## **St. Jude St. Jude Stiude**. crg/pronise s u m m e r 2 0 1 6

## Fighting Flu with a **Vitamin Boost** pg. 8

A Closer Look at **MELANOMA** pg. 2

Gene Therapy: Thinking Outside the Bubble pg. 12

> St. Jude Children's Research Hospital



#### Cover story

#### Fighting Flu with a Vitamin Boost

Can vitamins improve potency of the flu vaccine?

#### **Features**

#### A Closer Look at Melanoma

New clinic increases our knowledge about skin cancer.

A Philosophy of Giving For this couple, beneficence is a way of life.

A Seat at the Table Patient group helps plan clinical trials and other projects.

11

#### The Amazing Mr. Elephant

One stuffed animal and a walk to end childhood cancer.

Contact us: promisemagazine@stjude.org (901) 595-2125 Subscribe online: stjude.org/promise Connect with us on Twitter and Instagram: @stiuderesearch Facebook: St. Jude

Public Information: 1-866-278-5833, ext. 3306 Donations: 1-800-822-6344

#### SUMMER 2016

12

#### Thinking Outside the Bubble

Gene therapy offers hope for children born with SCID.

16

#### Picture Perfect

A study personalizes treatment for patients with a high-risk gene variation.

18

Next-Generation Education Graduate school brings fresh energy to campus.

#### **Research Highlights**

21

#### Discoveries and Achievements

Learn about the latest news at St. Jude.

#### Perspective

## 24

#### Vanna's Choice

When the time came to make a difference, Vanna White selected St. Jude.

The mission of St. Jude Children's Research Hospital is to advance cures, and means of prevention, for pediatric catastrophic diseases through research and treatment.

St. Jude Children's Research Hospital, American Lebanese Syrian Associated Charities, ALSAC and *Thanks and Giving* are registered trademarks.

St. Jude is an Equal Opportunity Employer. Articles may be reprinted with written permission. ©2016

St. Jude President and Chief Executive Officer James R. Downing, MD

ALSAC President and Chief Executive Officer Richard C. Shadyac Jr.

St. Jude Vice President of Communications and Public Relations Barry Whyte, PhD

**Director of Digital Media** Elizabeth Whittington

Editor Elizabeth Jane Walker

**Graphic Design** 

Jessica W. Anderson Ashley Broussard Timothy Hammond Jennifer Hardin Jerry Harris Brandon Stelter

**Contributing Writers** 

Kerry Healy John Juettner Mike O'Kelly Maureen Salamon Carole Weaver, PhD

#### **Photographers**

Peter Barta Seth Dixon Ann-Margaret Hedges Justin Veneman

#### **Editorial Advisory Board**

Justin Baker, MD Leah Brooks Christine Broughton Debbie Crom, RN, PhD Aditya Gaur, MD Hiroto Inaba, MD, PhD Josephina Ofiara Joseph Opferman, PhD Amy Scott Barry Shulkin, MD Carrie L. Strehlau Regina Watson Carole Weaver, PhD John Zacher

On the cover: Mabry Landstreet Photo by Peter Barta

Isaiah Mainer recently took part in the Pediatric and Adolescent Melanoma Referral Clinic created for children who were treated at other institutions."At St. Jude, we could fill in unanswered questions that we still had," says his mom.

## A Closer Look at Mismon. MELANORAL

\* -

By Elizabeth Jane Walker

#### A NEW CLINIC BRINGS FAMILIES FROM ACROSS THE NATION TO ST. JUDE TO INCREASE OUR KNOWLEDGE ABOUT THIS AGGRESSIVE TYPE OF SKIN CANCER.

Stephanie Mainer recalls with vivid clarity the day she received the phone call that changed her life.

"The sample we sent to the lab came back as cancer," the doctor told her. "But 3-year-olds don't get melanoma. So we're going to send it to a different lab."

That's when mother's intuition kicked in. Stephanie knew something was terribly wrong with Isaiah.

Originally, she and her husband had asked the doctor to remove a pinkish-red bump from the toddler's right cheek.

"Honestly, we wanted it removed for cosmetic reasons," she admits. "Skin cancer wasn't even on our radar."

A second report confirmed the diagnosis of melanoma, an aggressive type of skin cancer that affects only 400 children in the U.S. each year. Isaiah had two surgeries and received interferon therapy at a hospital in Texas. Although his treatment is now complete, his parents still have questions: "How often should he receive follow-up scans? Should we do blood work? Does he need to see an oncologist and a dermatologist?" And most importantly, "Will the cancer return?"

#### **Answers for Isaiah**

When the Mainers learned that St. Jude Children's Research Hospital was creating a Pediatric and Adolescent Melanoma Referral Clinic for children treated at other institutions, they jumped at the chance.

"Our new clinic offers a second opinion or guidance into the management of these very complex cases," explains Alberto Pappo, MD, director of the St. Jude Solid Tumor Division. "It's open to children with melanoma throughout the United States. All a physician has to do is make a referral. Families and their physicians may have questions about diagnosis, pathology,



Amanda and Nora Hosier consult with (from left) Joe Brigance, RN; Julie Jones, RN; Margaret Hussong, PNP; Ari VanderWalde, MD; Alberto Pappo, MD; Martin Fleming, MD; Teresa Wright, MD; Armita Bahrami, MD; and (not pictured) Sue Kaste, DO.

therapy or follow-up. We're providing this as a free service for them."

#### Sharing knowledge

Isaiah and four other children from Idaho, Minnesota, Georgia and Indiana were referred by their local physicians to attend the April 2016 clinic. The twoday event included medical exams by leading melanoma specialists, educational seminars, individual consultations with a panel of experts, and the opportunity to meet other families battling this rare cancer.

A leader in genomic research, St. Jude also invited participants to donate tissue samples to the hospital's Tissue Bank for use in future melanoma research. All five families agreed to take part in that project.

St. Jude provides travel, housing and meals for participants in the melanoma clinics, which will be held twice a year. Afterward, families and their referring physicians receive written reports that include treatment recommendations.

#### Advancing cures

As an important component of the St. Jude Strategic Plan, the melanoma clinic aims to advance cures by increasing our knowledge about this rare childhood cancer and sharing that information with patients and their physicians. St. Jude faculty and staff are currently making plans to create similar referral clinics for other rare diseases, such as thyroid cancer and adrenocortical carcinoma.

"Our goal is to accelerate progress for

some of the most aggressive and leastunderstood childhood cancers," explains James R. Downing, MD, St. Jude president and chief executive officer. "To do that, we must focus our efforts on diseases where progress has been limited.

"We cannot rest until every child with cancer can be cured."

#### A room full of experts

Amanda Hosier, mom of 11-monthold Nora, traveled from Indiana to attend the clinic. While all childhood melanoma is uncommon, Nora's is extremely rare. She was born with a small, blue lesion on the crown of her head. Doctors originally assumed the spot was caused by trauma from labor. But the lesion was actually melanoma, which had already spread to Nora's liver, lymph nodes, lungs and leg. Amanda and Nora attended the clinic to see if their current treatment plan is on the right course.

After an exam by clinic staff, Nora and her mom met with a multidisciplinary panel of experts that includes physicians from the University of Tennessee Health Science Center's College of Medicine and Le Bonheur Children's Hospital.

"All we ever hear about Nora is, 'She's one in a million.' There's no run-of-the-mill treatment plan for her," Amanda says. "So the panel discussion really exceeded my expectations. I've never before had the chance to have a radiologist, a surgeon, an oncologist, a pathologist, an RN and a dermatologist all in the same room



together so that I could ask questions about my child.

"They answered all the questions I had, and I'm in the process of following up on some of the things we talked about."

#### Knowledge is power

Isaiah's mother says the melanoma clinic helped put her mind at ease.

"After Isaiah's treatment, we've been following up with our local oncologist, but not a melanoma specialist," Stephanie says. "At St. Jude, we could fill in unanswered questions that we still had. The chance of recurrence was my biggest fear. Dr. Pappo cited some facts and figures that were really comforting. The chances of it coming back are very, very slim. When I asked him about long-term effects of interferon on Isaiah's teeth, Dr. Pappo researched our concern and discussed the results with us the next day. Everyone at St. Jude took their time and answered every question we had."

Stephanie also had the opportunity to connect with other families affected by melanoma and to attend an educational seminar. As the mom of an avid T-ball player, she was thrilled to learn one particular tip: "There's a product you can add to your laundry to make clothing sun resistant," she says. "For my little baseball player kid, that's great to know."

Six-year-old Isaiah excels in school, where he made straight A's in kindergarten. Talkative and energetic, he is quick to let St. Jude staff know that he plays first base and rover for his T-ball team, which won the T-ball World Series last year. He's also vocal about the attributes of reducing sun exposure by wearing hats and sunscreen.

"All because of cancer!" he warns, when referring to the small scar on his face. "Bad cancer!"■

The next St. Jude Pediatric and Adolescent Melanoma Referral Clinic will take place in November 2016. For more information, visit stjude.org/melanoma-consult-clinic.

BY KERRY HEALY

CA Philosophy of Giving

#### For one couple, beneficence has become a way of life.

Every good CEO is guided by a personal philosophy, and Bill and Michele Nuti are no different. The couple, who are native New Yorkers, are dedicated supporters of St. Jude Children's Research Hospital, and both are CEOs.

"Bill is the CEO of NCR Corp., and I am the CEO of the family," Michele quips.

Headquartered in Atlanta, Georgia, NCR is a global leader in consumer transaction technologies.

"The whole notion of giving back is central to NCR's culture and my personal business philosophy," Bill says.

The couple puts this principle into practice in their personal lives by supporting the hospital's lifesaving mission. They also made a generous gift to dedicate a conference room in the Marlo Thomas Center for Global Education and Collaboration in the Kay Research and Care Center at St. Jude.

"We love the idea that this building, equipped with amazing technology like the proton beam, is at the forefront in the battle against pediatric cancer," Michele says.

The Nutis are proud parents of a son, LB. "I love what Marlo Thomas says about giving thanks for the healthy children in your life and giving to those who are not. That means a lot," Michele says.

Since childhood, Michele has been a devotee of St. Jude Thaddeus, the patron saint of hopeless causes for whom the hospital is named. Her grandmother often prayed to the saint in difficult times.

"Over the years I became aware of the hospital's good work and started giving small amounts—whatever I could afford," Michele says.

Later, as Bill's career progressed, the couple established the Nuti Family Charitable Trust, from which St. Jude receives an annual grant.

"We see it as an investment in children's lives," Bill says. "St. Jude shows great leadership and integrity in everything they do, and that is what drives their great results."

The Nutis visited St. Jude in October 2014, and Michele says they were "blown away" by the passion, dedication and hope exhibited by every person they met.

"As a parent myself, the strength that I see in those parents is amazing," Michele says. "Bill and I are so proud and honored that we can help the children of St. Jude." ■



"I love what Marlo Thomas says about giving thanks for the healthy children in your life and giving to those who are not. That means a lot," says Michele Nuti, pictured with her son, LB, and husband, Bill.

"St. Jude shows great leadership and integrity in everything they do, and that is what drives their great results."

–Bill Nuti



## **A SEAT** AT THE TABLE By Elizabeth Jame Walker

One group of St. Jude patients helps HIV/AIDS researchers plan clinical trials and other important projects.

With hugs and laughter and enthusiastic chatter, several youngadult patients burst into a conference room at St. Jude Children's Research Hospital for a fun meeting with a serious purpose. These vibrant and engaged young leaders meet once a month to help clinicians and scientists nationwide improve the research and treatment of HIV/AIDS.

Each member of the Youth Community Advisory Board (CAB) is a St. Jude patient who has been affected by the disease. Under the guidance of Nurse Practitioner Carla London, this close-knit

group of seven to 10 patients provides feedback to investigators developing studies of youth with HIV. It's a duty the board takes seriously. And it's a service the researchers appreciate.

#### **Research** assistance

According to the Centers for Disease Control and Prevention, youth between the ages of 13 and 24 account for more than a quarter of all new HIV infections in the U.S., with more than half of "Every time I've gone to this group, they've provided something unique that we hadn't considered. They ask insightful questions that make us think."

Ronald Dallas, PhD

those individuals unaware they are infected.

Ronald Dallas, PhD, a clinical research scientist in St. Jude Infectious Diseases, has sought the CAB's input for grant proposals and clinical trials centered around medication adherence.

"Teens have many reasons for not taking their medications," he says. "They may have funky schedules. Or they may not see the importance of taking their meds, since they currently feel fine. Or they may not want their family or friends to know they have HIV. When we're designing a study to encourage teens to take their meds, it's great to have the CAB offer input."

Megan Wilkins, PhD, a clinical psychologist in Infectious Diseases, has consulted the group several times, including for one study evaluating body image in youth with HIV.

"The CAB gave really helpful feedback about the wording of questions and about acceptability among youth with HIV," she recalls. "In fact, their feedback was used to modify the wording of questions, the way we presented the protocol and our efforts to recruit patients."

The scientists view the CAB as an invaluable research partner.

"Every time I've gone to this group, they've provided something unique that we hadn't considered," Dallas says. "They ask insightful questions that make us think."

#### **Empowered to help**

The CAB has also offered input for protocols created through the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN), a national research network. Projects created by ATN institutions have the power to transform the treatment of HIV and AIDS. Many of those projects are focused on prevention research, since the U.S. has one of the highest rates of HIV infections in youth. According to the ATN, 3,300 young people are infected with HIV every day. The CAB members know the decisions they make have the potential to help change those statistics.

"The CAB is so important, because they give direct feedback to the principal investigators about things that need to be tweaked," London says. "What better group of people to give that feedback than those who are battling HIV themselves? I tell them all the time that they are vitally important because they have the authority to change the face of this disease and the interventions that are created to combat it."

#### A family and a voice

In addition to helping with research, the St. Jude Youth CAB reaches out to the community. They have spearheaded toy drives for children with HIV, organized dances for the hospital's Infectious Diseases staff and patients, and sent representatives to state and national HIV/AIDS meetings. The CAB members agree that the group empowers them, gives them a sense of purpose, and provides them with a way to give back to the institution that has offered them hope and understanding, as well as medical care.

Eighteen-year-old CAB member Miguel vividly recalls the day, three years ago, when he discovered he was HIV positive.

"I just froze," he recalls. "It was like a movie where I hit the 'pause' button, and I saw myself standing there with tears in my eyes. I was overwhelmed and disappointed, full of doubts and insecurities. But when I came to St. Jude, I felt like I was brought into a family. Everyone made me feel like I'm at home. I can talk to them about anything, and I feel loved when I come here.

"I'm thankful to be here and to be able to take part in the CAB," he continues. "This is a great opportunity for our voices to be heard."

Mabry Landstreet's experience reinforces the importance of St. Jude research focused on making the flu vaccine more effective.

## FIGHTING FLU with a Vitamin

Researchers investigate whether vitamins A and D can improve potency of the flu vaccine. JENNY and ALLAN LANDSTREET reminded themselves not to panic.

Their 2-year-old son, listless and feverish, had just been diagnosed with influenza, also called flu. But the couple's worries swiftly turned to their 4-year-old daughter, Mabry, who was receiving treatment at St. Jude Children's Research Hospital for acute lymphoblastic leukemia (ALL). Because Mabry's immune system was weakened from chemotherapy, flu might pose dangerous complications.

Common-sense measures, such as disinfecting household surfaces, washing hands frequently and keeping Mabry apart from her brother, helped allay the Landstreets' anxiety. Mabry's St. Jude doctors also prescribed an antiviral medicine to nip the illness in the bud. The strategy worked: Even though Mabry got flu, it took a fairly mild course, triggering only a low fever, runny nose and postponement of scheduled chemotherapy treatments.

"We were lucky," Jenny says, "because an illness that our body could fight could have been so much worse for Mabry."

#### Vitamins and infection

Mabry's experience reinforced the importance of St. Jude research focused on making the flu vaccine more effective.

According to the U.S. Centers for Disease Control and Prevention (CDC), influenza has killed as many as 49,000 Americans and about a half-million children worldwide per year. The CDC considers vaccination to be the best step to prevent flu. But during the 2015–16 flu season, the CDC reported that the flu vaccine was only 60 percent effective, underscoring the need to improve the vaccine's potency.

In a paper published in the journal *Clinical Vaccine Immunology*, a team led by Julia Hurwitz, PhD, of the St. Jude Infectious Diseases department, showed that vitamins A and D help boost the body's response to the flu vaccine. Now, clinical trials at St. Jude are exploring whether a simple supplement of those vitamins, given at the time of vaccination, can protect children from catching flu.

#### A and D to the rescue

Vitamins A and D are present in foods, and vitamin D is also made in the body in response to sun exposure. But changes in the U.S. diet are chipping away at the baseline levels of these nutrients. Hurwitz discovered this during previous research that tested vitamin levels in children and adults from Memphis.

"We found nutritional deficits, vitamins A and D among them," she explains. "Based on those findings, we began to question why the influenza virus vaccines were not working well, particularly in children in this city."

Hurwitz has long been interested in the activity of B cells, the white blood cells that circulate through our bodies and make antibodies to protect us from germs such as the influenza virus. If a person lacks healthy levels of vitamins, their B cells may not produce the antibodies our bodies require.

Hurwitz and her colleagues found that a shortage of vitamin A decreased the body's immune response to vaccines against



In the lab, Julia Hurwitz, PhD, showed that vitamins A and D help boost the body's response to the flu vaccine. Now, clinical trials at St. Jude are exploring whether a simple supplement of those vitamins, given at the time of vaccination, can protect children from catching flu.

respiratory viruses. So the scientists set out to see whether deficiencies in both vitamins A and D would worsen matters. That's what happened.

mats what happened.

In the lab, Hurwitz also found that giving vitamins A and D restored immune responses to the flu vaccine.

#### First-ever trial in humans

As a result of that research, St. Jude has launched a clinical study to examine immune responses to the flu vaccine in relation to vitamin levels and vitamin supplements.

The St. Jude FLUVIT trial is designed to find out whether children produce normal immune responses if they receive a vitamin supplement when they receive the flu vaccine.

Led by Nehali Patel, MD, of the St. Jude Infectious Diseases department, the study is enrolling 80 healthy children ages 2 to 8 over two to three flu seasons. Researchers first measure the vitamin levels present in the children's blood. Half of the children then consume a chewable gummy vitamin A and D supplement when receiving the flu vaccine. The other half receive a placebo supplement, or "dummy" gummy, at the time of vaccination.

Subsequent blood tests measure vitamin A and D levels in the children's blood. Scientists also check antibody responses against flu.

Parents keep food diaries to track the children's diets. And the parents' education levels and other socioeconomic factors are logged to find out whether these affect the children's nutritional status. By 2018, Hurwitz, Patel and their colleagues hope to show that when vitamins A and D are provided to children at the time of flu vaccination, there is an improvement in vaccine potency.

"People may not be willing or able to take vitamins on a daily basis, but this is just a one-time vitamin intervention that could be given when you get the flu vaccine to help improve response," Patel says. "So it's actually a very practical solution."

#### Potential worldwide benefit

Should all children receive vitamin A and D supplements when vaccinated against influenza?

If the St. Jude findings are positive and confirmed in larger studies, "we could consider changing policy so that everyone receives vitamins at the time of vaccination," Hurwitz notes. "Of course, we'd prefer that everyone simply had a good, nutritious diet, but that's hard to ensure.

"If we can demonstrate that vitamins make a difference in terms of vaccine efficacy, we can better protect children worldwide," she adds.

The beneficial ripple effects worldwide could be staggering. "We're a hospital that deals with catastrophic diseases of children, and flu is catastrophic," Hurwitz continues. "It is our mission to deal with serious disease and put an end to it."

Jenny Landstreet and her husband already knew that St. Jude research has contributed to a greater than 90 percent survival rate for children with ALL. But Mabry's recent experience with the flu left them especially grateful that St. Jude research efforts extend far beyond childhood cancers.

"You think they're doing research only to help find the cure for cancer, but you come to realize they're doing so much more research that could benefit not only Mabry, but kids for generations down the road," Jenny says. "I think research is the most important thing they do."

For more details about the study, visit stjude.org/fluvit.



Nehali Patel, MD, (pictured with 8-year-old Zariah Brooks) is leading a clinical trial that aims to enroll 80 healthy children, ages 2 to 8. Patel and her colleagues want to find out whether children produce normal immune responses if they receive a vitamin supplement when they receive the flu vaccine.

### The Amazing Mr. Elephant

If one toy elephant has the power to help St. Jude, just think what you can do.

#### BY JOHN JUETTNER

According to 7-year-old Cub Robertson, Mr. Elephant has the power to prevent bad dreams.

That power was put to the test in 2014, when Cub was diagnosed with acute lymphoblastic leukemia, the most common form of childhood cancer, and referred to St. Jude Children's Research Hospital for treatment. Mr. Elephant, a toy that has been with Cub since the day he was born, accompanies him to every appointment.

Mr. Elephant also helps Cub's family in their efforts to increase awareness of childhood cancer and raise funds for St. Jude. Last year, Cub's mom, Marilyn, signed up for the St. Jude Walk/Run to End Childhood Cancer near the family's hometown in the Midwest and recruited friends and family to join her team. Mr. Elephant's image was featured on the team's T-shirt.

The Robertson family used the event to educate their friends about childhood cancer.

"They were able to come to the walk because it's a neutral area to talk and learn about what Cub and our family are going through," Marilyn says.

Cub's treatment includes more than two-and-a-half years of chemotherapy. Families never receive a bill from St. Jude for treatment, travel, housing or food—because all a family should worry about is helping their child live.

"Once we arrived at St. Jude, it was like being enveloped with love and compassion," Marilyn says. "It was a nobrainer to do the event this year. It's now a part of life to support St. Jude and raise awareness for childhood cancer. It's a part of who we are. Even when Cub's all better, this experience will still be a part of us."

The St. Jude Walk/Run to End Childhood Cancer takes place in 61 cities this September, which is Childhood Cancer Awareness Month. Cub was unable to participate last year, but Marilyn is hopeful he will be able to join his family as they take part in the event this September.

"It's encouraging to see so many people out there for the same cause," she says. ■ MEMBERS OF THE SCID TEAM INCLUDE (FROM LEFT) MIKE MEAGHER, PhD; EWELINA MAMCARZ, MD; JAY LIEBERMAN, MD; AND BRIAN SORRENTINO, MD.

# **GENE HERAPY**<sup>By</sup> Elizabeth Jar Thinking Outside the Bubble

#### Gene therapy offers hope for children born with a rare immune disease called SCID.

*A father's hug. A mother's caress.* For children with severe combined immunodeficiency, or SCID, the embrace of a family member could be life threatening. Without treatment, most children with this rare immune disease die within the first two years of life.

Children with SCID lack the immune cells necessary to protect them from infection. In the 1980s, the media dubbed SCID as "bubble boy disease," in reference to a child who spent his brief life inside a sterile chamber to avoid infection. Between 40 and 100 infants in the U.S. are born with the disorder each year.

In 2013, Jose Orellana was one of those children. When a lingering ear infection failed to respond to antibiotics, a blood test

revealed SCID. The 9-month-old needed a bone marrow transplant as soon as possible. Upon arrival at St. Jude Children's Research Hospital, he was rushed to the ICU. Doctors fought to contain his dangerous respiratory infection while seeking a bone marrow donor.

"Jose was put in a plastic chamber completely in isolation," recalls his mom, Rosalina Orellana. "He received a special breathing treatment designed to kill the bacteria in his body and lungs. It was terrifying. I didn't know if he was going to survive."

Thankfully, an anonymous bone marrow donor was the perfect match for Jose, who is one of 13 SCID patients to have received transplants at St. Jude in the past few years. Today, Jose is an active 3-year-old who loves to play outside and interact with other people. When his mom recently learned St. Jude had developed a gene therapy treatment that may be safer and more effective than previous therapies, she was delighted.

"I can't tell you how elated I am for all the other children who have this disease," she says. "It's going to give them so much hope."

"We saw very high levels of correction—unprecedented levels for gene therapy."

– Brian Sorrentino, MD

#### The challenges of transplant

In April 2016, St. Jude scientists and their collaborators unveiled results of a study suggesting that a new kind of gene therapy is safe and effective for children with SCID-X1. Caused by a mutation in the *IL2RG* gene, SCID-X1 is the most common form of SCID.

In the past, bone marrow transplantation has been the most effective treatment for SCID. Through a transplant, a patient receives healthy blood stem cells from a donor. Once those blood-forming cells enter the bone marrow, they begin to create new, infection-fighting cells.

A transplant has the highest chance of success if the donor and the patient have matching tissue types. Unfortunately, twothirds of SCID patients lack fully matched donors. Generally, these children do not fare as well, with a third developing immune problems several years after transplant.

#### Enter gene therapy

To find a safer and more effective process for curing children with SCID, scientists turned to gene therapy. The process provides patients with the normal gene they lack. A carrier molecule known as a vector ferries the normal gene into the patient's bloodproducing stem cells. After infecting the cells, the virus' work is done, and it dies.

For more than a decade, St. Jude researchers have been toiling to perfect gene therapy. They developed tests to gauge vector safety. They re-engineered a lentivirus to transport the healthy gene into the body. And they created an entirely new process for manufacturing the vector in the Children's GMP, LLC, an on-site facility that produces biological products and drugs in accordance with federal safety regulations (see sidebar, page 15).

"Designing the vector took a couple of years; testing it for safety took two or three more," reflects Brian Sorrentino, MD, director of St. Jude Experimental Hematology. "And developing the safety data that led to FDA approval took five or six years. As a matter of fact, the Investigational New Drug application we submitted to the FDA was 4,000 pages long."

Mike Meagher, PhD, president of the GMP facility, reflects on the teamwork necessary to develop and manufacture vector for a project of this magnitude.

"We have 42 full-time staff, and everyone in the building played a role in the development and production of this vector," he says. "We take a lot of pride in what we do, and it's pretty cool when we get to see our products make a difference in the life of a child."

#### Unprecedented results

The goal of all that work was to create a gene therapy process that would save young lives. A recent clinical trial offered this option to a group of patients between 7 and 23 years of age for whom standard bone marrow transplant had failed. The results were astounding.

Previous gene therapy trials corrected only white blood cells called T cells. But the new treatment also corrected B cells and natural killer cells, which are crucial parts of the immune system.

"We saw very high levels of correction—unprecedented levels for gene therapy," Sorrentino says.



The adolescents and young adults in the study were treated at the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health (NIH). All of the patients had undergone bone marrow transplants that had failed to correct their immune function. In addition to using the lentiviral vector developed at St. Jude, the therapy included the first use in SCID of a chemotherapy drug called busulfan. This drug helps make room for the gene-corrected stem cells in the bone marrow.

Patients in the study experienced dramatic improvements as a result of the gene therapy. Although additional follow-up is necessary to confirm long-term effects, Sorrentino is optimistic.

"This rescue of the older children really had phenomenal results," he says. "All of the patients in the NIH study had transplants that failed, and we salvaged those transplant failures with gene therapy.

"It kind of turns things on their head."

#### Heading off immune problems

The next step is to offer this therapy to infants with SCID, before chronic infections have a chance to take a toll. A clinical trial using the new gene therapy process is now open at St. Jude for infants with SCID-X1 who lack matched sibling donors. Sorrentino is leading the project with Ewelina Mamcarz, MD, of St. Jude Bone Marrow Transplantation and Cellular Therapy, in conjunction with pediatric immunologist Jay Lieberman, MD, of Le Bonheur Children's Hospital.

As part of the study, doctors will first extract bone marrow cells from each participant. The infant will receive busulfan chemotherapy while scientists in the GMP treat the donated bone marrow cells with the lentiviral vector. Cells containing the corrected gene will then be infused back into the child's body. As the cells move into the bone marrow, they will create a new, healthy immune system. Children in the study will remain in the St. Jude Transplant Unit until their immune systems recover.

The hospital recently garnered national attention for its work with SCID. Earlier this year, St. Jude was designated a clinical center in the federally funded Primary Immune Deficiency Treatment Consortium, whose goal is to improve the outcome of patients with inherited immune disorders. And a conference in June of 2016 brought the world's top SCID researchers to campus to share the latest findings about newborn screening and treatment options.

After more than two decades of work on gene therapy, Sorrentino is enthusiastic about the future of children born with SCID.

"We believe it's possible that this new form of gene therapy will offer them the best available treatment for their disorder," he says. "And that's really exciting." ■





#### When time is of the essence

Situated on the campus of St. Jude Children's Research Hospital, the Children's GMP, LLC, develops and produces gene therapy vectors, vaccines and other biological products according to strict federal guidelines.

The 42 employees in the Good Manufacturing Practice (GMP) facility perform their task well, and they do it quickly. After all, children's lives are on the line.

GMP staff members manufacture the lentiviral vector used in the SCID clinical trials and transfer that genetic material into the patient's cells, which are then infused back into the patient.

The GMP enables St. Jude to provide such innovative treatments rapidly and efficiently.

"If we had to contract this out to a pharmaceutical company, we'd have to get in the queue and wait," says Mike Meagher, PhD, president of the Children's GMP, LLC. "We have the ability to develop and respond quickly and affordably. When you're dealing with children who have life-threatening diseases, days matter. We take that seriously. If we can get it done faster, that means the patient gets the product faster.

"Having a GMP facility at St. Jude makes a difference in people's lives," he continues. "And that's pretty cool." "Having a GMP facility at St. Jude makes a difference in people's lives. And that's pretty cool."

– Mike Meagher, PhD

GMP

## **Picture Perfect**

BY MIKE O'KELLY

#### St. Jude spearheads study that personalizes treatment for patients who inherit a high-risk gene variation.

Six-year-old Belinda "Bel" Mandy Goh Zhi Xuan gave her parents a friendly wave and flashed a bright smile as they snapped photos before she began her first day of school in January 2015. Pulling a sparkling pink backpack on wheels, Bel bounced into her first-grade classroom in Sarawak, a Malaysian state on the island of Borneo.

It was a snapshot moment for parents to treasure forever—a moment that inspired the work of researchers half-a-world away at St. Jude Children's Research Hospital in Memphis, Tennessee.

At age 4, Bel was found to have acute lymphoblastic leukemia (ALL). She began receiving treatment at the National University Hospital in Singapore, an institution with a long history of collaboration with St. Jude. But her white blood cell count plummeted and she developed infections after treatment with mercaptopurine, an essential chemotherapy drug. The standard 50-milligram dose was reduced to 15 milligrams, and eventually she was taken off the drug for a brief time. Unfortunately, the side effects returned each time she resumed treatment, even at these lower doses.

Bel's painful cycle of toxicity prompted her physician, Allen Yeoh, MD, who trained at St. Jude, to reach out to Jun J. Yang, PhD, of St. Jude Pharmaceutical Sciences. The two began studying the cause of Bel's unusual response to this drug in hopes of finding a potential solution for other children like Bel.

#### A medical mystery

For decades, St. Jude has been at the forefront of research in pharmacogenetics—the study of how genes affect a person's response to drugs. Most patients have no problem metabolizing mercaptopurine, which is part of a larger class of drugs known as thiopurines. However, previous St. Jude research found that patients with limited activity in an enzyme known as TPMT had problems breaking down thiopurines. That results in a toxic buildup of the medicine in the body, causing infections, anemia and bleeding.

Bel underwent pharmacogenetics testing for the TPMT

enzyme, but her levels of the enzyme were normal. So what was preventing her body from metabolizing the drug?

Yang and a team of international collaborators found the answer. His laboratory led research that included 270 children with ALL enrolled in clinical trials in Singapore, Guatemala and Japan.

Up to 25 percent of leukemia patients with East Asian ancestry in the trial had one of four variations that were found in a gene called *NUDT15*.

Because everyone has a unique set of DNA, each person has small differences in the genes that code for enzymes. The *NUDT15* gene tells the body how to break down thiopurines. Similar to earlier TPMT research, the study revealed that four variations in the *NUDT15* gene reduce the body's ability to metabolize the medicine. The variations were also common in other Asian and Hispanic populations.

#### Dialing down the dose

The research showed that the NUDT15 enzyme balances thiopurine activity by breaking down the excess drug and therefore helping prevent toxicity and other complications. Scientists learned the *NUDT15* variations caused a 74-to-100 percent loss of the gene's function. That led to a toxic buildup of the drug at standard doses.

Further testing revealed that Bel had the NUDT15 variant, which meant her treatment could now be tailored to avoid a severe drug reaction. Eventually, her physicians dialed down her dosage of mercaptopurine to a tolerable 2 milligram dose.

"She is back in school and doing great," Yang says. "It's gratifying to know that the research we do can make a positive difference in the lives of these young patients."

#### "It's gratifying to know that the research we do can make a positive difference in the lives of these young patients."

Jun J. Yang, PhD

#### Genetics and treatment

According to Yang, the study's findings will help clinicians develop more effective, personalized thiopurine therapy. Clinical evidence has shown that patients of Asian ancestry often cannot tolerate mercaptopurine dosages commonly used in the United States and Europe. "In the future, we hope patients like Bel will not have to endure these severe side effects, and that we can reduce the toxicity dramatically by knowing a patient's genetics in the beginning and using that information to guide treatment," Yang says.



Jun J. Yang, PhD (at left), Takaya Moriyama, MD, PhD, and their colleagues discovered that children such as Bel Xuan (facing page) who inherit certain versions of the *NUDT15* gene are extremely sensitive to an important family of anticancer drugs. A simple genetic test can help doctors choose the best dose of drug for these children.

# Next-Gen Education

#### THE NEW St. Jude Graduate School of Biomedical Sciences

brings fresh energy to campus.

#### **The fall of 2017**, a hand-picked group of students will walk into St. Jude and change it forever. Their lives will never be the same, either.

Those people will be the inaugural class of the St. Jude Graduate School of Biomedical Sciences, the first degreegranting program ever established on the campus of St. Jude Children's Research Hospital.

"It's going to be unique," says Stephen White, DPhil, the school's dean. "We've had a chance to design it from scratch. And we want the most ambitious and adventurous students."

#### An educational mission

Scientific research has always been central to the St. Jude mission of developing cures. But why establish a graduate school?

"People don't always realize that it's the trainees who do the hands-on experiments that give us those groundbreaking results," says faculty member Suzanne Baker, PhD, who leads the school's curriculum committee.

"Science is about asking questions, and we want people with open minds," she continues. "New, excited

#### **By Carole Weaver, PhD**

graduate students can bring a lot of energy and insight to a research program. They ask questions that a more experienced scientist might think they already know the answers to."

White agrees. "The school is designed to bring in fresh blood and new ideas—fearless people without preconceptions about how things should work," he says. "That's one of the great things students bring to a place."

In fact, St. Jude is no stranger to graduate students. Hundreds of outstanding students from affiliated institutions have received training at the hospital during their dissertation work.

However, the new PhD-granting program will be special. Crafted by St. Jude from the ground up, the school will reflect the hospital's mission and will provide a distinct educational experience. The class size will be roughly 10 students per year, so all interactions with faculty will occur in a small-group setting.

In the spring of 2017, the inaugural class will be handselected from a pool of top applicants from around the U.S. The students will begin their studies in early August. First-year courses will be taught by members of the St. Jude Graduate School faculty, internationally renowned

## eration

"I never had the chance to meet Danny Thomas, but I think the idea of having young people contribute and try to save the lives of kids would be something he would absolutely love."

Stephen White, DPhil, Dean
 St. Jude Graduate School of Biomedical Sciences

MARLO THOMAS CENTEI



KAY Research & Care

scientific and clinical investigators who will also serve as one-onone research mentors during the years of training ahead.

#### Creating nimble scientific leaders

To spark scientific creativity, simple textbook lessons will not be on the class menu. Students will immediately dive into high-level scientific literature that extends far beyond the usual topics found in first-year PhD training.

"The answer to curing disease is not just studying biology," White says. "That's an old idea. Modern scientists must be nimble-if a discovery is made, they need to be able to quickly adapt their research. So we have designed an innovative, challenging curriculum."

In addition to rigorous laboratory training, first-year students will work with clinical faculty in St. Jude clinics, where they will learn how treatment decisions are made. This integrated approach is designed to develop future scientific leaders who understand how lab discoveries become new therapies.

"We'll be attracting students who want to make an impact in pediatric cancer and other diseases," says Justin Baker, MD, of St. Jude Oncology. "By working with clinicians and patients, they can see the potential impact of their research findings, and that's meaningful.

"If you discover something in the lab it might lead to a publication," he adds. "But if you discover something in the lab that's immediately translated into a clinical protocol, patients' lives are changed quickly. There can't be anything more motivating than that."

#### An extraordinary environment

Sustained motivation is critical to success in science. But so is having the right research environment. To help students launch stellar careers, the graduate school will provide extraordinary resources, in keeping with the strong St. Jude tradition of supporting scientific discovery.

"I think they're going to be amazed by this-by St. Jude, the facilities, the atmosphere, how it's run," White says.

A major advantage will be the hospital's "core" research facilities, which offer state-of-the-art technologies and hands-on research support from trained experts. These resources give researchers freedom to rapidly explore promising scientific directions.

"With the St. Jude core facilities, we can do just about anything in biological and medical research that we need to do," White says. "There's nothing else on the planet to match them outside of a pharmaceutical company, and the students will have free access."

Another key success factor will be the close-knit research culture, which fosters the free exchange of ideas among scientists and clinicians across the institution.

"St. Jude has incredible facilities, unbelievable faculty, amazing opportunities," notes Suzanne Baker. "And the other thing we have is a collaborative culture. This is what really sets St. Jude apart."

#### A dedicated support team

As with any graduate program, faculty mentors will have an enormous impact on students' lives and work. But they are not the only critical support team. While construction crews were busy last year building new seminar and study spaces in the Marlo Thomas Center for Global Education and Collaboration, White was hard at work building a creative and energetic management team, which includes Senior Administrator Dayna Baker, Assistant Dean Racquel Collins, PhD, and Associate Dean Brian Walton.

"We have an opportunity to create a school in a research-driven institution on the leading edge of technology and innovation in delivering patient care," Walton says. "I am not sure there could be a more noble goal."

White says he believes the hospital's famous founder would have approved of such a goal. "I never had the chance to meet Danny Thomas," he says. "But I think the idea of having young people contribute and try to save the lives of kids would be something he would absolutely love."



Students will work with faculty in St. Jude clinics and labs. This integrated approach will help develop future scientific leaders who understand how lab discoveries become new therapies.



The graduate program's staff includes (from left) Racquel Collins, PhD, Brian Walton, Dayna Baker and Stephen White, DPhil.

## **highlights**



James R. Downing, MD

#### Downing receives national honors

James R. Downing, MD, St. Jude president and chief executive officer, has been elected to the American Academy of Arts and Sciences. Founded in 1780, the organization is one of the country's oldest learned societies and independent policy research centers. It convenes leaders from the academic, business and government sectors to respond to the challenges facing—and opportunities available to—the nation and the world.

Downing has also recently been appointed to a Blue Ribbon Panel to advise Vice President Joe Biden's National Cancer Moonshot Initiative through the National Cancer Institute. The Blue Ribbon Panel will serve as a working group of the presidentially appointed National Cancer Advisory Board and will provide scientific guidance from thought leaders, scientific experts and patient advocates in the cancer community.

"Collaboration is essential to fuel progress in science," Downing said, "and through efforts such as the National Cancer Moonshot Initiative, researchers will have new support to make the next push against cancer."

#### Designing an irresistible flu drug

The flu virus is a wily beast. Rapid changes in its genes make vaccines less effective, or help the virus resist common anti-flu medications.

New medications are needed to combat drug resistance, treat infected individuals and stop flu outbreaks before they spread. A research study from St. Jude has found promise in a new class of anti-influenza drugs that could form the basis of powerful new treatments.

L-742,001, an example of the new type of drug, gums up a bit of viral machinery that the flu virus uses to reproduce. The researchers found that even when grown for generations in the presence of this drug, the flu virus did not develop resistance.

"This finding is really an encouraging sign that under natural conditions the virus may not readily become resistant to this class of drug," said Richard Webby, PhD, of St. Jude Infectious Diseases.



To explore whether resistance could ever develop, the researchers gave evolution a shove by artificially changing the virus' genetic material. They found that resistance to L-742,001 could develop via changes to a specific "pocket" in the viral machinery.

The discovery may spark the development of even better drugs.

"We already have molecules that bind much, much better than L-742,001, and stay away from one of the pockets that could evolve resistance," said Stephen White, DPhil, of St. Jude Structural Biology. "And these findings give us more insight into designing drugs that avoid that region."

The findings were published in *Proceedings of the National Academy of Sciences (PNAS)*.

## **highlights**

#### Problems in cellular cleanup may contribute to lupus

Every day in the body millions of cells die. Some of those cells are old, worn out, unneeded or unwanted. Disposing of all those cells can be a challenge. Defects in the process have been linked to inflammatory disease and other health problems.

St. Jude scientists have discovered how problems in part of the disposal process may lead to the autoimmune disorder lupus.

Lupus occurs when the immune system mistakenly makes antibodies that attack healthy tissue. This causes widespread inflammation. People with lupus may also have life-threatening damage to the kidneys and other organs. The most common form of the disease is systemic lupus erythematosus, or SLE. About 322,000 people in the U.S., mostly young women, have SLE.

In the lab, researchers showed that defects in a cell digestion process called LAP can cause a lupus-like illness. LAP ensures that dead cells are digested and disposed of properly. The research showed that defects in LAP led to increased inflammation and other immune system changes seen in SLE.

"We hope the findings offer a window into the cause of this devastating disease in some patients," said Douglas Green, PhD, chair of the St. Jude Department of Immunology. He led the scientific team that discovered LAP in 2007.

"We also hope the discovery will pave the way for developing new strategies to prevent or reduce the inflammation and autoimmune response that characterize lupus," Green added.

The research was published in Nature.



Elaine Tuomanen, MD and Colin Kietzman, PhD

#### Insights into improving pneumonia vaccines

One of the deadliest living things on Earth is a tiny cell. A leading killer of children worldwide, the pneumococcus bacterium is responsible for pneumonia, meningitis, otitis media ear infections and other illnesses.

St. Jude researchers have discovered how an enzyme helps pneumococcus survive and become invasive in the body. The findings have profound implications for treatment and vaccine strategies.

The enzyme, LytA, helps pneumococcus quickly shed its outer layer, or capsule, soon after infecting a host. With no capsule, the bacterium can more readily escape the immune system's frontlines, enter host cells and spread into the bloodstream.

"The majority of antibacterial vaccines currently target the capsule to trigger the protective immune response," said Elaine Tuomanen, MD, of St. Jude Infectious Diseases. The results may explain why current vaccines are less effective in diseases where pneumococcus has less capsule, such as pneumonia and ear infections.

While preventing infection is a key goal, researchers also seek ways to block pneumococcus' spread after infection. "The pathway is new to microbiology and may provide clues for designing drugs to prevent invasive disease," Tuomanen said.

The findings were published in Nature Communications.



Mary Relling, PharmD (at left), and Chengcheng Liu, PhD

#### Risk factors found for leukemia treatment complication

Asparaginase is an important chemotherapy drug for treating acute lymphoblastic leukemia (ALL). Research suggests that patients who receive more doses of the drug are more likely to survive and avoid relapse.

But asparaginase is also a major cause of a serious and life-threatening condition called acute pancreatitis. This side effect occurs in 2 to 18 percent of ALL patients. Currently there is no way to predict which patients are most at risk in order to modify their treatment.

A study led by St. Jude has identified risk factors for asparaginaserelated pancreatitis. Researchers found that teens were more likely than young children to develop acute pancreatitis. Patients who received more asparaginase for a longer period were also at greater risk. So were patients with higher levels of Native American ancestry. And patients with a rare variation in a gene called *CPA2* had a dramatically increased risk of severe pancreatitis within weeks of receiving the drug.

"These findings, if confirmed, may help us better identify patients who are most likely to benefit from asparaginase and those who might be candidates for ALL treatment regimes that do not include the drug," said Mary Relling, PharmD, chair of the St. Jude Department of Pharmaceutical Sciences.

The research was published in the Journal of Clinical Oncology.

#### Diagnosing CNS-PNET tumors: Beyond the microscope

The first step to successfully treating a tumor? Figuring out what it is. And for some tumors, that is difficult.

One such example is a rare, aggressive childhood brain tumor called primitive neuroectodermal tumor of the central nervous system (CNS-PNET). These tumors are hard to diagnose under a microscope, complicating treatment choices.

A new study shows how widespread the problem is and points to a possible solution. Led by St. Jude and the German Cancer Research Center, an international research team used molecular techniques to compare hundreds of tumors classified as CNS-PNET to other known brain tumors.

What they found was surprising: Based on the molecular data, 61 percent of the CNS-PNET tumors could be reclassified as a different type of brain tumor. In many cases, the reclassification suggested a completely different treatment.

Of the remaining tumors, most fell into one of four distinct subgroups. Each had unique molecular patterns and genetic alterations.

"In time, these findings should help us assign patients to the appropriate clinical trial and to improve the design of clinical trials—particularly for precision medicines that target the newly identified genetic alterations," said Brent Orr, MD, PhD, of St. Jude Pathology.

The results were published in the journal Cell.

## Vanna's Choice

#### When the time came to make a difference, Vanna White selected St. Jude.

By Vanna White



My grandmother taught me to crochet when I was 5 years old. I always keep yarn with me, no matter where I am. If I go to a doctor's appointment, I crochet while I'm waiting. As soon as I board an airplane, I begin crocheting. If I'm behind the puzzle board at *Wheel of Fortune*, I'm crocheting—even if it's just for a two-minute break. So when Lion Brand<sup>®</sup> Yarns asked me to create my own lines of yarn, I said, "I'd love to do that, and I'd also like to give back. I want to find a charity that's near and dear to my heart."

Then I went to Memphis and toured St. Jude Children's Research Hospital.

During my visit, I met some of the patients and their parents. I learned that St. Jude saves the lives of children, but it also does tremendous research to find cures for cancer and other diseases. And the hospital takes good care of the whole family. The St. Jude staff members were warm and friendly and helpful. It was just amazing. Once you go to the hospital, how can you say no? So I said, "St. Jude is the one!"

I donate half of my proceeds from yarn sales to St. Jude. To date, we've donated more than \$1.7 million to the hospital. It warms my heart to be able to do that.

There are many reasons why I like St. Jude. Even though it's huge, it has a small, hometown feel—like a happy family. Having grown up in the South, it reminds me of my roots. It's also a first-class organization that does remarkable work.

My mother passed away from cancer, and many of my family members have had cancer. I'm fortunate to have two healthy kids. And I'm happy to do my part to help St. Jude help children get healthy. ■

Longtime Wheel of Fortune co-hostess and actress Vanna White is an avid crocheter who has her own lines of Lion Brand® premium yarns, called Vanna's Choice. A portion of each sale goes to St. Jude.

# <section-header><text>

St. Jude patient William, 10 months old

#### Establish a lifesaving legacy that costs you nothing now.

Remembering St. Jude with a gift in your will costs you nothing now, yet gives you the satisfaction of knowing the legacy of your compassion will continue into the future, helping to save the lives of children like William battling cancer and other life-threatening illnesses.

Begin your legacy today.

Call 1-800-910-3188 or visit stjude.org/legacy.





501 St. Jude Place Memphis, TN 38105

Non-Profit Org. U.S. POSTAGE PAID St. Jude Children's Research Hospital

#### **Pomp and Circumstance**

Ay'Jiona Williams is one of the proud kindergarten graduates who celebrated during the hospital's 2016 graduation ceremony hosted by the St. Jude School Program. Patients who had completed kindergarten during the school year donned caps and gowns, cheered on by their families and hospital staff. The ceremony featured a procession of the graduates, the presentation of certificates and a Class of 2016 slideshow.



## Finding cures. Saving children.