CHILDREN'S HOSPITAL LOS ANGELES

RESEARCHLA

2017

TIME IS BRAIN

Exploring new ways to prevent—and predict—epilepsy in children

CHILDREN'S HOSPITAL LOS ANGELES

RESEARCHLA

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ABOUT THE SABAN RESEARCH INSTITUTE

The Saban Research Institute encompasses basic, translational and clinical research at Children's Hospital Los Angeles—one of the few freestanding pediatric hospitals in the country where scientific inquiry is combined with clinical care devoted exclusively to children.

The Institute's interdisciplinary research explores the developmental origins of health and disease and addresses the most pressing issues of children's health.

Originally established in 1992, The Children's Hospital Research Institute became The Saban Research Institute in 2003 following a transformative gift in support of pediatric research made by Cheryl Saban, PhD, Haim Saban and The Saban Family Foundation. In fiscal year 2016, The Saban Research Institute received $26.1 million (prime and subawards) in National Institutes of Health (NIH) funding and $71.4 million in total funding. The Saban Research Institute ranks eighth in the nation among children's hospitals for NIH funding.

The Saban Research Institute and CHLA maintain strong scientific and strategic affiliations with the University of Southern California (USC) and the Keck School of Medicine of USC, where our physicians and scientists hold faculty appointments. The Institute's researchers also are involved in collaborative projects with academic institutions throughout the U.S. and abroad.

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Cover image: Earlier detection of the risk for epilepsy will improve long-term outcomes for children. See page 12 to learn more.

Kylie was diagnosed with a rare and aggressive form of leukemia. Her parents didn't know what to do. But her doctor did.

He offered Kylie treatment in a clinical trial that might give her a greater likelihood of remission. Her parents didn't hesitate. Now Kylie is doing well.

Please help kids like Kylie by supporting research at Children's Hospital Los Angeles.

Donate today
CHLA.org/FundResearch

A Message From Leadership

In light of all the discussions about health care policy and coverage, we've given a lot of thought to how the proposed changes would affect our patients. Some of the effects would be immediate, but others wouldn't become apparent until much later in the patient's life. Although you may have a lifetime to achieve a happy childhood, having a healthy childhood is a limited-time offer.

At Children's Hospital Los Angeles, we are working to achieve the healthiest childhood possible for each individual given the differences in genetics, environment and other factors.

"It's never too late to have a happy childhood."

– Tom Robbins

At The Saban Research Institute our investigators know that many adult diseases originate during those 18-plus years of childhood, making this time period especially crucial for maximizing the opportunity for health over a lifetime. In this issue of ResearCHLA, we profile several investigators who represent just a few of the hundreds who are working to provide children with a foundation of health by preventing or treating conditions as early as possible.

You will read how during the first moments of a patient's childhood—at the time of birth—something can go wrong, causing the newborn to suffer a lack of oxygen and putting the child at risk for cerebral palsy and neurodevelopmental disabilities. For these babies, Jessica Wisnowski, PhD, and Tai-Wei Wu, MD, are leading a study using therapeutic hypothermia combined with a medication that has neuroprotective properties. CHLA is the only hospital in Southern California able to offer this clinical trial.

We know that children with genetic disorders bear a significant burden, with many of these conditions putting the child at risk for early mortality. In this issue, you will read about Neena Kapoor, MD, and her use of a novel cellular therapy to treat a newborn patient suffering from severe combined immunodeficiency disorder. The child didn't just get better—he was cured.

Research done here goes beyond benefiting babies. As an example, our care for young athletes treated for concussions has led to studies on the differences in treatment required for the developing brain compared with what's needed for the adult brain. Building upon this research, Tracy Zaslow, MD, is leading our Children's Orthopaedic Center's Sports Concussion Program—the only one of its kind in Los Angeles.

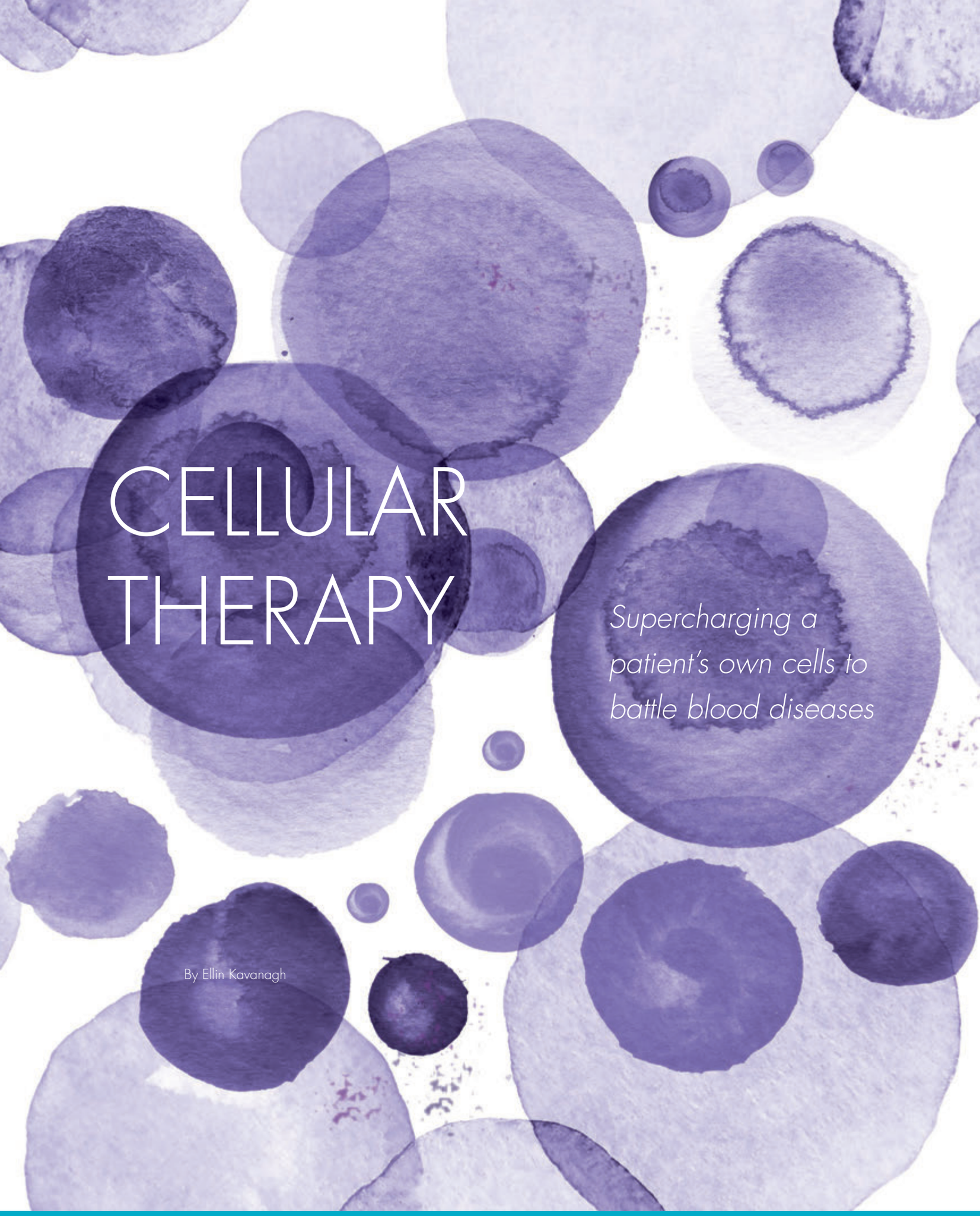
In these times when the cost of medical care is increasingly scrutinized, childhood stands out as the single best opportunity to produce the greatest return on dollars spent for health care. Through the work being done at The Saban Research Institute, our investigators are developing new standards of care so that health care accessed during childhood can pay dividends over a lifetime.

We hope that you enjoy this issue of ResearCHLA. We also hope that you will join us and our investigators by advocating for policies that support the integrity of funding for science and health care to ensure that every childhood is as healthy as possible.

Warmest regards,

Paul S. Viviano
President and CEO
Children's Hospital Los Angeles

Bradley S. Peterson, MD
Interim Director,
The Saban Research Institute
Director,
Institute for the Developing Mind



CELLULAR THERAPY

Supercharging a patient's own cells to battle blood diseases

By Ellin Kavanagh

"At CHLA, we can now offer potent immunotherapies to children with the most resistant cancers."

– Alan Wayne, MD

Cellular therapy is a treatment strategy that involves injecting living cells into a patient. For nearly 50 years, physicians have been using a type of cellular therapy, called bone marrow transplantation (BMT), that revolutionized treatment of cancer and blood diseases. BMT provides a way for patients to safely receive more aggressive, and often curative, treatment.

Cellular therapy may be poised to once again transform the treatment of cancer and blood diseases. Now scientists are taking a patient's or donor's blood cells and genetically engineering them to specifically target cancer cells and be more effective at battling disease.

"Despite the nearly continuous advances that have been made in the treatment of leukemia, this malignancy remains a leading cause of death in childhood," says Alan Wayne, MD, director of the Children's Center for Cancer and Blood Diseases at Children's Hospital Los Angeles and professor of Pediatrics at the Keck School of Medicine of the University of Southern California (USC). "At CHLA, we can now offer potent immunotherapies to children with the most resistant cancers."

Clinical trials for cancer

Alan Wayne, MD

Wayne is lead principal investigator on a multisite trial of chimeric antigen receptor T-cell (CAR-T) therapy for patients with relapsed or resistant acute lymphoblastic leukemia (ALL). He led an earlier CAR-T trial at the National Cancer Institute in which 14 of the 20 young patients treated achieved complete remissions. CHLA is one of a small number of sites offering this novel therapy to pediatric patients.

Michael Pulsipher, MD

Two other multicenter CAR-T trials at CHLA are being led by Michael Pulsipher, MD, section head of Blood and Marrow Transplantation, including an approach targeted at patients earlier in their disease phase with minimal residual disease. "There are many types of ALL with a poor outcome after BMT—we need to define patients where CAR-T cell therapy can either help or replace BMT," says Pulsipher.

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TARGETING RELAPSED/RESISTANT LEUKEMIA

RELAPSED LEUKEMIA IS OFTEN RESISTANT TO CHEMOTHERAPY.

CAR-T CELL THERAPY USES A PATIENT'S OWN IMMUNE CELLS TO SPECIFICALLY TARGET AND DESTROY LEUKEMIA.

Suits him to a T

Ninety percent of children diagnosed with acute lymphoblastic leukemia are cured. However, of those who relapse, only a minority survive long-term. So when Alexis Bonilla was 11 years old and his disease returned for the third time, his doctor immediately referred him to CHLA.

"I told Alexis' parents that the good news is we have a new therapy, and after being treated with it, your son has a 90 percent chance of remission," says Pulsipher. "The not-so-good news is that it might initially make him very sick."

Alexis' mom, Daysi Bonilla, and his stepdad, Jorge, agreed right away to have their son in the study.

Alexis Bonilla

Personalized medicine

A T-cell is a type of white blood cell that is part of our defense against viruses, bacteria, and to a lesser extent, cancer. CAR-T therapy harnesses the immune system by engineering the T-cells to specifically attack cancer cells. The opposite of a "one size fits all" strategy, this treatment is individually created for each patient using his or her own cells.

Alexis' blood was collected and sent to the lab so that his T-cells could be genetically engineered to produce a chimeric antigen receptor (CAR) on their surface. The receptor directs the T-cells to a protein, called CD19, present on leukemia cells. When the CAR-T cell connects with the CD19 protein, the leukemia cell is destroyed.

Alexis received several weeks of high-dose chemotherapy to kill as many leukemia cells as possible. Then his modified T-cells were reinfused.

Waiting to see what happens

"Ninety percent of patients develop a fever after the cells are infused," says Pulsipher. "It's a side effect that we want to see because it indicates that the CAR-T cells are functioning appropriately."

He explains that the greater the number of tumor cells a patient has, the greater the immune response. Sometimes, the battle between the supercharged T-cells and the large number of cancer cells becomes extreme, causing the patient's blood pressure to plummet.

This reaction, known as cytokine release syndrome, or "cytokine storm," occurred in Alexis. He was moved to the pediatric intensive care unit so that his response could be safely managed. "It was scary," says Daysi.

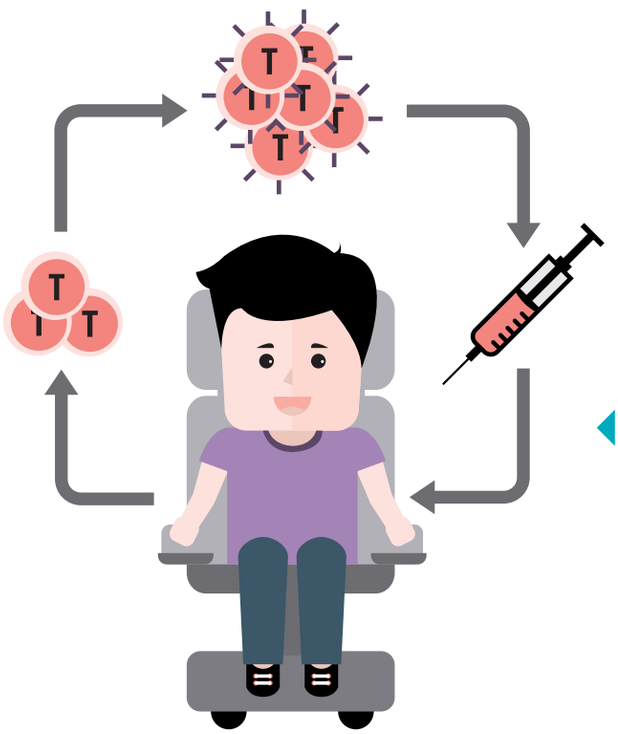
What's next for CAR-T?

When an investigational therapy is first introduced into the clinic, it is tested in people who have disease that is resistant to all other treatments—basically, the sickest patients.

"As we gain experience with CAR-T and trials are open to a wider variety of patients, I anticipate that we will see less-severe side effects in people with earlier-stage disease," says Pulsipher, who is also a professor of Pediatrics at the Keck School of Medicine of USC. Until then, he and his colleagues are glad to have this truly life-changing therapy to offer their most seriously ill patients.

Alexis made a rapid recovery. Two months after starting treatment at CHLA, he was ready to return home. He always bounces back, Daysi says.

"He wants life," adds Jorge.



Blood is removed from the patient and T-cells are separated out. The T-cells are sent to the lab, where the number of cells is expanded and a receptor is added to their surface. The modified cells are returned to the patient intravenously. The receptor acts to help the T-cells recognize and kill leukemia cells.

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"In the past, these babies did not have a chance—but now they do."

– Neena Kapoor, MD

The Match Game

Human leukocyte antigen (HLA) proteins are present on every cell in our body and are the primary way that the immune system distinguishes its own cells from foreign proteins—like another person's cells.

A successful stem cell transplant involves matching the patient's HLA tissue type with that of a donor. The closer the HLA match between donor and recipient, the better the chances of the transplant's success.

If the match is not close enough, the body will attack the donor cells and reject the stem cell graft. Or the immune cells from the graft can attack the recipient's body, resulting in a serious, potentially fatal condition called graft-versus-host disease. In a half-matched transplant, the possibility of graft-versus-host disease is increased because of the imperfect HLA match.

Beyond cancer

Neena Kapoor, MD

At CHLA, the reach of cellular therapy extends beyond cancer to diseases like severe combined immunodeficiency disease, sickle cell disease and other life-threatening blood disorders.

Neena Kapoor, MD, director of the Blood and Marrow Transplant Laboratory, is employing genetically engineered T-cells to make hematopoietic transplants like BMT safer for patients who lack a perfectly matched donor.

A child born with severe combined immunodeficiency disease (SCID) lacks the ability to fight off even the most benign infection. The condition is sometimes referred to as "bubble boy disease" because the child needs to live in a pathogen-free environment to survive.

Babies with this condition usually die of infection before their second birthday unless treated with a hematopoietic stem cell transplant that transfers immune cells from a donor. But what happens if a perfectly matched donor cannot be found?

Making a match

For ethnic minorities and those of mixed heritage, the chance of finding a full or "perfect" match is significantly less than it is for a Caucasian patient. "In a diverse community like Los Angeles, we needed to work toward finding other options for our patients," says Kapoor, who is also a professor of Clinical Pediatrics at the Keck School of Medicine of USC.

Since a child gets half of his or her genes from each parent, the half-matched transplant is an option for any child who has at least one living parent. Thanks to this technique, many children who lack a perfect donor match now have access to potentially lifesaving treatments.

"HALF-MATCHED" TRANSPLANTS

FOR ETHNIC MINORITIES AND THOSE OF MIXED HERITAGE, THE CHANCE OF FINDING A FULL OR "PERFECT" MATCH IS SIGNIFICANTLY LESS THAN IT IS FOR A CAUCASIAN PATIENT.

PARENTS ARE ALWAYS A HALF MATCH FOR THEIR CHILDREN SINCE THE MOTHER AND FATHER EACH CONTRIBUTE 50 PERCENT OF THE CHILD'S GENES.

"In the past, these babies did not have a chance—but now they do," says Kapoor.

She explains that although CHLA has been doing haploidentical, or half-matched, transplants for babies with SCID since 1980, there are now safer techniques for these high-risk transplants. Under Kapoor's leadership, CHLA is involved in a clinical trial testing ways to reduce the risk for children with malignant and nonmalignant blood disorders.

Adding a safety switch

"The half-matched transplant offers more patients an opportunity to be cured of their disease," says Kapoor. "To make the procedure safer, we remove the majority of T-cells—cells that are capable of recognizing self from non-self and can cause graft-versus-host disease. But removal of these cells from the graft can delay immune recovery and increase the risk of a potentially lethal infection."

To address these concerns, patients on the trial receive genetically modified T-cells that have been engineered to include a safety switch, or "suicide gene," which can be activated if the patient experiences significant signs of graft-versus-host disease. If that happens, a medication can be given that flips the safety switch, causing the reactive T-cells to self-destruct within hours.

This technique allows Kapoor and her colleagues to safely transplant a greater number of immune cells, which provides the patient with immune function much more quickly.

"Typically, patients spend four to six months in a sterile hospital room waiting for their immune system to rebuild," says Kapoor. "In this study, we can safely send them home just a few weeks after transplant."

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SEVERE COMBINED IMMUNODEFICIENCY DISEASE

CHILDREN NOT SCREENED AT BIRTH EXPERIENCE SEVERE RECURRENT INFECTIONS AND PREMATURE DEATH.

NINETY PERCENT OF CHILDREN IDENTIFIED THROUGH NEWBORN SCREENING SURVIVE WITH TREATMENT.

A newborn being tested for SCID

Need to know

Like every other baby born in the United States, Lawrence Hunt was screened for a variety of lethal conditions that are treatable but not clinically apparent at birth. Although newborn screening is federally recommended, the number of diseases screened for varies by state. Luckily, Lawrence was born in Apple Valley, California.

"California was one of the first states to screen for severe combined immunodeficiency disease," says Joseph Church, MD, division head of Clinical Immunology and Allergy at CHLA and professor of Pediatrics at the Keck School of Medicine of USC.

"Ninety percent of children identified through newborn screening survive with treatment. For children not screened at birth, however, survival drops significantly."

When Lawrence's parents arrived home with their newborn son, they received a call asking them to return to their local hospital to have the screening repeated. After the results were confirmed, the next call came from Church, who oversees notification and treatment referrals of infants born with SCID in Southern California.

Church also heads the Jeffrey Modell Diagnostic and Research Program for Primary Immunodeficiencies at CHLA. Jeffrey Modell was born with primary immunodeficiency disease. After he passed away, his parents, Vicki and Fred Modell, became advocates and established a foundation in memory of their son. The Modells and Church were among those responsible for California being one of the first states to routinely screen for immune disorders. By 2015, 34 states were screening newborns for immune deficiency diseases, with an additional eight states expected to begin this year.

Joseph Church, MD

Church asked the Hunts to come to the hospital for follow-up and treatment. At CHLA, Lawrence's parents learned that their son was born without an immune system, leaving him at high risk of developing a lethal infection. He required a hematopoietic stem cell transplant that would allow him to develop normal immune function.

"Soon, our baby was moved to the bone marrow transplant unit," recalls Christina Rwengo, Lawrence's mom. "He was kept in isolation while we waited for a match."

Unfortunately, no match was found.

A less-than-perfect match can be ideal

Kapoor met with the parents and told them that when a full match isn't found, centers like the one at CHLA have had success with half-matched transplants. Either biological parent could serve as the donor. Rwengo volunteered.

"Lawrence had never seen my face or his father's face—just our eyes—because we had to wear a mask whenever we were with him," she explains. "This was our first child. We wanted him to be able to see us, his mom and dad, and we wanted to bring him home."

Kapoor informed the parents about the clinical trial at CHLA, and they readily agreed to participate. In the study, Lawrence received the half-matched transplant plus some of his mom's white blood cells that had been genetically modified. These cells provided immunity until Lawrence's own immune system developed. As hoped, because of those additional cells from his mother, Lawrence was able to emerge from isolation and return home months sooner than he would have with standard treatment.

"He's a typical, happy 1-year-old," says his mom. "We are so grateful that Lawrence was tested for SCID at birth. Without the treatment he received at CHLA, he could have died from a minor cold. Instead, he's home."

Learn more about clinical trials available at the Children's Center for Cancer and Blood Diseases.

CHLA.org/CancerTrials

Finding New Therapies

Cellular therapy trials offer new options for patients with diseases previously considered untreatable. Investigators at the Children's Center for Cancer and Blood Diseases are continuing to expand the portfolio of clinical trials available. In fact, CHLA was recently named a Children's Oncology Group Phase 1 study site.

"It was a great honor being selected to be one of the 21 members in the National Cancer Institute-sponsored Children's Oncology Group Phase 1 consortium," says Alan Wayne, MD, "because it acknowledges the breadth and depth of experience with cancer and clinical trials at CHLA. We are proud to be one of the leading centers in the United States that offer breakthrough therapies to our patients."

TIME IS BRAIN

By Jennifer Marcus

Exploring new ways to prevent—and predict—epilepsy in children

For Douglas Nordli Jr., MD, chief of the Division of Pediatric Neurology at Children's Hospital Los Angeles, "time is brain." A recognized expert in the area of epilepsy, Nordli is acutely aware of the impact a certain type of febrile seizure can have on the developing brain. His research focuses on the early identification and aggressive treatment of children at highest risk.

Convulsions that happen during a fever, called febrile seizures, are fairly common, occurring in 2 to 4 percent of children under 5. Although the seizures are frightening to parents, most children who have simple febrile seizures develop appropriately and are not going to have other forms of neurological manifestations. Perhaps only 3 percent of them will develop epilepsy.

But Nordli is most concerned with febrile status epilepticus (FSE), a subgroup of prolonged or clustered febrile seizures. These seizures won't stop on their own, and even with medical intervention they may last for an hour or longer. FSE can occur in up to 5 percent of febrile seizure cases, and at least 40 percent of children who experience FSE will develop epilepsy.

"If we can predict which children are at risk for developing catastrophic epilepsy, we can take steps to prevent it."

– Douglas Nordli Jr., MD

By focusing on children with FSE, Nordli and his colleagues are working to answer a question that has long plagued neurologists: Why do people develop epilepsy?

For a decade, he and a team of specialists have been working on the National Institutes of Health-funded FEBSTAT study to determine the long-term consequences to the brain of prolonged febrile seizures in childhood. This multicenter, longitudinal study is led by Shlomo Shinnar, MD, PhD, from Montefiore Medical Center and the

Electroencephalography (EEG) tests are just one of the tools doctors use to diagnose and monitor epilepsy.

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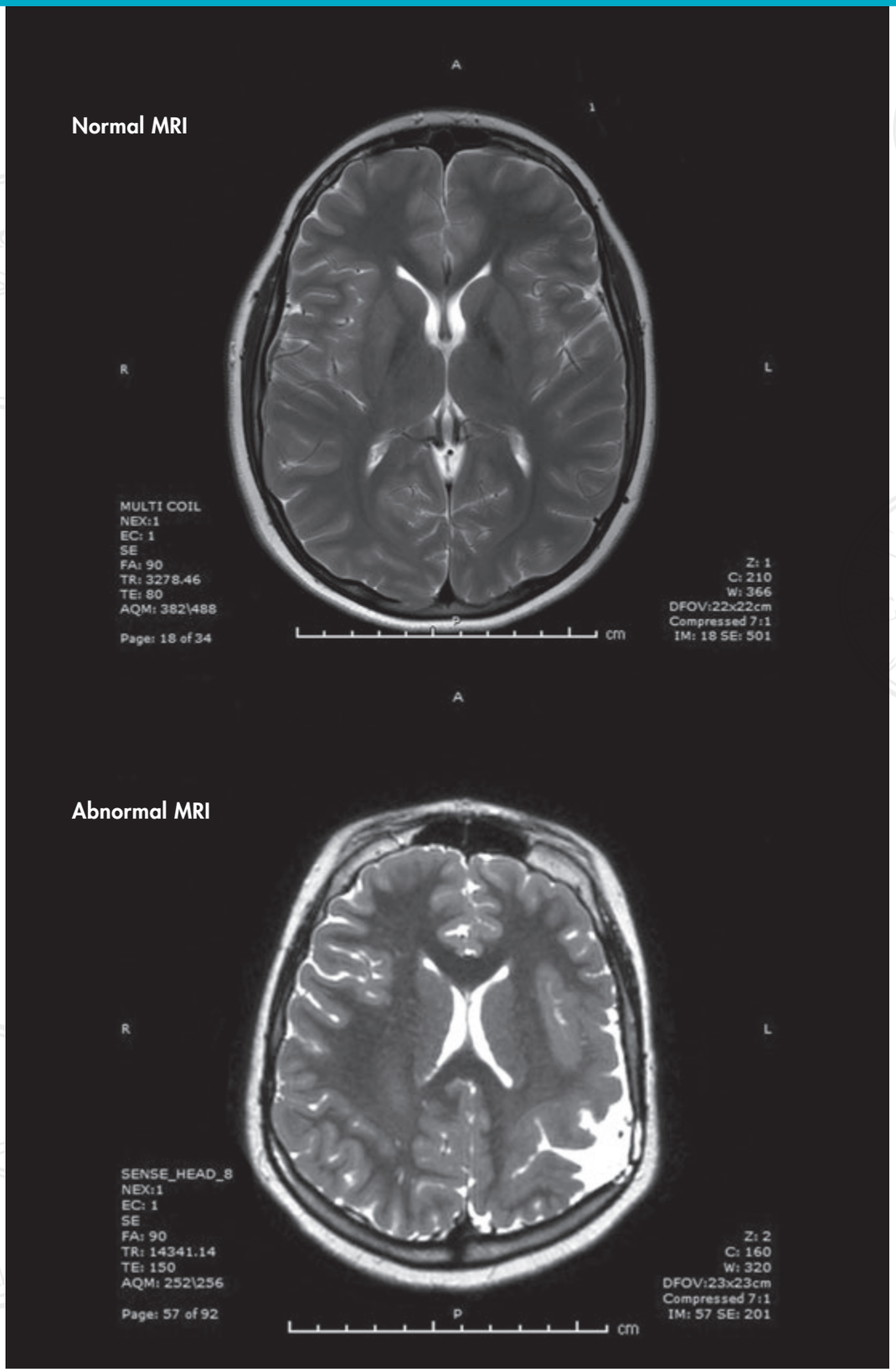


Neuroimaging techniques, such as magnetic resonance imaging (MRI), are used are used to detect any changes to the brain structure that may cause seizures.

Albert Einstein College of Medicine in New York City. Nordli has now brought CHLA into the study as well.

In the study, Nordli and his colleagues are using neurodiagnostic tools to look for abnormal patterns of brain waves and to study changes to brain structure that occur during prolonged seizures. They have observed that the patient's right hippocampus—a small region of the temporal lobe primarily associated with memory and spatial navigation—appears to be brighter and slightly enlarged during prolonged seizures. They also found abnormal electroencephalography (EEG) patterns in these children, indicating altered brain activity and even brain injury.

"These findings are moving us toward the development of a biomarker for epilepsy," says Nordli. "If we can predict which children are at risk for developing catastrophic epilepsy, we can take steps to prevent it."

Nordli, a professor of Clinical Neurology at the Keck School of Medicine of the University of Southern California, is also employing newer technologies. Estimating that 40 to 60 percent of epilepsy cases can be identified through gene sequencing panels, he is collaborating with geneticists at CHLA's Center for Personalized Medicine on next-generation sequencing. The goal: improve understanding of how the genome influences the development and function of the nervous system.

"With the advent of precision medicine and novel diagnostic tools, this is a pivotal time in the field of child neurology," says Nordli. "Time is brain—and earlier detection of the risk will mean better long-term outcomes for children."

Learn about epilepsy treatment at CHLA.

CHLA.org/EPILEPSY

Neurological Institute at CHLA

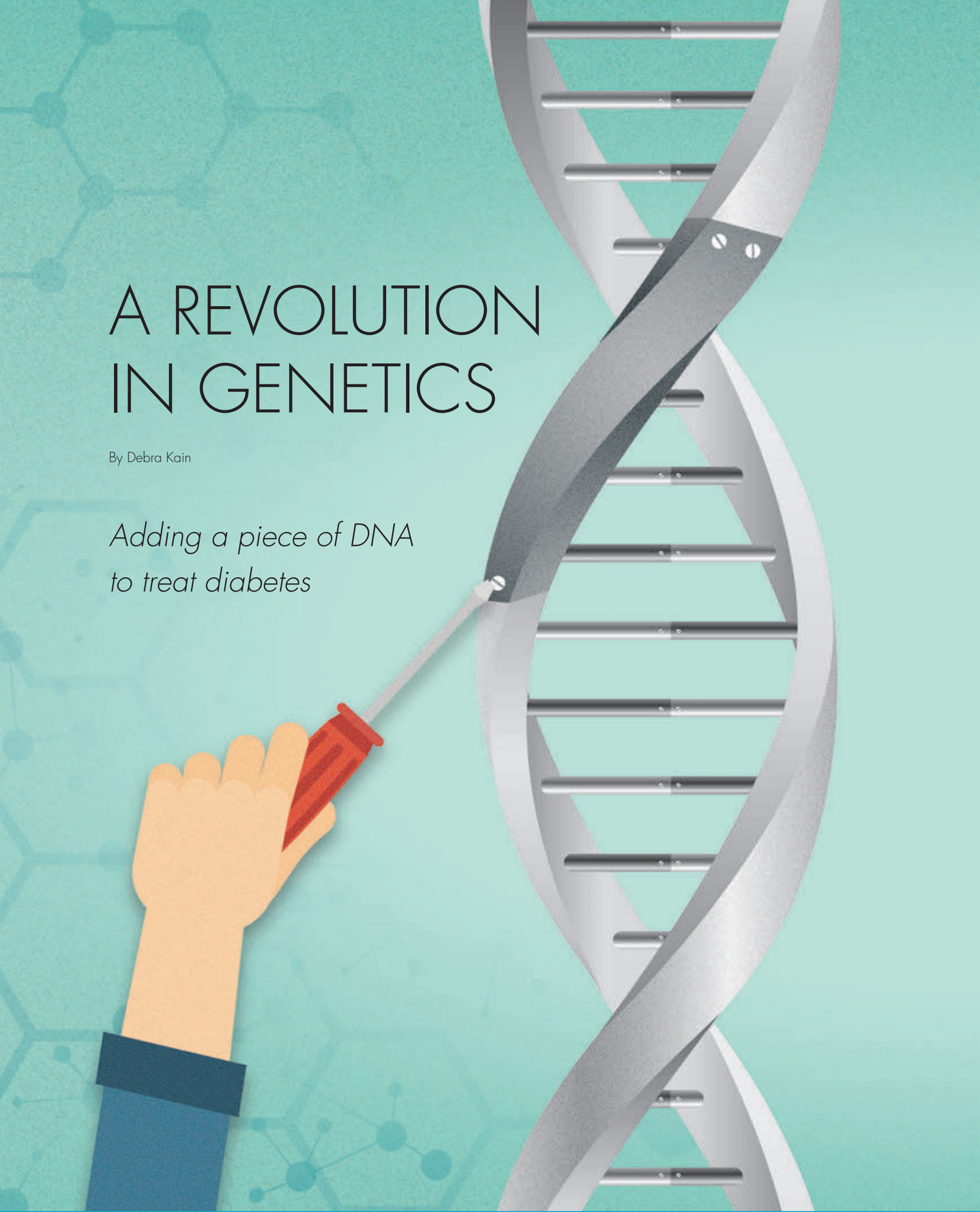
Douglas Nordli Jr., MD (left), and Mark D. Krieger, MD

Douglas Nordli Jr., MD, and Mark D. Krieger, MD, inaugural chair holder of the Billy and Audrey L. Wilder Endowed Chair of the Division of Neurosurgery, are co-directors of the newly established Neurological Institute at CHLA. The Institute provides a comprehensive continuum of care that brings together clinical services from Neurology, Neurosurgery, Psychiatry, Neuropsychology, Physical Therapy, Occupational Therapy, Dietetics and Social Work to support the care of children at CHLA.

A REVOLUTION IN GENETICS

By Debra Kain

Adding a piece of DNA to treat diabetes



A child develops a rare form of diabetes, due to the absence of a single piece of DNA in his genetic code. At Children's Hospital Los Angeles, a dedicated researcher is working to cure this young patient. How? With gene-editing technology called CRISPR-Cas9.

Just a few years old, CRISPR-Cas9 technology is transforming how scientists conduct medical research. Experts believe it can be used to edit the DNA in cells of any living thing. Senta Georgia, PhD, an investigator in the Division of Endocrinology, Diabetes and Metabolism at CHLA, hopes to use it to put the child's missing piece of DNA back in the proper place and cure his diabetes on a cellular level.

Changing DNA

DNA is made up of four chemical bases, pairs of which form the "rungs" of the twisted, ladder-shaped DNA molecule. These four base units are adenine (A), thymine (T), cytosine (C) and guanine (G). All genes are made up of stretches of these four bases, arranged in different order and length. The human genome contains approximately 3 billion of these base pairs.

Every cell in our body carries a copy of our genetic code or blueprint. Like letters in the alphabet form a word, the order of bases in a DNA sequence—A,T,C,G—form genes. RNA then translates these letters into messages that tell the cells how to produce proteins. When the letters are missing or truncated, the result is a mutation in the DNA.

CRISPR-Cas9 gene-editing technology allows scientists to edit a cell by precisely cutting out a specific sequence from among the billions of base pairs in that DNA code, and then repairing the mutation.

Creating new insulin-producing cells

The patient Georgia hopes to cure has three C's where there should be four. That single deletion caused what is called a "frame-shift mutation," which alters the way the sequence is read and results in an abnormal protein product.

Georgia discovered that the frame shift created a shortened code for the protein called Neurogenin 3 (Ngn3), which regulates the production of gut and pancreas hormone cells. In this case, the patient was born without the hormonal cells that are necessary for the absorption of food and nutrients in the intestine.

Senta Georgia, PhD, is using CRISPR-Cas9 technology in an effort to cure a child's rare form of diabetes.

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What is CRISPR-Cas9?

Injecting modified DNA into a cell.

CRISPR was first discovered in the DNA of bacteria in 1987, when scientists noticed a pattern of short, repeating, palindromic (reading the same forward and backward) DNA sequences separated by short, non-repeating "spacer" DNA sequences. Over the next five years, researchers realized that these repeats were present in many other single-celled organisms.

In 2012, scientists coined the term CRISPR, short for "clustered regularly interspaced short palindromic repeats," to describe the pattern. They figured out that the repeating DNA patterns, along with a family of "Cas" (CRISPR-associated) proteins and specialized RNA molecules, played a role in bacterial immune systems. The entire complex of DNA repeats, Cas proteins and RNA molecules is known as the CRISPR/Cas system.

The spacers were found to enhance the bacteria's immune system by creating a template of an invading virus that RNA molecules can recognize in the event of future infection. When the RNA molecule recognizes the foreign DNA, the CRISPR complex is guided to that particular sequence. There the Cas proteins, which act like a pair of specialized molecular scissors, precisely cut and disable the invader.

Also in 2012, scientists figured out how to hijack the bacteria's immune system to create a new gene-editing tool, building a CRISPR-Cas9 system that could be programmed to identify, cut and even replace any gene sequence.

"A lot of people don't realize that the gut is the largest endocrine, or hormone-releasing, organ in the body," says Georgia, who is also an assistant professor of Pediatrics at the Keck School of Medicine of the University of Southern California (USC). "So this patient must receive total nutritional supplements to stay alive."

Georgia is testing whether she can use CRISPR-Cas9 to correct induced pluripotent stem cells (iPSCs)—cells derived from the patient's own skin cells and reprogrammed back into an embryonic-like state, enabling the development of an unlimited source of any type of human cell. She will then use the corrected iPSCs to make new insulin cells for the patient.

The CRISPR technology will precisely cut out the section of DNA that is missing "C" and replace it with a new DNA segment created in the lab.

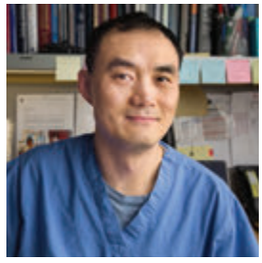
The new segment includes the missing molecule along with a copy of the remaining sequence. In the lab, the modified iPSCs are differentiated into insulin cells and then transplanted into mice to see if they can produce blood glucose.

"If this works the way we believe it will, the next step will be to seek funding and likely partner with a company for further testing, with the goal of finding a way to safely and effectively deliver cells that can create and secrete insulin as needed for this patient," Georgia explains. She adds that this process could also provide proof of principle for treating others with type 1 diabetes by creating new, insulin-producing beta cells.

Core findings

While Georgia aims to establish CHLA as a center for helping kids with genetic forms of diabetes, Di Tian, MD, PhD, a physician-scientist in the Department of Pathology and Laboratory Medicine, hopes that his core lab will become an important center for generating genetically modified disease models for biomedical research.

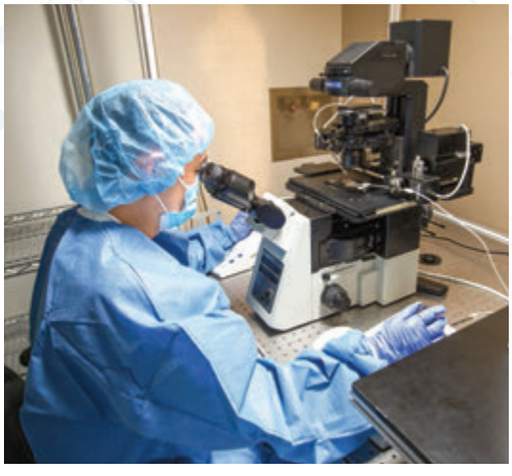
"Using this technology in a research context allows us to determine—in many cases for the first time—the underlying mechanisms for some developmental disorders."



– Di Tian, MD, PhD

"What CRISPR technology offers is higher efficiency with a higher success rate at a much lower cost," says Tian. He is using CRISPR-Cas9 to create several mouse lines to study multiple mutations that possibly cause autism spectrum disorder (ASD).

In just six months, two scientists in his core lab have created 10 lines. "This would have been inconceivable just a few years ago," he says, adding that without CRISPR he could never, with such efficiency, have been able to study the gene mutations that correlate to—and possibly cause—neurodevelopmental disorders. While at the Massachusetts Institute of Technology (MIT), Tian worked for nearly a year to establish just one mouse line through conventional gene targeting and careful crossbreeding.



Di Tian, MD, PhD, using Crispr-Cas9 gene-editing technology.

Tian, now an assistant professor at the Keck School of Medicine of USC, has been working to zero in on the causal gene or genes responsible for human chromosome 16p11.2 microdeletion syndrome. Chr16p11.2 microdeletion results in the loss of 30 genes of diverse functions and is one of the most common genetic abnormalities associated with ASD.

By systematically targeting each gene in a candidate genomic region one by one, he hopes to use CRISPR to identify the causal genes and molecular mechanism of this unique genetic disorder.

"Using this technology in a research context allows us to determine—in many cases for the first time—the underlying mechanisms for some developmental disorders," says Tian. "This information will provide clinicians and researchers new opportunities to develop therapies for these disorders and improve the lives of families affected."

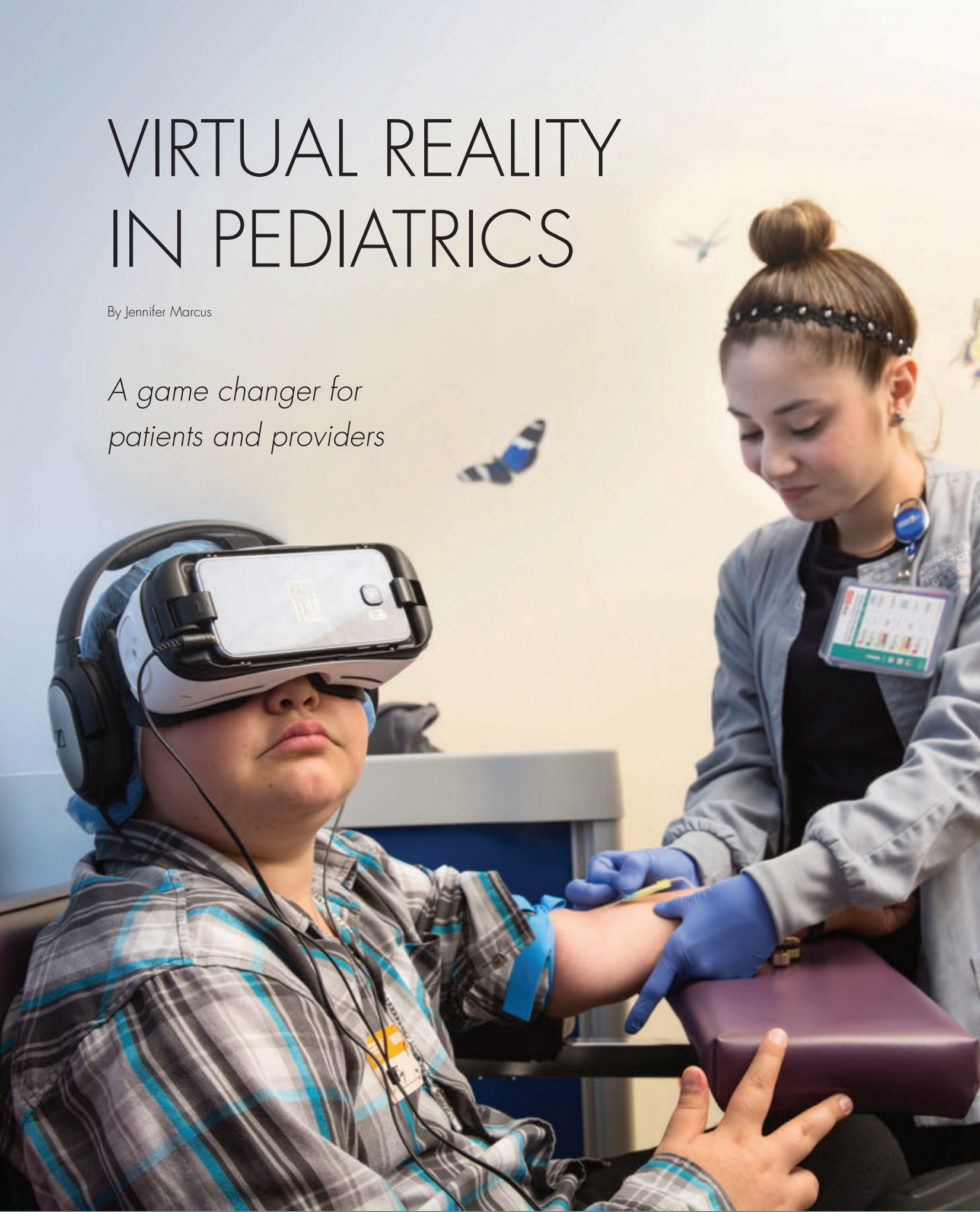
See how research conducted by Senta Georgia, PhD, could impact patients with diabetes.

CHLA.org/CRISPR

VIRTUAL REALITY IN PEDIATRICS

By Jennifer Marcus

A game changer for patients and providers



"Pain is not simple. Most people think pain is just about tissue damage, but the pain system is really a very complex and sophisticated network of signals cascading across many regions of the brain."

– Jeffrey I. Gold, PhD

An anxious adolescent showed up to have his blood drawn and was asked if he'd like to try virtual reality goggles. The boy agreed. A few minutes later he asked, "When are you going to take it?" According to Jeffrey I. Gold, PhD, the boy was surprised when he removed his headset and found that the blood sample had already been drawn and was on the table beside him.

In pediatric facilities throughout the country, children undergo necessary yet painful and distressing procedures every day, but very few non-pharmaceutical interventions have been determined to successfully manage the pain and anxiety associated with these procedures. To date, few clinical trials have been conducted to thoroughly study the effectiveness of these interventions.

Gold, a clinical psychologist and director of the Pediatric Pain Management Clinic in the Department of Anesthesiology Critical Care Medicine at Children's Hospital Los Angeles, has embarked on a new study to examine the effectiveness of virtual reality (VR) for children and adolescents undergoing painful procedures such as blood draws.

He and a team of researchers have hypothesized that patients using VR will report significantly less procedural pain and anticipatory anxiety, as well as lower heart rates and less behavioral distress, than patients receiving the standard of care, such as topical anesthetics.

"Pain is not simple," says Gold. "Most people think pain is just about tissue damage, but the pain system is really a very complex and sophisticated network of signals cascading across many regions of the brain. It is an integrated chemical, physiological and behavioral response."

A patient using virtual reality while having blood drawn

(continued on next page)

"Bear Blast"—a VR experience created for managing pain

AppliedVR, a software solutions company, is supplying specialized headsets for the study and working with Gold to design and develop content for the virtual reality experience. Gold, who is also a professor of Anesthesiology, Pediatrics, and Psychiatry and Behavioral Sciences at the Keck School of Medicine of the University of Southern California (USC), explains that not everything produced for VR is valid for managing pain. "We're testing an 'environment' here that's being developed especially for the purposes of pain management."

Immersive VR allows the user to become an active participant in a virtual world as it captures the visual, auditory and tactile senses, as well as the limbic sense of emotion. "When someone is fully engaged and immersed in a VR experience, they are releasing endorphins," he says. "These endorphins can produce an opioid response that markedly reduces the patient's subjective pain."

Given the significant concerns about problematic opioid use in the U.S., Gold is hopeful that evidence-based support for non-pharmaceutical interventions such as VR may lead to improved procedural pain management and a decreased need for narcotics.

"While it has not yet been extensively tested in a pediatric population, preliminary evidence suggests that VR may be particularly effective for pain management among children and adolescents," he says. It's also safer and a lot more fun.

See how Gold's research is helping kids manage pain.

CHLA.org/VRpain

"We're using wearable technology—like a Fitbit on steroids—to monitor physiologic responses such as heart and breathing rates … and comparing them to stress-level parameters from trainees using our modules."

– Joshua Sherman, MD

Just like the real thing

Although it doesn't occur often, emergency resuscitation is a high-stakes event in pediatric health care. Yet 80 percent of the pediatric emergencies nationwide are handled by medical professionals who lack significant training in pediatric emergency medicine.

"While everyone here at Children's Hospital Los Angeles is trained in pediatrics, when you consider the training provided to general EMS professionals—only 1 percent of their time is spent on pediatrics," says Joshua Sherman, MD, an emergency medicine physician with a penchant for simulation in medical education. In collaboration with Oculus, a technology company, Sherman is diving into the world of virtual reality to design a VR resuscitation training program. The goal is to prepare physicians in training for high-stress situations in pediatric emergency care.

Virtual reality headset

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Todd P. Chang, MD, MAcM, wears a motion-capture suit for animating digital characters in a hospital VR module.

Together with Todd P. Chang, MD, MAcM, another CHLA emergency medicine physician, Sherman is working closely with game developers at Oculus, providing the technical and medical direction to accurately re-create a resuscitation room. The virtual environment will serve as the foundation for resuscitation training modules and will come complete with all the furnishings, equipment, monitors and staff found in a resuscitation room, as well as noise and distractions that convey a sense of chaos and stress.

Once the environment is developed, the team will incorporate specially designed modules representing two high-acuity "code blue" scenarios, which are often encountered in a pediatric emergency room.

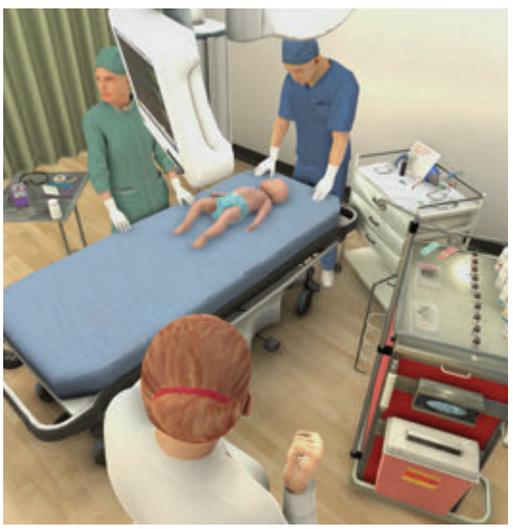
"Current methods of simulation training, including mannequins or screen-based computer games, are limited because the trainees don't necessarily feel the 'realness' of the experience," explains Chang, who is also an associate professor of Clinical Pediatrics at the Keck School of Medicine of USC. "The beauty of VR is that the simulation experience is entirely immersive—you literally put on a pair of VR goggles and you are instantly in the environment."

While wearing the goggles, a trainee sees the virtual resuscitation room in 360 degrees: Monitors are beeping, nurses and technicians are running in, and the patient's mother is pleading, "Please help my child!" The trainee proceeds through all the steps of managing the virtual patient's care in real time, and his or her performance is recorded and scored. At the end of the session, the trainee can review it and get instant feedback.

Once the game is fully developed, the investigators will run research studies to demonstrate its validity as a method of training and eventually compare it against the current standards of mannequin- and screen-based simulation training.

VR can also help solve the ethical challenge of placing a trainee in a high-risk resuscitation situation. Using the modules, trainees can practice working effectively in the medical environment while experiencing levels of stress and tension similar to what happens in an actual emergency department.

"We're using wearable technology—like a Fitbit on steroids—to monitor physiologic responses such as heart and breathing rates, and taking samples of salivary cortisol, a hormone marker



Scene from a hospital VR training module

Sherman with a trainee using the VR module

"The beauty of VR is that the simulation experience is entirely immersive—you literally put on a pair of VR goggles and you are instantly in the environment."

– Todd P. Chang, MD, MAcM

of stress, from providers in real-life emergency situations and comparing them to stress-level parameters from trainees using our modules," says Sherman, who is also an assistant professor of Clinical Pediatrics at the Keck School of Medicine of USC.

Sherman and Chang believe that if trainees can use VR to practice resuscitation under levels of stress similar to what they will encounter in a busy emergency department, they will be able to recall those reflexes and perform safely and effectively when they encounter the real thing.

Watch how Sherman and Chang's research is helping train providers for pediatric emergencies.

CHLA.org/VRmedEd

NEW WAYS TO BATTLE PEDIATRIC OBESITY

By Ellin Kavanagh

Weight-loss surgery (without the surgery)

Most of us have heard of weight-loss surgery. Perhaps we even assume to know how it works—by somehow magically reducing our food and calorie intake.

But it's likely we're wrong.

Rohit Kohli, MBBS, MS, joined Children's Hospital Los Angeles in September as head of the Division of Gastroenterology, Hepatology and Nutrition and as a principal investigator leading his own lab. Kohli's clinical specialty is obesity-related fatty liver disease, a condition that can progress to cirrhosis by the time a patient is a teenager. His National Institutes of Health-funded lab focuses on

Rohit Kohli, MBBS, MS, with a patient

"Basically, we are looking for a bariatric mimetic—something that produces the effect of surgery without the surgery."

– Rohit Kohli, MBBS, MS

pediatric obesity and investigates precisely how bariatric surgery for weight loss (also known as gastric bypass or sleeve gastrectomy) works.

"You've probably heard that bariatric surgery can reverse diabetes—which is one of the reasons it's being used in adolescents and teens to correct this chronic, debilitating disease," says Kohli, who is also an associate professor of Pediatrics (Clinical Scholar) at the Keck School of Medicine of the University of Southern California. "Most people think the surgery works because you make the stomach smaller or that you do something to the intestine so less nutrition is absorbed. Neither of these is true."

Research conducted during the past decade indicates that physical changes to the stomach or intestine are practically irrelevant. Rather, it is metabolic changes—alterations in the patient's own physiology—that result in weight loss. Surgery is only important because it initiates the crucial communication that alters metabolism.

Bile acids, important for fat metabolism, play a key role as signaling molecules, facilitating communication between molecular pathways. In 2014, Kohli and his colleagues co-authored a paper published in the journal Nature that demonstrated that animal models lacking an important bile-acid receptor didn't experience weight loss after surgery. Meanwhile, animals with the receptor did lose weight.

"This is the piece we want to exploit," says Kohli, "by identifying a medication that will initiate this signaling cascade, causing the child to lose weight and preventing type 2 diabetes and fatty liver disease, without the risk and expense of surgery. Basically, we are looking for a bariatric mimetic—something that produces the effect of surgery without the surgery."

Learn more about Kohli's research to help kids battle obesity.

CHLA.org/KOHLI

COOL IT

By Debra Kain

Saving babies' brains

When something goes wrong around the time of a baby's delivery, a new mom can go from the best day of her life to her worst nightmare. And the team at Children's Hospital Los Angeles may have only hours to intervene.

"In almost every case, there is no warning. Literally, in an instant, what was anticipated to be a beautiful birth becomes a life-or-death situation," says Jessica Wisnowski, PhD, of the Department of Radiology at Children's Hospital Los Angeles and assistant professor of Radiology and Neonatology at the Keck School of Medicine of the University of Southern California (USC).

Perinatal asphyxia, also known as hypoxic-ischemic encephalopathy (HIE), occurs when a newborn infant suffers a lack of oxygen during the birth process. Most commonly, it occurs in normal pregnancies, with complications arising just before or during birth—such as a drop in the mom's blood pressure, rupture of the uterus, premature separation of the placenta from the uterus or an umbilical cord wrapped around the baby's neck.

Confirming neuroprotective effects

Five years ago, clinicians and scientists from the Department of Radiology and the Division of Neonatology started a research study focused on perinatal asphyxia. Today, this project has grown into the multidisciplinary CHLA-USC Collaborative Research Program for Neonatal Hypoxic-Ischemic Encephalopathy, led by Wisnowski and Tai-Wei Wu, MD, an attending neonatologist at CHLA and an assistant professor of Pediatrics at the Keck School of Medicine of USC.

Without treatment, these babies often develop cerebral palsy or other severe complications, including blindness, deafness, intellectual impairments, learning disabilities and even death. Annually, more than half a million babies die from HIE worldwide, and an equal number are left with lifelong disabilities.

Therapeutic hypothermia

Therapeutic hypothermia, or targeted cooling of the brain, is the first-line therapy for neuroprotection in newborns with HIE. It involves cooling an infant's core body temperature down from 98.6 F to 92.3 F, starting as soon as possible after birth and continuing for 72 hours.

Physicians have known for a few decades that brain injury from HIE is an evolving process, disrupting metabolism at the cellular level. It is precisely because the underlying processes leading to cell death can take days, if not weeks, to develop that scientists have this window of opportunity to intervene with potential neuroprotective therapies to save brain cells.

Wisnowski explains that it's paradoxical that hypothermia works because "we are slowing down brain metabolism at the same time that the brain is trying to repair itself."

Published in 2015, the study confirmed hypothermia's neuroprotective effects on newborns with HIE. In the study, Wisnowski, principal investigator Stefan Bluml, PhD, and colleagues from both the Department of Radiology and the Steven & Alexandra Cohen Foundation Newborn and Infant Critical Care Unit (NICCU) at CHLA conducted magnetic resonance spectroscopy (MRS) studies on 31 newborns with HIE during hypothermia, and again after the infants were rewarmed.

The team of researchers, neonatal physicians and nurses transferred the babies and all of the cooling equipment to the MR scanner—in essence "bringing the whole NICCU down to the MRI suite."

"The biggest challenge we initially faced was getting these fragile babies down to the MRI and back to the NICCU without compromising the cooling in any way," says Wu. To achieve this, he developed a protocol that uses a huge battery—large enough to run two refrigerators. The battery provides portable power to cycle cold water through the cooling blanket that cocoons the infant.

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The team of researchers, neonatal physicians and nurses transferred the babies and all of the cooling equipment to the MR scanner—in essence bringing the whole NICCU down to the MRI suite.

The MRS imaging enabled the team to map what was happening biochemically in the brains of the infants while they were undergoing therapy. Researchers measured the concentrations of key molecules involved in the use and storage of energy, neurotransmission and oxidative stress.

Their findings showed that neuroprotection is achieved by realizing a specific balance between energy metabolism and neurotransmission. So far, the team has assessed more than 50 infants.

"We hope to obtain a better indicator of the child's prognosis," says Wu, whose interest in brain-temperature measurements laid the foundation for the research program. "Our goal is to categorize the degree and extent of brain injury, in order to better customize individual treatments and improve outcomes for these babies."

Transporting a premature infant and cooling equipment to the MRI suite

Jessica Wisnowski, PhD, and an infant at the MRI scanner

Enhancing neuroprotection

"But there is more that we can do," says Wisnowski. "Hypothermia is a first step, and with it we have been able to almost double the chance of a healthy outcome for newborns with HIE. However, about half of infants with HIE don't adequately respond to therapy. Although we know hypothermia helps, we don't fully understand how it helps or how best to aid those babies for whom hypothermia isn't enough to alleviate their brain injury."

Wu and Wisnowski are co-investigators on a new multisite study evaluating the use of a drug called erythropoietin (EPO) along with hypothermia. Though perhaps better known as a performance-enhancing drug banned from sports, EPO is a naturally occurring hormone secreted by the kidneys. Its function is to regulate red blood cell production.

EPO is frequently given to newborns to treat anemia of prematurity, and research has shown that it may also have neuroprotective effects. CHLA is the only institution in Southern California participating in this new trial.

In addition, CHLA researchers are working to develop a better understanding of hypothermia's impact. This could allow for a more tailored approach for its delivery, foster the development of early biomarkers, and direct additional neuroprotective therapies toward babies who are most likely to benefit.

"Most of us who devote ourselves to medicine do so for a reason," Wisnowski adds. "Before my mother passed away suddenly in 2014, she had spent more than two decades as a special education aide for children with neurodevelopmental disabilities—some of whom were born with HIE. Each day, I try to honor her legacy and our shared passion by helping to get us one step closer to ameliorating one of the most common causes of cerebral palsy."

Watch how therapeutic cooling is used to help protect a baby against brain damage.

CHLA.org/COOLING

FUNDING FOR RESEARCH

By Ellin Kavanagh

Leveraging thousands into millions

Whether through philanthropy or government grants, the right investment—made at the right time—can have a tremendous impact on research. Although funding a research program generally requires millions of dollars, smaller amounts of money can be used strategically to fill a gap or initiate a new project. Data generated from these research activities can then be leveraged to apply for significant National Institutes of Health (NIH) grants or to solicit larger philanthropic investments.

Leveraging $25,000 into $15 million

For Thomas Coates, MD, it started with a good idea. Coates treats patients with sickle cell disease. To develop new ways to help patients manage their condition, he needed to know what was happening in their smallest blood vessels—the areas where the characteristic crescent-shaped red blood cells cause obstructions. Nearly 20 years ago, there was no way to observe blood flow at that level.

That's where the good idea came in. Coates knew of a device called a laser Doppler flow meter, which was used in other applications to measure how fast particles were moving. He and his colleagues reasoned that a low-power laser could "see" beneath the skin well enough to measure the flow of red blood cells traveling through the capillaries. All he needed was the Doppler to test his hypothesis, but its $25,000 price tag put the essential piece of equipment out of reach.

Coates with the laser Doppler flow meter

"You can draw a line from that original gift to where we are today."

– Thomas Coates, MD

Fortunately, private philanthropist Genevieve Atoll stepped in and gifted the full amount. "You can draw a line from that original gift to where we are today," says Coates, section head of Hematology in the Children's Center for Cancer and Blood Diseases at Children's Hospital Los Angeles.

Today, he heads an investigation into the basic biology of sickle cell disease that is funded by a $9.5 million grant from the NIH. In fact, since purchasing the device that enabled Coates' lab to advance the knowledge of blood flow and vessel reactivity, the lab has continuously been awarded prestigious NIH funding, totaling more than $15 million.

"It represents a significant return on Mrs. Atoll's generous investment," says Coates.

He and his team discovered that when patients with sickle cell disease sigh, their blood flow drops and their vessels constrict—conditions that leave them vulnerable to sickle vaso-occlusion, strokes and extraordinary pain. All because of a simple sigh—something the average person does many times each day.

Subsequently Coates and his colleagues have identified many other factors that can cause blood vessels to constrict, including stress. They are investigating techniques to minimize a patient's stress, and with that, the incidence of sickle cell events.

"And we're still using the Doppler," Coates adds.

Learn more about sickle cell disease at CHLA.org/SickleCell

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"Science changes hearts and minds."

– Johanna Olson-Kennedy, MD

Olson-Kennedy shares a self-portrait created by one of her patients.

$340,000 helps generate $5.7 million

According to Johanna Olson-Kennedy, MD, medical director of the Center for Transyouth Health and Development at CHLA, "Early funding jump-started my career as a clinical researcher. I can't remember the amounts, but they weren't huge."

Olson-Kennedy received an intramural award—supported by private philanthropy and other sources—for $160,000 over two years. She used the money to fund the early stages of a cross-sex hormone study.

"I knew that I was onto something important because after six months, a lot of these kids were able to come off psychotropic medication, or they were no longer diagnosed with bipolar disorder or some other significant mental illness," says Olson-Kennedy. "We had begun moving these kids from 'survive' to 'thrive.'"

The information she collected from those first 101 patients had comprised the world's largest database of ethnically diverse transgender youth. Olson-Kennedy used the data to apply for an entry-level NIH award for mentored career development. Again, the amount was not large—$180,000 over two years. The new funding allowed her to continue the study in teenagers and to begin a second study, this time looking at the effect of hormone blockers on adolescents.

Experience with these two studies helped her craft another application to the NIH, for a multisite trial with Boston Children's Hospital, UCSF Benioff Children's Hospital San Francisco and Lurie Children's Hospital of Chicago. In 2015, the group was awarded $5.7 million, and Olson-Kennedy became lead principal investigator of the first NIH-funded study to evaluate the long-term outcomes of medical treatment for transgender youth.

"Science changes hearts and minds," says Olson-Kennedy. Even if you're not a millionaire, that's a worthwhile investment.

Read more about transgender medicine at CHLA.org/TRANSGENDER

"It doesn't always take a lot of money—just the right amount, right when you need it."

– Sonia Michail, MD

Michail holds a colonoscope, used to diagnose intestinal disorders.

Turning $5,000 into $2.3 million

For Sonia Michail, MD, a pediatric gastroenterologist at CHLA, the magic number was $5,000. That's what she needed to begin treating patients with intestinal disorders who were immunosuppressed and no longer responding to conventional treatment. Her patients were suffering from ulcerative colitis, Crohn's disease and Clostridium difficile infection—all diseases resulting from an imbalance between good and harmful bacteria in the gut.

At the time, she had been reading case reports about a procedure called a fecal microbial transplant, or FMT. Patients who had exhausted all other options were not just improving a little—they were being cured. Michail's previous research had focused on the gut bacteria of children with intestinal disorders and how it affects their response to treatment. FMT was a logical next step.

After developing a process for preparing and delivering the transplant, Michail encountered a hurdle with the Food and Drug Administration. Before she could begin investigating FMT to treat patients, she needed to hire a regulatory expert at a cost of $5,000.

Michail spoke with the Higgins Family Foundation, which she had worked with previously. Fortunately, the foundation supplied the necessary funding.

Treatment outcomes from her initial patients led Michail to consider initiating a clinical trial. Using the pilot data, she applied for an NIH grant to study FMT in patients with ulcerative colitis. In 2015 she was awarded $2.3 million to fund the study.

The Higgins Family Foundation has also agreed to provide financial support for an FMT trial in patients with Crohn's disease.

"That initial $5,000 is going to help change the lives of a lot of kids," says Michail. "It doesn't always take a lot of money—just the right amount, right when you need it."

Learn more about fecal transplants at CHLA.org/FMT

HEADS UP!

By Jennifer Marcus

Treating concussion in children and adolescents

Your son goes helmet to helmet with a linebacker in a school football game. Your daughter heads a soccer ball. What impact will these incidents have on each child's developing brain? Researchers at Children's Hospital Los Angeles want to find out—and help kids recover more quickly.

Between 1.6 million and 3.8 million sports- and recreation-related head injuries occur each year in the United States. While most concussions in adults resolve within seven to 10 days, children and adolescents often have longer recovery times, likely because of differences between mature brains and developing ones.

"Our comprehensive sports concussion team provides immediate access to state-of-the-art care, making CHLA the sports medicine home for student athletes."

– Tracy Zaslow, MD

In response to the increasing prevalence of families seeking care for these injuries, CHLA has developed the only pediatric concussion program in Los Angeles. This multidisciplinary program incorporates research and clinical care to provide the latest evidence-based assessments and treatment plans specific to the needs of school-aged patients.

Although concussion is a fairly common injury in children and adolescents, treatment guidelines have been based mostly on experience with college athletes and other adults. But because their brains are still developing, children and adolescents may be at increased risk for long-term effects. Also, this age group may manifest symptoms of injury differently than adults.

Kids are different from adults

Tracy Zaslow, MD

"Our comprehensive sports concussion team provides immediate access to state-of-the-art care, making CHLA the sports medicine home for student athletes," says Tracy Zaslow, MD, director of the Children's Orthopaedic Center Sports Concussion Program and assistant professor of Orthopaedic Surgery at the Keck School of Medicine of the University of Southern California (USC). "With the increased awareness of sports-related concussions, we see a lot of adolescents with this injury—both athletes and non-athletes—and we feel a responsibility to study more age-specific ways of diagnosing and treating our young patients."

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Kenneth Hartline, PsyD

Emotional aspects of concussion are the focus of a pilot study directed by Kenneth Hartline, PsyD, a pediatric neuropsychology fellow at CHLA. The study found a correlation between mood and recovery time, with mood—especially sadness during the initial visit—associated with a more prolonged recovery. While this assessment is preliminary, it guides CHLA's concussion team to intervene with psychological support sooner when needed.

Anita Hamilton, PhD

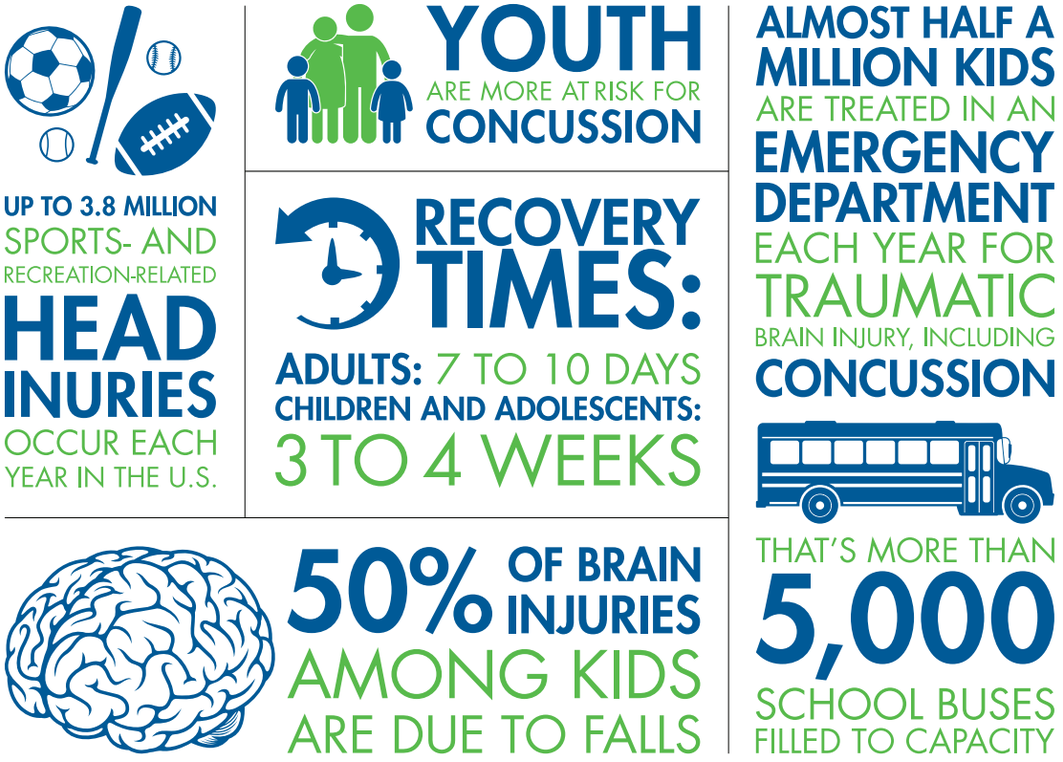
Pediatric neuropsychologist Anita Hamilton, PhD, is principal investigator of the concussion registry at CHLA, an effort to track the wide-ranging ways concussion can impact brain maturation, learning and psychosocial functioning. Hamilton studies neurocognitive and neuroimaging outcomes related to traumatic brain injury in children and adolescents. So far, the registry details nearly 250 patients. By collecting information about age, method of diagnosis, treatment and outcome, the research team can develop personalized, evidence-based care for future patients.

"While concussion is common among children and adolescents, there is still a lot we need to understand about the factors that impact recovery time and outcome," says Hamilton, who is also an assistant professor of Orthopaedic Surgery at the Keck School of Medicine of USC.

Kids are different from each other

"One of our clinical hypotheses was that high-achieving students would take longer to recover from concussion," says Zaslow. "But when we reviewed data from the registry, we found that wasn't the case." They found that children and adolescents identified as academically elite actually demonstrated an accelerated recovery course. These students also tended to seek treatment sooner and reported more anxiety-related symptoms than their peers.

The research team speculates that high-functioning students, who assume additional pressure to deliver stellar performance on and off the field, may possess internal factors such as greater cognitive reserves and resilience. These qualities may work in their favor to accelerate recovery and promote healthier outcomes following concussion.



What's next?

The Sports Medicine Program at CHLA is gearing up to begin a large-scale longitudinal study in partnership with the Harvard-Westlake School—a private high school in Los Angeles with approximately 1,600 students. The project, anticipated to begin in fall 2017, will follow participating students starting in seventh grade and continuing over a five-year period.

Bianca Edison, MD, MS

Led by Principal Investigator Bianca Edison, MD, MS, the project joins together multidisciplinary research workgroups at both institutions to better understand different factors that influence a student's academic and athletic performance, including nutrition, social activities, sleep habits and sleep disturbance.

"Surveying student athletes throughout the span of their middle and high school years will teach us a lot about typically developing adolescents and the many aspects that impact their development and what helps drive success in the classroom and on the field," says Edison, an attending physician in CHLA's Children's Orthopaedic Center and an assistant clinical professor of Orthopaedics at the Keck School of Medicine of USC. "Knowing about typically developing students in such detail will help us identify very subtle differences in young people with concussions so that we can intervene early and effectively."

Read more about our sports concussion clinic.

CHLA.org/CONCUSSION

At Children's Hospital Los Angeles, each of our patients has a different potential based on genetics, environment and other factors. All of our patients face challenges, and all have the capacity to realize their potential. For some, the treatment that will help them do that hasn't been invented … yet.

Being at a children's hospital provides our investigators the ability to witness these needs firsthand. They return to their labs to create treatments to help children like Jesus with unmet clinical needs.

Please support innovative research and discovery at CHLA.

Donate today
CHLA.org/FundResearch

Highlights

Tracy Grikscheit, MD

Tracy Grikscheit, MD, was awarded $7.1 million by the California Institute for Regenerative Medicine (CIRM) for her work toward developing a cellular therapy for the treatment of nerve disorders of the digestive system. Her goal is to develop an "off-the-shelf" cellular therapy to treat these disorders before patients require surgery, or to rescue patients who still have symptoms following surgery.

Robert E. Shaddy, MD, is now pediatrician in chief and senior vice president of Academic Affairs at Children's Hospital Los Angeles, and chair of the Department of Pediatrics at the Keck School of Medicine of the University of Southern California (USC). He will lead the search for CHLA's chief scientific officer as well as advance the strategic planning of our research enterprise.

Robert E. Shaddy, MD

Rohit Kohli, MBBS, MS

Rohit Kohli, MBBS, MS, was named chief of CHLA's Division of Gastroenterology, Hepatology and Nutrition. Kohli oversees all of the clinical, training and research efforts of the Division, which triages more than 9,500 patient visits. He comes to CHLA from Cincinnati Children's Hospital Medical Center, affiliated with the University of Cincinnati College of Medicine, and he has made significant contributions to the study of liver disease.

Vicente Gilsanz, MD, PhD, was named the 2016 Presidential Recognition Award winner by the Society for Pediatric Radiology. The award recognizes his contributions to the field, including his accomplishments in imaging research at the Children's Imaging Research Program of Children's Hospital Los Angeles, which seeks to advance the use of imaging technology to study pediatric disease.

Vicente Gilsanz, MD, PhD

Alan S. Wayne, MD

Curing Kids Cancer has initiated a $1.5 million endowment to fund the leukemia program at the Children's Center for Cancer and Blood Diseases under the direction of **Alan Wayne, MD**. A child named Killian was one of Wayne's patients at the National Cancer Institute, and his leukemia cells were found to be very sensitive to a new agent that was not yet available to treat children. After Killian lost his battle to leukemia, his parents created Curing Kids Cancer with the goal of providing critical funding to get targeted therapies out of the lab and into treatment as quickly as possible.

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Highlights (continued)

Lee Helman, MD

Lee Helman, MD, joined the Children's Center for Cancer and Blood Diseases as director of Basic and Translational Research. His responsibilities include setting strategic priorities, recruiting new investigators and organizing scientific teams. Helman comes from the National Cancer Institute at the National Institutes of Health, where he most recently served as scientific director for clinical research in the Center for Cancer Research.

David Cobrinik, MD, PhD, of The Vision Center at Children's Hospital Los Angeles was awarded a four-year grant totaling $1.665 million from the National Eye Institute of the National Institutes of Health to support his research to improve understanding of how cone photoreceptors in the retina develop.

David Cobrinik, MD, PhD

Douglas Vanderbilt, MD, MS

Douglas Vanderbilt, MD, MS, was awarded $3.5 million by the Department of Health and Human Services in support of the California Leadership Education in Neurodevelopmental and Related Disabilities (CA-LEND) Training Program. CA-LEND trains leaders, educates community providers and conducts research that promotes change for children with, or at risk for, neurodevelopmental disabilities.

Fariba Navid, MD, joined the Children's Center for Cancer and Blood Diseases in September 2016 as assistant director of the Clinical Trials Program and Children's Oncology Group Phase 1 & Pilot Consortium. Navid has extensive experience in research and pediatric early-phase drug development.

Fariba Navid, MD

Ellen Lien, PhD

Ellen Lien, PhD, of the Developmental Biology and Regenerative Medicine program, has been promoted to associate professor with tenure in the Department of Surgery at the Keck School of Medicine of USC. Lien's research focuses on cardiovascular development and regeneration.

Mark R. Frey, PhD, of the Developmental Biology and Regenerative Medicine Program, has been promoted to associate professor with tenure in the Departments of Pediatrics and Biochemistry & Molecular Medicine at the Keck School of Medicine of USC. Frey's lab is interested in the role of growth factor signaling in the intestinal response to injury and inflammation.

Mark R. Frey, PhD

Michele Kipke, PhD

A team of researchers led by **Michele Kipke, PhD**, at CHLA, and Thomas Buchanan, MD, and Jonathan Samet, MD, of the Keck School of Medicine of USC, received a prestigious Clinical and Translational Science Award from the National Institutes of Health (NIH). The $36.6 million grant will support continuation of the Southern California Clinical and Translational Science Institute (SC CTSI), the hub for community engagement in clinical and translational research at USC and CHLA.

Brent Polk, MD, was elected a fellow of the American Association for the Advancement of Science (AAAS), an honor bestowed upon AAAS members by their academic peers in recognition of their contributions to innovation, education and scientific leadership. This honor recognizes Polk for his distinguished contributions to the field of gastroenterology, particularly in understanding signal transduction mechanisms regulating intestinal growth and repair related to inflammatory bowel disease.

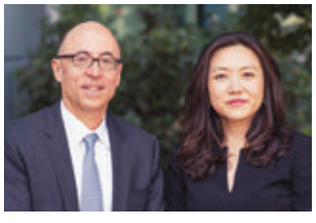
Brent Polk, MD

David Warburton, MD

David Warburton, MD, of the Developmental Biology and Regenerative Medicine program, was awarded more than $2.3 million from the Department of Defense Peer Reviewed Medical Research Program. The grant will support further study of lung injury and the development of an innovative endoscopic device for performing noninvasive, quantitative analysis of lung epithelial cell metabolism during lung injury—anticipated to significantly improve the respiratory health of military personnel in the field.

An innovative, first-in-pediatrics study, available only at Children's Hospital Los Angeles and led by **Leo Mascarenhas, MD, MS**, of the Children's Center for Cancer and Blood Diseases, will be enrolling children who have certain types of treatment-resistant cancer. The aim of this investigator-initiated Phase 1 trial is to test the safety, tolerability and metabolism of the drug Durvalumab in pediatric patients with solid tumors, lymphoma and central nervous system tumors.

Leo Mascarenhas, MD, MS



Alan Wayne, MD (left), and Erika Shin-Kashiyama, JD

The Therapeutic Advances in Childhood Leukemia & Lymphoma (TACL) consortium annual investigator conference was held this year at CHLA. The meeting was co-chaired by **Alan Wayne, MD**, **Deepa Bhojwani, MD**, and **Erika Shin-Kashiyama, JD**. The TACL consortium works to integrate translational laboratory research with early-phase clinical trials to speed the progress of innovative therapy development for children with cancer. This year, more than 50 investigators from 39 academic research institutions and four countries participated.

Honor Roll of Donors

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It is with heartfelt gratitude and pride that we recognize the following donors who made gifts of $1,000 and above during fiscal year 2015-16 to advance breakthrough research at Children's Hospital Los Angeles. We also extend deep appreciation to Cheryl Saban, PhD, and Haim Saban, as well as our many Associate and Affiliate groups, for their steadfast commitment to upholding the work of our dedicated investigators and expanding leading-edge studies at The Saban Research Institute. Through the generosity of our philanthropic community, we push the boundaries of science in order to advance treatments that improve the quality of life and build healthier futures for our young patients.

Despite our best efforts, errors and omissions in this list may occur. Please inform us of any inaccuracies by contacting Christian Nelson, assistant vice president, Stewardship and Donor Relations, at 323-361-1779 or cnelson@chla.usc.edu. For information on how you can provide philanthropic support, please contact Kerri Seibly, associate vice president, Foundation, at 323-361-1705 or kseibly@chla.usc.edu.

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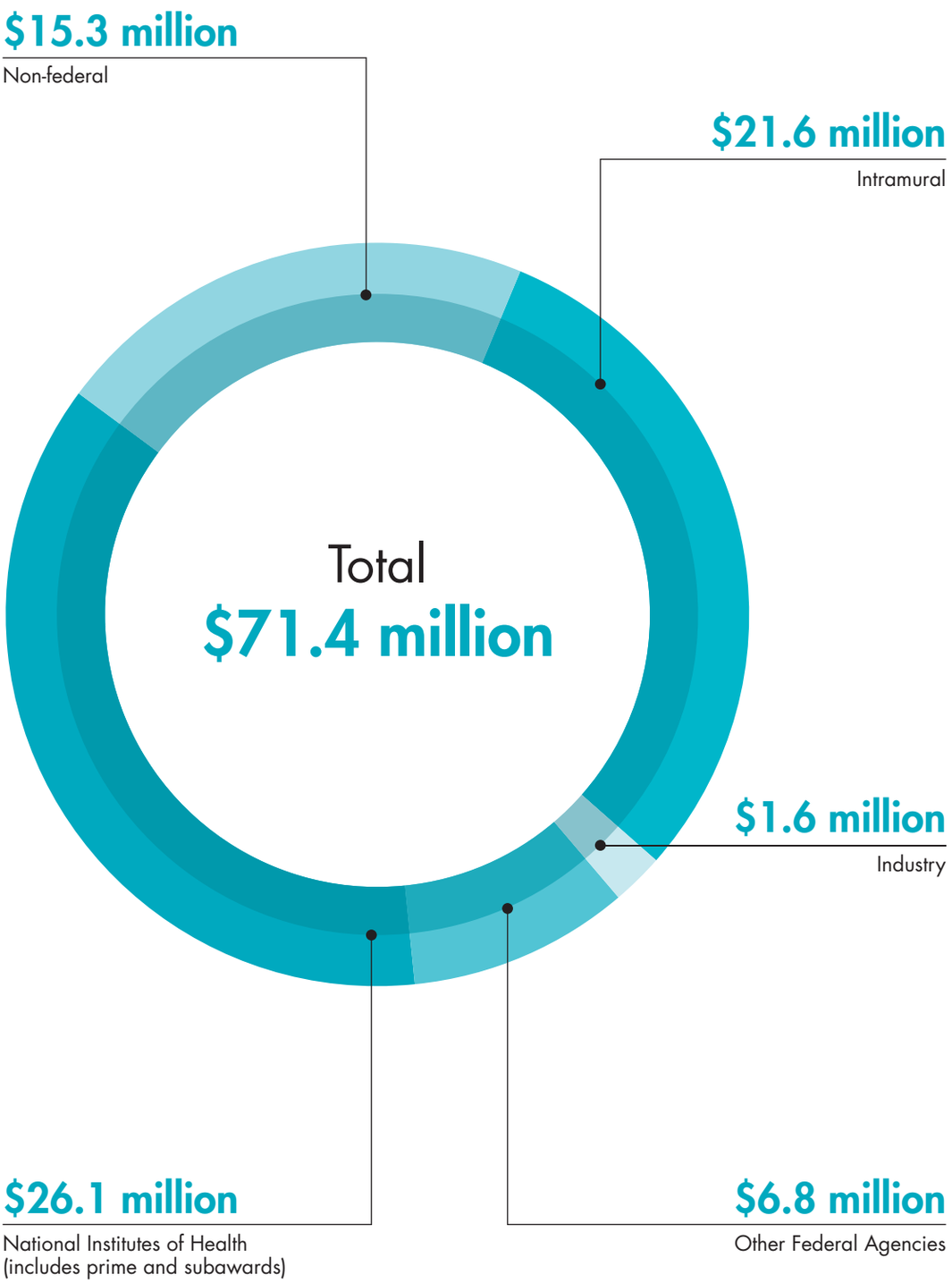

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