St. Jude St. Jude Stjude.org/promise winter 2016

He's a soccer player. A math whiz. **A pioneer.** Brendan is also one of the first cancer patients to enroll in **Genomes for Kids** *pg. 2*

In search of a cure: St. Jude enhances its **sickle cell program** *pg. 8*





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On the cover: Brendan Obioha Photo by Seth Dixon

PATIENT 2 PIONEER

St. Jude prepares to move whole-genome sequencing into the clinic.

By Elizabeth Jane Walker

Last summer, 10-year-old Brendan Obioha traveled from Nigeria to Memphis, Tennessee, to receive life-saving cancer treatment at St. Jude Children's Research Hospital. The young soccer player and math whiz has a rare blood cancer called biphenotypic leukemia.

The little boy arrived as a patient. But he quickly became a pioneer.

Brendan is one of the first children to enroll in a study that will lay the foundation for transforming childhood cancer therapy. That study is called Genomes for Kids.

Childhood cancer begins with a change-a mutation-in one or more genes. When it occurs only in a single cell of the body (known as a "somatic" mutation), the alteration may trigger the cell to grow uncontrollably and cause a tumor to form. Sometimes an alteration may be present in every cell of the body (known as a "germline" mutation). In this case, the mutation may increase the child's risk of developing cancer later in life. St. Jude research has shown that at least 8.5 percent of St. Jude cancer patients have germline mutations, which can be passed down through families (see sidebar at right).

The St. Jude – Washington University Pediatric Cancer Genome Project, which began in 2010, compared the genomes (the complete genetic blueprint) of both cancerous and normal cells from more than 800 children with cancer. That project provided important insights into some of the toughest childhood cancers. In the project's second phase, St. Jude developed new lab and computer facilities that would enable scientists to do clinical testing, analyze data and interpret its significance.

"The efforts to establish this one-of-akind clinical sequencing platform required a concerted effort over 18 months by molecular pathologists, computational biologists, computer science experts, pediatric oncologists, clinical geneticists, genetic counselors and medical ethicists," says James R. Downing, MD, St. Jude president and chief executive officer.

"We are thrilled that we've laid the

groundwork for moving this technology into the clinic," adds Jinghui Zhang, PhD, chair of St. Jude Computational Biology. "Our goal is to determine how best to tap its potential to improve patient care."

That's where Brendan comes in.

While he undergoes cancer treatment, he is also taking part in Genomes for Kids. This research study uses a technology called next-generation sequencing to pinpoint the specific gene changes that cause cancer to develop. Armed with those details, scientists will be able to understand more about why the tumors formed and learn how to treat them better.

"This gives us an opportunity to apply the kind of information we have learned from the Pediatric Cancer Genome Project to the actual clinic," explains Kim Nichols, MD, director of the new St. Jude Hereditary Cancer Predisposition Clinic.

St. Jude scientists expect Genomes for Kids to be the first step in a clinical genomics effort that

will usher in a new day—an entirely novel way of treating children with cancer and other life-threatening diseases.

All St. Jude cancer patients are now offered the opportunity to have their tumor and normal cell genomes sequenced as part of their routine workups.

Participants in Genomes for Kids agree to let researchers isolate DNA from part of their tumor—or bone marrow in Brendan's case—to look for changes in 565 cancerrelated genes.

To identify germline changes that could reveal whether the risk for cancer was inherited, St. Jude scientists currently look for alterations in 63 genes in the child's healthy tissue. These genes have been commonly associated with childhood cancer predisposition. The number of genes examined will increase in the coming years.

"The thing that is unique about St. Jude is the technologies we're using," Nichols says. "Other institutions that are doing genomic analysis are doing something called whole-exome sequencing, which only looks at a slice of the human genome—about 1 to 2 percent. At



James R. Downing, MD President and Chief Executive Officer

SURPRISING NUMBER OF YOUNG CANCER PATIENTS ARE PREDISPOSED TO THE DISEASE

When cancer is found in a young patient, parents often ask: "Why my child?"

New evidence suggests that some children may be born at an increased risk of developing cancer early in life. In a landmark study from St. Jude and Washington University in St. Louis, investigators closely examined the genetic makeup of 1,120 children with cancer. They found that 8.5 percent nearly one in 10—of those patients was born with genetic changes or mutations that increased their cancer risk.

These changes, called germline mutations, are found in the DNA of every cell, not just tumor cells. Such mutations were known to exist, but their frequency was a mystery.

"The study marks a turning point in our understanding of pediatric cancer risk and will likely change how patients are evaluated," says James R. Downing, MD, St. Jude president and chief executive officer.

These mutations can be used to help guide treatment and advance precision medicine. In some cases, entire families may benefit from genetic testing and counseling. St. Jude is now offering comprehensive genetic testing to its cancer patients as part of the Genomes for Kids clinical research study. This study is designed to lay the groundwork for transforming childhood cancer therapy through genomic sequencing.

If a mutation associated with increased cancer risk is found, children and families are referred to the St. Jude Hereditary Cancer Predisposition Clinic. There, a team of medical specialists work with families to understand and better manage their cancer risks.

The study, part of the Pediatric Cancer Genome Project, was published recently in the *New England Journal of Medicine*.



ST. JUDE USES THREE KINDS OF SEQUENCING TO PINPOINT AS MANY GENETIC ABNORMALITIES AS POSSIBLE:

1 WHOLE-GENOME

SEQUENCING. The genome includes the complete set of instructions to assemble and sustain humans. The genome is encoded in the DNA molecule carried in almost every cell. Whole-genome sequencing involves determining the exact order of the 3 billion nucleotides that make up human DNA.

2. WHOLE-EXOME SEQUENCING. The exome

comprises 1 to 2 percent of the genome and contains the more than 20,000 genes that encode the building blocks for life.

3. RNA SEQUENCING. This procedure reveals which genes are being turned on and at what level.

stjude.org/g4k



After completing cancer treatment, Brendan (pictured with Kim Nichols, MD, director of the St. Jude Hereditary Cancer Predisposition Clinic) anticipates returning to the soccer field and his school's robotics club.

St. Jude, when you have the tumor tissue tested, we're also doing whole-genome sequencing and RNA sequencing. We're looking at every part of the entire human genome, as well as every part of what is known as the 'transcriptome,' which is the RNA blueprint from which proteins are made. It's a comprehensive way to investigate the tumors for as many genetic abnormalities as possible."

Brendan's mom, Anita, says the possibilities are intriguing.

"This study is supposed to help to find out why cancer happens," she says. "I signed up to have them test the normal as well as cancerous cells. I want to know if the cancer was passed down or if we could have it in the future. I want to know why the genes change, what particular gene changes might be in our family. I'm really curious."

As part of the study, scientists are trying to determine the best ways to share testing results with families. After Brendan's genomic sequencing is complete, a doctor and genetic counselor will meet with his family to explain the results and how they may affect Brendan and his family. If he has a germline mutation that increases cancer risk, he and his family will receive care and counseling through the Hereditary Cancer Predisposition Clinic.

Nichols envisions creating a precision medicine pipeline, in which mutations are discovered in a child, a team of scientists identifies drugs that target those particular alterations, and the treatment is provided to the child.

"This is the bedside-to-bench-tobedside approach," Nichols says. "This comprehensive genomic analysis is something that you can only do at St. Jude. And this vision for the future is what makes St. Jude unique."

The Genomes for Kids research study is designed with tomorrow's patients in mind.

"We tell families that this study will not necessarily influence the treatment of their children today, but may be helpful for children in the future," Nichols says.

Anita says she hopes Brendan's participation may benefit others.

"Children don't deserve to have cancer," she says. "I want to help the world in any way I can. I would love it if my child's illness could help the doctors find ways to make it easier to treat other children.

"If we don't do these studies," she continues, "there's no way we can move forward. That's the way I see it." ■



"If we don't do these studies, there's no way we can move forward."

– Anita Obioha

Solving Mysteries of the Microbiota

By Chris Lewis

St. Jude scientists learn more about how bacteria affect colon cancer and the body's immune system.

How many bacteria inhabit your body: Thousands? Millions? Try again.

Trillions of organisms call your body home. The bacteria that populate your mouth, gut, skin and the rest of your body are known as the microbiota. And scientists estimate that these cells outnumber your body's cells 10 to 1.

The microbiota has become a hot topic recently, thanks in part to work conducted by immunologist Thirumala-Devi Kanneganti, PhD, of St. Jude Children's Research Hospital.

In one study, she and her colleagues explored the influence of diet on the microbiota, as well as on a variety of autoimmune disorders. Another study led to groundbreaking discoveries about colon cancer, which may provide hope to thousands of patients diagnosed with the disease each year.

Diet and disease

Scientists have long known that diet can affect disease. But until Kanneganti conducted her research, they did not understand exactly how that happened.

"When I started studying the microbiota more than 10 years ago, I was skeptical about whether it could be used to control diseases," Kanneganti says. "But seeing is believing. In our lab, I have seen several disease models in which we changed the microbiota and the disease outcome was different."

In particular, the St. Jude team found that diet can change the composition of bacteria in the intestines—which in turn can modify the immune response.

certain fatty acids carry their own risks, so identifying the specific components within the special diet would help scientists to check whether adding these components into a normal diet would be beneficial. Scientists were also happy to learn that a regular diet and antibiotics had a similar effect.

The confirmation that diet influences inflammatory disorder symptoms may extend beyond the lab to humans.

"By changing diet, we were able to prevent complete bone destruction," Kanneganti says. "We think diet modification is applicable to other diseases, too."

The microbiota and colon cancer

For years, an immune system protein called AIM2 remained a

Autoinflammatory diseases occur when the immune system does not work correctly. The innate, or inborn, immune system attacks the body's own tissues and causes inflammation.

Kanneganti and her

colleagues showed that a nutrient-rich diet offered protection from the bone destruction that accompanies osteomyelitis, an autoinflammatory bone disease that can affect children. The special diet restricted the development of Prevotella bacteria in the gut. These bacteria are associated with osteomyelitis, arthritis and other disorders. Of course, diets that have high levels of

When I started studying the microbiota more than 10 years ago, I was skeptical about whether it could be used to control diseases. But seeing is believing.

mystery to scientists, aside from the fact that it was absent in many types of cancer. Then Kanneganti led a team

that explored AIM2's influence on the microbiota. She and her collaborators discovered that AIM2 helps prevent colon cancer.

– Thirumala-Devi Kanneganti, PhD

The protein stops intestinal cells from uncontrolled growth—a hallmark of cancer. AIM2 also encourages "good" intestinal bacteria to flourish and prevents the growth of "bad" bacteria.

The discovery could offer hope to children and adults who have colon cancer or are at risk for the disease.

"By increasing AIM2 activity and providing patients with healthy

donor bacteria, colon cancer may be treated or even prevented," Kanneganti says. "This discovery could enable new treatments in the future."

Kanneganti says colon cancer may be prevented, or its progression slowed, by therapies that boost AIM2 activity and by giving patients healthy bacteria. By measuring AIM2 activity in patients who already have colon cancer, physicians may be able to predict how aggressive the cancer will be.

The scientists also found that AIM2 controls the abnormal growth of stem cells in the colon. Stem cells are immature cells that differentiate into adult cells and replace old or dying cells.

"We clearly showed that AIM2 is important in controlling stem cell proliferation," Kanneganti says. "This is a big breakthrough. It is intriguing to see how the microbiota can influence stem cell proliferation in the intestine."

Understanding the microbiota's role

Stanuo and a state

Kanneganti and her team intend to expand their study of the microbiota and determine how it can be manipulated to cure diseases.

"My goal is to understand the role of microbiota and how it modulates the outcome of cancer, bone diseases and some autoimmunity and skin problems," she explains. "By studying the role of the microbiota, we may not only be able to treat several diseases, including cancer and autoimmunity, but cure them as well."

SICKLE CELL DISEASE

By Elizabeth Jane Walker

Three-year-old Bryce Gross meets with Mitch Weiss, MD, PhD, Hematology chair, and nurse practitioner Nicole Dockery.

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A HOSPITAL'S COMMITMENT

St. Jude enhances its sickle cell program to look beyond symptom relief to a cure.

Adrienne Gross knows firsthand the sound a mother's heart makes when it shatters into a million glittering pieces. Hers did just that in September of 2013 when she learned that Bryce, her adorable newborn son, had a life-threatening disease.

Time began to move slowly. "This is not my life," she thought. "This is not my son. This is not my situation."

Although Adrienne knew she carried the trait for sickle cell disease, neither she nor her husband, Bruce, knew that he was also a carrier. That meant they had a 1-in-4 chance of having a child with the disorder. Bryce's older sister, Chloe, had been born without the disease.

"Everyone I knew who had sickle cell had died," Adrienne says. "I didn't know

anyone who had the disease and was living a normal life. I didn't even know how to process that information."

NIGHT AND DAY

Soon afterward, Bruce and Adrienne learned that St. Jude Children's Research Hospital was poised to help.

"Everything changed when we met with a staff member from St. Jude," Adrienne recalls. "A feeling of hope came over us. It was like, 'This is not the end of the world. We are going to walk through this journey with you, with Bryce. This is something that's going to be a part of your life, but it's not the end for your family or your son.'"

About 100,000 people in the U.S. have sickle cell disease, an inherited disorder that causes red blood cells to become hard and crescent-shaped, instead of soft and round. The misshapen cells block blood flow, causing intense pain, stroke, the need for blood transfusions and a shortened life expectancy. The disease can ravage the lungs, brain, heart, spleen, kidneys, eyes, joints, skin and liver. During Bryce's first year of life, his family visited the hospital regularly. At those visits, St. Jude staff educated them about the disease and introduced them to a family support group. Bryce experienced his first pain crisis at age 1. Soon afterward, he began taking a medication called hydroxyurea.

"Before he began taking hydroxyurea, his hands and feet would swell. He didn't want to be touched because he was in so much pain. Any change in his environment would make him sick," Adrienne recalls. "After he started taking the medication—it was like night and day.

"I know what it feels like to be low and scared and sad," she continues, "but now we have a normal life. Every now and then we go to the doctor or the hospital, but that



happens in people's lives who don't have to deal with sickle cell. We have learned how to be thankful. We celebrate the good days, and we count our blessings."

BUILDING ON A LEGACY

St. Jude scientists have been researching sickle cell disease for more than half a century:

- Before the hospital opened in 1962, its first research grant was awarded to Lemuel Diggs, MD, for the study of sickle cell disease.
- A St. Jude patient was the first person in the world to be cured of the disorder through a stem cell or bone marrow transplant.
- Sickle cell pioneer Winfred Wang, MD, of St. Jude Hematology, led nationwide research to advance the use of hydroxyurea in children.
- St. Jude scientists discovered ways to detect and prevent stroke risk in children with sickle cell disease.

St. Jude President and Chief Executive Officer James R. Downing, MD, is building on that legacy. He recently unveiled a plan to enhance the hospital's sickle cell program. It's great news for Bryce and for the 2,000 other children born with the disease in the U.S. each year.

SWEET RELIEF

Scientists and clinicians throughout St. Jude are seeking ways to provide the best possible care for children with the disease.

Hydroxyurea treatment. Twenty years ago, St. Jude clinicians pioneered the use of hydroxyurea to relieve the symptoms of sickle cell disease.

"It's been a long saga," recalls Wang, who has been at St. Jude since 1979. Wang headed the first national studies to use the drug in children. "We found that it's effective for symptoms and blood counts, and that it's reasonably safe to give hydroxyurea to very young children with sickle cell anemia."

Today, St. Jude researchers continue to refine the use of this drug. Jeremie Estepp, MD, of St. Jude Hematology, is currently leading a study to learn how to optimize the use of hydroxyurea and to maximize its short- and long-term benefits.

Precision medicine and pain relief.

Another faculty member, Mary Relling, PharmD, St. Jude Pharmaceutical Sciences chair, discovered a way to use genetic testing to determine which children should and should not receive codeine, a drug often prescribed to relieve the severe pain of sickle cell crises.

For most people, codeine works as intended. But the drug is dangerous for individuals who have an active gene that makes them metabolize codeine too quickly. And for about 10 percent of patients, the drug will not work at all.

"Now we know who benefits the most from codeine," says Mitch Weiss, MD, PhD, Hematology chair. "This is precision medicine, because by knowing a child's genetic status, we can decide which pain reliever is most likely to be safe and effective in that patient."

Sickle cell on trial. St. Jude research is ongoing to solve the problems of iron overload, stroke and learning disabilities that may accompany sickle cell disease. During the next few years, researchers will focus on further reducing complications, expanding the number of clinical trials available.

As part of one new study, St. Jude will sequence the genome of 1,000 patients with sickle cell disease (see "The Future Starts Now," page 12). Scientists will use data from that study to determine how genes affect sickle cell patients through their lifetime.

"Why are some patients sicker than others?" Weiss muses. "There's a strong genetic component to that. Through this study, we believe we can better understand the genetics."



optimize use of the sickle cell medication hydroxyurea.



DESTINATION: CURE

But the ultimate dream of St. Jude clinicians and researchers is to find a cure.

"Most programs in sickle cell disease have focused on decreasing symptoms," Downing explains. "Well, why not try to cure it? Can we use gene therapy to do that? Can we use gene editing to cure it? Can we find better drugs that would essentially reverse the disease? We're expanding our research efforts in those areas."

Stem cell or bone marrow transplant

is the only known cure for sickle cell disease. But this procedure requires a matched donor and poses dangers from infection and other side effects.

"We have much to learn about transplants and how to do them better for this population," Weiss says. That's why the hospital is working to develop a leading bone marrow transplantation program for children with sickle cell disease. This program will identify children who will benefit the most from transplants, develop new clinical trials to improve engraftment rates and devise ways to decrease transplant-related side effects.

Gene therapy replaces the mutated sickle cell gene with a normal gene. Sickle cell disease is caused by a change in the beta-globin gene. The resulting abnormal proteins cause red blood cells to adopt their sickled shape. Through gene therapy, scientists will insert a normal gene into a harmless virus that would transport that healthy gene into the cells' DNA.

Gene editing involves clipping out the mutant part of the faulty DNA and replacing it with a piece of normal DNA. St. Jude researchers are exploring this technique to edit the genome.

"There have been two revolutions in biology in the past 10 years," Weiss observes. "One is the ability to sequence the genome so easily, and we have taken advantage of that at St. Jude through our Pediatric Cancer Genome Project. The second revolution is the technique called gene editing. It holds great promise for changing a sickle cell mutation back to normal."

A MOTHER'S DREAM

PETER BARTA

Bryce's mom has often wondered whether she will see a cure for sickle cell disease in her lifetime.

"We know we are in the right place and at the right facility and with the right researchers, who believe there is a cure out there for these kids," Adrienne says. "Just to know that they are focusing on cures and having these conversations gives us hope." ■

> Sickle cell pioneer Winfred Wang, MD, (pictured with Lundan Brown) led nationwide research to advance the use of hydroxyurea, which is currently the only approved drug for the disease.

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THE UTURE STARTS NOW

By Elizabeth Jane Walker

Great Scott! When it comes to sickle cell disease, St. Jude researchers have their sights set on the future.

Like time travelers Doc Brown and Marty McFly in *Back to the Future,* Jane Hankins, MD, has her focus firmly set on a day that is yet to come. But instead of relying on a supercharged DeLorean time machine, Hankins depends on research to propel her toward her lofty goal: a cure for sickle cell disease. The hematologist from St. Jude Children's Research Hospital and her team are heading up a project that will extend decades into the future. And more than 450 children have already signed on for the ride.

It's an high-tech study with a lengthy name: Sickle Cell Clinical Research and Intervention Program, or SCCRIP for short. Children in this study agree to return to St. Jude for periodic checkups throughout their lives.

Not only will participants learn more about their own health, but they will help scientists gain long-term insights into a cruel disease. In addition, scientists will sequence the patients' genes to figure out how genetic changes affect disease severity.

"SCCRIP will help us understand how sickle cell disease progresses—what happens over time," Hankins explains.

Chris and Nichole Bridges have two daughters with the disease. The couple enrolled both 11-year-old Khirsten and 7-year-old Kaitlyn in SCCRIP.

"This study may help not only our girls, but other kids in the future," Chris says. "It could be next year, it could be 10 years, it could be 15 years down the line. But by following their growth, looking at their DNA, scientists can improve their quality of life and may actually find a cure."

WHEN LIGHTNING STRIKES

Individuals with sickle cell disease have a lifelong illness that can affect their blood, organs and bones, causing severe pain crises and increasing their risk of infections, anemia and stroke. Health problems for these patients generally escalate during young adulthood. Scientists do not know how to predict which children are destined for specific complications or who will be affected most severely.

The average life expectancy for a person with sickle cell disease remains in the mid-40s. For Hankins, that's simply unacceptable.

"They shouldn't be dying at that age," she says. "We need to understand why one person dies at 25 of kidney disease, and another at 40 of heart disease. If we follow a large number of patients long enough, we can start to understand that. Then we'll be able to pick out the kids who are at risk for certain complications 10 years down the line, 20 years down the line. We'll be able to find the early signs of trouble and take preventive action."

HELPING TOMORROW'S KIDS

St. Jude has created a comprehensive plan to help patients manage their disease. Until age 18, children and teens receive treatment—as well as education and counseling for their families—at St. Jude. At age 18, care transfers to one of the adult hospitals in Memphis, such as the Methodist Adult Comprehensive Sickle Cell Disease Center or the Regional One Health Diggs Kraus Sickle Cell Center. Clinicians in the adult program work with St. Jude staff to ensure that patients continue to receive the same level of care and those who enroll in SCCRIP will return to the hospital for medical follow-up every six years.

Data from this study will be used to help improve the health of future generations of children as well as provide information about the best way to make the transition from pediatric to adult care.

THE SKY'S THE LIMIT

Underlying the clinical program is a basic research question: How do genes affect the progression of disease or a patient's response to treatment?

That's what scientists aim to discover. By sequencing the genes of children with sickle cell disease, scientists expect to identify pivotal genetic changes and find out how they influence patient outcomes and complications.

"Not every patient with sickle cell disease gets every problem," says Mitch Weiss, MD, PhD, Hematology chair. "Some patients are sicker than others, and there's a strong genetic component to that."

Hankins says those findings could be the culmination of her life's work.

"Can I find one little marker, one gene, that tells me which child is going to die of heart disease at age 20?" Hankins says. "If we find those genetic markers, then we can work on fixing it."

Hankins is encouraged by the number of patients who have agreed to participate in SCCRIP. Her goal is to enroll every St. Jude sickle cell patient in the study. She is also extending the study to other Memphis hospitals and St. Jude affiliate programs.

"The sky's the limit, because the power is in the numbers, especially if you're



Chris and Nichole Bridges enrolled two of their daughters, (top left) 11-year-old Khirsten and (bottom left) 7-year-old Kaitlyn, in the study. St. Jude not only provides care for the girls, but also education for the entire family, including Khristia (at right), who does not have the disease.

doing genetic studies," she says. "If you're looking at DNA and trying to understand mutations, you really need a lot of patients to understand those changes."

IT'S THE POWER OF HOPE

Hankins says the SCCRIP study is different from sickle cell studies done elsewhere. Other programs generally follow children only until age 18 or 21, in spite of the fact that health complications skyrocket after that age. The genetic elements add depth to the study.

"I'm not sure you could pull this off anywhere else," Hankins says. "Now that we're following patients through adulthood, our numbers are growing very large. We have the infrastructure here at St. Jude to do the genome studies; we have a fantastic clinic infrastructure to collect all the clinical data. We have it all."

Chris and Nichole Bridges rely on St. Jude for their daughters' medical care, but they respect the value of long-term research and they keep their eyes on the future.

"My wife and I are always looking and waiting for the day that they call us and say, 'We've found the way to turn that sickle cell gene off," Chris says.

"Of course, as a dad, I want my children to outlive me, to live normal lives. With this study, we can be hopeful that this disease can someday have a safe and accessible cure for all." ■

FLEXING MENTAL MUSCLES

Computerized cognitive training improves attention and memory in childhood cancer survivors.



BY ELIZABETH JANE WALKER

s his fingers fly across the strings of his acoustic guitar, 17-year-old Cameron Blanchard muses upon a few of his greatest influences: Eric Clapton. Ed Sheeran. John Mayer. And his doctors at St. Jude Children's Research Hospital. A self-taught guitarist, Cameron aspires to a career in the medical field. He attributes that possibility—as well as the ability to write music and maintain a stellar grade point average—to St. Jude.

Cameron began experiencing academic problems during elementary school, soon after completing treatment for acute lymphoblastic leukemia (ALL).

"Two years later, the wheels fell off the bus," recalls his mom, Dana. "I had a child who was ready to give up on school. He thought he was dumb, but I knew he was intelligent. He just had to go about it in a different way."

Cameron's parents sought ways to solve his academic problems, but nothing seemed to help. Then St. Jude opened a study that featured a computer-based training program.

That intervention would make all the difference.

SEEKING SOLUTIONS

As many as 60 percent of children treated for brain tumors or ALL develop attention and learning problems as a result of their disease or its treatment. Stimulant medications can be effective, but they are not right for everyone. Therapist-led sessions may not be practical because of scheduling or geographical constraints.

Heather Conklin, PhD, of St. Jude Psychology, and her colleagues were determined to find a solution. They designed a study for children and teens who, like Cameron, experienced significant cognitive problems after cancer therapy.

Participants agreed to complete about 25 sessions of a

computer program called Cogmed Working Memory Training[®]. St. Jude researchers tracked the survivors' performance online and offered reinforcement through weekly telephone coaching sessions.

NOT YOUR BROTHER'S VIDEO GAME

Children in the study spent 30 to 45 minutes each day playing games led by a blue, roller-skating robot. The friendly creature introduced exercises that featured asteroids, space animals, twirling lights and other objects. Children relied on verbal or visual cues to recall specific sequences.

Conklin is quick to point out the difference between this software and a video game.

"First, the program is specific—targeting particular skills our patients need to work on," she says. "Second, it's intensive, requiring lots of repetition. Just like physical exercise, you must do it frequently for a sustained length of time in order to see results. Third, it's adaptive—meaning that the difficulty level changes based on performance."

"I had to push myself to do it," Cameron admits. "It seemed irrelevant at the time, but it helped me in ways I didn't realize until later."

GAME CHANGER

Children completing the training program enjoyed significant benefits in attention, working memory and processing speed.





"Cameron's approach to learning really changed," his mom says. "It was incredible."

The results were similar to those of children who take stimulant medications for attention deficit disorders.

"Typically, we don't see as much improvement with behavioral interventions as we

"It was incredible."

do with medication," Conklin says, "but in this case, we did." Scientists also saw changes in functional brain scans done before and after the program.

"We saw changes in activation that suggest participants are becoming more efficient at how they approach the tasks," says Conklin, who recently published results of the study in the *Journal of Clinical Oncology*.

"We think it means new connections are being made in the brain."

NEXT STEPS

Given the program's success with survivors, Conklin and her colleagues asked, "Why wait until they're having problems? Let's see if we can ward off issues rather than wait until they have them."

> That's just what they're doing. The hospital's latest clinical trial for the brain tumor medulloblastoma incorporates this computer-based training toward the end of therapy.

Cameron continues to benefit from his experience. In fact, he is spending his senior year of high school working on a capstone project titled "Late Cognitive Effects of Cancer Treatment on Children."

"Teachers might take one look at a kid like me and assume he hasn't ever been sick a day in his life," Cameron explains. "But my position is that these cognitive effects could be better understood by the educational system.

"Basically," he adds, "a better understanding leads to a decrease in difficulties." \blacksquare

From Old Drugs, New Hope

FHEOSON

St. Jude scientist redesigns an existing antibiotic to combat drugresistant infections ranging from tuberculosis to pneumonia.

By Maureen Salamon

His ancestors were blacksmiths, pounding pieces of metal into new and useful shapes. Today, Richard Lee, PhD, carries on his family legacy in a fascinating way.

As a scientist at St. Jude Children's Research Hospital, Lee now forges naturally produced chemicals into potential new drugs. He leads an international research effort that has transformed an old, weak antibiotic into a potential super-killer of drug-resistant infections that pose serious health threats to patients at St. Jude and beyond.

Lee's projects have used leading-edge technology to change the chemical structure of a 50-year-old antibiotic called spectinomycin and create new, more powerful drugs. These second-generation versions show promise in combating drugresistant tuberculosis (TB). The new drugs may also wipe out bacteria that cause other dangerous drug-resistant infections.

"I like making things, and I find an intellectual challenge in building molecules to fit into molecular targets. It's extremely rewarding," says Lee, who works in the hospital's Chemical Biology and Therapeutics department.

"Doing chemistry for medical purposes has always been appealing to me," he adds. "St. Jude is a great place to do this, and I love the mission."

Worldwide impact

Lee knows his work is linked to the well-being of patients around the world.

TB sickens about 500,000 children and kills 1.4 million people worldwide each year. Meanwhile, drug resistance is rising in common bacterial infections that cause pneumonia, meningitis, middle-ear infections and sepsis. Drug-resistant bacteria sicken 2 million U.S. residents yearly, causing 23,000 deaths.

But although the number of cases caused by drug-resistant bacteria is rising, the number of new drugs in the pipeline to treat these infections has dropped. This poses a challenge to the current standard of medical care.

Cancer therapies often suppress the immune system, leaving many St. Jude patients prone to secondary infections.

"An infection with drug-resistant bacteria can be life threatening to cancer patients and can alter the course of their cancer treatments," Lee says. "So infection control is a key part of making sure we have the highest survival rates possible.

"We're in a really bad situation because drug resistance is being spread rapidly by globalization."

Hard work and a spot of luck

To make their discoveries, Lee and his fellow scientists first created a 3-D, atomic-level model of how spectinomycin binds to ribosomes, which are part of the cell's machinery needed for protein synthesis. The scientists engineered spectinomycin by adding chemical groups that only bind to the bacterial ribosomes. One version of spectinomycin was effective against drug-resistant strains of TB. That version is known as 1599.

Lee and his colleagues showed how the structural changes in 1599 prevented TB bacilli from pumping it out of the cell. This resulted in 1599 accumulating to high enough levels in the bacilli to disrupt protein synthesis and trigger cell death.

As precise as the computer-aided process is, "I'm continuously amazed by how lucky we are when we work with modified natural products, as they tend to hit the most effective targets and work well in living systems," Lee observes. "There's a lot of serendipity in science, and I think a good scientist takes advantage of serendipity."

An infection with drug-resistant bacteria can be life threatening to cancer patients... Infection control is a key part of making sure we have the highest survival rates possible.

The new versions boast the added benefit of decreased toxicity compared with other protein synthesis inhibitors currently used to treat TB. These inhibitors work differently, making it unlikely to cause some of the serious side effects, such as hearing loss and low blood cell counts, which are associated with current therapies.

Breaking down barriers

Applying knowledge gained from his TB studies, Lee designed a second series of compounds. That research generated spectrinomycin compounds that are effective against a broader spectrum of drug-resistant bacteria. They include agents responsible for common childhood upper respiratory tract infections, including infections of the inner ear.

But there are many other hurdles to cross between testing the redesigned compounds in the lab and moving them into the clinic. Lee is focused on preclinical testing of these agents and creating oral versions of the new antibiotics—a process he predicts will take years.

But he's not fixated on the timeline, just the outcome.

"My job isn't to develop a drug, although I would love to make a drug," Lee says. "My job is to advance the options for therapy in the future. We're breaking down barriers, and we've potentially opened up a new class of antibiotic medicines." ■

highlights



From left: John Schuetz, PhD; Aaron Pitre, PhD; and Yao Wang

Discovery could ease lung disorder in at-risk newborns

The bile and bile acid that aid digestion and ensure good nutrition can make life uncomfortable for some pregnant women. Their babies may also be at risk for dangerous breathing problems.

The trouble begins during pregnancy when the normal flow of bile acid and bile from the liver is interrupted, causing a blockage. Bile acid is a key component of bile. The blockage leads to a buildup of both in the liver and blood stream. Women with the problem have itchy skin until the baby is born. But about 30 percent of the newborns develop life-threatening respiratory distress.

The disorder is called intrahepatic cholestasis of pregnancy. It affects as many as 5 percent of pregnant women with no history of liver disease. St. Jude research has dramatically improved our understanding of the problem. The study also identified a lead on how to protect newborns.

Working in a laboratory model of the human disease, scientists found evidence that bile acid can cross the placenta and build up in fetal lungs. The results also suggest bile prevents proper assembly of a chemical that helps keep newborn lungs inflated. Investigators found that blocking the reabsorption of bile acid in the intestines during pregnancy eased that risk.

"The results suggest it may be possible to develop drugs to reduce the risk of newborn respiratory distress by reducing bile acid levels in maternal blood and preventing its reabsorption in the intestines," said John Schuetz, PhD, Pharmaceutical Sciences vice chair. A report on this study appeared in the journal *Nature Communications.*

Scientists shine a light on dark proteome

Scientists at St. Jude, The Scripps Research Institute and other institutions recently announced the launch of the Human Dark Proteome Initiative. The project aims to foster research and collaboration about the proteins known as the "dark proteome."

The dark proteome is the collection of proteins in an organism that do not adopt defined 3-D structures and thus are currently "unseen," or "dark." These proteins are extensively involved in diseases ranging from heart and infectious diseases to diabetes, cancer, Parkinson's and Alzheimer's.

"Our goal is to raise awareness about the potential societal impacts of a broad-based research infrastructure for these understudied proteins," said St. Jude structural biologist Richard Kriwacki, PhD. "We also want to develop educational programs that will address the origins of and potential cures for devastating diseases affected by these proteins."



Jun J. Yang, PhD

Gene variations offer clues to cancer risk

A small change in a single gene suggests why childhood acute lymphoblastic leukemia (ALL) has turned up in two generations of one family. Research led by St. Jude investigators identified the change and found other young ALL patients had variations in the same gene.

The *ETV6* gene plays an important role in the blood system. St. Jude researchers discovered that one copy of the gene is altered in a family in which the mother and two of three children are survivors of childhood ALL.

All three childhood cancer survivors carry the alteration, which is predicted to cause the gene to malfunction. The daughter who is cancer free has the same alteration. The father does not have cancer and does not carry the alteration.

When researchers checked an additional 4,405 children with ALL they found almost 1 percent had changes in the same gene. Research is underway to understand the magnitude of the risk associated with *ETV6* variations and develop recommendations for monitoring affected children and families. The family in this study has received counseling and follow-up care through the St. Jude Hereditary Cancer Predisposition Clinic.

"The results also suggest that inherited susceptibility to pediatric ALL may be more common than currently believed," said Jun J. Yang, PhD, of St. Jude Pharmaceutical Sciences. A report on this study appeared in the journal *Lancet Oncology*.

How salad dressing mirrors cell function

Have you ever noticed how oil and vinegar separate into droplets on a salad plate? St. Jude scientists have evidence that cells use the same process to stay organized and work properly.

The discovery answers a basic question of cell biology. The finding also shows a possible new way to treat devastating degenerative diseases like amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease; frontotemporal dementia; and inclusion body myopathy.

The mechanism is called liquid phase separation. It leads oil and vinegar to separate in salad dressing. St. Jude researchers found that under certain conditions the process may also prompt proteins with particular designs to condense into droplets inside cells. The droplets are likely the basis for temporary cell structures like stress granules. Many important cell functions take place in such structures.

Until now, the way stress granules form was not well understood. Neither was their connection to certain mutations in patients with ALS and related diseases.

This study provides that link. The findings have also fueled interest in developing treatments for diseases like ALS that work by blocking granule formation.

J. Paul Taylor, MD, PhD, a Howard Hughes Medical Institute investigator and chair of St. Jude Cell and Molecular Biology, and Tanja Mittag, PhD, of Structural Biology, led the research, which appeared in the journal *Cell*.



Joshua Wolf, MD

On the line: preventing blockages before they develop

Nearly every child undergoing cancer therapy receives a central venous catheter, or central line. This tube is inserted into one of the large veins leading to the heart. The line provides the blood products, medications and fluids that kids need to battle cancer. But central venous catheters have their own risks, such as blockages that can lead to life-threatening problems.

For reasons that are unclear, about 40 percent of patients develop central line blockages that require clot-dissolving drugs to clear the lines, or surgery to replace them.

"We know that having a blockage—even one that is successfully treated—is associated with an increased risk of infection, other complications and even death," said Joshua Wolf, MBBS, Infectious Diseases.

If these occlusions were predictable, they might be preventable, but until now there has not been any way to determine which patients are at risk. Wolf developed a new technique to monitor the resistance in patients' central lines by measuring the pressure required for a saline solution to flow through the line. A significant increase in catheter resistance or evidence of turbulent flow was linked to a nearly seven-fold increased risk of developing a blockage within the next few days.

Wolf's research shows that monitoring catheter resistance may help clinicians prevent the problem by finding patients at risk and intervening early to treat the blockage before it occurs.

Results of the study were published in the journal PLoS One.

Skin cancer therapy also targets brain tumor subtype

A targeted therapy used to treat advanced skin cancer in adults is also effective against a subtype of the brain tumor medulloblastoma. As a result of recent research at St. Jude, this therapy is now included in the St. Jude clinical trial for newly diagnosed pediatric medulloblastoma patients.

The drug, called vismodegib, is designed to block a key protein in the sonic hedgehog (SHH) signaling pathway. There are four subtypes of medulloblastoma, each with different genetic alterations.

The SHH pathway is switched on in about 60 percent of medulloblastoma tumors in adults and 25 percent in children.

Giles Robinson, MD, Oncology, says not all children with the SHH subtype will benefit from vismodegib.

"But for the right patients, these results mark the beginning of a new era of targeted therapy," he said. "The findings also highlight the importance of ongoing research to identify the genetic alterations that define who the right patients are and help identify those most likely to benefit from this drug, as well as those for whom different therapy is needed."

The findings were published in the *Journal of Clinical Oncology.*



Giles Robinson, MD

FAMILY FIRST



One couple's generosity nurtures their St. Jude "family."

BY KERRY HEALY

For Charles and Connie Cotros, family comes first. Throughout Charles' successful career in the food industry, he and his wife adhered to that crucial priority.

"We really love each other and spend as much time together as we can," Connie says.

In 1974, Charles sold his family's business in Memphis, Tennessee, to Sysco, a national restaurant food and supply distribution company. In a career that spanned more than 30 years, he served in various leadership positions including being named chief executive officer in 2000. Upon his retirement in 2003, he became interim CEO of Allied Waste Services in Scottsdale, Arizona.

"I only agreed to take the position on the condition that I would come home every weekend," he says.

Charles and Connie put their St. Jude family first, too. "We grew up right down the street from St. Jude," Connie says. "We knew it was a great thing that hospital founder Danny Thomas was doing, and that it was going to be successful."

Lifelong supporters of the hospital, the couple participated in various events benefiting St. Jude, including sponsoring a gala in Houston, Texas. The couple also established a charitable trust to be distributed to several charities upon the death of the surviving spouse. "St. Jude's share was the most," Charles says.

"We've got to find a cure. I hope what we have done will also encourage others to help." — Charles Cotros

But then the plan changed.

"After we established the trust, we decided we wanted to see the good we are doing now, while we are still alive," Charles says.

So the couple released those funds

to support the new inpatient floors in the Kay Research and Care Center, the hospital's newest patient care facility. The gift celebrated the couple's 54th wedding anniversary and honored Connie's deep love of the hospital and its mission.

"Our hearts go out to every child battling cancer," she says. "We visit the hospital often, and we always feel thankful when we see the kids, but sorrow at the same time, for what they are going through."

"As wealthy as we are in America, we've got to find a cure," Charles says. "I hope what we have done will also encourage others to help."

In June 2016, the couple will unite their entire clan—three children, 11 grandchildren and their St. Jude family when they visit the hospital to celebrate the unveiling of the patient care space named in Connie's honor and their granddaughter's birthday.

"Those are the best times," Connie says, "when we are all together." ■

st. Jude.

tideo gamers unite to raise funds for

By John Juettner

Ben Moody (at right) plays video games with St. Jude patient Navada Eschete.

Video games are no longer just entertainment for kids. Today they benefit the patients of St. Jude Children's Research Hospital.

In the modern world of gaming, massive sports arenas fill with spectators who watch professionals play video games competitively. Internet-streamed broadcast channels, where people watch and interact with gamers as they play, are viewed by millions. The business outpaces the music industry by \$20 billion annually.

The gamers who earn a living playing these games are using their popularity to give back through St. Jude PLAY LIVE. Created two years ago, this video game charity event has raised more than \$1.5 million for the hospital.

"I believe that if we are fortunate enough to capture the attention of other people, we should use that time to make a positive impact on their lives as well as on other people," says Ben Moody, a Twitch broadcaster known as DizzyDizaster.

Broadcasters like Moody fundraise during dedicated charity streams when they ask viewers for donations to St. Jude. Often they include incentives to increase fundraising, such as broadcasting themselves playing video games while dressed as one of the game's characters.

"I run my live streams under the assumption that people are coming in to get away from the stress of their lives and are looking for an escape," says Moody, who has raised more than \$17,000 for St. Jude. "What better way to help people feel better than to use our awesome time together to benefit kids in need?"

St. Jude PLAY LIVE isn't just for the professionals. Anyone can play-either online or off-to raise funds and earn prizes and student service hours.

Moody visited St. Jude before the 2015 St. Jude PLAY LIVE event. Afterward, he described the experience to his viewers, who communicated with him through a chat feature.

"During the fundraiser, I even had several chat members tell me stories about their own children who were positively impacted by St. Jude," Moody says. "When I saw what a profound impact St. Jude was having, and how many incredible streamers were already on board, I knew this was the way for us to go."

To learn more about or participate in St. Jude PLAY LIVE, visit playlive.stjude.org.



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—Judi Didcoct

St. Jude patient Angelica, acute myeloid leukemia

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St. Jude Heroes

St. Jude patient Adam Cruthirds (in white cap) joined more than 21,000 other participants in the recent St. Jude Memphis Marathon weekend. The event raised \$8.2 million for the hospital.

Adam completed the half marathon with a group of classmates and their English teacher. Since Adam's diagnosis of acute lymphoblastic leukemia, he and his family and friends have raised more than \$130,000 for St. Jude.

"I've never seen anyone work so hard toward a goal, much less while undergoing chemo. Adam truly is a hero," said his mom.



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