

# Promise

Winter 2007



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# Promise

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St. Jude Children's Research Hospital's mission is to advance cures, and means of prevention, for pediatric catastrophic diseases through research and treatment. Consistent with the vision of our founder, Danny Thomas, no child is denied treatment based on race, religion or a family's ability to pay.

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*On the cover:* St. Jude patient Peter Martin. Story on page 14; photo by Peter Barta.

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# Highlights

MATT SIMMONS, COURTESY OF VIREIMAGE



Actor Jimmy Smits was one of several celebrities who helped St. Jude promote its third annual *Thanks and Giving* campaign through TV, movie and print ads. Pictured from left are Board member Tony Thomas, who produced the TV spots; Smits; Evelyn Homs of ALSAC Hispanic Marketing; and St. Jude patient José Meléndez, who appeared in the commercials with Smits.

## Heart of the matter

In laboratory studies, St. Jude investigators have discovered how cell walls from certain pneumonia-causing bacteria can cause fatal heart damage. Researchers demonstrated how antibiotic therapy can contribute to this damage by increasing the number of cell wall pieces shed by dying bacteria.

The study shows that pieces of cell walls from *Streptococcus pneumoniae* bacteria “hijack” a protein on the lining of the blood vessel wall and use it to slip out of the bloodstream and into the brain and heart. A report on this study appeared in the *Journal of Immunology*, November 2006. The findings explain why infection with *S. pneumoniae* often leads to temporary impairment of heart function. Elaine Tuomanen, MD, Infectious Diseases chair, says the findings also suggest a way to prevent this scenario from occurring.

Previously, her lab showed how cell walls can slip into brain cells.

## Hope when treatment fails

St. Jude clinicians have demonstrated an improved technique for blood stem cell transplantations that shows promise for children most likely to fail standard leukemia treatment.

The technique allows blood stem cells to come from parents or unmatched adult siblings; and it lessens the aggressive, toxic treatments that usually must accompany the transplant. This allows most patients with leukemia or non-cancerous blood disorders to receive transplants, according to Gregory Hale, MD, Bone Marrow Transplantation Division interim chief. A report on this work appeared in the *British Journal of Haematology*, October 2006.

## “Disorderly” proteins

St. Jude investigators have turned up the heat on “disorderly” proteins and confirmed that most of these unruly molecules perform critical functions in the cell. The St. Jude team completed the first large-scale collection, investigation and classification of intrinsically unstructured proteins (IUPs), a large group of molecules that play vital roles in cells’ daily activities.

The new technique for collecting and identifying IUPs is important because although scientists have been aware of the existence of flexible proteins for many years, they only recently realized that these molecules play important biological roles in the cell, according to Richard Kriwacki, PhD, of Structural Biology.

A report on this work appeared in the *Journal of Proteome Research*, October 2006.

## Best place to work

St. Jude has been named No. 1 in the “Best Places to Work in Academia” ranking by *The Scientist* magazine.

“We want St. Jude to be known as a place where doctors and scientists can do their best work,” said William Evans, PharmD, St. Jude director and CEO. “We like having *The Scientist* magazine’s verification that this is the case. This will help us continue to recruit and retain the best and brightest individuals to St. Jude, which is key to our continued success. I am also pleased that St. Jude continues to rank at the top based on citations of our publications, which is another indication that our people continue to define the forefront of treatment and research of catastrophic diseases in children.”

Complete survey results are published in the October 2006 edition of *The Scientist* magazine.

## ABCB6 is the key

St. Jude investigators have discovered that a protein called ABCB6 plays a central role in producing a molecule that is key to the ability of red blood cells to carry oxygen, of liver cells to break down toxins, and of cells to extract energy from nutrients.

The scientists showed that ABCB6 is lodged within the outer membrane of the cell’s energy powerhouse called the mitochondria; and that it ferries into mitochondria a type of molecule called a porphyrin, which is essential for life. The discovery of the location and function of ABCB6 solved the riddle of how porphyrins get into mitochondria so they can be used to make heme, said John Schuetz, PhD, of Pharmaceutical Sciences. A report on these results appeared in the journal *Nature*, September 2006.

## Survival rate increases

A team of investigators led by St. Jude has announced that improvements in the treatment of the childhood brain

cancer medulloblastoma have significantly increased the survival rate for children with this disease. The treatment increased the overall five-year survival rate for 86 children with average-risk medulloblastoma from 70 percent to 85 percent and raised the survival rate of 48 high-risk patients from 55 percent to 70 percent.

Investigators were able to achieve the improved survival rates while reducing the amount of radiation and length of chemotherapy following surgery in average-risk patients from levels used in standard treatments, according to Amar Gajjar, MD, co-chair of Oncology. A report on these results appeared in *Lancet Oncology*, September 2006.

## Solving a bacterial mystery

A 25-year quest to identify the first biochemical step that many disease-causing bacteria use to build their membranes has led to a discovery that holds promise for effective, new antibiotics against these bacteria. The finding is significant because the biochemical step the antibiotic would block is not used by humans. Therefore, such a drug would not cause dangerous side effects.

The discovery also demonstrated that the current textbook model to explain the critical biochemical steps in membrane creation represents a relatively minor pathway, according to Charles Rock, PhD, of Infectious Diseases. Scientists have used *E. coli* bacteria for many years as a model to understand the process, but *E. coli* is an unsuitable model for the important human pathogens, according to Rock.

A report on this finding appears in *Molecular Cell*, September 2006.

## Plot and subplot

The story of what makes certain types of bacteria resis-

tant to a specific antibiotic has a sub-plot that gives insight into the cause of a rare form of brain degeneration among children, according to St. Jude investigators.

The story is based on a study of the 3-D structure of an enzyme called pantothenate kinase, which triggers the first step in the production of coenzyme A (CoA). CoA plays a pivotal role in cells’ ability to extract energy from fatty acids and carbohydrates. Certain mutations in pantothenate kinase block its ability to function correctly. That diminishes the production of CoA and causes the neurodegenerative disease called pantothenate kinase associated neurodegeneration, according to Suzanne Jackowski, PhD, of Infectious Diseases. A report on this study appears in the journal *Structure*, August 2006.

## Predicting risks

Magnetic resonance imaging (MRI) could become a valuable tool for predicting the risk of muscle injury from radiation therapy. St. Jude investigators report that MRI can spot the immediate injury done by radiation therapy to the muscles of children undergoing radiation treatment for certain types of soft-tissue cancer. This indicates that MRI might one day be able to help doctors predict the amount of long-term damage that radiation may cause. A report on the findings appears in *Magnetic Resonance Imaging*, October 2006.

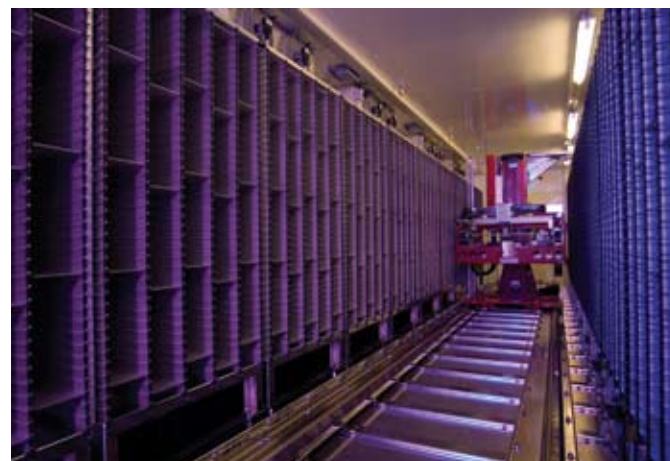
As radiation treatments become more advanced and complex, clinicians must have a way to anticipate the outcomes and side effects for individual patients to allow for avoidance or early intervention, according to Matthew Krasin, MD, of Radiological Sciences.

## Promise seeks your input

The editors of *Promise* would like your opinion about the magazine and suggestions on how to improve it.

Please log onto [www.stjude.org/promise](http://www.stjude.org/promise) and click on the reader survey. If you would like to be entered into a drawing for a St. Jude goodie bag, include your name and address in the survey.

PETER BARTA



St. Jude has a new storage facility that can hold up to 11 million vials of chemical compounds, which are essential for drug discovery. A robot maneuvers through the storage area and removes or replaces compounds that researchers use for their studies. The facility is the newest tool for members of the Chemical Biology and Therapeutics department.

The storage facility represents an exciting advance for St. Jude scientists who are working to discover molecules that hold promise for curing childhood cancer and other diseases.





Rose Marie and Gilbert Chagoury



# Ambassadors of Goodwill

By giving to a children's research hospital in Memphis, a Nigerian industrialist and his wife do the greatest good for children in need worldwide.

BY BETSY TAYLOR

FEW will ever be as successful as Gilbert Chagoury, but more impressively, he uses his gifts for the greater good of West Africans—and children in need worldwide.

Chagoury was born in Nigeria in 1946 to Lebanese parents. After marrying his wife, Rose Marie, he created a business to benefit all of West Africa. The Chagoury Group began as a flour mill but now includes construction, water bottling, telecommunications and international financing. It employs thousands in West Africa and prides itself on treating employees fairly.

Benevolence and social responsibility permeate every aspect of the Chagourys' lives. Gilbert and Rose Marie are known particularly for their philanthropy toward children's charities.

It's natural, then, that the couple came to know Danny Thomas and St. Jude Children's Research Hospital.

Gilbert and Rose Marie met Thomas at the St. Jude Hollywood Gala in 1980. The couple, who keep a home in

California, were attracted to the gala by what they knew of the St. Jude mission—and were even more impressed with what they learned.

"They embraced all of the good at St. Jude," says Gilbert's cousin, Gisele Chaghouri. "They appreciated that so much of the money raised goes to research and not administrative costs."

Gilbert also felt a kinship with hospital founder Danny Thomas. "Gilbert was drawn to Danny's personality, his leadership and his human side," Chaghouri says. "He quickly came to feel that Danny was like a father, and I know that Danny felt the same—that Gilbert was like a son to him."

Throughout the 1980s and 1990s, the couple helped fund the St. Jude Hollywood Gala. Their generosity has not gone unrecognized.

"In 1985 my father honored Gilbert with what he considered the highest award, which was the Founder's Award," says Thomas' daughter Terre Thomas. In 1988 Rose Marie was named the

hospital's Woman of the Year, and in 1990 Gilbert was named Man of the Year.

"They loved our parents, and our parents loved them," Terre says. "They are truly wonderful people."

The couple has continued to support St. Jude by underwriting the food and beverages for all four years of *Runway For Life*®, the hospital's premier Los Angeles fund-raiser. The event was co-founded by Terre Thomas and close family friend Robert Ellis in 2002 as a way to continue the work of Danny Thomas in the Los Angeles area. Since its inception, the event has raised more than \$5.25 million thanks to the commitment of people like the Chagourys.

"The Chagourys have been our 'Guardian Angels,' which is the highest title we can give anyone," Terre says. "Their generosity, commitment and enthusiasm are enough to light a city. We've truly been blessed to have them in our lives as our friends and in our efforts to save the lives of the children of the world."●

# Spreading Hope

BY BETSY TAYLOR

An encounter with Danny Thomas years ago planted the seed of giving for Walter and Pat Arnell.



Through a combination of excellent research and clinical care, "St. Jude gives these children hope," says Walter Arnell, PhD, when explaining why he and his wife, Pat, endowed a chair at St. Jude Children's Research Hospital.

Pat Arnell remembers when up-and-coming comedian Danny Thomas spoke at St. Andrews, her California high school. "We all thought that he was very funny," she recalls. Thomas spun yarns and spoke of his devotion to St. Jude Thaddeus, the patron saint of hopeless causes. That was almost 60 years ago, before Thomas had realized his remarkable rise to stardom and success. If he harbored dreams of building a hospital in Memphis, he didn't mention them.

Pat thought his visit was a nice distraction from schoolwork and nothing more. Yet, years later, she and her husband would fund an endowed chair at St. Jude Children's Research Hospital, the

hospital borne of Thomas' promise to the saint.

Walter Arnell, PhD, was once academic dean of engineering at California State University at Long Beach. He taught what is today known as engineering psychology, the science of designing better machine systems by using knowledge of how humans sense, store and process information. It's heady stuff, and scientists can get lost in their work. The popular professor made quite an impression on one of his students.

"He thought I looked lonely," Walter says, "and he set me up on a blind date with his friend Pat."

The date went extremely well. Last year, the couple celebrated their 50th wed-

ding anniversary. They have two daughters and four grandchildren.

After positions at the University of Hawaii and University of Arizona, Walter now refers to himself as "retired and tired," but he's not inactive. He and his wife have begun a second life making documentaries and collecting miniatures. They also discovered St. Jude.

Twenty years ago, Pat found that her ailing mother was a dedicated St. Jude supporter. Remembering her encounter with Thomas, Pat took up the cause. She and Walter, who gradually increased donations as they learned more about St. Jude, appreciated that most of the money raised goes directly to helping the children and that medical findings are shared freely and globally.

The couple's genuine interest led to a tour of the hospital and a meeting with Michael Kastan, MD, PhD, Cancer Center director. "We immediately liked him," notes Walter. "He was full of vim, vigor and enthusiasm—you could see his leadership."

Pat and Walter decided to establish an endowed fund to support Kastan's work, which has provided breakthroughs that could affect the hospital's ability to treat a broad range of catastrophic diseases.

While the scientific problem-solving at St. Jude appeals to the Arnells, their emotional ties to the hospital first inspired them to get involved.

"By taking science and applying research, St. Jude gives these children hope," Walter says. It's an alchemy that Danny Thomas well understood. For Thomas, faith and intellect went hand-in-hand. Belief in the power of prayer led him to found a research hospital that has saved countless children's lives, and the Arnells have become a special part of this mission.●



BY ERIC SMITH

## St. Jude restores hope and happiness for Nigerian teenager.

i

t's late afternoon in small-town Ohio, and a 16-year-old boy scurries off the soccer field to take a phone call.

The high school sophomore catches his breath and politely answers questions, though it's obvious from the short replies he'd rather be back on the field.

After a few moments, the call is finished. He can again focus on soccer, then algebra equations later that night, then dance lessons later that week, then basketball tryouts later that semester.

To anyone nearby, there's nothing unusual or special about this scene. Teenagers everywhere bounce from one activity to the next and talk on cell phones without missing a beat.

But to this young man and his family, the moment is nothing short of miraculous—a significant step on the long journey that crossed an ocean and required a vital detour at St. Jude Children's Research Hospital in Memphis, Tennessee.



# Kayode's Joy

### What's in a name?

The journey began far away, on the Nigerian coast in 1990, when Oluwatosin and Adekunle Owodunni had their first child, a son they christened Kayode (pronounced *KAH-yo-deh*). The name means “he brought joy” in Yoruba, one of many languages spoken in Nigeria.

From the beginning Kayode Owodunni (*o-wo-DOON-nee*) seemed destined to spread happiness to those around him: his parents, siblings, classmates, anyone who caught a glimpse of his bright eyes and warm smile.

Kayode found happiness, too. He had friends at school, a loving family at home, a passion for soccer and an uncanny knack for mathematics.

“He’s a very shy, quiet, loving child,” says his mother, Oluwatosin (*o-loo-wah-TO-seen*). “He likes to play soccer. He likes going to church. He likes everything.”

For the first 13 years of his life, Kayode relished it all. He discovered music. He idolized Nigeria’s soccer stars. He dreamt of places he’d visit someday. Kayode had even decided to become a doctor, perhaps an oncologist, like one of his uncles in the United States.

His parents were elated with the way their son was growing up and becoming a young man.

“He is a lovely boy,” says his father, Adekunle (*ah-deh-KOON-lah*). “He is a golden child for me.”

Then one day, out of nowhere, Kayode’s boundless energy evaporated. His light began to fade. His joy began to subside.

### Off to America

Kayode had no idea what was wrong, only that he was tired all the time. He visited the nurse at his Nigerian boarding school but didn’t tell his parents right away about feeling fatigued.

“I couldn’t do the activities like I did before,” he says. “I thought I just got lazy or out of shape.”

When the malaise persisted, the nurse alerted his family. Oluwatosin took him to a local doctor, whose initial diagnosis was malaria—not surprising since the disease is widespread in Nigeria and since Kayode had such symptoms as a distended stomach and fever. But doctors eventually determined Kayode had acute myeloid leukemia (AML), in which cancerous cells accumulate in the bone marrow, replace normal blood cells and spread throughout the body.

Kayode was incredulous: “I thought maybe they did the wrong thing or something because I didn’t think I could have that,” he says.



“The chance of surviving AML in Nigeria is zero,” observes Kayode’s mother. But thanks to St. Jude, the young artist, athlete and scholar forsees a colorful and promising future.

But he did. And Oluwatosin knew she had to get her son out of Nigeria.

“The chance of surviving AML in Nigeria is *zero*,” she says. “Even though we were spending lots of money at the best hospital in Nigeria, the doctors there were telling me his chances were zero.”

So the Owodunnis made plans to get Kayode across the Atlantic to the United States, where another one of Kayode’s uncles also was a doctor. As he prepared for the long trip, Kayode lamented that he would experience America for the first time in a hospital room.

“I always wanted to come here,” Kayode says, “but I didn’t want to come here sick.”

### The Nigerian connection

Soon after Kayode settled in with his aunt and uncle in Ohio, the journey took an unexpected twist when doctors at the hospital there said he needed to be at St. Jude for a bone marrow transplant. Kayode would be uprooted once more.

Kayode and his mother, who was a potential marrow donor, visited St. Jude in August 2004 and were comforted when they met Kayode’s doctor, Usman Yusuf, MD, a fellow Nigerian.

“You see one of your compatriots, and you have to feel like you’re at the right place,” Oluwatosin says. “Dr. Yusuf gave me the assurance that everything would be OK.”

The treatment team at St. Jude performed what is known as a haploidentical or “haplo” stem cell transplant, which uses the parent as a donor. The team harvested stem cells from Oluwatosin’s bloodstream and infused them into Kayode, hoping that the transplanted cells would create a new, healthy immune system that would fight the leukemia.



“That is what St. Jude is an expert in,” says Yusuf. “We’ve done more haplo transplants in children than any center in the United States.”

The procedure went well, according to Yusuf, who was impressed with the strength and determination of the young transplant recipient.

“He never complained,” Yusuf says. “He’s a very patient young man, very stoic, even when he’s hurting. And he’s always grateful for whatever is being done for him.”

## Spreading cheer

Kayode was grateful not only for the medical treatment he received at the hospital, but also for the academic and emotional attention. Among many others, St. Jude teacher Erin Brick and social worker Melanie Russell did their best to make Kayode and his mother feel at home.

Brick provided scholastic structure and companionship for Kayode, and the student reciprocated with a daily dose of cheer for his teacher.

“He was a bright spot in my day—every day that he was here,” Brick says. “I think he did as much for me as I did for him.”

Meanwhile, Kayode regularly borrowed Harry Potter books from Russell and returned them promptly before taking the next installment in the series. Russell was amazed at Kayode’s maturity level, which she believed exceeded that of most American teens.

“He is charming in a natural, genuine way,” Russell says. “He seems happy on the inside, and that shows.”

After the transplant, Kayode’s happiness indeed returned, thanks to St. Jude doctors and staff welcoming and curing him when he was far from home and down to his last chance.

“I am very happy,” Kayode says. “Anybody would be happy if you survived something like that.”

## Healthy once again

St. Jude saved Kayode’s life, but it also became a place for him to explore his creative side. He had dabbled with drawing for a few years, but while recovering from surgery, he began to hone his ability. During one stay, he painted a picture of his mother, who was taken aback by her son’s newfound talent.

“I was surprised because I didn’t know he could draw so well,” says Oluwatosin, whose portrait now hangs in Brick’s classroom.

Art is just one of Kayode’s many gifts. His favorite subject in school is algebra, and Brick was impressed with his aptitude and affinity for a subject many dislike.



Kayode solves algebra problems with Erin Brick, his St. Jude teacher. At right are examples of his artwork—a self portrait and a rendering of his mother.



Kayode currently lives in Ohio and travels to St. Jude every few months for checkups. When he’s not in Memphis, the teen can often be found on the soccer field. He plays forward for his high school’s junior varsity team, and though he is limited to 15 minutes each half to prevent fatigue, he eagerly awaits the day he can compete on an equal basis with his teammates.

“I like being treated like everyone else,” he says.

Kayode has become active in his relatives’ church and enjoys running the video camera during worship services and working with young children. He even took up hip hop dance, and he sends tapes of himself to his parents in Nigeria, who delight in seeing their son dancing with girls in the class.

“I remember the times I used to see him in the bed, and he couldn’t do anything because he was so weak,” Oluwatosin says. “Now I can see him be an active child again, a healthy boy again. So I say, ‘Thank you, God.’”

## Thankful for St. Jude

Life in Ohio isn’t perfect for Kayode. He likes his new school but misses his parents and younger brother and sister. He likes the plentiful trees in his new hometown but misses traditional Nigerian foods like *iyun*, a dish of pounded yam.

His parents and siblings also miss Kayode, but they realize that he still needs to be near St. Jude and they know that this stage of his life is a blessing.

“I’ll be forever grateful to all the people who helped one way or another just for Kayode to be alive today,” Adekunle says. “I give glory to God.”

Kayode also gives glory to God, and then he gives a message of hope to any child whose life takes a detour because of cancer or some other catastrophic disease.

“Everything will be all right if you’re at St. Jude,” Kayode says. “It’s the best place to be.”

Sixteen years ago, Oluwatosin and Adekunle Owodunni named their first-born son Kayode with hopes he would lead a long, prosperous, happy life. Thanks to St. Jude, Kayode’s journey continues—and his joy endures. ●

# The Missing Link

A promising new treatment for a childhood eye cancer might also give hope to adults with breast, prostate, colon or lung cancer.

BY BONNIE KOURVELAS

No matter who you are, or where you are as you read this, you have probably been touched in some way by cancer. Most likely, you encountered breast, prostate, colon or lung cancer—the “big four” that strike the largest number of adult victims. Perhaps you dread that you, or a loved one, might have to endure cancer and the ravages of chemotherapy.

But scientists have encouraging news: A discovery at St. Jude Children’s Research Hospital may lead to the elimination of traditional chemotherapy for some forms of cancer—quite possibly in our lifetime. Imagine tiny doses of medicine inside microscopic bubbles that race through your bloodstream and

release medication only at the tumor site. The treatment could end baldness, nausea, vomiting and other side effects of chemotherapy.

This scenario has become possible because of recent research conducted at St. Jude. But scientists weren’t studying adult cancers when they made the discovery; they were studying retinoblastoma, a rare form of cancer that strikes the developing eyes of children.

## Blocking MDMX

Retinoblastoma occurs in about 300 children in the United States every year (in comparison, breast cancer strikes more

than 200,000 Americans). Yet retinoblastoma holds a clue to unlocking what may be the future of cancer treatment.

With retinoblastoma, physicians often must remove the affected eye. If the disease strikes both eyes, doctors face the prospect of saving the child’s life at the expense of eyesight.

“These are extremely difficult cases for doctors and especially for parents: to make that call, to balance the child’s life against the cancer,” says Michael Dyer, PhD, of St. Jude Developmental Neurobiology. “We’re going to go beyond that. My ultimate dream would be that someday no child would lose an eye to this disease.”





Dyer recently published a paper in the journal *Nature* explaining the latest breakthrough in his research, with implications that reach far beyond retinoblastoma.

The paper is based on a discovery in Dyer’s laboratory that overturned an accepted belief among scientists about apoptosis—cell suicide—in retinoblastoma. Apoptosis is the way the body rids itself of abnormal cells that might become cancerous.

Until now, retinoblastoma experts thought that a mechanism called the p53 pathway triggered apoptosis in other types of cancer cells, but not in retinoblastoma. The St. Jude team not only proved that the p53 pathway is activated in early-stage retinoblastoma, but that excessive levels of a molecule called MDMX keep p53 from killing unhealthy cells that can grow into tumors.

The St. Jude team used a specific molecule to block MDMX, allowing cancerous cells to commit suicide. When that worked, the team applied the molecule directly to retinoblastoma tumors in the lab. The process worked—the molecule reduced the retinoblastoma tumors without the side effects of traditional chemotherapy.

Then Dyer’s team modified the treatment, combining the molecule with topotecan, an investigative drug that is used to treat retinoblastoma. This two-drug targeted treatment was even more effective, reducing tumor size significantly more than any other combination of chemotherapy drugs.

This success suggests that direct delivery of the drugs to a patient’s eye could also reduce tumor size.

If blocking MDMX results in the death of retinoblastoma cells, then the process might work in other tumors, too. Some forms of breast, lung, prostate and colon cancer are caused by abnormally large quantities of MDMX in the cells, so knocking out MDMX could trigger those tumors to commit suicide. Finding a way to deliver the drug directly to those tumors would eliminate the need for traditional chemotherapy and would target the drugs precisely where they are needed.

“Traditional intravenous chemotherapy can make patients very sick,” Dyer



**Mary Ellen Hoehn, MD, of the Ophthalmology Division, Surgery Department, examines Alex Moore, who is undergoing treatment for the eye cancer retinoblastoma. A laboratory discovery may lead to the elimination of traditional chemotherapy for retinoblastoma and some other forms of cancer.**



**“If a localized, targeted drug for retinoblastoma is perfected, it could be applied to a child’s eye by an ophthalmologist,” says Matthew Wilson, MD, of St. Jude Ophthalmology Division, Surgery Department. “That wouldn’t require the cost and intensive hospitalization that’s required now.”**

explains. “It kills the cancer cells, but it also causes stress in other organs where there is no cancer. With retinoblastoma, the entire body is exposed to chemotherapy just to get a little bit of drug inside your eye. What I wanted was to find the one genetic weakness in the tumor cell and exploit it with a drug that only targets the tumor, and then deliver that drug directly to the eye where it is needed.”

## Beyond chemo

Now that researchers know which molecule will block MDMX and allow

tumor cells to die, the next step is to find an even better drug combination to do that. Dyer and his colleagues have joined forces with Kip Guy, PhD, chair of the newly established Chemical Biology and Therapeutics department at St. Jude.

“Mike works on the signaling pathways in retinoblastoma,” Guy says. “As a chemist, one of my research specialties was working on compounds that regulate protein interactions. This project was a wonderful opportunity to bring that expertise to bear on discovering small molecules, drug-like molecules, that are active in disease.”



**Michael Dyer, PhD, and colleagues (from left), Nikia Laurie, PhD, and Stacy Donovan, PhD, both of Developmental Neurobiology and Chie-Schin Shih, MD, of Oncology, are part of a St. Jude team of physicians and researchers who are making exciting progress toward improving the treatment of retinoblastoma.**

Guy’s staff oversees a library of thousands of chemical elements that can be mixed and matched in endless combinations, sometimes in containers no larger than pin heads. Among those chemicals, St. Jude researchers hope to find the mix that will knock out retinoblastoma tumors. When they do, they may pave the way for drugs that will knock out the much more common forms of cancer—ones that kill adults as well as children.

“Sometimes in studying rare childhood diseases, you come up with discoveries which will lead to new treatments that can have a much broader impact,” Dyer explains.

Drug companies were not interested in developing drugs for retinoblastoma, because it affected such a small number of people. But now that a link has been established to more common forms of cancer, Dyer believes pharmaceutical companies will be interested in finding new drugs to target MDMX.

Someday, not only will there be new drugs, but there will be new and better ways to deliver them, predicts Beth McCarville, MD, of Radiological Sciences.

“We are looking at ways to better visualize tumors with ‘microbubble’ ultrasound contrast agents,” McCarville says. “These contrast agents are small spheres that are about the size of a red blood cell and contain a gas that can be seen on ultrasound images. They can be safely injected into a vein in the arm and then they travel through the blood stream to the tumor.

“We are looking at ways to design the microbubbles so that they also contain chemotherapeutic agents,” she continues. “Once the microbubbles are visualized in the eye tumor we can use the ultrasound wave to break the bubble open and deliver the chemotherapy directly to the tumor.”

“I suspect some even more creative ways will be developed,” Dyer adds, “and

I think that’s going to be where cancer treatment goes in the future.”

Recent discoveries at St. Jude also have implications for children around the world. Kids in developing countries have a higher risk of dying from retinoblastoma.

“The cost can be prohibitive in developing countries, and few have the facilities and doctors to manage the side effects associated with intravenous chemotherapy,” observes Matthew Wilson, MD, of St. Jude Ophthalmology. “However, if a localized, targeted drug for retinoblastoma is perfected, it could be applied to a child’s eye by an ophthalmologist. That wouldn’t require the cost and intensive hospitalization that’s required now.”

“You look worldwide and it’s a shame that children are dying of this disease when they don’t have to,” Dyer says. “And someday they won’t. That’s what’s really exciting to me.”●



# Boo!

PHOTOS BY PETER BARTA

Boo who? That's the question every year when St. Jude patients crowd the hospital's corridors for the highly anticipated Halloween extravaganza. It's all about smiles and fantasy as kids and their families wander from area to area, laughing at caregivers, high-fiving researchers, showing off inventive costumes and, of course, collecting treats.

Employees transform clinics, departments—and themselves—into new and glorious incarnations. One staff member floats by as an ethereal jellyfish; nearby, an entire clinic morphs into a wonderland where imaginations run wild.

For one zany day, patients and employees are replaced with cowboys and clowns, penguins and princesses, superheroes and space creatures. One kid drags his "friend" along—an IV pole dressed as a ghost. Another patient pirouettes through the crowd in a diaphanous ballerina costume.

It's fun; it's wacky; and it's just one more way that St. Jude employees help "their" kids capture the magic of childhood.







PHOTOS PAGES 14-15 BY PETER BARTA

# Through Pete's Eyes

Valuable lessons can be learned by looking through the eyes of a 3-year-old.

BY RUTH ANN HENSLEY

If the eyes are, indeed, windows to the soul, perhaps that explains why Peter Martin's are so beautiful. It is a rare thing to become transfixed by another's gaze. But to look into Peter's eyes is like diving off a cliff into a sea of sapphire blue before realizing your feet have left the ground. It isn't just the color of his eyes or the way they light up his face that is so engaging; it's the wisdom they reflect—a sage sense of “knowing” that is rarely found when staring into the ocular orbs of a 3-year-old.

Maybe Peter knows a few things we don't. Maybe he knows that it's OK to hug someone, even if you've just met them; that you should feel compassion when you hear a baby cry, even if it belongs to a stranger at the mall; and that it's important to live with passion, even if nobody else shares your love of goats and all things yellow.

Of course, there are some things Peter doesn't know. He doesn't know that the rare brain tumor that brought him to St. Jude Children's Research Hospital

represents only 2 percent of all childhood brain tumors; that treating toddlers with brain tumors is extremely challenging; and that his chances for surviving this disease are less than 30 percent.

But to look into the eyes of Peter, who his mother Kellei lovingly refers to as “a funny little man,” one is quickly comforted and quietly inspired. We are reminded that beautiful, old souls can reside in tiny, young people who can reach out and touch your heart forever—and that's all anybody needs to know.

## Through a glass darkly

“I remember seeing the technician's face through the window, when Pete was getting his first CAT scan,” Kellei recalls of the evening Pete's brain tumor was discovered. “The technician had a really strange look on his face. Then another person came in to look at the screen and got that same strange look, and then another and another. At that point, I knew.”

As a baby, Pete was as able and agile as any infant. But when he turned 22 months old he began walking with a limp. He was also exhibiting cold-like symptoms, even though no one else in the family was ill.

Kellei remembers discussing Pete's condition with her husband, Jeff. “I actually told him, ‘I think it's in his head,’” she says.

In a sense, that was the opinion of Pete's pediatrician.

“They thought it was an inner ear infection that was interfering with his equilibrium,” Jeff explains.

The pediatrician instructed the family to watch Pete during the weekend. “But that wasn't good enough for me,” Kellei says. “It was a Friday afternoon, and we were trying to play with him. He couldn't run. He was stumbling and vomiting, and I said, ‘That's it. We're taking him back to the pediatrician.’”

After performing tests and observing the tiny boy for several hours, the perplexed pediatricians ordered a CAT scan.

“St. Jude is the only place that sensed the urgency of our situation. I'm certain if we had stayed home, our son wouldn't be here right now.”

That's when the Martins' worst fears were confirmed.

The pediatrician emerged from the room on the other side of the glass, the same glass that Kellei and Jeff had peered through during Pete's scan; the same glass that reflected their dread and sorrow with each strange look that met their gaze.

“Your son has a mass—a large mass—in his brain,” the doctor said.

The tumor was larger than a golf ball. “In a little head that's a big thing that shouldn't be there,” Kellei says.

The diagnosis was pineoblastoma (pronounced PINE-e-oh-blast-OH-muh), an extremely rare tumor of the pineal region of the brain, affecting 25 to 50 children per year in the United States. The pineal gland produces melatonin, which plays a role in the body's circadian rhythms (light and dark cycles) and affects hormones that regulate the onset of puberty.

“Most pediatricians will go their entire career and never see anything like it,” Jeff says.

“It was not only a night we will always remember, but the doctor and the hospital staff will, too,” Kellei adds.

## Looking for help

As the news of Pete's condition sank in, a pediatric oncologist discussed a protocol, or scientific treatment plan, with the Martins. “It was the national protocol for basically any brain tumor,” Jeff says.

The doctors said that Pete's tumor was inoperable; the amount removed during the biopsy, which wasn't much larger than a grain of sand, was all they were comfortable removing. They told the family to go home for a week and then bring Pete back for chemotherapy.

Meanwhile, Pete's family leapt into action. “My sister was on the Internet constantly searching for answers. All of



**Whether he's laughing at goats or peeking out of a bamboo thicket, Peter is a constant delight to his family and friends. “No matter what the outcome of all this is, I'll never second guess our choice to come here,” Jeff says. “St. Jude is the place we needed to be. We're lucky that we found it.”**

the information she found indicated we had to get the tumor out before starting treatment,” Kellei says. “That was our

rush against time. We had one week to find someone in this country who could remove that tumor.”

The Martins sent Pete's medical records to pediatric neurosurgeons across the country and received a wide range of responses.

“Some were great about giving us their opinions; others wouldn't say anything besides, ‘Be here on this date’; and some wanted to charge us \$500 to review the scans before giving us any information,” Jeff says.

## A glimpse of hope

Then Kellei's sister found the St. Jude Web site, and they discovered a brain tumor protocol that looked like a perfect fit. “I thought, ‘This is just what we need,’” Kellei recalls. Pete's pediatrician gave an immediate referral, the Martins sent Pete's records to St. Jude via overnight delivery and the next day they received a call from neurosurgeon Frederick Boop, MD, of the St. Jude Surgery department.

“He introduced himself and said, ‘We have to get that tumor out,’” Kellei recalls with a sigh of relief. “That was exactly what we were waiting to hear.”

One week later, Pete underwent surgery to remove the tumor. Performing surgery on the pineal region is extremely dangerous because of its precarious location. It is located deep inside the brain on the midline, slightly above the brainstem. But after six hours of cautiously removing tiny fragments of the tumor bit by bit, the neurosurgeon successfully excised approximately 90 percent of it.

“We found out his tumor had grown 50 percent in that week we were searching for someone to remove it,” Kellei says. “St. Jude is the only place that sensed the urgency of our situation. I'm certain if we had stayed home, our son wouldn't be here right now.”

Upon recovery, Pete immediately began the St. Jude protocol, a collaborative project with the Pediatric Brain Tumor Consortium that targets children under the age of 3 with malignant brain tumors. Pete's Oncology team included postdoctoral fellow Stephen Laughton,





“We were apart from Hailey (pictured above with Peter) for about a month, and it was breaking our hearts,” Jeff says. “We knew we needed to go through this together, as a family. I went home to get Hailey, and when we returned, Peter had a smile on his face for about three days straight.”

MD, and attending physician Alberto Broniscer, MD.

“The reason the study is aimed at children this young is because the risk of giving them radiation to the whole brain (the standard in older children) presents a great danger of creating long-term developmental problems,” Laughton explains. “So the primary strategy of this protocol is on the application of intensive chemotherapy, supplemented by conformal [targeted] irradiation.”

A novel aspect of the study involves the injection of a drug called mafosfamide directly into the spinal fluid.

“The risk of these types of tumors is that they metastasize and spread,” Laughton explains. “That’s why it’s important in young infants like Pete to find alternatives to whole-brain irradiation, because that is what would normally prevent the spread.”

## Windows to truth

Since Pete began his treatment in the fall of 2005, he has undergone 20 weeks of chemotherapy, followed by six



“We really don’t know how much time we have with Pete,” Jeff says. “So you can either spend your time crying about it, wondering why and feeling sorry for yourself; or you can live it up and enjoy life because there’s a chance that he’s going to make it.” Peter makes the most of his time with Alberto Broniscer, MD, Oncology, and postdoctoral fellow Stephen Laughton, MD; and with his mom on a whirling carousel.

weeks of conformal radiation and 20 more weeks of chemotherapy. Pete’s cancer is in remission with no sign of spreading beyond its original site and no evidence of cancerous cells in the fluid surrounding the brain.

If you were to meet Pete, he would be quick to tell you in his small but firm voice, “I’m almost through with my chemo.” But can he possibly understand what he is saying?

“He is one of the smartest 3-year-olds I have ever met,” says a member of his

treatment team, Morgan Hayes, RN. “He is definitely wise beyond his years.”

Unfortunately, even old souls don’t know what the future holds. But when you peer into the deep, blue windows of Pete’s sweet spirit, you can see in his eyes the love he has for his parents and 5-year-old sister Hailey; the joy he has for life; and the contentment of a little boy who knows he is loved beyond measure—and that’s all anybody needs to know. ●

# Lollipops Not Included

BY CARRIE L. STREHLAU

**St. Jude adds a new department and embarks on an exciting project. In an unprecedented effort, select adult survivors will return to St. Jude for regular clinic visits—for the rest of their lives.**

In one episode of the popular television show *Friends*, a 30-something character named Ross Geller is embarrassed to admit that he still visits his pediatrician. At the end of Geller’s appointment, the physician gives him a lollipop for being a good patient; Geller accepts the candy with a wide grin. Lollipops might not be included, but St. Jude Children’s Research Hospital is about to welcome back its own population of adults to walk the halls again as patients.







Through the St. Jude Life program, select adult survivors will return to St. Jude for actual clinic visits—for life. “The objectives of St. Jude Life are to describe the occurrence and timing of selected late effects as the age increases for the survivor population, as well as to identify treatment, genetic, demographic, behavioral and psychosocial related predictors,” says Leslie Robison, PhD. Robison chairs the Epidemiology and Cancer Control department and serves as principal investigator of the national Childhood Cancer Survivorship Study, which is now anchored at St. Jude.

When St. Jude opened in 1962, its sole focus was on saving lives. As scientific knowledge progressed, clinicians and researchers placed more emphasis on not only saving patients, but also making sure they survived longer. Today, St. Jude focuses on creating treatments that will prolong life and help reduce long-term side effects.

That’s where the hospital’s After Completion of Therapy (ACT) Clinic steps in—following St. Jude survivors after they “graduate” from St. Jude to track their health progress and their quality of life. This clinic now has a new ally in its survival quest. Working side by side with the clinic is the Epidemiology and Cancer Control department. Its creation greatly increases the hospital’s ability to include preventive medicine in its overall mission.

“St. Jude has some of the most outstanding research in cancer prevention and control focusing on aspects like health behaviors, sleep fatigue, end of life, general health status and quality of life,” says Leslie Robison, PhD, department chair and principal investigator of the national Childhood Cancer Survivorship Study (CCSS), which is now anchored at St. Jude. “We want to expand upon the existing strengths of St. Jude, establish new areas of research and create a sys-

tem that will facilitate and maintain our research initiatives.”

### St. Jude Life

One of those new initiatives is “St. Jude Life.” In an unprecedented effort, select adult survivors—whether they are 28, 48 or 68—will have the opportunity to be like Ross Geller and return to St. Jude for actual clinic visits—for life.

“St. Jude has been in the enviable position of being able to do highly detailed clinical evaluations of its survivors through the ACT Clinic because of our ability to bring patients back to be evaluated,” Robison explains. “But there is a limit on that. After a given point, the clinic discharges patients as alumni, and they are released back to their local health care providers. What we are going to do now is expand that through St. Jude Life. The initiative will establish a lifetime group of adult survivors of childhood cancer.”

According to Robison, a number of institutions have been able to carry out more detailed clinical evaluations, but their ability to do that declines with time mostly because they no longer have access to the patient population. Within the CCSS, physicians have effectively fol-

lowed patients for long periods but relied heavily on self-reports.

By combining St. Jude Life with the CCSS efforts, St. Jude survivorship research will cover the entire spectrum of long-term follow-up. The results can be used by all St. Jude researchers as they develop treatment plans and conduct research to prolong and improve survival of children with catastrophic diseases.

“The objectives of St. Jude Life are to describe the occurrence and timing of selected late effects as the age increases for the survivor population, as well as to identify treatment, genetic, demographic, behavioral and psychosocial related predictors,” Robison says.

More than 4,000 adult survivors—including some 630 who are at least 30 years past diagnosis—will be invited to return to St. Jude for initial clinic visits. Chaired by Melissa Hudson, MD, director of the Cancer Survivorship Division, the pilot program will launch in early 2007, targeting 500 patients in the first six months.

“We want to approach these very valuable patients not only to get maximum participation, but also in a way that they feel they are deriving benefit from participating in St. Jude Life,” Robison says. “These first 500 are going to be from very high-risk populations. St. Jude

## More than 4,000 adult survivors—including some 630 who are at least 30 years past diagnosis—will be invited to return to St. Jude for initial clinic visits.

researchers are identifying these populations to carry out small, focused pilot projects to generate the preliminary data that will tell us whether or not we should invest in research initiatives in a much broader sense within some of these higher risk groups.”

Within the next four to five years, St. Jude will welcome 2,500 survivors to participate in St. Jude Life. “The frequency of follow-up for each person will depend on risk profiles,” Robison says. “We’re estimating that we will try to find a happy medium of seeing patients, on average, once every two years.”

### Partners for life

To increase the number of survivors who participate in these studies, St. Jude is partnering with select institutions to create a consortium that can carry out randomized intervention studies.

“Identifying high-risk populations is an essential goal, but once you identify who is at the highest risk, then it becomes essential that we develop interventions,” Robison says. “St. Jude has a number of researchers engaged in carrying out intervention trials; however, we want to ramp that up so we can do multiple trials in a much shorter time frame.”

A shorter time frame means faster results that can be translated into how to treat young patients currently undergoing treatment.

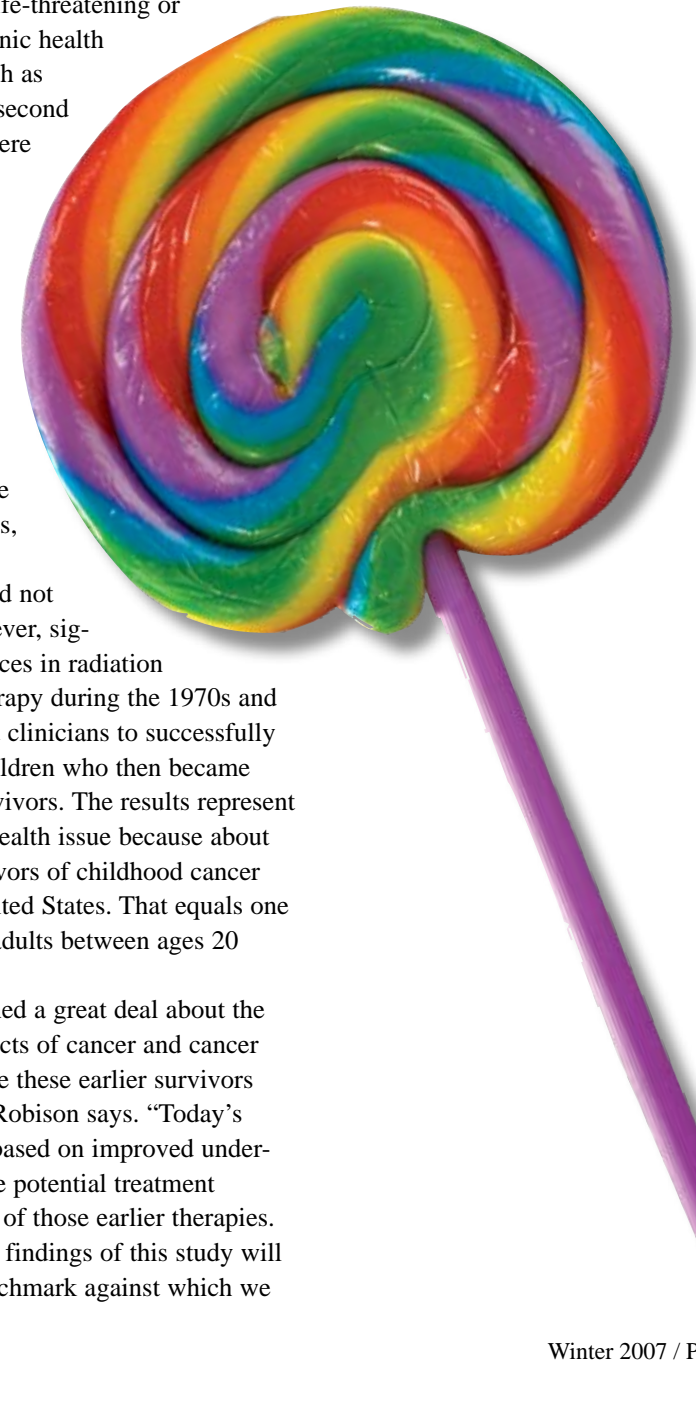
According to a recent study in *The New England Journal of Medicine*, almost three-fourths of adult survivors who had pediatric cancer diagnosed in the 1970s and 1980s have—or will develop—chronic health problems related to their cancer or its treatment. Robison is the study’s senior author.

The findings were based on interviews with survivors, questionnaires completed by those survivors and analyses of their cancer treatments. Compared with their siblings, adult survivors of childhood cancers were eight times more likely to have severe, life-threatening or disabling chronic health conditions such as heart attacks, second cancers or severe learning problems.

The high rate of health problems found among survivors in this study reflects the fact that before the early 1970s, most children with cancer did not survive. However, significant advances in radiation and chemotherapy during the 1970s and 1980s enabled clinicians to successfully treat many children who then became long-term survivors. The results represent a significant health issue because about 270,000 survivors of childhood cancer live in the United States. That equals one of every 640 adults between ages 20 and 39.

“We learned a great deal about the long-term effects of cancer and cancer treatment since these earlier survivors were cured,” Robison says. “Today’s therapies are based on improved understanding of the potential treatment complications of those earlier therapies. Therefore, the findings of this study will serve as a benchmark against which we

will be able to compare future outcomes of patients who are now receiving therapies that are more advanced and, we hope, less toxic. We expect these newer patients to have fewer and less severe long-term health problems.” ●







# EXPRESSIONS OF Survival

BY ERIC SMITH

Cancer survivors return to St. Jude to share stories of hope.

In the spring of 1962, time was running out for Dwight Tosh, a 13-year-old boy with Hodgkin disease. The prognosis was so bleak that doctors in Arkansas had given up on his chance for survival.

Needing a miracle, Tosh's family heard about a newly opened pediatric cancer center in Memphis, Tennessee, called St. Jude Children's Research Hospital.

Tosh was quickly transferred to the hospital, becoming the 17th patient in the facility's brief history. And thanks to the

treatment he received at St. Jude during the next few years, Tosh became one of its first cancer survivors.

Now 58 years old, cancer free for more than 40 years and among the thousands cured at St. Jude, Tosh returned last fall to pay tribute to the place that saved his life.

Tosh and his wife, Joan, along with 500 other survivors and family members, celebrated the hospital's 10th annual Survivors Day by reuniting with fellow patients, reconnecting with doctors and nurses, and recounting the myriad ways St. Jude has answered their prayers.

Although Tosh was the oldest survivor to return, he describes an unbreakable bond that develops among those treated at St. Jude—regardless of race, religion or age.

"I see the other survivors and I know, even though we shared a different time and a different era, that we all have the same thing in common," Tosh says. "We were all patients here—at a place that was our last hope."

## A special place

The theme for Survivors Day 2006 was "Expressions of Survival," and everyone who returned to the hospital had the opportunity to express their gratitude to St. Jude for helping them beat cancer.

Survivors came from near and far with stories to share about overcoming the obstacles of childhood cancer and then moving on to lead productive lives. But this day also held the promise of catching up with old friends.

PHOTOS BY ANN-MARGARET HEDGES



*"Not all of us made it. But the fact is, if we hadn't had the hospital, none of us would have made it. St. Jude gave us a fighting chance."*

Carol Jones of Arkansas returns for Survivors Day almost every year to give thanks for the care and compassion she received as a patient in the 1970s and to check on fellow survivors.

"St. Jude is a special place for me," Jones says. "I like coming back and seeing some of the same people again—seeing how they're doing, seeing their status."

The outlook for childhood cancer patients has improved greatly since the hospital opened its doors 45 years ago. In that time St. Jude has worked hard to cure childhood catastrophic diseases, and those efforts have raised cancer survival rates from less than 20 percent in 1962 to about 70 percent overall today.

Survivors are monitored by the hospital's After Completion of Therapy (ACT) Clinic, which helps survivors stay healthy through education, check-ups for cancer-related complications and outreach with community providers. Clinic Director Melissa Hudson, MD, knows the clinic's role grows each time a patient earns alumnus designation, which occurs when patients no longer come back to the hospital for regular monitoring.

"We provide health education regarding the survivor's cancer history, cancer-related health risks and health screening based on the specific treatment the survivor received," Hudson says. "This information is used to prepare the survivor and community providers who will assume care when the survivor is made an alumnus. We emphasize to our survivors that staff is available in the Alumnus Program Office to assist alumnus survivors who develop health issues or other problems later in adulthood. The ACT Clinic can help them in such areas as health education counseling, organizing treatment summaries and health screening recommendations, and assisting with referrals to community adult health care providers and other services."

Survivors of Hodgkin disease and the eye cancer retinoblastoma were of particular concern for Hudson and her colleagues at this year's Survivors Day. Special educational workshops were held for survivors of those diseases to address unique health issues they may face.

## A fighting chance

Many participants compare Survivors Day to a family reunion, and that was especially true for Franz and Kathy Hoerdemann of Illinois. They were patients at St. Jude together as children in the 1970s; after reconnecting as adults, they wound up falling in love and getting married.

The Hoerdemanns were thrilled to attend Survivors Day as husband and wife, to see the hospital's numerous changes and to hear how St. Jude has improved cancer survival rates.



**Dwight Tosh (pictured with his wife, Joan) arrived at St. Jude in 1962, just months after the hospital opened its doors. Tosh was the 17th patient admitted to St. Jude. He returned to campus last fall for the 10th annual Survivors Day celebration. Now 58 years old, Tosh was happy to pay tribute to the place that saved his life.**

"It's interesting to see how everything's progressed," Kathy observes.

"It's great to come back now and see the strides that have been made because of the knowledge they've gained from us and other survivors," adds Franz.

They weren't alone in showing their appreciation for St. Jude. Jason Schwartz of Louisiana, a patient in the 1990s, was so inspired by the medical staff that he decided to become a doctor. Now a 24-year-old med student, Schwartz figures that his time as a St. Jude patient—and now as a survivor—will make him a more empathetic doctor.

"I could be a benefit to other people by having experienced it myself," he says.

For Tosh, who finished his treatment before many of his fellow survivors were even born, memories of the experience have faded in the past four decades.

Still, he remembers meeting Danny Thomas and the Three Stooges. He remembers being wheeled through a tunnel from St. Jude to the old St. Joseph Hospital for radiation. And he remembers his mother sleeping in a recliner next to him each night, never leaving his side.

As Tosh reminisces, he takes a moment to reflect on what St. Jude has meant to the multitude of people whose hope was restored in their darkest hours.

"Not all of us made it," Tosh says. "But the fact is, if we hadn't had the hospital, *none* of us would have made it. St. Jude gave us a fighting chance."●



**"The ACT Clinic can help survivors in such areas as health education counseling, organizing treatment summaries and health screening recommendations, and assisting with referrals to community adult health care providers and other services," says Melissa Hudson, MD, ACT Clinic director.**





St. Jude researchers  
prepare to knock out a  
rare form of leukemia.

PHOTOS BY PETER BARTIA

# Ready to Rumble

SENSITIVITY can be considered good or bad, depending on the situation. If a doctor is described as sensitive, that’s a positive attribute. If a prizefighter is stuck with the label, it’s not so good. But when it comes to the treatment of a rare form of acute lymphoblastic leukemia (ALL), researchers at St. Jude Children’s Research Hospital are on the verge of delivering a knockout punch. They are studying a way to make ALL cells sensitive to an effective treatment to which they were becoming resistant.

Now that’s a form of sensitivity even a heavyweight contender can celebrate.

When St. Jude opened its doors in 1962, the survival rate for pediatric ALL was a dismal 4 percent. Today, 94 percent of newly diagnosed ALL patients can expect to be long-term survivors. ALL is the most common form of childhood cancer. Approximately 12,500 children will be diagnosed with cancer each year, and of this number a whopping 30 percent will receive a diagnosis of ALL.

BY LIN BALLEW

However, within this group of 30 percent is a small subset of patients with an extremely rare and devastating form of leukemia known as Philadelphia chromosome-positive ALL (Ph+ ALL). Less than 5 percent of the total pediatric leukemia population has this form of the disease, and their prognosis is still poor.

## Preparing for the fight

This rare subset of leukemia occurs when two chromosomes fuse to form an

oncogene (a cancer-stimulating gene) called the BCR-ABL kinase. BCR-ABL sets off a cascade of signals that drive ALL cells to divide rapidly, resulting in cancer formation. However, in order for things to reach that point, the BCR-ABL kinase must bob and weave to avoid the body’s natural defense mechanisms, such as tumor suppressor genes. These cancer-combating genes recognize when a cell is responding to abnormal signals and cause the affected cells to commit suicide, thus knocking the cancer out cold.

Charles Sherr, MD, PhD, co-chair of Genetics and Tumor Cell Biology and a Howard Hughes Medical Institute investigator, has studied such tumor suppressor genes for a number of years. One such gene, *ARF*, would normally take out the BCR-ABL enzyme with one punch. But *ARF* is frequently absent in patients with Ph+ ALL. Sherr and his colleagues, Richard Williams, MD, PhD, of St. Jude Oncology, and Martine Roussel, PhD, of Genetics and Tumor Cell Biology, have carefully examined how *ARF* loss speeds ALL progression.

One drug that has shown promise in the fight against this rare form of ALL is imatinib, also known as Gleevec®. This drug blocks BCR-ABL’s ability to signal cells to divide rapidly. But laboratory models of Ph+ ALL established by these investigators revealed that removal of the *ARF* gene greatly enhances the aggressiveness of BCR-ABL-induced ALL and contributes to imatinib resistance.

Thus, determining an effective treatment for Ph+ ALL isn’t as simple as delivering a one-two punch. The researchers also discovered that leukemia cells that had not responded to imatinib therapy still displayed sensitivity to the drug.

“Paradoxically, the resistance is not due to a change in the tumor cells themselves but instead reflects an altered relationship between the tumor cells and the body,” Sherr says.

## Delivering the K-O

So what is the secret to delivering a knockout treatment?

The critical issue is to determine the basis of the imatinib resistance.

According to Sherr and Williams, inactivating *ARF* enables ALL cells to thrive in the bone marrow even when the cancer-stimulating signals from BCR-ABL are blocked by imatinib. Thus, finding drugs that work hand in hand with imatinib to limit survival of the tumor cells should prove effective in treating this rare form of ALL.

“When children have this disease, it’s very aggressive, and they generally don’t respond as well to conventional treatment,” Williams says. “Tragically, some of these children still die, despite receiving the maximum therapy available.”

One of the unique aspects of this research is its scope. While Ph+ ALL is rare in children, it accounts for about one-third of adult ALL cases, with an equally poor prognosis. This is in stark contrast to chronic myelogenous leukemia (CML),

a disease also caused by the BCR-ABL kinase. In CML, where the *ARF* gene is intact, imatinib therapy is remarkably successful in keeping almost all patients in long-term remission; infrequent drug resistance that develops is usually due to acquired mutations of the BCR-ABL oncogene within the leukemia cells.

Scientists’ ultimate, long-term goal is to use the genetics of these leukemias to target their treatment. “Although it is ambitious to think about putting *ARF* back into the cells,” Williams says, “our efforts have already given us an enhanced understanding that is bringing us closer to developing effective treatments to fight these leukemias.”

With these insights comes the hope of winning the final round against cancer and knocking it out for good. ●



## WHAT’S A HOWARD HUGHES MEDICAL INSTITUTE INVESTIGATOR?

HHMI investigator Charles Sherr, MD, PhD, (at left) and colleague Richard Williams, MD, PhD.

The team led by Charles Sherr, MD, PhD, is funded in part by the Howard Hughes Medical Institute (HHMI). St. Jude has two HHMI scientists, which is quite an honor, since the institute currently funds only 330 researchers, all of whom are selected competitively.

Founded in 1953 by aviator and industrialist Howard Hughes, HHMI funds researchers at 70 institutions throughout the United States. The generous funding allows the scientists at host research centers to collectively sponsor approximately 2,500 research associates, technicians and support personnel.

Sherr has been an HHMI investigator since 1988. His salary, and that of his team, is paid by the institute, which allows St. Jude donor dollars to go further. HHMI gives its investigators great latitude in choosing projects and charting the direction of their research.

“It allows me the intellectual freedom to follow my intuition, take risks and hopefully discover something worthwhile,” Sherr says.

When Sherr’s research changed direction early in his involvement with the institute, he thought it prudent to advise HHMI. “They told me, ‘We are paying for you, not for the project,’” Sherr recalls.

Investigators are reviewed every five years by a distinguished senior scientific advisory board, and the researchers must defend their research. Brenda Schulman, PhD, of Genetics and Tumor Cell Biology and Structural Biology is also a current HHMI investigator; James Ihle, PhD, Biochemistry chair, held the title for nine years.



# Perspective

## Math + Kids = Hope

“There is such a sense of hope at St. Jude, and that feeling stays with you long after you leave the doors of that wonderful place.”



Actress Danica McKellar (pictured with patient Luseane Kahalelei Pese) helps St. Jude through her involvement in the hospital's Math-A-Thon® fund-raising program.

Acting is my first and truest love, but I've always had a passion for mathematics—which is why St. Jude Children's Research Hospital's Math-A-Thon® program is such an amazing fit. Since I graduated from UCLA with a degree in math and published a math theorem, I have found ways to keep math as a hobby. I've been answering math questions for

students on my Web site [www.danicamckellar.com](http://www.danicamckellar.com) for several years now; I absolutely love being a role model and helping kids and young adults understand math.

Last year, my publicist told me that St. Jude wanted me to be the spokesperson for the Math-A-Thon program. I had known about St. Jude for a long time, and to combine such an amazing cause with my love of math education was one of the easiest, fastest decisions I've ever made.

Almost immediately, I flew to Memphis to learn more about St. Jude. Quite simply, I was blown away. I have visited other children's hospitals, but St. Jude is completely different. They do amazing, cutting-edge research to help kids with even the rarest cancers, but the environment simply does not feel like a hospital. Colorful murals and creative activity centers are around every corner. I never even

saw a wheelchair; in fact, the patients being pulled around the hospital in bright red wagons and riding on tricycles left an indelible image of joy in my mind. Everyone, patients and parents alike, seemed to be genuinely happy.

Even the kids who were tired from chemotherapy looked content, like they truly felt taken care of. I believe that has

BY DANICA MCKELLAR

to do with the fact that the parents don't have to worry about whether they can afford treatment, and are able to focus on being there for their kids in an atmosphere of love and healing. There is such a sense of hope at St. Jude, and that feeling stays with you long after you leave the doors of that wonderful place.

I couldn't be more thrilled to be the Math-A-Thon spokesperson. By participating in Math-A-Thon, kids know that they are raising money that directly helps kids their own age who are struggling with cancer. Kids need to learn the importance of volunteerism and giving back. I hope that all of the teachers and parents who read this article will do what they can to bring Math-A-Thon to their schools. It's such an overwhelmingly win-win activity for both the kids in the classroom and the kids at St. Jude.

Needless to say, I am so grateful that a place like St. Jude exists. I am thrilled to be a part of its support system, and I hope we can all help it thrive for years and years to come.

*An accomplished actress, writer, producer and award-winning director, Danica McKellar's recent projects include starring in Lifetime Movie Network's multi-media series Inspector Mom and releasing a yoga and meditation DVD Daily Dose of Dharma. In 2007, she will publish MATH DOESN'T SUCK, a book that uses hip and entertaining examples to teach girls and their parents how to master many concepts that are introduced in middle school—the time when girls begin to shy away from math. ●*

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