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JUSTIN VENEMAN

A Tale of Two Vaccines

Two common childhood infections kill hundreds of thousands of children each year. St. Jude is creating vaccines to combat both croup and RSV.

By Elizabeth Jane Walker

When 5-year-old Laniah Harris began to cough and swipe at her nose one blustery February day in 2011, her mom, LaToya, pulled out a tissue. "Laniah must have caught a cold," LaToya thought. But within 48 hours, the little girl was fighting for her life in the Intensive Care Unit.

Laniah had nearly completed leukemia treatment at St. Jude Children's Research Hospital when she acquired the respiratory syncytial virus (RSV) infection. For most children, the infection is merely an annoyance, causing mild, cold-like symptoms. But for babies in the first year of life and children with cancer, the virus can spread to the lungs—often with deadly consequences.

"RSV is really a nasty virus," says Charles Russell, PhD, of St. Jude Infectious Diseases. "Within the first years of life, almost everyone has gotten infected with RSV, which causes at least 150,000 deaths a year."

St. Jude researchers and clinicians want to shield all children from the dangers of RSV. That's why scientists are developing vaccines to prevent RSV as well as croup. Caused by the human parainfluenza virus type 1 (hPIV1), croup causes a lung infection with a characteristic barking cough and can be dangerous in young toddlers. Infections by these two viruses kill hundreds of thousands of children each year. Currently, no vaccines exist to prevent infection; once a child is infected, the treatment is costly and often ineffective.

The secret weapon

The secret weapon of the St. Jude vaccine project is a particle called the Sendai virus (SeV). The physical structure of this particle closely resembles that of hPIV1. Scientists use SeV as a decoy to fool the immune system into thinking it is being attacked by hPIV1. Immediately, the body's B cells and T cells prepare a counter-attack. When the real virus later invades, the system is poised to destroy it.

Allen Portner, PhD, of St. Jude Infectious Diseases, began conducting basic research on SeV in 1968. Decades later, he met with Julia Hurwitz, PhD, of Infectious Diseases and other colleagues to discuss the possibility of using SeV as a croup vaccine. After years of lab work, the vaccine was ready for Phase I testing.

"Vaccine development is a slow, arduous process,"

Once tethered to life support because of an RSV infection, Laniah Harris (at left) is now a proud kindergarten graduate. St. Jude scientists are developing vaccines to prevent RSV and croup, so that no other child must endure what Laniah experienced.

PHOTOS BY PETER BARTA

Michael Meagher, PhD, vice president of Therapeutic Production and Quality and president of the Children's GMP, LLC, leads the production phase of the vaccine project. St. Jude was the first pediatric health facility in the world to have on-site capability to manufacture highly specialized lifesaving products such as the hPIV1 and SeVRSV vaccines.

Elisabeth Adderson, MD, of St. Jude Infectious Diseases visits with Arthur Russell and his mom, Mimi. Arthur participated in the croup vaccine clinical study. Although the SeVRSV vaccine is not ready for testing, scientists continue to recruit healthy children for the croup vaccine study.

PETER BARTA

Portner explains. "From the day a vaccine is conceived in the laboratory until it reaches the pharmacy shelf to be dispensed is, on average, about 22 years."

The late Jerry Shenep, MD, of St. Jude helped initiate the world's first human study using SeV. The vaccine was successfully administered to adults at gradually increasing doses; the vaccine has also been tested in healthy children between the ages of 3 and 6. Elisabeth Adderson, MD, of St. Jude Infectious Diseases is now helping to advance the study. Phase I testing involves intensive attention to safety issues. The next two phases involve larger groups of participants. Eventually, scientists test the vaccine's protective efficacy against infection as compared to a placebo.

And the results thus far?

"Indications are that the vaccine is completely safe," Portner says.

Why create vaccines for RSV and hPIV1?

Respiratory syncytial virus (RSV)

- Most common cause of bronchiolitis syndrome in infants
- Causes **70,000–120,000** hospitalizations annually in U.S.
- Causes **150,000** deaths globally each year
- No standard, effective treatment
- Current preventive measures are extremely costly, yet insufficient

Human parainfluenza virus type 1 (hPIV1)

- Most common cause of croup in infants and toddlers
- Causes approximately **30,000** hospitalizations annually of children younger than 3 years in U.S.
- Ventilator required for about 1 to 2 percent of those children
- No curative treatment

Engineering a second vaccine

The existing St. Jude croup vaccine uses an unmodified laboratory strain of SeV. Creating an RSV vaccine using SeV, however, requires genetic engineering. A technique called reverse genetics has enabled researchers to modify SeV to piggyback the *RSV F* gene. By introducing that gene into the SeV carrier, scientists ensure that the immune system makes preparations to foil any future incursions by both RSV and hPIV1. The new vaccine, known as SeVRSV, has the potential to target both viruses at once.

Russell is helping Hurwitz and Portner advance the SeVRSV vaccine. It is being produced in the Children's GMP, LLC, an on-site facility that manufactures biologics and drugs under stringent federal regulations. Once the product has been manufactured to meet FDA specifications, Phase I safety testing of SeVRSV can begin. The project has already attracted interest from the National Institutes of Health (NIH) as well as from the pharmaceutical industry.

Prescription for success

Other research facilities worldwide have attempted to create vaccines against RSV, to no avail. Hurwitz cites several reasons why St. Jude may succeed where others have failed. First, the vaccine uses the SeV particle as its backbone, instead of the human RSV particle.

"Scientists elsewhere have taken RSV and tried to make it weaker—they culled it, adapted it or mutated it so that it wouldn't cause disease in humans," she says. "They've never been able to reach the fine balance you need to ensure both safety and efficacy."

Another attribute of the SeVRSV vaccine is that it is administered through the nose, much like the FluMist® influenza vaccine. "You get a long-lasting immune response in the nose," Hurwitz explains, "which blocks the virus at its point of entry. A single dose of this vaccine will induce long-term immunity, as opposed to some protein vaccines that require one or more booster immunizations."

Finally, the new vaccine appears to be safe.

"We have every indication that SeVRSV will be extremely safe in humans, and so we have both safety and efficacy on our side," she says. "Our approach seems to be on target.

"We want to see 100 percent immunogenicity, meaning that when unprotected children receive the SeVRSV vaccine, they will generate protective antibody responses against RSV and hPIV1," she continues. "In

Allen Portner, PhD (at left), Charles Russell, PhD, and Julia Hurwitz, PhD, of Infectious Diseases have been working on a project to create a new vaccine, known as SeVRSV. This vaccine will protect children against both RSV and hPIV1, which causes croup.

the lab thus far, it has been 100 percent effective at inducing protective antibodies."

Worldwide protection

Hurwitz, Russell and Portner believe that SeVRSV may hold the key to eradicating RSV and croup from the general population—thus protecting children like Laniah Harris from dangerous infections. After enduring a month on the ventilator, fighting for every breath, Laniah gradually improved. With the help of St. Jude staff, she relearned how to walk and began to regain her fine motor skills.

In May of 2012, Laniah took a deep breath and strode down the aisle at the St. Jude kindergarten graduation. As the 6-year-old bestowed an endearing, gap-toothed smile upon the cheering audience, her mom looked on with pride. Not only had Laniah completed cancer treatment and survived her harrowing bout with RSV, but she had also completed kindergarten.

From the vantage point of the beautiful young graduate—and for other children who may someday be able to avoid RSV altogether—the future is rosy, indeed. ●

What makes the St. Jude vaccines unique?

- Produced in the Children's GMP, LLC, on the St. Jude campus
- Administered through the nose, rather than by injection
- Designed to offer safe, long-lasting immune response
- Should eliminate the need for booster vaccinations
- Laboratory tests indicate that virtually all children who lack protection against RSV or croup will benefit from SeVRSV vaccination.

Prescribing Gets Personal

Scientists are mining the genetic code to better match patients and medications now and in the future.

By Mary Powers

SETH DIXON

Pain management for 5-year-old Bo Carter is child's play, thanks to the science of pharmacogenetics.

His broad smile signals that 5-year-old Joshua "Bo" Carter is having a good day. Before beginning the family's weekly trip to St. Jude Children's Research Hospital where he undergoes treatment for acute lymphoblastic leukemia (ALL), Bo's mother packed his favorite superhero action figures and a selection of small race cars. Now Bo makes the toys zoom through a hospital play area as he waits to start treatment. During the two-hour intravenous immune-system boost, Bo will pass the time by watching *Tom & Jerry* cartoons.

This week has been easy for Bo, who is more than halfway through an expected two-and-a-half years of cancer treatment. It has offered a break from chemotherapy that consists of vincristine and other drugs. Vincristine is part of the chemotherapy cocktail that helped St. Jude push its long-term ALL survival rates to 94 percent. The drug works by preventing or slowing the growth of cancer cells, but it can also cause severe pain.

Thanks to a multidisciplinary St. Jude research team, Bo's doctors have new tools to help them select the best medication to manage his pain. Those tools include an automatic computer warning that appears on screen if a health care provider attempts to prescribe the drug codeine. A genetic test done shortly after Bo began cancer treatment showed that codeine would not ease his pain. The test revealed that Bo belongs to the estimated

Pharmacogenetics unites the fields of genetics and pharmacology to better understand how small differences in genes affect a person's response to drugs. The St. Jude PG4KDS project uses pharmacogenetics as a tool to help improve medication safety and effectiveness.

10 percent of the population who lack the gene that makes the enzyme needed to activate codeine into the pain-reliever morphine.

Now when he receives vincristine, Bo goes home with alternate pain relievers.

"I had no clue that genes could affect whether or not a drug like codeine gave you any relief," says Michelle, his mom. "I just know that life gets back to normal when he is feeling better, and he's up playing and running around."

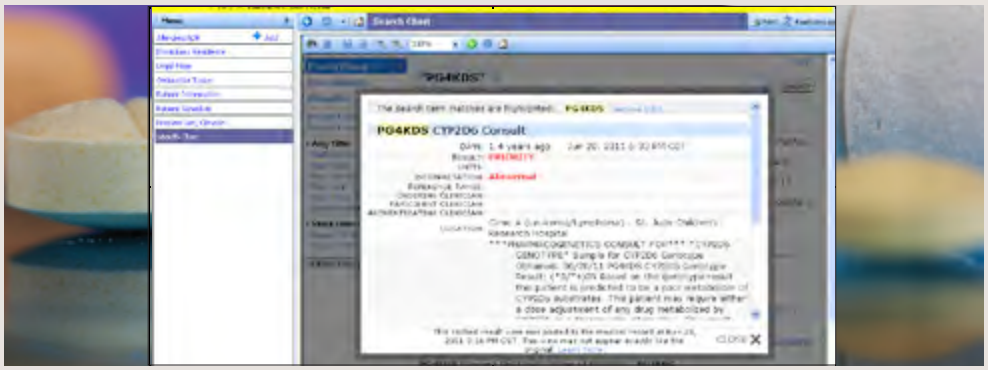
Understanding differences in drug response

The science of pharmacogenetics has made personalized medicine possible for patients like Bo. Pharmacogenetics got its start in the 1950s when investigators realized certain medicines were more likely to trigger side effects in specific ethnic groups. Scientists also showed that the side effects tended to be inherited. Pharmacogenetics shows how countless small differences in genes affect each person's response to drugs—good, bad or indifferent.

In the 1990s, St. Jude researchers offered an important early example of pharmacogenetics' power to improve patient care. A team led by William E. Evans, PharmD, now St. Jude director and chief executive officer, linked life-threatening complications associated with an important family of cancer drugs to variations in a single gene. The gene was *TPMT*. It carries instructions for making an enzyme of the same name that metabolizes medicines known as thiopurines. The variations mean that as many as one in 10 patients may need a lower dose of the drugs; one in every 400

Pharmacogenetics and PG4KDS

- Pharmacogenetics brings together the fields of genetics and pharmacology to improve understanding of how genes affect a person's response to drugs.
- PG4KDS, an ongoing St. Jude study, opened in 2011 using pharmacogenetics as a tool to help improve medication safety and effectiveness.
- The project uses a blood test to check for variations in 225 genes associated with differences in how drugs impact the body. Genes will be added to the medical records when evidence is sufficient to use the results to help guide patient care.
- Results for two genes, CPY2D6 and TPMT, are added to the patient's medical record, such as the one pictured above. The genes influence how many drugs work in the body and helps determine whether or not patients benefit.
- The study creates a process for deciding when to add results for other genes.
- PG4KDS also gives patients and families a voice in the process.



- Scientists develop tools to help health care providers use those results to guide medication decisions now and in the future.
- PG4KDS has enrolled more than 500 St. Jude patients battling cancer, HIV and different blood disorders.

CPY2D6

- This gene carries instructions for making an enzyme that plays a role in the activity of about 25 percent of commonly used drugs.
- More than 100 variations have been identified in this gene.
- The differences affect if and how as many as one in 10 patients respond to those drugs.

TPMT

- This gene carries instructions for making an enzyme that breaks down a family of drugs known as thiopurines.
- Several thiopurines are important for the treatment of leukemia and lymphoma.
- Differences in TPMT mean as many as one in 10 persons might benefit from a lower dose.

SETH DIXON

Pharmaceutical Sciences Chair Mary Relling, PharmD, discusses expansion of the PG4KDS study with James Hoffman, PharmD, the hospital's medication outcomes and safety officer.

individuals needs a substantially smaller amount to avoid potentially deadly side effects.

Today, work continues to identify which of the estimated 18 million gene variations in the human population plays an important role in drug response. So far, investigators have tied differences in hundreds of genes to differences in the activity of particular drugs, including how they are metabolized and transported. St. Jude researchers are at the forefront of a national effort to develop ways to translate the research into clinical tools.

"There are now several medications that are so strongly affected by genetic variation; if we can test patients before they are treated with those medications, we have an opportunity to choose a better drug or a better dose of the drug right from the start. For these medicines, using genetics to inform prescribing means that therapy is safer and more effective," says Mary Relling, PharmD, St. Jude Pharmaceutical Sciences chair. "Because these medications are used for a number of different diseases, pharmacogenetics is not just important for children with cancer."

Advances in gene tests mean that for a few hundred dollars it is now possible to screen 225 genes for about 1,900 differences implicated in drug metabolism. The technology meets the high standards for use in the clinic, not just in the research laboratory. One gene can impact the workings of as many as 30 or 40 different drugs. The lower cost now makes it possible to test such genes early in treatment so results are available before prescribing medications. Because genetic test results are lifelong, a single test can offer prescription guidance throughout a patient's life.

From research findings to clinical applications

The challenge is developing a system to integrate the information into clinical care. Busy doctors need a way to use complex genetic test results for prescription decisions and to keep up with new findings.

St. Jude launched the ongoing PG4KDS study to develop solutions. Relling is the principal investigator of the study, which has enrolled more than 500 patients, including Bo, since opening in 2011. Ultimately all St. Jude patients will have a chance to join.

PG4KDS uses a blood sample to check for variations in 225 genes. Currently, results for two genes are added to a patient's medical record. For now the remaining pharmacogenetic results are stored in a research database. Relling and her colleagues say additional genes, with rules linked to the drugs they affect, will be added to patient medical records when evidence is strong enough. Tools must also be available to help medical providers use the results to make prescribing decisions now and for years to come. Relling leads an international group, the Clinical Pharmacogenetics Implementation Consortium, which is writing rules to help expand use of pharmacogenetic testing as a tool to improve patient care.

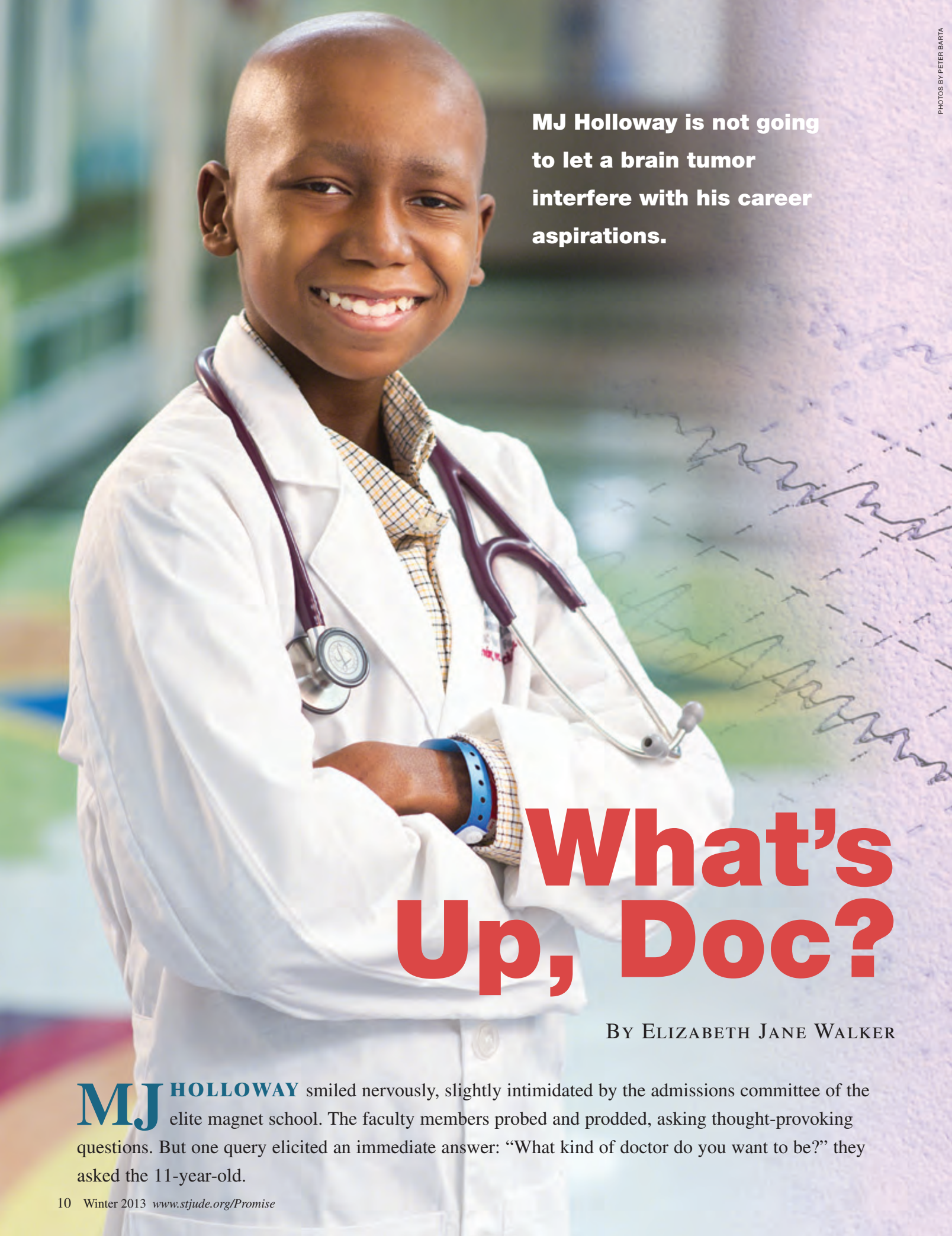
"We want to be the bridge between research and clinical care," explains Kristine Crews, PharmD, of Pharmaceutical Sciences.

PG4KDS is having an impact. Tools developed for the study and the hospital's switch to electronic medical records are helping translate the genetic test results into patient care decisions. The changes include automatic computer alerts that signal a clinician to change a medication dose or pick a different drug.

"Pharmacogenetics helps us act earlier to avoid complications and, in the case of patients like Bo, ease symptoms," says Hiroto Inaba, MD, PhD, Oncology. For Bo and his family, pharmacogenetics has not only made cancer a little easier to endure but has also raised questions about whether the same variations might influence other family members' responses to medication.

St. Jude parents played an important role in designing PG4KDS. Because patients and parents want to understand how tests might impact their care now and in the future, they can receive test results directly as they are added to the medical record.

Parents of St. Jude patients also helped create an educational video about PG4KDS. Visit *www.stjude.org/pg4kds* to watch the video. ●



PHOTOS BY PETER BARTA

MJ Holloway is not going to let a brain tumor interfere with his career aspirations.

What's Up, Doc?

By Elizabeth Jane Walker

MJ HOLLOWAY smiled nervously, slightly intimidated by the admissions committee of the elite magnet school. The faculty members probed and prodded, asking thought-provoking questions. But one query elicited an immediate answer: "What kind of doctor do you want to be?" they asked the 11-year-old.

"Nothing in life is impossible to overcome or achieve if you just put your mind to it," the aspiring neurosurgeon told his classmates during his elementary school commencement address. "You should always set your goals very high and dream impossible dreams."

"I want to be a pediatric neurosurgeon," MJ confidently responded.

"I want to prevent brain tumors, and I want to cure them. I want to be able to experience finding a cure for an incurable disease."

Ironically, four days later, the academically gifted fifth grader would experience his first headache. Two weeks later, a pediatric neurosurgeon would remove a tumor from MJ's brain.

Give me a sign

When MJ's headaches began in February of 2012, his parents, Lisa and Maurice Sr., immediately realized something was awry. The intensity of his headaches worsened as the frequency increased. Lisa, a university faculty member with a doctoral-level nursing degree, recognized that her son's headaches did not fit the typical pattern for migraines. After two weeks, a CT scan indicated a malignant tumor called pineoblastoma lodged deep within MJ's brain.

After removing the mass, surgeons in South Carolina asked the couple where they wanted to take their son for further treatment.

"I've been donating to St. Jude Children's Research Hospital since I became a nurse, so I knew about it, but I didn't really know about it," Lisa says. "So even as a nurse practitioner, I was lost. I used to be a pediatric ICU nurse, and I once worked with a federal government task force studying cancer in adults. But never in a million years would I ever have guessed that I'd be one of the parents."

Lisa prayed for guidance. "Give me an obvious sign," she said.

"In one day, five total strangers called me and said, 'You need to go to St. Jude,'" Lisa says. All of the individuals had heard about MJ's plight through mutual acquaintances or word of mouth. One couple who were both physicians contacted me. Their son had been treated at St. Jude, and they said, 'Go.'"

Later that day, the Holloways received a referral and began making plans to travel from South Carolina to Memphis.

Lessons in courage

At St. Jude, MJ received six weeks of radiation therapy, followed by a break during which he returned

As I'm going through my cancer treatment, I definitely have some fears, but courage is a quality that says, 'I'm afraid, but I know I can do this and everything will turn out OK.'"

home to deliver the commencement address at his elementary school. The diminutive class president climbed upon a stool and peeked over the podium. With a maturity that belied his years, MJ proceeded to dispense pearls of wisdom to his peers.

"Character is a choice," he told them. "You build on your character in positive and negative ways every time you make a choice.

"Guys, be committed," he continued, "because commitment is the characteristic that takes you from a dreamer to a doer."

What is pineoblastoma?

- This maligant brain tumor arises in cells of the pineal gland, located near the center of the brain. The pineal gland produces melatonin, a substance that helps control our sleeping and waking cycle.
- Pineoblastoma is extremely rare. Only 10–40 children in the U.S. are diagnosed with pineoblastoma each year.
- Symptoms may include headaches, nausea, vomiting, weakness on one side, change in sleep habits or personality, unexplained weight loss or difficulty looking upward.
- Treatment consists of surgery, followed by radiation and chemotherapy.
- At St. Jude, chemotherapy is accompanied by an autologous stem cell transplant (an infusion of the patient's own cells), which replaces blood-forming cells that were destroyed by treatment.

"We're thrilled every single time MJ comes through the clinic," says Giles Robinson, MD, of St. Jude Oncology. "He has got a bright smile and has tolerated chemotherapy incredibly well. MJ's extremely smart, and he should have a very, very bright future."

PHOTOS BY PETER BARTA

Then he drew upon his own experiences.

"Have courage in everything you do," he told his fellow graduates. "Just because you have courage doesn't mean you can't be afraid. Sometimes it's OK to be afraid. As I'm going through my cancer treatment, I definitely have some fears, but courage is a quality that says, 'I'm afraid, but I know I can do this and everything will turn out OK.'"

There was not a dry eye in the house.

A bright future

Returning to St. Jude, MJ began the chemotherapy phase of his protocol. Each of the four cycles of high-dose chemotherapy was followed by an autologous stem cell transplant.

"That means he received his own stem cells," explains Giles Robinson, MD, of St. Jude Oncology. "This process helps patients recover relatively more quickly from chemotherapy. Before MJ began treatment, we gave him a medicine to boost his stem cell count; then we took some of his blood and removed the stem cells, storing them for future use. Two days after he finished each chemotherapy cycle, he received the stem cell replacement."

Robinson and his colleagues say they look forward to their interactions with the aspiring physician.

"We're thrilled every single time MJ comes through the clinic," Robinson says. "He has got a bright smile and has tolerated chemotherapy incredibly well. MJ's extremely smart, and he should have a very, very bright future."

MJ and former President Bill Clinton found a bit of common ground when they met one another at St. Jude last summer. "I'm a former president, too," commented MJ, who was president of his fifth-grade class back in South Carolina. "It's a hard job, isn't it?" Clinton commiserated.

MJ shares a quiet moment with his mom and dad.

Kaci Richardson, a teacher in the hospital's School Program, has helped MJ sustain his academic progress throughout treatment. Richardson works with teachers at MJ's home school to ensure that he completes his rigorous, accelerated curriculum.

"He's in all honors classes," Richardson says. "MJ is extremely intelligent, but he's also mature for his age. When he comes to school, he doesn't want to play around. He's here to work as soon as he arrives.

"He talks about his desire to be a doctor," she continues, "and he's quite smart enough to do that."

Faith, focus and fundraising

During his treatment at St. Jude, MJ has kept a journal. His mom, not to be outdone, has written a fictional children's novel based on their experiences at St. Jude. In Lisa's book, magical characters fight a terrible disease, which can only be vanquished with the help of family, love, loyalty and faith.

"There's so much magic going on around St. Jude," she says. "This place is amazing. St. Jude does much more for us than they really know. We couldn't have left our home for treatment if it were not for the way this place is set up. It's not just the housing and the food and covering the medical bills—it's so much deeper than that. At St. Jude, I can totally focus my care on MJ, and that makes all the difference in the world."

As a university professor, Lisa says her future students will benefit from MJ's journey.

"I've already started rewriting my teaching curriculum to include some of the things I've learned about compassion here," she says. "I teach medical surgical nursing to 250 nursing students a year. St. Jude has taught me much about that topic, and I want to pass that on to my students."

She is also an advocate for the hospital itself.

"Even being in health care, I never really thought about what this children's research hospital was all about and what it was doing," Lisa admits. "You get these things in the mail that ask you to donate $25. You sign it, and you donate the $25, but you don't know exactly where that money's going. I've talked to everyone who donates back at home and said, 'Up your ante, because what they're doing with this money is so wonderful. What they do for the families and for the children is amazing.'"

A doctor in the house

MJ says that his experience has only reinforced his medical school aspirations.

"I want to do it even more than I did before," he says.

Armed with determination and drive, MJ is poised to take another piece of advice he offered to his classmates during his commencement address: "Nothing in life is impossible to overcome or achieve if you just put your mind to it," he told them. "You should always set your goals very high and dream impossible dreams." ●

Lanasha Gray celebrates with family and hospital staff during her No Mo' Chemo celebration. What comes next for Lanasha and other childhood cancer survivors? That is what St. Jude researchers are trying to determine.

After the **Confetti** Falls

By Mary Powers and Elizabeth Jane Walker

St. Jude research doesn't stop when treatment ends. Studies conducted by our faculty and staff are uncovering new details about the long-term issues facing childhood cancer survivors.

The No Mo' Chemo celebration is a joyful rite of passage—a colorful and melodic event signifying the completion of treatment. But St. Jude Children's Research Hospital continues to care for its patients long after the confetti has been swept up and the last strains of the No Mo' Chemo song have faded away.

As more children survive childhood cancer, the hospital's researchers feel an increasing obligation to develop cures that minimize long-term side effects. Survivors share their experiences with the hospital's scientists, who in turn educate community health care providers about the screenings and tests that childhood cancer survivors need in order to lead long and healthy lives.

On the following pages, you'll find a few recent St. Jude studies that offer new details about the long-term effects of childhood cancer and its treatment.

PETER BARTA

No mo' extra scans

St. Jude investigators recently found that routine pelvic computed tomography (CT) screenings are unnecessary for most survivors of Wilms tumor, a type of kidney cancer that occurs in children. In medical centers nationwide, Wilms survivors have received pelvic scans as part of standard follow-up treatment. Eliminating extra scans will reduce their lifetime exposure to radiation and minimize their chance of developing treatment-related cancers.

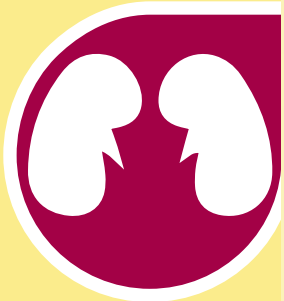
The research is the largest study to date exploring the benefits of regular pelvic CT screening for patients who have completed treatment for Wilms tumor.

"The results show there is no need for continual pelvic imaging of patients with stage I or stage II Wilms tumor, which account for about two-thirds of all children with Wilms," says Sue Kaste, DO, of St. Jude Radiological Sciences. "Pelvic relapse is a rare event in these patients. This study found that if Wilms tumor recurs in the pelvis, survivors usually experience symptoms, which aid in diagnosis."

Additional research is needed to determine the best monitoring approach for higher-risk Wilms tumor survivors, including those who were older or had more advanced disease when their tumors were discovered. Investigators say other imaging approaches, including MRI and ultrasound, may be reasonable alternatives that do not involve radiation.

What is Wilms tumor?

- A type of kidney cancer that occurs in children.
- Cure rate exceeds **90%**.
- Pelvic relapses are rare.



Eliminating pelvic CT imaging for survivors would:

- Reduce survivors' radiation dose by **34–45%**.
- Minimize cancer risk caused by radiation exposure.
- Help control health care costs.

Survivors, take heart

The heart of the matter

80% of children with cancer will live into adulthood.

47% of childhood cancer survivors were exposed to anthracyclines and/or chest irradiation.

172,000 childhood cancer survivors received treatment that could affect the heart.

Thousands of adult survivors of childhood cancer received treatment that may put them at risk for heart problems. Recent St. Jude research indicates that these adults may benefit from revised guidelines to identify those in danger of heart failure.

Children who received chest-directed radiation therapy or certain chemotherapies, such as the anthracycline class of drugs, are at increased risk of reduced left ventricular function. Greg Armstrong, MD, of St. Jude Epidemiology and Cancer Control and his colleagues found that current national screening guidelines based on echocardiography may overestimate the heart function of childhood cancer survivors when compared to another test called cardiac magnet resonance (CMR) imaging. As a result, echocardiography may miss up to 75 percent of survivors who need more comprehensive cardiac evaluation and possible treatment of heart muscle problems known as cardiomyopathy. Treatment-related cardiomyopathy sets the stage for heart failure.

Echocardiography and CMR imaging use different methods to calculate ejection fraction, which measures the strength of the heart's main pumping chamber. Although cost and availability limit its usefulness, CMR imaging is the best method for measuring the ejection fraction.

This scores an A+

St. Jude researchers recently found that survivors of childhood acute lymphoblastic leukemia (ALL) treated with chemotherapy alone—rather than chemotherapy plus cranial irradiation—performed as well as healthy children on most tests of intellectual functioning, academic performance and related skills.

Scientists reached that conclusion after analyzing how 243 St. Jude ALL survivors fared on a battery of tests measuring intelligence, learning and memory. The outcome was good news for childhood ALL survivors. The findings indicate that dropping radiation therapy, once a standard part of ALL treatment, reduced the risk to survivors of treatment-related cognitive deficits. An earlier St. Jude study, called Total Therapy XV, showed that childhood ALL could be cured without cranial irradiation.

"These results suggest that not only have pediatric ALL survival rates remained high, with better than 90 percent of patients still alive 10 years after diagnosis, but that survivors also have better cognitive outcomes when radiation is eliminated," says Heather Conklin, PhD, of St. Jude Psychology.

Survivors still faced challenges, including a greater risk for attention problems. Researchers plan to continue monitoring the survivors to determine how or if the cognitive challenges they face change with age.

Think again: Cognitive skills after ALL treatment

20% of acute lymphoblastic leukemia (ALL) patients at other institutions receive cranial irradiation.

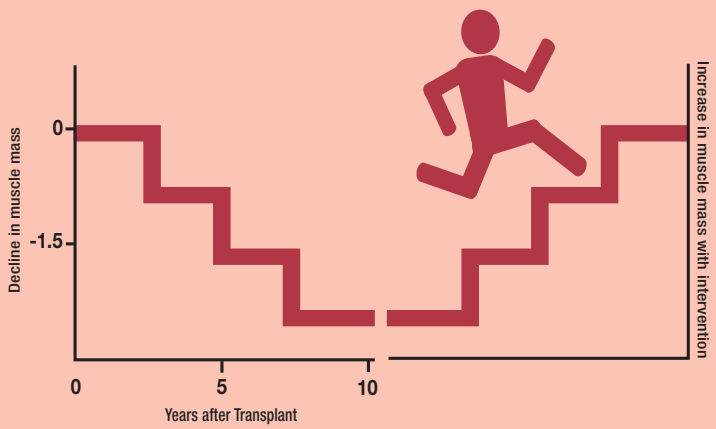
0% of ALL patients in the St. Jude Total Therapy XV received cranial irradiation.

94% was the survival rate of St. Jude ALL patients in Total Therapy XV.

243 ALL survivors' cognitive skills were analyzed. Most performed as well as healthy children on most tests of functioning and academic performance.

BMT and muscle mass

Bone marrow transplant survivors may benefit from nutrition counseling and exercise training to help regain muscle strength as they recover.



BMT survivor, make a muscle

Childhood cancer survivors whose treatment included bone marrow transplantation might benefit from such efforts as additional nutrition counseling and exercise training to help preserve muscle as they age, according to St. Jude researchers.

The study of St. Jude transplant patients found body mass index (BMI) fell significantly in the decade after transplantation as survivors lost lean mass but not fat. BMI is calculated using a person's weight adjusted for height. A major component of lean mass is muscle.

The change leaves survivors at increased risk for later

Preventing colorectal cancer

St. Jude researchers recently found that the colorectal cancer risk facing aging childhood cancer survivors is linked to the dose of abdominal radiation they received as children and the amount of the colon that was irradiated.

While previous studies have linked childhood radiation therapy to an increased risk of second cancers, this analysis showed the risk of colorectal cancer was associated with the radiation dose.

The odds jumped 70 percent for each 10 units of absorbed abdominal radiation survivors received as part of their childhood cancer treatment. Investigators also reported for the first time that the greater the volume of colon tissue exposed to radiation, the greater the risk of a colorectal cancer diagnosis. In addition, researchers associated treatment with drugs known as alkylating agents with a nearly nine-fold increased risk of secondary colorectal cancer.

The results also underscore the importance of cancer screenings and possibly the need to revisit current screening guidelines. "Childhood cancer survivors are at higher risk of developing this cancer, but they can take steps to protect themselves," says Kerri Nottage, MD, of St. Jude Hematology. "Colonoscopy offers a proven method of detecting colorectal cancer early, offering the best chance of cures."

Radiation dosage and colorectal cancer risk

11x Childhood cancer survivors are 11 times more likely than other Americans to develop colorectal cancer before age 40.

Colorectal cancer odds increase:

70% for each 10 units of absorbed abdominal radiation received during treatment.

9x if child received chemotherapy with drugs called alkylating agents.

Early detection with colonoscopy offers survivors and others the best chance of detection and cures.

health problems, including diabetes, musculoskeletal disorders and heart disease, said Hiroto Inaba, MD, PhD, of St. Jude Oncology.

Wing Leung, MD, PhD, chair of Bone Marrow Transplantation and Cellular Therapy, adds that the results will likely shape care of future transplant patients.

"The novel finding of substantial reduction in lean mass is alarming and useful for the development of preventive and remedial strategies for this group of survivors," he says. The research underscores the importance of assessing lean body mass as well as BMI during long-term follow-up.

Beam of Hope

St. Jude builds the world's only proton center dedicated solely to the treatment of children.

By Mike O'Kelly

Beth Elliott colorfully compares her first proton therapy treatment session to watching a scene from a science fiction movie unfold around her. Although the pristine white walls and state-of-the-art equipment conjure up images from the future, the technology will soon be a reality on the St. Jude Children's Research Hospital campus. The hospital is currently building the world's only proton center dedicated solely to the treatment of children.

Part of a $198 million project to enhance the hospital's clinical and laboratory facilities, the St. Jude Proton Therapy Center is slated to open in 2015.

The new center will greatly enhance the hospital's ability to conduct research optimizing the use of proton therapy in children.

"This facility will enable us to complete important trials while providing the support that only St. Jude can provide to patients," says Larry Kun, MD, chair of St. Jude Radiological Sciences.

"It's exciting to hear that St. Jude is building its own proton therapy center," adds Beth, who participated in a St. Jude protocol that involved traveling to Florida for treatment. Beth was found to have a rare brain tumor known as craniopharyngioma when she was a college sophomore. After six weeks of daily proton therapy, which lasted from one to two hours each, Beth's tumor is now smaller.

"St. Jude has given Beth hope, and that was more than any other therapy could offer," says Beth's mom.

Precise treatment

Beth's doctor, Thomas Merchant, DO, PhD, division chief of St. Jude Radiation Oncology, says proton therapy represents the next logical step for the hospital as it remains a world leader in the research and treatment of brain tumors and radiation therapy. Proton therapy can deliver high radiation doses directly to tumors while sparing normal tissues and reducing the side effects of traditional X-ray therapy. Proton therapy's chief advantage is the ability to control its depth and intensity in tissue. The more precise the beam, the more targeted the therapy.

"It's very important that we deliver precise

continued on page 20

SETH DIXON

What is proton therapy?

The medical use of protons for cancer therapy was first proposed in a paper by physicist Robert R. Wilson, PhD, in 1946. Within a decade, protons were being used to treat patients with certain cancers. As technology developed, proton therapy treatment became a more viable option for treating both adult and pediatric cancer patients.

Proton therapy offers tremendous advantages compared to X-ray technology because it is more precise and may be used to deliver a potentially higher dose of radiation to the tumor with fewer side effects. By confining radiation exposure to the tumor itself, the pinpointed therapy reduces a person's risk of experiencing toxic effects on major organs and of developing secondary cancers later in life.

Beth Elliott, who received proton therapy in Florida as part of a St. Jude protocol, receives a checkup from Thomas Merchant, DO, PhD, division chief of Radiation Oncology. "It's exciting that St. Jude is building its own proton therapy center," Beth says.

treatment to children, and we've designed our facility in such a way that when it opens in 2015, it will have the smallest beam in the United States," says Merchant, who toured leading proton centers throughout the world in researching the project.

Merchant also took a sabbatical to the famed Paul Scherrer Institute in Switzerland to learn more about developing a proton therapy program for children with cancer. "We are certain this will take our treatment protocols to the next level," he says.

Benefiting families

St. Jude patients began participating in proton therapy clinical trials in 2009 through the hospital's relationship with the University of Florida Proton Institute. The initial group of patients involved children less than 4 years of age with brain tumors who might benefit most from the tissue-sparing ability of proton therapy. In the last 18 months, children of all ages with craniopharyngioma, a rare brain tumor, have been sent for treatment using proton therapy. Families like the Elliotts, who came to St. Jude from California, arrive in Memphis understanding that they have to make another trip to receive treatment.

"It's been wonderful to be able to offer the treatment to our patients at the facility in Florida, but it's a huge challenge for the families to have to uproot again," says St. Jude social worker Melanie Russell. "When we have our own treatment facility here, it will be so much easier for our families."

A goal realized

Kun says the hospital's plan to build a dedicated proton therapy center on campus has been a long-term goal. Most proton beams throughout the U.S. use scatter-beam technology to deliver protons to the patient. This treatment concerns clinicians because it may deliver potentially harmful doses of radiation to regions in which vital organs and brain functions are developing. The St. Jude facility will be tailored exclusively for children, using a pencil-beam scanning technology that is accurate to the millimeter level.

"The goal is to use proton beam radiation to deliver relatively high radiation doses to very confined areas while sparing closely contiguous structures that are critical in the brain and other areas of the body without underdosing the tumor," Kun says.

In addition to treating brain tumors, the new technology will also be used to treat Hodgkin lymphoma and other solid tumors such as Ewing sarcoma, neuroblastoma and retinoblastoma. Treatment sessions may range from 20 minutes to an hour. More than half of the procedures will require patients to receive anesthesia prior to treatment. Each patient will undergo an MRI scan to confirm the tumor's location. The patient will then be placed on a treatment couch and moved into the proton therapy vault.

"The proton room will be arranged in such a way that the patient will always be visible to the staff through dedicated monitors," Kun says.

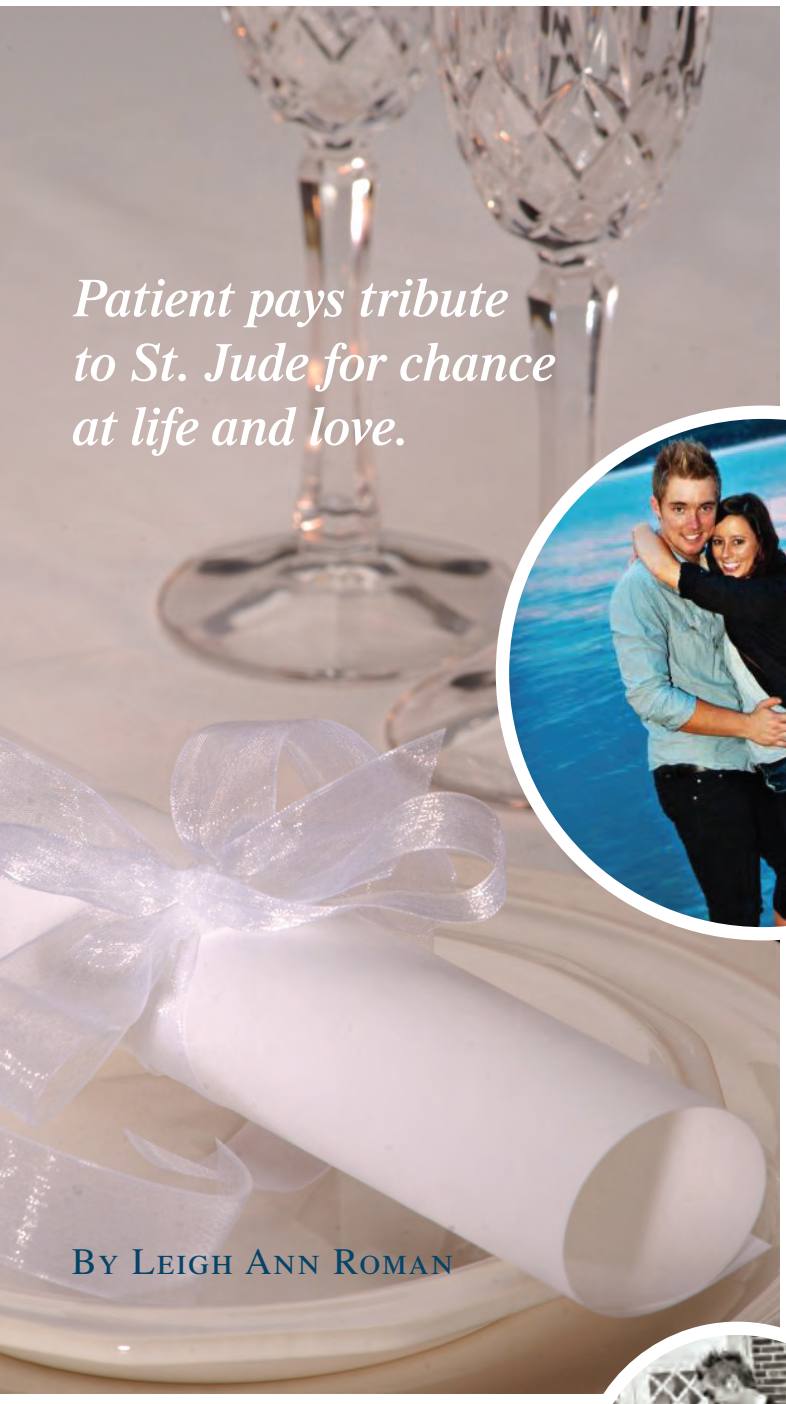
After treatment, patients will periodically undergo positron emission tomography (PET) scans to confirm the accuracy of doses that were delivered. The proton center will be staffed with dedicated therapists, trained nurses and a sedation team as well as a team of highly trained radiation physicists and the engineers who manage the beam.

With its two large, subterranean vaults, the St. Jude Proton Therapy Center requires a deeper building than has ever been built in the Memphis area. The new tower housing the facility will also include expanded surgical suites, an advanced Intensive Care Unit, the new Computational Biology department and a global education and collaboration center. ●

Above: **This conceptual rendering depicts the St. Jude Proton Therapy Center.**

Below: **Construction is underway on the seven-story facility that will house the Proton Therapy Center, as well as other clinical and laboratory facilities.**

In Tribute



Patient pays tribute to St. Jude for chance at life and love.

By Leigh Ann Roman

A series of miraculous coincidences put Adam Duggan in a church on December 18, 2010, to marry Kate Marler.

Exactly 23 years before—on December 18, 1987—Adam's mother had taken 18-month-old Adam to the pediatrician for symptoms similar to a stomach virus. While he was being X-rayed, the toddler moved. Instead of discarding that image, the technicians examined it. There was a tumor behind his heart. It was neuroblastoma, a tumor of the sympathetic nervous system.

Fortunately, the cancer was discovered then, because Adam later learned that his symptoms were related to a virus, rather than the tumor. He was referred to St. Jude Children's Research Hospital, where doctors decided to remove the tumor. When the surgeon who was scheduled for the procedure got the flu, a former St. Jude doctor, who had pioneered Adam's lifesaving surgery, came out of retirement to perform the procedure. Adam returned to St. Jude for check-ups until he was 18.

On their special day in 2010, he and Kate chose to pay tribute to St. Jude by making their wedding favor a scroll that recognized the hospital's mission and let guests know how to make a donation to St. Jude. The wedding favors are part of the St. Jude Tributes program, which includes memorial and honor cards to recognize loved ones, and specialty cards that take note of a variety of occasions, including weddings, Mother's Day, graduations and holidays. The program's support for St. Jude has grown from $2 million 15 years ago to $17 million in 2012.

"I am a walking testament to the fact that the money from donors and events is not being wasted," says Adam, who now works for ALSAC, the fundraising organization for St. Jude. "I look forward to speaking with donors every day and being able to share firsthand what their donations are doing—and have done—for the children of St. Jude."

As he grew up, Adam had talked about working for St. Jude. In July 2012, he and Kate moved to Memphis for his job with ALSAC. Kate and Adam are expecting their first child, a boy, this month.

"St. Jude means many different things to my family and me," Adam says. "To my parents, it means having their baby boy. To my grandparents, it means having their grandson. To my wife, it means having her husband and a baby on the way; and to me it means having an opportunity to make a difference. I am so happy to be able to give back to the hospital that gave me so much." ●

To learn more about how you can send a St. Jude tribute, visit stjude.org/tributes.

As part of the St. Jude Tributes Program, Adam and Kate Duggan presented their wedding guests with keepsake scrolls that encouraged guests to support St. Jude. "I am happy to be able to give back to the hospital that gave me so much," Adam says.

Research Highlights

New treatment options for Ph-like ALL

St. Jude scientists have identified new genetic alterations underlying a high-risk subtype of leukemia that could be effectively targeted with existing therapies.

The study focused on a subtype of acute lymphoblastic leukemia (ALL) known as Philadelphia chromosome-like ALL (Ph-like ALL). This subgroup accounts for as much as 15 percent of childhood ALL. While approximately 90 percent of newly diagnosed ALL patients are cured with current treatments, only 63 percent of patients with Ph-like ALL are alive and cancer-free after five years.

The research identified new alterations in genes that regulate how cells grow and proliferate.

Investigators also showed that the leukemia cells were sensitive to the drugs imatinib and dasatinib, which are already being used against other leukemias, but not this subtype. The findings suggest patients with Ph-like ALL may benefit from the addition of these drugs to current chemotherapy regimens.

"One of the next steps will be to continue work on laboratory tests to rapidly identify patients whose cancer cells carry these alterations and to develop clinical trials to test targeted therapies," said Charles Mullighan, MBBS (Hons), MSc, MD, Pathology, a corresponding author of the study, which appeared in the journal *Cancer Cell*.

Colorful creations

During All of Me Week at St. Jude, patients and their siblings engaged in a variety of activities to express themselves. Anthony Lopez (at right) loads up a roller with fresh paint during a project in which participants decorated a giant canvas with their handprints and footprints. The final result was on display during a special reception that featured the canvas as well as videos, poems and songs created during the week.

Exciting AMKL discovery

Research led by the St. Jude Children's Research Hospital–Washington University Pediatric Cancer Genome Project has identified an abnormal gene responsible for almost 30 percent of a rare subtype of acute myeloid leukemia (AML) that has a grim prognosis. The subtype, acute megakaryoblastic leukemia or AMKL, accounts for about 10 percent of AML.

The finding offers the first evidence of a genetic mistake that gives rise to a significant percentage of AMKL cases in children. The discovery paves the way for desperately needed treatment advances.

The study identified an abnormal protein that sets certain blood cells on the path to AMKL. The protein is the product of a fusion gene created when pieces of *CBFA2T3* and *GLIS2* are brought together by the rearrangement of chromosome 16. The fusion gene, found only in children with AMKL, identifies those at high risk for a poor outcome.

"The discovery of the *CBFA2T3-GLIS2* fusion gene in a subset of patients with AMKL paves the way for improved diagnostic testing, better risk stratification to help guide treatment and more effective therapeutic interventions for this aggressive childhood cancer," said James Downing, MD, St. Jude scientific director. Downing was corresponding author of a report on this study, which appeared in the journal *Cancer Cell*.

To learn more about the genome project, visit *www.pediatriccancergenomeproject.org*.

Focusing on Glomulin

A faulty gene linked to a rare blood vessel disorder has led St. Jude scientists to discover a mechanism involved in determining the fate of possibly thousands of proteins working inside cells. The findings highlight a potential new approach for developing treatments for glomuvenous malformations, which result in veins that cause discolored raised skin lumps that can be painful and disfiguring.

The study provides insight into one of the body's most important regulatory systems, the ubiquitin system. Cells use it to get rid of unneeded proteins. Problems in this system have been tied to cancers, infections and other diseases.

Researchers demonstrated how a protein named Glomulin binds to a key component of the regulatory system. Scientists showed not only where Glomulin binds but also how binding shuts down a biochemical cascade that tags unnecessary proteins for dismantling.

"We believe Glomulin may represent the tip of the iceberg. There could be many proteins that work in this fashion," said Brenda Schulman, PhD, of St. Jude Structural Biology and a Howard Hughes Medical Institute investigator. She was senior and corresponding author of a report on this work that appeared in the journal *Molecular Cell*.

The risk of swine viruses

St. Jude-led research has found evidence that the main strains of the influenza virus circulating in North American pigs have the potential to not only infect and sicken humans, but to spread easily from person to person.

The study focused on triple-reassortant influenza A swine flu viruses, which contain genes from human and bird as well as swine flu viruses. These viruses have caused sporadic illness in individuals who came in contact with infected pigs, but the viruses have not spread from person to person.

In the journal *PLoS Pathogens*, researchers published evidence that this pattern could change. If confirmed, the findings suggest the strains pose a risk to humans. The work also highlights a potential new method of identifying risky swine flu viruses.

"This study underscores the need to track flu viruses in swine and step up efforts to contain viruses that pose a risk to humans," said the paper's corresponding author, Richard Webby, PhD, Infectious Diseases.

During the 2012 Survivors Day Conference, cancer survivor Jarred Falor displayed a photo of himself with St. Jude founder Danny Thomas. Honoring the hospital's 50th anniversary, the conference featured dynamic panel discussions with distinguished medical experts, cancer researchers and advocates, as well as other survivors of childhood cancers. View the event's webcast at *www.stjude.org/survivors2012.*

A better way of testing

Early treatment response is a powerful predictor of long-term outcome for young patients with acute myeloid leukemia (AML). That information can help physicians decide if a more intensive approach is needed. Research led by St. Jude investigators has identified the best test for measuring that response and guiding therapy.

The method uses a laboratory technique called flow cytometry, which makes it possible to identify a single cancer cell in 1,000 normal cells in patient bone marrow. St. Jude investigators were instrumental in developing the test to identify extremely low levels of cancer called minimal residual disease.

Researchers showed that checking for minimal residual disease by flow cytometry is better than two other widely used methods for predicting AML patient survival. The results help identify who might benefit from more intensive therapy, including bone marrow transplantation.

"These results will help establish flow cytometry testing for minimal residual disease as a routine tool for guiding therapy of acute myeloid leukemia and identifying patients early who are at risk of treatment failure," said Hiroto Inaba, MD, PhD, of St. Jude Oncology. He was the first and corresponding author of an article on the topic that appeared in the *Journal of Clinical Oncology*.

Writing the **Next Chapter**

One couple embarks on a new phase of life, helping St. Jude build support and awareness.

By Kerry Healy

Retirement is allowing Bob and Eileen Hutton to turn the page on an exciting new chapter of life. This literary analogy is particularly apt since Eileen, a librarian, spent much of her career building an audiobook empire. As the Huttons begin writing their next chapter, the children of St. Jude Children's Research Hospital are fortunate to be among the main characters.

Bob and Eileen embarked on this new phase with an overwhelming sense of gratitude for all the blessings of life: a happy marriage of 49 years, two successful careers, two wonderful children and two grandsons.

"We really have led charmed lives," Eileen says. "Helping the children of St. Jude is our way of giving back."

A serendipitous move propelled Eileen to the top of the audiobook world. In 1989, Bob's flourishing career as an engineer in the machine tool industry prompted a relocation to Michigan. While searching for a school librarian position, Eileen's interest was piqued by an ad for a small audiobook publishing company.

"I thought it was a cool concept. I'd never heard of an audiobook before," she says.

Eileen went on to become co-owner and vice president of Brilliance Audio. Her talent for signing big-name authors, such as Nora Roberts, Dean Koontz and Danielle Steele, helped Brilliance Audio become the largest independent audiobook publisher in the United States.

In 2007, she and her partner sold Brilliance Audio to a large, online retailer, and Bob and Eileen retired to Hilton Head Island, South Carolina.

"The last time we saw snow was in our rearview mirror," Eileen jokes.

As former residents of Detroit—the city where St. Jude founder Danny Thomas began his show business career—Bob and Eileen are extremely familiar with the hospital's mission.

"My mother and my aunt sang backup on a radio show in the 1930s with Danny," Bob recalls. So when the couple created a charitable remainder trust with proceeds from the sale of Brilliance Audio, it was an easy decision to make St. Jude one of the main beneficiaries.

Now St. Jude will become an even bigger focus of the Huttons' post-career story, because Eileen has accepted a nomination to serve on the ALSAC Leadership Council (ALC). She will join other distinguished supporters as an ambassador for ALSAC, the fundraising organization for St. Jude.

"I am honored to serve on the ALC," Eileen says. "Building support and awareness is critical for St. Jude to continue to fulfill its mission, because as Danny said, 'No child should die in the dawn of life.'"

With each visit to the hospital, the Huttons' life story and the St. Jude story become more intertwined. Bob explains, "When you walk through the hospital and you see the joy in these halls, how can you not want to be a part of that?"

As enthusiastic supporters of the St. Jude mission, Eileen and Bob Hutton have established a charitable remainder trust that benefits the hospital. The couple are also dedicated to building support and awareness for St. Jude.

St. Jude patient Addison:
Sweet baby girl

The very fact that you are holding this magazine is proof that you care. In fact, it is because of you that kids like Addison will have a fighting chance to experience the beautiful moments of their lives. Yes, because of you. Your legacy gift is a powerhouse in terms of research and care. It will allow researchers and doctors to continue to peel away the layers of pediatric cancer and other deadly childhood illnesses. Let this be your legacy: that one day no child will die in the dawn of life. Join St. Jude in finding cures and saving children.

Begin your legacy today. Call 800-910-3188 or visit stjudelegacy.org.

St. Jude Children's Research Hospital
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CHANGE SERVICE REQUESTED

October 2012 marked the end of chemotherapy for Auburn University football player Shon Coleman, whose battle with acute lymphoblastic leukemia was chronicled in the autumn 2010 issue of *Promise* (to read that story, visit *www.stjude.org/still-in-the-game).* At far right: Coleman pauses with Deepa Bhojwani, MD, of St. Jude Oncology at his recent No Mo' Chemo celebration.

SETH DIXON

Finding cures. Saving children.