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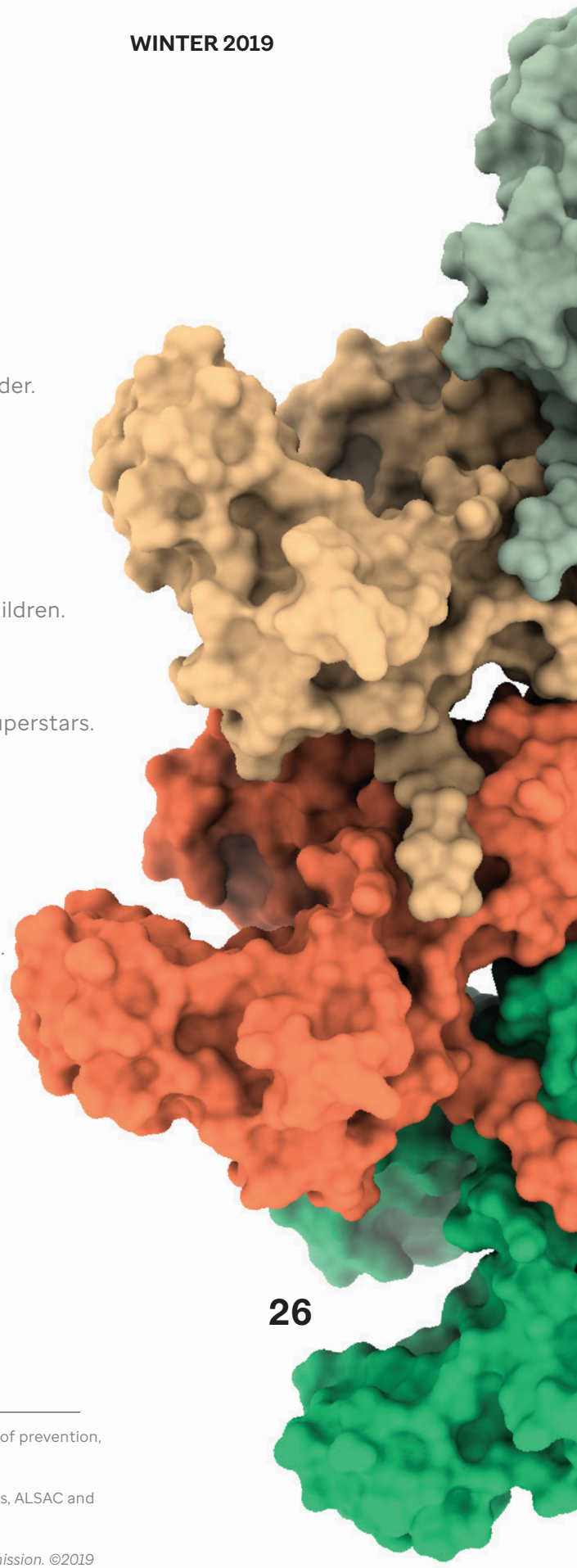

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The mission of St. Jude Children's Research Hospital is to advance cures, and means of prevention, for pediatric catastrophic diseases through research and treatment.

On the cover:
Photo of Graham Robertson by Seth Dixon

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SHARING SMILES

Foundation supports St. Jude care and research.

By Zack McMillin

For Philip Wenk, appreciation for the mission of St. Jude Children's Research Hospital began 45 years ago when he was a student at the University of Tennessee College of Dentistry.

St. Jude had recently announced a dramatic increase in childhood leukemia survival rates and a major hospital expansion was underway.

"It really had that startup feel," Wenk recalls.

Now, as president and CEO of Delta Dental of Tennessee, Wenk marvels at what generous people across the nation have helped build.

"I tell my friends, 'You need to tour St. Jude,'" Wenk says. "When I walk through St. Jude, I get that tingle in my back, because you know you are in the presence of greatness."

Delta Dental and the company's Smile180 Foundation have provided about $2 million in support of treatment, research and awareness:

- **Support for the hospital's onsite dental clinic**, including a renovation, helps St. Jude control and minimize patients' dental problems.
- **A $1 million gift for the St. Jude Graduate School of Biomedical Sciences** helps ensure the training of tomorrow's scientists.
- **Sponsorship of several St. Jude events**, including benefit concerts This Show Saves Lives and the St. Jude Jam, raises funds and awareness for the hospital.

Because Delta Dental and Smile180 have helped increase access to dental care in underserved communities, Wenk identifies closely with the hospital's commitment to freely share its research.

"It sends the message to the world: Don't hide your light under a basket," Wenk says. "When people think about giving to St. Jude, I hope they think about everything St. Jude is giving to the world."

Wenk's son survived non-Hodgkin lymphoma as a young man. Having seen firsthand how those medical bills added up, Wenk says it means the world that families never receive a bill from St. Jude.

"I know these parents are so scared of their child dying," Wenk says. "To know there is no cost for treatment has a huge effect on their psyche. Instead of worrying about finances, they can focus on helping their child heal." ■

Learn how to include St. Jude in your charitable goals and financial plans: Call 1-800-910-3188 or email giftplanning@stjude.org.

Science Alliance

Married St. Jude researchers broaden collaboration to develop a novel medication for PKAN, a life-threatening neurological disorder.

By Maureen Salamon

They finish each other's sentences, so perhaps it's not surprising that the lab discoveries of scientists and spouses Charles Rock, PhD, and Suzanne Jackowski, PhD, are complementary.

For nearly 40 years, the couple has carefully choreographed experiments in the Infectious Diseases department at St. Jude Children's Research Hospital. Their recent work mobilized four labs in three departments to create a new

More than chemistry

Suzanne Jackowski, PhD, and Charles Rock, PhD, united colleagues across St. Jude to develop a treatment for PKAN, a devastating disease with no effective treatment. "We really like the project because it blazes new ground, but in the end, getting something to help kids is wonderful," Rock says.

medication for a devastating neurological disorder that strikes only three of every 1 million people.

Known as PKAN, or pantothenate kinase-associated neurodegeneration, the progressive, life-threatening disease has had no effective treatment. The disorder typically develops in toddlers and can be misdiagnosed as epilepsy or muscular dystrophy.

Rock and Jackowski doggedly characterized the enzymes that are key to triggering PKAN and discovered how they are regulated.

Inspirations for the research

Jackowski paints a poignant picture of young PKAN patients she's met through advocacy groups and clinical centers in the U.S. and Europe.

"They continue to smile through their disabilities," she says. "They keep trying to participate even when they can't say the words they try to vocalize. When they raise their hands, they can't control their arms.

"Many of these children have a hard time telling jokes but still laugh at their own jokes," she continues. "They're not shy; they're just like the kids at St. Jude. Their positive attitude is amazing."

Discovery leads to treatment

Moved by the plight of young patients struggling to walk, speak and swallow, Jackowski, Rock and their collaborators have developed a treatment that raises hopes of easing symptoms and extending the lives of PKAN patients.

"It's a brand-new mechanism of action that's never before been described," says Jackowski, who, like Rock, joined St. Jude in the early 1980s.

"We really like the project because it blazes new ground, but in the end, getting something to help kids is wonderful," Rock says. "We think it's a significant achievement, and everyone on the team is really pumped."

Oil shortage

Thought to occur when nerve cells lack enough coenzyme A (CoA), PKAN results from mutations in the *PANK2* gene. The shortage of CoA in the body is a problem that can't be overstated, according to the scientists.

"It's so intertwined with central energy metabolism," Jackowski explains.

"It's the universal oil that lubricates the engine of life," Rock adds.

The twosome joined forces with colleagues in the Structural Biology and Chemical Biology and Therapeutics departments to outline a novel treatment approach to increase those CoA levels.

Search for the perfect drug

The team, which included Stephen White, DPhil, and Richard Lee, PhD, developed a class of small molecules called pantazines. The molecules activate the other PANK proteins to compensate for the missing CoA. But first, the researchers spent several years weeding out medications that weren't good candidates. The team scoured the St. Jude library of more than 500,000 drug-like molecules to find those that might be effective.

To qualify, a drug had to check several key boxes: be able to cross the blood-brain barrier to reach affected nerve cells, work in pill form and cause few side effects. The drug also needed to activate enzymes instead of inhibiting them – which happens to be the opposite effect of most available drugs, Rock says.

"It was a big chore," he recalls. "This isn't a cure that corrects the genetic defect; this is a bypass of that genetic defect. The plan from the beginning was for patients to be on this drug for the rest of their lives."

High hopes for helping kids

Structural biologists at St. Jude showed that compound PZ-2891 temporarily locks PANK in the "on" position to promote CoA production in cells.

St. Jude patented the pantazines for use in treating CoA disorders, and planning has begun for clinical safety trials.

Rock and Jackowski say they're gratified their work may help PKAN patients and their families desperately hoping for successful treatments,

"We were provided the resources here at St. Jude to pursue this work and try to make a difference in their lives," Jackowski says. "Hopefully we'll be able to help a lot of kids." ■

Watch video: bit.ly/science-alliance

LOCATION, LOCATION, LOCATION.

The greatest predictor of survival for a child with cancer is where that child happens to live. St. Jude and World Health Organization join forces to change that sobering fact.

By Karlisa Cryer

PHOTOS BY JERE PAROBEK

Progress toward the goal
"St. Jude hasn't finished what we started in 1962, so we are continuing to work toward that goal of a day where no child should die in the dawn of life," says Carlos Rodriguez-Galindo, MD (at right), St. Jude executive vice president and Global Pediatric Medicine chair, shown with Gabriel Alessandro Mayorga Hernandez.

As an 11-year-old living in the capital city of El Salvador, Gabriel Alessandro Mayorga Hernandez was an avid soccer player. One day, he suddenly lacked the energy to complete a match. A doctor's visit revealed he had acute lymphoblastic leukemia.

Flash forward to September 2018, as Gabriel, now a healthy 16-year-old, takes center stage at a United Nations General Assembly meeting — part of a momentous announcement between St. Jude Children's Research Hospital and World Health Organization (WHO).

Gabriel's astounding recovery is due in part to the fact that St. Jude forged partnerships with El Salvador's government and nonprofit sector long before his birth. As a result, the survival rate for childhood cancer in that country has skyrocketed.

Now, St. Jude and WHO have launched an effort with an ambitious goal: to cure at least 60 percent of the children with six of the most common cancers by 2030.

"It's a daring dream, but one that's within our reach. In science and medicine, collaboration is the engine that drives progress," says James R. Downing, MD, St. Jude president and chief executive officer. "Imagine what great feats we can achieve together, working across disciplines, across borders and around the world.

"Together, we will give children the best hope for their futures — no matter where they live."

Hope for all children
St. Jude National Outreach Director Marlo Thomas addresses participants gathered at the United Nations headquarters.

Answers to a global problem

Several years ago, St. Jude leadership took stock of the state of childhood cancer care by asking a simple question: How do we accelerate progress? They looked for gaps in knowledge and opportunities to advance care for childhood cancer and other deadly diseases.

What did they learn?

The greatest predictor of survival for a child with cancer is where the child happens to live.

Globally, the figures are staggering. Each year, more than 300,000 children and adolescents are diagnosed with cancer. Most children in developed countries, such as the United States, survive their disease. But 80 percent of children worldwide live in low- and middle-income countries.

In those areas, less than 20 percent survive.

Downing and Carlos Rodriguez-Galindo, MD, St. Jude executive vice president and Global Pediatric Medicine chair, created a blueprint for transforming those odds. The program is called St. Jude Global.

Partnership to save young lives

St. Jude Global develops multi-faceted networks to improve access to care, enhance quality of care and create sustainable infrastructures worldwide. The hospital's global efforts have been enhanced by joining forces with WHO, an entity with the standing, history and expertise to further expand reach and impact.

The first step of this partnership occurred in March 2018, when WHO named St. Jude as its first Collaborating Center for Childhood Cancer.

Six months later, leaders from St. Jude and WHO met at the United Nations to announce the global childhood cancer initiative.

Fulfillment of a dream

The global childhood cancer partnership will combine St. Jude expert technical support and resources with WHO authority working with governments and leaders across health systems regionally and globally.

"Our new endeavor with WHO brings together the strengths of the two organizations to expand services, capacities and partnerships for tackling childhood cancer," Downing explains. "It's my hope that by uniting St. Jude, World Health Organization and our global partners, we can transform the international landscape of childhood cancer – and save many more lives of children, now and for years to come."

Rodriguez-Galindo says the new initiative allows the hospital to take the logical next step toward fulfilling its mission.

"St. Jude was established by the entertainer Danny Thomas more than half a century ago," he says. "The son of Lebanese immigrants, he had a unique perspective on our responsibility to one another. It doesn't mean we need to restrict our efforts and our vision to children in Memphis, Tennessee, or the United States. St. Jude hasn't finished what we started in 1962, so we are continuing to work toward that goal of a day where no child should die in the dawn of life." ■

> "Imagine what great feats we can achieve together, working across disciplines, across borders and around the world."
>
> *– James R. Downing, MD*

Collaborating to cure
James R. Downing, MD, St. Jude president and chief executive officer, and HRH Princess Ghida Talal of Jordan discuss the World Health Organization collaboration.

Cancer Chameleon

Is a chameleon blue or green or both? Is a rare leukemia AML or ALL?

Mixed-phenotype acute leukemia shows its true colors, thanks to St. Jude research.

By Jane Langille

When 16-month-old Graham Robertson began taking two naps per day and eating a bit less, Holly and Colby Robertson took note, but their son otherwise seemed fine. Then one day during a grocery outing, Graham pinched his finger and tried to scream, but passed out instead.

"That was our big sign something was wrong," Holly says.

The couple rushed Graham to the Children's Hospital at Saint Francis in Tulsa, Oklahoma, a clinic affiliated with St. Jude Children's Research Hospital.

"They said Graham had a rare leukemia," Holly recalls, "and flew us to Memphis two days later."

Kaleidoscope of features

Graham had mixed-phenotype acute leukemia (MPAL), a subtype that accounts for only 2 to 3 percent of all acute leukemia cases.

The best treatment for MPAL has puzzled the medical community because the disease has aspects of both acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). Just as a chameleon morphs from blue to green, the features of MPAL can change with time or treatment, enough to switch the diagnosis from one acute leukemia to the other.

Long-term survival for children with MPAL is 50 to 75 percent, compared with about 94 percent for ALL and 65 to 75 percent for AML.

"Selecting the right treatment is important," says St. Jude oncologist Hiroto Inaba, MD, PhD. "If we treat ALL with AML therapy or vice versa, patients do not do as well as we would hope."

ALL treatment involves less intensive chemotherapy for two to two-and-a-half years. By contrast, AML treatment requires more intensive chemotherapy over about six months. About a third of children with AML require bone marrow transplants.

Finding the best treatment

When the Robertsons arrived at St. Jude in August 2016, Inaba and other investigators were already collaborating on an international study examining whether patients with MPAL experienced better survival rates with ALL or AML therapy. The data, published in the journal *Blood*, indicated outcomes were superior with treatment traditionally used for ALL.

Researchers have proposed updating World Health Organization's classifications of **acute leukemia** to include three new MPAL subtypes, including the two identified in this study.

High spirits, high hopes

Thanks to St. Jude research, Graham Robertson and other children with rare, high-risk leukemias have more reasons to smile.

PHOTOS BY SETH DIXON

Chuckles, giggles and grins

Three-year-old Graham Robertson shares a laugh with his clinical fellow, Dave Cervi, DO, PhD.

Conferring about cures

Jeffrey Rubnitz, MD, PhD (at left), and Thomas Alexander, MD, joined Hiroto Inaba, MD, PhD, and Charles Mullighan, MD, MBBS, in discovering the genetic basis of mixed-phenotype acute leukemia.

The researchers **identified genetic mutations** defining the two most common subtypes of MPAL. Until this study, the genetic basis of these subtypes had been unknown.

Jeffrey Rubnitz, MD, PhD, chief of the St. Jude Leukemia/Lymphoma Division, started Graham on ALL therapy.

"We were scared, but Dr. Rubnitz gave us confidence," Colby says. "He told us to take things one step at a time with the less-invasive approach and see how Graham responds."

True colors

In another international study, St. Jude researchers including Inaba; Rubnitz; pathologist Charles Mullighan, MD, MBBS; former clinical fellow Thomas Alexander, MD, and others helped uncover the genetic underpinnings of MPAL.

"We discovered progenitor cells that can turn into either myeloid or lymphoid cells," Mullighan says. These newly identified "immature" blood stem cells explain why MPAL cancer cells can have both myeloid and lymphoid features.

In a 2018 paper, published in the journal *Nature,* the investigators also reported genetic mutations defining the two most common subtypes of MPAL called B/myeloid and T/myeloid. Until this study, the genetic basis of these subtypes had been unknown.

The scientists found that some children with MPAL may benefit from targeted therapies already in existence.

"We see only two or three cases of MPAL each year at St. Jude," Inaba says. "Through these internal and international collaborations, we have been able to conduct much larger studies and discover important insights to help us optimize treatment plans for these children."

As a result of this study, St. Jude will continue its collaborations with the Children's Oncology Group, which is formally examining MPAL outcomes using ALL therapy and its relationship to genomic features. Researchers have also proposed updating World Health Organization's classifications of acute leukemia to include three new MPAL subtypes, including the two identified in this study.

Graham had B/myeloid MPAL with an *MLL* gene rearrangement. A couple of

months after he began ALL therapy, his minimal residual disease was negative, confirming Graham was on the best treatment path.

Bright future

Graham receives weekly treatments in Oklahoma, at the St. Jude Affiliate Clinic at The Children's Hospital at Saint Francis. He returns to Memphis for milestone checkups. Soon, his 120 weeks of ALL therapy should be complete. With the cancer in remission, Graham's prognosis is promising.

Like many 3-year-olds, Graham has a big imagination. When he's at St. Jude, he likes to wave to the statue of hospital founder Danny Thomas. At home, he "cooks" for his parents with toy vegetables and sings "Johnny B. Goode" while playing his toy guitar.

Thanks to St. Jude international research, more children like Graham with rare, high-risk leukemias are getting back to their lives and looking forward to more promising futures.

As Chuck Berry might have sung, "Go, Graham, go, go!" ■

What is mixed-phenotype acute leukemia?

Mixed-phenotype acute leukemia (MPAL) incorporates features of two forms of leukemia: acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). The term "mixed phenotype" means "both types."

- MPAL is rare: Only 2-3% of all acute leukemia cases are MPAL.
- It can change from MPAL to AML or ALL, or vice versa.
- It grows very quickly.
- It can be hard to treat.
- The survival rate is 50–75%, compared with about 94% for acute lymphoblastic leukemia.
- St. Jude scientists recently discovered the mutations that cause MPAL's two most common subtypes.
- The mutations occur early in blood cell development.
- Researchers from St. Jude also found why MPAL has both myeloid and lymphoid features.
- Based on these findings, clinicians will be able to design more effective treatments for children with MPAL.

Investigators discover how guardian T cells help combat flu in infants and young children.

FLU FIGHTERS

By Mike O'Kelly

It may start with a runny nose that leads to a cough. Then a fever and the aches slowly settle in – a multitude of unwelcome symptoms that by themselves are enough to raise concern in the parents of an infant. When Liz Carter's 5-month-old daughter, Morgan, developed these symptoms in 2016, Liz suspected Morgan had the flu.

A visit to the pediatrician confirmed her suspicions. The doctor prescribed Tamiflu, and the combination of early administration of the medicine and rest helped Morgan recover quickly in a few days.

"I kept her at home and just kept her warm, trying to comfort her until she got well," Liz says.

Because Morgan was not yet 6 months old – when most babies are able to receive their first flu vaccination – she was especially vulnerable to flu. Liz was also concerned because Morgan has sickle cell disease, for which she receives treatment at St. Jude Children's Research Hospital.

Kids with sickle cell disease and other disorders have an elevated risk for flu-associated death.

Morgan was fortunate. Each year, hundreds of U.S. children die of influenza. According to the Centers for Disease Control and Prevention, the 2018–2019 flu season already has the highest number of flu-related deaths in children since national reporting began.

Paul Thomas, PhD, of St. Jude Immunology, and his colleagues are working to better understand how the immune system helps infants battle this dangerous disease. The findings may help clinicians save more lives.

ANN-MARGARET HEDGES

Risky business
Liz Carter vividly remembers the flu experience of her daughter, Morgan. Now a toddler, Morgan fought flu when she was only 5 months old. The 2018–2019 flu season already has the highest number of flu-related deaths in children since national reporting began.

Developing systems

Flu is dangerous for people of all ages, but it is more often lethal in infants than in older children and healthy adults because infants have smaller lungs and weaker immune systems. Thomas' laboratory studied a group of unconventional T cells as part of a collaboration with the St. Jude Department of Bone Marrow Transplantation and Cellular Therapy. The scientists found that patients who had stem cell transplants recovered these unconventional T cells faster and with higher magnitude than did other patients.

"When we looked at other types of cells, we didn't find any other cell type that predicted a good outcome," Thomas says. "That got us thinking that these cells play an important role in the developing immune system."

Because the immune systems of transplant patients develop much like those in infants, the researchers sought to further examine the effects of the unconventional T cells on the infant immune system.

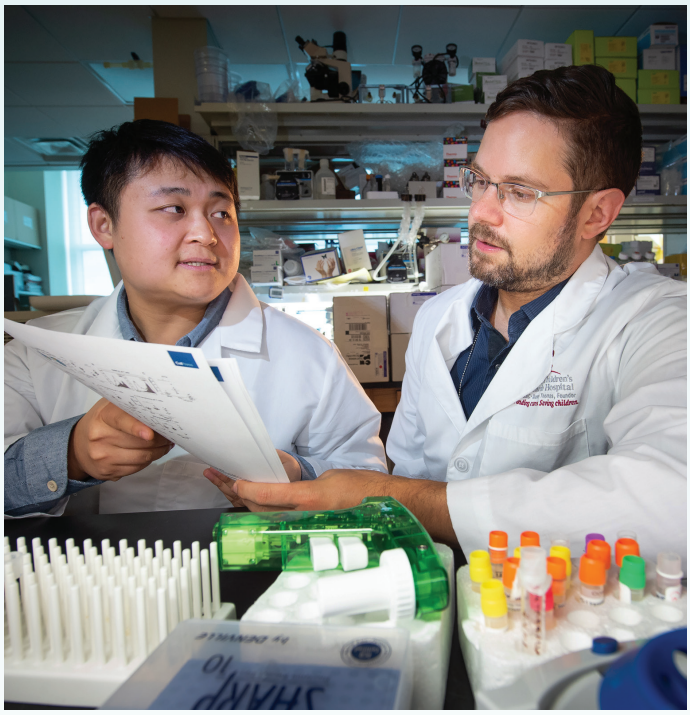
An unusual finding

T cells are responsible for helping the immune system form and for regulating responses to viruses and other illnesses. The unconventional T cells are named according to the protein chains that form their surface receptors. The T cells Thomas and his colleagues examined are known as gamma-delta T cells. Unlike conventional T cells, gamma-delta T cells develop before birth. These cells are found in the blood, lungs, gut and skin.

"Since gamma-delta T cells are the first immune cells we develop, we thought they might be special," said Xi-zhi Guo, a graduate student in Thomas' laboratory. "Their role may be to help right after birth while conventional T cells are still developing."

Previous research had shown that gamma-delta T cells were more likely to cause inflammation than to promote tissue repair, but this recent study revealed something unexpected.

Previous research had shown that gamma-delta T cells were more likely to cause inflammation than to promote tissue repair, but this recent study revealed something unexpecte



SETH DIXON

Laboratory discoveries to save lives
Graduate student Xi-zhi Guo (at left), Paul Thomas, PhD, and their colleagues discovered how the immune system strives to protect the lungs of the youngest flu patients. The findings may help clinicians save more lives.

The researchers already knew gamma-delta T cells in flu-infected models produced high levels of a signaling protein called interleukin-17A. Thomas and his colleagues learned an increased amount of that protein triggered a surge in another signaling protein known as interleukin-33 in cells lining the lungs. Interleukin-33 then goes to work, recruiting other immune cells to produce a growth factor called amphiregulin, which promotes lung repair.

Nasal wash samples from infants infected with flu showed a similar connection between increased interleukin-17A and better patient outcomes.

Beyond influenza

The findings suggest that the immune systems of infants and adults take different approaches to restoring lung function. Thomas and his team would like to better understand the makeup of the immune response in infants and determine which interventions might lead to better results in the future.

"Relying on gamma-delta T cells and the amphiregulin pathway to help restore lung function could have broad-based therapeutic benefits — not just for flu, but for other viruses such as respiratory syncytial virus, adenovirus or hand-foot-and-mouth disease," Thomas says. ■

DANCE OF THE T CELLS

CAR T-cell therapy transforms a lowly immune cell into a potential superstar.

By Elizabeth Jane Walker

IN HER IMAGINATION, ZOEY SMITH floats like a dandelion puff across a stage, leaping and pirouetting with other joyful ballerinas. At only 30 pounds, 4-year-old Zoey looks as fragile as spun glass, but she is a mighty little soul.

For the past three years, an aggressive blood cancer has been her unwelcome partner, twirling her around and around and around in a frenzied dance of chemo and relapses.

"Zoey's had leukemia four times in three years," says her mom, Whitney Wadkins, "and she's relapsed four times."

A new therapy at St. Jude Children's Research Hospital holds hope for many children who, like Zoey, have cancer that returns or is hard to treat. Known as CAR T-cell therapy, this tactic involves engineering a patient's disease-fighting T cells to home in on cancer cells and destroy them. Once established in the body, these turbo-charged cancer fighters have the ability to continue their work for years to come.

Immune cells on the move

As you read these words, powerful immune cells in your body are on the move, searching for intruders. If those cells perceive an interloper, they'll mount an attack. That scenario happens with infections all the time. But here's the catch: A

> "With this immunotherapy approach, we can specifically target only the cancer cells and not other parts of the body. We hope to help patients avoid the long-term complications of chemotherapy. We also hope to cure patients who currently cannot be cured with conventional therapies."
>
> *– Stephen Gottschalk, MD*

En pointe
Zoey Smith (pictured with Crystal Brothers of Ballet Memphis), received an early version of CAR T-cell therapy. Scientists say a new clinical trial called SJCAR19 offers exciting improvements over other CAR therapies.

PETER BARTA

Next steps
Stephen Gottschalk, MD, Bone Marrow Transplantation and Cellular Therapy chair, and his colleague Aimee Talleur, MD, head the SJCAR19 clinical trial.

> "CAR T-cell therapy is very powerful. It puts the vast majority of patients who are treated with it into remission."
>
> *– Aimee Talleur, MD*

tumor cell can camouflage itself so the immune system doesn't recognize it. As a result, the cancer cell is free to reproduce uncontrolled, crowding out healthy cells.

CAR T-cell therapy helps the immune system "see" the tumor cells. Because this kind of treatment reprograms the individual's own T cells, the dose must be manufactured specifically for each patient.

"You can't just call the pharmacist and say, 'Send me immunotherapy,'" says Stephen Gottschalk, MD, chair of St. Jude Bone Marrow Transplantation and Cellular Therapy. "It's a complex endeavor where we have to collect immune cells from the patient, make them in the laboratory and then infuse them back into the patient."

Exacting sequence of steps

When doctors believe a child has cancer that will respond to CAR T-cell therapy, their first step is to collect T cells from the patient's blood. Those cells are then transported to a manufacturing facility. There, scientists add a chimeric antigen receptor (called a CAR) to the surface of each T cell. This receptor will act like a heat-seeking missile to search for a specific protein on the cancer cell's surface.

Meanwhile, in the hospital, the patient may receive several days of chemotherapy to prepare for the new cells.

Once the engineered cells are infused into the patient, they get to work. The genetically modified T cells roam around in the body. When they discover tumor cells, the T cells multiply and bind to the cancer cells, destroying them.

"CAR T-cell therapy is very powerful," says Aimee Talleur, MD, of Bone Marrow Transplantation and Cellular Therapy. "It puts the vast majority of patients who are treated with it into remission. To be able to make someone's own immune system work better is pretty incredible and remarkable."

A living drug

Unlike chemotherapy, which kills cells indiscriminately, CAR T-cell therapy is a living drug. The cells can replicate for many years, identifying and demolishing cancer cells if a relapse occurs.

"With this immunotherapy approach, we can specifically

target only the cancer cells and not other parts of the body," Gottschalk explains. "We hope to help patients avoid the long-term complications of chemotherapy. We also hope to cure patients who currently cannot be cured with conventional therapies."

CAR T-cell therapy had its genesis at St. Jude many years ago, when then-faculty member Dario Campana, MD, PhD, and his colleagues found a molecule that helped the immune system attack leukemia cells. The treatment Zoey received was a direct outgrowth of that discovery — the first CAR T-cell therapy to receive FDA approval. Zoey received that version of therapy.

"There's still a lot to learn about CAR T-cell therapy," Talleur says, "including how the cells behave once they're infused into a patient and how this correlates with clinical outcomes."

Now, St. Jude has developed a new CAR T-cell product for children with leukemia that has returned or has never responded to treatment.

The next generation: SJCAR19

Unlike the therapy Zoey received, the new CAR product is manufactured on the St. Jude campus — in the Children's GMP, LLC, a facility that manufactures biological products for patient use.

Gottschalk and Talleur are heading the clinical trial, called SJCAR19. St. Jude scientists have made important changes they believe will offer significant improvements over past CAR T-cell therapies.

"Our manufacturing process is a little bit different," Talleur explains. "We think these cells will last longer in the body than cells from other CAR T-cell therapies. We believe this product will be even safer for patients and will be more effective in killing cancer cells. Through SJCAR19, we also want to answer questions about the patient and caregiver experience.

"Our goal is to improve on existing therapies, and better design and implement future CAR T-cell therapies for a variety of cancer types."

Gottschalk and Talleur report that other CAR clinical trials are also in the planning stages at St. Jude. These include therapies for children with acute myeloid leukemia, solid tumors or brain tumors.

The dance continues

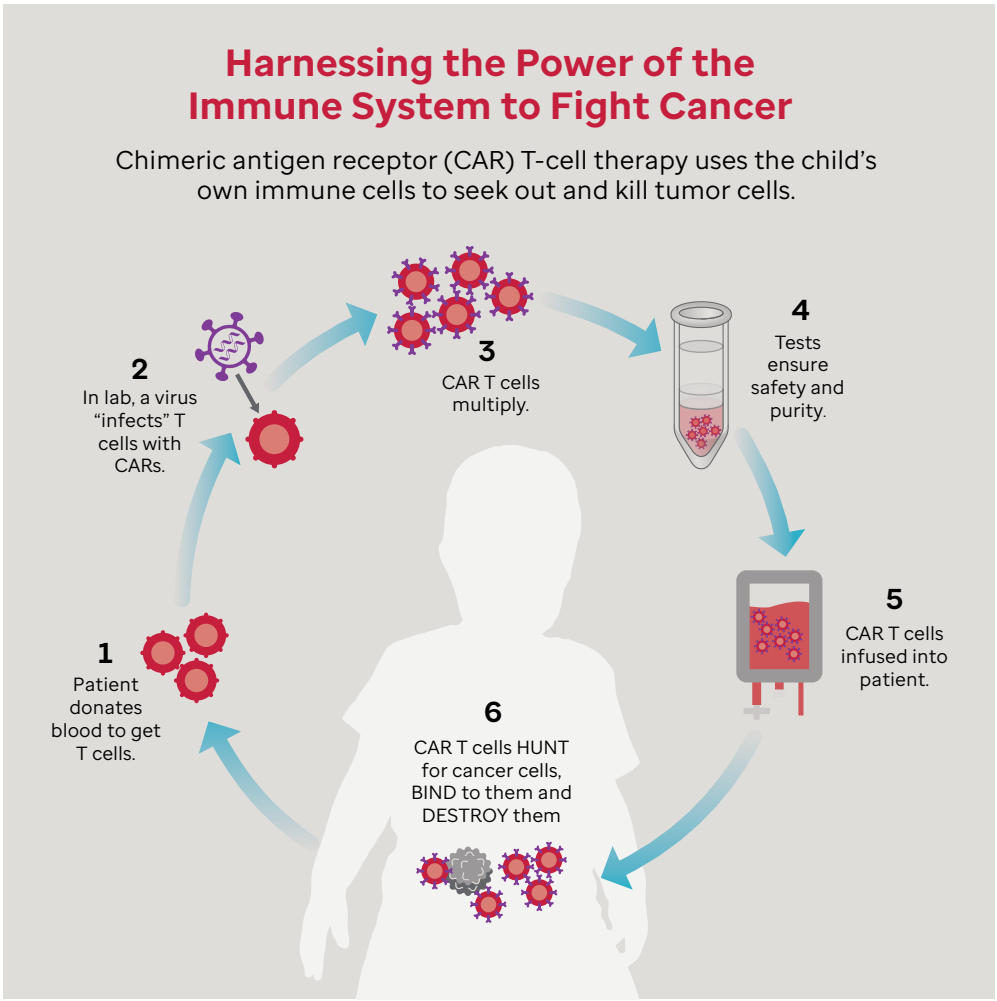
While doctors and researchers work to create new and more effective CAR T-cell therapies, Zoey continues the important work of a little girl, practicing her ballet moves, coloring pretty pictures and lovingly caring for her little brother.

"No, you can't go outside," she admonishes her dolls. "There are germs. Your ANC is 600, and you're doing pretty good, but you have to go to clinic next week."

Zoey's mom emphasizes that continued CAR T-cell research is crucial.

"So many children are dying way too early," Whitney says. "We've seen it firsthand. It's sad to know that parents are losing their children because there are no other options for them.

"It's super-important to find new advancements to save our children."■



Dawn of a

Relapsed brain tumors have been difficult to treat,

By Corey Carmichael

The founder of St. Jude Children's Research Hospital said it first: ***"No child should die in the dawn of life."*** So when doctors created a new plan to save children with the most aggressive brain and spinal cord tumors, the choice was clear: The clinical trial would be called SJDAWN.

"We called it DAWN as a play on Danny Thomas' phrase," explains St. Jude oncologist Giles Robinson, MD, "but we also wanted to signify a new age of treatment."

This study aims to improve cure rates for children with malignant brain tumors that fail to respond to treatment or that return after therapy. Most clinical trials for such children evaluate only one drug. SJDAWN proposes a new approach to treating these tumors. Clinicians will combine promising therapies based on tumor type and the molecular characteristics of the child's tumor.

New Era

but a new approach at St. Jude offers a **ray of hope**.

Journey to St. Jude

SJDAWN is designed for patients like Chelsea McKita, whose brain tumor has returned three times in 11 years.

Chelsea still remembers that day in the seventh grade, when her parents arrived at the principal's office to check her out of school after a CT scan startled her physicians.

"Cancer was not on my mind whatsoever," she says. "I remember seeing my parents sitting there, but don't remember anything after that until we were halfway to the hospital in Pittsburgh. Even then, brain surgery was not on my mind."

Doctors found a golf-ball sized mass at the base of her brain. Chelsea had medulloblastoma, a brain tumor that starts at the base of the skull, but also tends to spread to other parts of the brain and to the spinal cord.

After surgery, chemotherapy and radiation, Chelsea was declared cancer-free in spring 2008. Unfortunately, that's not where her cancer journey ended.

Medulloblastoma returned during her junior year of college. This time, the tumor lodged at the base of her spine and the frontal lobes of her brain. Nearly a year later, Chelsea was once again in remission.

It would not be long before the cancer came back yet again, just as she returned to college in August 2017.

"I feel like the hospital experience has been my life since I was 13," Chelsea says. Then her family found St. Jude.

JUSTIN VENNEMAN

Moving discoveries into the clinic
Giles Robinson, MD (at right), consults with Chelsea McKita, who has enrolled in SJDAWN.

> "It's fantastic that we can look at the molecular construct of tumors and potentially dictate therapy."
> ***– Giles Robinson, MD***

With knowledge comes options

"We had a biopsy done in June of 2018 at the National Institutes of Health," says Chelsea's mother, Heather McKita. "Before that biopsy, we had all these straws to grasp at with clinical trials, but that biopsy took all of our straws down to one – and that was St. Jude."

SJDAWN proposes a new approach to treating malignant brain tumors that fail to respond to treatment or that return after therapy. Clinicians combine promising therapies based on the tumor's type and molecular characteristics.

The only clinical trial that could offer Chelsea hope was SJDAWN.

Robinson is the primary investigator for SJDAWN and treats brain tumor patients at St. Jude. He is optimistic about how enriched molecular analysis and genomic sequencing can provide new targets for treatment and can teach oncologists more about these tumors.

"It's fantastic that we can look at the molecular construct of tumors and potentially dictate therapy," Robinson says. "The more we do it and the more we understand, the more targets we're going to find, the more potential medicine to help these patients."

The one-two punch

Once a team of pathologists, led by Brent Orr, MD, PhD, analyze a patient's tumor, they help the oncologists assign the child to one of three treatment arms tailored for that tumor type.

Each treatment plan is based on a "doublet" therapy, combining two drugs. Every child in SJDAWN receives a medication called ribociclib. This drug is a cell-cycle inhibitor, which prevents the signal (the cell cycle) that tells a cancer cell to grow and divide. If scientists can stop this process, they can stop the tumor's progression.

Clinicians combine this cell-cycle inhibitor with a helper drug tailored to each child's tumor type and treatment group. This type of drug combination has been tremendously successful in treating adults with breast cancer. In that case, ribociclib was combined with estrogen therapy.

In SJDAWN, one of three helper drugs is given along with ribociclib. These drugs are called gemcitabine, trametinib and sonidegib. Gemcitabine has been used to treat adults with ovarian, breast, lung and pancreatic cancer. The other two drugs have been approved by the FDA to treat adults with certain types of skin cancer.

Leading the way

In the lab, St. Jude tumor cell biologist Martine Roussel, PhD; Clinton Stewart, PharmD, of Pharmaceutical Sciences; and other scientists showed that the cell-cycle inhibitor would be a viable option when paired with the helper drugs used in SJDAWN. With ribociclib as the base, the team hopes to block the transition of the cancer cells' growth cycle and stop the rapidly dividing cells.

"Most successful cancer treatments have used a cocktail (or mixture) of medicines because aggressive cancers tend to be resistant to single medicine therapy since the cancer cells have a lot of built-in escape routes. This doublet therapy is not that much different in theory, but the drugs are newer and hopefully more precise at killing these particular brain tumor cells," Robinson explains.

After many years of treating children with recurrent brain tumors, Amar Gajjar, MD, chair of St. Jude Pediatric Medicine, sees this type of therapy as a positive step for treating children who otherwise might have no hope for cures.

"We've got a big initiative at St. Jude to use targeted combination therapies," Gajjar says. "It's positioning our program and our institution to lead the way in providing new therapeutic approaches." ■

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St. Jude redefines diagnostic 'gold standard'

Recent St. Jude findings suggest that whole-genome sequencing should be used for all children with cancer.

This process involves determining the exact order, or sequence, of the 3 billion chemical bases that make up human DNA.

The method isn't widely used because of cost and time constraints.

Most pathology departments that issue sequencing results look at only a panel of several hundred genes. That approach can miss many important mutations. More advanced institutions may look only at the whole exome and whole transcriptome. The exome encodes instructions for assembling proteins. The transcriptome identifies the genes that are expressed. Together, those two methods can find 78 percent of cancer-causing mutations.

But when St. Jude researchers combined whole-genome sequencing with those two approaches, 99 percent of mutations were identified.

Whole-genome testing is now offered to every new St. Jude cancer patient.

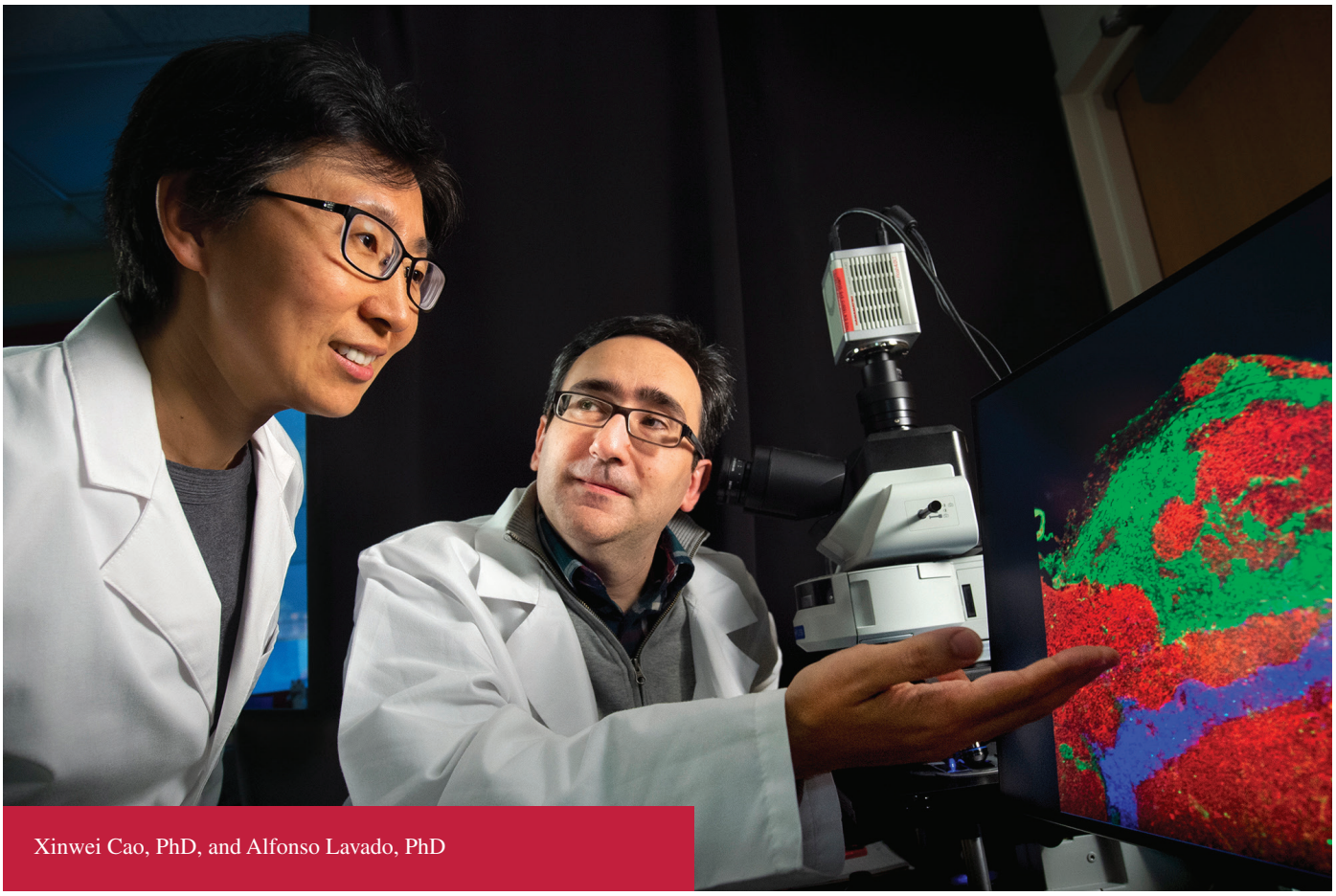
Scientists shared these findings in the journal *Nature Communications*. Data from the study are also available in St. Jude Cloud's PeCan portal.

PETER BARTA

Awareness and education

Hailey Skonhovd of St. Jude Infectious Diseases helps Sarosh Khan learn how to extract DNA from a strawberry during Childhood Cancer and Sickle Cell Awareness Month. The hospital offered an array of activities for patients and their families. St. Jude employees took part by volunteering for events, donating blood and platelets and wearing "We Honor You" T-shirts.

SETH DIXON



Xinwei Cao, PhD, and Alfonso Lavado, PhD

How Hippo pathway may affect solid tumor growth

Like detectives tracking a serial killer, St. Jude scientists have identified a novel mechanism that may explain how two oncogenes promote the growth and spread of solid tumors.

The research focused on two proteins called YAP and TAZ, which activate gene expression and drive cell growth. YAP and TAZ are controlled by the Hippo signaling pathway.

But how YAP/TAZ contributes to tumor growth and spread had been unclear.

One possible answer? Hypertranscription.

"Rather than activating a few genes involved in cell proliferation, activation of YAP/TAZ caused a global increase in gene transcription activity, or hypertranscription," said Xinwei Cao, PhD, of St. Jude Developmental Neurobiology,

Researchers are using results of this study to explore how YAP/TAZ activation may influence development of other solid tumors. The findings appeared in the journal *Developmental Cell*.

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Taking palliative care to the world

Health care providers from 29 countries recently traveled to St. Jude to learn about pediatric palliative care. The course was part of the St. Jude Global Academy.

Following that event, St. Jude hosted the second Interdisciplinary Pediatric Palliative Oncology Symposium. Experts and a panel of bereaved parents covered a host of challenging subjects. These included communication of difficult news, ethical issues in pediatric oncology, management of pain and complex symptoms, legacy building and bereavement care. More than 400 health care providers attended.

Immune housecleaners morph into cancer fighters

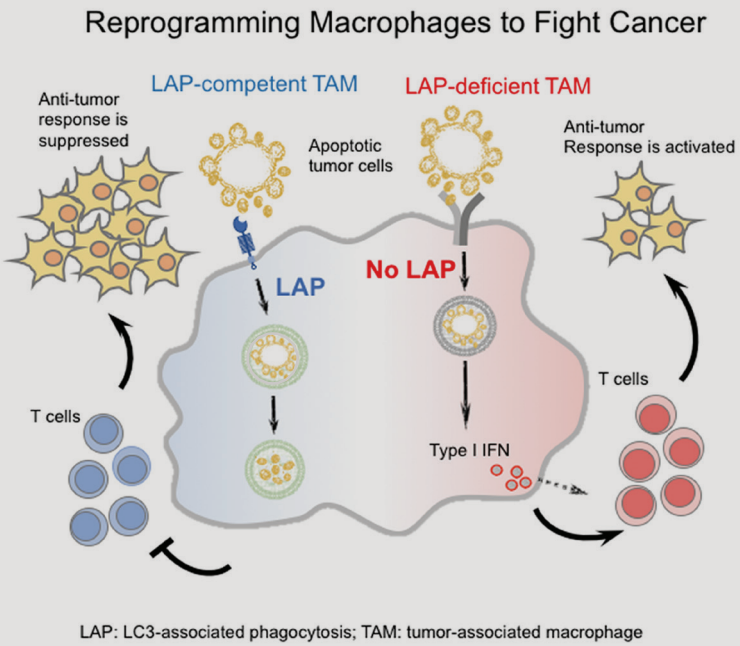
Ever let dishes pile up while you deal with a crisis? Scientists at St. Jude have a new strategy to reprogram certain immune cells inside tumors so that they focus on killing cancer cells rather than tidying up after tumor cells die.

The plan involves a process the scavenger immune cells use to digest the dead and dying tumor cells they pick up for disposal. Researchers showed that disabling the process in the immune cells transformed them from housecleaners to cancer fighters.

Doug Green, PhD, St. Jude Department of Immunology chair, and his colleagues discovered the process, known as LAP, in 2007. He also led this research. (LAP is short for LC3-associated phagocytosis.)

"Understanding this fundamental process holds a key to future treatments," Green said. "We have already embarked on approaches to applying our findings."

The research appeared in the journal *Cell*.



LAP: LC3-associated phagocytosis; TAM: tumor-associated macrophage

PETER BARTA

Zhaoming Wang, PhD

Small risks may have big impact on breast cancer odds

Female survivors of childhood cancer have among the highest breast cancer rates of any group. Using data from the St. Jude LIFE study, scientists found common genetic variations that can help identify those who have a higher risk for breast cancer.

The research focused on 170 common genetic variations. Individually, each confers a small breast-cancer risk. But together, they can double the breast-cancer risk for women who survived childhood cancer. The threat is greatest for those under 45 years of age.

"When combined with screening for rare mutations in breast cancer predisposition genes, these findings are expected to help identify high-risk pediatric cancer survivors who currently go unrecognized," said Zhaoming Wang, PhD, of St. Jude Epidemiology and Cancer Control and Computational Biology.

The findings were published in the journal *Clinical Cancer Research*.

PETER BARTA

Boo! Who?

Superheroes, cartoon characters and magical creatures filled the St. Jude corridors during Halloween 2018. Employees turned the hospital into a trick-or-treat extravaganza for children such as 2-year-old Grayson Farrier (pictured). Hundreds of patients and their siblings made stops along 54 booths decorated by St. Jude and ALSAC employees. Staff from each department also took part in reverse trick-or-treating, delivering candy to inpatients.

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What can salad dressing tell us about cancer? Think oil and vinegar.

The process explaining why oil and vinegar separate in salad dressing may also play a role in prostate cancer and other solid tumors.

St. Jude scientists found that mutations in the tumor suppressor gene *SPOP* contribute to cancer by disrupting a process called liquid-liquid phase separation. This process is the reason oil and vinegar separate in salad dressing.

The SPOP protein binds unneeded or unwanted proteins so they can be tagged for destruction. *SPOP* mutations were known to disrupt binding and lead to a buildup of cancer-promoting proteins in sensitive cells.

"This study shows for the first time that mutations in the tumor-suppressor *SPOP* disrupt phase separation and that tumor-suppressor function can be influenced by phase separation at all," said Tanja Mittag, PhD, of St. Jude Structural Biology.

The findings appeared in the journal *Molecular Cell.*

PETER BARTA

Rainforest comes to life through sequin project

Thanks to 1.2 million sequins that fill the space between the Chili's Care Center and Kay Research and Care Center, the rainforest has come to life at St. Jude. The swirling patterns of shiny sequins ripple like water, offering a shimmering display for the hospital's patients and staff.

Map unveils secrets of brain development

St. Jude researchers have created a massive database of the changes in gene activity of individual cells in the cerebellum during development and immediately after birth. The cerebellum, a key brain control center, contains more than half of all nerve cells in the central nervous system.

The St. Jude project created a high-resolution map. It allows scientists to view the genomic changes cells undergo as the cerebellum develops.

The research provides a basis for understanding the origins of brain disorders caused by errors in development. The database will enable scientists to trace the cellular origins of certain childhood brain tumors.

Researchers worldwide can interact with the data through the St. Jude Cell Seek interface.

A report on this project appeared in the journal *Current Biology*.

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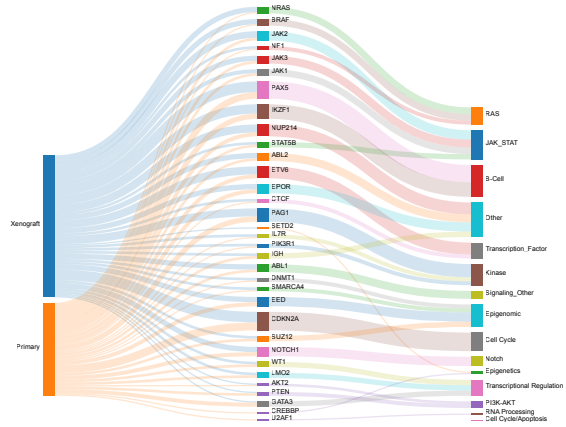


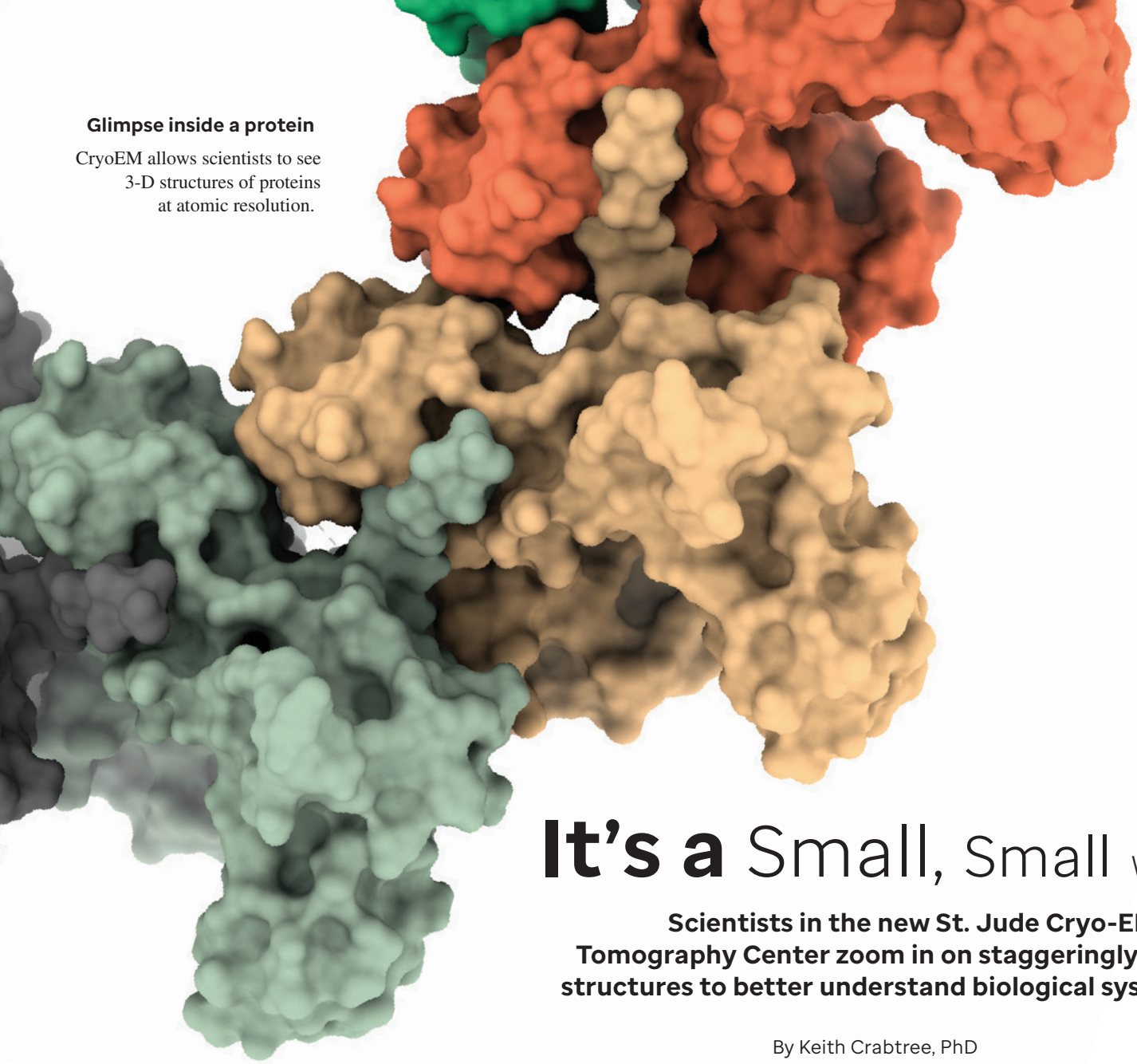
New resource will advance leukemia research

St. Jude has created the world's largest collection of acute leukemia models from children and adults.

PROPEL (Public Resource of Patient-derived and Expanded Leukemias), aims to advance global research in acute leukemia. The project shares unique, patient-derived xenograft samples with researchers worldwide.

PROPEL samples are offered free of charge to researchers. Recipients have no obligation to collaborate, which is unique in the research community. The xenografts, and the matching primary patient samples, include detailed genome sequencing data. They also often contain drug-response data.

"Despite therapeutic advances and improved outcomes, we must make progress to cure leukemia with more effective, less-toxic therapies tailored to each type of leukemia," said Charles Mullighan, MD, MBBS, of St. Jude Pathology. "We hope to accelerate discovery and cures for leukemia and improve long-term outcomes for survivors."



Glimpse inside a protein

CryoEM allows scientists to see 3-D structures of proteins at atomic resolution.

It's a Small, Small World

Scientists in the new St. Jude Cryo-EM and Tomography Center zoom in on staggeringly small structures to better understand biological systems.

By Keith Crabtree, PhD

A Titan Krios electron microscope with a Volta phase plate. *Check.*

A Talos Arctica electron microscope (which, like the Krios, is equipped with K3 direct electron detector and energy filter). *Check.*

A Vitrobot and a plasma cleaner for sample preparation. *Check.*

These are only a few of the items required to assemble a world-class cryo-electron microscopy (cryo-EM) center.

St. Jude Children's Research Hospital opened such a facility in 2018. In the Cryo-Electron Microscopy and Tomography Center, scientists can zoom in to see 3-D molecular and cellular images at atomic resolution.

How small is that?

Well, atoms measure about one ten-billionth (1/10,000,000,000) of a meter.

Now, *that's* small.

Just look at the thing

In 1960, a scientist from Caltech proposed a new field of "small-scale" physics. "It is very easy to answer many of these fundamental biological questions," said Nobel laureate Richard Feynman, PhD. "You just look at the thing."

Feynman challenged physicists to increase the power of electron microscopes. For decades, X-ray crystallography was the main technique for imaging proteins — the building blocks of cells. Then came the cryo-EM resolution revolution. Suddenly, scientists were able to see proteins that had once been too floppy or wiggly to image.

At St. Jude, Liang Tang, PhD, director of the Cryo-EM Center,

> “By knowing the 3-D structure of a protein — for example, one that carries a disease-causing mutation — scientists will be able to better understand how the protein works.”
>
> *– Liang Tang, PhD*

calls the hospital’s new electron microscope a “monster.”

Located in the Danny Thomas Research Center, the Titan Krios nearly fills one of two rooms dedicated to this equipment. The smaller Talos Artica is in the other room.

The Krios sits atop a platform designed to pick up and absorb ambient vibrations — voices, footsteps, even a dropped mug. White Lego-like panels filled with flowing water hang from the wall to regulate room temperature, since electrons are sensitive to temperature. With this equipment, scientists can render high-resolution pictures of many kinds of molecules, including membrane proteins.

World-class resource

It’s crucial that scientists be able to scrutinize the structures of biomolecules, especially membrane proteins, which are targeted by many drugs.

“Membrane proteins are typically difficult to capture with X-ray crystallography,” says Stephen White, DPhil, dean of the St. Jude Graduate School of Biomedical Sciences and former Structural Biology chair. “But with cryo-EM, you can access membrane proteins really well.”

In cryo-EM, a tiny bit of a protein sample is frozen by plunging it into liquid ethane. Then an electron gun shoots electrons through the protein molecules at a high speed while a detector captures them. A computer algorithm sorts the resulting images, and a software program — averaging hundreds of thousands of molecules — creates a 3-D composite image in ultra-high resolution.

A complete toolset

“Cryo-EM is probably the most powerful tool you can have in structural biology,” says Charalampos “Babis” Kalodimos, PhD, St. Jude Structural Biology chair.

Nevertheless, in order to build the world’s premier structural biology program, Kalodimos and his colleagues require additional tools to study the structure and dynamics of large molecules.

“We’re investing heavily in complementary techniques,” Kalodimos says, “because you need to have the complete toolset.”

The St. Jude toolset includes not only cryo-EM but also nuclear magnetic resonance spectroscopy, X-ray crystallography, single-molecule imaging and mass spectrometry.

In 2019, St. Jude will install one of the world’s most powerful magnets for the study of biomolecules.

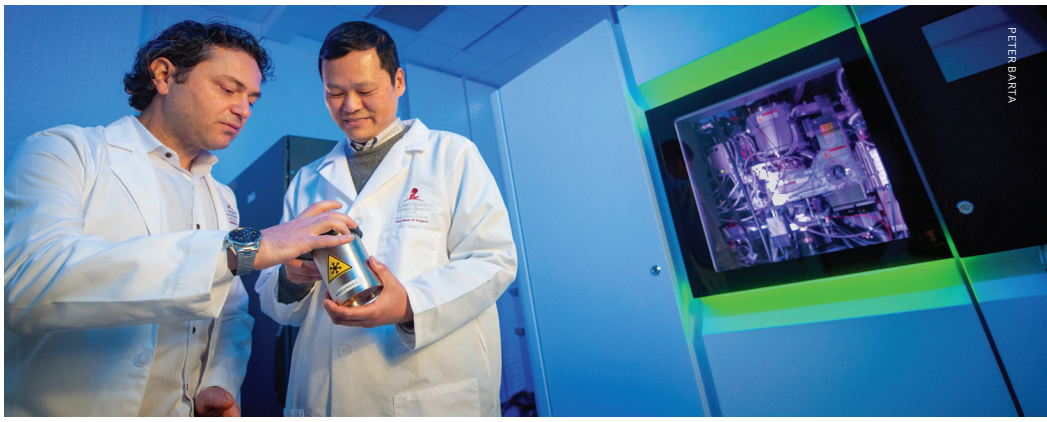
“This integrated approach,” Kalodimos says, “gives us confidence that we will be able to tackle any biological system, no matter how challenging.”

Using cryo-EM to advance cures

Some pathways to developing new medicines and preventing catastrophic diseases are already known.

“By knowing the 3-D structure of a protein — for example, one that carries a disease-causing mutation — scientists will be able to better understand how the protein works,” Tang says. “This may enable scientists to find ways to manipulate its function and interfere with the occurrence or progression of the disease.”

With a complete toolbox, St. Jude scientists are equipped to “just look at the thing,” to increase their understanding of miniscule biological systems and to design new medicines and therapies. ■



The resolution revolution
Charalampos “Babis” Kalodimos, PhD (at left), St. Jude Structural Biology chair, and Liang Tang, PhD, director of the Cryo-EM Center, examine a sample that will be analyzed using the Talos Arctica electron microscope, situated behind them. With this equipment, scientists can zoom in to see 3-D molecular and cellular images at atomic resolution.

TOUCHDOWN St. Jude

Football stars turn fundraising champs for the hospital.

By David Williams

The seeds were sown in study hall. They sprouted at St. Jude Children's Research Hospital.

It sounds more like a parable than a game plan for a football team to win a national championship. But it's just how Lausanne Collegiate School teammates Isaac Weiss and Eric Gray drew it up.

Lausanne, a Memphis private school with a tradition of football dominance, raised more than $19,000 for St. Jude to win the 2018 Touchdowns Against Cancer national championship. The Lynx were led by seniors Weiss, the kicker with an eye toward the Ivy League, and Gray, one of the nation's top-rated all-purpose backs.

"Being a good football player is half of you," says Gray, who decided to dedicate his season to St. Jude after a study-hall conversation with Weiss. "You've also got to be a good person."

Gray's touchdowns raised more than $3,000 for the kids of St. Jude; Weiss' kicks accounted for more than $11,000.

Touchdowns Against Cancer is a national fundraising program in which St. Jude partners with MaxPreps, a website covering high school sports, and Pledge It, a sports fundraising site. Donors pledge a specific amount per touchdown – or field goal and extra point, in Weiss's case – or make a one-time donation.

"Basically, my thought process is, this could be my last year playing football," Weiss says. "No one's going to remember a high school career playing football, but doing something like Touchdowns Against Cancer and Pledge It really lets me leave something after I'm done."

As they hoisted the Touchdowns Against Cancer trophy during a visit to the St. Jude campus, the Lynx had an 8-0 record and a No. 1 state ranking. They'd won 35 straight games overall – a streak that began with Weiss' debut as the team's kicker.

"They're leaders, obviously, within our football program. But they're leaders within our school community," says Lausanne coach and athletic director Kevin Locastro. "They're kids who have really good heads on their shoulders. They come up with good ideas and good concepts, and they're not scared to execute them." ■

Your legacy can help cure childhood cancer

St. Jude patient Antonio, acute lymphoblastic leukemia, with his mom

Create a lifesaving legacy with St. Jude

Leaving a gift in your will to St. Jude Children's Research Hospital® costs you nothing now, yet gives you the satisfaction of knowing your legacy can lead to a future where no child dies from cancer. If you have already included St. Jude in your will, please let us know so we can plan for future generations of children like Antonio who will need our pioneering research and lifesaving care.

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Run for a reason

More than 26,000 runners and walkers recently laced up their shoes for the 2018 St. Jude Memphis Marathon Weekend, the largest single-day fundraising event for St. Jude.

Over 40,000 spectators cheered on participants in five races, ranging from a full marathon to a 5K. The event involved 4,000 volunteers and 6,500 St. Jude Heroes, who raised $11.2 million for the hospital.

Don't miss your chance to take part in the next St. Jude Memphis Marathon Weekend, slated for December 7, 2019. Registration will open in May for St. Jude Heroes who commit to fundraising, and general registration will begin in June.

Sign up for email updates about the 2019 event: *stjude.org/marathonupdates.*

SETH DIXON