Promise
A publication of St. Jude Children’s Research Hospital  Spring 2007

Features
4  Life’s Work
   Ellis and Janet Harrell
5  The Hero Next Door
   Running for a reason
6  The Finish Line
   Evan Sanders’ most grueling race
10  A Global Mission
   Ethics in motion
12  Traveling Toward a Cure
   Neuroblastoma discoveries
15  Shattering the Syndrome
   Discovery offers hope for millions
18  The Color of Hope
   Patients Judah and Jada Lindsey
22  Foundation for the Future
   Training the scientists of tomorrow

Highlights
2  News and Achievements

Perspective
24  James M. Davis
   Partners for Life
Fatty acid detectors

Just as homes have smoke detectors, cells have an enzyme that responds to a buildup of fatty acids by triggering production of a key molecule in the breakdown of those acids, according to a St. Jude investigator. This process provides the cell with energy while reducing the chance that excess fatty acids will accumulate, the researchers said. The discovery explains how the fatty-acid-sensing enzyme PanK2 tailors production of this key molecule, coenzyme A (CoA), to the energy demands of the cell, according to the report’s senior author, Yong-Mei Zhang, PhD, Infection Diseases. Understanding PanK2 function is important because mutations in this enzyme cause an inherited neurodegenerative disease called PanK-associated neurodegeneration. A report on this work appears in the January 30 issue of Proceedings of the National Academy of Sciences.

Parkinson’s and pi

The degeneration of brain cells that occurs in Parkinson’s disease may be caused by either externally provoked cell death or internally initiated suicide when the molecule that normally prevents these fatal alternatives is missing, according to laboratory studies by St. Jude investigators. Parkinson’s disease is a disease in which nerve cells in a part of the brain called the substantia nigra die.

One molecule that prevents damage to the substantia nigra is an enzyme called GST pi (“pie”). This molecule acts like a brake at the crossroads of several biochemical pathways, any one of which can lead to Parkinson’s disease, the researchers reported in the February 6 issue of Proceedings of the National Academy of Sciences.

The findings suggest that measuring levels of this enzyme might be an effective way to determine individuals at risk for developing this disease, according to the report’s senior author, Richard Smeyne, PhD, Developmental Neurobiology.

Order among disorder

The secret to the ability of a molecule critical for cell division to throw off the protein yoke that restrains its activity is the yoke itself—a disorderly molecule that seems to have a mind of its own, say investigators at St. Jude, Innsbruck Medical University (Austria) and Max Planck Institute (Martinried, Germany).

The researchers showed that the disorderly protein yoke, called p27, participates in its own destruction. The finding explains how CDK2 normally shrugs off p27. Once free of p27, CDK2 can participate in a specific step of cell division. This also explains how some abnormal enzymes cause this to occur prematurely, putting cell division into overdrive—a state that produces cancer.

Richard Kriwacki, PhD, Structural Biology, is a co-author of a report on this research which appears in the journal Cell, January 2007.

Passing the baton

The freeze-frame image of a molecular relay race—in which one enzyme passes off a protein like a baton to another enzyme—illustrates how cells control some vital functions, according to a team of St. Jude investigators.

A report on this work appears in the January 25 issue of Nature. The St. Jude discovery explains how a simple chemical link between molecules called a thioester bond works like a baton in a relay race, controlling the handoff of the NEDD8 protein from one enzyme to another. In the cell, this NEDD8 relay race triggers a number of biochemical reactions, one of which takes the brakes off cell division, allowing cells to multiply. These thioester bonds are chemical links between two biological molecules that form when a sulfur atom on one of the molecules binds to an atom that is part of the other molecule.

Understanding how the thioester bond switch works is important not only because it explains a critical step in the NEDD8 handoff of one enzyme to the next, but also because similar enzymes run relays with other important protein batteries, said the report’s senior author, Howard Hughes Medical Institute investigator Brenda Schulman, PhD, of St. Jude Structural Biology and Genetics and Tumor Cell Biology.

Another reason to roll up your sleeves

The yearly influenza vaccine that health officials urge people to get each fall might also offer certain individuals some cross protection against the H5N1 virus, commonly known as bird flu, according to St. Jude investigators.

Scientists found in a laboratory model that the virus protein N1, one of two or more proteins present in the annual flu shot, can act as a vaccine itself and trigger some cross protection against H5N1; and that some human volunteers already had antibodies directed against the same part of this virus.

“The jury is still out on whether the seasonal flu vaccine is definitely a reliable way to offer people some protection from H5N1, but our initial results suggest to us that this is a research trail worth following,” said Richard Webby, PhD, Infectious Diseases. Webby is senior author of a report on this study that appears in the February 2007 issue of PLoS Medicine.

Finding their “niche”

St. Jude researchers have found a vulnerable spot in brain tumors they are trying to exploit to improve the treatment of these cancers and prevent tumors from returning. The researchers showed in laboratory studies that brain tumors appear to arise from cancer stem cells (CSCs) that live within microscopic, protective “niches” formed by blood vessels in the brain; and that certain drugs can disrupt these niches, depriving the tumors of their source of cancer cells. CSCs are cells that continually multiply, acting as the source of tumors.

“These niches might also protect CSCs from chemotherapy and radiation therapy,” said Richard Gilbertson, MD, PhD, Developmental Neurobiology.

“This could help explain why tumors that rapidly produce new blood vessels are clinically aggressive and how brain tumors reappear following treatment.” Gilbertson is senior author of a report on this work that appears in Cancer Cell, January 2007.

Attack of the modified cells

St. Jude researchers showed in a laboratory model that genetically modified cells can be used to treat neuroblastoma tumors. These cells seek out sites harboring cancer cells and are modified to activate a chemotherapy drug directly at those sites, according to investigators at St. Jude and their colleagues at City of Hope National Medical Center (Duarte, California) and the University of British Columbia (Vancouver, Canada).

Neuroblastoma is a solid tumor that arises in the part of the nervous system outside the brain.

A report on this work appears in the December 20 issue of the Web-based journal PLoS ONE.

Since the drug, called CPT-11 (irinotecan), is already used to treat cancers, doctors and scientists already know how the drug behaves in humans. That knowledge should make it easier to translate these laboratory findings to the clinic. Mary Danks, PhD, of St. Jude Molecular Pharmacology, is the report’s senior author.

Score one for the immune system

In the lab, St. Jude investigators demonstrated a way that might reduce the time it takes for a bone marrow transplant to rebuild a child’s immune system, and so reduce the risk of potentially fatal viral infections that can occur during this time.

The St. Jude finding is important because children whose own bone marrow stem cells have been destroyed by chemotherapy or radiation treatments for cancer routinely undergo bone marrow transplantation. Reducing the time it takes for the immune system to regenerate blood cells called T lymphocytes would be an important step in reducing infection risk in these children and improving their long-term outcomes, says Raymond Barfield, MD, PhD, of Bone Marrow Transplantation.

A report on this work appears in the journal Stem Cells, February 6, 2007.

For more details about St. Jude research, visit www.stjude.org/media.
Ellis and Janet Harrell believe that God gives you the gift of life, and hard work makes it meaningful.

By Betsy Taylor

Ellis Harrell has never taken a halfhearted approach to life. He grew up on a farm in Goldsboro, North Carolina, which taught him that good things come from hard work.

“I learned early on that you get out of something what you put into it,” Ellis says.

Once he came of age, he was drafted into the Army. He served in the military police from 1952–54 and was stationed for a time in Germany.

By the end of his two-year stint, he knew one thing for sure: He hated taking orders. “I wanted to be my own boss, live my own life,” he says.

Ellis is a self-starter with an inquisitive nature, and he doesn’t shy away from calculated risks. For these reasons and others, the start of his first business—well drilling—led to a dizzying array of other successful ventures, including home finance, mini-storage unit supply, car washes and commercial property sales.

His faith in God has allowed him to overcome the normal fears of trying something new. In this sense, he is like the late entertainer Danny Thomas, who, in devotion to St. Jude Thaddeus, the patron saint of hopeless causes, forged ahead with plans for a children’s research hospital without a speck of medical or administrative experience.

Ellis’s wife, Janet, complements her husband’s hands-on, entrepreneurial nature.

“She’s just been a good mate who gives me moral support and stands by me in the business and my life,” Ellis says. “We go to church together and visit family. She’s a good soul mate.”

Thankful to God for their large and loving family, the couple decided to share their good fortune. For years to come.

“When I came to see a St. Jude Children’s Research Hospital television special in 2004, they contacted the hospital. Ellis and Janet wanted to help substantially, but first they needed to see St. Jude for themselves.

“Having a little extra in life is an awesome responsibility,” Ellis says. “You have to do a little investigation and be confident that your money is going where it will do the most good.”

The couple visited Memphis in 2005 to speak with St. Jude doctors about cutting-edge research. They also toured Target House, a home away from home for St. Jude families. “I was impressed with the way they treat the whole family, not just the child,” Janet says.

This confidence inspired a generous cash gift and a specific bequest in their estate plans that will benefit St. Jude kids for years to come.

“To be able to reach into the life of a child and a family and give hope and healing is very gratifying,” Ellis says.

“The door opened for this opportunity when Danny Thomas was so inspired to create St. Jude. Let us be inspired to carry the torch for support.”

To learn more about making a gift to St. Jude or other planned giving opportunities, call Gift Planning at (800) 395-1087 or e-mail giftplanning@stjude.org.

The Hero Next Door

St. Jude Heroes are regular people who raise money for St. Jude while participating in sports they love.

By Betsy Taylor

Heroes no longer need capes, but stretchy tights still help in cold weather.

In 1999, a group of marathon aficionados in the Washington, DC, area decided to link their favorite sport with fundraising for St. Jude, urging family and friends to sponsor their participation in the Marine Corps Marathon.

They called themselves St. Jude Heroes, and they raised thousands of dollars.

Since then, the definition of a St. Jude Hero has expanded to include people who, in the name of St. Jude, want to push themselves to accomplish fitness goals through competitive sports.

If this definition seems inclusive, it’s meant to be.

“Less than 1 percent of the population are marathon runners,” says Marianna Webster, national program marketing representative for ALSAC/St. Jude. “The Heroes program has grown to embrace something much broader. It’s become a fitness initiative so that everyone who participates can feel motivated to reach their goals.”

Many find the Heroes program a therapeutic way to honor loved ones who have suffered from cancer. Heroes now include family teams, those with physical challenges, grandparents, former patients and others. “Everyone can be a hero,” explains Webster.

Last year, the Heroes program garnered $1 million; this year’s tally has already surpassed $1.5 million. Heroes may compete in any sport from swimming to mountain climbing, but the lion’s share of Heroes choose racing as their sport of choice.

In 2005, the Hudson Valley Heroes for St. Jude Kids running team raised $7,000, and last year the group drummed up more than $14,000 through its participation in the St. Jude Memphis Marathon.

“The contributions went beyond what we ever envisioned,” says team member Liz Irwin, “and it keeps building.”

The Heroes receive support through the program’s Web site to help them hit their fitness and fundraising targets, a log book to record training progress and information about St. Jude to share with sponsors. Heroes have access to a virtual training module that provides a fitness assessment and a tailored daily training regimen. They may also set up their own customizable Web sites to keep in touch with sponsors as their sporting event date approaches.

Many Heroes dedicate their personal sites to those who have fought cancer, including St. Jude patients. (See related story about Hero and St. Jude patient Evan Sanders, page 6)

Mike Creed of Missouri ran the 2006 St. Jude Memphis Half Marathon for a patient named Brandon who had lost his leg to osteosarcoma.

“I thought, ‘There’s my guy. I’m going to do it for him,’” Creed says.

Program organizers provide incentives for Heroes who reach their goals, including St. Jude apparel and airline vouchers, but that’s a bonus. The patients are the ones who motivate these athletes.

“I’ve run six of these [before becoming a Hero]. I’ve run them just for me—to try to better my time and that kind of thing,” Creed says. “Now I have a reason.”

To learn more about the St. Jude Heroes program, visit www.stjudeheroes.org.
The 14-year-old, curly haired boy wearing bib No. 6193 blends in with the sea of runners who have braved this chilly December morning to compete in the St. Jude Memphis Marathon, Half Marathon and Memphis Grizzlies House 5K.

Like them, he sports cold-weather gear and running shoes. Like them, he settles into a suitable pace. And like them, he digs deep for every breath and every stride along a course that winds through the heart of the city.

Despite similarities with 8,600 other participants, the 14-year-old, curly haired boy wearing bib No. 6193 has separated himself from the pack—but not by building a lead, breaking the tape and collecting prize money.

In December 2005, Evan Sanders watched thousands of runners stream by Target House during the St. Jude Memphis Marathon. Ravaged by disease and its treatment, the former athlete had little more than 80 lbs. on his 5-foot-9-inch frame. Evan resolved to run the race the following year. But first, he had to outrun cancer.

With the help of St. Jude, Evan Sanders wins the most important race of his life.

By Eric Smith
No, he has set himself apart simply by putting on that cold-weather gear, lacing up those running shoes and taking that first step toward the finish line. Because eight months ago he lay in a hospital bed at St. Jude Children’s Research Hospital recovering from four surgeries. Eight months ago he was in a race against cancer.

On your mark…

In 2004 Evan Sanders was a 12-year-old boy with straight hair. Life at home with his parents, Richard and Julie, older half-brother, Marty, and younger sister, Nicole, was typical for an ambitious, active preteen. When Evan wasn’t devouring books or doing homework, he was bustling from one athletic field to the next. He played soccer, baseball, and basketball; he ran track and cross-country; he even swam. A naturally gifted athlete, Evan made a name for himself by regularly winning agility and physical fitness contests. Along with talent, Evan possessed a competitive fire that burned whenever he stepped into a batter’s box, toed a starting line or kicked a soccer ball. So when his back started hurting, neither Evan nor his parents worried. All athletes, especially multi-sport ones, get bumps and bruises, aches and pains. He took pain relievers twice a day and went about his life. “We thought it was muscular,” Evan says, “just a really bad pull or something.” When the medicine wreaked havoc on his stomach, he stopped taking it and began playing through the pain. As one of the starting pitchers on his baseball team, Evan tweaked his throwing mechanics and relied on his arm to do all the work, a dangerous habit for a young athlete who’s still growing and developing. When he couldn’t pitch, he would play shortstop and third base, excelling in the field and at the plate.

Evan’s doctor, Lisa McGregor, MD, of St. Jude Oncology (see photo of McGregor, page 14), recalls his visit to the hospital six months later for routine procedures. “He returned for follow-up and the mass was back, more aggressive than it had been previously,” McGregor says. A biopsy and scan in February 2005 revealed a large, malignant tumor in Evan’s back. The diagnosis this time was osteosarcoma, the most common type of bone cancer in children. The way it progressed in Evan, however, was decidedly uncommon.

“Evan’s is a very rare situation,” McGregor says. “Osteoblastoma is rare in itself, and then to have it recur and be classified as an osteosarcoma is even rarer.” The surgeons removed this new menace and resected Evan’s spine for a second time. Clinicians hoped chemotherapy and radiation would shrink whatever cancer might remain. Those treatments, which began in March, two days before his 13th birthday, were especially rough. Evan lost his hair, his appetite and his patience for the entire ordeal.

Evan doesn’t remember much about this time at the hospital, but he recalls being unpleasant to staff because he was hurting so bad and because he was ready to resume his life. McGregor understood. “When Evan first came here, he was in a lot of pain, and of course nobody is the nicest when they are in so much pain,” she says. “He was not used to being in a medical world, and he didn’t like to be stuck with needles. He was a normal kid.”

The home stretch

Evan spent his time at St. Jude doing as many normal things as possible. He became a master of the board game Connect Four. He read dozens of books—from The Da Vinci Code to Eragon to A Series of Unfortunate Events. He bought two guitars, one acoustic and one electric. And when he felt OK, Evan and his father played disc golf, attended baseball games or checked out country music concerts.

Evan took advantage of the good days, but he also knew how much he was missing. By December 2005, Evan had already missed all of seventh grade and half of the eighth. The avid runner, who had been away from his sport for a year to remove the remainder of one of his thoracic vertebrae that was tainted with dead tumor tissue and bone fragments from previous surgeries. This time he healed more quickly. During recovery he decided it was time to think about training for that promise he had made to himself just five months prior. “I said, ‘I am definitely going to be able to run again,’” he recalls. “It didn’t hurt to walk, so I shouldn’t hurt to run.”

Two months later, Evan indeed started running. He began training with his high school’s cross-country team in the evenings. His father ran alongside, to pace Evan and get him back up to speed. Richard and Julie were impressed—but not all surprised—with their son’s determination and willingness to work himself back into shape. “You know, some kids try to take shortcuts,” Julie says. “Evan is not a kid to take shortcuts.”

Meanwhile, Evan gained weight, and his hair started to grow back, darker and curlier than before. He refused to have it cut.

1:46:26

On this chilly December morning in downtown Memphis, the 14-year-old, curly-haired boy sporting bib No. 6193 crosses the finish line at 1 hour, 46 minutes, 26 seconds. That time is now Evan’s personal record for the half marathon—a 13.1-mile, leg-burning, lung-busting task that challenges even the healthiest runners.

When the results are posted, he sees that he placed 11th out of 34 runners in the 11-15 age group. Evan also beat his father.

“They made it clear from the beginning that they were proud of him and it and him.”

That kick came from deep inside Evan, who wasn’t competing for awards or accolades, but to reclaim the life that was halted two years earlier. “The last time I was running on pure adrenaline because I was ready to finish, ready to get done and go to sleep,” says Evan, who recently turned 15.

Although Evan ran the race as a St. Jude Hero—someone who pledges to raise money for the hospital (see related story on page 5)—he admits he wasn’t doing it for anyone but himself. Thanks to his efforts and those of St. Jude, there will be a second chance to do that.

“This one was for me,” he says. “I’m going to do it every year, and then it’s going to be for the hospital. But the first one was for me, because that was my goal—to finish.”

In the end, cancer simply couldn’t keep up with Evan Sanders. You might say he left cancer and all its sodal companions in the dust.
A Global Mission

By helping hospitals in developing countries form research ethics committees, St. Jude opens the door to sharing lifesaving knowledge with the world.

By Ruth Ann Hensley

Imagine if you will, a young boy around the age of 9 bouncing a soccer ball on his knees, first left, then right, getting just enough lift to squat down beneath the ball and bounce it off the top of his head. With a victorious grin, he nonchalantly catches the ball and plops down in the grass welcoming the sun to warm his tired muscles. Moments later his mother calls for him to come inside and do his homework. He moans later his mother calls for him to come inside and do his homework. He moans later.

This boy is not so different than any other 9-year-old boy except that he lives in El Salvador. That means if he were to receive a diagnosis of acute lymphoblastic leukemia, his chances of survival would be 39 percent less than a child who lives in the U.S.—and that’s an alarming difference.

The disparity in the quality and availability of health care between high- and low-income countries has challenged the global medical community for years. One of the primary obstacles developing nations face is that they have little or no access to oversight organizations like research ethics committees (RECs), groups that protect and oversee the rights of people participating in scientific treatment plans. Without such a committee in place, a hospital cannot participate in research studies with hospitals in more affluent countries.

Through its International Outreach Program, St. Jude Children’s Research Hospital has formed a collaboration with a children’s hospital in El Salvador that is paving the way for hospitals around the globe to form their own RECs. Through a process called “twinning,” St. Jude is mentoring low-income countries so they can reach national and international ethics compliance standards. That way, these hospitals can participate in research aimed at curing catastrophic childhood diseases—and that makes all the difference in the world.

Research ethics in motion

“Most hospitals in other countries have hospital ethics committees, but they are not prepared to review research protocols,” explains Miguela Caniza, MD, of St. Jude Infectious Diseases and International Outreach. “There is a different set of standards required when the protection of human subjects is involved.”

When International Outreach partner site Hospital Nacional de Niños Samuel Bloom (Hospital Bloom) in San Salvador, El Salvador, expressed an interest in participating in research protocols with St. Jude, Caniza realized the Salvadoran hospital was not prepared. They did not have an REC in place, therefore barring the possibility of research collaboration.

Caniza, who describes herself as a problem solver, took the REC formation ball by the horns and used consultancy funds to finance it. In a mutual interest in the project, she asked, “Why don’t you just come to St. Jude and let us figure out a way to get this done?” Caniza recalls.

Making it happen

So she did. Although it was Maron’s first attempt to establish an REC, her visit to St. Jude marked Hospital Bloom’s third such effort since 1995. The St. Jude Institutional Review Board (IRB), a committee responsible for ethical and regulatory oversight of all research involving human participants, guided Maron through the numerous steps of the process.

When she returned to El Salvador, Maron partnered with Wilfrido Clara, MD, then chief of clinical research at Hospital Bloom. “All of this was new to us and very intimidating, and we had no other model in the country,” Maron explains. “We had to learn on the job, talk to local authorities and register our REC.”

After Maron and Clara completed an online research ethics course, took a Family Health International course in Guatemala and trained members of Hospital Bloom’s REC, the hospital obtained a Federal Wide Assurance in 2004. This assurance, granted by the U.S. Department of Health and Human Services, allowed Hospital Bloom to collaborate with U.S. institutions like St. Jude.

Successful formation of the REC brought the issue of research ethics to the forefront in El Salvador. This inspired the Salvadoran Vice Minister of Health José Emesto Navarro Marin, MD, to push for establishment of a national REC, which was formed in 2005.

Sharing the knowledge

“St. Jude is a global resource,” says Raymond Barfield, MD, PhD, of St. Jude Bone Marrow Transplantation and chair of the St. Jude Ethics Committee. “It’s absolutely imperative, especially when treating children, to pay attention to ethical issues and to share that message with the world.”

That is where the process of twinning comes into play. ‘Twinning is a long-term collaborative relationship between a high-income and a low-income institution that fosters the sharing of knowledge, resources, technology and ideas. The process encourages the creation of alliances between private and public entities, including the government.

Barfield, who worked with Caniza in strengthening the Hospital Bloom REC, says this is not a “big brother” relationship.

“It’s very much a back and forth educational experience,” he says. “We have a standard that we set in this country for research ethics and we insist that people reach it. But when we operate at an international level, we have to take into consideration numerous factors and barriers such as cultural, social and religious practices, languages and what we call ‘respect for persons.’ It’s negotiating these kinds of complexities that is so important for an institution like St. Jude that wants to conduct research and share knowledge.”

“Twinning with institutions in other countries allows us to develop culture-sensitive research initiatives,” says Raul Ribeiro, MD, International Outreach director, whose vision the team of Barfield, Caniza and Scott Howard, MD, of St. Jude International Outreach, credit with the initiative’s success. “We think this collaboration can serve as a model for other countries in Central America.”

In fact, it already has. Plans are underway to participate in a research study with Hospital General Pediátrico Niños de Acosta Ñu, in Paraguay, South America, which does not have an REC.

“St. Jude would like to do this,” Caniza asks with a knowing grin. “Create one!”

Hospital Bloom will share the information learned from St. Jude by forming a twinning partnership with the Paraguayan hospital. But St. Jude will still be involved in the process, which is viewed as one piece to a larger, global mission.

“This project is my passion. It’s like when you preach something and someone is converted,” Caniza reasons. “I’ve already sent my REC books to Paraguay—so I am preaching actively and will continue to spread the word.”
Laboratory studies by Jill Lahti, PhD, of Genetics and Tumor Cell Biology, show that a drug called interferon-gamma (IFN-gamma) sensitizes tumors, making them more responsive to chemotherapy and thereby easier to cure. “It has the potential to be the next step forward,” Lahti says. “Our studies suggest it could enhance response to existing chemotherapy drugs.”

Walk, then run

Scientists already knew that IFN-gamma causes cancer cells to undergo apoptosis, or cell death, in part, by stimulating them to make a molecule called caspase-8.

Lahti and her research team took the understanding a step further by showing that the drug not only sensitizes neuroblastoma tumors to chemotherapy, but that it also may be effective in doses appropriate for children.

The second most common pediatric solid tumor, neuroblastoma accounts for up to 10 percent of all childhood cancers. It typically occurs in infants and children under 5 years old.

Neuroblastoma tumors originate from neural crest cells, called neuroblasts, in the sympathetic nervous system, which runs from the base of the neck to the tailbone. The tumors can appear anywhere along the chain, but are generally found near the adrenal glands, which are located on top of the kidneys and in the chest.

As many as seven out of 10 cases are not discovered until symptoms appear, at which time the cancer usually has spread to other parts of the body.

“We’ve spent a number of years looking at the mechanics of neuroblastoma,” Lahti says. “With neuroblastoma, the cells grow a little faster than normal cells, but the real problem is that they don’t die like they should when something goes wrong or in response to chemotherapy. We started to examine why they didn’t die, and we discovered that caspase-8, a major cell-death-inducing protein, is preferentially turned off in many advanced-stage neuroblastoma tumors.”

The caspase-8 molecule is turned off in about a third of neuroblastoma patients, and, in many cases, the disease has reached this late, advanced stage and spread before diagnosis. At that late stage, genes have typically lost the ability to express caspase-8, which is required for chemotherapy drugs to induce the cancer cells to commit suicide.

So St. Jude researchers explored a way to “turn on” caspase-8.

Many pathways, one destination

“We’re finding that the more pathways you can target at one time, the more effective the chemotherapy is going to be,” Lahti says. “The idea is to upregulate (or reactivate) death pathways so that the chemotherapy actually kills the cells.”

Cell death occurs in two ways: It can be triggered by a signal from outside the cell’s surface that is transmitted inside the cell wall, or it can be caused by the cell...
recognizing that it is abnormal and choosing to destroy itself. Researchers found that caspase-8 worked in both death pathways.

“Most things target one pathway or the other, but caspase-8 is one of the few molecules that works in both ways to kill a cell,” Lahti explains. “That’s where the interferon comes in. We can use a low dose to stimulate the cells making the molecule caspase-8, which then triggers cell death by both pathways in response to chemotherapy drugs that attack those cells.”

Administered at high doses, IFN-gamma can cause severe side effects, but at the low doses Lahti and the team used, the side effects are minimal—a skin to a case of the flu.

For the study, the researchers exposed a series of different cultures of neuroblastoma cells to IFN-gamma for five minutes. The single-dose treatment triggered caspase-8 production in all cells that previously were not producing this molecule as well as in three out of six neuroblastoma cultures that were already producing high quantities of caspase-8. The increase in caspase-8 occurred within 16 hours and lasted for up to nine days.

Most importantly, the treatment made the cells almost three times more sensitive to the chemotherapy drug doxorubicin.

Moving forward

The investigators also used a technique called gene microarray analysis to identify genes that were affected by IFN-gamma. “Altered activity of these genes by both pathways in response to chemotherapy drugs that attack those cells,” Lahti says.

The findings from the year-and-a-half study raise questions for use in future therapies.

“Interferon up-regulates the immune system,” Lahti cites as an example. “Can we take advantage of that? What else do we know about the biology that we can capitalize on? Can we add drugs to that or change the order in any way to make it even more effective?”

St. Jude researchers are now discussing the possibility of testing IFN-gamma in a clinical trial. The hospital treats up to two dozen new neuroblastoma patients annually. Nationwide about 650 new cases—about one in 100,000 children—occur every year. To enroll the appropriate number of patients in the trial and to share research efforts, St. Jude would partner with other institutions across the nation.

“The cure rate for late-stage neuroblastoma patients is relatively low,” Lahti says. “Something that leads to even a 10 to 20 percent increase in the cure rate is significant.”

The right direction

For Heather Burford, there is a moment of relief knowing that Brady is at the halfway point of his treatment. “It’s been some years,” she says, recalling Brady’s stomach ache which lead to the neuroblastoma diagnosis; a rush surgery to remove the tumor in his adrenal gland; and months of grueling treatment. Adding to the anxiety, Brady’s arm was fractured in a car accident, putting him in a cast for weeks while undergoing treatment.

“That’s a lot for anyone to go through, and Brady has managed it all before he turned 4,” Heather says. McGregor, Brady’s physician agrees. “He’s a tough little cookie. Now it’s just a matter of waiting to move to the next step,” she says. “Hopefully one day IFN-gamma will improve the efficacy of chemotherapy for neuroblastoma, but it often takes years of research both in the laboratory and in patients to translate such an exciting finding into a benefit for our patients. We are only beginning that process.”

Once Brady’s immune system recovers from his transplant, he will start the second phase of treatment, a 16-month rotation between two oral chemotherapy drugs, topotecan and retinoic acid.

After an initial period of monitoring his response to the new regimen, the Burfords will be able to go home, returning to St. Jude monthly for scans.

The thought thrills Heather. “Brady has gone through so much, and now we’re finally at the point that we can go home,” she says. “It’s another step in the right direction.”

With the development of IFN-gamma treatment, researchers may someday make the road home even easier to travel for patients like Brady.
metabolism, a group of conditions—obesity, insulin resistance, high blood pressure, low levels of good cholesterol and high blood sugar levels—that occur together. These conditions can increase the risk of serious complications like type 2 diabetes, heart attack and stroke. Metabolic syndrome affects up to one in four adults in the United States, and its occurrence is increasing in developing countries like India and China where people are adopting Western lifestyles, diets and behaviors.

Eating a balanced diet, exercising, maintaining a healthy weight and avoiding tobacco can reduce the risks associated with metabolic syndrome, but what if a treatment were available to help prevent the disorder? Researchers at St. Jude— in collaboration with scientists at Washington University School of Medicine in St. Louis, Missouri— have found that chloroquine, a drug commonly used to treat malaria, shows potential as a treatment for metabolic syndrome. This finding may also help insulin-dependent diabetics reduce their insulin requirements.

**Fragments of questions**

The key to chloroquine’s effectiveness against metabolic syndrome is a protein called ATM—known to researchers for its role in the cell’s response to stress and DNA repair. ATM has been studied its role in the cell’s response to stress called ATM—known to researchers for its role in the cell’s response to stress and DNA repair. ATM has been studied its role in the cell’s response to stress, in particular DNA damage,“ Kastan says. “DNA damage is very important in several aspects of cancer biology,” Kastan says.

The researchers began this journey of discovery with studies of a rare, recessive genetic disorder called ataxia telangiectasia (A-T). A-T is a complex disorder in which children experience a progressive neurodegeneration and other abnormalities. The disease causes devastating damage to the part of the brain that controls muscle function and coordination; patients with A-T are also at high risk for developing certain cancers, immunological disorders and lung problems. Because of this correlation, St. Jude created the world’s only clinic specifically designed to treat children with A-T and cancer.

“Several years ago, we found that the ATM protein, made by the gene that is missing in A-T patients, plays a role in insulin signaling and how cells respond to insulin,” Kastan says. “The reason we looked at that is because we knew from our work with A-T patients that some of them tend to have a strange type of diabetes. So, we explored the reason for this. In looking at insulin signaling, we found that the ATM protein—which is an enzyme—can get activated by insulin in certain cell types.”

Also, parents of A-T patients have been reported to have a higher incidence than normal of cardiovascular disease. Kastan wondered: With the link between insulin and ATM—and the apparent responses are important determinants of whether cancers start, of how tumors respond to therapy, and of the toxicities experienced by patients receiving cancer therapies. Thus, how cells respond to DNA damage is very important in several aspects of cancer biology,” Kastan says.

The researchers began this journey of discovery with studies of a rare, recessive genetic disorder called ataxia telangiectasia (A-T). A-T is a complex disorder in which children experience a progressive neurodegeneration and other abnormalities. The disease causes devastating damage to the part of the brain that controls muscle function and coordination; patients with A-T are also at high risk for developing certain cancers, immunological disorders and lung problems. Because of this correlation, St. Jude created the world’s only clinic specifically designed to treat children with A-T and cancer.

“Several years ago, we found that the ATM protein, made by the gene that is missing in A-T patients, plays a role in insulin signaling and how cells respond to insulin,” Kastan says. “The reason we looked at that is because we knew from our work with A-T patients that some of them tend to have a strange type of diabetes. So, we explored the reason for this. In looking at insulin signaling, we found that the ATM protein—which is an enzyme—can get activated by insulin in certain cell types.”

Also, parents of A-T patients have been reported to have a higher incidence than normal of cardiovascular disease. Kastan wondered: With the link between insulin and ATM—and the apparent increase in cardiovascular disease in the parents of A-T patients—would ATM play a role in insulin resistance and cardiovascular disease? Because this type of research is not done at St. Jude, Kastan called a colleague to help.

“I partnered with a scientist at Washington University who is an expert in insulin signaling, insulin resistance with type 2 diabetes, atherosclerosis, and fat build-up in the central part of the body, which are all part of metabolic syndrome?” The answer was that the ATM protein, made by the gene that, which happens in up to 1 in 100 Americans, made metabolic syndrome much worse. Missing both copies, as occurs in A-T patients, is even worse.

In 2003, Kastan’s laboratory published a paper in the journal Nature about how ATM works and how it gets activated by DNA damage. The study described how a critical early step in a cell’s response to DNA damage, a chemical modification of ATM, allows the enzyme to initiate a series of events that ultimately halt the growth of a damaged cell and help the cell survive.

The finding was important because DNA damage caused by radiation and environmental toxins can lead to mutations or cell death and can also contribute to the development of cancers. At the same time, the researchers discovered that the drug chloroquine could activate the ATM enzyme in cells without causing DNA damage. The St. Jude/Washington University team reasoned that if loss of ATM makes metabolic syndrome worse, then perhaps activating ATM would make it better. The researchers asked whether chloroquine could improve the symptoms of metabolic syndrome. They found that low doses of chloroquine could reduce blood pressure, decrease hardening and narrowing of the arteries, and improve blood sugar tolerance.

The next step was to determine if chloroquine helps by activating ATM. “Loss of ATM made symptoms of metabolic syndrome worse,” Kastan says. “We found that chloroquine made it better and did so by working through ATM.” According to Kastan, medical literature already contains a great deal of information showing that humans can take chloroquine safely and generally tolerate the drug well.

“The results of our studies suggest that we may be able to provide people with these protective benefits using very low and perhaps infrequent doses of such a drug,” Kastan says. “The good news is that chloroquine is a proven drug. It’s used frequently for treating malaria as well as for certain autoimmune diseases. Here we have a drug that can impact a disease that affects 10 percent of the population.”

Meanwhile, the researchers have been looking closely at how ATM and chloroquine work together to make the drug effective. The results of their studies are showing promising results. “We just received funding for a new clinical trial, and we’re very excited to see if the processes activated by chloroquine can effectively treat one of the most common health problems of modern industrialized society,” says Clay Semenkovich, MD, professor of Medicine, Cell Biology and Physiology at Washington University. “We already know that chloroquine is safe and well-tolerated, and our results suggest we may only need very low and perhaps infrequent doses to achieve similar effects in humans.”

How do all of these studies relate back to cancer? Children with A-T—such as A-T gene. Kastan’s colleagues in the St. Jude Epidemiology and Cancer Control department have found that survivors of childhood cancer have a high frequency of metabolic syndrome when they get older. The findings may lead to useful treatment options for these patients.

“The fact that our patient population has a significant problem with metabolic syndrome has been well documented in our After Completion of Therapy clinic,” Kastan says. “When they get older, chil-
The crayon is fat and shiny...and gloriously, impossibly red. What 2-year-old can resist a crimson Crayola® and a blank palette? Jada Lindsey certainly can't. Grasping the waxy tool in dexterous fingers, the toddler quickly and decisively decorates her family’s home—a brilliant slash of scarlet emblazoned along the hallway, culminating in flamboyant squiggles on the doors and walls of the family room.

Daddy is not amused. At the same time, he breathes a sigh of relief. Jada is active and healthy. She’s able to select her favorite hue from a box of crayons and—in less than three minutes—redecorate the house. “This is what we fought for—the opportunity to be normal,” Roy Lindsey says with a rueful chuckle. “It’s been a very long road.”

Jada (facing page) and Judah Lindsey are reflected in mirrors as they produce “masterpieces” for their mom, who is also a survivor of the eye cancer called retinoblastoma.
or eye cancer. Because of the delay in obtaining treatment, the tumor had ravaged Jobie’s eye, which had to be removed.

Nearly three decades later, when Jobie would reach adulthood and move to Louisiana, that scenario would occur again.

Déjà vu
Before Jobie and Roy Lindsey married, they discussed her medical history. “The doctors told me that my cancer is not hereditary, because it was unilateral (occurring in only one eye) and I was the first one in my family to have it,” Jobie told Roy. Barrett G. Haik, MD, chief of the St. Jude Ophthalmology Division, says Jobie’s odds of carrying an abnormal retinoblastoma gene were, in fact, low. Only one out of 10 individuals with unilateral disease carries the defective gene.

“We didn’t know until recently how to tell who that one out of 10 was,” Haik says. “We can now do it via a blood test. But when Jobie was treated, there was no way to know for sure.” Unfortunately, Jobie had the gene. She was unaware that her children would have a 90 percent chance of inheriting that gene, and each child who received it would have a 90 percent chance of developing cancer.

In 2001, Jobie gave birth to a boy, named Judah. Every so often, Roy glimpsed a peculiar reflection in his infant son’s eye. “It never occurred to me that this could be the kind of cancer that Jobie had,” Roy says, “but it just kept bothering me.” Jobie took the baby to the pediatrician several times, but the doctor treated the young mother like a hypochondriac. Finally she became insistant.

“I told the pediatrician about our concerns,” Jobie recalls. “He did a test to see if Judah could pick up a raisin from a table and whether he could distinguish which object was which. Then he took a light, flashed it in Judah’s eyes, and said, ‘I don’t see anything.’ He was kind of sarcastic. I said, ‘We have a family history of eye cancer. Can I have a referral to an ophthalmologist, please?’

‘I’m not writing a referral if there’s nothing wrong,’” the pediatrician replied.

A nurse overheard the conversation. After the doctor left the examining room, she handed Jobie a slip of paper.

“Here’s the name of an ophthalmologist who should be able to help you,” she said.

Dark days
Jobie took Judah to the ophthalmologist that afternoon. As Roy glanced into Judah’s eye, he saw “crystals,” or small pieces of tumor. Doctors used cryotherapy to eradicate those seeds. Only six weeks after that procedure, more crystals appeared. Once again, the Lindseys had a child with a bilateral (occurring in two eyes) retinoblastoma. But because they had discovered the problem early, they increased their odds of preserving Judah’s sight.

Jada had just begun receiving chemotherapy in New Orleans when Hurricane Katrina hit. The Lindseys brought the Lindseys to Memphis so that Jada could continue her cancer therapy and Judah could obtain regular follow-up care. At St. Jude, Jada required additional treatments, including radioactive implants, to save her eyes. Today, the family travels to St. Jude every month for checkups.

“One of the biggest miracles is that Jada had bilateral disease, and yet she didn’t lose any vision,” Jobie says. “The care at St. Jude has been tremendous,” Roy adds. “When we go up there, the nurses are constantly hugging Jobie, and they know our kids by name. When we’re at home, they call us. There’s a constant dialogue. It gives us a sense of security to know that St. Jude is always with us.”

Spectrum of care
Although Judah and Jada are cured of retinoblastoma, clinicians at St. Jude are not through caring for them. As the children enter adolescence and adulthood, they will require counseling to educate them about their risk of developing second cancers and of passing the abnormal gene to their offspring.

“These children have the germinal mutation, so they have a 50 percent chance of passing it on,” Haik says. “The same retinoblastoma gene that controlled their susceptibility to eye cancer will also make them susceptible to other cancers. They will need to be screened all their lives, because they have a 50 percent risk of getting another cancer by age 50.”

One bright spot in the scenario is the hospital’s ability to conduct sophisticated genetic screening on the St. Jude campus. In the past, St. Jude sent blood samples to distant labs, which was expensive and time consuming. As the number of retinoblastoma cases increased, clinicians recognized the need to perform genetic testing at St. Jude. Michael Dyer, PhD, of Developmental Neurobiology and Sheila Shortleff, PhD, of Molecular Pathology developed a new process that allows scientists to sequence the entire gene quickly and precisely.

“We tested the technique and confirmed that our test is extremely accurate,” Rodriguez-Galindo says. “In keeping with our focus on providing family care, we are now able to test patients, families, siblings and offspring to determine whether they have the genetic mutation.”

A commitment to education may also ensure that children receive diagnoses more quickly than Jobie and Judah did. “The odds of a pediatrician seeing a child with this disease are about one in a lifetime,” Haik says. “Part of our job is to educate ophthalmologists and pediatricians so that these kids receive the best possible care.”

Color them thankful
With three children ranging from 2 years to 5 years old, the Lindsey household is lively and noisy and wonderfully normal. “Judah is boisterous; he wants to be just like me,” Roy says. “Joe is a party animal who just wants to have a good time. Jada is the cunning one. One minute she’s taking toys from her sister and the next minute she’s giving you the biggest kiss you’ve ever gotten in your life. Everybody tells us, ‘That girl’s gonna break you!’”

Jobie can’t help but smile when she considers her clear-eyed daughter’s penchant for color. “She’s used to going to St. Jude, where murals cover many of the walls,” Jobie explains. “But there’s no doubt about it: She’s stuck on that red crayon—no other color but red.”

After examining Judah, the St. Jude treatment team met with the Lindseys. Matthew W. Wilson, MD, of Ophthalmology, Carlos Rodríguez-Galindo, MD, of Oncology and Haik agreed that the left eye should be removed. The family returned to New Orleans for the operation, which was followed by laser therapy and cryotherapy (freezing treatments), to eliminate tumors in the right eye. Today, Judah has excellent vision in his right eye.

Multicolored miracle
A year later, Jobie discovered that she was pregnant again.

“Jada has given us a shy smile as she hugs her mom during a visit to St. Jude. ‘One of the biggest miracles is that Jada had bilateral disease, and yet she didn’t lose any vision,’ Jobie says.

According to Barrett Haik, MD, chief of St. Jude Ophthalmology, Judah (in foreground) and Jada have a 50 percent chance of passing on the genetic mutation that causes retinoblastoma. For that reason, St. Jude emphasizes genetic education. To see a new educational booklet about retinoblastoma, visit www.stjude.org/retinoblastoma; then click on ‘What is Retinoblastoma?’

the family met with a team of surgeons in New Orleans. “We need to remove his eye tomorrow,” they said.

“At those words, I felt like I turned into a big blob of …not jelly…but something that is viscous and more like a big pool of oil,” Roy says. “I was sliding, falling to the floor. I was losing it, and it just didn’t make sense.”

Reeling with shock and desperate to save their son’s eye, Roy and Jobie insisted on obtaining a second opinion. Their physicians sent them to St. Jude Children’s Research Hospital. When the Lindseys arrived at St. Jude, they were overwhelmed to meet parents of children who were in various stages of treatment for retinoblastoma.

“That first day was such therapy for us,” Roy says. “The most amazing thing was to see the fight inside the kids. A fighter always remembers the fight. They were the biggest support group that any person could have. Suddenly we began developing hope that this was going to work out. It was invigorating.”

20 Promise / Spring 2007

Spring 2007 / Promise 21
By training the scientists of tomorrow, St. Jude ensures that more children will be saved, more cures will be discovered. One postdoctoral research fellow explains why he chose St. Jude as the place to learn and collaborate and grow.

One of the most meaningful experiences in life is to wake up each morning with the desire to go to work, knowing that your daily accomplishments will have a positive impact on the lives of others. I’ve been privileged to feel that way throughout my training as a postdoctoral research fellow at St. Jude Children’s Research Hospital.

After earning a doctorate in biochemistry and medical sciences at the University of Nebraska Medical Center, I had two options for advancing my career: to look for a research position in the pharmaceutical industry; or to undergo an industrial biomedical setting, such as clinical care at St. Jude. Such immense diversity within a single institution affords fellowships from nearly 80 countries are being trained in pediatric-based research or clinical care at St. Jude. Such immense diversity within a single institution affords all fellows the opportunity to establish collaborative efforts and friendships.

Through the institution’s communication networks, fresh ideas are born, freely exchanged, discussed and built upon to further advance the pace of scientific discovery. Such collaboration speeds the translation of basic research discoveries into lifesaving clinical treatments—the so-called “bench-to-bedside” philosophy. What makes a postdoctoral fellowship at St. Jude so attractive and unique? Perhaps the most important benefit of being a part of the St. Jude family is the people with whom I’ve had the opportunity to work. More than 300 postdoctoral fellows from nearly 80 countries are being trained in pediatric-based research or clinical care at St. Jude. Such immense diversity within a single institution affords all fellows the opportunity to establish collaborative efforts and friendships.

When one arrives at St. Jude, another attribute becomes apparent: the personal association between the St. Jude staff and the patients and their families. All patients and families, the physicians and nursing care staff, the researchers, technicians and support staff enter through the same front door, walk the same hallways and eat together in the same cafeteria. Such close association gives St. Jude staff a daily appreciation of how important their work is, since the beneficiaries of that work walk among them.

In addition, St. Jude has a wide variety of advanced technological tools available to postdoctoral fellows. The facilities at St. Jude are second to none. The institution has numerous core services that streamline the research process, among which are bioinformatics (the computer-based analysis of molecular structures), DNA sequencing, electron microscopy and cell-sorting analysis. While many other institutions must outsource such services, St. Jude has had the foresight to offer them within the institution. This significantly speeds the research process and fast-tracks new discoveries.

The institution’s dedication to advanced technology is also evident in the development and maintenance of state-of-the-art laboratories that facilitate not only efficient research but also good communication between investigators. Postdoctoral fellows are encouraged to present seminars to faculty, staff and peers as a means to brainstorm ideas and establish networks that advance and support the science.

The hospital is committed to guide the scientific pioneers of tomorrow through postdoctoral research training fellowships. Such a commitment is a significant investment in the treatment of children with catastrophic diseases. Training that starts at St. Jude does not end there; postdoctoral fellows at St. Jude apply their training in subsequent professional endeavors, carrying on the mission of St. Jude.

It’s a dream to be a scientist at a place where the focus is on supporting and facilitating research. St. Jude is a place of hope that promotes cutting-edge research on behalf of children with catastrophic diseases. I’m extremely proud to be a part of this endeavor and will forever be indebted to St. Jude for the privilege of training in this institution’s laboratories, working with faculty and staff, and walking the hallways with the children and their families.

“Patients, families and staff enter through the same front door, walk the same hallways and eat together in the same cafeteria,” says Steven Zatechka Jr., PhD, of Biochemistry. “Such close association gives St. Jude staff a daily appreciation of how important their work is, since the beneficiaries of that work walk among them.” Pausing from their work are four of the hospital’s more than 300 postdoctoral fellows: (clockwise, from left) Zatechka; Zachary Baquet, PhD, of Developmental Neurobiology; and Aaron Shater, PhD, and Meenu Ramanatha Pillai, PhD, both of Immunology.
“Some people can roll up their sleeves and go to work to help St. Jude, but most of us facilitate the hospital’s mission by turning our heartfelt partnership into dollars.”

Nothing in the world is more important than having vibrant communities and, of course, healthy, happy children. Shortly after Stanford Financial Group opened offices in Memphis, we became well acquainted with the impact St. Jude Children’s Research Hospital has in the United States and around the world. Since we have offices in 12 countries, we were excited to learn that St. Jude shared so much of our global footprint. One way we could give back is through supporting the hospital’s international outreach efforts. This is an area that matches up to who we are and the footprint we have, especially in Latin America. In conjunction with that decision, St. Jude became our corporate charity of choice worldwide. This summer we will expand on that partnership as we become title sponsor of the Stanford St. Jude Championship. The importance of St. Jude hit home recently when the daughter of one of our employees was found to have leukemia. Here we are, partnering with one of the finest institutions of its kind in the world, and lo and behold, one of our families is a direct recipient of the hospital’s healing powers.

Why support St. Jude? First of all, we’re custodians and stewards of many wonderful blessings, and with that stewardship comes a huge responsibility. Individuals looking for a place to invest in the future should consider St. Jude—a place that takes care of business.”

James M. Davis is director and chief financial officer of Stanford Financial Group, which this year becomes title sponsor of the Stanford St. Jude Championship. The PGA TOUR event will occur June 4-10 in Memphis.

Your legacy can be her future.

You can play a vital role in helping secure a healthy future for children battling cancer with a gift to St. Jude Children’s Research Hospital through your will. Join others who share the desire to leave a legacy of hope to catastrophically ill children by considering a bequest gift to St. Jude. To learn more about these special gifts and the Danny Thomas—St. Jude Society recognizing these contributions, please call us at 800-395-1087, visit www.stjudelegacy.org or complete the enclosed postage paid envelope today.

Ensure that our research continues until the day we have conquered childhood cancer. The promise of your charitable legacy helps make it possible.

Who loves a party? St. Jude kids do! And did they ever party on Fat Tuesday. In the spirit of Mardi Gras, patients, siblings and staff tossed shiny beads, donned outrageous masks and spread the fun throughout the hospital.