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### Promise

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# Promise

A publication of St. Jude Children's Research Hospital Summer 2015



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On the cover: Allie Johnson Photo by Ann-Margaret Hedges St. Jude scientists' discoveries offer hope for some of the tiniest and most vulnerable patients—babies with a rare and aggressive form of leukemia.

#### By Ginger Porter

When a newborn is placed in mom's arms for the first time, the introduction begins: "Hello, world." An assessment commences—hair, nose, pretty eyes, 10 fingers, 10 toes. That's followed by more detailed numbers: length, weight, respiration rate, heart rate. The tiny, one-of-a-kind individual has captured hearts. Doctors, nurses and family agree: this baby is perfect.

Researchers at St. Jude Children's Research Hospital are working to make sure precious infants like these have the best chance at life even when the genetic underpinnings are not perfect.

#### NIPPING LEUKEMIA IN THE BUD

Alterations in a gene named *MLL* cause a rare but highly aggressive subtype of acute lymphoblastic leukemia (ALL) in infants. About eight out of 10 infants with ALL have a chromosomal rearrangement that fuses the *MLL* gene to a gene on another chromosome. The fusion process leads to production of an abnormal protein. And that protein holds the key to converting normal blood cells to leukemia cells.

The resulting disease causes ominous changes to the central nervous system, resulting in bumps on the scalp, lesions extending deeply into the brain, and leukemic cells in the spinal fluid. The longterm survival rate for babies with this subtype of leukemia, which is known as MLL-R, is a dismal 28 to 36 percent.

For doctors and researchers at St. Jude, that survival rate is simply unacceptable.

The St. Jude – Washington University Pediatric Cancer Genome Project has yielded the most comprehensive DNA analysis yet of childhood ALL, with some surprising results. St. Jude scientists discovered that infants with MLL-R had few other genetic changes besides the chromosomal rearrangement. In fact, the subtype had one of the lowest mutation rates of any cancer.

"This is one of the rare subtypes of pediatric

ALL where there has been little progress in the last 15 years," says James R. Downing, MD, St. Jude president and chief executive officer. "These results show we need to develop drugs that target the abnormal proteins produced by the *MLL* fusion gene or that interact with MLL fusion proteins to shut down the cellular machinery."

#### FOILING THE FUSION

St. Jude researchers are working to identify current drugs and design therapies that will boost cure rates for children with the MLL-R subtype.

Tanja Gruber, MD, PhD, of St. Jude Oncology, is one of those scientists. She is studying the effects of two drugs in combination with standard chemotherapy. The two drugs block the action of proteasomes, which are cellular complexes that break down proteins. By inhibiting the proteasomes, Gruber and her colleagues hope to halt the *MLL* fusion process altogether.

"To improve survival in these patients, we need to shut down the MLL fusion protein," Gruber explains.

The drug combo is the backbone of a clinical trial Gruber recently opened for patients whose *MLL* subtype leukemia returned after treatment. That clinical trial is called REL-MLL. A second study for newly diagnosed infants is scheduled to open this summer. Other sites throughout the

United States plan to offer that St. Jude study, which is titled Total Therapy for Infants I or TINI.

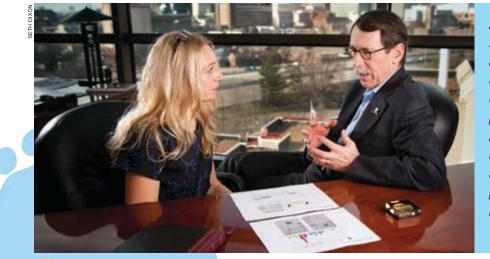
Gruber and her colleagues are also working with scientists in St. Jude Chemical Biology and Therapeutics to identify other compounds that are effective against the MLL-R subtype.

#### SIGNIFICANT STATS

St. Jude research suggests that in infants the *MLL* rearrangement requires very few cooperating mutations to cause ALL. By contrast, in older children, *MLL*-rearranged leukemia requires many more cooperating mutations. St. Jude scientists suspect that in infants the *MLL* fusion occurs in a unique blood stem cell that no longer exists in older children. This early blood stem cell is easily transformed to leukemia by the *MLL* rearrangement.

"This may also be why it is so much harder to cure the infants," Gruber says. "The cancer cell originates from a prenatal blood stem cell that has the ability for robust growth and longevity and is resistant to standard chemotherapy. There is still a lot of work that needs to be done to determine if that is, indeed, the case."

St. Jude is dedicated to raising the 28 to 36 percent survival rate for MLL-R so that parents of a new baby only have to concern themselves with simpler numbers: "10 fingers, 10 toes." ■



James R. Downing, MD, St. Jude president and chief executive officer, and Tanja Gruber, MD, PhD, of St. Jude Oncology, discuss recent progress in treating babies with a high-risk leukemia subtype, called MLL-R. Gruber recently opened a clinical trial for patients whose disease has returned after treatment.







The St. Jude Endocrine Clinic helps families gain the confidence and knowledge they need to spread their wings.

Like fledglings perched on the edge of a nest, patients and families often feel nervous when they contemplate leaving the security of St. Jude Children's Research Hospital. But as children move into adulthood, their medical needs change. A new program eases the transition to adult care for patients in the St. Jude Endocrine Clinic.

The clinic sees children, teens and young adults who are at risk for hormone problems related to their treatment or tumors. Many of these patients require lifelong hormone therapies. Others need ongoing screening to monitor for hormone problems.

Wassim Chemaitilly, MD, director of the St. Jude Endocrinology Division, notes that St. Jude handles nearly every detail of care for patients and their families.

"The mission of St. Jude is to provide the maximum support to patients and their families. Because of that, some of our patients have not performed, for many years, basic tasks related to their health care needs within their communities—tasks such as filling prescriptions in their local pharmacy or calling a doctor's office to set up appointments," he says. "We must provide them with tools to self-advocate and to navigate the health care system."

#### **BIRD'S EYE VIEW**

Enter Endocrine physician assistant Karen Clark and Hematology social worker Margery Johnson.

During the past few years, they have worked on a quality improvement project through the St. Jude Evidence-based Practice Fellowship. The project involves helping adolescent and young adult endocrine patients make the transition to adult endocrinologists.

"The idea of seeking services elsewhere is anxiety provoking because they get good care at St. Jude, and they know everybody. It's hard to know how or where to start to establish community-based care again," Johnson says.

And yet, the shift is necessary.

"We're pediatric providers, and there are benefits and therapies available through adult endocrinologists that we're not able to offer," Clark explains.

Sixteen-year-old Nayla Bandealy's mom is a nurse, and her dad is a doctor. Ten years ago, when Nayla was diagnosed with the brain tumor medulloblastoma, her family turned to St. Jude. Like a warm blanket, the hospital's staff provided comfort and security along with world-class treatment.



Even though Nayla's parents work in the health care field, they do not relish the thought of transitioning to adult endocrinology care.

"The best place for her has been St. Jude," says Nayla's mom, Maria. "They know what to do. They know her history, and they have taken such good care of her. They have given us hope."

#### SOFT LANDINGS

When Clark and Johnson began to design a transition program, they turned to the experts: patients and their families. With their input, the duo designed a simple checklist that includes a series of tasks for patients to complete over a two-year period and resources to assist them.

"This helps patients understand that transition is a process over time, and not a one-time event," Clark says.

During the first year, patients use the checklist to identify a primary care physician and an adult endocrinologist: *check*. To acquire insurance: *check*. To make medical appointments, manage their own medicines, get refills and complete other health-related tasks: *check, check, check, check*.

The second year, patients learn about obtaining referrals, scheduling new-patient visits and gathering information to share with community providers. Finally, after visiting with their adult endocrinologists, patients have their last appointment in the St. Jude Endocrine Clinic. Staff members ensure that the transfer is proceeding smoothly and assist with any final details.

"Afterward, we remain available to families and their providers," Clark says. "We're happy to answer questions regarding screening recommendations, offer advice or help them understand what to expect in the future."

#### **GROWN AND FLOWN**

Letting go can be challenging, but also exciting. "This transition program is a great thing. It's time for

him to handle health on his own," one mom told Clark. Another parent said, "I think it's wonderful that you are staying on top of this planning."

Johnson and her colleagues have begun working with St. Jude families to introduce the transition program for patients in other areas of the hospital.

"The goal is to empower 16-, 17- and 18-year-olds to start doing some of these things themselves," she says.

As for Nayla Bandealy, she has already checked several items off her list. She and her parents have identified a primary care physician and a gynecologist who will take care of her after the transition. She knows her medical history and is taking steps to ensure that she remains healthy throughout adulthood. She's nearly ready to fly.

# Changing Hues

By Elizabeth Jane Walker

A spectrum of discoveries in St. Jude labs and clinics offer promise for patients with Ewing sarcoma.

In a classroom at St. Jude Children's Research Hospital, five bright-eyed firstgraders crowd around a table, paying rapt attention to their teacher. In response to a question, 7-year-old Allie Johnson confidently raises her hand.

During the next 45 minutes, Allie enthusiastically answers queries about days of the week, aces a fractions lesson and properly categorizes the term "rainbow" as a compound word. Tucking wispy hair behind her ear, she joins her classmates in reciting the rainbow's hues: red, orange, yellow, green, blue, indigo and violet.

Then, using crayons and blunt-tipped scissors, the little girl with the iridescent smile carefully creates a rainbow of her own—a symbol of hope after a storm.



St. Jude Ewing sarcoma patient Allie Johnson delights in creating rainbows, such as this painting.

#### The glowering sky

For Allie, the clouds began to gather in 2014, after a playground tumble.

"I fell off the really tall monkey bars at school," Allie explains. "My back kept hurting, and they found out I had a tumor. At a hospital in Oregon, they took out some of my tumor. Then I came to St. Jude."

The pain that Allie and her parents originally attributed to a fall was actually a tumor wrapped around her lower spine. Allie had a type of bone cancer called Ewing sarcoma, which had also spread to her lung. Instead of pursuing standard treatment in Oregon, her parents, Richard Johnson and Kelli Gambucci, opted to enroll Allie in a clinical trial at St. Jude.

"From my research about St. Jude and everything they're doing for children, it was a no-brainer," says Allie's dad, Rich Johnson. "We quickly realized we'd made the right choice. I have nothing but wonderful things to say about St. Jude and the progress that they've made and the loving care that my daughter and my family get while they're there."

Thus far, Allie has responded well to treatment, which has involved chemotherapy.

"She's a great example of how remarkable the response can be to therapy," says her St. Jude oncologist, Tamara Chang, MD. "She has very minimal disease left right now, and we're only 18 weeks into therapy, which is awesome."

After undergoing surgery to remove the remaining tumor, Allie will receive radiation therapy.

"She's spunky and bright and adorable," Chang says. "She's always cheerful, even when she's not feeling well. She's a rock star."

#### A new direction

Throughout the hospital, doctors and researchers are collaborating to find better ways to treat Ewing sarcoma, which has an overall survival rate of 75 to 80 percent. For children whose disease has spread or has returned after treatment, the outlook is grim: 15 to 20 percent survive.

"Over the past 20 years, there has been no significant improvement in outcomes," says Michael Dyer, PhD, a Howard Hughes Medical Institute investigator and co-leader of the St. Jude Developmental Biology and Solid Tumor Program. "The idea of taking the chemotherapy that we already use for childhood cancer and mixing it up and intensifying doses just doesn't work. We need new therapeutics."

Several years ago, experimental drugs called PARP inhibitors were developed to treat breast cancer and ovarian cancers in adults. PARP inhibitors interfere with a process called DNA repair.

"These drugs were never on the radar for childhood solid tumors," Dyer says.

But when scientists tested PARP inhibitors against different tumor types, Ewing sarcoma tumors were vulnerable to the compounds.

"Nobody expected that," Dyer says. "It led to a firestorm of activity."

Dyer and his colleagues subsequently discovered that Ewing sarcoma cells have problems repairing DNA damage. The St. Jude team quickly opted to exploit that weakness. They combined DNAdamaging chemotherapy with PARP inhibitors.

The results were dramatic. In the lab, the combo excelled at killing Ewing sarcoma tumors.

Using a special dosing schedule developed at St. Jude, not only did the combo have fewer side effects than traditional treatments, but it also killed Ewing cells more efficiently.

"This is truly a game-changer," Dyer says, "building on the research that has been done at St. Jude in the past."

#### Sifting the spectrum of mutations

Meanwhile, across campus, computational biologist Jinghui Zhang, PhD, helped lead an international collaboration to explore the genetic landscape of Ewing sarcoma. The results were astounding. Scientists not only pinpointed frequent mutations that occur together in this cancer, but they also identified a subtype of Ewing that is linked to a poor prognosis.

The research provides the most comprehensive picture to date of the genetic changes that help Ewing sarcoma grow and, in many cases, recur. The work took place as part of the St. Jude – Washington University Pediatric Cancer Genome Project, in conjunction with the Institut Curie-INSERM through the International Cancer Genome Consortium.

"This is an important step toward developing more effective diagnosis and treatment," Zhang says.

Zhang and her colleagues already knew that mutations in *STAG2* and *TP53* genes played a role in some cases of Ewing sarcoma. But the recent study proved that children who have both of those mutations also have a lower chance of surviving their disease.

Fortunately, the PARP inhibitor combo appears to be effective against this subtype. In the lab, the combination therapy was effective against 70 percent of Ewing sarcoma tumors that featured the *STAG2* and *TP53* mutations.

#### True colors

Dyer and his colleagues moved quickly to share their findings with the world.

"We want other scientists to have access to our data," Dyer says. "I think this kind of open communication is really important. All of the data is in an open database—every dose, every blood count, every image. It's all freely available."

St. Jude has rapidly moved the research from the lab to the clinic.

Based on the St. Jude findings, Dana-Farber/Harvard Cancer Center in Boston changed an existing Ewing clinical trial to incorporate a third drug. St. Jude is now a collaborator on that study, which is designed for teens and young adults.

A second clinical trial opened in the spring of 2015 at St. Jude. In that study, children with hard-to-treat or recurrent Ewing sarcoma will receive the PARP inhibitor talazoparib with a standard chemotherapy drug called irinotecan.

"It's an exciting time for us," observes Beth Stewart, MD, of St. Jude Oncology, who played an important role in the project. "About 11 months after our laboratory study was completed, the clinical trial opened. In the past, it could take from five to 10 years before discoveries in the lab made it to pediatric patients. Our supercomprehensive research shortened that length of time so that the right drugs are getting to the right patients much more quickly.

"At St. Jude, there's a very nice relationship between those doing the research and those who are designing the clinical trials for patients," Stewart continues. "There are very few places that do that as well as St. Jude does. It's a true blessing for me to have the opportunity to work at such an institution—where we have such phenomenal resources and incredible collaborators right within the doors of our own hospital."



Computational biologist Jinghui Zhang, PhD, recently helped lead an international collaboration to explore the genetic landscape of Ewing sarcoma.



Another St. Jude team quickly moved their Ewing discoveries from the lab to the clinic. Those researchers included (from left) Anang Shelat, PhD, Michael Dyer, PhD, and Beth Stewart, MD.

## Pot of gold

While teams of doctors and researchers explore the mysteries of Ewing sarcoma and work to develop better treatments, Allie Johnson pursues her own activities, which are just as important to her.

Those pastimes include preparing the perfect cup of pretend tea for an unlikely group of friends.

"My brother is not invited to my tea parties," says Allie, with a mischievous smile. "Only my animals and my mom are invited. The ones who come to my tea parties are Purple Monkey and Shadow the dog, and three fake people. They're my dolls. Their names are Josey, Medium Josey and Small Josey."

When she's not hosting tea parties, undergoing treatment or attending school—she's a voracious reader—Allie spends her time building extravagant Lego creations, carefully applying makeup to her mom's face, and dreaming of the day when she can return home to Oregon. There, she will enjoy a party with her school friends, ride her bicycle, eat strawberries from the garden and get a kitten. Those simple activities are, for Allie, rewards at the rainbow's end.





When she's not hosting tea parties for Purple Monkey, Shadow the dog, and her "three fake people," Allie Johnson (at right) spends time with her little brother, Richie.

### "lam"

#### By Jaxon Hindman

I am strong and hopeful.

- I wonder how many kids are there? I hear the frustration and anger of other families and children.
- I see the pictures of survivors hanging on the walls.

I want them to find a cure.

I am strong and hopeful.

I pretend I'm Danny Thomas.
I feel his arms leaning out to hug me.
I touch my head and feel nothing.
I worry if it will ever come back.
I cry when I'm in pain.
I am strong and hopeful.

I understand what the doctors tell me. I say, "Never give up Hope." I dream one day I'll work there. I try to be strong for my family. I hope no more kids go through what I went through. I am strong and hopeful.

## Jaxon's Journey

When Jaxon Hindman fell to the floor during a dodgeball game at school last year, he lost consciousness for an instant. Then he brushed himself off and returned to class.

"My head was really hurting afterward," Jaxon recalls. Throughout the day, the pain increased. "When I went to lunch, all the noise and commotion made it hurt a lot worse."

Cresta Hindman, a nurse, suspected her son had a concussion. She and her husband were shocked when tests revealed a brain tumor called medulloblastoma. Ironically, the dodgeball accident may have saved Jaxon's life, because it led to an early diagnosis.

"We say that ball was God's divine intervention, because the ball was lightweight and should never have knocked him down," Cresta says.

Jaxon's teachers and principal signed the ball and delivered it to him during his treatment.

Now 13 years old, Jaxon returns to St. Jude for regular checkups. He is back to playing basketball and hopes one day to work at St. Jude.

# SOURCE CODE

St. Jude scientists discover the genetic basis of the side effects that sometimes accompany cancer treatment

#### By Sarah Webb

Two-year-old Skylar Ebanks loves to give and receive hugs and kisses. She reaches out to touch the faces of new people that she likes. But her short life has been a health rollercoaster.

When Skylar was just 5 weeks old, her parents noticed that her forehead was swollen and she was sleeping too much. Her family traveled from their home in the Cayman Islands to Florida for medical care.

Skylar had a brain tumor called ependymoma.

After an operation that partially removed the tumor, she traveled to St. Jude Children's Research Hospital. There, Skylar had another operation and went through an experimental course of chemotherapy to treat her cancer. Although the experimental course can involve radiation treatment, her parents were allowed to opt out of radiation due to Skylar's age.

However, shortly after starting chemotherapy, Skylar faced yet another challenge. Cisplatin, one of the drugs used to kill her cancer cells, had permanently damaged her hearing.



Skylar's mother, Mechon Ebanks, remembers the day she learned about her daughter's hearing loss.

"I cried my eyes out," she recalls. But she also knew that such setbacks can be part of the process of treating cancers effectively. Skylar's doctors changed her treatments to an alternate therapy.

St. Jude doctors and researchers have been studying genes to better understand which patients might be most likely to develop side effects from particular chemotherapy drugs. The lessons they learn could change therapies for future patients.

Knowing the gene variations that leave children susceptible to treatment side effects will help doctors address problems a child might face. That information will enable researchers to develop safer therapies. It will also help physicians choose treatment combinations that maximize the ability to fight cancers while minimizing the risk of side effects.

#### Delicate balance

Cancer therapies often include powerful drugs. Their ability to kill disease also means that they can cause unintended harm to other cells. Treatment remains a balancing act. If doctors administer too much of a therapy, it can cause damage, says Jun J. Yang, PhD, of St. Jude Pharmaceutical Sciences. "But if you don't give enough," he says, "the tumor comes back."

The ways that individuals respond to these drugs can vary widely. Researchers can trace some of those differences to the age of the patient or the dose of the drug. But even after scientists consider these factors, sometimes one patient tolerates a treatment regimen well, while another experiences a devastating side effect, Yang says.

Those findings suggest that differences in patients'



William Evans, PharmD (at right), of St. Jude Pharmaceutical Sciences, and his colleagues (from left) Kristine Crews, PharmD and Barthelemy Diouf, PhD, PharmD, found that more than half of patients who inherited two copies of a certain version of the CEP72 gene developed nerve damage called peripheral neuropathy.

genes could be important. Now that the success rates for childhood cancer treatments have improved, doctors can turn some of their attention to improving quality of life after treatment.

"These kids are often very young, and we want them to have full, productive lives after cancer therapy," Yang says.

Cisplatin remains an important drug for treating pediatric brain tumors like Skylar's. However, hearing loss is one of the most worrisome side effects. Hearing loss occurs more often in the youngest children, which can significantly interfere with language development and learning. However, Yang notes there is variability both in who experiences this side effect and in the severity of the hearing loss. movements like walking and eating with a fork and knife. The symptoms often, but not always, end after treatment, Evans says. But the pain can lead patients to delay or stop treatment before completion.

Now that St. Jude survival rates for ALL have reached 94 percent, researchers hope to lower the toxicity and improve quality of life while continuing to implement new treatments that advance cure rates closer to 100 percent.

Evans and his colleagues wanted to see if specific genes were linked to the pain and movement problems of this group of patients.

"If we found that, it may provide a way to identify the kids at greatest risk, and it also might give us some clues on how we might mitigate the toxicity," he says.

Knowing the gene variations that leave children susceptible to treatment side effects will help doctors address problems a child might face. That information will help researchers develop safer therapies.

To look for a genetic cause, Yang took a snapshot across all the genes of children in a St. Jude clinical trial whose brain tumors had been treated with cisplatin. He and his team looked for differences that occurred in the children with hearing loss. They found that changes in one particular gene, called *ACYP2*, popped up consistently in these children.

Right now scientists don't know much about what this gene does and why it is linked to hearing loss from cisplatin therapy, Yang says. But research is underway at St. Jude to answer these questions.

#### Precision medicine

Meanwhile, other studies looking at genes linked to therapy side effects are moving closer to the clinic.

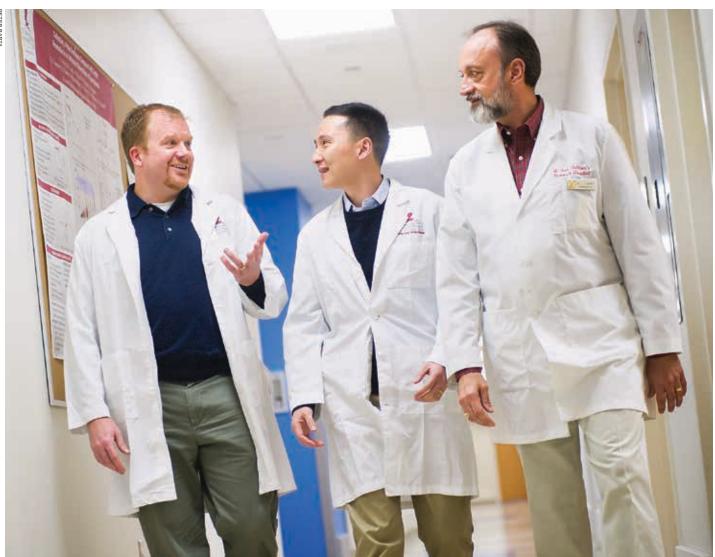
William Evans, PharmD, of St. Jude Pharmaceutical Sciences, and his colleagues recently looked at side effects from vincristine, a drug that physicians give up to 40 times during a child's treatment for acute lymphoblastic leukemia (ALL).

These side effects occur in about one-quarter of children treated for ALL, and it most often shows up as nerve damage in the hands and feet. This condition is called peripheral neuropathy. Sometimes the damage leads to pain and tingling, and it can also interfere with coordinated The scientists compared the genes from two groups of children: one group from a St. Jude clinical trial and the other group from another national clinical trial. They found that patients who inherited a certain form of the *CEP72* gene had a higher risk and greater severity of vincristine neuropathy.

In laboratory tests, Evans and his team confirmed that cells with a specific version of this gene were more sensitive to vincristine. This drug works by interfering with the same steps in cell division that the CEP72 protein contributes to—a process known as microtubule formation. Patients at highest risk of neuropathy inherited a form of the *CEP72* gene that produces lower amounts of the CEP72 protein, making them more sensitive to vincristine.

"It makes biological and pharmacological sense that these changes would make cells more sensitive to vincristine," Evans says.

Based on those results, Evans and his colleagues are planning a new clinical trial that will give children who carry this particular genetic signature doses of vincristine that are one-third lower. Their research indicates that this lower dose will be high enough to kill cancer cells but low enough to prevent nerve damage in the hands and feet.



#### Continued support and care

Although the ongoing research may not help Skylar regain her hearing, Mechon is grateful that what St. Jude researchers are learning could help future children with pediatric brain tumors. Since Skylar's treatments, the little girl has been learning to live with her hearing loss. Her family has nicknamed her hearing aid "Roger," and "he" helps her experience the sounds that surround her. Her hearing loss has slowed her learning and development, Mechon says. At home in the Cayman Islands, Skylar participates in music and speech therapy weekly as part of her ongoing recovery.

In addition, Skylar and Mechon will spend eight weeks at St. Jude this summer for an intensive therapy program tailored to Skylar's developmental needs.

"St. Jude isn't just looking at cancer treatment," Mechon says. "They're also looking at post-treatment and paying attention to quality of life." ■ Researchers (from left) Giles Robinson, MD, Oncology; and Jun J. Yang, PhD, and Clinton Stewart, PharmD, of Pharmaceutical Sciences; found that variations in a gene named ACYP2 were associated with as much as a four-fold greater risk of cisplatin-related hearing loss.

# SIFTING NEEDLES FROM HAYSTACKS

First, St. Jude pioneered a test that could pinpoint one leukemia cell among 10,000 normal cells. Now that test is helping guide therapy—with spectacular results.

#### By Jon W. Sparks

One of the challenges in treating cancer is figuring out how intense the treatment should be for a patient.

A team led by Ching-Hon Pui, MD, Oncology chair at St. Jude Children's Research Hospital, recently demonstrated that measuring the number of leukemia cells in patient bone marrow early in treatment can help determine how intense the chemotherapy needs to be for patients with acute lymphoblastic leukemia (ALL).

"This is the most powerful way to identify high-risk patients who need more intensive therapy. It also helps us avoid over-treating low-risk patients," Pui explains.

The procedure evaluates a patient's response to treatment. The test measures minimal residual disease (MRD)—the number of leukemia cells that remain during and after the first phase of treatment, which is called remission induction therapy. MRD testing is done on the 19th and 46th days of induction treatment when, Pui says, "we can identify patients who will have very, very good treatment outcomes without intensive therapy."

Those patients can receive low-intensity therapy, which lowers the risks of treatment-related side effects.

Children with higher MRD results require more intensive therapy for cures. Thanks in part to this method, 94 percent of children with ALL survive their disease.

St. Jude is the first hospital to pioneer the use of MRD to help guide treatment.

#### A crisis and a plan

For 8-year-old Gayatri Linga, the test provided good news and helped doctors plan the best course of treatment.

In mid-October of 2013, Gayatri had begun complaining of pain in her legs. Although her dad, Vijay, is an oncologist in Hyderabad, India, he did not suspect cancer in his own child.

"I've seen many sick children at the hospital," he

says, "and she was not having those signs. No continuous fever, no bleeding, no spots."

Gayatri had just gotten over chicken pox. A doctor suggested the complaints were due to a postviral infection. "After four to five days, she had bleeding from her nose so heavy we couldn't stop it," recalls Gayatri's mom, Saritha.

A blood test revealed ALL.

"My husband knew about the survival rates at St. Jude," Saritha says. "He knew that it had the best survival data for leukemia. So he wanted to get her treated there."

#### Welcome discovery

After obtaining a referral, Gayatri and her parents made the 30-hour flight to Memphis, Tennessee. Much uncertainty remained. The family knew that St. Jude was the best place to go, yet they did not know much else about the hospital.

Gayatri's parents were so concerned about getting her to St. Jude and into treatment that they had not thought about how they were going to manage the costs.

"After the third day, the doctors were discussing my daughter's case and they said, 'You will not pay; the treatment is provided at no cost to you," Saritha says. She and her husband were stunned and relieved to realize that donors from around the world had made their St. Jude experience possible.

"Until I came here, I never knew that the treatment quality someone could get would be so good," Vijay says.

#### Sweet remission

The MRD test showed that Gayatri was a candidate for standard-intensity therapy. For two-and-a-half years, she will continue to receive treatment every week. Her parents are optimistic.

"Now she is in remission; now she is cancer free," Saritha says.

A St. Jude study about MRD published in the journal *Lancet Oncology* showed that MRD testing twice, instead of multiple times during the 2.5 years of treatment, was enough to guide therapy. Not only does that save money, but it also helps children avoid the discomfort and risk of repeated bone marrow aspirations.

The MRD test can detect even one leukemia cell among 10,000 normal cells. But that's not good enough for Pui and his team.

They plan to further fine-tune the test, so that hospitals



This is the most powerful way to identify high-risk patients who need more

intensive therapy. It also helps us avoid over-treating low-risk patients.

-Ching-Hon Pui, MD, Oncology chair



Gayatri Linga

worldwide can use it to separate high-risk patients from those who can be cured with lower levels of treatment. Pui and his colleagues hope the use of MRD tests can also extend beyond children to adults.

"Research is needed to determine if even more sensitive methods of MRD measurement can improve our precision in predicting outcomes," Pui says. "It is also important to develop simple methods that maintain or increase the reliability and can be readily extended to all laboratories and, hence, all patients."

# Signs and Sub

For decades, the genetic basis of pediatric melanoma was a mystery. But St. Jude scientists recently discovered the molecular signatures of three pediatric melanoma subtypes.

By Chris Lewis

It was supposed to be a routine physical—nothing out of the ordinary. But that all changed when Summer Bate's family physician discovered something unusual: a large mole on her upper back.

The eighth-grader had known about the mole for years, but had never given it a second thought. Summer's physician encouraged her to visit a dermatologist as soon as possible. Summer's mother, Kristy Harvey, scheduled the appointment. But when Summer got the chance to travel to Colorado, the appointment was cancelled.

Neither Summer nor her mom thought of the mole again until several years later, when the teen noticed that a white ring had developed around the spot. Nearly four years after the original appointment had been cancelled, she finally visited a dermatologist.

A biopsy revealed melanoma, the most dangerous type of skin cancer. Summer was only 17 years old.

"It was a complete shock," Kristy says. "Summer always used sunscreen and was the first person in our family to ever be diagnosed with melanoma."

#### Melanoma on the rise

Pediatric melanoma is quite rare, even for blonde girls with pale skin like Summer.

In fact, on average, only 400 people in the U.S. aged 19 or younger are found to have melanoma each year, according to the National Cancer Institute. Unfortunately, this incidence rate has risen steadily in recent decades, by upwards of 2 percent annually, primarily in those ages 15 to 19.

To better understand pediatric melanoma and improve treatment, Alberto Pappo, MD, and Armita Bahrami, MD, of St. Jude Oncology, led research to improve understanding and treatment of the three most common subtypes. The effort was part of the St. Jude Children's Research Hospital – Washington University Pediatric Cancer Genome Project, which used nextgeneration, whole genome sequencing to determine the molecular signatures of pediatric melanoma for the first time.

#### Banning the rays

Scientists studied 23 melanoma patients, who were between 9 months and 19 years old. The investigators focused on a pediatric melanoma subtype that is identical to adult melanomas when viewed under the microscope. They also examined a subtype that arises in large moles present at birth, as well as a spitzoid melanoma subtype, which is often difficult to diagnose.

"We found that conventional melanoma is essentially the same disease in children and adults, with DNA changes caused by sun damage," Pappo says. "Most of those patients carry a mutation of the *BRAF* gene, which is similar to the melanoma of many adult patients."

He says these findings further emphasize the importance of adopting

# types

sun protection habits at a young age.

The team also noticed that children and teens who were born with large moles had a mutation in a gene known as *NRAS*.

"Although this type of melanoma is rarer, it is usually very aggressive and difficult to treat," Pappo explains. "But treatment options may improve, since we have now targeted a gene mutation that each of those patients had."

#### **Predicting spitzoids**

In the meantime, the behavior of the most common subtype of pediatric

melanoma, spitzoid, is especially challenging to predict.

"Childhood spitzoids are typically not as aggressive as conventional melanomas, so perhaps they should not be treated as aggressively as conventional melanomas are," Bahrami observes. "Still, some of them have an unpredictable course and can be aggressive."

Bahrami identified a genetic marker known as a *TERT* promoter mutation. This discovery may help scientists pinpoint children who have the aggressive type of spitzoid that requires more intensive therapy.

The recent St. Jude findings make Pappo optimistic that young melanoma patients will be included in the pipeline of new drugs much earlier than they are currently.

"We need to make it easier for young people to try promising treatments that are being studied in

More than 9 out of 10 young patients with conventional melanoma had DNA changes caused by sun damage. St. Jude scientists emphasize that sun protection must start early and should be a lifelong habit. adults," he says. "Clinical trials should start including younger patients who have conventional melanoma as well, since our study has demonstrated these patients share many genomic similarities, when compared to adult patients."

#### Made in the shade

Summer says her experiences with pediatric melanoma have ultimately been positive. Her tumor was surgically removed at St. Jude more than three years ago. She also received interferon therapy for 36 weeks. Then a new melanoma lesion developed, which was surgically removed.

Summer's disease has been in remission since August of 2012.

She completed her final semester of high school through the St. Jude School Program. Currently, she is in college, pursuing her goal of becoming a sign language interpreter.

"My experiences at St. Jude have definitely changed my life," Summer says. "I have learned to not take anything for granted. You never know what can happen, so you need to live every day the best you can and stay as positive as possible."



Pediatric melanoma survivor and aspiring sign language interpreter Summer Bate teaches sign language to her oncologist, Alberto Pappo, MD, during a recent checkup. Facing page: How to sign the word "hope."



Pappo and Armita Bahrami, MD, of St. Jude Oncology, discuss their recent discoveries, which shed new light on melanoma's three most common subtypes.



#### By Kerry Healy

The proceeds from the sale of a rare, limited-edition sports car are helping St. Jude Children's Research Hospital in its race to find cures for children battling cancer and other lifethreatening illnesses.

The 1953 Fiat 8V Super Sonic was auctioned in 2011 for the benefit of the children of St. Jude by the oldest son of the late Benny Caiola.

Caiola, who was widely known for owning one of the world's most extensive collections of Ferraris and other Italian sports cars, immigrated to the United States at age 17 from

## to save Lives

his small village in Sicily at the end of World War II. Benny worked his way up from construction work to owning one of the most successful real estate development companies in Manhattan. He never forgot his humble beginnings and remained a gracious and giving person to all who knew him.

Today, his sons and daughter operate the family business and continue their father's compassionate and benevolent example. When Benny passed away from cancer in 2010, his son and namesake, Ben Caiola III, decided to honor his life by helping the children of St. Jude.

The rare Fiat was purchased at auction for \$1.7 million, which Ben is using to fund and name the SIM CT suite in the St. Jude Chili's Care Center, where children receive computerized tomography scans that help doctors to identify and analyze the most intricate details of a child's cancer.

"I know my father would want me to do this," Ben says.

In May 2013, he and his stepmother, Bettina, visited St. Jude to see the plaque honoring his late father and mother and recognizing his contribution. "I have no words. It was overwhelming to see the children who are getting treatment, yet at the same time smiling, happy and playing. We love what St. Jude does. No costs are incurred by the sick child, and the families are taken care of, which is amazing to me," Ben says.

The inscription on the plaque reads: "In honor of Benny Caiola, Jr. and Rose Caiola. May their compassion bring health and happiness to those who walk these halls."

"My parents taught us that we are here to help people in need," Ben says. "I feel so grateful that I am able to do this."



The auction of a 1953 Fiat 8V Super Sonic generated funds that are being used to fund and name the Chili's Care Center SIM CT suite. Touring the hospital are (above, left) Ben Caiola III and his stepmom, Bettina.

#### *stjudeatwork.org* helps companies who want to include St. Jude in their workplace giving programs.

By Leigh Ann Roman

# **IECTING** to St. Jude at work



Brett Guzdziol is an employee champion for St. Jude at his employer, Zurich North America.

#### Encourage your workplace to support the hospital: **visit** *stjudeatwork.org*

Brett Guzdziol can thank his mother and a dedicated doctor for the opportunity to grow up with one of his best friends—his sister, Mikayla.

Mikayla was born with an acute respiratory virus. Several doctors said nothing could be done for the baby. But her mother persisted and found the doctor who cured Mikayla.

"She is one of my best friends, and I can't imagine growing up without her," Guzdziol says.

When he learned that his employer, Zurich North America, offered the opportunity to donate to charity through a workplace-giving program, he knew he wanted to support a charity for health care or children.

"St. Jude does both, and it was a perfect fit," he says.

Zurich is one example of how companies across the U.S. support St. Jude through employee giving and matching company gifts.

A recent addition to the St. Jude employee giving program is *stjudeatwork.org*, a website that provides information and a virtual toolkit for companies who want to include St. Jude in their workplace giving programs. The site, which includes input from Zurich employees, offers engaging ideas for fundraising at work, including bake sales, a fun run at the office, an ugly sweater contest and an office trivia competition.

Zurich selects an executive champion and two employee champions to promote each of its core charities. Guzdziol, 28, is an employee champion for St. Jude. In that role, he visited St. Jude where he was "blown away" by what he saw, although he had read about the hospital's pioneering research and exceptional care.

"St. Jude goes to extreme efforts to ensure that the kids still have a childhood and that their families can remain close during that time. That was what left me so inspired," he says. "That is what sets St. Jude apart from any other charity."

St. Jude is the No. 1 charity supported through Zurich's A Time For Giving campaign, says Andrea Davis, program manager for community investment at Zurich.

"The idea of helping provide sick children with innovative treatments that will give them the best chance to live a full, healthy life—in an environment where the family is supported—makes it a natural draw for many Zurich employees to support St. Jude," Davis says.

Working together to help St. Jude children also builds employee relationships. "One thing I didn't expect when I started doing this was the feeling of

connectedness with other colleagues," Guzdziol says. "It's a nice benefit."

## Research Highlights

#### **Taylor named Howard Hughes Medical Institute investigator**

J. Paul Taylor, MD, PhD, chair of St. Jude Cell and Molecular Biology, has been selected as a Howard Hughes Medical Institute (HHMI) investigator. He is one of 26 scientists nationwide chosen for the recognition from more than 1,000 applicants. There are approximately 330 HHMI investigators in the United States, and Taylor will become the fourth of these investigators currently working at St. Jude.

Investigators selected for the program by HHMI are some of the country's top biomedical researchers, demonstrating creativity, innovation and excellence in their areas of study. Taylor is an expert in the fields of cell and molecular biology, neurological diseases and genetics.

"In science, really big payoffs come when you stick your neck out," Taylor said. "HHMI support will allow my team to be creative and take chances, which will hopefully lead to ground-breaking scientific contributions. I am honored to be named an HHMI investigator, and am looking forward to collaborating with the other investigators to further advance scientific innovation."



Taylor joins St. Jude researchers Charles Sherr, MD, PhD, Brenda Schulman, PhD, and Michael Dyer, PhD, in holding HHMI investigator designations. Taylor begins his appointment in September.



#### A lifetime of achievement

Winfred Wang, MD, of St. Jude Hematology, is the recipient of the 2015 American Society of Pediatric Hematology/Oncology Distinguished Career Award. A gifted physician and noted investigator, Wang conducts research on blood disorders such as sickle cell disease. He joined St. Jude in 1979. This national award recognized Wang for the dramatic impact he has made on the field through his research, education, patient care and advocacy.

#### Scientists find defects caused by brain tumor mutations

Understanding how genetic changes disrupt cell function is a key step in developing better cancer treatments. Researchers use the details to target defects that support cancer cells. The goal is to create precise treatments that save lives with fewer side effects.

Scientists from St. Jude joined forces to find defects caused by two mutations in the DDX3X gene.

The findings built on earlier work from the St. Jude Children's Research Hospital – Washington University Pediatric Cancer Genome Project. That study found that *DDX3X* is often altered in patients with medulloblastoma, particularly those with the WNT subtype of the brain tumor.

Medulloblastoma is the most common childhood brain tumor. For decades, doctors treated medulloblastoma as a single disease, even though it has four different subtypes. Thanks in part to St. Jude researchers, that is changing. The latest findings may help advance those efforts.

"The defects we found could provide the basis for

developing specific therapies for patients with these mutations," said Eric Enemark, PhD, of St. Jude Structural Biology.

He and Janet Partridge, PhD, Pathology (pictured with Enemark above), led the research. The study appeared in the Journal of Molecular Biology.

#### Preserving the power of glucocorticoids to fight leukemia

Steroids called glucocorticoids are part of chemotherapy that has transformed treatment of the most common childhood cancer. Today 94 percent of St. Jude patients with acute lymphoblastic leukemia (ALL) will become long-term survivors. But those whose cancer cells are resistant to steroids may not fare as well.

St. Jude scientists searched the cancer genomes of ALL patients to find out how some leukemia cells could resist steroids.

In leukemia cells that resisted the drugs, the genes *CASP1* and *NLRP3* were more active. *NLRP3* 

makes a protein that works like an "on" switch for *CASP1*. When scientists reduced *CASP1* activity, the steroids worked better against leukemia cells. Scientists also found out why extra *CASP1* helped cells resist the drugs.

"The search is on to find small molecules that could help reverse glucocorticoid resistance," said William Evans, PharmD, Pharmaceutical Sciences. "Glucocorticoids are used to treat asthma, rheumatoid arthritis, colitis and other autoimmune disorders, so these results may benefit a wide range of patients."

The study appeared in the journal Nature Genetics.



## Perspective

### The Beauty of Giving

"Any little thing I can do to help a child is a beautiful gift," says supermodel and actress Lily Aldridge.

#### By Lily Aldridge



Lily Aldridge models the T- shirt she designed to benefit St. Jude during last year's Childhood Cancer Awareness Month.

My two-and-a-half year old daughter is the light of my life, my little angel. She's a little firecracker. Right now, she's all about arts and crafts. There's glitter all over our house all the time, but it's the best, most beautiful glitter I've ever seen.

Anything to do with children has always touched me deeply. And any little thing I can do to help a child is a beautiful gift.

Several years ago, my husband [Kings of Leon frontman Caleb Followill] and I decided we should visit St. Jude Children's Research Hospital. It was an emotional, amazing and eye-opening experience: seeing how state-of-the-art everything is, the incredible care the children get, and how happy and vibrant the facilities are.

We learned that a parent does not pay one bill, not one airfare, not one meal for their child. Every little detail was planned so that a family had nothing to worry about but getting their child better.

We went into one of the research facilities, and a scientist told us, "We're researching this rare cancer. There's not much known about it, because it's so rare that researching it wouldn't be profitable for pharmaceutical companies."

I was shocked.

Then the scientist told us, "All the research we're doing for this cancer is public, so other hospitals use that information. We're trying to get this cancer eliminated, so it doesn't exist anymore."

Since that visit, my husband and I have done what we can to help. A portion of the ticket sales from his band goes to St. Jude. And each time I have an opportunity to represent a charity, I always pick St. Jude. I've never found a charity that does more important work than St. Jude. It makes my life happier knowing that I can do something to help.

The care and love and hard work that St. Jude puts into eliminating cancer are so important. You might think, "It's just a dollar, and what can a dollar do?" But a dollar from a million people is a huge donation. It's life changing. It will save lives.

Supermodel and actress Lily Aldridge has supported St. Jude in numerous ways, ranging from participating in *St. Jude Give thanks. Walk.* and providing social media support to designing a clothing line whose sales benefited the hospital. "I knew that I wanted to help St. Jude continue its lifesaving mission, so that the children and their parents could realize their dreams."

-Nora Martinez

### Your gift gives back.



St. Jude patient Charlee at age 3 myelodysplastic syndrome

#### Meet your financial needs and help the children.

By including St. Jude in her estate plans, Nora Martinez is providing for her loved ones and helping to ensure that the lifesaving work of St. Jude doesn't stop until no child dies from cancer. Her legacy of compassion will continue to carry her values forward for future generations.

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





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#### Hope through change

Two-year-old J'mari Caldwell greets one of more than 500 monarch butterflies that fluttered into a clear, blue sky during Ependymoma Awareness Day at St. Jude. The event is designed to raise awareness about ependymoma—a rare cancer of the brain or spinal cord that affects both children and adults.

The event was a collaboration between St. Jude and the Collaborative Ependymoma Research Network (CERN) Foundation. CERN is a dedicated group of scientists and adult and pediatric neuro-oncologists working in concert to find a cure for ependymoma.



## Finding cures. Saving children.