children's Hospital – Our Lady of the Lake Regional Medical Center
Medical Director Emeritis • Shelia Moore, MD
Medical Director •Jeffrey Deyo, MD, PhD
Vandy Black, MD
Catherine Boston, MD
Katherine Montgomery, NP
Jessica Templet, PA-C

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

HUNTSVILLE, AL
Huntsville Hospital for Women & Children – Huntsville Hospital
Medical Director • Jennifer Cox, MD
Heidi Simpson, CRNP

JOHNSON CITY, TN
Niswonger Children's Hospital – Johnson City Medical Center
East Tennessee State University
Medical Director • Kathryn Klopfenstein, MD
Marcela Popescu, MD
Cathleen Cook, MD
Angela Willocks, RN, MSN, C-FNP

PEORIA, IL
Children's Hospital of Illinois – OSF Healthcare System
University of Illinois College of Medicine at Peoria
Mary-Beth Ross, MD
Karen Fernandez, MD
Ruben Antony, MD
Pedro de Alarcon, MD, Chair of Pediatrics
Jaime Libes, MD
Angela Herman, MD
Medical Director • Kay Saving, MD, Medical Director, CHOI

SHREVEPORT, LA
Feist-Weiller Cancer Center – LSU Health Sciences Center – Shreveport
Medical Director • Majed Jeroudi, MD
Samer Kaylani, MD

SPRINGFIELD, MO
Mercy Children's Hospital – Springfield – Mercy Health System
Medical Director • Remi Fasipe, MD

Carolyn L. Russo, MD

ACADEMIC DEPARTMENTS

BIOSTATISTICS

Chair
James M. Boyett, PhD; Endowed Chair in Biostatistics • Statistical design and analysis of clinical trials

Members
Cheng Cheng, PhD • Statistical methods in cancer genomics and genetics
Stanley B. Pounds, PhD • Development of statistical methods for genomics studies
Deo Kumar S. Srivastava, PhD • Clinical trials, robust methods, survival analysis

Associate Members
Yimei Li, PhD • Statistical analysis of complex imaging data
Arzu Onar-Thomas, PhD • Phase I-II designs, survival analysis, Bayesian statistics
Jianrong Wu, PhD • Design and analysis of preclinical and clinical trials
Liang Zhu, PhD • Survival analysis and longitudinal data analysis

Assistant Members
Guolian Kang, PhD • Statistical genetics/genomics, modeling of complex data
Li Tang, PhD • Measurement error & classification, longitudinal modeling
Hui Zhang, PhD • Statistical methods for psychological research

CELL & MOLECULAR BIOLOGY

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

Associate Members
Stacey K. Ogden, PhD • Mechanisms of Hedgehog signal transduction
Joseph T. Opferman, PhD • Regulation of cell death and mitochondrial function

Assistant Member
Hans-Martin Herz, PhD • Regulation of transcription and enhancer activity

COMPUTATIONAL BIOLOGY

Chair
Jinghui Zhang, PhD; Endowed Chair in Bioinformatics • Genomic sequence analysis and visualization

Assistant Members
Xiang Chen, PhD • Genetic and epigenetic data integration by machine-learning approaches
Charles Gawad, MD, PhD[2] • Cellular and genetic origins of childhood cancers

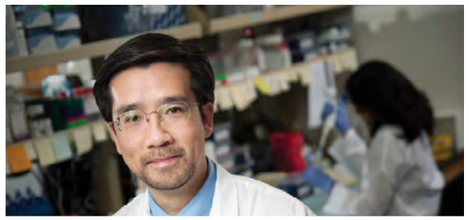
DIAGNOSTIC IMAGING

Interim Chair
Larry E. Kun, MD; Clinical Director; John & Lorine Thrasher Endowed Chair in Radiation Oncology • Improving diagnosis and therapy of brain tumors

Members
Sue C. Kaste, DO • Skeletal toxicities in childhood cancer survivors
Robert A. Kaufman, MD • Optimization of CT dose in children with cancer
Mary E. (Beth) McCarville, MD • Solid tumor imaging & contrast-enhanced ultrasonography
Zoltán Patay, MD, PhD • Brain tumor characterization by sophisticated quantitative MRI
Wilburn E. Reddick, PhD • White matter injury in leukemia and CNS tumors
Barry L. Shulkin, MD • PET imaging and evaluation of pediatric tumors

Associate Members
Mikhail Doubrovin, MD, PhD • Radiotracer imaging–based techniques of pediatric solid tumors
Kathleen J. Helton, MD • Cerebral perfusion & white matter connectivity in sickle cell disease
Claudia M. Hillenbrand, PhD • Novel MR techniques in solid tumors and sickle cell disease
Robert J. Ogg, PhD • Imaging assessments of brain function in CNS and ocular tumors
Scott E. Snyder, PhD • Design of radioactive diagnostic agents for functional medical imaging

Assistant Members
Samuel L. Brady, PhD • Medical physics; optimizing CT image quality
Jamie L. Coleman, MD • Ultrasound and CT/MR imaging of pediatric solid tumors
Julie H. Harreld, MD • Magnetization transfer MR imaging and cerebral perfusion
Scott N. Hwang, MD, PhD • Brain tumors, quantitative imaging, computational modeling
Noah D. Sabin, MD, JD • Imaging of brain tumors and acute effects of therapy
András Sablauer, MD, PhD • Imaging informatics and computerized tumor modeling



BONE MARROW TRANSPLANTATION & CELLULAR THERAPY

Chair
Wing H. Leung, MD, PhD; Endowed Chair in Bone Marrow Transplantation & Cellular Therapy[1]

Member
William E. Janssen, PhD • Immunotherapy, therapeutic application of engineered cells

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

Assistant Members
Lea C. Cunningham, MD • Drug discovery and development of preclinical models
Mari H. Dallas, MD • Cord blood transplantation and immune reconstitution
Christine M. Hartford, MD[1]
Ewelina K. Mamcarz, MD • Transplantation in patients with nonmalignant diseases
Asha B. Pillai, MD • Immunobiology of alloregulation, engraftment, & GVHD
David R. Shook, MD[1]
Brandon M. Triplett, MD • Hematopoietic cell transplantation

CHEMICAL BIOLOGY & THERAPEUTICS

Chair
R. Kiplin Guy, PhD; Robert J. Ulrich Endowed Chair in Chemical Biology & Therapeutics • Chemical biology and orphan disease drug discovery

Member
Richard E. Lee, PhD • Development of new chemotherapeutic agents

Associate Members
Taosheng Chen, PhD • Small-molecule transcription factor drug discovery
Naoaki Fujii, PhD • Medicinal chemistry, chemical biology, PDZ domain
Philip M. Potter, PhD • Anticancer drug hydrolysis by carboxylesterases
Scott E. Snyder, PhD[2] • Design of radioactive drugs for medical imaging

Assistant Members
Fatima R. Rivas, PhD • Organic chemistry synthesis/natural product discovery
Anang A. Shelat, PhD • Multiscale modeling of biological and chemical data

Research Associate
Tudor Moldoveanu, PhD[2] • Programmed cell death in health and disease

DEVELOPMENTAL NEUROBIOLOGY

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

Members
Suzanne J. Baker, PhD • Signaling pathways driving childhood high-grade glioma
Michael A. Dyer, PhD; Richard C. Shadyac Endowed Chair in Pediatric Cancer Research • Retinal development, retinoblastoma, and pediatric solid tumor translational research
Richard J. Gilbertson, MD, PhD[1]
Richard J. Smeyne, PhD • Role of viruses, inflammation, and oxidative stress in neurodegeneration
Jian Zuo, PhD • Auditory hair cell function and regeneration in mice

Associate Members
Xinwei Cao, PhD • Growth control during neural tube development
David J. Solecki, PhD • Cell polarity in neuron precursor differentiation
Stanislav S. Zakharenko, MD, PhD • Learning and memory, synaptic mechanisms of schizophrenia

Assistant Members
Fabio Demontis, PhD • Protein homeostasis and stress sensing in skeletal muscle aging
Young-Goo Han, PhD • Hedgehog signaling and primary cilia in brain development and tumorigenesis
Paul A. Northcott, PhD • Genomics and developmental biology of childhood brain tumors
Jamy C. Peng, PhD • Epigenetic regulation of stem cell functions

Research Associates
Myriam Labelle, PhD • The role of platelets in cancer metastasis
Liqin Zhu, PhD • Stem cells in normal liver development and malignancy

[1]No longer at St. Jude
[2]Secondary appointment

ACADEMIC DEPARTMENTS

EPIDEMIOLOGY & CANCER CONTROL

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

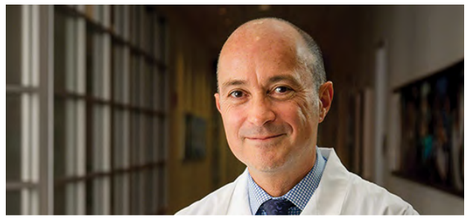
Members
Cheryl L. Cox, PhD • Health promotion, early/late effects of treatment
Daniel M. Green, MD • Adverse cardiac & reproductive effects of therapy
Melissa M. Hudson, MD[1]; Endowed Chair in Oncology – Cancer Survivorship • Health outcomes after childhood cancer
Kevin R. Krull, PhD • Neurocognitive outcomes of pediatric cancer
Kirsten K. Ness, PT, PhD • Functional limitations among cancer survivors
Yutaka Yasui, PhD • Genetics and risk of therapy-related outcomes

Associate Members
Gregory T. Armstrong, MD, MSCE • Pediatric neuro-oncology and cancer survivorship
I-Chan Huang, PhD • Patient-reported outcomes measurement after pediatric cancer

Assistant Members
Tara M. Brinkman, PhD • Psychosocial outcomes of pediatric cancer
Todd M. Gibson, PhD • Risk factors for late effects after pediatric cancer
Daniel A. Mulrooney, MD, MS[1] • Cardiovascular outcomes of cancer therapy
Rohit P. Ojha, DrPH • Infection-associated outcomes among childhood cancer survivors

Research Associates
Matthew J. Ehrhardt, MD, MS[1] • Late effects of childhood cancer therapy
Carmen L. Wilson, PhD • Late effects of childhood cancer therapy

Adjunct Members
Lisa M. Klesges, PhD • Behavioral epidemiology
Robert C. Klesges, PhD • Cancer prevention and control in adults & children



GLOBAL PEDIATRIC MEDICINE

Chair
Carlos Rodriguez-Galindo, MD, Four Stars of Chicago Endowed Chair in International Pediatric Outreach • Global medicine; pediatric solid tumors

Members
Sima Jeha, MD[1] • Childhood leukemias, developmental therapeutics
Monika L. Metzger, MD, MSc[1] • Hodgkin & non-Hodgkin lymphomas, leukemias, IOP
Ching-Hon Pui, MD[1]; Fahad Nassar Al-Rashid Endowed Chair in Leukemia Research • Biology and treatment of childhood leukemia

Associate Members
Miguela A. Caniza, MD[1] • Infection care & control, international outreach
Ibrahim A. Qaddoumi, MD, MS[1] • Low-grade gliomas, retinoblastoma, telemedicine

Assistant Member
Catherine G. Lam, MD, MPH[1] • International outreach, solid tumors, improving adolescent outcomes

GENETICS

Chair
Gerard C. Grosveld, PhD; Albert & Rosemary Joseph Endowed Chair in Genetics Research • The role of chromosome translocations in cancer

Members
Alessandra d'Azzo, PhD; Jewelers for Children Endowed Chair in Genetics and Gene Therapy • Intracellular degradation in development & disease
Peter J. McKinnon, PhD • DNA damage responses in the nervous system
Guillermo C. Oliver, PhD[2]

Associate Member
Beatriz Sosa-Pineda, PhD[2]

HEMATOLOGY

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

Members
Arthur W. Nienhuis, MD • Genetic therapy of hematological diseases
Brian P. Sorrentino, MD; Wall Street Committee Endowed Chair in Bone Marrow Transplant Research • Gene therapy and hematopoietic stem cell biology
Winfred C. Wang, MD • Sickle cell disease, bone marrow failure

Associate Members
Jane S. Hankins, MD, MS • Sickle cell disease, transfusional iron overload, transition to adult care
Ulrike M. Reiss, MD • Bleeding disorders, thrombosis, bone marrow failure

Assistant Members
Wilson K. Clements, PhD • Vascular/hematopoietic development & leukemia
Jeremie H. Estepp, MD • Thrombosis and anticoagulation, sickle cell disease
Shannon L. McKinney-Freeman, PhD • Mechanisms of hematopoietic stem cell development
Kerri A. Nottage, MD, MPH[2]

IMMUNOLOGY

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

Members
Hongbo Chi, PhD • Cellular signaling in innate and adaptive immunity
Peter C. Doherty, PhD; Nobel Laureate; Michael F. Tamer Endowed Chair in Immunology • Molecular and cellular analysis of $CD8^+$ T cells
Thirumala-Devi Kanneganti, PhD • Mechanisms of host defense and inflammation
Peter J. Murray, PhD[1] • Control of inflammatory responses

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

Assistant Members
Mark Bix, PhD[2]
Benjamin A. Youngblood, PhD • T-cell memory differentiation and exhaustion

INFECTIOUS DISEASES

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

Members
P. Joan Chesney, MD • Education and training; bacterial pathogenesis
Patricia M. Flynn, MD; Deputy Clinical Director; Arthur Ashe Endowed Chair in Pediatric AIDS Research • HIV/AIDS and infections in children with cancer
Walter T. Hughes, MD[3]
Julia L. Hurwitz, PhD • Vaccine-induced immunity
Suzanne Jackowski, PhD • Phospholipids and coenzyme A in health and disease
Peter J. Murray, PhD • Control of inflammatory responses
Charles O. Rock, PhD • Membrane phospholipid metabolism
Stacey L. Schultz-Cherry, PhD • Pathogenesis of influenza and astrovirus infection
Richard J. Webby, PhD • Influenza virus pathogenicity
Robert G. Webster, PhD[3]

Associate Members
Elisabeth E. Adderson, MD • Fellowship director, clinical trials management
Miguela A. Caniza, MD • International outreach
Aditya H. Gaur, MD, MBBS • Clinical research in pediatric HIV infection
Hans Haecker, MD, PhD • Signal transduction of Toll-like and TNF receptors
Charles J. Russell, PhD • Respiratory viruses: disease, cures, & prevention

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

Research Associates
Akinobu Kamei, MD • Innate and adaptive immunity to *Pseudomonas aeruginosa*
Amber M. Smith, PhD • Kinetic modeling of influenza and bacterial coinfection

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; Scott & Tracie Hamilton Endowed Chair in Brain Tumor Research • Novel treatments for children with brain tumors

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

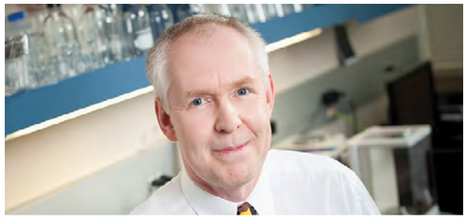
Associate Members
Gregory T. Armstrong, MD[1] • Pediatric neuro-oncology and cancer survivorship
Richard A. Ashmun, PhD[1] • Applications of flow cytometry & cell separation
Justin N. Baker, MD • Pediatric palliative and end-of-life care
Alberto Broniscer, MD • Biology and treatment of high-grade gliomas
Tania A. Gruber, MD, PhD • Pathogenesis of infantile leukemia
Hiroto Inaba, MD, PhD • New therapeutic strategies for leukemia
Ibrahim A. Qaddoumi, MD, MS • Low-grade gliomas, retinoblastoma, telemedicine
Carolyn Russo, MD • Palliative and supportive care

Assistant Members
Rachel C. Brennan, MD • Retinoblastoma, novel therapeutics, renal tumors
Patrick K. Campbell, MD, PhD • Histiocytic disorders; chronic myeloid leukemia
Sara M. Federico, MD • Drug development, pediatric soft-tissue sarcomas
Kevin W. Freeman, PhD • Genetic interactions that give rise to neuroblastoma
Charles Gawad, MD, PhD • Cellular and genetic origins of childhood cancers
Mark E. Hatley, MD, PhD • Origins of pediatric sarcomas
Chimene Kesserwan, MD • Cancer predisposition
Catherine G. Lam, MD, MPH • International outreach, solid tumors, improving adolescent outcomes
Deena R. Levine, MD • Pediatric palliative and end-of-life care
Daniel A. Mulrooney, MD, MS• Cardiovascular outcomes of cancer therapy
Giles W. Robinson, MD • Origin & genomics of medulloblastoma, translational studies
Karen D. Wright, MD[2]

Research Associates
Michael Bishop, MD • Osteosarcoma, bone and soft-tissue sarcomas, rhabdoid tumors
Matthew J. Ehrhardt, MD, MS • Late effects of childhood cancer therapy
Elizabeth Stewart, MD • High-risk pediatric solid tumors, preclinical translational research

[1]Secondary appointment
[2]No longer at St. Jude
[3]Emeritus

ACADEMIC DEPARTMENTS



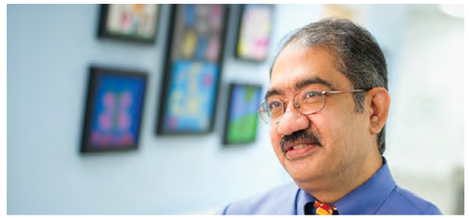
PATHOLOGY

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 • T-cell regulation, autoimmunity
Randall T. Hayden, MD • Clinical microbiology of immunocompromised hosts
Jesse J. Jenkins III, MD • Childhood tumor diagnosis by molecular techniques
Michael M. Meagher, PhD; Vice President, Therapeutic 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 • Genomic profiling of acute leukemia
Ching-Hon Pui, MD[1]; 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 • p53 function in tumor suppression & tumorigenesis

Associate Members
Armita Bahrami, MD • Pathology of bone and soft-tissue tumors
John K. Choi, MD, PhD • Transcription factors in acute leukemias
Tanja A. Gruber, MD, PhD[1] • Pathogenesis of infantile leukemia
Laura Janke, DVM, PhD • Pathology of mouse models of disease
Mondira Kundu, MD, PhD • Role of autophagy in erythroid maturation & anemia
Janet F. Partridge, PhD • Chromosome segregation, heterochromatin assembly
Richard J. Rahija, DVM, PhD • Animal models of human disease

Assistant Members
Elizabeth Azzato, MD, PhD • Molecular pathology and clinical genomics
Jeffrey M. Klco, MD, PhD • Genomic and functional characterization of acute myeloid leukemia
Vasiliki Leventaki, MD • genomic alterations in pediatric lymphomas
Leta K. Nutt, PhD • Metabolic regulation of cancer cell death
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 • Investigative pathology of human cancers



PEDIATRIC MEDICINE

Interim Chair
Amar J. Gajjar, MD[1]; Scott & Tracie Hamilton Endowed Chair in Brain Tumor Program • Novel treatments for children with brain tumors

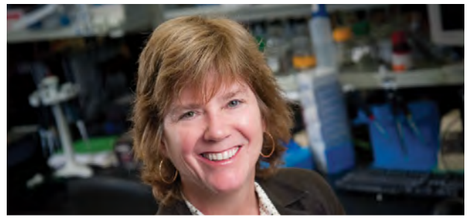
Anesthesiology
Doralina L. Anghelescu, MD • Pain management, anesthesia risks, palliative care
Kyle J. Morgan, MD • Palliative care, NSAIDS after bone marrow transplantation
Luis A. Trujillo Huaccho, MD • Regional anesthesia & anesthetic approach in high-risk cases
Becky B. Wright, MD • Pain management techniques, peripheral nerve blocks

Critical Care Medicine
R. Ray Morrison, MD; Chief • Pediatric critical care, myocardial protection
Lama Elbahlawan, MD • Pediatric critical care, acute lung injury

Endocrinology
Wassim Chemaitilly, MD; 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 Mandrell, PhD, RN, PNP; Director • Biological mechanism of symptoms associated with cancer and cancer therapy



PHARMACEUTICAL SCIENCES

Chair
Mary V. Relling, PharmD; 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 • Mechanisms of human variation in drug response
John D. Schuetz, PhD •Regulation & function of ABC transporters
Clinton F. Stewart, PharmD • Pharmacology of anticancer drugs in children

Associate Members
Sharyn D. Baker, PharmD, PhD[2]
James M. Hoffman, PharmD • Medication safety and outcomes
Alex Sparreboom, PhD[2]
Jun J. Yang, PhD • Pharmacogenomics of anticancer agents & drug resistance

PSYCHOLOGY

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

Members
Melissa M. Hudson, MD[1]; Endowed Chair in Oncology – Cancer Survivorship • Health outcomes after childhood cancer
Kevin R. Krull, PhD[1] • Neurocognitive outcomes of pediatric cancer

Associate Members
Heather M. Conklin, PhD • Cognitive outcomes of childhood cancer treatment
James L. Klosky, PhD • Health behaviors in cancer survivorship

Assistant Members
Tara M. Brinkman, PhD[1] • Psychosocial outcomes of pediatric cancer
Valerie M. Crabtree, PhD • Sleep disruptions in children with cancer
Lisa M. Ingerski, PhD[2]
Jerlym S. Porter, PhD, MPH • Transition from pediatric to adult care in sickle cell disease
Jane E. Schreiber, PhD • Neurobehavioral functioning in children with medical disorders

Research Associates
Lisa M. Jacola, PhD • Neurobehavioral outcomes in children treated for cancer
Victoria W. Willard, PhD • Social outcomes in children with cancer

RADIATION ONCOLOGY

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

Member
Larry E. Kun, MD; Clinical Director; John & Lorine Thrasher Endowed Chair in Radiation Oncology • Improving diagnosis and therapy of brain tumors

Associate Members
Jonathan B. Farr, PhD • Proton therapy and dosimetry
Chia-Ho Hua, PhD • Image-guided radiation therapy and normal tissue effects
Matthew J. Krasin, MD • Developing radiation therapy strategies and toxicity profiles for pediatric sarcomas

Assistant Members
John T. Lucas Jr., MS, MD • Brain tumors, neuroblastoma, proton therapy, clinical trial design
Christopher L. Tinkle, MD, PhD • Brain tumors and sarcomas
Weiguang Yao, PhD • Proton therapy and cone beam computed tomography

STRUCTURAL BIOLOGY

Chair
Stephen W. White, DPhil; Endowed Chair in Structural Biology • DNA repair, catalysis, and structure-based drug discovery

Members
Richard W. Kriwacki, PhD • Structural basis of tumor suppressor function
Brenda A. Schulman, PhD; Dr. Joseph Simone Endowed Chair in Basic Research • Cellular regulation by ubiquitin-like proteins

Associate Members
Donald Bashford, PhD[2]
Eric J. Enemark, PhD • Molecular mechanisms of DNA replication
Junmin Peng, PhD • Application of proteomics to ubiquitin biology and human disease

Assistant Member
Tanja Mittag, PhD • Dynamic protein complexes in signal transduction

Research Associate
Tudor Moldoveanu, PhD • Programmed cell death in health and disease

SURGERY

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

Members
Bhaskar N. Rao, MD • Surgical management of sarcomas and rare tumors
Stephen J. Shochat, MD[3]

Assistant Members
Israel Fernandez-Pineda, MD • Musculoskeletal sarcomas, vascular tumors, minimally invasive surgery
John A. Sandoval, MD[2]

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

Adjunct Members
Frederick A. Boop, MD; St. Jude Chair in Pediatric Neurosurgery
Barrett G. Haik, MD, FACS • Diagnosis and treatment of ophthalmic cancers
Mary Ellen Hoehn, MD • Pediatric ophthalmology
Paul D. Klimo Jr., MD • Pediatric neurosurgery
Max Langham, MD; St. Jude Chair in General Pediatric Oncological Surgery
Michael D. Neel, MD • Pediatric orthopedic oncology
Jerome W. Thompson, MD, MBA • Pediatric otolaryngology
Robert D. Wallace, MD • Pediatric plastic surgery
Mark Williams, MD[2]
Matthew W. Wilson, MD; St. Jude Chair in Pediatric Ophthalmology

[1]Secondary appointment
[2]No longer at St. Jude
[3]Emeritus

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Bing Bai, PhD, Structural Biology
Jesse Bakke, PhD, Chemical Biology & Therapeutics
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Julia Behnke, PhD, Tumor Cell Biology[1]
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Wenting Zheng, PhD, Pathology

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Esther Knapp, MD
Arun Modi, MD[1]
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Malek Baassiri, MD
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NEURO-ONCOLOGY FELLOWS
Omar Chamdine, MD[1]
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Anna Vinitsky, MD

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Chi Zhang, Structural Biology
Yunqian Zhao, Pathology
Yumei Zheng, Structural Biology
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[1]No longer at St. Jude
[2]Promoted to staff position

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[1]No longer a member
[2]Nonelected member
[3]July–December, 2015
[4]Ex officio voting member
[5]January–June, 2015

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[1]January–October, 2015
[2]No longer at St. Jude
[3]October–December, 2015
[4]November–December, 2015

This panel of physicians and scientists, serving during 2015, fostered the institution's development through discussion with faculty members, reports to the Board of Governors, and advice to the President and CEO on scientific and clinical research directions.

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OPERATIONS & STATISTICS

OPERATIONS	
Operating expenses[1]	$745.3 million
Number of employees[2]	4073
RESEARCH STATISTICS	
Grant funding[1]	$98.4 million
Peer-reviewed original research publications	660
Faculty members	252
Postdoctoral fellows	309
Clinical residents and fellows[3]	206
Graduate research scholars	82
CLINICAL STATISTICS	
Number of beds[4]	68
Outpatient encounters[5]	291,953
Inpatient admissions	3177
Total inpatient days	17,813
Patients enrolled on therapeutic trials	1186
Patients enrolled on nontherapeutic trials	6016 on prospective trials
	1843 on tissue-banking protocols
	8061 on retrospective protocols
Number of protocols open to accrual in 2015	788
Number of active therapeutic trials	216
Number of active nontherapeutic trials	196 prospective trials
	5 tissue-banking protocols
	572 retrospective protocols

[1]Data represents the period July 1, 2014 – June 30, 2015.
[2]Data is from July 1, 2015.
[3]Data includes 65 full-time St. Jude fellows and 141 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.

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Departments of Scientific Editing
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St. Jude Children's Research Hospital

ALSAC • Danny Thomas, Founder

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