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SJELOIT
INTERNATIONAL
STUDY TAKES
AIM AT DEADLY
BRAIN TUMOR

SOFT
LANDINGS
PATIENTS MAKE
THE LEAP FROM
HOSPITAL TO
HOME

MINDS
OVER
MATTER
RESEARCH
COLLABORATIVES
UNITE GLOBAL
EXPERTS

featuring
PAWS
AT PLAY
RUFFLECTIONS
FROM THE
HOSPITAL’S CANINE
CLINICIANS

St. Jude Children’s Research Hospital
St. Jude is leading the world in research on the causes and treatments for pediatric cancer and other life-threatening diseases.

CASSIDY OTTO & PUGGLE
NOW THAT 8-year-old Alana Davis has completed treatment for Hodgkin lymphoma, she has more free time for playing outside. The new Transition Oncology Program (see page 20) is designed for children like Alana.

Emily Browne, DNP, director of TOP, understands the challenges of moving from hospital to home. “Children have to go back to school,” she says. “Parents have to go back to work. They’ve got to figure out what their new normal is. We want to make sure they feel supported during that time.”
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Research reveals structural details of chaperones

For the first time, St. Jude scientists have mapped the structure of chaperones. These molecules are found in all cells. Chaperones bind to proteins to prevent them from malfunctioning. The work reveals how a chaperone attaches to a protein to protect it from going bad and causing disease.

The findings help us understand how the cell defends against mistakes in which proteins can unfold, misfold or form toxic clumps. Before this work, scientists did not know the structural details of how chaperones and their proteins link.

“Proteins are first formed as string-like molecules, but with the help of chaperones fold into the globular shapes that give them specific functions,” said Charalampos Kalodimos, PhD, St. Jude Structural Biology chair. “The basic structural knowledge gained by studying a range of chaperones will increase our understanding and may lead to clinical applications.”

Scientists used nuclear magnetic resonance spectroscopy to study the protein structure. Chaperones are over-produced or mutated in cancers and neurodegenerative diseases, altering their structure. For this work, the team looked at a three-part chaperone machine found in every cell, Hsp40-Hsp70-NEF, and its attached client protein.

Science published a report on this study.
at greatest risk: kids with cancer, people over 65, and those who are pregnant or obese. Also at risk are those who have chronic illnesses, including diabetes and asthma.

Scientists from St. Jude and the University of Georgia will lead a team funded by the National Institutes of Health. Their goal is to develop better flu vaccines, especially for the most vulnerable populations.

“The goal is to develop vaccines that are more broadly protective against multiple flu strains. Our priority is vaccines to safeguard populations we know will develop more severe disease if infected,” said Stacey Schultz-Cherry, PhD, who co-directs the Center of Excellence for Influenza Research and Surveillance at St. Jude.

INFLUENZA VACCINES are the best way to protect against flu infections and serious, even deadly, complications. But there’s room to improve.

In a good year, flu shots prevent infections in 70%–90% of healthy children and adults under age 65. The vaccine is less effective for those

Do vitamins A and D help the flu vaccine work better? It depends.

VITAMINS A AND D influence the immune system. Researchers suspected these vitamins might affect how well children respond to the flu vaccine. However, earlier studies by other scientists showed mixed results.

A new St. Jude study may have the answer. Baseline vitamin levels are rarely studied in flu vaccine research. But scientists found that baseline vitamin A and D levels were linked to immune responses to the vaccine.

A clinical trial studied the flu vaccine and vitamin supplements in children 2–8 years old. Children got two doses of the vaccine, either with a vitamin A and D supplement or with a placebo.

“Baseline vitamin A and D levels each influenced the flu vaccine-induced immune response and the effect of high-dose vitamin supplements,” said Julia Hurwitz, PhD, of St. Jude Infectious Diseases.

A report on this work appeared in Viruses.
Exercise may give the brain a boost

IMPROVING cancer survivors’ physical fitness may boost their thinking and learning skills. A St. Jude study reveals more about this link.

“Survivors are more likely to have limited ability to exercise,” said Kirsten Ness, PhD, of Epidemiology and Cancer Control. “Physical activity can have a positive effect on cognitive ability.”

This work relied on the St. Jude Lifetime Cohort (St. Jude LIFE) study. The scientists tested 341 childhood leukemia survivors and 288 control subjects.

“Even minor changes like going from sitting to walking for 30 minutes can have an effect,” said Nicholas Phillips, MD, PhD, of Epidemiology and Cancer Control.

A report on this work appeared in the journal Cancer.

Total 16 lowers ALL relapse rate

UP TO 10% of children with acute lymphoblastic leukemia experience a relapse of their disease. St. Jude researchers recently announced results of the Total Therapy Study 16. This clinical trial tested strategies for lowering the relapse rate. Extra doses of chemotherapy in the cerebrospinal fluid improved disease control in the central nervous system (CNS) without adding toxicity.

On the previous clinical trial, Total 15, the CNS relapse rate was 5.7% for high-risk patients. But on Total 16, the CNS relapse rate for a similar group of patients was reduced to 1.8%. The addition of extra therapy to control CNS disease did not cause extra toxicity.

“In cancer research, leukemia always leads the way,” said Ching-Hon Pui, MD, St. Jude Oncology chair. “St. Jude is at the forefront of a new era of cancer treatment where therapies are optimized to provide the maximum benefit to all patients, even those at the highest risk.”

The Journal of Clinical Oncology published a report on this work.
Reimagining beta-thalassemia and its treatment

Beta-thalassemia is one of the world’s most common blood disorders. Researchers noticed it shares similarities with brain disorders such as Alzheimer’s disease. Both involve abnormal proteins that build up in cells.

St. Jude scientists turned that observation into a possible treatment approach. They found a drug called rapamycin that’s widely used to treat other diseases. This drug is also used with patients undergoing organ transplants.

In the lab, researchers showed the drug eased symptoms of beta-thalassemia. The drug also helped reduce the build-up of toxic proteins in developing blood cells from people with beta-thalassemia.

“The next step is to design a clinical trial to test whether rapamycin is safe and effective for treating people with beta-thalassemia,” said Mitchell Weiss, MD, PhD, St. Jude Hematology chair.

A report on this work appeared in Science Translational Medicine.

Step aside Marie Kondo, the genome is the real organizational expert

“When understanding the way cells organize their genomes during development will help us understand their ability to respond to stress, injury and disease,” said Michael Dyer, PhD, St. Jude Developmental Neurobiology chair.

The researchers are using the same approach to study how the genome is organized in the cerebellum. That’s where the most common malignant childhood brain tumor develops.

Study data and an instructional video are available to researchers worldwide. These are offered through St. Jude Cloud, an online, cloud-based data-sharing resource.

A report on this work appeared in the journal Neuron.

WHEN IT COMES TO organizing, even experts like best-selling author Marie Kondo could learn from the genome. The genome is the blueprint for life. That blueprint is encoded in the DNA molecule. Human DNA from a single cell measures about 6 feet long.

Packaging turns it into a microscopic instruction manual that fits into the cell nucleus.

St. Jude researchers used the latest technology to make a 3D map of a mouse genome. The work focused on cells in the developing retina and revealed surprises about gene regulation. The map gives scientists a way to track how cells package DNA and how that packaging affects whether and when genes are expressed.

Understanding the way cells organize their genomes during development will help us understand their ability to respond to stress, injury and disease,” said Michael Dyer, PhD, St. Jude Developmental Neurobiology chair.

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A report on this work appeared in the journal Neuron.
HOW DO YOU create a drug for a target that does not exist? This question underlies research on cancers driven by the loss of a gene, such as rhabdoid tumors. Eighty percent of these tumors are driven by loss of the gene SMARCB1. These aggressive cancers can arise in the liver, kidney or parts of the central nervous system. Between 20 and 25 people are diagnosed with malignant rhabdoid tumors in the U.S. each year.

A team led by Charles Roberts, MD, PhD, St. Jude Comprehensive Cancer Center director, looked at these tumors through a wider lens to search for new targets. “We used a library of existing drug compounds and CRISPR technology to look for dependencies gene by gene,” he said. “This showed us which targets rhabdoid tumors need to survive.”

Scientists found that a class of drugs called receptor tyrosine kinase inhibitors can slow the growth of rhabdoid tumors. These drugs target growth-factor receptors, including the proteins VEGFR, PDGFR, FGFR and HGFR/MET.

Researchers also found that the gene PTPN11 is needed for rhabdoid tumors to survive. This makes the gene a possible target for therapy. Cell Reports published a report on this work.

Taking a wider view reveals potential targets for rhabdoid tumors

**CELLS ARE BOMBARDED** with a dizzying array of stimuli. St. Jude researchers have found a molecule that helps cells respond to that info.

The molecule is DDX3X. Scientists showed for the first time that DDX3X helps decide the fate of immune cells. If DDX3X is available, stressed cells can form compartments that help them survive or that activate a cell-death pathway. The choice helps regulate the immune system, including inflammation. DDX3X might also offer a new way of treating autoinflammatory diseases.

Those disorders play a role in some of the leading killers of the modern era, including cancer, heart disease and diabetes.

“The findings make DDX3X an attractive target for designing drugs to modify the stress response to restore balance to prevent chronic inflammation and other diseases,” said Thirumala-Devi Kanneganti, PhD, of St. Jude Immunology.

The journal Nature published a report on this work.
Jett Ramsey is part of an international study testing a new chemo drug. This drug prevents medulloblastoma cells from repairing themselves after damage caused by other chemotherapies.

By Maureen Salamon
JETT RAMSEY may only be 4 years old, but already he’s mastered the yin and yang of emotional balance. Some days he’ll sweetly grab his mom’s cheeks and profess his love for her. Other days, the California boy fights with his two older brothers and peppers his conversation with zingers and wisecracks.

But Jett’s feisty side has been particularly useful during the past year in helping him weather rigorous treatment for medulloblastoma, the most common brain cancer in children. And when his tumor came back despite surgery, radiation and chemotherapy, Jett’s grit was again called to the mat.

He is part of an international clinical trial led by St. Jude that aims to increase the arsenal of treatments against the disease. The study, called SJELIOT, is testing a new chemo drug called prexasertib. The drug prevents medulloblastoma cells from repairing themselves after damage caused by other chemotherapies. Researchers hope this medication will strengthen the blow to cancerous cells when used with mainstay treatments.

“My husband and I feel this trial is the best option for Jett because it provides the most hope,” says Jett’s mom, Amy Ramsey. “It also allows Jett to be normal. He’s happy, he doesn’t feel sick, and he seems like a normal kid right now. That’s huge.”

IMPROVING OUTCOMES

SJELIOT aims to enroll about 100 patients whose medulloblastoma tumors didn’t get better with treatment or came back afterward. About 350 children and adolescents are diagnosed with medulloblastoma in the U.S. each year. More than a decade ago, St. Jude researchers led research that showed medulloblastoma is not just one disease, but has four distinct subtypes caused by specific genetic mutations. Those subtypes are named wingless (WNT), sonic hedgehog (SHH), Group 3, and Group 4. Survival rates vary widely from one subtype to another. About 95% of children in the WNT subgroup enjoy long-term survival, compared to about 50% of patients in Group 3. Overall, about 70% of patients survive beyond five years.

Hoping to attain the higher treatment success rates of the WNT subtype, St. Jude researchers led a variety of studies in recent years to increase treatment options and reduce side effects. SJELIOT will include children with more aggressive subtypes, like Jett’s.

“The thing to know about medulloblastoma therapy is we have a good foundational therapy on which to build,” says St. Jude oncologist Giles Robinson, MD, who leads SJELIOT. “This foundation cures many but not all, and it produces some unwanted side effects.

“What we’re trying to do at St. Jude is take that standard therapy and make it better,” he continues, “whether by reducing some of the treatments that cause toxicities or by creating more innovative and, hopefully, better additions to therapy—such as that of SJELIOT—to give to a patient who’s more likely to relapse.”

CHAIN OF SUCCESS

SJELIOT was several years in the making. It launched after an Australian researcher identified prexasertib as a test-worthy medication against medulloblastoma. More research performed globally by St. Jude and other collaborators found the drug to be potent against aggressive subtypes of medulloblastoma cells. The trial includes children at St. Jude and nine other centers in Australia and Germany.

Before a patient can take part in the study, pathologists determine which subtype of tumor the child has. Patients whose tumors are Group 3, Group 4, SHH or an undeter-
The positive results we saw, along with other preclinical work, suggested that all recurrent medulloblastomas could benefit from this therapy,” Robinson explains. “You don’t ever want somebody to relapse or recur with disease,” he adds. “You want to get it right the first time. I think we can easily foresee that if we’re seeing success on a relapse trial, that’s going to lead to success at treating the disease in general.”

NO ESCAPE FOR CANCER CELLS
Researchers want to learn how well prexasertib is tolerated in children and the effects it may have on medulloblastoma. Jett and other patients receive prexasertib every two weeks, along with one of two standard chemotherapy drugs, gemcitabine or cyclophosphamide.

Adults with other types of malignant tumors have tolerated prexasertib well. These observations fueled the idea that children with cancer might also benefit. The trial will last for two to three years, during which Robinson and his St. Jude collaborators can also determine if prexasertib has a helpful effect on attacking medulloblastoma tumors. If the medication works against tumors that have come back or not responded to standard treatments, it may also be tested as a front-line treatment in newly diagnosed patients.

“For many years, we’ve known chemotherapy is a good agent to use against medulloblastoma,” Robinson says. “But unfortunately, cancer cells have the ability to repair themselves and escape the damage chemotherapy has caused.

“Prexasertib interferes with the repair pathway the cancer cells are manipulating,” he adds. “By instigating damage with chemotherapy and then using prexasertib, we’re hoping to see the disease melt away in comparison to using chemotherapy alone.”

SUPERSTARS
In the meantime, Jett’s participation in SJELIOT allows him to spend a lot of time at home with his parents and brothers between treatments, playing in what his mom calls his “wild man” ways and tooling around his family’s large property on his favorite ride-on truck.

When Jett first arrived at St. Jude in fall 2018, he resisted being poked and prodded. Today, he understands that his clinical team is there to help.

“He’s a good sport. He’s amazing,” Amy says. “Now, looking back, I see there was this fight in him that has gotten him through all this. He’s still Jett… he’s still crazy little Jett. We call him Jett Fighter.”

Robinson praises Amy; her husband, Chris; and others who travel this road with their children.

“I have the ultimate respect for the parents who go through this,” Robinson says. “They’re the superstars. They care about the things that are most important in life—and that’s their children.”

For Amy, the respect reflects right back to St. Jude.

“We’re thankful there’s a place like St. Jude for these kids. We’re grateful there are other options,” she says. “Yes, it’s a sacrifice for me to be here and be away from my family and my home and my other kids, but I feel like I’m giving Jett the best care he could possibly get.”
The next-generation lattice light-sheet microscope, or LLSM, is the high-tech version of a handy tool with more than one function. The term lattice explains the intersection of ultra-thin sheets of laser light; the equipment will also feature adaptive optics, a technology borrowed from astronomers.

Instead of the stars, neuroscientists will be able to see biological systems.

“The new microscope will allow scientists to see for the first time incredibly small features of cells deep within tissues or tumors,” says Michael Dyer, PhD, Developmental Neurobiology chair at St. Jude Children’s Research Hospital.

St. Jude developmental neurobiologists David Solecki, PhD, and Daniel Stabley, PhD, recently acquired a first-generation LLSM for the department’s Neuroimaging Laboratory, a core resource comprising neurobiologists, imaging experts and data scientists. The resolution of this equipment surpasses that of conventional light microscopes. The current LLSM also uses less laser light than other microscopes. Laser light can be toxic to delicate cells.

“The next-generation LLSM will allow scientists to see cellular dynamics with extraordinary clarity,” Solecki says. Dyer, Solecki and Stabley are working with teams at three external labs on the project, the brainchild of Nobel laureate Eric Betzig, PhD, from the University of California, Berkeley.

Like a multi-tool, the next-generation LLSM will smoothly switch from one mode to another, permitting scientists to select different tools derived from decades of technological advancements. St. Jude scientists may one day develop targeted therapies for life-threatening childhood diseases using this technology.

For years, Dyer has studied retinoblastoma, a type of eye cancer that affects young children. When the teams of scientists in this project complete their work, he expects to gain new insight into the biological systems that underpin retinoblastoma—thanks to this handy, high-tech tool.

by Keith Crabtree, PhD
Bridge to a Healthy Future

St. Jude helps survivors build lifelong relationships with their primary care providers.

By Maureen Salamon
TIM FOLSE, MD, OFTEN ENTERS an exam room at St. Jude Children’s Research Hospital and offers a handshake to a long-term survivor. But he was taken aback when a 37-year-old Hodgkin lymphoma survivor gripped his hand and held on. The patient had suddenly realized that Folse’s father (also a doctor) had diagnosed the patient’s cancer 30 years before.

That powerful moment emphasized more than the shared profession of father and son. It also highlighted the mighty ripple effects of follow-up care for adult survivors of childhood cancer.

More than 500,000 childhood cancer survivors live in the U.S. today. St. Jude closely tracks and educates its survivors. The hospital also helps them build relationships with primary care providers in their hometowns. By receiving regular medical care throughout their lives, survivors can have the best health possible.

CREATING A ROADMAP
Research shows that about 98% of childhood cancer survivors have at least one chronic health condition as a result of cancer or its treatment. The long-term side effects can range from problems with the heart or lungs to the development of new cancers.

St. Jude wants to help survivors stay on top of their health. That’s why the hospital provides a detailed survivorship care plan that survivors can share with their hometown doctors or nurse practitioners. Each health care provider can read that plan to learn about the survivor’s history and health risks. The plan also outlines which medical tests are needed and when.

“We try to leave no stone unturned as far as giving patients information about how to access care or other resources,” says Folse, clinical director for St. Jude LIFE long-term follow-up study and the After Completion of Therapy (ACT) Clinic.

St. Jude patients visit the ACT Clinic until either age 18 or 10 years after diagnosis, whichever is later. ACT “graduates” receive three-ring binders that contain their survivorship care plans and information from their initial diagnosis and treatment. The binder also includes tips on insurance coverage, fertility treatment, disability programs, scholarships and other topics.

OVERCOMING HURDLES
In spite of careful planning, obstacles sometimes arise. Hometown doctors and health insurers may not understand why a survivor requires certain medical tests at an early age. For instance, a girl whose cancer therapy includes chest radiation faces a risk of breast cancer that’s 25-times higher than that of the average woman. As an adult, this survivor needs mammograms and breast MRI scans every year starting eight years after radiation or at age 25, whichever is later.

If physicians or insurers disagree with this testing schedule, St. Jude can step in. Staff members will explain the reasons, based on data from St. Jude and the Children’s Oncology Group, a clinical trials group supported by the National Cancer Institute.

“I see it as a unique privilege to be able to provide education to patients and hometown doctors,” Folse says. “Primary care doctors will be better equipped if we can continue to increase their exposure to the needs of our survivors. Even after four years of medical school, three years of family medicine residency and 20 years of community family medicine, I had very little knowledge of the long-term late effects risks that can be due to childhood cancer treatment.”

Going to bat for patients years after their cancer treatment ends isn’t unusual for St. Jude. But survivors are also urged to stand up for themselves to ensure they receive the best follow-up care.

“They need to be their own advocates,” Folse says.

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Read your survivorship care plan.
Schedule recommended tests.
Share the plan with your hometown medical providers.
Sign up for the St. Jude patient portal at www.stjude.org/mystjude.
Then, tell your providers how to log in. They’ll find details about your history and the tests you need.
Encourage your providers to call St. Jude with questions at (901) 595-3658.
Change providers if they refuse to follow your survivorship care plan. Check out the Late Effects Directory of Services at childrensoncologygroup.org.
Contact St. Jude if your doctor or insurance company hesitates to provide suggested screenings. St. Jude staff will explain to them why the guidelines must be followed.
If you have medical issues, let St. Jude know so they can update your survivorship care plan.

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Survivors: Take control of your health

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stjude.org/promise • 13
MONDAY MORNINGS ARE RUFF. It’s cold and raining when my mom, Brittany, turns on the light to awaken me. But as much as I’d like to sleep, there’s important work to do.

My pal Huckleberry and I work at St. Jude Children’s Research Hospital in the new St. Jude Paws at Play program. We make the day a little easier for patients—whether helping them relax during procedures, demonstrating how to take medicine or climbing on a mock scanner to show them MRIs aren’t scary.

Brittany is my primary handler, and I live at her house. She’s a Child Life specialist on the inpatient Solid Tumor and Neuro-Oncology unit. Huckleberry and his handler, Shandra, visit kids in Diagnostic Imaging and the H Clinic.

PAWS OF PURPOSE
Huckleberry and I were born to do this job. We’re both 2 years old. I like to remind him that I’m older—by 18 days. Before we joined St. Jude, we lived at a service dog school, where we began our training when we were 4 days old.

I remember the day Huckleberry and I met our St. Jude handlers. They cried tears of joy when they met us. Huckleberry and I don’t really cry, but we do wag our tails a lot. Our tails wagged a lot that day. And guess what? I rode in an airplane on my way to Memphis. I even got to look out the window. Sorry about the nose prints.

WORKING LIKE A DOG
Mondays are bath day for Huckleberry and me. Afterward, I lie on my fluffy bed in an office in the Bone Marrow Transplantation and Cellular Therapy unit. That’s where Ashley works. I sometimes make visits with her since she’s my secondary handler.

My first patient today is a 9-year-old girl. I join the girl and her family for a walk around the fifth floor of the Kay Research and Care Center. We look out the windows at a rainforest of more than 1 million sequins—an art display on the side of the buildings. The wind rustles the sequins to create a rippling effect. It reminds me of my hair blowing in the wind when I chase my favorite red ball.

RUFFLECTIONS
Later, I’m off to a meeting with Brittany and Ashley. Guess who’s there? Huckleberry. We share stories about our weekends and then relax for a bit. As I take a little rest, I think back to our first day at St. Jude.

Huckleberry and I started that day by having photos taken for our employee ID badges. I made sure they got my good side. Then we met the big guy—Dr. James Downing, St. Jude president and CEO. He loves dogs, and he was happy to meet us.

Then we met our co-workers in a special Town Hall meeting. As we entered the auditorium, hundreds of employees snapped photos and greeted us. Huckleberry and I knew we were in the right place.

HEELING AND HEALING
I awaken from my daydream as the meeting ends. Brittany and I stroll to Cassidy Otto’s hospital room, where we see our friends from Rehabilitation Services. They’re trying to encourage Cassidy to get out of the bed and walk.

Cassidy is tired and a little scared. She doesn’t want to try. Brittany and I approach the bed, and the girl smiles at me. I learn Cassidy has a dog, so here’s my chance. As
we get closer, she reaches out to pet me.

We spend the next few minutes getting to know each other. Cassidy agrees to stand with the help of a walker—but only if I’m nearby. Then she surprises all of us. As I pace alongside her walker, the brave girl moves across the room to a couch.

Brittany lets me jump on the couch to snuggle with Cassidy. The girl pets me some more and makes playful faces. My new friend sticks her tongue out to mimic my long tongue.

Later, the therapist says that without my help, Cassidy wouldn’t have walked today. My new friend is one step closer to walking on her own.

As we return to the office, Brittany slips me a treat and says, “Good boy, Puggle.” I’m grateful for the treat, but the real reward was seeing the determined look in Cassidy’s eyes as she moved steadily toward her goal. That’s why I’m here. 🐾
FOR DECADES, scientists at St. Jude Children’s Research Hospital have made steady progress in finding cures for children with life-threatening diseases. In spite of numerous discoveries and advancements, we still have gaps in our knowledge. These diseases are incredibly complex and understanding them requires expertise from many scientific fields.

That’s the reason St. Jude launched Research Collaboratives as part of the strategic plan. What if we brought together the world’s experts, regardless of where they work, to tackle some of the toughest questions related to pediatric catastrophic diseases? Via funding provided by St. Jude, these Collaboratives unite the focus of star scientists from many different institutions to focus attention on pediatric disease and to collaborate with our own St. Jude scientific stars. These projects are chosen based upon the potential to transform science and medicine. The Research Collaboratives go to the heart of the St. Jude mission.

On the following pages, you’ll find a snapshot of the first four initiatives St. Jude has funded to foster these extraordinary collaborations.
Gene editing for sickle cell disease

**Sickle Cell Disease** is the most common inherited blood disorder in the U.S. About 900 patients turn to St. Jude for treatment for this disease, which causes chronic pain, organ damage and early mortality. Since sickle cell disease is caused by a single mutation, could gene-editing techniques cure it?

**Mitchell Weiss**, MD, PhD, St. Jude Hematology chair, leads the hospital’s sickle cell collaborative, which consists of several teams of scientists.

“We’re exploring different approaches for genetic correction,” he explains.

Within the next couple of years, Weiss anticipates that the Hematology department and the Bone Marrow Transplantation and Cellular Therapy department will open a St. Jude-based clinical trial that uses the gene editing protein CRISPR-Cas9 to induce gamma globin. This protein’s expression can inhibit the harmful effects of sickle cell disease. That clinical trial represents the first generation of gene editing therapies and will create a clinical research infrastructure for testing new gene editing technologies in the future.

To develop these new technologies, Weiss has joined forces with Shengdar Tsai, PhD, of St. Jude Hematology; and Shondra Pruett-Miller, PhD, who directs the St. Jude Center for Advanced Genome Engineering (CAGE), in a project supported by the St. Jude Research Collaboratives.

Other renowned innovators in the field of gene editing have also joined the collaborative. They are Daniel Bauer, MD, PhD, of Boston Children’s Hospital; Gerd Blobel, MD, PhD, of Children’s Hospital of Philadelphia; Keith Joung, MD, PhD, of Massachusetts General Hospital; David Liu, PhD, of the Broad Institute of Harvard and MIT; and John Tisdale, MD, of the National Heart, Lung, and Blood Institute.

“A few months is a long time in the fast-moving field of genome editing,” Weiss says. “We’re working with our collaborators to develop the next generation of genome editing techniques that will fuel future clinical trials for treating blood diseases and other genetic disorders.” Gene editing tools developed through the collaborative are being made available to all St. Jude researchers through the CAGE.

Chromatin regulation in pediatric cancers

**IN 2010**, St. Jude teamed with Washington University in the Pediatric Cancer Genome Project—the world’s most ambitious effort to discover the origins of childhood cancer and seek new cures. As part of that project, scientists compared the complete genomes from cancerous and healthy cells of more than 800 childhood cancer patients.

As a result, researchers have made groundbreaking discoveries on the genetic factors driving some of the most challenging childhood cancers. A particularly surprising finding is that one of the most common pediatric cancer mutations takes place in a class of genes called chromatin regulators.

“Chromatin regulators function to tell other genes when to turn on and off, similar to foremen at a construction site,” says **Charles Roberts**, MD, PhD, executive vice president and director of the St. Jude Comprehensive Cancer Center. “We’re beginning to learn that mutations in chromatin regulators contribute to cancer by causing mistakes in the control of genes that determine whether a cell continues to divide or matures to perform a specific job. While it is clear that disruption of chromatin control is at the heart of many cancers, our understanding of this process is still rudimentary.”

Roberts has assembled a team of scientists, including St. Jude pathologist Charles Mullighan, MBBS, MD, and developmental neurobiologist Paul Northcott, PhD. Joining them are Scott Armstrong, MD, PhD, of Dana-Farber Cancer Institute, and Rockefeller University cell biologist David Allis, PhD. Together, they are pooling their expertise in biochemistry, gene regulation, and chromatin structure and function.

“Together we hope to understand the mechanisms of chromatin regulation and how they drive cancer with the long-term goal of developing better therapies,” Roberts says. “Chromatin regulators also play a role in adult cancers, so discoveries by our team could transform the entire field.”
3D genomics of pediatric cancer

Can new insights on how DNA is packaged shed light on the biology of pediatric cancers?

Every human cell has about two meters of DNA wound up in a tight package inside the nucleus. For genes to be activated or suppressed, they must come into physical contact with other genes.

Scientists have discovered that a ring-like structure made of proteins, called the cohesin complex, holds bits of DNA together and controls how the genes are expressed. Mutations in the cohesin complex are present in pediatric acute myeloid leukemia, T-lineage acute lymphoblastic leukemia and neuroblastoma.

St. Jude scientists have been collaborating with world-renowned colleagues at other institutions for many years to understand these processes. Now, they are pooling their expertise and tapping into the latest next-generation sequencing technologies to discover how mutations in structural regulators like CTCF and cohesin drive cancer development.

Jinghui Zhang, PhD, St. Jude Computational Biology chair, heads the team, which includes St. Jude colleagues Suzanne Baker, PhD, of Developmental Neurobiology; and John Easton, PhD, and Brian Abraham, PhD, of Computational Biology.

Collaborating experts from other institutions are Richard Young, PhD, of the Whitehead Institute and Massachusetts Institute of Technology; Kimberly Stegmaier, MD, of the Dana-Farber Cancer Institute; and Thomas Look, MD, of Dana-Farber/Harvard Cancer Center. In total, the group combines expertise in gene regulation in pediatric cancers, next-generation sequencing techniques and advanced genomic analysis.

“These mutations have not been well studied yet because the recently developed sequencing and analysis techniques are complex,” Abraham says. “By applying these methods to many models, we hope to better understand the mechanisms causing cancer.”

Zhang notes: “By identifying a new vulnerability in gene expression, we may be able to identify novel targets for the development of future therapies.

“In the meantime, our datasets will be a valuable resource for the pediatric cancer research community.”

Biology of liquid organelles

Did you label and color the parts of the cell in science class? Then you understand there are distinct structures inside cells, such as the nucleus and mitochondria.

But cells also contain liquid droplets. For many years, scientists could not explain them. Then, a decade ago, researchers discovered that these “liquid organelles” form by condensation, similar to how droplets of oil and vinegar form in salad dressing.

“Today, we know that liquid organelles directly or indirectly control most cellular functions,” says J. Paul Taylor, MD, PhD, St. Jude Cell and Molecular Biology chair and Howard Hughes Medical Institute investigator. “We suspect that a large number of diseases, including cancer and neurodegenerative disorders, are caused by disturbances in how liquid organelles assemble.”

In 2013 and 2017, Taylor and his St. Jude colleagues discovered gene mutations in a specific liquid organelle that cause amyotrophic lateral sclerosis and frontotemporal dementia. They also found that some of these same mutations drive certain cancers such as leukemia and Ewing sarcoma.

“We’ve begun to tease apart the underlying biology of liquid organelles, but there’s much still to learn,” Taylor says. “If a gene mutation changes the viscosity of a liquid organelle, does that cause disease? If so, we need to understand that process.”

To find answers, Taylor invited Tanja Mittag, PhD, and Richard Kriwacki, PhD, both of St. Jude Structural Biology, who collaborated with Taylor on previous discoveries of gene mutations in liquid organelles, to join the team. Biomedical engineers Rohit Pappu, PhD, at Washington University and Clifford Brangwynne, PhD, at Princeton University are contributing their expertise in biophysics to explore how liquid organelles assemble.

“No single lab has all the skills necessary for this work,” Taylor says. “Our group has been highly productive and published many papers since we started two years ago. We’re finding answers that no one lab could have answered on its own.”
By Elizabeth Jane Walker
IMAGINE YOU’RE FLYING in a private aircraft. Initially nervous, you relax into your comfy seat, as waiters offer food and drinks.

Then comes the announcement you knew would come eventually: You must jump out of the plane midair. You’re terrified at the prospect. Who will offer guidance for this leap? What awaits you on the ground? How can you prepare?

A similar sense of anxiety grips many patients and families as they prepare to return home after cancer therapy at St. Jude Children’s Research Hospital. For months or even years, St. Jude has provided housing, food and medical treatment. Their care team has held them close—anticipating their needs, calming their fears. Suddenly, the family faces the daunting task of returning home: a place where doctors, nurses, psychologists, physical therapists and pharmacists will no longer be accessible at a moment’s notice. Where bullies may lurk on the playground. Where the specter of a relapse is only a breath away.

Now there’s a parachute to ease those worries and provide patients and families with a soft landing. It’s called the St. Jude Transition Oncology Program, or TOP.

PRE-FLIGHT JITTERS

For two-and-a-half years, Trevor Shinall received treatment for acute lymphoblastic leukemia (ALL) at St. Jude. About 10 weeks before the fifth-grader completed therapy, his mom, Kelly, began to feel nervous.

“I was excited for him to be done, but it was also scary,” Kelly says. “Trevor was having some side effects. He was extremely thin. He had some drop foot, weakness in his legs and shaking in his hands. I thought, ‘What’s going to happen when we get home? We’re going to be done with this cancer, and he’ll be cured, but what about all this other stuff going on?’”

One day, a TOP appointment appeared on their schedule. During that meeting, Kelly and her husband, Terry, met Nurse Practitioner Sandra Jones, who explained how the TOP team would connect the family with resources.

“She answered my questions and gave me a lot of information about nutrition, since Trevor’s weight was so low.”

TOP’s rehabilitation coordinator ensured that Trevor had occupational therapy and physical therapy appointments awaiting him in his hometown. Today, Trevor is back in school and has joined the soccer team, returning to St. Jude every few months for checkups.

PACK THE PARACHUTE

Established in 2018, the TOP team helps patients and their families make the leap from hospital to home. Active treatment is complete; families visit the hospital periodically to ensure the patient remains cancer free.

“Just because they’re finished with therapy doesn’t mean it’s going to be smooth sailing,” says Emily Browne, DNP, RN, who directs TOP. “It’s exciting, because they’re done with this phase, but it can be unsettling. Children have to go back to school. Parents have to go back to work. They’ve got to figure out what their new normal is. We want to make sure they feel supported during that time.”

The TOP team includes nurse practitioners, psychologists, social workers, rehabilitation coordinators and school liaisons. The team also coordinates with a physician in the child’s primary care practice to provide ongoing care. Here’s how the TOP team helped Trevor.

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Support and resources
Nurse Practitioner Sandra Jones was one of the TOP staff who helped guide Trevor Shinall and his family through the transition from hospital to home. Jones and the rest of the team worked together to connect the family with the resources they needed.

TANDEM JUMP
As an ALL survivor who was diagnosed during high school, Browne can empathize with patients facing the end of therapy.

“For me, those first couple years off therapy were rough,” she recalls. “There was a lot of anxiety over every little cold and sinus infection. I’d think, ‘Oh my gosh, what if I relapse?’ I was no longer getting medicine all the time or having my labs checked—and yet, I was expected to bounce right back into life. It was a very confusing time for me.”

Browne acknowledges that every family has its challenges and struggles.
“I’ve had some families tell me, ‘Gosh, this was harder than the diagnosis,’ and other families who jump right back into life and school easily,” she says.

The TOP staff tailors their offerings to each family’s needs. Preparations begin well in advance of the return home, so that the patient and family have ample time to begin the transition and receive the support they need.

“We want them to be the happiest and healthiest they can be,” Browne says.

**PULL THE CORD**

April Parker and her husband, Ryne, spend their days chasing 16-month-old Turner, an active toddler who recently completed therapy for neuroblastoma, a cancer of nerve tissue. April says the TOP program’s social worker put her in touch with a mentor—a parent who could offer practical suggestions and a listening ear.

“I had so much anxiety and fear as Turner came off treatment,” April admits. “When you’re at St. Jude, nurses and doctors are available 24/7, if you need them. My mentor was able to help calm my fears and reassure me that leaving the hospital wasn’t a bad thing. She gave me lots of encouragement and advice. She also helped me connect back to the real world, after being at St. Jude for so long.”

April says the TOP program helped smooth the way for their return home. Browne set up a psychology appointment to ensure Turner was on track with social and cognitive skills. She also sent Turner’s hometown pediatrician a detailed summary of the child’s treatment, as well as follow-up recommendations and contact information. Browne continues to call the family about once a month to find out if any issues require attention.

“It’s reassuring to know that we can reach out to her if we have questions,” April says, “and if there’s an immediate need she’ll help find someone in our area to meet it. This program is great because it helps me feel like we’re supported even when our St. Jude team doesn’t have their eyes on us every day.”

**Encouragement and advice**

The TOP team smoothed the way for Turner Parker to return home after his treatment for neuroblastoma. Members of the team helped ensure Turner was on track with social and cognitive skills, served as a liaison with his hometown physician and followed-up with regular phone calls to check on Turner’s progress.
The Rise of LANDO

Research yields an unexpected discovery—named after an unlikely hero in a galaxy far, far away.

By Erin Podolak
**How do researchers** at a children’s hospital make a discovery about Alzheimer’s disease, a disorder associated with aging? By following the science.

Led by Douglas Green, PhD, St. Jude Department of Immunology chair, a group of scientists were investigating how the immune system responds to cancer. They were studying autophagy, a process where a cell consumes pieces of itself to recycle nutrients and clear away damaged or unneeded parts. It’s a cell’s way of cleaning up.

Several proteins are involved in autophagy. To find out whether autophagy might play a role in immune response, the researchers focused on the LC3 protein in microglial cells. These cells are the primary immune cells of the brain and central nervous system.

That’s when science threw them a curveball. The researchers made a discovery—one with implications for cancer immunotherapy, but also for Alzheimer’s disease.

“You can expect your research to take you in one direction, but then the science pulls you in another,” Green says. “Following where the results lead can bring forward some truly fascinating discoveries.”

**Alzheimer’s and LC3**

The researchers discovered that LC3 helps microglial cells move proteins through their membrane in a process called endocytosis. LC3-associated endocytosis, or LANDO, enables microglial cells to clear away beta-amyloid protein. A buildup of this protein is one of the factors underlying the establishment and progression of Alzheimer’s disease.

Imagine a car wash. Receptors on the surface of microglial cells bind to beta-amyloid proteins like cars hook into the track of an automatic carwash. The cars bring with them dirt and debris that gets cleared away in the wash, much like beta-amyloid that is consumed by microglial cells. When the beta-amyloid is disposed of, the receptors return to the microglial cell surface like glistening cars returning to the road.

A car wash needs hardware to attach the car to the track. Similarly, LANDO requires several proteins to help it do its job. The proteins, called Rubicon, Beclin1, ATG5 and ATG7, decline with age as their expression decreases. This explains how in older individuals LANDO can start to lag behind, unable to clear the beta-amyloid protein.

**Eureka moment**

The researchers realized what they had found. Activating LANDO appears to offer protection against neurodegenerative disease, guarding against toxic neuroinflammation and neurodegeneration, including memory problems.

“Turning on LANDO in microglial cells could form the basis of a new type of therapy, where cells are able to increase their ability to clear away beta-amyloid, reducing neuroinflammation,” explains Bradlee Heckmann, PhD, a postdoctoral fellow in Green’s lab.

Although the link between Alzheimer’s disease, beta-amyloid proteins and LANDO is clear, the pathway is still relevant for research into how the immune system responds to cancer. Inhibiting LANDO could also help boost the effectiveness of cancer immunotherapies.

“At St. Jude we care deeply about the health of children, and we still care about them even when they get much older,” Green says. “We think that our discoveries on Alzheimer’s disease will bring us back to insights into pediatric brain cancers. Following the science is the St. Jude way. We never know where discoveries will lead us.”

**Naming a discovery**

In biology, discovering something new often means you get to name it. Green and Heckmann named their find LC3-associated endocytosis, but they wanted an acronym that might resonate more with scientists and the public.

Talking it over with their colleagues one evening, the researchers found their conversation flitting back and forth between their work in the lab and the latest movie in the Star Wars saga.

As the conversation flowed, Green mentioned the character Lando Calrissian, who is a smuggler and pilot in the films. Eventually it clicked for Green, and LC3-associated endocytosis became LANDO.

What convinced Heckmann that the acronym was fitting were the images of LANDO at work in microglial cells.

“The image of red-stained beta-amyloid protein and microglial cells stained green against a black background looked like something from Star Wars,” he says.

**Douglas Green, PhD**

**Bradlee Heckmann, PhD**

**Galaxy of discovery**

When St. Jude scientists made a momentous discovery, they named their discovery LANDO, after a Star Wars pilot and daring leader.
Destination: Information

By Mike O’Kelly

St. Jude uses sophisticated technology to understand disease and share data with the global community.
**SCHOLARS HAVE SHARED** their findings in academic journals for more than three centuries. The first journal was a 12-page pamphlet published in France in 1665. Since that time, scientific findings have filled leather-bound books and glossy magazines with a common goal of documenting and inspiring research.

Today’s scientists have a wealth of information available at their fingertips—a data revolution that is changing the landscape of medicine and research.

St. Jude Children’s Research Hospital is helping drive this new age of information-sharing, providing a roadmap for investigators complete with data, tools and resources.

**IN THE CLOUD**

In early 2020, the institution marks the 10th anniversary of the St. Jude–Washington University Pediatric Cancer Genome Project (PCGP). This landmark initiative set the stage for huge leaps in our understanding of the origins of disease. Researchers sequenced the genomes of more than 800 patients to find the genetic factors behind the most common pediatric cancers.

Recognizing the need for a more sophisticated resource, the institution launched St. Jude Cloud in 2018. This resource allows users to study the world’s largest whole genome-based pediatric cancer repository and to analyze genomic data with advanced tools and visualization methods. The portal houses more than 10,000 whole genomes.

“Our idea was to enable users by developing tools and make it easier for institutions that do not have huge computing infrastructures to analyze data,” says Jinghui Zhang, PhD, St. Jude Computational Biology chair.

**PROTEIN PAINT AND PECAN PIE**

One of these tools, a web application called ProteinPaint, provides snapshots of gene mutations from pediatric cancer that alter the genetic instructions for encoding proteins. This allowed researchers a first-time glimpse of these details.

St. Jude scientists also developed a free, online system to search the millions of variations in a patient’s genome. The portal—Pediatric Cancer Variant Pathogenicity Information Exchange (PeCanPIE for short)—can find mutations linked to inherited disorders. Just like St. Jude Cloud, the data is freely available.

**PROPEL AND CSTN**

The success of St. Jude Cloud has spawned other sharing tools targeted at specific diseases and patient research. Last year, the hospital unveiled PROPEL—one of the world’s largest collections of leukemia samples from children and adults. PROPEL samples are available at no cost to researchers with no obligation to collaborate. St. Jude sends investigators the samples along with the data.

The hospital teamed with the Howard Hughes Medical Institute in 2017 to create the Childhood Solid Tumor Network, the world’s largest collection of pediatric tumor samples. This free resource includes samples and data aimed at advancing treatment and research of pediatric solid tumors.

**SURVIVORSHIP AND SICKLE CELL**

St. Jude Cloud also hosts two new portals for scientists studying childhood cancer survivorship and sickle cell disease.

The survivorship portal offers clinical and genomic data from thousands of childhood cancer survivors in the St. Jude Lifetime Cohort study. The portal includes de-identified data of more than 3,000 study participants along with genomic information as well as demographics, diagnoses, outcome and treatment.

“Our goal is to accelerate the rate of discovery in pediatric cancer survivorship research,” says Leslie Robison, PhD, St. Jude Epidemiology and Cancer Control chair. “We’re convinced the best way to achieve this is by using St. Jude Cloud to make the data from the St. Jude Lifetime Cohort Study available to the global research community.”

St. Jude has sequenced the DNA of about 500 patients with sickle cell disease to help determine why complications vary among individuals. This disorder is caused by the mutation of a single gene, but genetic modifiers influence outcomes such that some patients are sicker than others.

“We are examining potential associations between the sequencing data and specific clinical complications of our sickle cell disease patients to identify and study genes that affect their outcomes. Ultimately, understanding sickle cell disease modifier genes should lead to new, individualized therapies,” says Mitch Weiss, MD, PhD, St. Jude Hematology chair. “The portal is making some of that information available publicly so that other investigators can use the information to do similar work.”

**FUTURE DESTINATIONS**

As technology and data sequencing evolve, St. Jude will continue to develop ways to understand the biology of disease while providing information freely to the world.

“We are on the path of increasing the dimensionality of our genomic data resources,” Zhang says. “In addition to a data repository, St. Jude Cloud will be more of an integration portal for all different types of data relevant to pediatric cancer.”

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TWENTY-SEVEN YEARS. FOUR STATE CHAMPIONSHIPS. HUNDREDS OF STUDENT-ATHLETES. As a teacher and softball coach, I tell my students that good things happen if you work hard. But that doesn’t just mean wins and losses on the field. For me, the ultimate victory occurs when I send kids out of my program into the world to do great things.

Sometimes I wonder what would have happened to some of those kids if St. Jude Children’s Research Hospital had not made my future possible.

I was 13 when I learned I had acute lymphoblastic leukemia. My cancer didn’t go into remission as quickly as the doctors would have liked. The cranial irradiation and 30 months of chemo robbed me of my teenage years, as well as my shoulder-length hair (it was the ’70s, after all).

Eventually I returned to a normal life, graduating from college and marrying Cecelia, who is also a childhood cancer survivor.

I think about St. Jude every day. I also think about the children who went before me. My cancer cure occurred because St. Jude patients in the 1960s and early 1970s participated in research.

Now I feel a responsibility to give back. I donate money to St. Jude every month, but taking part in survivorship research is the best way I know to make a difference.

Each time I arrive at St. Jude and see the amazing research facilities, I know that behind those walls, great things are going on.

St. Jude has remained a part of my family’s life and will forever. My brother constantly fundraises for the hospital. Even my daughter, Darbi, is a supporter. She knows that if I hadn’t received treatment at St. Jude, she wouldn’t be here. One day, when I’m gone, my daughter will carry on the love and care that I have for St. Jude.
R is for Robot

DUANE CURRIER AND OTHER SCIENTISTS in the High-Throughput Bioscience Center at St. Jude use robots to automate the screening of hundreds of thousands of compounds to discover potential new drugs.

St. Jude patients recently named the newest robot, who now goes by Max. Patients also helped name the hospital’s other robots: Billy, Saver and Widget. Max allows scientists to capture images of cells on multiple channels while keeping the cells alive for long periods of time.
Art for all

Even the coldest winter day is glorious in the area between Chili’s Care Center and the Kay Research and Care Center. Ducks paddle across brilliant blue water as 1.2 million sequins shimmer in the breeze. Artists are submitting the 12,000-square-foot mosaic mural to Guinness World Records.

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