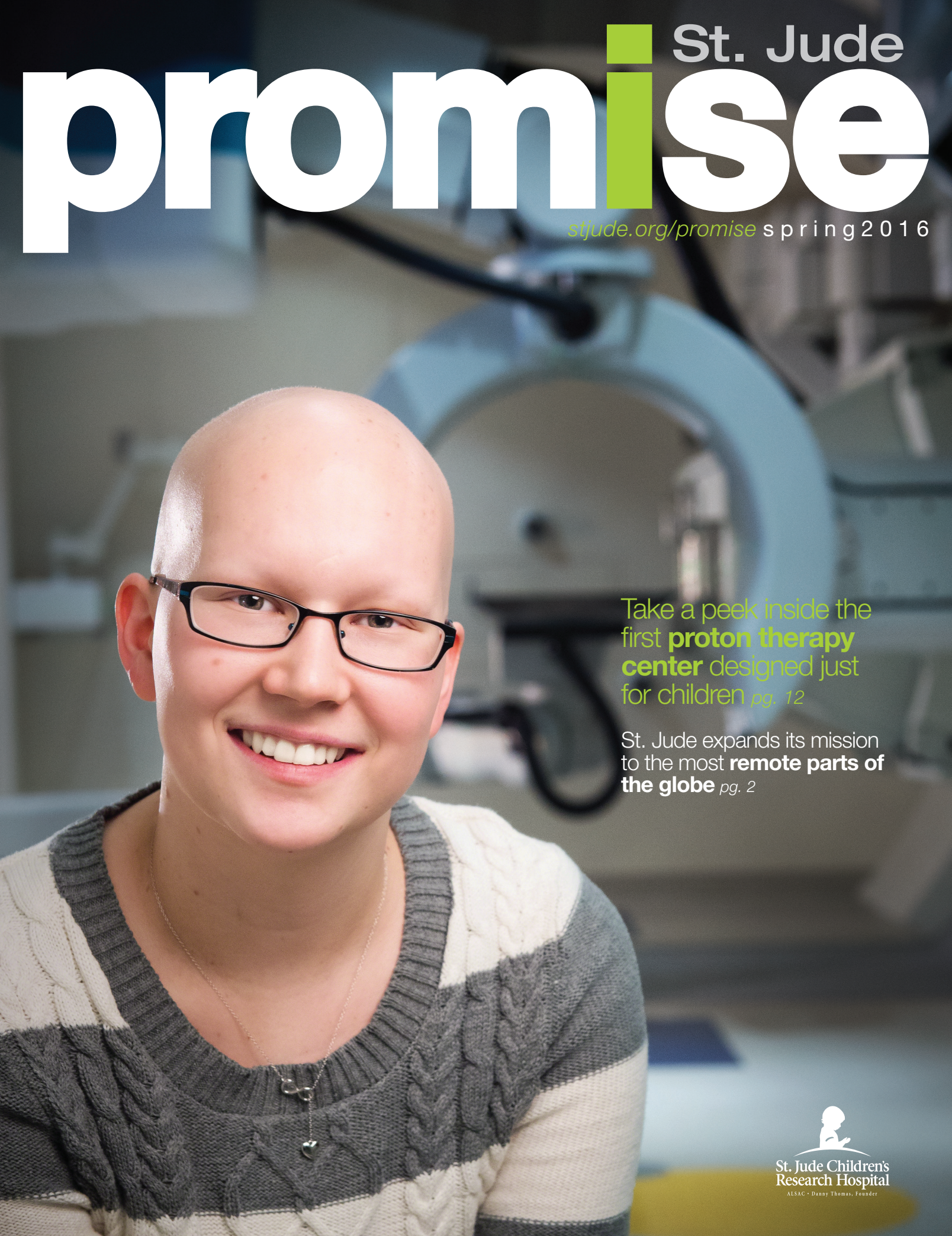

St. Jude promise

stjude.org/promise spring2016

Take a peek inside the first **proton therapy center** designed just for children *pg. 12*

St. Jude expands its mission to the most **remote parts of the globe** *pg. 2*

St. Jude Children's Research Hospital
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SPRING 2016

Research Highlights

On the cover:
Kennedy Adamowich
Photo by Peter Barta

The mission of St. Jude Children's Research Hospital is to advance cures, and means of prevention, for pediatric catastrophic diseases through research and treatment.

Taking St. Jude to the

In a daring new initiative, St. Jude prepares to take its research and clinical care to the 80 percent of kids worldwide who lack access to quality cancer care.

By Ginger H. Porter

SETH DIXON

Carlos Rodriguez-Galindo, MD, St. Jude executive vice president and Global Pediatric Medicine chair

WORLD

The little boy with the liquid brown eyes is shy and solemn as he awaits his turn for treatment in an El Salvador cancer clinic. Thanks to a partnership with St. Jude Children's Research Hospital, he has a fighting chance at surviving his disease. But that scenario is not the case for tens of thousands of other children in low- and middle-income countries worldwide.

This year, more than 80 percent of all children with cancer in the U.S. will be cured. That's great news. But Carlos Rodriguez-Galindo, MD, St. Jude executive vice president and Global Pediatric Medicine chair, has fixed his gaze on the horizon—far beyond the hospital's campus.

"We do very well, but we are only reaching out to a small percentage of children with cancer in the world," he says. "About 80 percent of children with cancer worldwide don't have access to the St. Jude level of care. And that gap is only going to increase as the numbers of children with cancer continue to rise in the developing world.

"Solving the global pediatric cancer problem," he says, "is the next frontier."

Extending the reach

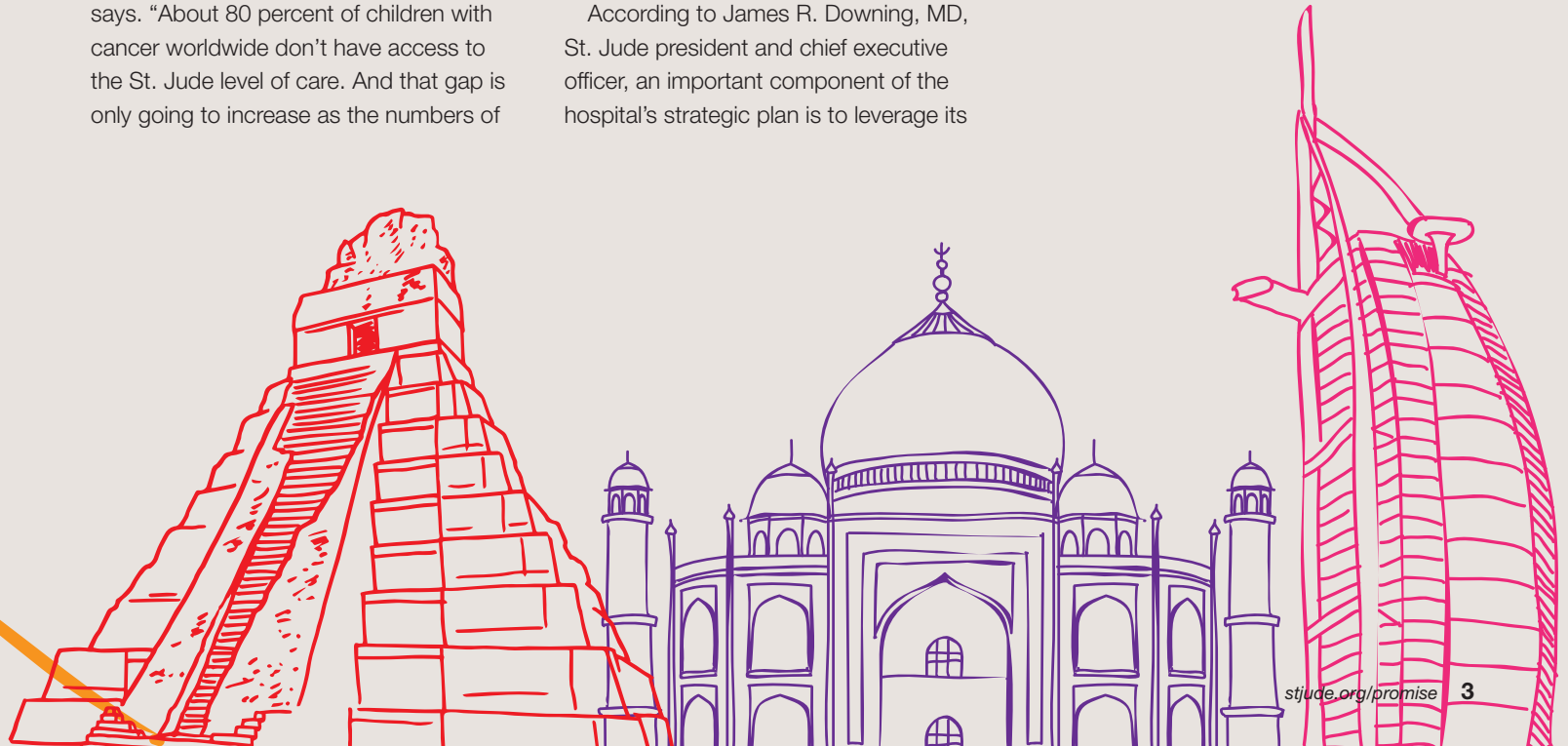
St. Jude has spent more than five decades perfecting its approach to pediatric cancer treatment. Technology, developmental therapeutics, surgeries, multidisciplinary approaches, child psychological support and family services are customized for each patient. The hospital's research and clinical care has been shared with hospitals around the world, and patients have come to St. Jude from many countries.

But now, the mission is expanding, as St. Jude extends its medical footprint to the farthest reaches of the Earth.

According to James R. Downing, MD, St. Jude president and chief executive officer, an important component of the hospital's strategic plan is to leverage its resources, position and knowledge to accelerate progress worldwide.

"We are in a position to set up global collaborations—big efforts others can't do," he explains. "We want to define how to treat cancer patients across the globe and

PETER BARTA



teach clinicians and investigators around the world how to do this."

Children first

Throughout his career as a pediatric oncologist, Rodriguez-Galindo has always had a simple goal: "I want to bring my expertise and my knowledge to all children, regardless of where they are.

"How can we develop treatments to do that?" he says. "That's the major challenge."

For nearly two decades, the hospital has gradually increased its international presence, establishing 24 partner sites in 17 countries. The progress has been extraordinary, but thousands of children in countries around the world still lack access to adequate diagnosis and care.

Building on existing successes, the hospital's new initiative, St. Jude Global, will address that challenge. St. Jude staff will develop models to advance the quality of research and care to children everywhere. Local and regional leaders in developing countries will be trained and fostered. St. Jude will also provide educational tools for program growth and research, while creating an infrastructure to sustain that growth.

"My hope is that by the end of the next decade, we will have been able to guarantee access to quality care to all children with cancer in the world," Rodriguez-Galindo says.

Beyond twinning

Previously, the hospital's international outreach efforts relied on a model called twinning to develop partnerships with medical institutions in other countries. This process pairs St. Jude experts with local health providers and community leaders in other countries, sharing expertise and promoting self-sufficiency.

"This is a very effective approach, but we need to go beyond that," Rodriguez-Galindo says. His aim is to provide measurable outcomes to check program progress and to be more strategic. One way to do that will be through developing new consortia, or regional networks, that encompass not only education and regional capacity building, but also research methods.

There are many questions that keep Rodriguez-Galindo up at night.

"Is the cancer we're seeing in the Middle East or Africa or Central America the same that we see here?" he asks. "Are the causes of cancer different? Do ethnic or racial backgrounds or environmental factors determine what kinds of cancer we see? How can we improve access to care to all children with cancer and blood disorders in the world in a way that is sensitive to the socioeconomic environment without lowering our aims? How can we develop new models for care and bring innovation to the bedside? And most importantly, how can we do all this without losing our patient-centered approach?"

Answering those kinds of questions is the job of the new Global Pediatric Medicine Department.

"We need to have a corps of physicians or researchers who can generate these kinds of answers and then help build programs and strategize at regional and national levels," Rodriguez-Galindo says.

He aims to recruit faculty whose focus will be to conduct research in global health, with the ultimate goal of improving access to care and quality of care for all children with cancer and blood disorders.

A true global alliance

The St. Jude Global Alliance will consist of the following consortia created by

STACEY SCHULTZ-CHERRY, PHD

"We are in a position to set up global collaborations—big efforts others can't do."

– James R. Downing, MD
St. Jude president and chief executive officer


PETER BARTA

"If anyone has the capacity, the vision, the mission and the dream to reach every single child in the world, it's St. Jude."

– Carlos Rodriguez-Galindo, MD

St. Jude during the past two decades as well as newly created partnerships:

- **The Asociación de Hemato-Oncología Pediátrica de Centro América (AHOPCA)** provides education and training and fosters pediatric cancer collaborations throughout Guatemala, Honduras, El Salvador, Nicaragua, Costa Rica, the Dominican Republic and Panama. The organization has standardized treatment regimens across participating institutions, with thousands of children treated on AHOPCA-funded clinical trials.
- **The Pediatric Oncology East and Mediterranean Group (POEM)** is a network of physicians, scientists and health care professionals from more than 50 childhood cancer centers across the Middle East, northern Africa and southern Asia. The network includes St. Jude partner sites in Armenia, Bahrain, Egypt, India, Iraq, Iran, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Palestine, Saudi Arabia, Syria, Tunis, Turkey, United Arab Emirates and Yemen.
- **The National Childhood ALL Study Group in China** has been created to ensure that Chinese children with acute lymphoblastic leukemia (ALL) receive the best possible treatment. Since 2005, St. Jude has collaborated with physicians at Beijing Children's Hospital and Shanghai Children's Medical Center. Those efforts led to establishment of the National Childhood ALL Study Group in 2014. Through that initiative, 20 medical institutions in China will treat 1,200 to 1,500 children with ALL per year.
- **The Consorcio Latinoamericano de Enfermedades Hematooncológicas Pediátricas (CLEHOP**) was born as a result of the success of AHOPCA's program for the treatment of children with Hodgkin disease. Those excellent results triggered interest to extend this work to other parts of Latin America. CLEHOP integrates collaborative groups from Argentina, Peru, Ecuador, Mexico, Venezuela and Brazil to expand beyond the treatment of Hodgkin disease and become a true Latin American cooperative group.
- **The Prevencionistas e Infectólogos para Cáncer Infantil en América Latina (PRINCIPAL)** consortium integrates 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.
- **New consortia** will be created in the near future. For instance, plans are in the works to create and strengthen groups similar to AHOPCA in Southeast Asia and South America. These consortia will integrate regional capacity-building strategies, training programs and research to improve the care and increase the cure rates of children with cancer and blood disorders.

No corner unexplored

The hospital's goals are ambitious and bold—but Rodriguez-Galindo believes they are achievable.

"We are prioritizing the global approach to childhood cancer, taking St. Jude to the world," he says. "But at the end of the day, our outcomes will be about patients. We do what we do because of the kids; they are the ones who inspire us.

"If anyone has the capacity, the vision, the mission and the dream to reach every single child in the world, it's St. Jude." ■

Tyler's Treehouse

A little boy's legacy may help save the lives of kids with a rare brain tumor.

By Rachel Schwartzberg

This year marks the 10th anniversary of the passing of Tyler Scott, a small boy who left a giant legacy. Through a foundation his family created, Tyler has touched the lives of children he would never have had the chance to meet.

In 2006, 5-year-old Tyler began having problems with his hand. Soon his family learned he had an extremely rare and aggressive brain tumor known as diffuse intrinsic pontine glioma (DIPG). Doctors suggested that Howard and Dana Scott take their son to St. Jude Children's Research Hospital.

"From the moment we arrived at St. Jude, we felt we were in good hands," Dana says. "The entire staff was wonderful. We felt they were truly invested in our child—above and beyond what we might have expected."

Unfortunately, St. Jude doctors had to deliver terrible news: "There was really nothing they could do for him," Howard says. "They worked hard on getting him home, so his brothers could say goodbye."

Because of its location, DIPG is virtually impossible to remove or biopsy—and therefore little was known about it. After Tyler's death, his parents allowed St. Jude researchers to use tissue from his tumor as part of a study to learn more about the disease.

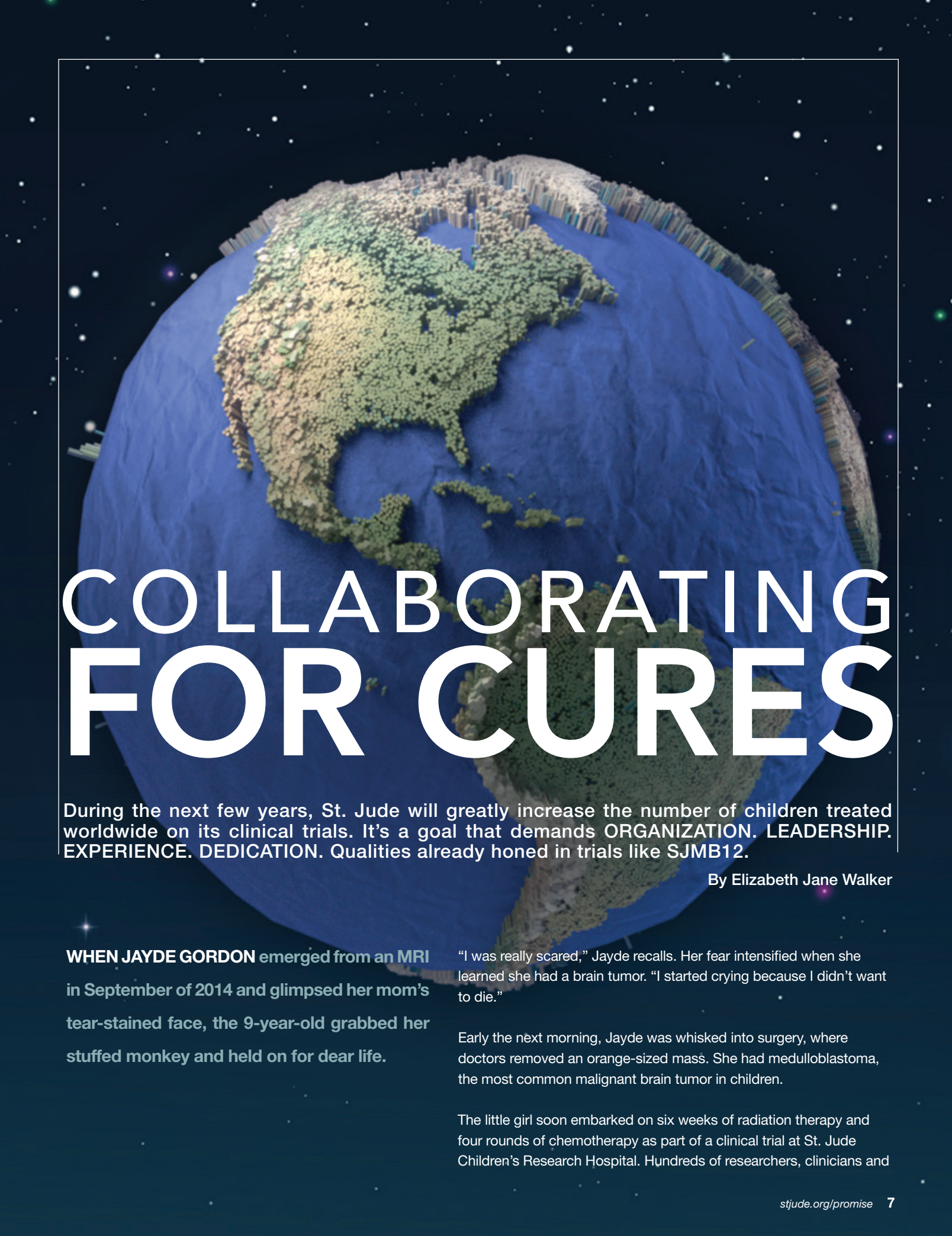
The Tyler's Treehouse Foundation—named for the tree house that friends constructed to fulfill Tyler's last wish—funds further research into DIPG.

The Scott family and their friends host Tyler's Treehouse fundraisers, such as a 5K run and pool party, and a golf tournament and auction.

"The foundation plans to provide a grant to St. Jude every year until they find a cure," Howard says.

The Scotts and their sons, Chase, Bryce and Aidan, are gratified to know that Tyler's Treehouse is helping "accelerate timelines," as Howard puts it.

"St. Jude is now growing tumor samples in the lab and hitting them with different drugs to see what works," Howard says. "Researchers at St. Jude have also discovered a common mutation found in the DIPG tumors from most children with the disease. The scientists are looking for more targeted treatments to offer hope to these children and families. We're proud to be part of that." ■



COLLABORATING FOR CURES

During the next few years, St. Jude will greatly increase the number of children treated worldwide on its clinical trials. It's a goal that demands ORGANIZATION. LEADERSHIP. EXPERIENCE. DEDICATION. Qualities already honed in trials like SJMB12.

By Elizabeth Jane Walker

WHEN JAYDE GORDON emerged from an MRI in September of 2014 and glimpsed her mom's tear-stained face, the 9-year-old grabbed her stuffed monkey and held on for dear life.

"I was really scared," Jayde recalls. Her fear intensified when she learned she had a brain tumor. "I started crying because I didn't want to die."

Early the next morning, Jayde was whisked into surgery, where doctors removed an orange-sized mass. She had medulloblastoma, the most common malignant brain tumor in children.

The little girl soon embarked on six weeks of radiation therapy and four rounds of chemotherapy as part of a clinical trial at St. Jude Children's Research Hospital. Hundreds of researchers, clinicians and

> "We are using this combined approach to assess risk—a first in North America—to match patients with the radiation dose, chemotherapy agents or novel therapies targeting specific subtypes that we believe offers the best hope for long, rewarding lives."
>
> — Amar Gajjar, MD
> St. Jude Neuro-Oncology director
> *(pictured with Damien Chiasson-Larson)*

other professionals had toiled for years to create this study, which is helping to find new treatments for young patients with medulloblastoma.

Accelerating progress

The St. Jude clinical trial in which Jayde enrolled is headed by Amar Gajjar, MD, director of St. Jude Neuro-Oncology, and Giles Robinson, MD, of St. Jude Neuro-Oncology. That study, known as SJMB12, is offered at St. Jude and 20 collaborating centers spread from the U.S. and Canada to Australia and New Zealand.

By including other institutions in studies such as SJMB12, St. Jude can gather data more quickly and accelerate progress toward cures.

During the next six years, St. Jude plans to double the number of non-St. Jude patients enrolled in collaborative studies such as this one. What is involved in creating such a project? Years of research. Mountains of paperwork. Teams of dedicated professionals united by a common goal.

It's an undertaking of mammoth proportions—but for the scientists, staff and families involved, it's well worth the effort.

Subtypes and survival

When Jayde was born in March of 2005, St. Jude scientists were already conducting research that would one day help save her life. Researchers soon proved that medulloblastoma was not one disease—as scientists had always assumed—but had four distinct subtypes caused by specific genetic mutations. Those subtypes are named sonic hedgehog (SHH), wingless (WNT), Group 3 and Group 4. Survival rates vary widely from one subtype to another.

"In the past, some patients did very well and some did poorly—and we didn't know why," Gajjar says. "Subtypes help explain why cure rates varied so widely."

Children with medulloblastoma once received one-size-fits-all treatment. But now therapy could be based partially on subtype. Children with the WNT subtype, such as Jayde, might be cured with less-intensive treatment, allowing them to avoid many of the long-term side effects that plagued earlier generations of patients. Kids with more aggressive subtypes could receive more intensive treatment, increasing their chances for cures.

Armed with these new findings, scientists and clinicians teamed up to create a sophisticated clinical trial, named SJMB12. This study would take into account the subtype as well as other factors, such as whether the tumor could be surgically removed, what the tumor looked like under the microscope, and whether the cancer had spread to other parts of the brain and spinal cord.

"We are using this combined approach to assess risk—a first in North America—to match patients with the radiation dose, chemotherapy agents or novel therapies targeting specific subtypes that we believe offers the best hope for long, rewarding lives," Gajjar says.

From lab to clinic

Many research studies fed into the SJMB12 clinical trial. For instance, Robinson and his colleagues discovered that a targeted therapy used to treat skin cancer was also effective against the SHH subtype of medulloblastoma in adults. Now St. Jude patients with the SHH subtype receive that medication as part of treatment.

"This is the first targeted therapy for medulloblastoma," Robinson explains. "Targeted therapy is potentially very exciting because, as the name implies, it's hitting a specific target. It may have less toxicity than previous treatments."

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Martine Roussel, PhD, of St. Jude Tumor Cell Biology, worked with Anang Shelat, PhD, of St. Jude Chemical Biology and Therapeutics, to pinpoint two other drugs that were ultimately featured in SJMB12. And Clinton Stewart, PharmD, of St. Jude Pharmaceutical Sciences, led experiments to determine the exact doses of drugs to use in the clinical trial. (See related story in summer 2014 *Promise*.)

Marshaling the troops

An army of doctors, researchers, nurses, project managers and other staff members helped write the clinical trial, negotiate the use of drugs used in the study and manage the thousands of details that accompany a project of this magnitude.

An internal scientific review committee, the St. Jude Institutional Review Board, and industry and government agencies weighed in to ensure the trial was scientifically sound and met safety regulations. Teams of St. Jude staff created the study's infrastructure, which included building an electronic database and entering orders into the electronic medical record.

For an international clinical trial like SJMB12, St. Jude employees carefully select collaborating sites. They visit each location in person to ensure that the institutions have the experience required to run a sophisticated study, have access to electronic medical records, possess essential equipment and facilities, and can provide top-notch clinical care. Throughout the trial, St. Jude employees work closely with the collaborating centers to ensure that the trial proceeds smoothly.

> Because medulloblastoma affects a relatively small number of children worldwide, progress is accelerated when institutions work together.

Because medulloblastoma affects a relatively small number of children worldwide, progress is accelerated when institutions work together.

"The more sites you have, the faster you can complete your trial," explains Mary Griffin of St. Jude Neuro-Oncology. "A multi-institutional trial like SJMB12 requires a lot of time and effort to develop. But it allows St. Jude to expedite enrollment and it allows the other facilities to offer this therapy to patients in their areas.

"It's a huge operation," Griffin continues, "involving more than 100 people at St. Jude. From initial concept to enrolling the first patient can take about a year and a half. We're working to compress our timeline for future studies."

A global consortium

The infrastructure and expertise used in St. Jude collaborative trials such as SJMB12 will soon be expanded and enhanced as the hospital invites a dozen of the world's top pediatric programs to help develop similarly complex clinical trials for some of the toughest cancers.

"For some childhood cancers, each institution might see only a couple of cases a year," observes James R. Downing, MD, St. Jude president and chief executive officer. "Individually, nobody can make much progress. But if St. Jude leads a consortium of institutions to design these protocols and run them, we can make the kind of progress that nobody has been able to make before."

Building on success

Jayde Gordon is the walking, talking, dancing beneficiary of St. Jude research and clinical care. Because she had the WNT subtype of medulloblastoma, she received reduced doses of chemotherapy and radiation therapy. Even so, the treatment was challenging.

"Chemo is the worst," she proclaims. "It was not fun."

Now 11 years old, Jayde *(pictured on page 11)* returns to St. Jude for checkups every three months. She and her mom say it's like going home.

"St. Jude is family now and always will be," says Jayde's mother, Kristy Pelt. "You cannot find a more loving and compassionate and caring staff. And the fact that it's a research hospital is so important to us."

Kristy knows the research conducted at St. Jude helped save her daughter's life. And Jayde's participation in SJMB12 will help doctors create even better treatments for children worldwide.

"I know I didn't coin the phrase," Kristy says, "but St. Jude is the best place you never want to be." ■

ANN-MARGARET HEDGES

> "Targeted therapy is potentially very exciting because, as the name implies, it's hitting a specific target. It may have less toxicity than previous treatments."
>
> — Giles Robinson, MD
> St. Jude Neuro-Oncology
> *(pictured with Totti Do)*

PETER BARTA

ONE STUDY, MANY FACETS

The SJMB12 clinical trial evaluates many issues that arise as children move through treatment, such as:

Learning and memory. As survival rates have improved, quality-of-life issues have become crucial. SJMB12 addresses some of those aspects, including fatigue, as well as learning and memory problems. Heather Conklin, PhD, of St. Jude Psychology, and her colleagues are working to alleviate the learning and memory issues of many brain tumor survivors. To do that, researchers are using a computer program specially designed to increase attention, working memory and processing speed. (See related story in winter 2016 *Promise.)*

Cardiac fitness and cognitive health. Kiri Ness, PhD, of St. Jude Epidemiology and Cancer Control, designed a 12-week exercise intervention designed to improve aerobic fitness in SJMB12 participants. "It's prescribed based on the children's individual abilities so nearly any child can participate no matter how tired they feel. We also have hope that it will improve their cognitive health," Ness explains. "We want to encourage these kids early to be physically active and remain so throughout their lives."

Children in the exercise component also wear a device that measures their physical activity and sleep. "We'd like to prevent long-term side effects, as opposed to having to remediate problems when survivors show up with them later in life," Ness says.

Checking connections. Researchers have found that medulloblastoma patients experience changes in the white matter tracts that connect different regions of the brain. Gene Reddick, PhD, of St. Jude Diagnostic Imaging, uses a process called diffusion tensor imaging to assess those connection patterns, determine how they differ from those of healthy children, and pinpoint how the connections change during treatment.

A new way to identify subtypes. According to Zoltan Patay, MD, PhD, of St. Jude Diagnostic Imaging, each medulloblastoma subtype may be unique in appearance and location of origin. Patay is cataloging the appearance and locations of these subtypes so that clinicians worldwide can more easily diagnose the subtypes and determine treatment.

Making predictions. Julie Harreld, MD, of Diagnostic Imaging, uses magnetization transfer imaging to look at gray matter, the tissue where information is processed in the brain. She and her colleagues use this technique to pinpoint the areas that have been damaged relative to others.

"The nice thing is that a lot of these imaging objectives use the same imaging sequences," Harreld says. "So we are very efficient in using those sequences to investigate many things."

PHOTOS BY ANN-MARGARET HEDGES

Julie Harreld, MD (at left) and Gene Reddick, PhD, use high-tech imaging techniques to examine changes that occur in the brains of children with medulloblastoma.

Kiri Ness, PhD, has designed a 12-week exercise intervention to improve aerobic fitness in children like 9-year-old Jaycee Richard.

Jayde Gordon

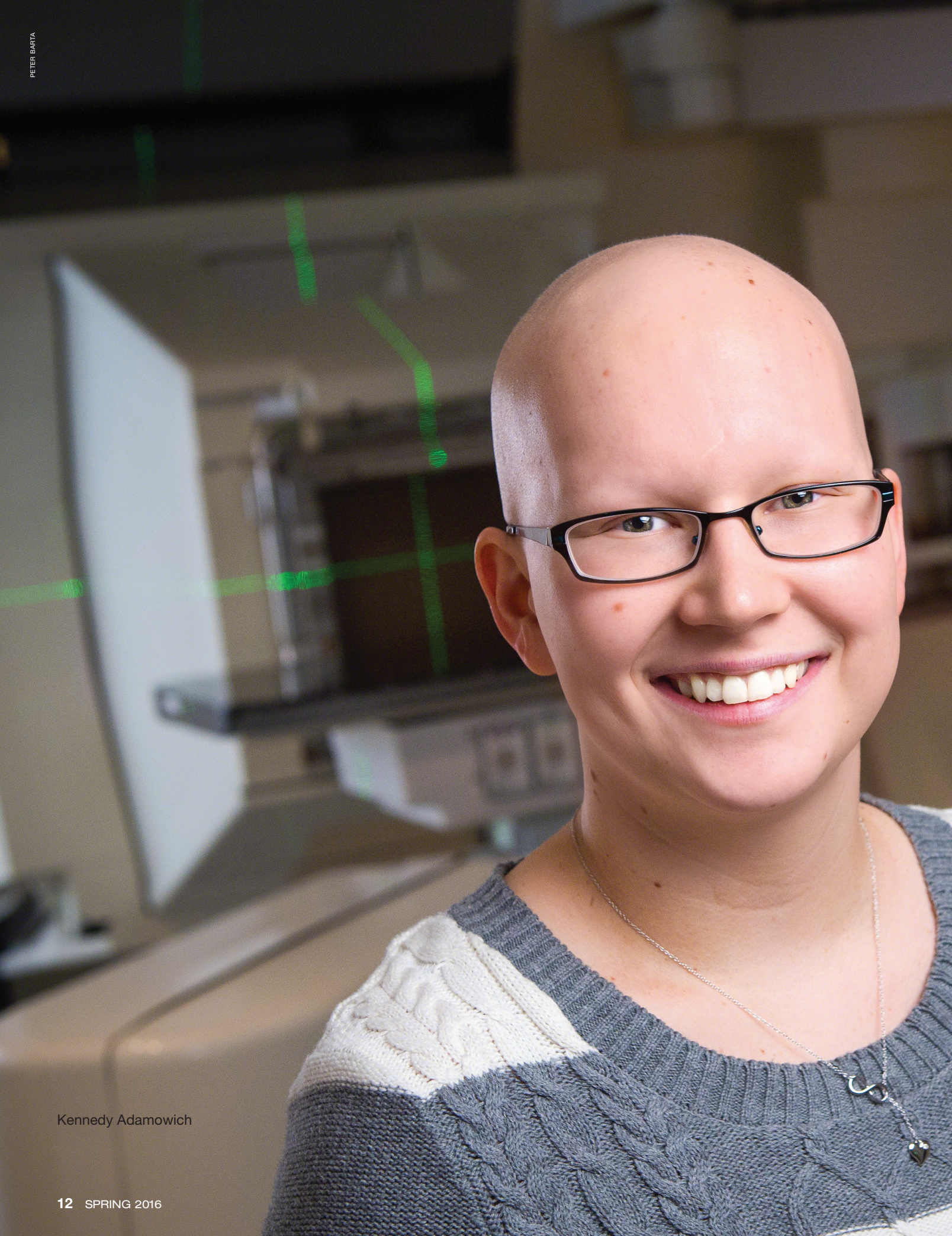
THE RESEARCH CONTINUES

In the first months of 2016, St. Jude scientists published studies that shed new light on two subtypes of medulloblastoma:

Martine Roussel, PhD, and **BaoHan Vo, PhD**, both of St. Jude Tumor Cell Biology, worked with colleagues in Germany to identify a protein interaction that leads to Group 3 medulloblastoma, the subtype with the worst prognosis. A report on this research appeared in the journal *Cancer Cell*. The scientists found that a protein called Miz1 binds to the Myc protein to drive the cancer's growth. St. Jude researchers are working to discover drugs that target this interaction and stop the spread of Group 3 tumors.

Paul Northcott, PhD, of St. Jude Developmental Neurobiology, led an international research team that pinpointed cells that likely give rise to Group 4, the most common subtype of medulloblastoma. About half of all children with medulloblastoma have this subtype. The finding will likely help scientists develop more effective targeted therapies against Group 4 tumors. Scientists working on the project also identified a new pathway that may drive Group 3 tumors. Results of the study were published in the scientific journal *Nature*.

PETER BAPTA



Kennedy Adamowich

think POSITIVE

By Elizabeth Jane Walker

St. Jude opens the first proton therapy center just for children.

Kennedy Adamowich is an optimistic young woman. So it's no surprise that she would be the first patient at St. Jude Children's Research Hospital to receive a treatment that involves positively charged particles—protons—to treat cancer.

Last summer, a scan revealed massive tumors in Kennedy's hip and lung. When local physicians estimated her survival odds as between 5 and 20 percent, the news pierced her mom's heart like a blade.

"Stop crying," the pragmatic teen said to her mom. "I need you to call my work and tell them I won't be in.

"It hit my family harder than it hit me," Kennedy explains. "My attitude was that it's going to work out fine."

Kennedy soon learned St. Jude was putting finishing touches on the world's only proton therapy center designed solely for the treatment of children. And she would be the first person to benefit from that treatment.

PHOTOS BY PETER BARTA

The power of protons

Just as a spider shoots a gossamer line with incredible accuracy, the St. Jude proton therapy equipment propelled sub-atomic particles into Kennedy's tumor with phenomenal precision. This level of accuracy also minimized damage to her healthy tissues and organs.

Located 60 feet underground, the new St. Jude Red Frog Events Proton Therapy Center harnesses the power of protons to treat brain tumors, Hodgkin lymphoma and other solid tumors. Kennedy compares the treatment area to a spaceship from a sci-fi movie.

"The machine that takes my scans looks like a little port that you can pass through and it will transport you somewhere," she says. "They even play the *Star Wars* theme song to clear everybody out of the room before the treatment begins."

Opened last fall, the $90 million facility is an engineering marvel in which success relies on both dizzying speed and absolute stillness. Protons moving at 60 percent the speed of light must hurtle toward a target that is utterly still and precisely positioned.

In order to be effective, protons must be accelerated to extremely high speeds. Created from hydrogen gas and guided through a linear accelerator, the protons then pass into a circular device called a synchrotron. The particles whirl around the synchrotron 8 million times per second—the equivalent of 4.5 revolutions of the earth per second. The emerging proton beams attack tumors with exquisite control, thanks to a three-story-tall, 100-ton framework called a gantry, which enables 190-degree rotation around the patient.

Unlike traditional radiation therapy, which passes through both tumor and the healthy tissue beyond it, proton therapy enables clinicians to "paint" the dose, layer by layer, stopping at the tumor's edge.

Although the proton beam is impressive, Thomas Merchant, DO, PhD, St. Jude Radiation Oncology chair, says it is only one component of a remarkable system.

"It's not just the beam," he explains. "It's everything that surrounds it: How the patient is set up, how the dose is calculated, the imaging that we use to confirm the position of the patient. There's no room for error here."

Sub-millimeter accuracy

Today, one of the hospital's three proton therapy rooms throbs like an artery, rock music pulsing as a new patient, Breydon Hammer, undergoes a rehearsal for treatment that will begin next week. The teen has chosen tunes that put him at ease during the session, in which he discusses his upcoming treatment with a Child Life specialist, two radiation therapists, a radiation oncologist and a radiation physicist. Once all of Breydon's questions have been answered, he climbs onto the treatment table, nestling into a foam couch that has been customized for his body. An individualized mask stabilizes his head.

As Merchant watches the interaction, he points out attributes of the new system.

"Our verification imaging system is entirely novel," he observes. "We have the first gantry-independent, robotic cone-CT system ever deployed in a proton therapy setting in the U.S."

Once Breydon is situated, the only movement is his index finger, tapping a staccato beat as staff members continue their adjustments. Soon, the cone beam CT scanner will produce a 3-D image of his brain.

Clinicians will compare those images to previous scans to ensure that Breydon is in the exact spot for treatment. If minor tweaks are necessary, an automatic patient positioning system will move the couch so that the position is perfect. A special camera system will monitor the couch and do a final correction before treatment begins.

"The patient set-up needs to be accurate, and we have to know the position of the proton beam precisely," Merchant

Radiation therapists (from left) Chance Taylor, Carla LaFosse and Andrew Saunders verify Breydon Hammer's position before his proton therapy treatment begins.

explains. "It's not humanly possible to put someone in exactly the same position every day. The system helps correct for variations in day-to-day set-up. Patients lose weight or gain weight; slight shifts can occur. Most proton centers rely on a pair of two-dimensional images to verify the position of the patient. We use the most advanced form of verification imaging, cone-beam CT, to determine a patient's position for treatment. We believe there is no patient positioning system in the U.S. that is more accurate than the one we have installed in our proton therapy facility."

As soon as the patient is situated, all staff members leave the room, keeping the child under constant video surveillance throughout the treatment. During the actual proton beam therapy—which lasts only a few minutes—advanced control systems guide the finely focused beams so that they conform to the shape of the tumor.

Proton pro

Kennedy received proton therapy 38 times, with sessions averaging about 30 minutes from arrival to departure.

"I had the treatment five days a week," Kennedy explains. "It was weird and not weird at the same time. You lie on this foam bed and they line you up using lasers and CT scans. When it comes time for the actual proton therapy, you can't feel the protons going in, but you can hear the machine. It's kind of like the sound a shovel makes as it's scraping the ground when you're shoveling snow."

Kennedy received her treatment in one of the facility's two gantry rooms, which feature a moveable "scanning" beam. The center also includes a fixed-beam room, as well as anesthesia areas and a recovery room. Families entering the center descend a musical staircase into a rainforest-themed waiting area that was designed with input from parents on the St. Jude Family Advisory Council.

Beam of hope

St. Jude has a long history of excellence in defining the best ways to use radiation therapy for childhood cancers. Proton therapy will usher in an entirely new era.

"This is not only going to advance our ability to cure patients, but it's going to make sure that every child has the best chance for living a long and productive life, free of the complications that can occur as a result of therapy," observes James R. Downing, MD, St. Jude president and chief executive officer.

About 100 patients will receive treatment during the facility's first year of operation, with the number gradually increasing during subsequent years. Merchant's goal is to incorporate proton therapy into every clinical trial for which it is applicable, as well as into collaborative trials with other institutions.

After 20 years of working at St. Jude, Merchant says he derives a deep sense of fulfillment by introducing a treatment that has the potential to give hope to many families.

"We treat some of the most difficult cases, and we enjoy the challenge," he says. "That's what it's all about. If it's a difficult case, we believe St. Jude is the best place for treatment."

Kennedy says the only side effect she has noticed from proton therapy has been a slight redness of the skin. "It was just like a little sunburn," she says, "but it wasn't super bad."

But the best thing?

"We actually saw shrinkage of the tumor," she says, a smile unfurling across her face. "I had to be the optimistic one in the beginning. And now look at where we are." ■

LEARN MORE about St. Jude proton therapy: *stjude.org/proton-therapy-at-st-jude*

Making Data Beautiful

PETER BARTA

Jinghui Zhang, PhD, Computational Biology chair (at left), confers with research scientist Xin Zhou, PhD.

An elegant Web tool developed at St. Jude makes it easy for any scientist to explore cancer genome data.

By Carole Weaver, PhD

Scientists love data. But even the bravest can feel daunted when faced with billions of pieces of it. And what good is big data if nobody uses it?

This question is becoming increasingly important in childhood cancer research. As technologies like genome sequencing move into the clinic, avalanches of data are emerging about DNA changes that occur in childhood cancers. Now, the challenge is to get scientists excited about sifting through all that data to make new discoveries and advance cures.

Jinghui Zhang, PhD, has a simple solution: make it easy, and make it fun.

"How do you make using the data an enjoyable experience, rather than having to fight and struggle with the tools to make them work?" she asks. As chair of St. Jude Computational Biology, Zhang is an expert at analyzing big data to make big discoveries about childhood cancers.

With this goal in mind, she and her research team set about revolutionizing how scientists everywhere access and explore pediatric cancer data. The result is an elegant new Web application called ProteinPaint.

A luxury vehicle—with an incredible engine

ProteinPaint is like a sleek luxury car, beautiful to look at and a pleasure to drive. With a couple of clicks on clean, simple visuals, a scientist can be drawn into deep data about a particular childhood cancer and its most common genetic alterations.

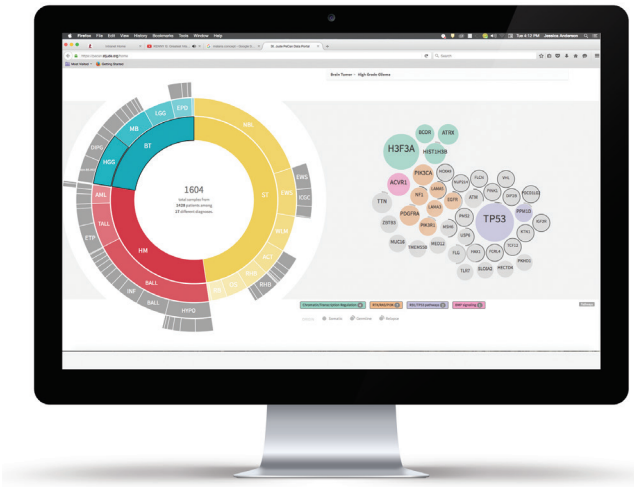
"You don't need to learn anything first—you can go directly and use it, and the interface is intuitive," Zhang notes. "During the exploration, users can gain knowledge about the complexity by themselves—it is a visual-based navigation process that is intuitive to human nature. That's what we tried to capture."

But it's not just the sleek exterior that makes the tool stand out. It's what's under the hood.

ProteinPaint is powered by the largest pediatric cancer database in the world, a data portal developed at St. Jude called PeCan. Through this incredible engine, ProteinPaint delivers information on nearly 27,500 genetic alterations from more than 1,000 pediatric cancer patients.

Adult cancer data is available too, and can be compared with pediatric data with a single click. Researchers can also upload and explore their own data sets using the tool.

Jinghui Zhang, PhD, has a simple solution: make it easy, and make it fun.



A global resource for discovery

With ProteinPaint, Zhang hopes to empower more researchers to take the critical next steps: Use genomic data to make more accurate diagnoses. Learn how different DNA changes contribute to cancer. Develop precision therapies tailored for the genetic makeup of a patient's cancer.

"We want this to be the definitive resource for genomic information for the pediatric cancer community," Zhang says. "Collectively we can better understand, using our combined knowledge, what contributes to cancer." ■

WATCH THE VIDEO: ***stjude.org/protein-paint-video***
TRY IT OUT: ***https://pecan.stjude.org***

Birth of a Research Tool

Several years ago, ProteinPaint was just a gleam in the eye of a St. Jude researcher. Matt Parker, PhD, a former postdoc in Jinghui Zhang's lab, designed an early version of the application to share data from the St. Jude – Washington University Pediatric Cancer Genome Project. While popular, the tool was limited in the amount of data it could show at one time.

Then, in early 2015, Xin Zhou, PhD, (pictured on facing page) joined St. Jude. Within two weeks, he had cranked through six new versions of ProteinPaint to create a winning design. "Each time I got an updated version, Jinghui and I would look at it together and discuss whether this new approach could do something more valuable," Zhou says.

"When we came up with this design, we had a very happy moment," he adds.

Further refinements moved quickly. The application was soon published in the prominent journal *Nature Genetics* and released for global use by the scientific community.

"It's unusual to have the creativity coupled with quick productivity," Zhang observes. "It wasn't because it was a simple task; it's because Xin is so great."

Zhou is too modest to use such superlatives, but he's not afraid to think big.

"Some have called ProteinPaint a premium experience to look at cancer datasets," he says. "This is a nice way to describe it." His new effort is to expand ProteinPaint to display new types of data on each cancer and culprit gene, increasing its value as a discovery tool.

Even now, a team of data wranglers is busy behind the scenes, making continual updates. Data for nearly 200 new genetic alterations, called gene fusion events, have been added to the database since its first release, with more coming through the pipeline.

"There's so much that can be done," Zhou says, a hint of excitement in his voice. "And the data's already there."

St. Jude Tells Malaria to BUZZ OFF

Spread by mosquitoes, malaria is a worldwide killer of children. St. Jude scientists and clinicians have teamed up to create a potential new malaria drug that could save untold lives.

By Maureen Salamon

Armand Guiguemde, PhD, remembers only the blistering fever and throbbing headache.

As a 9-year-old boy in the West African country of Burkina Faso, Guiguemde had no idea his intense symptoms signaled one of the world's leading killers of children: malaria. Fortunately, his grandfather had the insight to seek prompt medical care for Guiguemde, sparing him from a coma or even death.

More than three decades later, Guiguemde's experience has come full circle with his participation in an effort by St. Jude Children's Research Hospital to attack malaria, which claimed about 438,000 people globally in 2015.

Caused by *Plasmodium* parasites spread through the bites of infected Anopheles mosquitoes, the scourge has outwitted existing medications. Children under age 5, whose immune systems are especially vulnerable, constitute more than 70 percent of malaria-related deaths worldwide.

St. Jude scientists have headed an international collaboration to develop a fast-acting, single-dose malaria drug they expect to be a game-changer on a global scale. Although hospital staff have led similar projects for vaccines and gene therapy initiatives, this is the first "soup-to-nuts" small-molecule project at St. Jude—in which a novel compound is created in the lab and brought to clinical trials.

"Many kids my age died of malaria when I was a child, and it's great to know that now we may be able to prevent that from happening for the next generation," says Guiguemde, now 42, and a malaria researcher in St. Jude Chemical Biology and Therapeutics. "Malaria's still a big killer. So whatever we can do to save lives is going to be a dream come true for me."

PETER BARTA

Fast-acting compound

Kip Guy, PhD, barely dared to dream a decade ago that his long effort to discover a new malaria drug could pay off with such a stunning prospect. Chair of St. Jude Chemical Biology and Therapeutics, Guy leads a team focused on discovering new drug leads that work against the molecular targets that fuel disease.

Malaria control has been increasingly difficult because of emerging drug resistance. But by 2010, St. Jude researchers and their international colleagues had found new starting points for drug discovery. Scientists tested the effectiveness of more than 300,000 chemicals against the malarial parasite. The team identified nearly two dozen families of molecules as possible drug-development candidates.

With these starting points in hand, Guy organized a consortium of laboratories, including key collaborators at Rutgers University; the University of California, San Francisco; and the University of South Florida. Within two years, the team had identified a winning compound: Known as (+)-SJ733, the agent tricks the immune system into rapidly destroying red blood cells infected with the malaria parasite but leaves healthy cells unharmed.

Even more compelling is the compound's speed. It killed 80 percent of malaria parasites within 24 hours. No parasites were detectable after 48 hours.

"We were quite surprised at how rapidly it acted *in vivo,*" Guy says. "In fact, that really energized the whole project team to push much harder on the compound. It moved from a project of interest to something we thought was at the front edge of all the available malaria drug candidates in the world. I think that's actually proven to be the case."

"For most medicinal chemists, you're lucky if this kind of breakthrough happens once in your career," he adds. "I'm 25 years into doing this, and it's the first time for me."

Avoiding drug resistance

Malaria remains among the top threats to children in the developing world. In fact, according to the World Health Organization, the disease kills one child in Africa every minute. Yet, financial investments in malaria research petered out in the mid-20th century, after the disease was eradicated in Europe and the U.S. Interest rebounded in the last 15 years, as the malaria parasite began to outsmart the mainstay drugs that had beaten back death rates.

Existing frontline drugs seem to be losing effectiveness among malaria patients in Asia. Guy says this could set up a terrifying scenario in which drug resistance spreads throughout the developing world.

"We roughly halved the number of children dying each year, due to the introduction of those drugs in Africa," he explains. "If we lose that backbone therapy, we could go back up to 1 million or 1.5 million children dying every year. It's a horrifying prospect."

That's why it's especially valuable that (+)-SJ733 is part of an entirely different class from existing drugs.

The new compound should skirt the drug resistance chipping away at other medications' power. The potency of (+)-SJ733 is driven by host responses to the treated, infected red blood cells. The agent also works in both the blood and sexual stages of the disease, extending its punch beyond treatment to blocking transmission between patients.

"I would put it in a very unusual category with a small number of other anti-malarials," Guy says. "This is a property we've all been looking for."

Armand Guiguemde, PhD (at right), discusses the hospital's malaria research efforts with Kip Guy, PhD, Chemical Biology and Therapeutics chair.

The compound killed 80 percent of malaria parasites within 24 hours. No parasites were detectable after 48 hours.

According to the World Health Organization, malaria kills one child in Africa every minute.

ANN-MARGARET HEDGES

Testing the compound

Now underway is the first phase of a clinical trial that may make (+)-SJ733 an exciting new prospect in the malaria clinical realm.

Dubbed the BUZZOFF Trial—a catchy nod to enemy mosquitoes—the study's kickoff phase is based in Memphis and involves 30 healthy adults. Clinicians are examining the safety and potential side effects of escalating doses of (+)-SJ733 among these volunteers. This phase, which should continue through the summer, will also measure blood levels of the drug. The goal is to establish which dose consistently leads to a therapeutic level.

On the heels of this data will be the trial's next phase, which will be based in Australia. This part of the study will test (+)-SJ733 in groups of eight to 12 people.

After being infected with a strain of malaria known to respond to standard treatment, the volunteers in Australia will be carefully observed while their blood is tested every 12 hours for malaria activity. Once such activity is detected, they'll be given the therapeutic dose of (+)-SJ733 that was established in the trial's first phase. With blood tests continuing, the volunteers will receive standard anti-malarial drugs a few days later regardless of whether they ever develop symptoms of the disease.

"We're among the few pediatric-focused research facilities that have the scientific expertise in the basic science area to be able to have such drug discovery and then the resources on campus to take it through early-stage drug development," says BUZZOFF principal investigator Aditya Gaur, MD, of St. Jude Infectious Diseases.

"We also have the clinical research infrastructure to be able to design and execute the first human trial," he adds. "It's something unique to a very small group of academic institutions."

Gaur points out that dozens of employees in a wide variety of departments and organizations worked in tandem to design and oversee the thousands of details required to launch the clinical trial.

"The phrase, 'It takes a village,' is so applicable to this experience," he says. "The unsung heroes of everyday clinical research are the ones who make these studies possible."

Worldwide impact

Gaur anticipates that a few more years will pass before the breakthrough malaria pill (+)-SJ733 gains U.S. Food and Drug Administration approval and is ready for the market. But he, Guiguemde and Guy are keeping their eyes on the prize, eagerly anticipating the compound's contribution to malaria control.

While it may be a cure in itself, it's more likely to be an important part of a combination of drugs, says Gaur, who, until 1996, worked as a pediatrician in India, where malaria is common.

"I think the expectation would be that a single dose does 80 or 90 percent of the job, and then combined with another medication, provides a successful treatment of malaria that's starting to become resistant to current drugs," Gaur says.

Guy has high hopes for the eventual impact of (+)-SJ733.

"I think if we put this drug in the clinic and it works, it's going to positively affect the lives of a lot of children," he says. "That's exactly the kind of legacy that our hospital's founder, Danny Thomas, wanted."■

LEARN MORE about Armand Guiguemde, PhD:
stjude.org/Guiguemde

PETER BARTA

BUZZOFF principal investigator Aditya Gaur, MD, (at right) discusses nuances of the clinical trial with the study's first healthy volunteer, Joshua Wolf, MD, of St. Jude Infectious Diseases. "As a clinical researcher, I jumped at the opportunity to put my money where my mouth is," says Wolf, who usually has the role of recruiter instead of research participant.

PETER BARTA

Charles Mullighan, MBBS, MD, and Illaria Iacobucci, PhD, of Pathology

Study offers clues to precision treatments for leukemia

One of the biggest success stories in pediatric oncology is the effort to cure acute lymphoblastic leukemia (ALL). Its survival rates have risen above 90 percent. However, survival remains poor for children with treatment-resistant forms of the disease.

Enter a possible game-changer: A new study led by St. Jude on a tough-to-treat form of ALL called Ph-like ALL. In revealing genetic secrets of the disease, the study has identified promising treatment options in existing drugs.

Cancer cells in this form of ALL have a broken chromosome that gets put back together incorrectly. The study revealed four similar rearrangements of that chromosome occurring in different patients. The rearrangements created a shortened version of a gene called *EPOR*. All led to the same thing: white blood cells proliferating out of control.

"To our knowledge, this is a previously unknown mechanism for leukemia," said Charles Mullighan, MBBS, MD, of St. Jude Pathology.

Now for the good news: the researchers were able to counter these issues with an existing drug called ruxolitinib. In the lab, ruxolitinib also enhanced the function of other chemotherapy drugs.

"We think these findings provide a useful road map for planning more accurate testing of combination chemotherapies," Mullighan said. In fact, one such clinical trial will take place at St. Jude. The research was published in the journal *Cancer Cell*.

Promising drug tames immune system

SETH DIXON

Kim Nichols, MD
Oncology

The immune system is built to protect the body. But an overactive immune system can do just the opposite. For patients with hemophagocytic lymphohistiocytosis (HLH), extreme immune activity can cause life-threatening inflammatory reactions.

If standard treatment fails, patients are left with few choices. Now, a promising new option has emerged from a study led by St. Jude and published in the journal *Blood*.

In patients with HLH, a massive buildup of white blood cells can cause a "cytokine storm," which triggers a dangerous inflammatory reaction. By recreating this scenario in the lab, researchers were able to search for drugs that reduced inflammation.

The scientists homed in on molecules called JAKs, which enable cytokines to carry out their normal functions. "We reasoned that inhibition of these JAKs might diminish inflammation and lessen disease," said Kim Nichols, MD, of St. Jude Oncology.

They were right. Inhibiting JAK function with a drug called ruxolitinib reduced both inflammation and its negative effects. Since ruxolitinib has been well studied for many years in the treatment of other conditions, it is an attractive candidate for HLH clinical trials.

"It is our hope that by incorporating JAK inhibitors, we can improve the cure rate for children and adults suffering from this devastating and often life-threatening disorder," Nichols said.

SETH DIXON

Tara Brinkman, PhD, Epidemiology and Cancer Control

Understanding long-term effects of treatment

Lifesaving treatments for childhood brain tumors are a double-edged sword. While destroying cancer cells, therapy can also take a toll on the developing brain.

Unprecedented research from St. Jude has shed new light on what this can mean for adult survivors of pediatric brain tumors. Researchers brought 224 survivors back to St. Jude, where they had been treated as children, for extensive testing and assessment.

While sobering, the results provided critical insights. Decades after treatment, many brain cancer survivors experienced deficits in intelligence, memory, educational achievement and employment. Radiation therapy to the brain and spine increased these risks, but was not the only contributing factor.

The findings will guide efforts to prevent and alleviate such problems in survivors. One key goal: Catch them early.

"We hope to help these kids while they are on therapy, to prevent the onset of some of these neurocognitive difficulties," said Tara Brinkman, PhD, of St. Jude Epidemiology and Cancer Control. "For survivors who have finished therapy, we want to develop ways to address the problems so they don't become as severe as what we are seeing with our current adult survivors."

The research, published in the *Journal of Clinical Oncology*, was part of St. Jude LIFE, a study that brings childhood cancer survivors back to the hospital for health screenings throughout adulthood.

Parental influence extends to drug response

Doctors know patients sometimes respond quite differently to the same drug. St. Jude is a leader in studying how differences in the makeup of the genes inherited from each parent influence how patients react to certain drugs. St. Jude is also a pioneer in using the information to guide clinical care.

An international research team led by St. Jude scientists has discovered how such inherited differences can cause serious problems during leukemia treatment.

The scientists showed that patients who inherit certain versions of a gene named *NUDT15* were more sensitive to an important family of anti-cancer drugs. The drugs, called thiopurines, cause serious side effects in these patients.

Researchers discovered that these patients were less able to metabolize the drugs. This, in turn, increased the risk that the drug would build up in the patients' bodies and amplify side effects.

Scientists found that high-risk versions of the gene are more common in people across Asia and those of Hispanic ancestry. These findings help explain why Asian and Hispanic patients often cannot tolerate thiopurines at standard doses.

"The results suggest that in the future we can improve the safety and effectiveness of chemotherapy by screening patients for the high-risk versions of the gene and using the information to adjust the dose of the drug," said Jun J. Yang, PhD, of St. Jude Pharmaceutical Sciences.

A report on this research appeared in the journal *Nature Genetics*.

THE PERFECT GIFT

By John Juettner

Sometimes the best gift of all is one that helps others. For donors like Kat Watson, the Birthdays for St. Jude program is icing on the cake.

Kat Watson was a high school freshman when her mother, Pam Clinger Frye, received a cancer diagnosis.

Watson watched her mother lose her battle, an experience she says she wouldn't wish on anyone.

Watson did her best to turn her grief into something positive. When she decided to dedicate her 19th birthday to St. Jude Children's Research Hospital, she thought about what it would have been like if the roles had been reversed: What if she had been the one with cancer—how would that have affected her family? Watson recalls watching her mother worry about bills, fighting to keep family life as normal as possible during treatment.

"I wanted to help other people not to have to worry about that," Watson says.

Because she knew that no family ever receives a bill from St. Jude for treatment, travel, housing or food, she decided to make a difference by supporting St. Jude.

"I thought that was genius, and I wanted to be able to help as much as I could," Watson says. "St. Jude relies on donors, and I wanted to be one of those donors to help a child not worry."

When Kat Watson blew out 19 candles on her most recent birthday cake, her celebration benefited the kids of St. Jude.

Watson raised $1,515 this past September through the Birthdays for St. Jude program, in which St. Jude supporters simply set up personal fundraising pages at *stjude.org/birthdays* and ask friends and family to donate to the hospital as a birthday gift.

Watson, who hails from Austin, Texas, and studies multi-media journalism at Oklahoma State University, discovered Birthdays for St. Jude while searching *stjude.org* for internship opportunities.

"Even though it wasn't interning, I would still be helping other people by helping fundraise for the kids who are burdened by cancer, and are taken away from their childhood, somewhat, to be thrown into this terrible situation," Watson says. "I wanted to help make it easier for them and their families."

Watson had never fundraised on her own before—she had only helped out at events hosted by others. That made her a little nervous at the start of her efforts. But after experiencing tremendous support from friends and family, Watson plans to dedicate her birthday to St. Jude again. ■

Find out more about donating your birthday and pursuing other personal fundraising opportunities: ***stjudetributes.org***

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St. Jude patient Elizabeth, acute lymphoblastic leukemia

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—Jim & Carol Di Lorenzo

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Science Scholars of Tomorrow

Nearly 100 Memphis-area high school students and teachers recently visited St. Jude to get an exclusive look at science in progress. The Science Scholars of Tomorrow Symposium showcased how the scientific method, as a means of problem-solving, is put into practice by St. Jude researchers.

"Your generation will provide the doctors, nurses, scientists and many others who will continue the path to discovery and to healing," James R. Downing, MD, St. Jude president and chief executive officer, told the students.


SETH DIXON

Finding cures. Saving children.