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Promise

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A Targeted Effort

Promising drug offers targeted therapy for children with high-risk acute myeloid leukemia.

By Mike O'Kelly



arshitha Bhandaru wriggles across an examination table wearing a smile as bright as the fluorescent lights that illuminate the cozy room inside the Leukemia and Lymphoma clinic at St. Jude Children's Research Hospital. A playful shadow on the table's crinkling white paper mirrors the 14-month-old's every move. Harshitha's father, Muraly, and her mother, Chandana, steady the toddler while her 6-year-old brother, Praneeth, employs an amusing variety of methods to elicit grins from his younger sister.

In two days, Harshitha will receive a bone marrow transplant to treat high-risk, relapsed acute myeloid leukemia (AML).

When she was 3 months old, Harshitha was found to have leukemia cutis—an abnormal proliferation of white blood cells or leukocytes that create lesions under the skin. Tiny bumps formed on her body and face. Four rounds of chemotherapy sent the AML into remission, but by summer 2011, a large lump had developed on her forehead. The cancer had returned.

"Harshitha started chemotherapy again, but it was no use," Muraly says. "The bumps continued to get bigger, and she had more leukemic blasts in her blood."

As treatment options became ineffective, Muraly desperately searched the Internet for alternatives. He found the St. Jude website during a 2 a.m. search. After receiving a referral, the family arrived at the hospital days later. Hoping to achieve remission and make a transplant possible, physicians enrolled Harshitha in a treatment study designed specifically for relapsed AML.

Phase I

Using research gleaned from the laboratory of Sharyn Baker, PharmD, PhD, of St. Jude Pharmaceutical Sciences, oncologist Hiroto Inaba, MD, PhD, had developed a Phase I study of 11 children with leukemia who had relapsed or failed to respond to therapy.

The patients received the drug sorafenib as part of multi-drug therapy that included the conventional chemotherapy drugs clofarabine and cytarabine. Clinicians administered sorafenib twice a day during the study's first week. For days eight through 12, the

St. Jude oncologist Hiroto Inaba, MD, PhD, plays with Harshitha Bhandaru during a checkup. children received that medication plus the standard chemotherapy drugs; afterward, the patients received only sorafenib.

Leukemic blast cells decreased in 10 of the children after the study's eighth day. Eight patients experienced remissions following the combination of sorafenib with clofarabine and cytarabine. A ninth child had a partial remission.

The goal of the combination therapy is to achieve remission—a level of less than 5 percent of leukemic blasts in the bone marrow. These remissions were obtained not only in all five patients with a rare *FLT3-ITD* genetic mutation, but also in four of the six patients without the mutation such as Harshitha.

"For these patients, sorafenib offers hope for the first time that their disease can be controlled so that they can be considered for a bone marrow transplant," Inaba says.

Replacing the diseased bone marrow with cells from a healthy donor currently offers such high-risk AML patients the best chance for cures.

Harshitha's protocol was based on the results of that Phase I study. A week after beginning the treatment plan, her bumps disappeared. After a month, her leukemic blasts were drastically reduced and her AML was in remission—meaning that she could now receive a transplant.

"St. Jude has taken care of everything. They helped to save my daughter's life," Muraly says.

Bridging lab and clinic

Stories like Harshitha's are made possible at St. Jude through partnerships between researchers in the laboratory and health care practitioners in the clinic who are all on the same campus.

"Communication and teamwork are important here at St. Jude," Inaba says. "When I visit other places to explain our research, I talk not only of the close distance between the buildings that allows us to bridge clinical and basic research, but I talk about the value of collaboration."

Inaba and Baker worked together to first identify a signaling-inhibiting drug for use in the study. Sorafenib is a tyrosine-kinase inhibitor, which means that the drug targets the tyrosine family of proteins and the receptors on the surface of cells where the proteins act. Mistakes in these proteins, including FLT3-ITD, are associated with the unchecked growth and survival that characterizes cancer.

Baker's laboratory had already shown that combining sorafenib with cytarabine produced a strong anti-cancer effect against human AML cells in the laboratory and in a model of the disease. Sorafenib had also been approved for use by the Food and Drug Administration in the treatment of adults with kidney and liver cancers.



Findings by Sharyn Baker, PharmD, PhD (at left), of Pharmaceutical Sciences and her team (which includes Christina Drenberg, PhD, and Steven Zatechka, PhD, above) enabled oncologist Hiroto Inaba, MD, PhD, to develop a new protocol for children whose leukemia had relapsed or failed to respond to therapy.

Baker's research found that sorafenib is metabolized differently in adults and children, resulting in higher levels of a compound with potent toxicity against normal and leukemia cells. Because of the differences, St. Jude investigators made adjustments to the treatment and closely monitored patients to avoid temporary but debilitating skin complications.

In the laboratory, Baker's team pinpointed the exact combination of drugs that proved most effective.

"We looked into the mechanisms of why treatment might be more effective when they are given together," Baker says. "There can be many mechanisms, but we focused on efflux pumps, which are drug transporters that sit on the cell membrane. Drugs like sorafenib can prevent cytarabine from being pumped out of the leukemic blasts. When you combine the drugs, sorafenib allows cytarabine and its active metabolites to accumulate and get more anti-tumor activity."

There is still more to be learned about sorafenib's effects and when to properly administer it, Baker says. Observations made through application in the clinic are used as a checklist in the laboratory to determine which methods should be investigated further and what should not be pursued.

"These are questions and issues that we are looking at now in our laboratory models," Baker says. "We still have a lot to learn about the drug and its role in AML and how best to combine it with chemotherapy and with other targeted agents."

If these results are confirmed in larger studies, the drug will mark a new era in the treatment of AML and offer new opportunities for patients like Harshitha.

WriTinG The NexT ChApTer

By Mary Powers

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For many years, St. Jude researchers have been investigating the connection between genetics and pediatric cancer. Those approaches continue to have dramatic implications for clinical care.

ore than 25 years have passed since a St. Jude Children's Research Hospital investigator published the first scientific paper describing a genetic abnormality in a childhood cancer. Now a new generation of researchers is hard at work using modern technology to mine the genome for clues about cancer that can be translated into new and better tools for treating these diseases.

The genome is the complete set of instructions needed to assemble and sustain life. In humans this instruction book is written in the four-letter alphabet of the DNA molecule (T-C-G-A). The estimated 3 billion letters of the human genetic code are organized into 23 chromosomes carried in nearly every cell.

Long before the entire human genetic code was first deciphered, St. Jude investigators were focusing on missteps in that code. In the 1980s, the hospital expanded its efforts to understand the role genetic alterations play in cancer, investing in the faculty, equipment and facilities to take advantage of new technologies that made searching the genome easier. Dr. William E. Evans, St. Jude director and CEO, says that by the 1990s the benefits were evident.

"St. Jude investigators made a number of key discoveries

about childhood cancers and pharmacogenomics that were diagnostically important and potentially therapeutically important as well," he says.

The list includes Evans' own research that showed normal genetic variation could dramatically affect how patients responded to certain drugs.

Pinpointing DNA defects

A recently published study from Evans' laboratory identified a defect in the DNA repair system. That mistake might leave some young leukemia patients less likely to benefit from a key chemotherapy drug and at greater risk of relapse. Knowledge of the defect might eventually be used to help identify a new group of high risk leukemia patients.

The work focused on a protein named MSH2, which is involved in DNA repair. Earlier work had linked low levels of MSH2 to an increased risk of certain cancers. Low MSH2 was also associated with resistance to mercaptopurine, a drug that is a backbone of childhood acute lymphoblastic leukemia (ALL) treatment.

The most recent study identified the cause of low MSH2 levels. Investigators demonstrated that the *MSH2* gene contained no errors and the leukemia cells were making MSH2 protein.

When researchers screened DNA from 90 newly diagnosed



Postdoctoral fellow Barthelemy Diouf, PhD, and his colleagues are using information gleaned from the human genome to find better ways to diagnose and treat cancer.

ALL patients at nearly 1 million spots in the genome, they found ALL cells from patients with low MSH2 protein were missing at least one of four genes that regulate the breakdown of MSH2 in cells. As a result, the MSH2 was being eliminated more rapidly and the DNA repair system in the leukemia cells operated less efficiently.

A check of the cancer cells of another group of St. Jude ALL patients found that about 12 percent were missing at least one of the same genes involved in the breakdown of MSH2. Scientists also found evidence that one or more of the genes that play a role in MSH2 levels in cells are missing in more than 13 percent of adults with a form of colon cancer and 16 percent with adult ALL.

"If confirmed, this suggests a patient's MSH2 status might someday be used to guide treatment," says the paper's first author, Barthelemy Diouf, PhD, a postdoctoral fellow in Evans' Pharmaceutical Sciences laboratory.

Improving clinical care

Another recent example of how laboratory research aids efforts to improve clinical care involved the work of Suzanne Baker, PhD, and postdoctoral fellow Barbara Paugh, PhD, both of Developmental Neurobiology; Alberto Broniscer, MD, of Oncology; and their colleagues. The investigators led an international study that explored a different tumor's genome for insight into that tumor's biology and wound up with promising new treatment targets.

The study was the largest ever of a rare brain tumor known as diffuse intrinsic

pontine glioma (DIPG). The results helped launch a Phase I study of an experimental drug against DIPG and related tumors. That is good news, since survival rates for children with this tumor remain low.

For this study, scientists checked for deletions or additions of genetic material at more than 1 million locations across each tumor's genome. The results revealed that approximately one-third of the tumors included extra copies of a gene that promotes cell division and survival. A clinical trial using a drug designed to specifically counteract the increased activity associated with excess copies of this gene is currently underway at St. Jude. Other genetic changes identified in these tumors will likely provide the basis for planning additional clinical trials.

Across the St. Jude campus, other researchers are also writing chapters in the history of childhood cancer in the 21st century. Those investigators include Richard Gilbertson, MD, PhD, who heads the hospital's Comprehensive Cancer Center, Kip Guy, PhD, Chemical Biology and Therapeutics chair; Peter McKinnon, PhD, of Genetics; Mary Relling, PharmD, Pharmaceutical Sciences chair; Charles Mullighan, MD, of Pathology; and James Downing, MD, the hospital's scientific director, who is also leading the St. Jude Children's Research Hospital -Washington University Pediatric Cancer Genome Project.

The next chapter

The past few decades of genomic work helped set the stage for the Pediatric Cancer Genome Project. Launched in 2010, the three-year project aspires to sequence the complete normal and cancer genomes of 600 children and adolescents with some of the most challenging and least understood types of leukemia and tumors of the brain, spine and other cancers of the bone, muscle and connective tissue.

The project is on target to meet that goal, with important discoveries already emerging.

"To date we have completed the sequencing of more than 220 pediatric cancer samples," Downing says. "A detailed analysis of the data has revealed major new insights into the genetic lesions that underlie some of the most aggressive cancers seen in the pediatric populations, including acute leukemia, brain tumors and solid tumors. These findings will ultimately change the way we diagnose and treat these specific cancers."

Scientists are using the information to identify changes that play a central role in the tumor's formation, spread or survival. The answers are revealing new differences between adult and childhood cancers, providing insights into cancer biology and giving clues about novel ways to use existing chemotherapy agents. The lessons learned will likely help lay the foundation for a new era of personalized therapy.

"When it comes to cancer, we still do not know which genes are the bad actors or the most important mutations in genes or even the genes that are mutated in most cancers," Evans says. In the coming months and years, more exciting discoveries are sure to occur—advancements that will continue to offer patients around the world reasons for hope. ●

Sweet Relief

Where does a family turn when their son is given a zero percent chance of survival?

hen Chris and Ginger Braun discovered that their infant son had a brain tumor, they were overwhelmed not with terror or dread, but with a feeling of relief.

"You probably don't hear many parents say that it was a relief to be told their child has cancer," Ginger says, "but Carson was almost lifeless. He was 1 year old and couldn't hold his head up. We had been trying for months to find out what was wrong." BY ELIZABETH JANE WALKER

Carson and his twin, Cameron, were born prematurely in February of 2003. In the fall of that year, Carson began having frequent bouts of crying and vomiting. After visiting the pediatrician three times in one week, the baby underwent a CAT scan at a hospital in Louisiana.

"First, they told us that he had a huge brain tumor and probably wouldn't make it," Ginger recalls. "Then they told us that it was probably a birth defect. They even sent the scans to other hospitals to try to get a diagnosis. We got nothing, nothing, nothing."

Doctors inserted a shunt to remove fluid that had accumulated in Carson's brain and sent him home. The day after the twins' first birthday, his condition took a turn for the worse.

"He wouldn't wake up; he was pretty much lifeless," Ginger says. "We rushed him to the hospital, where they put him in the ICU and told us they didn't know whether he would make it or not."

This time, a biopsy indicated that Carson had a type of malignant brain tumor called nodular medulloblastoma.

"By that point, he was like a newborn baby," Ginger says. "He couldn't eat or hold his head up, and he only weighed 15 pounds."

Lifesaving treatment

The Brauns learned that St. Jude Children's Research Hospital had a treatment plan that might save their son's life.

"The doctors told me, 'He has a 30 percent

chance of survival,' and I thought, 'Great! Thirty percent is fantastic when I've been told that he has a zero percent chance back home,''' Ginger recalls.

She and her husband already knew a little about St. Jude before arriving in Memphis. Soon after their marriage, Chris and Ginger had begun buying tickets for the St. Jude Dream Home[®] Giveaways in their area.

"We had heard about the hospital and wanted to support it by buying one of those tickets," Ginger says, "but we never imagined that we would



have to take one of our children there.

"We were scared to death to walk through the doors of that place," she continues. "It was so overwhelming, but they took good care of us from the first moment. My biggest concern was my family. I said, 'I can't do this without having both of my kids with me. Can Cameron come, too?' and the people at St. Jude said, 'Yes, we strive to keep families together.' What a relief that was."

In February of 2004, neurosurgeon Robert Sanford, MD, removed the tumor, which was the size of a large orange. Carson received 20 weeks of chemotherapy, including some treatments administered directly into the fluid surrounding his brain and spinal cord. That regimen was followed by five weeks of radiation therapy and 20 additional weeks of lessintensive chemotherapy.

Once Carson completed his treatment, he faced extensive therapy to gain skills that he had not yet developed. Because he had been so weak and sick during his first two years of life, Carson had not learned how to eat solid food. When he was 3 years old, he began eating pudding and banana baby food.

"He didn't like the texture of food," Ginger explains. "It was a long process and took lots of therapy to get that child to put anything in his mouth."

Benefiting from progress

During a routine checkup in January of 2011, Chris and Ginger learned that their son had developed a second cancer—a tumor unrelated to the

medulloblastoma. This time, he had a grade II meningioma, a slow-growing brain tumor that originates in the meninges, the membranes covering the brain and spinal cord. As they grow, meningiomas can compress adjacent brain tissues.

"It had been six years since his original diagnosis. You never think this is going to happen," Ginger says.

"Carson is truly a miracle," says Ginger Braun, "and it's all because of St. Jude."



Carson receives a checkup from Ibrahim Qaddoumi, MD, and Pediatric Nurse Practitioner Liz Burghen. The active 8-year-old has made dramatic strides since his first visit to St. Jude, when he was unable to eat food or hold up his head.

The Brauns discovered that surgical technology had improved significantly since Carson's first bout with cancer. Neurosurgeon Frederick Boop, MD, now had access to a new imaging technique called intraoperative MRI (iMRI).

In the past, surgeons removed only the tumor that they could see; afterward, the patient would receive an MRI to determine whether the entire tumor had been removed. The iMRI, however, enables a surgeon to examine the tumor and confirm its successful removal while the patient is under anesthesia. If any additional tumor remains, it can be removed immediately.

"We have a computer system that allows us to do an MRI before surgery and build a 3-D computer model of the child's brain and his tumor," Boop says. "We can point to a location on the model and it shows us where we are inside the brain. So if we have a tumor that's deep in the brain and the surface looks normal, we can use that system to tell us what the best trajectory to the tumor is. We used that process on Carson."

Oncologist Ibrahim Qaddoumi, MD, says the 8-year-old's prognosis is good. "Because we were able to remove the entire tumor, the chance of the meningioma returning is low. Survival is not an issue anymore. Now we're concentrating on further improving his quality of life."

Windows on the world

One sunny Saturday morning seven years ago, Chris, Ginger and their sons gazed out of the hospital window as thousands of people ran past the campus during the St. Jude Memphis Marathon and Half Marathon. "For hours, runners streamed by," Ginger says. "I was amazed. I thought, 'Wow—all of these people are doing this for the kids!' I said, 'I can do that. I am *going* to do it."

Carson completed his treatment the following March. In December of 2005, Chris and Ginger laced up their running shoes and competed in the 5K race that is held in conjunction with the marathon. Participation in that event provided Ginger with further inspiration.

"When I got to the finish line and saw the halfmarathon runners, I said, 'I can do more than this for these kids. If they can endure the treatment and the days of being so sick, I can run a half marathon. I am going to do it."

And so it began. In December of 2011, Ginger once again laced up her shoes and participated for the seventh consecutive year. Her goal? To raise \$10,000 for the hospital that saved her child's life.

"We want to give back because they gave so much to us," she explains. "Most people know that St. Jude provides treatment, food and housing, but they don't know about the little behind-the-scenes things, like the gift cards that we used to buy groceries; like the fully furnished apartment at Target House, which included two brand-new cribs and a Pottery Barn changing table for the twins. We had everything we needed to take care of both of our kids and to make sure that we could stay together as a family."

On the run

Today, it's hard to believe that the active and cheerful second-grader ever struggled to attain basic milestones.

"Carson is a social butterfly. He makes friends easily, and everybody loves him," observes his mom. Fascinated by computers, Carson spends hours playing computer games. He also enjoys swimming and riding his bike. Ginger attributes Carson's achievements to sheer determination.

"He's headstrong," she says. "His attitude is, 'By golly, I can do it, and you are not stopping me.' At one point, the doctors warned us that he might never be able to sit up on his own. Today, he runs.

"Carson is truly a miracle," she continues, "and it's all because of St. Jude." ●

The Science of Support

One couple champions the importance of research to the

St. Jude mission.



Bob and Mary Jane Engman pause with Mary Relling, PharmD, Pharmaceutical Sciences chair, after the unveiling of their plaque outside of the pharmacogenomics laboratory last summer.

Rengman received the Cardinal Stritch Donor of the Year Award from the ALSAC/St. Jude Boards of Directors and Governors last summer, but it was a gift they received after the award ceremony that they cherished most.

"On our way out of the door, a gentleman pushing his wife in a wheelchair stopped me," Bob recalls. "He said, 'You made it possible for us to have our daughter eight years longer than we would have.""

The couple credited St. Jude with allowing their daughter to survive those extra years, and the Engmans for helping make that care possible. The gentleman removed his St. Jude tie and handed it to Bob as a gesture of appreciation. "It brought tears to our eyes," Mary Jane says.

For nearly three decades, the Engmans have supported the hospital's research and patient care. In 2000 they endowed the John Rodman Lectureship in

By Janice Hill

Pharmaceutical Sciences and in 2010 made a generous gift naming the pharmacogenomics lab of William E. Evans, PharmD, St. Jude director and CEO, and Mary Relling, PharmD, Pharmaceutical Sciences chair.

The Engmans began supporting St. Jude in the early 1980s. "We were personally impressed by its reputation in care and that children can go there for free," Mary Jane explains. Soon the hospital's research also captured their interest and support.

An engineer and entrepreneur, Bob believes science is the answer to many issues that plague mankind. A few years ago he read two books that piqued his interest in biology, genetics and the value of DNA research to determine the causes and best treatment for diseases. "I became excited about the pharmacogenomics research taking place at St. Jude," he says.

A graduate of the University of Utah, the same institution where Relling earned her doctorate, Bob began his career in the 1950s just as magnetic amplifiers and transistors were introduced, and he quickly became interested in their potential. In 1974 he founded Opto 22, which became the major supplier of liquid-filled, solid-state relays for large-frame computer disc drives. The company is now run by their son, Mark. Bob and Mary Jane also have two other children, Carrie and Elaine.

The couple first visited St. Jude in 2006. "We fell in love with the place, from the way children are treated to the amount of research that is being accomplished," Bob recalls. "I am very impressed by the way St. Jude is run—it is a flat (non-hierarchal) organization where everyone speaks with everyone else. Doctors and patients eat together. That is the same way we ran our company."

The Engmans recommend that everyone visit the hospital. Bob says, "You will immediately realize the value of science in alleviating suffering." ●

Promise and Hope

Promesa y Esperanza unites the Hispanic community in support of St. Jude



St. Jude patient Emilio Garabito (at right) participates in a *Promesa y Esperanza* radiothon. Since its inception in 1997, the program has raised more than \$74 million for St. Jude.

The incredible success of the *Promesa y Esperanza* (Promise and Hope) radiothons in the Hispanic community has launched fundraising for St. Jude Children's Research Hospital into the open arms of Latinos throughout the United States.

"Promesa y Esperanza has helped build the platform for Hispanic efforts at the national and regional level for ALSAC," says Evelyn Homs, senior director of multicultural marketing for ALSAC, the fundraising organization for St. Jude.

Promesa began in 1997, with just three participating radio stations. Fifteen years later, 106 radio stations in 65 markets are involved in the Spanish-language fundraiser, which has generated more than \$74 million in donations and pledges for the kids of St. Jude.

Univision Radio, the top Spanish radio network in the United States, has partnered with St. Jude for 14 years. "At the core of the Hispanic community is a strong value in families and children," says Univision Radio President Jose Valle. "The St. Jude mission

By Leigh Ann Roman

tugs at the heartstrings of many Hispanics—that no child is ever denied treatment because of a family's inability to pay."

"At St. Jude, we take care of the child and family," Homs adds. "Our mission resonates strongly with this culture."

ALSAC's bilingual regional event staff is key to the success of *Promesa* and other fundraising efforts among Hispanics, Homs says. Thanks to their cultural connections, the staff can leverage their radiothon relationships into Hispanic involvement with other St. Jude fundraisers.

Maria Cardenas Hultine, senior bilingual event marketing representative for ALSAC in Atlanta and a former St. Jude patient, has seen that happen in her region. The Hispanic Clear Channel radio station in Atlanta helped with the *St. Jude Give thanks. Walk.*TM in November by running on-air promotions, forming a walk team and broadcasting from the event.

Valle also sees the impact of Univision's radiothon on listeners.

"The response from our listeners has been overwhelming,"

he says. "Events such as the galas, triathlons and walkathons have increased in size and fundraising, thanks to the phenomenal name recognition the radiothon has generated for St. Jude."

Despite the dominance of the Internet in this digital age, radio remains the most valuable medium to access the Hispanic community.

"Radio is still providing information to the community that is hard to get in their own language," Homs says. "Every time there is a Hispanic event in the community, radio is bringing it to them."

The Hispanic population nationwide has increased from 35.3 million in 2000 to 50.5 million in 2010, according to the U.S. Census. Hispanic donors make a sizeable contribution to overall ALSAC fundraising, with more than \$35 million attributed to 394,005 donors through Hispanic programs for fiscal year 2011, Homs says.

And once Hispanics start giving to St. Jude, they continue. "Our partner stations commit with their hearts," Hultine says, "and they understand we value their help." •

Research Highlight

Gene therapy achieves early success against hemophilia B

St. Jude researchers have developed a treatment that offers hope to patients with the bleeding disorder hemophilia B. In a recent clinical trial conducted at the University College London (UCL), symptoms improved significantly in hemophilia B patients following a single gene therapy treatment.

The findings mark the first proof that gene therapy can safely reduce disabling, painful bleeding episodes in patients with the blood disorder. Results of the Phase I study appeared in the *New England Journal of Medicine*.

Hemophilia B is caused by an inherited mistake in the gene for making a protein called Factor IX, which is essential for normal blood clotting. Previous efforts to ease hemophilia B symptoms by introducing a correct copy of the gene had been unsuccessful. The current study used a harmless virus as the vector to deliver the Factor IX gene along with additional genetic material into each patient's liver. The vector used in the study was produced at the Good Manufacturing Practices facility on the St. Jude campus. The approach was jointly pioneered by St. Jude and UCL, initially in the lab of study co-author Arthur Nienhuis, MD, of St. Jude Hematology.

As is often the case with experimental therapies, this study was conducted in adults to ensure the treatment was safe and effective. Plans are to include children in future trials. Because they have not yet experienced the joint damage and other complications of the disease, children undergoing gene therapy will likely benefit even more than adults do.

"These results are highly encouraging and support continued research. More patients are scheduled to be enrolled in future trials scheduled to begin later this year," said the study's senior author, Andrew Davidoff, MD, St. Jude Surgery chair.

> "These results are highly encouraging and support continued research."



In-house screening reduces stroke risk

Gail Fortner, RN (above), uses an ultrasound to measure blood flow in arteries leading to a child's brain. The procedure, known as transcranial Doppler (TCD) ultrasound, is the most effective tool for predicting primary stroke in patients with sickle cell anemia.

Sickle cell patients at St. Jude undergo annual TCD screenings at their regular clinic visits. Most sickle cell centers require patients to go to radiology or neurology appointments to have the test done.

With the knowledge obtained from TCD screenings and the treatment offered to those considered to be at high-risk for strokes, clinicians are able to prevent stroke in many children with sickle cell anemia.

"Today, 99 percent of our high-risk patients ages 2 to 16 are screened for stroke. In published data from other institutions, that number is from 49 to 58 percent," Fortner said.

She and Beth McCarville, MD, Radiological Sciences, are training Brazilian and Jamaican physicians who will be collaborating with St. Jude and Baylor College of Medicine on a future multicenter trial. This will be the first NIH-funded international sickle cell disease clinical trial and the latest example of the hospital's collaboration on research that helps to improve the quality of life for sickle cell patients.





Molecule serves as key in some protein interactions

St. Jude structural biologists Brenda Schulman, PhD (center), Daniel Scott, PhD, and Julie Monda have identified a mechanism that facilitates some protein interactions that are workhorses of cells. In the process, they have also found a potential new cancer drug development target.

The discovery involves a chemical known as an acetyl group. About 40 to 80 percent of human proteins have this chemical added to the amino acid at one end of the protein during a process known as N-terminal acetylation. Although it has long been recognized that proteins are N-terminally acetylated, until now it was unknown how that process could serve specific functions.

The researchers showed that much like a key must fit precisely to work a lock, the acetylated end of one enzyme fits perfectly into a deep pocket on the surface of another protein. The connection helps accelerate the activity of a protein complex that is involved in regulating cell division and that has been linked to cancer. The research appeared in the journal *Science*.

The findings have potential implications for drug discovery and for understanding basic mechanisms governing the interaction of possibly thousands of proteins, said Schulman, who is also a Howard Hughes Medical Institute investigator.

"The work presents a major new concept in protein-protein interactions," she said. "This raises the question of whether similar 'keys' on thousands of different proteins also unlock doors to allow them to function."

Brain tumor research yields new treatment options

St. Jude investigators have pioneered a new approach to drug development and have identified dozens of potential new treatments for ependymoma, a rare tumor of the brain and spine.

The new system combines the latest drug screening technology with the first accurate laboratory model of the tumor.

Using the method, researchers have identified new and existing drugs as possible ependymoma treatment candidates. The drugs were identified by screening 5,303 existing medicines, natural products and other compounds for activity against the tumor, which affects children and adults.

The list of candidate drugs included 5-fluorouracil (5-FU), which has been widely used to treat adult cancers but has not been formally tested against ependymoma.

Based on study results, St. Jude is now planning a clinical trial of 5-FU in young ependymoma patients, said senior author Richard Gilbertson, MD, PhD, Comprehensive Cancer Center director.

The work was published recently in the scientific journal *Cancer Cell*.

Researchers hope to use the same system to expand chemotherapy options for patients with other cancers. Rather than waiting years for clinical trial results, this system promises to take just months to provide key information about a drug's effectiveness and optimal administration.

Based on study results, St. Jude is now planning a clinical trial of 5-FU in young ependymoma patients.

Research Highlights



Study addresses survivors' neuromuscular problems

Kirsten Ness, PhD (above), of St. Jude Epidemiology and Cancer Control, is principal investigator of research that is spurring efforts to address the neuromuscular problems of some cancer survivors.

In a study recently published in the journal *Cancer*, Ness and her colleagues found that high doses of two drugs widely used to treat children with acute lymphoblastic leukemia (ALL) left nearly half of adult survivors in their mid-30s with walking, balance and other limitations typical of someone decades older.

The study is the first to document the association between high doses of methotrexate and the muscle, joint and nerve problems that affect some long-term survivors of childhood ALL. Adult survivors whose treatment included high cumulative doses of the drug vincristine were also identified as being at increased risk of reduced ankle flexibility, reduced leg strength and difficulty walking.

The information was collected as part of the St. Jude LIFE study that provides ongoing clinical follow-up to thousands of St. Jude cancer survivors.

"These survivors do not complain of pain or numbness, but many have evidence of a mild motor neuropathy that affects their ability to walk and leaves them at risk for a variety of problems later in life," Ness said.

Simple stretching and strengthening exercises may help ease the problems, she added.

Nasal flu vaccine safe for young cancer patients

New St. Jude research demonstrates that both the flu shot and the nasal vaccine are safe for use in young cancer patients. The finding is important because the influenza virus poses a severe risk to cancer patients with immune systems weakened by their disease and treatment. Flu can also cause life-threatening illness and delay chemotherapy.

The new findings will not change recommendations that pediatric cancer patients receive flu shots, which deliver a vaccine made from killed flu viruses, rather than nasal vaccines, which use a different form of influenza virus to trigger a protective immune response. But the research should ease any lingering concerns that pediatric cancer patients will contract flu following direct or indirect exposure to the nasal vaccine.

The vaccine, which is marketed as FluMist, uses live, but weakened flu virus to trigger protection.

The study is the largest yet to compare the safety of the two flu vaccines. Patricia Flynn, MD, Infectious Diseases, was senior author of a paper on this topic, which appeared in the *Journal of Infectious Diseases*.

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Let us eat cake

Both *Promise* magazine and St. Jude Children's Research Hospital are celebrating anniversaries. This is the 50th issue of *Promise*, which was launched in 1998. This year, the hospital also celebrates a monumental milestone—five decades of finding cures and saving children. Look for a special issue marking the hospital's anniversary in April of this year...and go ahead: Celebrate!

Outreach program is national model

A marquee outreach program developed at St. Jude is a national model for raising awareness about sickle cell disease, the world's most prevalent genetic disorder.

Approximately one in 12 African Americans has sickle cell trait. Sickle cell disease is also prevalent among those of Caribbean, Latin American, Mediterranean or Middle Eastern descent.

The Know Your Sickle Status program, or K.Y.S.S., provides free educational programs and screenings to families affected by sickle cell trait and sickle cell disease. K.Y.S.S. offers awareness education to at-risk populations, particularly teenagers and young adults.

"If one parent has sickle cell trait and the other parent has sickle cell trait or any other abnormal hemoglobin trait, the couple has a one-in-four chance of having a child with sickle cell disease. That's why it is important for people to know their status," said Yvonne Carroll, RN, director of Patient Services in St. Jude Hematology.

Coordinated by Charlotte Hoyle of Hematology, the peer education component of K.Y.S.S. targets African-American teenagers and young adults who are at risk for having children with sickle cell disease. St. Jude has one of the largest sickle cell centers in the country. Approximately 800 patients, from infants to teenagers, are treated at the center.

To access sickle cell resources and materials at St. Jude, visit *www.stjude.org/sicklecell*.

Hormone research may lead to more targeted drug development

Research led by St. Jude scientists advances a strategy for taming the side effects and enhancing the benefits of steroids and other medications that work by disrupting the activity of certain hormones.

The approach relies on a small molecule developed at St. Jude. In this study, scientists showed that a compound known as SJ-AK selectively blocked the activity of genes in a cell signaling pathway regulated by thyroid hormone. SJ-AK also affected cells growing in the laboratory, reducing cell proliferation as well as the production and secretion of a growth hormone regulated by thyroid hormone.

The research appeared in the journal ACS Chemical Biology.

The findings raise hope that compounds like SJ-AK will lead to drugs with more tailored effects by selectively controlling signaling pathways that switch genes on and off.

"This study offers the first evidence that it is possible to shut down a portion of the signaling network activated by a particular hormone," said the study's senior author, R. Kiplin Guy, PhD, chair of Chemical Biology and Therapeutics at St. Jude.

Such selectivity could lead to a new generation of medications with greater effectiveness and fewer side effects. The new treatments could include steroids that fight leukemia or suppress the inflammation associated with autoimmune disorders without affecting metabolism or bone strength.

"This study offers the first evidence that it is possible to shut down a portion of the signaling network activated by a particular hormone."

Perspective

Stuck Like Glitter

Sometimes children need more than medical treatment. They need glue and paint and crayons...and someone to listen.



Patient Coralie Martinez joins Patty Stephens at an arts-and-crafts table in the leukemia/lymphoma waiting area.

As a volunteer at St. Jude Children's Research Hospital, I spend a lot of time covered in glitter. Every Wednesday, I have fun doing arts and crafts with families at the hospital. For several days afterward, I'll find glitter stuck to my face, my clothes, my skin. But that's not the only thing I take with me when I leave each week. I think about those families—their challenges, their stories. And often, I remember my brother.

In 1963, my little brother died of leukemia in a North Carolina hospital. My mother had heard of the new hospital named St. Jude, but she had other children and no family support, so traveling to Memphis was impossible. It probably wouldn't have mattered anyway, because during that era only 4 percent of children survived leukemia. My brother was $3\frac{1}{2}$ years old when he passed away.

I worked as a nursing assistant at St. Jude in 1978, while attending nursing school. Occasionally, I'd meet children who reminded me of my brother. Survival rates were still low in those days, and it became difficult for me to see those children. After graduation, I spent my nursing career working at other hospitals, eventually taking early retirement because of multiple sclerosis.

I feel like my little brother still leads me places. In 2004, I returned to St. Jude as a volunteer, where I was assigned to the outpatient leukemia/lymphoma area, working with children who have the same disease that my brother had. Sitting at that table, doing arts and crafts, children and their parents relax and open up. They talk about what's going on in their lives, and I just listen. Sometimes having someone to hang around with is all you need.

Coming from a medical background, I appreciate all that St. Jude does for these families. St. Jude provides housing, travel expenses and amazing medical care. The cost for cancer treatment is staggering, but St. Jude covers those costs.

When my brother got sick, he was handed a death sentence. Today, children with the same kind of cancer have a 94 percent survival rate, which to me is mind-blowing. St. Jude uses its resources wisely in order to make those kinds of medical advances. I wish that all donors would visit St. Jude to see how their money is being spent. If they walk through the hospital for just a few minutes, they'll know that they're making a wise investment.

I love spending time with the children at St. Jude. Together, we paint and we glue and we color. We laugh and talk and make a mess. I think about what my family went through decades ago, and I see how much St. Jude offers these children. And I reach for that glitter.

A hospital volunteer since 2004, Patty Stephens serves as president of the St. Jude Auxiliary, which provides volunteer support and raises funds for the hospital. She is also the 2011 winner of the Sheryl K. Nienhuis Memorial Volunteer Service Award. From St. Jude patient to survivor, Micah 10 years old



She was given more than hope. She was given another chance.

When Micah was 11 months old, she got sick and lost the ability to stand. She was referred to St. Jude Children's Research Hospital[®], where doctors found she suffered from stage IV neuroblastoma. Her treatment included radiation and surgeries to remove the tumor.

Today, Micah is cancer free, thanks to support from friends like you. She takes part in the After Completion of Therapy program at St. Jude, which helps her and other patients stay healthy as post-treatment survivors. Now Micah can focus on her dreams of being a designer and an actress when she grows up.

You can help St. Jude continue its lifesaving mission and make the difference of a lifetime by creating your own legacy through your estate plans. Your wishes will be honored to help ensure that St. Jude never stops looking for cures that save children.

Call us at 1-800-395-1087 or visit us online at www.stjudelegacy.org.



Micah, pictured at age 1 neuroblastoma



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CHANGE SERVICE REQUESTED

Supermodel Cindy Crawford recently toured St. Jude, where she spent time with patients and families. Crawford is a long-time supporter of the hospital and is dedicated to continuing to raise awareness about the St. Jude mission in 2012 and beyond. Crawford is joined by (from left) JaLise Fleming, Raul Calix, Arianna O'Neal and Evan Hamilton.



Finding cures. Saving children.