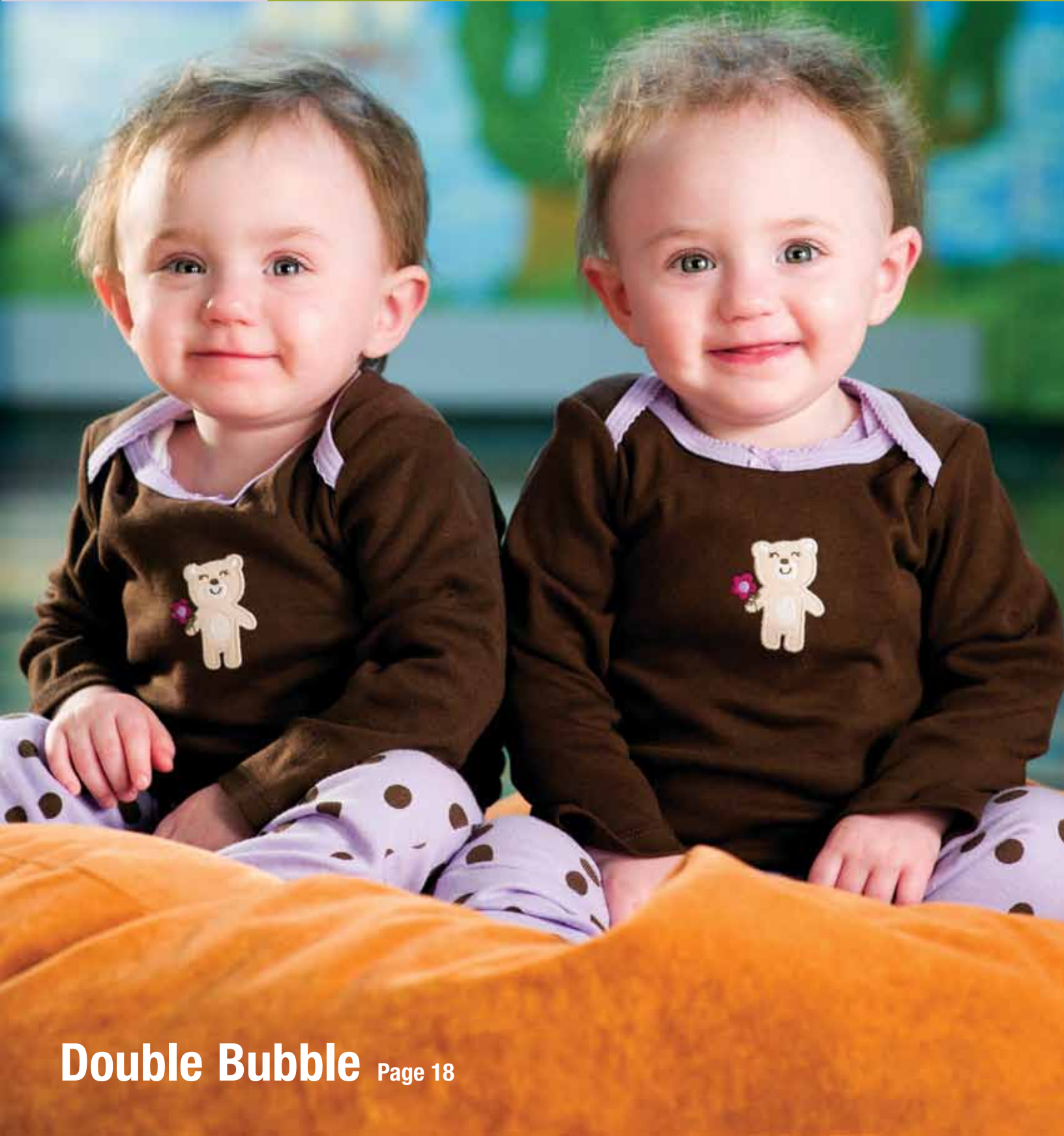


Promise

SPRING 2011



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Promise

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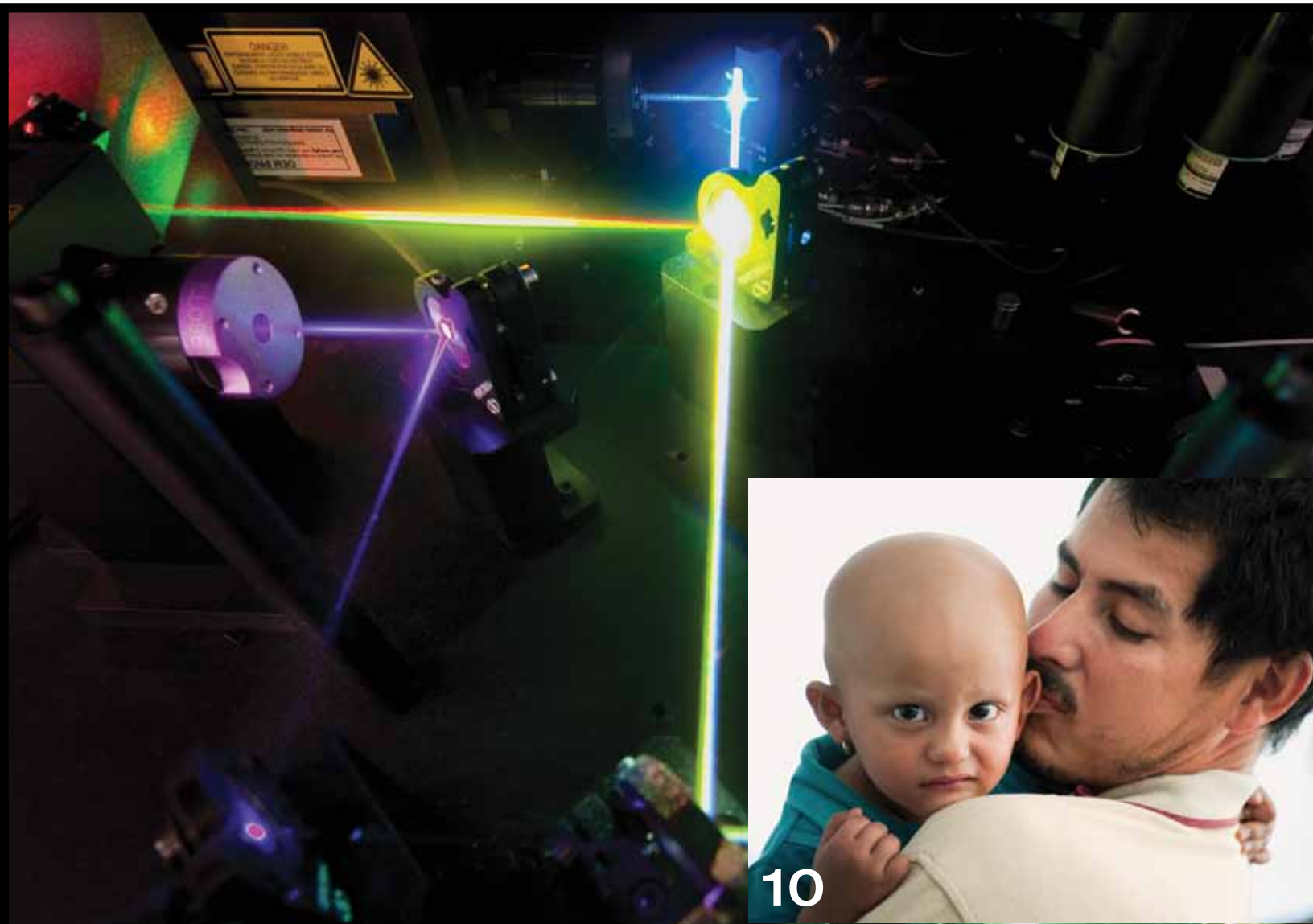
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Patients (from left)
Madisyn and Addisyn Million.
Photo by Peter Barta.

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Highlights

Uncovering genetic diversity

New research shows that defective genes and the individual leukemia cells that carry them are organized in a more complex way than previously thought.

The findings challenge the conventional scientific view that cancer progresses as a linear series of genetic events and that all the cells in a tumor share the same genetic abnormalities and growth properties. A report on this work appeared in a recent edition of the scientific journal *Nature*.

The results are expected to open the way for discovering how genetic abnormalities transform normal cells into leukemic cells as well as aid understanding of how cells at different stages of that genetic evolution respond to therapy or contribute to relapse. The findings also underscore the importance of developing therapies capable of eradicating the diverse population of cancer cells present in all cancer patients.

“Now we need to extend this work to identify genetic changes present at low levels in patients at diagnosis that confer a high risk of treatment failure and relapse,” said Charles Mullighan, MD, PhD, Pathology. He is co-first author of the study with Faiyaz Notta, PhD, Ontario Cancer Institute and the University of Toronto.

In this study, researchers demonstrated that the leukemia cells taken from patients with acute lymphoblastic leukemia (ALL) are composed of multiple families, or subclones, of genetically distinct cancer cells. Investigators discovered that cells that propagate the disease and potentially survive therapy persist through generations, sometimes acquiring additional genetic alterations and branching off to form genetically distinct cancer subclones. Some of these genetic families dominate, which sometimes makes it appear that the leukemia cells have only one set of genetic abnormalities. Other ALL subclones are extremely rare, explaining why they were not detected using different techniques.

“Overall, the study proved that many leukemias comprise multiple subpopulations of cells with different genetic alterations, and that these genetic alterations may evolve over time,” Mullighan said.



PETER BARTA

St. Jude makes *FORTUNE* list

St. Jude Director and CEO Dr. William E. Evans announces that the hospital has been recognized by *FORTUNE* magazine as one of the “100 Best Companies to Work For.” This is the first year St. Jude has been included in the publication’s annual list (*see related article, page 24*).

“St. Jude employees rank pride in the hospital’s mission—finding cures, saving children—as one of the top reasons St. Jude is a great place to work,” Evans said. “For our employees, working at St. Jude is much more than a job.”

St. Jude currently has more than 3,600 faculty and staff. Evans says the mission gives them a unique sense of purpose.

“Employees are proud of their work because it has special meaning,” Evans said. “A key to our success is attracting outstanding people and giving them a place to do their best work. We are successful because of our people and the partnership we have with our patients and our donors. Employees embrace the mission and espouse the culture of St. Jude, which is one of compassion, collaboration and innovation.”

*“For our employees,
working at St. Jude is much
more than a job.”*



Clinician wins AACR award

The American Association for Cancer Research recently presented St. Jude Oncology Chair Ching-Hon Pui, MD, with the 2011 Joseph H. Burchenal Memorial Award for Outstanding Achievement in Clinical Research.

Pui played a key role in treatment protocols that raised cure rates of acute lymphoblastic leukemia (ALL) from about 70 percent in the early 1980s to an unprecedented 90 percent at St. Jude today. His work has shown that cranial irradiation, once regarded as a standard treatment for ALL, can be omitted altogether, thus sparing patients from devastating side effects and enhancing their quality of life.

“One of Dr. Pui’s great strengths, beyond his unsurpassed wealth of knowledge about treating leukemia, is that he brings together a broad array of scientists and clinical investigators to participate in developing and conducting new ALL treatment protocols,” said Dr. William E. Evans, St. Jude director and CEO. “He is like a great conductor drawing together the best musicians to create something that is extraordinary and far greater than any one person playing alone.” For more about Pui’s recent research, see page 6.



PETER BARTHA

Molecular switch controls migration

David Solecki, PhD, Developmental Neurobiology, and his colleagues have identified key components of a signaling pathway that controls the departure of neurons from the brain niche where they form and allows these cells to start migrating to their final destination. Defects in this system affect the architecture of the brain and are associated with epilepsy, mental retardation and perhaps malignant brain tumors.

The findings provide insight into brain development as well as clues about the mechanism at work in other developing tissues and organ systems. The report appeared recently in the journal *Science*.

“Neurons are born in germinal zones in the brain, and the places they occupy in the mature brain are sometimes quite a distance away. The cells have to physically move to get to that final destination,” Solecki said. “If the process is compromised, the result is a devastating disruption of brain circuitry that specifically targets children.”

The findings may also offer clues about the spread of malignant brain tumors. Solecki said some types of the pediatric brain tumor medulloblastoma share similarities with immature neurons and seemingly fail to depart the cerebellar germinal zone.

Why flu attacks young adults

In spring 2009, a novel H1N1 influenza virus emerged in Mexico and became a pandemic. Although extremely young children were most likely to become infected, young adults were more likely than either much younger or much older individuals to develop life-threatening complications.

New research led by Jon McCullers, MD, Infectious Diseases, suggests the young adults may have been susceptible to complications because earlier flu infections primed them for a mismatched immune response to the novel virus.

The study focused on the role that sugar molecules

known as glycans play in shaping the immune response to flu. As flu viruses circulate, glycans are added to the proteins studding the viral coat. The process, known as glycosylation, may help the virus elude antibodies programmed to destroy it. In the absence of normally protective antibodies, other immune responses mediated by T-cells caused damage to the lungs instead of the virus. A paper on this work appeared in the *American Journal of Respiratory and Critical Care Medicine*.

If confirmed, the findings raise new questions about how to factor glycosylation into the design of future flu vaccines.

Highlights

Ancestry links relapse risk

The first genome-wide study to demonstrate an inherited genetic basis for racial and ethnic disparities in cancer survival linked Native American ancestry with an increased risk of relapse in young leukemia patients. The work was done by investigators at St. Jude and the Children's Oncology Group (COG).

Along with identifying Native American ancestry as a potential new marker of poor treatment outcome, researchers reported evidence that the added risk could be eliminated by administering an extra phase of chemotherapy. The study involved 2,534 children and adolescents battling acute lymphoblastic leukemia (ALL), the most common childhood cancer. The work appeared in the journal *Nature Genetics*.

The children were all treated in protocols conducted by St. Jude or COG. Although the overall cure rate for childhood ALL now tops 80 percent, and is close to 90 percent at St. Jude, racial and ethnic disparities have persisted. Based on self-declared status, African-American and Hispanic children with the disease have often fared worse than their white and Asian counterparts. This is the first study to use genomics to define ancestry, rather than relying on self-declared racial or ethnic categories.

"To overcome racial disparity you have to understand the reasons behind it," said the study's first author, Jun Yang, PhD, of Pharmaceutical Sciences. "While genetic ancestry may not completely explain the racial differences in relapse risk or response to treatment, this study clearly shows for the first time that it is a very important contributing factor."

The research identified a possible mechanism linking ancestry and relapse. Hispanic patients, who have a high percentage of Native American ancestry, were more likely than other patients to carry a version of the *PDE4B* gene that was also strongly associated with relapse. The *PDE4B* variants were also linked with reduced sensitivity to glucocorticoids, medications that play a key role in ALL treatment.

"This is just one example of how ancestry could affect relapse risk," said the study's senior author Mary Relling, PharmD, St. Jude Pharmaceutical Sciences chair. "It is likely that many other genes are involved."

"While genetic ancestry may not completely explain the racial differences in relapse risk or response to treatment, this study clearly shows for the first time that it is a very important contributing factor."



SETH DIXON

Taking the mission to Mongolia

Yuri Quintana, PhD (at left), director of Education and Informatics in St. Jude International Outreach, visits with Lama Arjia Rinpoche, director of both the Tibetan Center for Compassion and Wisdom in Mill Valley, California, and the Mongolian Buddhist Cultural Center in Bloomington, Indiana. The Lama Rinpoche was seeking guidance and best practices as his organization prepares to establish a Wellness Medical Center in Mongolia to provide free health care to the underserved in the nation's capital of Ulaanbaatar. At St. Jude, he and his colleagues learned about the hospital's approach to medical and educational outreach.



ANNE MARGARET HEDGES

Scientists meet immune cell riot squad

If regulatory T cells are the immune system's police force, stepping in as needed to control the immune response, work led by St. Jude researchers recently identified a subset of the specialized white blood cells that may serve as the riot squad.

The new cells are called "induced T regulatory population making IL-35" or iTr35 cells. Research from the laboratory of Dario Vignali, PhD, Immunology vice chair, and his colleagues, showed that iTr35 cells are created from more common less-specialized immune cells known as conventional T cells. Natural regulatory T cells generate iTr35 cells to help them put the brakes on an immune response.

Investigators also determined that a cytokine called interleukin 35 (IL-35) played a pivotal role in iTr35 creation and activity. Vignali's laboratory discovered IL-35 in 2007. It is one of a small number of cytokines that suppress rather than stimulate the immune response. The recent study showed that IL-35 could convert activated conventional T cells into powerfully suppressive immune cells that used IL-35 as the main weapon of suppression. The research appeared in the journal *Nature Immunology*. Vignali is the senior author and Lauren Collison, PhD, a postdoctoral fellow, is the first author.

Novel technique tracks immune response

Like a coach shuffling the starting lineup as the season progresses, a key component of the immune system's strategy for recognizing virus-infected cells often changes during the course of an illness, St. Jude researchers report. The change might help regulate the immune response.

St. Jude investigators developed a technique to track changes in the gene expression of key regions of two proteins known as the alpha and beta chains. Those proteins make up the unique receptor that covers a T cell's surface and determines the immune cell's ability to recognize and target cells infected with viruses or bacteria. Scientists used the approach to show production of the RNA message for the receptor's alpha chain changed in most T cells as infection with influenza A virus progressed.

"We had never previously been able to ask such detailed questions about the alpha chain in the immune response," said Immunology Postdoctoral Fellow Pradyot Dash, PhD, lead author of a paper on this topic that appeared in the *Journal of Clinical Investigation*.

The paper's senior author, Paul Thomas, PhD, Immunology, said the findings will advance understanding of T cell biology and the receptor's role in shaping the immune response. Investigators hope the results will include more effective vaccines, new immune therapies and insight into the origin of autoimmune disorders.



PETER BARTIA

Hands-on science

Students from Bellevue Middle School, the hospital's Adopt-a-School partner, recently visited St. Jude to participate in an interactive science fair as part of Research Tech Week. Shelly Jackson (center) and Stacie Woolard, PhD, of Tumor Cell Biology help a student understand the properties of polymers by showing him how to make homemade slime out of laundry detergent, glue and water.

Things Are Looking Up for Teens with ALL

St. Jude boosts cure rates for older teens with acute lymphoblastic leukemia.

BY ELIZABETH JANE WALKER

West Rountree's friends hugged and high-fived one another, tilting purple mortarboards at rakish angles and snapping photos with cell phones. As he filed into the auditorium with his 260 classmates, West fought against nausea and a bone-deep exhaustion. How, he wondered, would he be able to endure his high school commencement exercises?

"I walked across the stage, and before the ceremony was over, I went home," West recalls. During a graduation cookout that evening, he slipped away from his well-wishers and collapsed into bed, burning with fever. When his condition persisted the following day, his family took him to the hospital. To their shock, a bone marrow test revealed acute lymphoblastic leukemia (ALL).

"I didn't know much about leukemia," West says. "I thought little kids and old people got it. I didn't know that people my age got it."

While West's friends packed their suitcases for a senior trip to Florida, the new graduate embarked on a different kind of journey. Within hours of his diagnosis, West boarded a plane bound for St. Jude Children's Research Hospital in Memphis, Tennessee.

Building on past success

For nearly 50 years, St. Jude

researchers have been seeking a cure for ALL. Each study has built on the success of preceding protocols—refining, tweaking, moving treatment outcomes inexorably higher. In spite of that progress, ALL cure rates for older teens have been disproportionately lower than those for younger children. A dozen years ago, teens like West had only a 59 percent chance for a cure, compared with an 88 percent rate for children ages 1 through 14.

Because of individualized treatment and supportive care, those numbers have skyrocketed. In a recent report in the *Journal of Clinical Oncology*, St. Jude investigators announced a nearly 30 percent increase in the survival rate for ALL patients who were 15 to 18 years old when their cancer was found. The five-year overall survival rates were 88 percent for those teens and 94 percent for younger children. The patients' quality of life increased as well, thanks to the

elimination or reduction of drugs that cause such long-term side effects as infertility and second cancers. The St. Jude study, called Total XV, also eliminated cranial irradiation, which had traditionally been used to prevent central nervous system relapse. Radiation to the brain can cause problems with attention, behavior and learning. Investigators were thrilled to discover that radiation could be removed without affecting cure rates.

Ching-Hon Pui, MD, St. Jude Oncology chair, cites several reasons that teens have traditionally had lower ALL survival rates than younger children. Older teens are more likely to have high-risk subtypes of the disease, to experience more side effects from treatment, and to have cancer cells that are resistant to chemotherapy drugs.

"Another reason is treatment adherence," Pui observes. "When the kids are young, their parents make sure that they take their medicines."

PETER BARTA

But teens may not be compliant with the treatment. They may decide they don't want to risk being nauseated if, for example, they have a party the next day. So they won't take their medicine. Also, when ALL is in remission, the teens begin to feel good; they think they're cured, and they stop taking their medicine."

Teens and toxicity

The past year has been extremely challenging for West.

"My third methotrexate high-dose treatment was the hardest part thus far," he says. "I had super nausea and other problems. I couldn't eat for five days."

Pui says that teens like West often experience severe

side effects from treatment.

"Almost every toxicity is more common in older teenagers," Pui says. "In general, they do not tolerate chemotherapy very well. They have more side effects from the same treatment we give to younger children."

The reason behind the toxicity is that teenagers process drugs in a different way than younger children do.

"When you give a dose of a medication to an older child, their blood levels of that drug are actually higher than they are in younger children who get the same dose of the drug," explains Mary Relling, PharmD, Pharmaceutical Sciences chair. "So we're walking a tightrope.

On the one hand, if we give teens more medications, they'll have more side effects and more toxicity. On the other hand, if we give them less of the anti-cancer drugs, they might be at a higher risk for relapse because their leukemia cells are more resistant to the anti-cancer drugs."

In Total XV, St. Jude clinicians introduced several elements that destroyed leukemic cells yet minimized side effects.

"We used a combination of genetic testing and pharmacologic testing," Relling says. "For every single child, we individualized the amount of methotrexate to reach a specific target plasma level."

Dosages of other drugs were adjusted, as well, based on risk



West Rountree regains his strength with the help of Terry Wilson of St. Jude Rehabilitation Services. Thanks to St. Jude research and clinical care, the survival rate for older teens with ALL has skyrocketed.

status. Following the initial phase of treatment, clinicians evaluated the minimal residual disease, or MRD, status of each patient to decide how to further individualize therapy. Pioneered at St. Jude, the MRD screening technique can detect even one malignant cell among 100,000 normal cells. The test allows clinicians to evaluate how well a child has responded to therapy and to predict the risk of relapse. St. Jude is the first institution to use MRD to guide therapy for front-line leukemia protocols. If a child has residual leukemia at the end of remission induction therapy, the disease is reclassified as higher-risk and a more intensive course of treatment is given.

Following directions

Patients with ALL must take multiple drugs by mouth for three years. Teens offer many reasons for skipping their oral medications. They may honestly forget. They may hope to minimize nausea or hair loss. They may believe that they can forego their medicine if they are feeling better. Or they may just be going through a rebellious phase.

Pui, Relling and their colleagues have heard all of the excuses. Nevertheless, they know that treatment adherence is crucial. To ensure that teens receive optimum treatment, the investigators require regular intravenous administration of drugs. Patients also receive chemotherapy directly into the spinal canal, so that the drug can penetrate the blood-brain barrier. Clinicians counsel with the teens, encouraging them to take their oral medications regularly.

“We pay close attention to treatment adherence,” Pui says. “We give at least one drug intravenously each week and we monitor the blood levels of drugs regularly so



SETH DIXON



PETER BARTIA

Ching-Hon Pui, MD, Oncology chair, Mary Relling, PharmD, Pharmaceutical Sciences chair, and their colleagues have increased the ALL survival rates for older teens by 30 percent through the use of sophisticated patient monitoring and risk-adjusted chemotherapy.

that we can identify patients who are not taking the oral medications. If the levels aren't high enough, we sit down with the patient and talk about improving compliance. The next time we check, we'll find out that they are taking the medicine.”

Child's play

Even though West towers over most St. Jude patients—and many staff members—the tall, lanky teen is enrolled in a pediatric treatment plan. Research has shown that survival rates are better for teens who are treated on pediatric rather than adult protocols. That success may be due to the more intensive therapy and the higher emphasis on treatment adherence.

“There has been controversy in the past over the best way to treat adolescents with ALL,” Relling says. “Should they be treated on pediatric treatment protocols or on adult treatment protocols? Our findings further cement the conclusion that these children really should be treated on pediatric treatment protocols.”

Teen patients have a set of unique needs when compared to young children or adults. At St. Jude, clinicians and researchers unite to identify and address those needs.

“We have a dedicated team

for each type of cancer,” Pui says. “Everybody at St. Jude specializes in a specific type of cancer—from the social worker to the doctors, dietitians, pharmacists, nurse practitioners, nurses and physical therapists. We individualize our therapy based on pharmacokinetics, pharmacogenetics and pharmacodynamics. That cannot easily be done by any institution. It has to be done by an institution as sophisticated as St. Jude.”

The results speak for themselves.

“We were pleased to find that close to 90 percent of older adolescents can be cured with chemotherapy without the need for bone marrow transplantation,” Pui says. “Importantly, not only do we have the highest cure rate, but our patients survive with good quality of life because they don't get any radiation.”

West Rountree still has a long way to go before he completes his leukemia treatment. He eagerly anticipates the day that he can resume his life: Go on a vacation to replace the senior trip he missed; dust off his skateboard and try out a few moves; hang out with his friends; jump-start his future. “When I get finished with this, I'm going to college,” he says. “I'm still trying to decide what I want to be.” ●

It's a Small World, After All

GREG BLOOMBERG



ANN-MARGARET HEDGES



At left: MikrosTik co-owners Arnis Riekstins and John Tully support the St. Jude Children's Research Hospital – Washington University Pediatric Cancer Genome Project. **Above:** John and Andra Tully with their children, Martin and Helen. Since 2007, Helen has been battling rhabdomyosarcoma.

Tiny Helen Tully inspires a global partnership that spans 5,000 miles and the 3 billion base pairs of the human genome.

On first glance, a technology company with 70 employees in Riga, Latvia, may appear to have little in common with a pediatric research hospital in Memphis, Tennessee. But closer examination reveals several similarities between MikrosTik® and St. Jude Children's Research Hospital. Both are at the forefront of their fields, share a passion for innovation and use communications technology to bring progress to far parts of the world.

But their strongest bond is a charming 3-year-old girl named Helen, who adores her puppy, named Cookie, and loves to get her nails painted her favorite color—pink.

Helen came to St. Jude three years ago with rhabdomyosarcoma, an aggressive cancer of the soft tissue. Her treatment has included chemotherapy, brachyradiotherapy and most recently a stem cell transplant, completed in December of 2010. Helen is the daughter of Andra and John Tully Jr.

John co-founded MikrosTik with his partner and co-owner Arnis Riekstins. The Latvian company provides wireless ISP systems for Internet connectivity in many countries around the world. Now, MikrosTik is partnering with St. Jude to help uncover the mysteries of how childhood cancers begin and grow in children like Helen. The company has provided \$1.5 million in sponsorship support of the hospital's cancer research and the St. Jude Children's Research Hospital – Washington University Pediatric Cancer Genome Project.

"We are honored to have this incredibly special

company embrace the St. Jude mission," says Richard C. Shadyac Jr., CEO of ALSAC, the fundraising organization for St. Jude. "Their partnership is particularly significant because of their personal connection to the mission and speaks to the urgency of research into the genetic causes of childhood cancer."

The most ambitious initiative of its kind, the Pediatric Cancer Genome Project will sequence the normal and cancer genomes of more than 600 childhood cancer patients during a three-year span. The project will allow scientists to identify the genetic mutations that lead to childhood cancer and will provide a foundation for discovery for diagnostic and treatment advancements.

"It's a privilege and honor to partner with St. Jude on this important effort," Riekstins says. "We see firsthand how St. Jude has tailored a cutting-edge protocol for Helen and how the staff provides incredible patient care that includes the entire family. This dedication to quality matches the values of our company and confirms the importance of our commitment."

Despite her treatment, Helen remains buoyant, bantering with her nurses at the hospital. Her father is a native Memphian, and Helen loves being with her grandmother, who lives near the hospital.

This little girl, who links her father's technology company on the Daugava River with St. Jude on the Mississippi River, has a unique quality for bringing people together. Affectionate and fun loving, she simply smiles and says, "Come here—Let me give you a hug."●

Hospital without Walls

BY MARY POWERS

St. Jude partner sites extend
cures to children worldwide.



PHOTOS BY PETER BARRIA

As he does early on most Wednesday mornings, Raul Ribeiro, MD, director of the St. Jude International Outreach Program (IOP), settles in to trade ideas and advice with colleagues about the care and treatment of young leukemia patients.

For 90 minutes, he discusses the blood cancer that has derailed the lives of a half-dozen individuals. He and the other clinicians evaluate bone scans, view images of white blood cells, and discuss treatment of a patient battling both cancer and tuberculosis. Ribeiro listens to patient histories, reports of lab results and measures of treatment response. He fields questions about whether one patient needs an immediate bone marrow transplant, whether an 11-year-old needs another bone marrow biopsy and what to try next for a patient who has had a disappointing initial treatment response.

Such discussions play out countless times every day as health professionals work to bring the art and the science of medicine to the patient's bedside. This conversation involves participants scattered across the globe. Some, like Ribeiro, speak from offices on the St. Jude campus. Others are an ocean and six time zones away in Morocco.

The North African nation is home to three of the hospital's international partners, which expand the St. Jude mission of finding cures and saving children. What began in 1993 with a request to help replicate the St. Jude model in El Salvador has become an international effort involving partnerships with 20 hospitals in 15 countries.

This year those sites will serve about 2,000 new patients and provide care for thousands more. But the program affects many more and has become a model for other organizations working to advance pediatric cancer treatment worldwide.

"St. Jude has helped demonstrate that cancer is curable, even in developing countries. That evidence is changing government policies worldwide," Ribeiro says.

Battling childhood cancer is finally starting to appear on the agenda even in developing countries.

The connection also benefits St. Jude. Physicians adapt treatments developed at St. Jude for use in situations where the need dramatically exceeds local resources. Investigators have used tissue donated from partner sites for research advancing the understanding of leukemia and the eye tumor retinoblastoma. The links have also helped Ribeiro and other St. Jude investigators understand and treat adrenocortical carcinoma, a rare tumor of the adrenal gland.

Global problem

This year cancer will be diagnosed in about 160,000 children around the globe. For the estimated 20 percent in the U.S., Europe or other parts of the developed world, the odds of a cure approach 80 percent. But for the remaining 80 percent, the outlook can be bleak. Some countries still lack a children's cancer specialist. Cures are often restricted to those with the resources to travel abroad for treatment. In many nations, cancer patients are stigmatized and providing patients

with adequate pain control remains a dream.

The International Outreach Program has tackled this disparity by pioneering a cooperative approach called twinning. This process pairs St. Jude experts with local health providers and community leaders in other countries. Although some families travel to St. Jude, many now receive treatment closer to home. Twinning is more efficient, less disruptive and allows the benefits of care to reach thousands. All patients treated at the partner hospitals also benefit from the IOP's emphasis on infection control, enhanced nursing education and greater local medical expertise.

Working together

Each partner site must have a medical institution that can ensure all children have access to treatment, a physician dedicated to the effort and the fundraising support of a local nonprofit dedicated to childhood cancer. In return, physicians, staff and patients at the partner locations gain access to St. Jude experience and assistance. In addition to serving as mentors, St. Jude employees offer the



Mae Dolendo, MD (center), local medical director of the partner site at Davao Medical Center in the Philippines, confers with Raul Ribeiro, MD (at left), International Outreach director, and George Velez, administrative director, during a recent visit to St. Jude.

expertise and connections needed for local physicians to improve cure rates and conduct research to find solutions to their unique challenges.

Weekly webinars, based on geography and cancer diagnosis, allow clinicians to discuss the care of particular patients. St. Jude has helped with diagnostic testing, trained nurse educators and developed computer software to support research into local or regional needs. Partners also obtain advice about building grassroots financial support.

The efforts are paying off.

“We have seen tremendous progress in terms of access to care in a relatively short period of time,” Ribeiro says.

Cure rates are also rising. In El Salvador, the five-year survival rate for children with acute lymphoblastic leukemia (ALL) rose from 10 to 60 percent during the first five years of the partnership between St. Jude and Hospital Benjamin Bloom in San Salvador. In Guatemala City, a partner since 1997, childhood cancer cure rates climbed from 25 to 60 percent. The rates rose from 29 to 70 percent at the St. Jude partner hospital in Recife, Brazil.

Physicians at the Central American partner sites collaborated on a strategy that dramatically reduced treatment abandonment by bone tumor patients. An internationally accepted system for matching the intensity of leukemia treatment with the capabilities of the local health care system grew out of efforts to adapt St. Jude leukemia therapies for use in El Salvador.

During St. Jude visits to partner sites, staff noticed numerous deaths from infection among children whose immune systems had been weakened by

chemotherapy. In response, Miguela Caniza, MD, who heads the IOP’s infection control program, launched an educational program that trained about 150 infectious diseases specialists in Latin America. Other efforts have focused on reducing hospital-acquired infections through mentoring of physicians and nurses, improved access to hand sanitizer and better techniques for administering injections. A demonstration project helped one partner hospital save about \$3,000 monthly simply by doing a better job separating biohazards from other waste. The effort cut the hospital’s costs and improved safety. The savings are being reinvested into patient care.



In El Salvador, the five-year survival rate for children with acute lymphoblastic leukemia rose from 10 percent to 60 percent during the first five years of the partnership between St. Jude and Hospital Benjamin Bloom in San Salvador. In Guatemala City, childhood cancer cure rates climbed from 25 percent to 60 percent. The rates rose from 29 to 70 percent at the St. Jude partner hospital in Recife, Brazil.

The IOP’s mission prompted Kyle Johnson, PhD, to switch his professional focus from basic science to clinical care. Johnson earned a doctorate in molecular and cell biology and now works in the program’s infectious disease effort. He spearheaded the biohazards project.

“Doing even a little has a big impact on the health care being delivered. I’ve been helped a lot in my life, so this is a way for me to give back,” Johnson explains.

Partners in progress

The approach of pairing institutions from developed and developing nations to support quality, locally sustainable

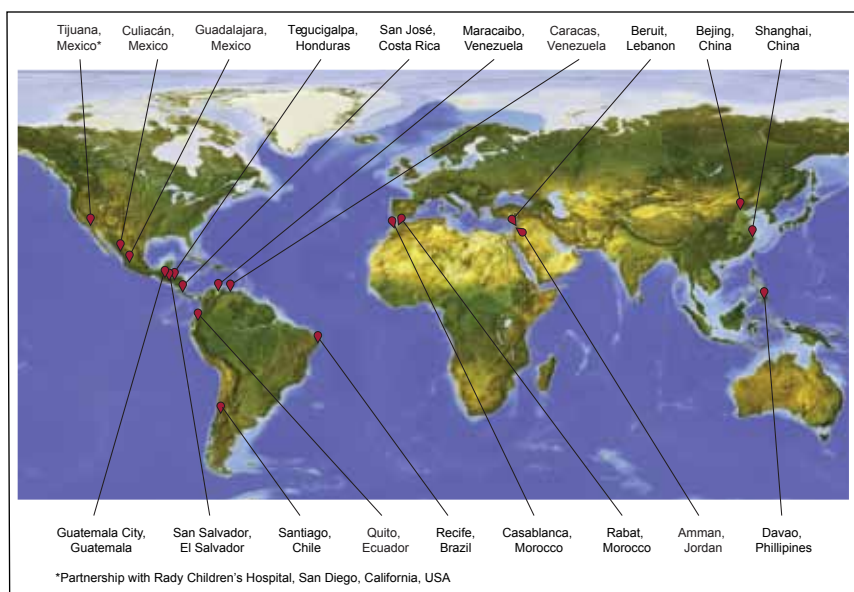
health care has become an international model.

“It makes you realize that the impact of what we do is really felt by a lot of people around the world,” says Scott Howard, MD, director of IOP’s clinical trials.

After Sheri Spunt, MD, Oncology, traveled to Singapore, Lebanon and Jordan last year to participate in conferences and visit partner sites, she was struck by the international reach of St. Jude. Not only was much of the hospital’s research being discussed, but the partners brought health providers together to identify their own solutions.

“The biggest impact of the work we do may be in these other places, helping other physicians take what we have learned here and apply it to their situation at home,” she says.

The partnerships have also underscored the reputation of St. Jude as a hospital without



walls. Sima Jeha, MD, Oncology, was attending an international leukemia conference in Asia when a colleague remarked, “St. Jude is known everywhere, from the highest mountain to the deepest ocean. There is always a family or a doctor or a patient who has been directly touched or treated or counseled by someone at St. Jude.”

Jeha, who graduated from the American University of Beirut, joined St. Jude in 2003. Today her duties include serving as director of the IOP’s Middle East Program.

“Many people would love to be involved in twinning programs, but they lack the institutional support we enjoy,” she says. “We cannot thank ALSAC and the donors enough for what they do.”

Howard likens the St. Jude efforts to shoring up a leaky dam.

“We are working on a small hole called childhood cancer, while other larger groups are working on bigger holes, like malnutrition or the lack of clean drinking water,” he says. “It would be nice if there were twice as many people working on childhood cancer.”

Lighting new candles

The breadth of the IOP makes it exceptional internationally. Ribeiro says the challenge has been handling the requests for help. “Once we documented our success in El Salvador, requests for help poured in from around the globe,” he says.

St. Jude officials responded by launching www.Cure4Kids.org in 2002, a free clearinghouse for scientific and clinical information on childhood cancer for health providers worldwide. The website hosts about 50 online conferences every month, including the weekly meetings that unite St. Jude faculty with physicians at partner sites in Morocco and around the world. About 26,000 health providers in 175 countries have registered with the site. The hospital has developed and shares other free tools, including a database to aid collaboration and research at partner sites.

But Jeha says it is not enough to simply make information available online. Health providers in many parts of the world do not have access to the latest medications, laboratory facilities or skilled support staff. Visiting partner sites not only helps

St. Jude faculty understand the challenges colleagues there face, but often helps bring providers together to collaborate on solutions.

When Spunt visited the St. Jude collaborating site in Singapore, she learned the depth of the challenges physicians face.

“Their questions did not lend themselves to easy answers but required problem solving, since often the recommended treatment is not immediately available,” she says.

St. Jude officials are now looking for new ways to advance the hospital’s mission. Through its alliance with Rady Children’s Hospital in San Diego, St. Jude helped create a new five-bed childhood cancer treatment unit at Tijuana’s General Hospital in Mexico. Ribeiro says such multi-institutional efforts may help expand health care in some of the world’s poorest countries.

“We are starting to see more patients being diagnosed with cancer in urban African cities. These children have curable cancers, but no access to care or even proper pain control,” he says.

Meanwhile, work continues to nurture and expand expertise at current partner institutions. Steady improvement in each one will foster not only greater access to care, but improved access to the kind of treatment that has pushed long-term survival for St. Jude ALL patients to 94 percent. The vision is for a new, expanded network of national and regional centers of excellence staffed by local experts searching for answers to local problems.

“It is like lighting a candle from one flame. The partnership program allows us to spread that light all over the world,” Jeha says. ●

Beyond Words

At St. Jude, Miguel Betances Lee has brushed up on his English. Thanks to faith, optimism and a dedicated clinical team, he has also mastered the language of hope.

BY ELIZABETH JANE WALKER



"We have to be positive—to say, 'I can beat the cancer. I can fight, win,'" says Miguel, shown here with Yen Pham, RN. "With God's help and the help of my family and doctors, I'm going to be healthy again."

During English language classes in the Dominican Republic, Miguel Betances Lee conjugated verbs, memorized vocabulary words and chuckled at American idioms. But he did not learn the terms "malignancy" or "limb-sparing procedure" until he arrived at St. Jude Children's Research Hospital in March of 2010. That is when his total immersion classes really began.

Many high school students prefer to spend Saturday mornings snuggled in their beds, catching up on lost sleep. Miguel's typical weekend schedule was much more arduous. Every Saturday for a year, he boarded a bus and traveled two hours to participate in four-hour English classes. For a teen aspiring

to a career as a software designer, the sacrifice seemed like a good investment in the future.

"English is a global language—the language of commerce," he explains. "People may be Chinese, German or Portuguese, but they usually know English."

Language classes were not Miguel's only passion.

"Basketball, baseball, soccer, chess—I played everything," he says. "And math—trigonometry, algebra—I love it, I love it, I love it."

In November of 2009, the athlete and honor student began experiencing pain in his thigh. An ultrasound indicated a muscle problem. Several months passed; his discomfort increased. When a local physician diagnosed



Miguel and his St. Jude English instructor, Tracy Long, work on a language exercise together. Long is one member of an extensive team that has helped Miguel and his family cope with a confounding array of medical, cultural and language challenges.

chondrosarcoma, a cancer of the cartilage, Miguel's family traveled to a hospital in Florida for a second opinion. There, they learned that he actually had a malignant bone cancer called osteosarcoma. By that time, the tumor had grown substantially. Doctors explained that treatment would require high-dose chemotherapy and the possible amputation of his leg. There was no time to lose. Miguel's family obtained a referral to St. Jude.

The language of teamwork

As soon as Miguel arrived in Memphis, his St. Jude clinical team leapt into action.

"Miguel had a massive tumor and needed treatment immediately," recalls Nurse Practitioner Nancy

Bailey. "He was in a lot of pain and had extremely high blood pressure. It was evident right away that he was in too much pain to be managed by our usual oral medications."

Members of the hospital's Pain Management Service administered a nerve block to control his pain so that he could begin chemotherapy.

An extensive team of professionals helped Miguel's family cope with a confounding array of medical, cultural and language challenges. He and his parents met with staff ranging from interpreters and social workers to clinical pharmacists and chaplains. Child Life Specialist Cara Sisk offered to help Miguel with relaxation techniques and assisted him in creating a video to send to his

friends in the Dominican Republic. "Even in hard times, he had a positive, upbeat attitude," she recalls.

Dietitian Whitney Orth from Clinical Nutrition monitored Miguel's nutritional intake and needs. "When his chemotherapy got intense, we talked about the best foods to eat," she says. "The chemo can cause mouth sores; it can make you really nauseated. Even if you want to eat, it can be difficult."

"All the people were so charming, so sweet and helpful," Miguel says. "We thanked God for them."

The language of faith

Miguel knew that he must eventually undergo an operation to remove the tumor. He and his

family prayed that the chemotherapy would kill as much of the cancer as possible so that an amputation could be avoided. Miguel's surgeons, Michael Neel, MD, and Bhaskar Rao, MD, hoped to perform a limb-sparing operation, in which the diseased bone would be replaced with a prosthesis; yet, the tumor's location, size and proximity to major nerve pathways made amputation probable.

"I had faith that I would not lose my leg," Miguel says. "I prayed to baby Jesus every day."

When Miguel went into surgery, he knew that amputation was a strong possibility.

"It was tedious," recalls Rao, who was one of the first surgeons in the U.S. to perform limb-sparing operations and has completed nearly 300 such procedures. "Normally, this surgery takes up to three hours. This one took seven or eight. I separated the nerves and the vessels from the tumor, and Dr. Neel put in the prosthesis."

The surgeons emerged from the operating room exhausted but exhilarated. Chemotherapy had killed more than 90 percent of the tumor, and they had preserved Miguel's leg.

The language of optimism

Miguel's journey was far from over. Because limb-sparing surgery involves stretching the nerves, he experienced excruciating discomfort, called neuropathic pain. Once again, the Pain Management Service stepped in to help.

"Neuropathic pain is common after limb-sparing surgery," explains Doralina Anghelescu, MD, Anesthesiology. "It's almost like an amputation where you've cut the nerves and the patient has phantom limb pain. In this case, the limb is still there, but the nerves have



Miguel chats with Nurse Practitioner Nancy Bailey and Alberto Pappo, MD, during a recent checkup. "We've been able to deal with all the complications of therapy, and now Miguel has a functional limb, no pain and a normal heart," Pappo says.

been traumatized so the children have a shooting, tingling, burning, needles-and-pins pain for up to two to three months. Miguel's persistent nerve irritation was difficult to treat, requiring many layers of treatment."

As suddenly and abruptly as it had arrived, the pain disappeared.

Miguel also experienced cardiac complications, an extremely rare side effect of one of the chemotherapy drugs. His oncologist, Alberto Pappo, MD, designed a new treatment regimen in conjunction with Miguel's cardiologist, Vijaya Joshi, MD.

"Miguel's recent tests came back completely normal," Pappo reports. "We've been able to deal with all the complications of therapy, and now Miguel has a functional limb, no pain and a normal heart. Things are looking rosy for him."

The language of hope

A keen sense of humor, strong family support and a steadfast faith have helped Miguel weather the storms of cancer treatment. He has also demonstrated extraordinary determination. Physical Therapist Terry Wilson helped Miguel strengthen his muscles before surgery and regain his strength and range of motion afterward.

"Miguel has a lot of energy; he's outgoing and engaging and friendly," Wilson says. "Even when he's in a

lot of pain, he still keeps a positive attitude toward his rehabilitation. Miguel says he works out regularly in the gym at Target House. I can tell that he follows through, because he's making great progress."

Tracy Long, Miguel's English instructor for the past year, has marveled at the teen's attitude as well as his aptitude for languages. "His English is incredible," she says, "and he's the most amazing young man. It's my job to encourage and inspire him, but I'm the one who's always encouraged and inspired. Miguel has a special inner light and a spirit that will not let him see the negative. He and I have had discussions about how hard some days are, but he tells me you have to look for the positive; it makes a difference when you choose that. His attitude is just fabulous, despite all that he has been through."

Whether he's conversing in English or Spanish, Miguel speaks the language of hope.

"I try to never give up and to set an example for the other kids," he says. "If I can do it, they can, too. Everyone here is going through a hard time. We have to try to keep the faith; to keep praying; to never give up. We have to be positive—to say, 'I can beat the cancer. I can fight, win. With God's help and the help of my family and doctors, I'm going to be healthy again.'" ●

Inspired to Aspire

Motivated by the courage of one St. Jude patient, an Arizona company embraces the Give thanks. Give hope.™ campaign.

BY AMANDA MCGEE ROBBINS

For the associates of Arizona-based Fry's Food Stores, supporting St. Jude Children's Research Hospital started with one child. They were deeply moved by an *Arizona Republic* story about an Arizona teen receiving brain tumor treatment at St. Jude.

"Her personal story touched many hearts," said Jon Flora, president of Fry's. "We were inspired by her courage and bright personality. And we were touched by her family's commitment to find a cure and support her."

The story inspired the employees to learn more about St. Jude, which progressed to a desire to do more to support the hospital's mission.

Fry's had been involved as a sponsor in local St. Jude fundraisers: with the Stars of Hope—Handbags for Hope Luncheon in Scottsdale and with *Country Cares for St. Jude Kids*® radiothons in Cottonwood, Yuma and Flagstaff. But,

with renewed enthusiasm, Flora and his associates made the commitment in 2010 to bring the Give thanks. Give hope.™ campaign into Fry's 121 stores.

Now in its third year, the annual campaign spans the months of April and May, when patrons at participating businesses, such as Fry's, can purchase a \$1 pinup or add a donation to their purchases at the register. One hundred percent of the proceeds benefit St. Jude.

"We are so thankful for our generous partners' support of the annual Give thanks. Give hope. campaign," said Richard C. Shadyac Jr., CEO of ALSAC, the fundraising organization for St. Jude. "Each dollar donated by customers of these businesses helps in the fight to find cures for cancer and other deadly childhood diseases so that children in communities everywhere will have a second chance at life."

The opportunity to provide hope to children battling cancer and other deadly diseases is a strong motivator for all the employees of Fry's, including senior management. To help inspire his team, Flora held a contest during the campaign, in which the top fundraiser got to trade jobs with Flora for a day.

"The reason this worked is that Jon made it fun and helped provide education about St. Jude. His commitment was a key factor in driving the fundraiser," said Pam Giannonatti, Fry's community affairs/consumer services manager.

The efforts paid off. In Fry's first year in the campaign, the company raised \$214,000 to support the hospital. In addition to asking for donations in stores, Fry's associates also held additional fundraisers, from a garage sale to offering root beer floats for St. Jude donations.

"Our associates were thrilled to be able to help the children and know that 100 percent of the proceeds would help give hope to children battling deadly diseases," Flora said. "By supporting St. Jude, Fry's and its employees hope to make life a little better for these young patients. Our hope is that the future will be brighter due to St. Jude's continuing research efforts."

For more information about Give thanks. Give hope. and for a complete list of all participating retail outlets, visit www.stjude.org. ●

©2011 ALSAC. Jon Shadyac Jr. (CEO of ALSAC) and Pam Giannonatti (Fry's community affairs/consumer services manager) are pictured. (01/11)

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Through the Give thanks. Give hope.™ campaign, patrons at participating businesses can purchase \$1 pinups, such as the one above, or can add donations to their purchases at checkout. One hundred percent of the proceeds benefit St. Jude.

Double Bubble

BY MIKE O'KELLY



Because of a rare and potentially fatal disease, the Million sisters hardly knew one another. The identical twins lived in separate apartments, were treated in different examining rooms, underwent transplants on opposite ends of the hospital. Now Madisyn and Addisyn are together at last.

Identical twins Addisyn and Madisyn Million frolic together now like they have spent every second of their 17 months within an arm's reach of each other. Addisyn, the younger twin, sometimes sits back and observes her older sister at play. If Madisyn falls down, Addisyn chuckles. It's a happy laugh borne out of familiarity with one another, which is surprising given the fact that the toddlers spent one-third of their lives separated from each other as a result of severe combined immunodeficiency (SCID). This life-threatening disease is often called "bubble-boy disease" after a famous case in which a boy with the disorder lived for 12 years in a plastic, germ-free bubble.

Double jeopardy

When she learned she was expecting twins, Emily Million was excited about welcoming tiny additions to her family, but slightly overwhelmed with the thought of the dual responsibilities. She and her husband, Labron, had a 6-year-old daughter, Aliyah, and Emily hoped for two more girls.

"I come from a family of mostly girls, so I was excited to have twin girls," Emily says.

Although the babies were small and arrived earlier than expected in November 2009, both girls were healthy at first. Babies with SCID usually develop a light cough and some intestinal problems in the first few months of life. They are also slow to put on weight, but Addisyn and Madisyn displayed no excessive symptoms until they were 5 months old.

Emily took the girls to a pediatrician after both twins experienced respiratory problems. When a combination of antibiotics, breathing treatments, allergy medicines and steroids showed limited effect, the pediatrician determined the girls had bronchiolitis, an inflammation of the small air passages of the lungs. During the next few days, Madisyn improved, but Addisyn struggled to breathe, sleep and eat.

As Addisyn's condition worsened, she was admitted to a local hospital but was soon transferred to the intensive care unit of a nearby children's hospital. Because she was expending so much energy trying to breathe, Addisyn was put on a respirator to let her body rest while immunologists worked to determine the underlying cause of her symptoms.

"In the ICU, the staff came in every day at 5 a.m. and did X-rays," Emily says. "Every day the X-rays were a little worse or the same."

After a negative cystic fibrosis test, an immunologist found that Addisyn had a severe case of pneumonia, known as pneumocystis jiroveci pneumonia (PJP). PJP is a hallmark of babies born with immune deficiencies. Additional tests revealed Addisyn had SCID, a rare disease that is among the most severe of the primary immune deficiency syndromes. Because Addisyn was an identical twin, Madisyn was tested

and was also found to have the same immune disorder. Since the only treatment for SCID is a bone marrow transplant, the twins' immunologist referred the girls to St. Jude Children's Research Hospital.

Search for a match

SCID is marked by a vulnerability to infectious diseases and the need for strict isolation from the outside world. If not treated early, SCID patients rarely survive past their first birthdays.

"There are several genetic disorders that can cause SCID, but all of them result in a severe defect in the number or function of T cells, the cells that fight viruses and fungi," explains Mary Ellen Conley, MD, of St. Jude Immunology.

The twins' admitting physician, St. Jude oncologist Brandon Triplett, MD, vividly recalls their arrival at the hospital.

"Addisyn and Madisyn had no detectable T cells when they got here," Triplett recalls.

The medical team immediately placed Madisyn in an isolated room in the hospital's Bone Marrow Transplantation (BMT) unit. Addisyn spent four days in ICU before moving to the BMT unit.

"Addisyn's condition was extremely fragile when she arrived in the ICU, but she improved quickly," says Ray Morrison, MD, St. Jude Critical Care division chief.

Physicians found that Addisyn had a mutation in a gene for the receptor for a growth factor called IL7. This novel mutation had never been reported before, says Wing Leung, MD, PhD, director of the St. Jude Bone Marrow Transplantation and Cellular Therapy program. Because the *IL7* gene was abnormal, Addisyn's body could not produce infection-fighting T cells, which are vital to the body's immune system.

In the two decades before the Millions' arrival, St. Jude had treated 21 SCID patients, with four receiving bone marrow transplants from siblings. The remaining patients had received transplants from their parents, who are known as "half-matched" donors. The twins' older sister, Aliyah, was not a match, and no matches were found on the national donor registry. That meant either Emily or Labron must donate stem cells to save their daughters' lives. The couple mutually decided that Emily would donate to allow Labron to remain at home and continue working.

Half and half

Before the transplants, the twins received individually designed chemotherapy to prevent their immune systems from rejecting their mother's stem cells and to encourage the engraftment process. A week before the transplants, Emily arrived in the hospital's Medicine Room to begin the first of

St. Jude saved the lives of Addisyn (below) and Madisyn (facing page). "I thank God for working a miracle in my girls," their mom says. "I can't thank St. Jude staff members enough for what they do—not only for my girls, but for every patient who walks through the doors."



six consecutive days of granulocyte-colony stimulating factor (G-CSF) injections to stimulate her bone marrow into producing more white blood cells. Emily experienced the shot's common side effects of flu-like symptoms. On the fifth day, she sat in a chair in the hospital's Blood Donor Room to prepare for the five-hour extraction of her blood stem cells.

"I was honored to donate," Emily says. "You can't move at all, but when you think of why you are sitting there and what you are doing it for, it's not that bad. 'Children go down there and donate to themselves all the time,' I thought, so that made it a lot easier."

Nurses inserted an intravenous needle into each of Emily's arms; blood was then withdrawn from one arm, passed through a machine designed to trap the white blood cells and infused back into the other arm. On the sixth day, Emily underwent the same process for five more hours.

"She had to donate to two patients, so we had to split the cells," Leung explains. "We had never done that before at St. Jude."

Research technicians split the 20 million cells in half, with each twin receiving a total of 10 million cells during their two infusions. The technicians also removed the T cells from Emily that might create rejection problems and left behind cells known as natural killer, or NK cells, to encourage the engraftment process.

A solitary split

While the donor cells grew, the twins recovered in isolated rooms on opposite ends of the hospital's BMT unit. Because the girls were identical, had the

same last name and were enrolled on the same protocol, staff members took extraordinary precautions to avoid confusion. Each twin had a separate nursing team so that when medicine arrived from the Pharmacy or blood from the blood bank, it was given to the right patient.

"Madisyn and Addisyn's situation was unique," says Jenn Wallace, Madisyn's primary nurse practitioner. "We had to be careful to focus on our individual patient and to ensure the details of her medical course were handled properly."

When entering the babies' rooms, each family and staff member wore a gown, mask and gloves to protect the girls' developing immune systems. Emily credits Labron's mother and stepmother for coming to Memphis and helping during the two-month period when both girls were in the transplant unit.

"It was strict isolation," Emily says. "We couldn't pull down our masks to give them a kiss or to show them who Mommy is—that was kind of tough. The nurses were really nice about stepping in and giving us a break when we needed one."

The twins' inpatient stay in isolation ended in July 2010, just 19 days after their transplants—the fastest on St. Jude record.

"Because the chemotherapy we prescribed was gentle but very good to help engraftment, the twins recovered their blood counts quickly with no side effects requiring a long hospital stay," Leung explained.

After discharge, each child was housed in a separate apartment in the hospital's patient housing facility, Target House, to minimize cross infections. Although the girls were not in strict isolation, they still could not be near

each other. Visitors were also limited.

During the day, Emily divided her time between the girls, but at night, she usually slept with Addisyn. The babies visited the hospital twice a week, each on separate days.

In mid-October, Addisyn's nurse practitioner, Ken Burnette, delivered the news that the Millions had waited 120 days to hear: "Dr. Leung says you can go home," Burnette said.

"It was kind of like a dream, and I thought I didn't hear him right,"



Nurse Practitioner Ken Burnette takes a moment to play with Addisyn.



Emily recalls. “I made him write it down on a piece of paper.” The girls also set the record for leaving Memphis the earliest after a transplant for SCID.

Reunited

The twins traveled to St. Jude for biweekly check-ups until January of this year. It took a few months for them to become reacquainted after so much time apart. At first, the girls treated each other like strangers with no special bond.

“Being identical twins, everybody thought they wouldn’t forget each other, but I think they did,” Emily says. “It might have been because they were so young and didn’t get to know each other before.

“I thank God for working a miracle in my girls,” Emily continues. “I can’t thank St. Jude staff members enough for what they do—not only for my girls, but for every patient who walks through the doors.”

Emily says the girls play together now like they were never separated, and each one has a curious interest in the other. They return to St. Jude for monthly check-ups and, since their immune systems are now normal, for vaccinations. The St. Jude visits will be yearly after the first anniversary of the transplant in May.

Now cured of SCID, the girls should have no restrictions and should be able to handle infections and function like any other children.

“I think these girls really exemplified how collaborations between families and the St. Jude staff can turn a deadly disease into a disease that can be cured,” Leung says.

“One day you have no hope; the next day, someone is telling you it can be fixed—and fixed quickly.” ●

Madisyn walks through the St. Jude corridors, with a little help from Nurse Practitioner Jenn Wallace.

Right On

BY ELIZABETH JANE WALKER

For decades, scientists have been mistaken in their assumptions about two childhood brain tumors. Thanks to St. Jude research, they're now on the right track.



ANN-MARGARET HEDGES

cancer while another would not. Why did these children have such variable responses to therapy?

“Back in 2005, we used genomic technologies to show that medulloblastoma is not one disease,” he explains. “We started to carve this apparently single disease into subgroups that shared similar genetics and similar clinical behaviors.”

Researchers have used this same technique for a number of adult diseases such as lung cancer and liver cancer.

“But the obvious elephant-in-the-room question was, ‘Where do those subgroups come from?’” Gilbertson says. “If there are different subgroups, how do we get them? Is this all one disease that comes from the same place and ends up being different? Or are these different diseases, but we just call them the same thing because they arise in a similar part of the body and look alike under the microscope?”

Paul Gibson, PhD (at left), Richard Gilbertson, MD, PhD, and their colleagues recently discovered that the most common malignant childhood brain tumor, medulloblastoma, is actually several different diseases.

Your mother stands corrected. Sometimes two wrongs do, in fact, make a right.

Once upon a time—not long ago—scientists regarded medulloblastoma as a single disease. They were also confident that this malignant brain tumor always originated in cells located in the cerebellum.

The scientific community was wrong on both counts.

Developmental neurobiologist Richard Gilbertson, MD, PhD, of St. Jude Children’s Research Hospital led research teams that disproved these well-known “facts.” For the past several years, he and his team have been trying to figure out why one child would be cured of brain

Asking the right questions

A couple of years ago, an international team led by Gilbertson began asking those questions about ependymoma, the third most common brain tumor in children. The researchers suspected that the cancer known as ependymoma was actually several diseases that were intrinsically different from the start.

Gathering 204 ependymoma samples from patients in the U.S., Europe and Canada, the team conducted the world’s most comprehensive analysis of the ependymoma genome. As part of that study, scientists developed a method for tracing the molecular origins of different

cancers, expanding the number of ependymoma subtypes to nine and identifying more than 200 genes that may cause the tumor to develop or spread. Scientists identified *EPHB2* as the first gene proven to cause ependymoma. The team also created the first laboratory model for the disease and pinpointed the stem cells responsible for specific subtypes. In July of 2010, the researchers published their findings in the journal *Nature*.

As a result of that study, Gilbertson and his team collaborated with Kip Guy, PhD, St. Jude chair of Chemical Biology and Therapeutics, to screen thousands of drugs to find a compound that would be effective against ependymoma. Scientists used the model created in Gilbertson's lab to test the compound. The scientists were surprised to discover that a drug that has long been used to treat colorectal and breast cancer was also effective against ependymoma.

"There are about 300 FDA-approved compounds out there for cancer," Gilbertson says. "If you wanted to test those in kids with ependymoma, it would take years. But our new model enabled us to screen all of those drugs to see if any of them had value. We discovered that this drug is highly potent for kids with ependymoma. We would never have known that if not for the new model."

Clinicians are already using the compound in the clinic and expect to incorporate it into the next St. Jude clinical trial for ependymoma.

Growing up

Flush with success, Gilbertson and his colleagues applied similar techniques to medulloblastoma, the most common brain tumor in children. The investigators concentrated their efforts on the wingless (WNT) and sonic hedgehog subtypes of medulloblastoma. These subgroups derive their peculiar names from the biochemical pathways that are activated in the resulting tumors. Together, the two subtypes account for about 40 percent of medulloblastoma tumors.

First, scientists used gene expression mapping to determine where the hedgehog genes were expressed. Not surprisingly, they were expressed in the cerebellum. But scientists were shocked to discover that the WNT genes were expressed far from the cerebellum—on a distant, lower part of the brainstem. Cells in that area had never before been linked to cancer.

"When you scan kids with medulloblastoma, they always have tumors in the cerebellum, which is why everyone thought the cancer started there," Gilbertson says. But St. Jude scientists noted that there were many children whose tumors also attached to the brainstem.

"We thought those tumors started in the cerebellum

and grew down into the brainstem," says postdoctoral fellow Paul Gibson, PhD, first author of a paper on this research that appeared in a recent issue of *Nature*. "We now know that the WNT subtype begins in the brainstem and grows up into the cerebellum. It completely changes the way that people think about medulloblastoma and opens up a new way of thinking about treatment."

The right track

Children with WNT tumors fare extremely well. "We've cured almost every kid at St. Jude with that disease," Gilbertson says.

In contrast, WNT's dangerous cousin, sonic hedgehog, tends to attack extremely young children and has a lower survival rate. Now that scientists can differentiate between the two subtypes, they hope to tailor treatment accordingly. In the past, all children with medulloblastoma have received cranial irradiation, which can result in cognitive deficits. Older children with the disease may also encounter fertility problems when they become adults. Scientists aim to develop novel, less-toxic treatments for children with the WNT subtype so that they avoid such harsh side effects.

The medulloblastoma findings may transform the diagnosis and treatment of the disease. In fact, children in the hospital's upcoming medulloblastoma clinical trial will benefit from this research.

"Our next step will take this work and apply it to clinical practice."

"We are pretty confident that we can pick out the good actors and the bad actors," Gilbertson says, "so our next step will take this work and apply it to clinical practice." That protocol is slated to open in the summer of 2011.

These latest discoveries bring Gilbertson one step closer to fulfilling his personal aspirations.

"My ambition when I was at medical school was to cure at least two of the top brain tumors in kids—that remains my goal," he says. "It's not an unrealistic pipe dream. We have great science and a great clinic right at each other's doorstep, and they interact beautifully. I could not do this science anywhere else in the world. Thanks to the terrific and unique environment at St. Jude, I'm beginning to believe that we will someday do it."●

Perspective

BY CAROL COLETTA

A Rare Combination

What makes St. Jude a great place to work? The mission.



Several years ago, as part of a research project, I needed to talk to some talented, highly educated people in Memphis to obtain their observations and to learn about their attitudes toward the city. St. Jude Children's Research Hospital allowed me to meet with a group of postdoctoral fellows. What a phenomenally impressive group of people from around the world!

During that meeting, I was reminded of what a wonderful asset St. Jude is to Memphis. Of course, the patient care at St. Jude is tremendous. But researchers at St. Jude are making extremely important contributions not only to Memphis, but to the world. I'm constantly reminded of what a big footprint St. Jude has in the minds of Americans as well as to people abroad. The hospital does great work that is acknowledged by so many. That makes me really proud as a Memphian.

If you look at *FORTUNE* magazine's recent list of the nation's 100 best companies to work for, you'll find St. Jude listed (*see related story, page 2*). There are not many nonprofits on that list, so I think it's particularly exemplary that St. Jude is recognized.

St. Jude doesn't offer the perks evident at most of the corporations on that list. But the hospital has something even more important: a powerful mission. Many of the for-profit companies try to overlay a strong mission on top of a profit goal. Thousands of people in this country go to work every day and think, "Why am I here? What is the real meaning of this? What's the real meaning of my life if most of it is spent in this particular workplace?"

No one has to wonder that at St. Jude.

A strong sense of mission is reflected in the way St. Jude employees perform and the way they relate to their jobs. St. Jude staff members know exactly why they come to work every day.

The work that St. Jude employees do is amazing. One of the special benefits of donating to the hospital is the knowledge that not only are you helping individual patients and supporting their care, but you're also leveraging that by supporting research that could help hundreds of thousands of other children.

So it seems to me that St. Jude offers the best of all worlds. It's not just the cerebral "Here's the research that we're investing in," or it's not just, "Here's patient care" but it's a rare combination of both. To me, that's enormously exciting.

Carol Coletta is president and CEO of CEOs for Cities, a civic lab of today's urban leaders catalyzing a movement to advance the next generation of great American cities. She has spent a decade hosting and producing the nationally syndicated public radio show Smart City. Named one of the world's 50 most important urban experts by a leading European think tank, Coletta is also a recipient of Lambda Alpha International's International Journalism Award for her work with CEOs for Cities and Smart City Radio.

Your gift will make a difference for generations to come.



St. Jude patient Lindsey with daughter Audrey and mother Ginny
(inset) Lindsey at age 10, in treatment at St. Jude for acute lymphoblastic leukemia.



Thanks to donors like you, patients like Lindsey were given a second chance at life. Her mother Ginny was given the gift of becoming a grandmother when Lindsey became the proud mother of a healthy, growing daughter.

Since 1962, St. Jude Children's Research Hospital® has helped families with children in the fight of their lives against cancer and other deadly diseases. St. Jude has become one of the world's premier pediatric cancer centers. Because our groundbreaking research is freely shared, the benefits of our unsurpassed care can reach children in communities around the world.

Learn more about how you can help St. Jude continue its lifesaving mission by creating your own legacy with your bequest, will or a gift. 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, visit us online, or complete the enclosed postage paid envelope today.

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The art of caring

Singer, songwriter and actress Gloria Estefan (second from left) and her husband, musician and producer Emilio Estefan (third from right), participated in an arts-and-crafts activity during a recent visit to Target House. Among the patients they met were (front row, from left) Ana Mendez, Cameron Palton, Rylie Wilson, Reese Coffin, Christian Otero and Ella Aulik; (back row, from left) Miguel Betances Lee and Jose Melendez. The Grammy award winners also toured the hospital and visited with inpatients during their visit.



Finding cures. Saving children.