

CHILDREN'S HOSPITAL LOS ANGELES

RESEARCHLA



2019



WHOLEHEARTED

Surgeons at CHLA are tapping into regenerative medicine to give newborns with a rare heart defect a better chance at a longer life.



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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 2018, The Saban Research Institute received \$22.6 million in National Institutes of Health (NIH) funding and \$72.3M in total extramural 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 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.

We are often asked why a children's hospital would make research a priority.

The implication is that caring for seriously ill children is a sufficiently large mandate. At CHLA, we recognize that basic, translational and clinical research has the ability to improve every aspect of the care we deliver here in Los Angeles, as well as enhance the impact we have on the health of children around the world.

In this issue of ResearCHLA, you will read about the transformational work of our investigators to fill unmet clinical needs, increase access to new and existing therapies, and make life safer for young people both in and out of the hospital:

- For infants born without intestinal nerves, the best that pediatric medicine can currently offer them is one treatment option, with only a 50 percent chance of success. CHLA surgeon and scientist Tracy Grikscheit, MD, recently completed a proof-of-concept study to tackle this condition. While other labs are developing custom cell therapies that are expensive and take months to prepare, Dr. Grikscheit and her team are creating a therapy that could treat virtually any infant who has the disorder, without the wait.
- While adult oncologists have long benefited from the use of gene panels to help with diagnosis and treatment decisions, pediatric oncologists have been unable to leverage this approach since the existing panels were specific to adult cancers. To fill the gap, Jaclyn Biegel, PhD, and an interdisciplinary team of experts working to personalize cancer care for children developed OncoKids®, a next-generation sequencing-based panel that can identify the genetic cause of pediatric cancers. A young patient, whose tumor threatened to claim her life within the day, instead went home with her parents because of OncoKids.

- A unique team of scientists led by Bradley Peterson, MD, is analyzing the effect of repeated head impacts on high school football players. Although head impacts in professional and college football players have been studied, little is known about the effects on adolescent brain development. Results from Dr. Peterson's study could have far-reaching effects, not just for young athletes, but for any adolescent who experiences head trauma.

At CHLA, our mission is to create hope and build healthier futures. Research allows us to fulfill that mission through work done in the lab, the clinic and the community. Please join us in carrying out this mission by supporting and advocating for the health and welfare of young people everywhere.

Warmest regards,



Paul S. Viviano

Paul S. Viviano
President and Chief Executive Officer
Children's Hospital Los Angeles



Pat Levitt

Pat Levitt, PhD
Vice President, Chief Scientific Officer and
Director of The Saban Research Institute,
Simms/Mann Chair in Developmental
Neurogenetics (CHLA); W.M. Keck Provost
Professor of Neurogenetics (USC)

Meet Pat Levitt, PhD, inaugural chief scientific officer at Children's Hospital Los Angeles.

Pat Levitt, PhD, accepted the position of vice president, chief scientific officer (CSO) and director of The Saban Research Institute on July 1, 2018. He holds the Simms/Mann Chair in Developmental Neurogenetics at the Institute of the Developing Mind at Children's Hospital Los Angeles, and is engaged in both basic and clinical research.

He recently answered a few questions about what's next for research at CHLA.

Who is conducting research at CHLA?

Research is being conducted by basic and translational scientists, clinician-scientists, nurses, physicians, and investigators in the community. Our goal is to weave all of these elements into a single culture that represents the full range of our research diversity.

What's first on your agenda as CSO?

Our first step is to complete a strategic plan for research. A strategic plan will inform how we are going to grow and develop the research enterprise and the infrastructure we need to support those activities.

What do you expect will be significant aspects of the plan?

In this process we will look for ways to increase alignment between what is happening in research and what is happening in the clinic.

Another aspect of the plan will be to recognize that the quality of a research enterprise can be measured by the promise of its trainees—clinical research fellows, postdoctoral fellows and graduate students. We want to create a more integrated training environment with people competing to come here. We want the very best young scientists choosing CHLA.



Pat Levitt, PhD

Faculty recruitment will be pivotal to our success. Initially, we will focus on established scientists. We will continue to create a cadre of mentors who can effectively guide junior faculty and also help attract great clinical research and postdoctoral fellows. We will also continue to develop our own top-tier investigators.

The clinical enterprise has already started planning for growth. Similarly, on the research side we need to take a critical look at growing our infrastructure, while ensuring access to leading-edge technology. Those investments will be accounted for as part of the plan.

What outcome do you anticipate?

By creating an operational framework with specific goals, and providing better opportunities for people to get together who have common interests but use different approaches—thinking about challenging research questions in different ways—magic can happen.

Bringing clinician-scientists and basic scientists together, in the same way that we bring different disciplines together, will be challenging but very exciting. 🌀

ENGINEERING NEW ORGANS FROM LIVING CELLS

By Anna Azvolinsky

A novel, cell-based therapy for babies with intestinal disorders moves closer to a first-in-humans trial.

Tracy Grikscheit, MD, is a fixer. In the operating room at Children's Hospital Los Angeles, she specializes in helping babies born with severe bowel dysfunction. She's one of the leading pediatric surgeons specializing in intestinal disorders, and saving the lives of infants is a major part of her job.

Grikscheit, an attending surgeon at CHLA, often operates on babies born with an intact intestine that is not functioning adequately. The infants' intestines are either missing or deficient in the crucial nerves and other supporting cells needed to produce muscle contractions that move food through the gut, and ensure proper digestion, nutrient absorption and waste disposal.

This group of disorders, called enteric neuropathies, is named for the enteric nervous system (ENS), a complex, tangled web of nerves within the intestine that is needed not only for the gut's motility but also for essential gut hormone secretions and blood flow.

Without the ENS, stool becomes immobile—stuck in the intestine—and causes pain, gastrointestinal symptoms and infections. Individuals can be born without some or all of these neuronal cells layered within the intestine. The cells can also be injured or destroyed after birth, sometimes as a result of other diseases or conditions.

This is what Grikscheit has set out to fix.

Limited options for some babies

"The ENS is an incredibly diverse neural network that some call the second brain," says Grikscheit, who is also an associate professor of Surgery at the Keck School of Medicine of USC. "It acts as traffic signals for the intestine and is also like a watchman for the neighborhood, making sure the intestine is happy and healthy."

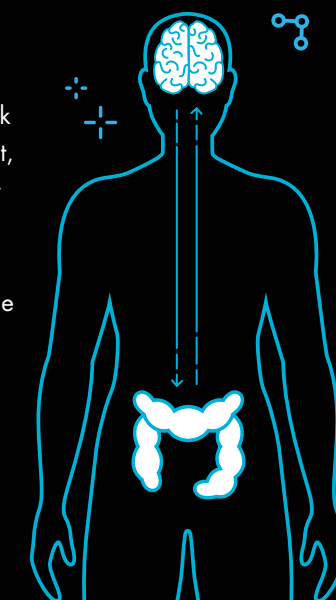


Tracy Grikscheit, MD (left), and Deven Patel, MD

Right now, Grikscheit's options in the operating room are limited. She can remove sections of intestine that lack nerve function while retaining the part that works. But even after one or more surgeries, most of these babies will continue to experience difficulties with bowel movements and be left prone to intestinal infections—some of which can be fatal.

And for the rare infant born with no enteric nervous system at all, the only option is an entire intestinal transplant—which has only a 50 percent chance of success. There are no other treatments for the underlying cause of these disorders.

This is not good enough for Grikscheit, who heads a regenerative medicine laboratory focused on tissue engineering within The Saban Research Institute of CHLA.



◀ The ENS is an incredibly diverse neural network that some call the second brain.

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Potential treatment for all babies

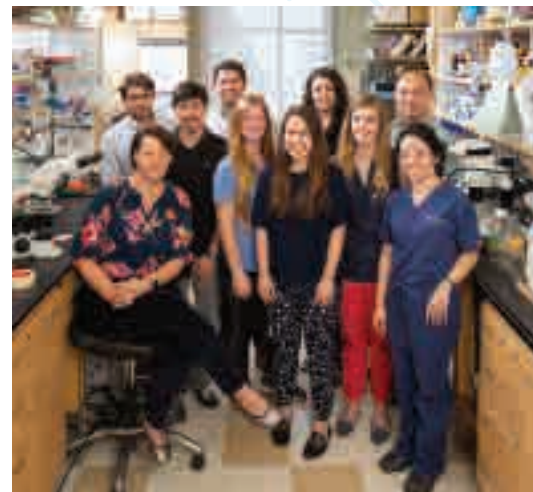
Grikscheit and her team are working on a potential fix—a cell-based therapy that could help virtually any infant with this disorder.

Together, the team has developed a process that takes human pluripotent stem cells—a type of cell derived from adult cells and capable of becoming any type of specialized cell—and differentiates them into precursors for the missing nerve cells essential for proper intestinal function.

The cells would sit in the freezer and could be thawed and delivered into a newborn baby missing some or all of the enteric neurons. Just as they would in normal development in utero, the cells would begin to differentiate and migrate down the length of the intestine, rebuilding the enteric neuronal network.



Induced pluripotent stem cells that have been stained with trypan blue and placed in an agarose block



Tracy Grikscheit, MD (left), and members of her lab

Outside of Grikscheit's lab, other cell therapies in development are derived from individual patients. But custom-made therapies can be prohibitively expensive, and the process to retrieve a patient's cells, revert them to stem cells and then differentiate them into enteric precursors would take months—too long for a newborn with a blocked bowel to wait.

Instead of trying an individualized method, Grikscheit and her team are developing cells that could be used to treat any baby. To develop the therapy, called advanced stem cell enteric neuropathy therapy (ASCENT), Grikscheit received a grant last year for \$7.1 million from the California Institute of Regenerative Medicine (CIRM) Translational Research Program.

The ENS in humans is made up of some **500 million** neurons.

"This was a proof of concept that we can introduce a new nervous system into an organ that didn't previously have one and that the two can function together."

—Jason Spence, PhD

Proof of concept

Together with a collaborator, Jason Spence, PhD, at the University of Michigan, Grikscheit recently added the enteric neural progenitor cells to a human tissue-engineered intestine, demonstrating that the progenitor cells could restore nervous-system function to a lab-grown human intestine. The engineered intestine was able to produce the movements needed for normal gut function. "This was a proof of concept that we can introduce a new nervous system into an organ that didn't previously have one and that the two can function together," says Spence.

Grikscheit is now working to show that adding the progenitor cells into animal models without an ENS can also restore intestinal function. The evidence is promising. Her lab already has shown that, when injected into the intestines of pigs, the cells are able to migrate and differentiate into at least some of the ENS cell types.

Progressing toward a clinical trial

Her lab is also busy preparing quality-control measures on the enteric progenitor cells to make sure that a sufficient quantity and quality of cells can be made to begin a first-in-human clinical trial.

The trial would test whether these cells, when injected into the small intestine, could migrate and differentiate, establishing the ENS. Initially, testing would be performed in a small number of infants with severe cases of enteric neuropathies, such as Hirschsprung disease.



Laura-Marie Nucho, project manager for ASCENT, loads a scaffold with stem cells.

The trial would be notable—the first pediatric trial investigating a cell-based therapy derived from pluripotent stem cells, and the first therapy of any kind to be tested for enteric neuropathy.

"When I speak to parents, the thing they want to know is when I can fix their child," says Grikscheit. With her breakthrough research and translational work, she hopes she will have a much better answer for them soon. ✨

To learn more about this research, visit CHLA.org/GrikscheitLab

A Better Look Into a Baby's Brain

By Melinda Smith

New, noninvasive imaging techniques use existing technology to provide a better view into the brains of newborns.

A new, noninvasive imaging technique developed at Children's Hospital Los Angeles improves neonatal brain imaging by 50 percent. The technology, called Time STAMP, aids neurosurgeons treating neonates for hydrocephalus—a buildup of fluid in the brain and the second-leading cause of pediatric brain surgery.



Matthew Borzage, PhD

"Blockages in cerebrospinal fluid (CSF) flow that cause hydrocephalus are smaller than the tip of a pencil, making it difficult to pinpoint the location of the obstruction with

current imaging techniques," explains Matthew Borzage, PhD, an investigator in Neonatology at Children's Hospital Los Angeles. Nationally, about half of hydrocephalus patients must return for a second surgery within a year. Clearer imaging could mean fewer repeat surgeries and more targeted strategies for care.

To develop a better imaging solution, Borzage worked closely with Stefan Bluml, PhD, as well as with neurosurgeons and radiologists at CHLA in a unique collaboration. The result

was Time STAMP, an innovative protocol that is used with existing MRI machines. The new technique greatly improves the signal-to-noise ratio—resulting in an image that is 50 percent clearer and brighter than what current scanning methods produce. This allows radiologists to better diagnose—and more precisely locate—obstructions in CSF flow, arming neurosurgeons with more accurate information prior to surgery.

"I hope to see this technology travel from CHLA to institutions across the country," Borzage says. "Time STAMP is noninvasive and doesn't require any new or specialized hardware, so it can be implemented immediately—and help patients anywhere."

This research was recently published in *Child's Nervous System*, the official journal of the International Society of Pediatric Neurosurgery. In addition to Borzage and Bluml, CHLA authors include Skorn Ponrartana, MD; Benita Tamrazi, MD; Marvin Nelson, MD; J. Gordon McComb, MD; and Wende Gibbs, MD, from the Keck School of Medicine of USC. [✦](#)

To find out more about this work, visit [CHLA.org/BorzageResearch](https://chla.org/BorzageResearch)

Time STAMP

(Static Tagging And Mono-contrast Preservation)



Time STAMP is noninvasive and works with existing MRI machines for easy adoption.



One out of every 1,000 newborns has hydrocephalus, or fluid buildup in the brain. That's more common than spina bifida or brain tumors.



50 percent of all babies with hydrocephalus nationwide must return for a **second surgery within a year**.



This new brain imaging solution from CHLA results in images **50 percent brighter and clearer** than other current scanning methods.

Better images will mean fewer repeat surgeries for vulnerable newborns.



WHOLE HEARTED

By Candace Peason

Surgeons at Children's Hospital Los Angeles are tapping into regenerative medicine to give newborns with a rare heart defect a better chance at a longer life.

Jasmine Garcia and her parents, Amy Guillen and Ray Garcia, find themselves unexpectedly on the leading edge of science. Jasmine came into this world on Dec. 22, 2017, at a robust 8 pounds, 10 ounces and 19.5 inches long—statistics that on the surface concealed a big problem within her tiny body. Jasmine was born with half a heart.

She is one of about 1,000 children diagnosed in the United States each year with hypoplastic left heart syndrome (HLHS). In this rare and complex congenital heart defect, the left side of the heart is severely underdeveloped and can't do its job of pumping oxygen-rich blood from the lungs to the rest of the body.

There is no cure for HLHS. However, a sophisticated surgical intervention introduced three decades ago reroutes the heart's plumbing to enlist the right ventricle as the main pumping chamber to the body. Unfortunately, this workaround is not a permanent solution.

Personalized medicine for HLHS

Now a bold experiment is attempting to supercharge that pioneering surgery with the power of stem cells. The goal: create a stronger heart that may help postpone or even prevent future heart failure in HLHS children. "This marks a paradigm shift in the way we are thinking about



Jasmine Garcia, following her first open-heart surgery.

these congenital heart defects," says Ram Kumar Subramanyan, MD, PhD, cardiathoracic surgeon and regenerative medicine investigator in the Heart Institute at Children's Hospital Los Angeles. "We have gotten so good at surgically caring for these patients, who better to push the envelope with biological therapy?"

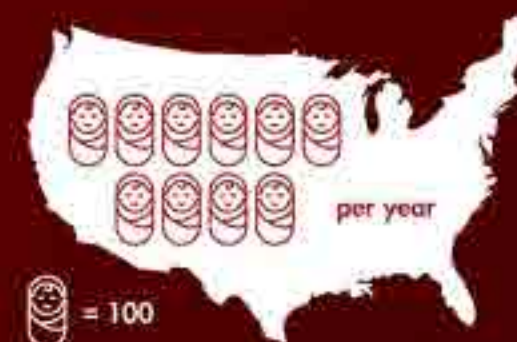
Pushing the envelope includes participating in the multicenter HLHS Consortium, launched by the Mayo Clinic in Minneapolis with a phase I clinical trial to test the safety and feasibility of using a baby's own umbilical cord blood cells to trigger the growth of new heart muscle.

A Second Chance

In September 2017, 20 weeks into her pregnancy, Guillen went for what she thought would be a routine ultrasound at a local hospital. When doctors spotted the signs of HLHS, they sent her and Garcia to the Heart Institute, where specialists confirmed the diagnosis.

"It was very hard to hear at first," says Guillen. Then Subramanyan told the parents about the stem cell study. They signed on immediately. "I couldn't see any downside," Guillen adds. "I believe this is a second chance for our daughter and her future."

That second chance is taking place at one of the leading, high-volume treatment centers for complex HLHS cases. The Heart Institute first performed the three-part surgery in 1992.



About **1,000 children** are diagnosed with **hypoplastic left heart syndrome** in the U.S. each year.

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"Today, we have better approaches to protect the heart and brain during surgery, and the surgical techniques have been refined significantly," says Vaughn Starnes, MD, co-director of the Heart Institute.

Yet even the most advanced techniques and cardiothoracic critical care apparently can't beat the passage of time.

As HLHS children grow older, their reconstructed hearts have been working overtime. By adolescence, many survivors are showing signs of cardiopulmonary deterioration. For some, that means the need for a heart transplant. "We're looking at new and alternative approaches to tackle this vexing problem," says Starnes.

Those novel approaches include investigating cellular and molecular-level factors that impact HLHS outcomes. "What if we can teach the right ventricle to grow extra muscle while it still can?" says Subramanyan. The question is based on the finding that the newborn heart appears capable of making new muscle cells for the first year or so—"before we lose that ability for the rest of our lives."

A team approach to move further, faster

No one center alone can accumulate enough patients to accelerate innovation. "The HLHS Consortium enables us to take the science and technology and teams of people to other centers of excellence, and interact with more families at more locations," says Timothy Nelson, MD, PhD, director of the Todd and Karen Wanek Family Program for Hypoplastic Left Heart Syndrome at the Mayo Clinic.

The Consortium is a group of strategically located centers with the unique capacity to implement the study procedures. Working together, up to seven regional centers will enroll about 20 children. CHLA is the only West Coast member organization. "We want to be at the forefront in treating this complex disease process," says Starnes. "We're proud to be part of this select group of institutions."

At 5 days old, Jasmine had her first open-heart surgery at CHLA. A sample of her umbilical cord blood was collected at birth, then processed at the Mayo Clinic to create highly concentrated stem cells. Those cells were frozen and stored until Jasmine's second reconstructive surgery



Left to right: Vaughn Starnes, MD, Ram Kumar Subramanyan, MD, PhD, and Parag Wong, MD, of the Heart Institute at Children's Hospital Los Angeles with Timothy Nelson, MD, PhD, of the Mayo Clinic

at 6 months of age. On July 9, 2018, Jasmine underwent her second surgery. On that day, the stem cells that had been collected previously were delivered directly into her heart.

Once injected, the stem cells don't actually become new muscle—"they're not the seed," explains Subramanyan, "they're the fertilizer." Current thinking, based in part on pre-clinical studies, is that the stem cells stimulate the muscle tissue that already knows to multiply.

Jasmine's third surgery will take place at about 3 years old. She and other newborns in the study will be monitored closely as they grow. If the investigators' hypothesis is correct, they will see these hearts getting stronger, evidenced by thickening of the heart wall.

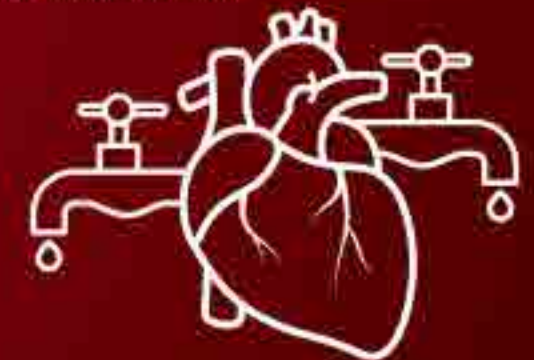
"I feel very hopeful," Gullen says with a smile. "I have read about stem cells having amazing promise in other diseases. Why not the heart?"

To learn more about the HLHS clinical trial, visit CHLA.org/HLHS



Kalle Mosey, RN, examines infant Jasmine Garcia as her mother, Amy Gullen, looks on.

TWO PUMPS IN ONE



The healthy human heart is a muscle with two hardworking pumps. The right ventricle normally pumps oxygen-poor blood from the heart to the lungs. The left side receives oxygenated blood from the lungs, then sends it out to the entire body. When the left side is underdeveloped, as in hypoplastic left heart syndrome (HLHS), that blood flow is impaired. With surgery, the right ventricle takes on the duty of pumping oxygenated blood to the entire body.

In a healthy heart, the left ventricle is thick with muscle. But the right ventricle has less muscle, making it less equipped for this strenuous job. By injecting stem cells into the right ventricle of a baby with HLHS, scientists hope to increase muscle in this area, making it better able to perform the double duty required.

Listen Up: Reducing Hearing Loss Caused by Chemotherapy

By Jennifer Jing

Investigators develop a strategy for minimizing ototoxicity while maximizing treatment effectiveness.

For children and adolescents with cancer, permanent hearing loss is a frequent side effect of common chemotherapy medications. Although lowering the dosage of chemotherapy may reduce these harmful effects, that can cause the cancer treatment to be less effective.

Researchers at Children’s Hospital Los Angeles have been leading the search for a safe way to prevent chemotherapy-induced hearing loss in pediatric patients—without compromising the effectiveness of treatment. That’s particularly important for children because the ability to hear is critical for acquiring language, learning in school, establishing social skills and achieving proper psychosocial development. Any disruption to hearing at an early age may lead to lifelong functional disability.

In a recent multicenter study, David R. Freyer, DO, MS, explored the effects of sodium thiosulfate—a powerful antioxidant—in preventing hearing loss among children undergoing chemotherapy with cisplatin. Cisplatin is a common chemotherapy drug used to treat many childhood and adult cancers.

Freyer found that the incidence of hearing loss was reduced by about half in children treated with cisplatin plus the antioxidant, compared with cisplatin alone. He also found that the greatest benefit of the antioxidant treatment was seen in children younger than 5 years of age. These children are most susceptible to, and most affected by, hearing impairment.



David R. Freyer, DO, MS (left), and Etan Orgel, MD, MS

As director of the Survivorship and Supportive Care Program in the Children’s Center for Cancer and Blood Diseases, Freyer is working closely with CHLA colleague Etan Orgel, MD, MS, to expand on this discovery and look into other compounds that may offer hearing protection during cancer treatment.

“Until now, hearing loss was an unavoidable fact for most patients undergoing chemotherapy,” says Freyer. “Our findings are an important step toward developing a strategy that not only effectively treats cancer, but also greatly improves the quality of life for pediatric cancer survivors.”

To learn more about this work, visit CHLA.org/FreyerResearch and CHLA.org/OrgelResearch

“Until now, hearing loss was an unavoidable fact for most patients undergoing chemotherapy. Our findings are an important step toward developing a strategy that not only effectively treats cancer, but also greatly improves the quality of life for pediatric cancer survivors.”

– David R. Freyer, DO, MS

THE ADOLESCENT BRAIN ON...

FOOTBALL

By Jennifer Marcus

Do repeated sports-related head impacts have cumulative effects on the developing brain?



Max Herman

rang out in alarm. Max was taken off the field for the remainder of the game.

Fortunately, Max's school is participating in a unique research study to assess the effects of repeated sports-related head impacts on the developing brain. So in addition to the standard checkup, Max also received a brain scan as part of his participation in the study.

Besides having the only pediatric concussion program in Los Angeles, Children's Hospital Los Angeles also has an active research program focused on the developing brain. Led by Bradley S. Peterson, MD, director of the Institute for the Developing Mind at The Saban Research Institute of Children's Hospital Los Angeles, a team of investigators has partnered with Crescenta Valley High School to follow young athletes over the course of their entire high school sports careers using a variety of tools—including brain imaging, cognitive and behavioral tests, and helmets equipped with electronic sensors to record head movement and any blows received during football games.

Study participants so far include 40 high school football players and a control group of 40

athletes not involved in contact sports—such as runners, swimmers and tennis players—with no prior history of concussion. The same number of players will be recruited each year as freshmen and followed throughout the course of their high school careers.

"There are still many unanswered questions about the effects that repeated head impacts have on children and adolescents," says Peterson. "Currently, we do not know whether the adolescent brain is more or less vulnerable than the adult brain to repeated head impacts."

To answer this question, Peterson has assembled a unique team of experts, including Tracy Zaslow, MD, medical director of CHLA's Sports Medicine Program and director of the Pediatric Sports Concussion Program and Clinic; Ravi Bansal, PhD, an expert in brain image processing technologies at CHLA; David A. Baron, MEd, DO, director of the Global Center for Exercise, Psychiatry and Sport in the Department of Psychiatry at the Keck School of Medicine of USC; and Cynthia A. Bir, PhD, director of the Biomechanics Injury Research Laboratory at USC.

"The brain has its own natural repair mechanisms just like any other organ in the body."

— Bradley Peterson, MD

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Members of the research team (left to right): Karen Li, Kelsey McAlister, MS, Zachary Toth, MPA, Bernice Flores, Patricia Baron, David Baron, MEd, DO, and Bradley Peterson, MD



Establishing a baseline for each player

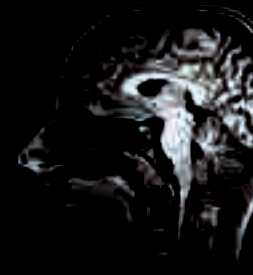
In one of the most distinctive aspects of the study, researchers are conducting magnetic resonance imaging (MRI) scans and cognitive and behavioral tests on participants at the beginning of each football season, including prior to the freshman year, before any head impacts have been sustained. This information establishes a critical baseline against which they can compare subsequent data each year, as well as within 36 hours of any suspected concussion.

The objective is to assess how the number and magnitude of head impacts affect the long-term developmental trajectory of brain structure and function in football players relative to the group of control athletes.

In the lab

According to Peterson, the information gathered by the MRI scans and cognitive tests throughout the study will reveal new and important details about how the brain develops differently in adolescents with and without repeated head impacts. It will also provide information about the brain's natural protective and repair mechanisms in response to the impacts.

"The brain has its own natural repair mechanisms just like any other organ in the body. It's critically important to understand how the brain is able to protect itself and repair minor injuries on its own. We're also looking at how these intrinsic processes may be aided by factors that can be controlled, such as hydration, nutrition, and the amount and quality of sleep," says Peterson. The investigators are looking at brain structure,



▲
Coronal, sagittal and axial brain scans



Rendering of the football helmet with sensors

connectivity, function, blood flow, metabolism and myelin content—the fatty substance that coats the white matter in the brain and enables information to be transmitted along nerve cells quickly and accurately.

"A lot of evidence suggests that myelin and the portions of nerve cells it covers are disrupted by repeated head impacts," says Peterson. "We're interested in finding out how this affects critical-thinking skills, problem solving and emotional development, and we're especially interested in learning how to protect myelin for these kids."

On the field

Study participants like Max are issued state-of-the-art football helmets equipped with highly sensitive electronic sensors—now commonly worn by college and professional athletes. The sensors record all movements of the head and especially impacts to the head, including those not strong enough to cause a concussion.

"During any football practice or game, each student has many head impacts, and those vary by position on the team," explains Peterson. "Certain player positions have more frequent and severe impacts, but we're measuring all the athletes and getting critical readings on every single movement of a player's head."

The research team will obtain very detailed measures of every hit, along with detailed video recordings from five angles across the football field, for every practice and every game. For each head impact, the study team will know the direction, speed and rotation of head movements, as well as the accelerations and decelerations that cause the brain to jostle around inside the skull.

Biomechanics experts on the research team will be able to analyze these measures to understand what kinds of head motions create the biggest problems for the athletes.

In life

"We're working to keep these kids healthy and safe and able to continue participating in contact sports," says Peterson.

Armed with the breadth of data being collected, he is confident that the detailed analyses his team conducts will be able to identify the kinds of injuries that are most harmful to the brain, and what kinds of tackles and other football maneuvers are more dangerous than others. This will hopefully inform policies regarding training practices and rules and regulations governing the game, resulting in improved player safety.

In spite of the hard hit Max took last season, his MRIs and other tests came back normal, allowing him to get back to math, guitar and his dream of pursuing a football scholarship.

According to Max's mom, Nicole Herman, Peterson's work is making a difference in how she feels about her son playing football. The intense monitoring that study participants receive "makes me feel a whole lot safer about letting my son go out there and play contact sports." 🦋

To learn more about this research, visit CHLA.org/PetersonLab

TRANSFORMING THE LIVES OF PATIENTS WITH HEMOPHILIA



By Sara Nafie

For some patients, a new medication helps bleeding episodes decline from 30 each year – to zero.

Ivan Molina, 17, was diagnosed with hemophilia A when he was 9 months old. As soon as he started to crawl, the condition's telltale signs began to appear through bruises on his arms and legs. At that time, he was referred to Guy Young, MD, director of the Hemostasis and Thrombosis Center at Children's Hospital Los Angeles. A few years later, Ivan's younger brother, Diego Garcia, now 13, was also given the life-changing diagnosis.



Left to right: Diego, age 3, and Ivan, age 6

The boys' maternal grandfather passed away from the condition when he was just 32, so their mom, Mayra Molina, knew there was a chance her children might inherit it. Yet nothing could have prepared her for the all-consuming responsibility of taking care of one child, and then another, with hemophilia.

Unfortunately, both Ivan and Diego developed inhibitors, or antibodies, to factor replacement therapy. To stop a bleed, intravenous bypassing agents—medications that circumvent the need for coagulation factor and take a different route to clotting—had to be given as often as every two to three hours. For each occurrence, the need for this around-the-clock diligence typically lasted three or four days. Mayra recalls that her older son had several serious bleeds in his joints every year.

"Sometimes they'd get pain during the day but not want to stop playing, like most boys, so they'd finally come to me at night saying, 'Mom, it hurts. I can't take it.' We'd then start a 25-minute setup to make sure everything was sterile, prep the medication, then try to find a vein," Mayra recalls. "This would be at 2 or 3 in the morning, and sometimes it would be both boys but at different hours in the middle of the night. It was really, really difficult."

Mayra started hearing about a new medication for hemophilia a few years ago. At their very next appointment, she told Young, who treats both of her boys, "If the study opens at CHLA, I want my kids on it." Looking back she says, "I had hoped this would be the thing that changed everything, and so far it has."

Ivan started taking emicizumab in April 2016 as part of the HAVEN 1 study, and Diego began the drug as part of HAVEN 2 in August of the same year. In less than three weeks, the drug's benefits were obvious. Ivan's bruises disappeared and the swelling in his joints decreased. It has now been more than a year since the family has had to wake up in the middle of the night to treat a bleed.



This photo, taken in 2012, shows Diego standing behind Ivan, who spent much of his life in a wheelchair until he began treatment with emicizumab.

(continued on next page)

“He has not used his wheelchair in over a year now. Well, actually, that’s not true. Last summer we were moving into a different apartment, and he used his wheelchair as a dolly to load boxes.”

— Mayra Molina

Equally remarkable is that emicizumab is a simple, once-a-week injection into any area of fat on the body. A relentless and meticulous procedure that used to take hours and days to manage now has become a 10-second weekly routine.

In the five years before the study, Mayra estimates Ivan spent about 50 percent of his time in a wheelchair; in fact, the only time he “walked” to school was in his wheelchair with his mom pushing. Within the first month on the new medication, Ivan started trying to walk, and now he regularly walks a mile to school and a mile home every day.

“He has not used his wheelchair in over a year now,” Mayra says. “Well, actually, that’s not true. Last summer we were moving into a different apartment, and he used his wheelchair as a dolly to load boxes. All these years we have had to live in a first-floor apartment or somewhere with wheelchair access. And last week he carried 30-pound boxes up to our new third-floor apartment!”

Before taking emicizumab, Ivan was depressed, overweight and seemingly hopeless about his future. “It was like all he could do was watch his body deteriorate,” Mayra reflects. Today he is motivated, physically fit, getting A’s and B’s in high school and doing the “normal teenage



Left to right: Diego, Ivan and their sister, Angelina, in September 2017

things” his mom never imagined for him—including having a steady girlfriend. “I don’t want to say it’s a cure, but if kids like mine are not having bleeds, they are no longer dealing with hemophilia.”

To find out more about this research, visit CHLA.org/YoungLab

A New Way to Treat Hemophilia

Approximately 20,000 people in the United States are living with hemophilia A, a genetic bleeding disorder caused by a deficiency in the clotting protein called factor VIII. For these people, what might otherwise be a minor bump or bruise can quickly become a life-threatening bleeding episode. In severe cases, spontaneous and recurrent bleeding in the same joint—most frequently the ankle, elbow or knee—leads to progressively debilitating pain and physical impairment.

Despite their inability to produce factor VIII naturally, most people with hemophilia A with access to factor replacement therapy have a normal life expectancy. But replacement factor VIII has a short half-life and must be administered intravenously two or three times per week to maintain normal coagulation, and even more frequently during an active bleed.

In about 30 percent of cases, patients develop antibodies or “inhibitors” that prevent replacement factor from working. Hemophilia A with inhibitors, therefore, must be treated with so-called bypassing agents that take a different pathway to coagulation and circumvent the route that is blocked by inhibitors. These agents promote blood clotting but are much less effective than replacement factor at stopping active bleeds.

In 2017, the U.S. Food and Drug Administration (FDA) approved an innovative new therapy, emicizumab, that revolutionized the treatment of hemophilia A with inhibitors. Guy Young, MD, director of the Hemostasis and Thrombosis Center at Children’s Hospital Los Angeles, is part of the international team of hematologists that conducted the pivotal phase 3 clinical trials on this medication.

In these multicenter phase 3 studies, called HAVEN 1 and HAVEN 2, emicizumab was proven to be dramatically more effective than conventional therapies for preventing bleeding in patients with hemophilia A with inhibitors. Emicizumab is also easier to administer than bypassing agents since it is given subcutaneously (an injection under the



Guy Young, MD

skin rather than into a vein) and only once a week, rather than multiple times every week.

HAVEN 1 is now complete, having enrolled 109 males ages 12 years and older with hemophilia A with inhibitors. Children’s Hospital Los Angeles, which treats the largest number of pediatric hemophilia patients in California, was one of the highest-enrolling sites in the world.

Results from HAVEN 1, published in the *New England Journal of Medicine* on July 10, 2017, were dramatic: Individuals treated with emicizumab experienced 87 percent fewer bleeds compared with patients treated with on-demand bypassing agents, and 79 percent fewer bleeds compared with prior prophylactic bypassing agents. Significantly, no anti-drug antibodies were detected.

HAVEN 2 is an ongoing follow-up study of emicizumab for patients younger than 12. Preliminary results are equally as promising as those from HAVEN 1. “This is the most significant advancement I have seen during my 20 years working in the field of hemophilia,” says Young, who is also a professor of Pediatrics at the Keck School of Medicine of USC.

Based on final results from HAVEN 1 and preliminary results from HAVEN 2, Genentech’s application for FDA approval of emicizumab was granted priority review and breakthrough therapy designations. Final approval of emicizumab under the trade name Hemlibra was announced on Nov. 16, 2017.

“Before this medication was licensed and widely available, we had families flying in from all over the country to get access to it,” says Young. “Patients had been bleeding up to 30 times per year—to see that number drop to basically zero is really something.”



Nearly a third of patients with hemophilia develop antibodies. These “inhibitors” prevent clotting factors from doing their job.

A New Tool for Studying Communication Deficits in Autism

By Ellin Kavanagh

A signal-processing program enhances the ability to study vocalizations in a mouse model.

Much of what we know about diseases and how to treat them comes from the use of models that allow scientists to study a specific condition. However, for autism spectrum disorder with behavioral diagnostic criteria—such as social communication deficits—the development of models can be challenging.

Vocalization plays a significant role in social communication in many species, including mice, which vocalize during friendly social encounters. By linking vocalizations with the animal's behavior and genetics, scientists have created a model for studying the behaviors and the impact of genes associated with autism.



Pat Levitt, PhD


“Understanding the complicated vocalizations of mice and how they relate to their social behavior will be crucial to advancing vocal and social communication

research, including understanding how genes that affect vocal communication relate to genetic mutations in children with disorders like autism,” says Pat Levitt, PhD, Simms/Mann Chair in Developmental Neurogenetics and vice president, chief scientific officer and director of The Saban Research Institute of Children's Hospital Los Angeles.

This painstaking and time-consuming process of analyzing vocalizations has recently gotten a lot faster and more innovative. In a unique collaboration with Levitt, researchers Allison Knoll, PhD, of CHLA and Shri Narayanan, PhD, of the Viterbi School of Engineering at USC have developed a novel signal-processing tool called Mouse Ultrasonic Profile ExTraction, or MUPET.

The new tool enables unbiased, data-driven machine learning analysis of tens of thousands of vocalizations, and the researchers' findings were published in the journal *Neuron*.

The investigator team is now able to rapidly analyze enormous amounts of mouse communication data, identify subtle differences in vocalizations, and link them to behavioral conditions occurring at the same time. The analytical software has been made available to all researchers and is now being used by dozens of laboratories around the world.

“This advance has made translational research to understand neurodevelopmental disorders more powerful—testing potential interventions that address social and emotional challenges that typically include communication disturbances,” says Levitt, the W.M. Keck Provost Professor in Neurogenetics at the Keck School of Medicine of USC. 

To find out more about this research, visit [CHLA.org/LevittLab](https://chla.org/LevittLab)

“Understanding the complicated vocalizations of mice and how they relate to their social behavior will be crucial to advancing vocal and social communication research, including understanding how genes that affect vocal communication relate to genetic mutations in children with disorders like autism.”

– Pat Levitt, PhD

ZIPPY: THE VIRTUAL RESEARCH NAVIGATOR

By Jeff Weinstock

Researcher Michele Kipke is hoping a kindly cartoon robot will help draw cautious, underrepresented minorities into clinical trials.



You wouldn't know by its neutral orange-and-gray countenance and flat tone, but Zippy the robot is passionate about its mission.

Zippy follows Ava, a teenage patient with diabetes, through the halls of Children's Hospital Los Angeles, hoping to engage her in a conversation about clinical trials.

"Keep your research studies to yourself!" Ava says. "I know what happens. Once you go on a study, you never come back."

A self-described medical research robot programmed to help humans learn about research studies, Zippy understands Ava's anxiety. The kind and well-meaning robot praises Ava's skepticism and tries to alleviate her fears by explaining the rights and protections assured to participants in clinical trials. Zippy is presented as a helper, not as a doctor or nurse, nor with any particular identity, so the information the robot provides is better received by a distrustful teen.

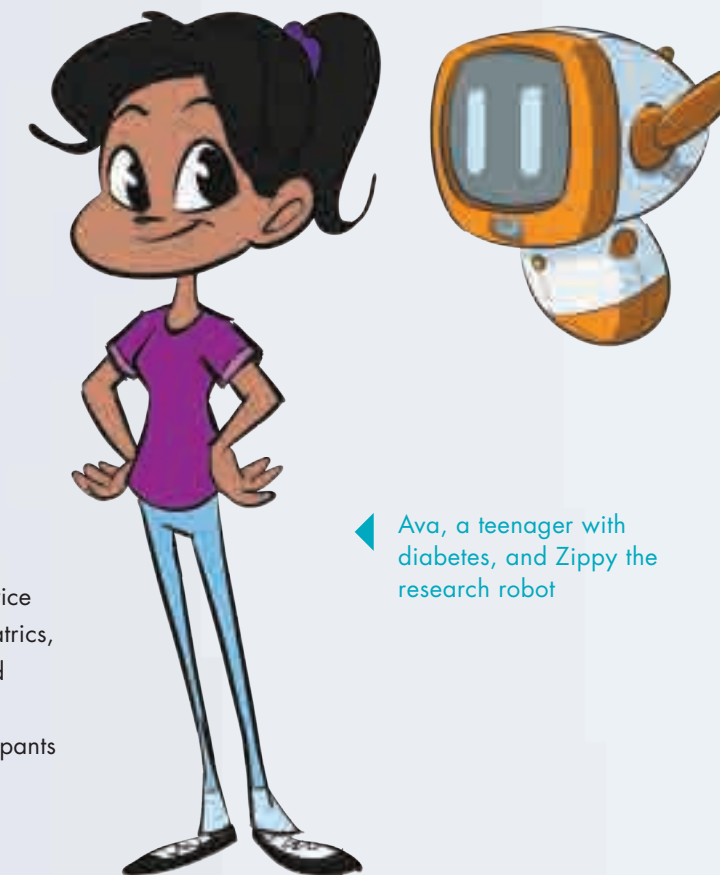
In spite of herself, Ava is intrigued. "I have more questions," she says. "I have more answers," Zippy replies. The two walk off together, continuing their dialogue. Whether she says yes or no to participating in a research study, Ava will have the information she needs to make an informed choice, and Zippy will have done its job.

Although this is a scripted cartoon being played out on a YouTube page, it's the hope of Michele Kipke, PhD, and her team at The Saban Research Institute of Children's Hospital Los Angeles that it will be repeated in real-life encounters. Kipke, the hospital's vice chair of Research in the Department of Pediatrics, is counting on Zippy's wisdom, empathy and charm to increase diversity in enrollment in CHLA's research studies, where white participants outnumber participants of color by 4-to-1.

"As a result, our clinical trials don't provide enough information about the health of communities of color," Kipke says, "and we don't know if we're going to get the same positive benefits in African-American or Latino populations."

This isn't a problem specific to pediatric studies or to CHLA. Kipke says minorities are also underrepresented in adult research studies nationwide.

Patients from minority communities have long been reluctant to participate in research, due in part to a history of abuse in past studies. Kipke cites the most egregious examples, such as the Tuskegee Airmen—African-American World War II pilots who were experimented on without their knowledge—and Henrietta Lacks, an African-American woman who, in 1951, did not consent to the use of her cells, which are still being used in cancer research today.



◀ Ava, a teenager with diabetes, and Zippy the research robot

(continued on next page)

The Many Faces of Zippy



Happy

Sympathetic

Confused

Surprised

Angry



Michele Kipke, PhD

Kipke says conversations with local families have confirmed that suspicions persist, even though the research process is now highly regulated and includes many

patient protections. Although researchers—including Kipke—are working to correct the imbalances in clinical trials by increasing participation among communities of color, those changes don't happen easily or quickly.

"We know patients are mistrustful," Kipke says. "They're also afraid of some sort of unintended consequences occurring down the road. What they don't know is that they have rights as participants. We need to shed light on the protections for patients while explaining the importance of research to families."

Enter Zippy, Ava and other supporting players in a series of videos developed through the Virtual Research Navigator Project. The videos are looking to build what Kipke terms "research literacy," a better understanding of what research studies are and a greater willingness among patients to join them. If families have questions that aren't addressed in the videos, Zippy can respond to their queries through a website. Kipke and her team developed the content working with engineers and animators at USC's Institute for Creative Technologies, within the university's Viterbi School of Engineering.

The videos are essentially animated tutorials well-disguised as cute narratives. In each, the polite but earnest robot Zippy interacts with Ava, your classic eye-rolling teen, and her parents—addressing their concerns about clinical studies and taking on issues of privacy, enrollment, consent and the importance of research participation.

In one video, titled "Benefits," Ava shuts down Zippy's pleas. "Save your battery," she says. When Ava expresses concern about being part of a research study, Zippy explains the protections in place, but doesn't push. "Do what you feel is right," the robot says.

Ava comes around: "OK, I can at least listen to what the doctor has to say."



Project Manager Dayo Akinyemi, MPH, a member of Kipke's staff, and potential research subject, Mei Diaz, go over matters with Zippy.



Ava tries to ignore Zippy, the persistent robot.

And that, Kipke says, is her goal for the videos. She's not looking for an instant yes from families, but rather hoping to provide them with the resources to make an informed decision, "so that when they're sitting with their pediatrician who says, 'Your daughter with type 2 diabetes would be eligible for this clinical trial,' they are more willing to listen."

Kipke's team has completed the pilot phase of the project and is now moving ahead with making some adaptations to the platform for use in multiple children's hospitals in the U.S.


Although diversity among research participants has been a longstanding problem, Kipke says it has taken on more importance as health care moves toward precision medicine. "We're trying to figure out what works best for whom, and why, and in which real-world health care settings. The only way we can do that is if we have data from everybody."

That may be ambitious, but it's only a means to Kipke's ultimate objective, which is to accelerate the research pipeline—the course from discovery in the lab to actively improving child health.

That effort is the ongoing work of the Southern California Clinical and Translational Science Institute, another collaboration between CHLA and USC, underwritten by a \$36.6 million grant from the National Institutes of Health.

On average it takes 20 years for new breakthroughs to be translated into treatments and then put into use. "That's too long," Kipke says. Testing medications and other treatments for safety and efficacy is crucial, but the process needs to be shortened and barriers to getting people into research studies—such as their fear and mistrust—need to be eliminated.

"If the goal is to speed up the research pipeline, part of that is how you engage people in clinical trials," Kipke says.

And if Zippy is successful at its job, "people" will include everyone. 

To find out more about this work, visit CHLA.org/KipkeLab

"We're trying to figure out what works best for whom, and why. ... The only way we can do that is if we have data from everybody."

— Michele Kipke, PhD

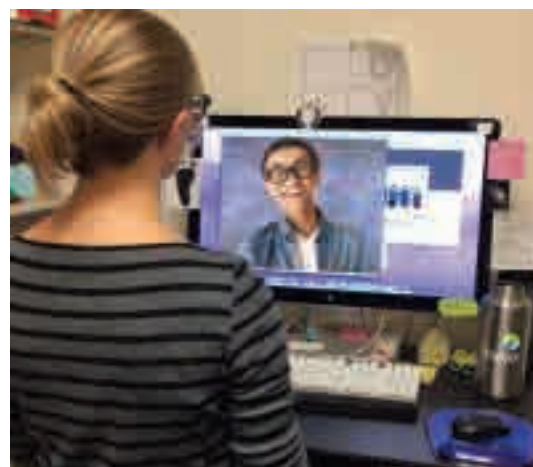
The Doctor Will See You NOW

By Melinda Smith

Telemedicine can be used to tackle chronic diseases like type 1 diabetes in difficult-to-treat patient populations.

The American Diabetes Association (ADA) recommends that patients visit their doctor four times a year to monitor diabetes control and optimize therapy. Patients devote hours or even days to these appointments, missing school or work several times a year. Jennifer Raymond, MD, MCR, the clinical diabetes director at Children's Hospital Los Angeles, foresees a future in which appointments are better accommodated to patients' schedules.

Raymond is using the growing field of telemedicine—treating patients remotely—to improve the care of adolescents and young adults with type 1 diabetes.



A virtual medical appointment

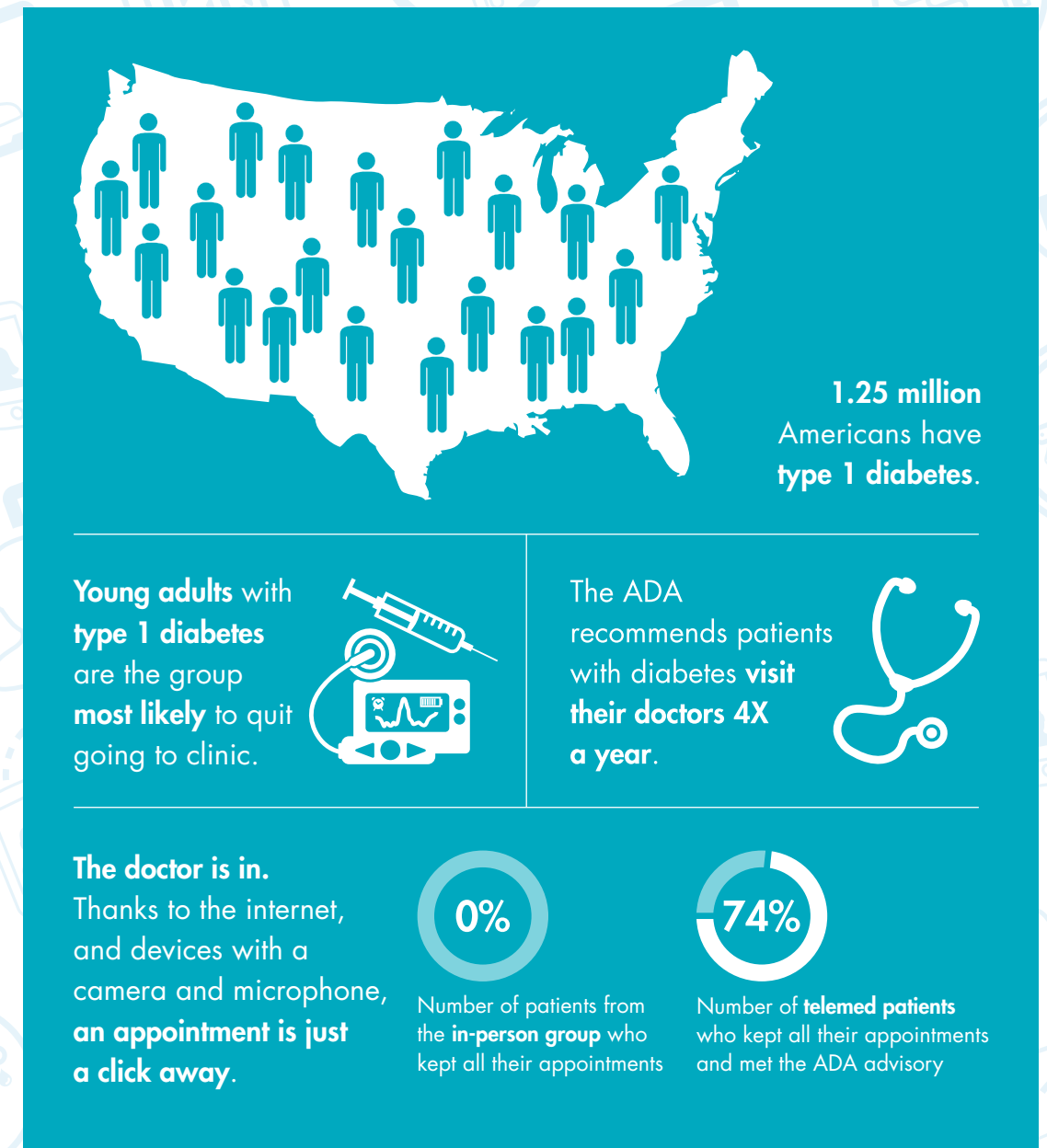
"I want to help young adults with type 1 diabetes obtain proper health care while respecting their academic, work and social priorities," says Raymond, who is also an associate professor of Clinical Pediatrics at the Keck School of Medicine of USC.

She conducted a pilot telemedicine study with young adults—the age group where clinic attendance drops the most. Patients had blood drawn at local facilities and uploaded data from glucose monitors and other diabetes devices through secure software. Then, using devices equipped with internet, a camera and a microphone (e.g., laptops, tablets and smartphones), patients simply clicked a link to begin their "virtual appointment."

The result was a drastic improvement in clinic attendance: 74 percent of patients in the virtual appointment group met the ADA recommendation for quarterly appointments, while none of the patients in the in-person group did. Significantly, they also increased their engagement outside of appointments, actively seeking medical care and advice—a rare trait for this age group.

"We need medical care to be more patient-centered," Raymond says. "Innovations in technology and clinical care models are helping us meet that need."

To learn more about this research, visit CHLA.org/JenniferRaymond



WHAT A DIFFERENCE A DAY MAKES

By Anna Azvolinsky and Ellin Kavanagh



A 2-year-old with a rare cancer benefits from a team of experts, personalized medicine and the right clinical trial.

"We thought she had a bug bite," says Christina Lowry, "but it turned out to be cancer."

Christina and her husband, Joe, initially noticed a mass on their daughter Michelle's neck in October 2017, when she was just over 2 years old. Michelle's pediatrician prescribed a course of antibiotics in case the mass was a swollen lymph node resulting from an infection. When the antibiotics didn't work, Michelle was referred to a local hospital for a biopsy, which came back positive for sarcoma. That's when the Lowry family came to Children's Hospital Los Angeles.



Mikako Warren, MD

Prior to beginning treatment, CHLA pediatric pathologists Mikako Warren, MD, and David Parham, MD, performed a detailed analysis of Michelle's tumor, revealing that it was a low-grade spindle cell sarcoma. The standard treatments of surgery and radiation were ruled out because of the location of the tumor.



David Parham, MD

Fortunately, the clinical team had access to specialized testing to help guide this very challenging treatment decision. Called OncoKids®, this unique next-generation, sequence-based panel is able to identify the genetic alterations most commonly found in pediatric cancers. OncoKids could determine whether Michelle would be eligible for any targeted therapies offered as part of a clinical trial.

The test was developed by CHLA's Center for Personalized Medicine, which is led by Jaclyn Biegel, PhD, chief of the Division of Genomic Medicine in the Department of Pathology and Laboratory Medicine at CHLA.

Changing conditions

While the team waited for the results of the OncoKids panel, Michelle was discharged

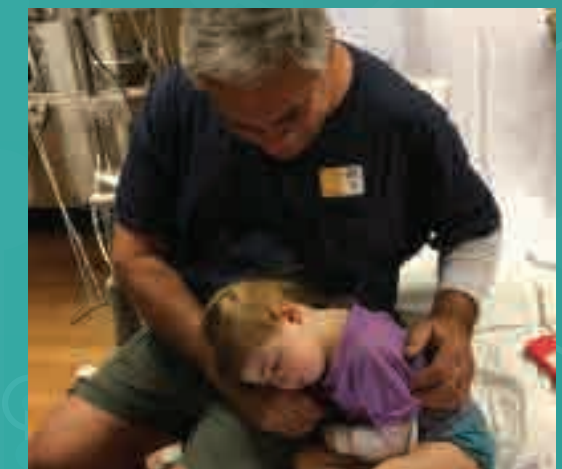


Jaclyn Biegel, PhD

so the family could celebrate Thanksgiving together at home. "Michelle loves Christmas, and since we didn't know what the future would hold, as soon as we got home we began decorating," says Christina. "It made her happy." One week later, Michelle was not her usual self and her parents became concerned. On the morning of Friday, Dec. 1, they returned to CHLA.

"When we last saw Michelle, she had good energy and was very active," recalls her oncologist, Rachana Shah, MD, MS. "But when her parents brought her into the Emergency Department, the right side of her face was swollen and she was having trouble breathing." Worried that Michelle's condition could quickly deteriorate, Shah admitted her to CHLA's Pediatric Intensive Care Unit.

It turns out Michelle's breathing difficulties were caused by the tumor, which had grown so rapidly in just a matter of days that it was now blocking 50 percent of her airway.



Michelle with her grandfather before receiving an experimental drug at CHLA

(continued on next page)

“The experimental therapy was a lifesaver for Michelle.”

— Rachana Shah, MD, MS



The partially blocked airway also meant that Michelle could not be fully sedated for a procedure. Surgery was not an option anyway, since the tumor was wrapped around the windpipe and major blood vessels of the lungs. The sarcoma was also impinging on Michelle’s nerves and causing upper-arm and facial weakness.

The team overseeing Michelle’s care considered a few possible options. The surgical team was standing by in case the situation became dire enough that Michelle needed an extreme intervention. Extracorporeal membrane oxygenation, called ECMO, could bypass her heart and lungs to provide proper blood oxygenation and carbon dioxide removal, if her breathing became even more compromised. Alternatively, Shah and the oncology team



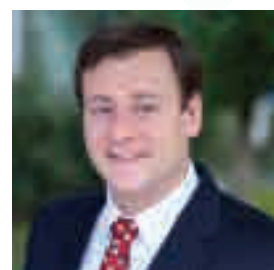
Leo Mascarenhas, MD, MS

considered initiating emergency chemotherapy. “She was so critically ill that we needed to do something to get her stabilized and buy more time,” says Shah.

Critical timing

Leo Mascarenhas, MD, MS, deputy director of the Children’s Center for Cancer and Blood Diseases and head of the Oncology section of CHLA’s Division of Hematology, Oncology and Blood and Marrow Transplantation, leads a clinical trial at CHLA evaluating an oral drug called larotrectinib.

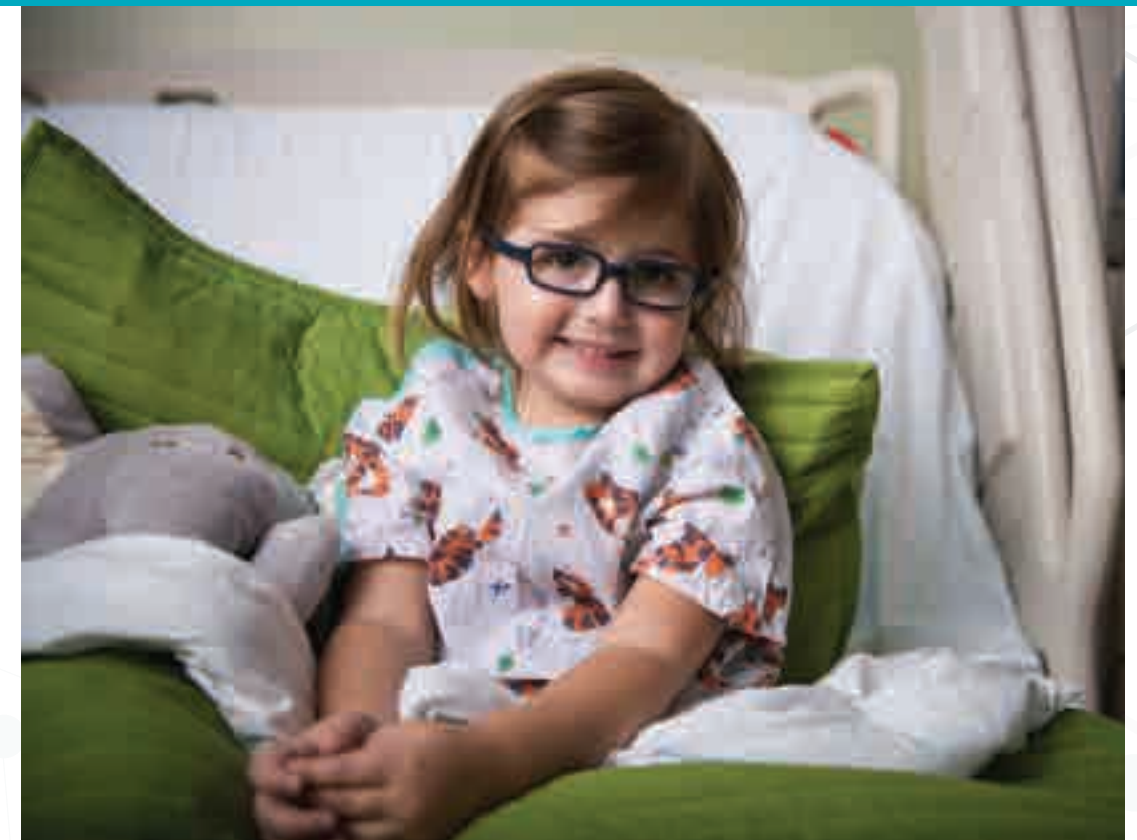
The medication targets tumors that express an NTRK fusion—a hybrid oncogene formed from two separate genes that can drive tumor growth. Mascarenhas had been collaborating on a manuscript, subsequently published in the *New England Journal of Medicine*, reporting on the high rate of success and low incidence of side effects associated with the drug. Suspecting that Michelle’s tumor might harbor an NTRK fusion, he requested that the molecular testing be expedited.



Matthew Hiemenz, MD

At 7 p.m. that same day, Biegel and her colleague Matthew Hiemenz, MD, a molecular genetic pathologist at CHLA, analyzed the results of the OncoKids testing and identified a TPM3-NTRK1 fusion in Michelle’s tumor. “We had this critical information we needed, right when we really needed it,” says Shah. This finding meant that Michelle was eligible for a specialized phase 1 clinical trial, only offered at CHLA and a few other sites in the country.

For the Lowrys, the offer of a clinical trial really made them stop and think. “It’s not like solving a mathematical equation, where 2 plus 2 always equals 4,” says Christina. “In this case, every patient is different. You don’t really know how it will go. How can you prepare yourself for this? You can’t. You just have to move ahead—and we did.”



Michelle after beginning treatment on a phase 1 clinical trial

With the parents’ consent, Mascarenhas called the trial’s national study director and filed an official report declaring that Michelle was eligible to participate. Although all clinical trials are highly regulated, phase 1 studies such as this are particularly rigorous. Fortunately, approval from the pharmaceutical company, Loxo Oncology, came that same night.

The next hurdle was getting the medication. Clinical trial medications are stored in a special investigational pharmacy, which is only staffed on weekdays. But after the team reached out, an investigational pharmacist came in on Saturday to prepare the twice-daily suspension doses Michelle would need.

“She was given her first dose exactly 17 hours after we received the molecular diagnosis—a process that typically takes one to two weeks,” says Mascarenhas.

Good news, finally

Michelle responded to the medication within 24 hours, exceeding her doctors’ expectations. Remarkably, after being in critical condition on Saturday morning, she was able to go home with her family on Tuesday. “The experimental therapy was a lifesaver for Michelle,” says Shah.

Two months later, a scan revealed that her tumor had shrunk by approximately 60 percent. According to Michelle’s father, the tumor has gotten so small that it is difficult for the radiologists to measure. Michelle will continue to receive the drug as part of the clinical trial until she has a maximal response or the tumor disappears completely.

Based on other positive outcomes like Michelle’s, the FDA granted accelerated approval of larotrectinib on Nov. 26, 2018. [✦](#)

To learn more about OncoKids, visit [CHLA.org/CPM](https://www.chla.org/cpm)

In the News



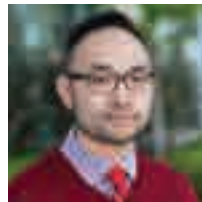
Rosemary She, MD (left), and Jeffrey Bender, MD

Jeffrey Bender, MD, and co-author **Rosemary She, MD**, of the Keck School of Medicine of USC, reported on using elimination communication, also known as natural infant hygiene, to toilet-train their infant daughter from birth. The perspective paper was published in *Pediatrics* and received national media coverage from outlets such as *The Washington Post* and *Reuters Health*.

Jesse Berry, MD, and **Jonathan Kim, MD**, showed proof of concept for a safe, minimally invasive liquid biopsy for retinoblastoma, using fluid that is removed from the front of the eye during localized injection of chemotherapy. Their study, published in *JAMA Ophthalmology*, shows potential for future diagnostic and prognostic applications and was covered by numerous media outlets, including *Stat News* and *MedPage Today*.



Jesse Berry, MD (left), and Jonathan Kim, MD



Todd P. Chang, MD, MAcM

CBS National News featured **Joshua Sherman, MD**, and **Todd P. Chang, MD, MAcM**, on their use of virtual reality to safely teach medical residents how to approach life-or-death scenarios in pediatrics—allowing the trainees to experience the stress of the real-life experience. **Marie La Fortune, MD**, who had tested VR as a study subject, demonstrated the technology. *USA Today* also did a feature story on this project.

Jay Desai, MD, and **Bradley Peterson, MD**, reported that stuttering is linked to reduced blood flow in the area of the brain associated with language. Their study was published in the journal *Human Brain Mapping* and was covered by a wide range of national and international news outlets, including *U.S. News & World Report*, *NIH Medline Plus*, *the Daily Mail*, *BBC World Service* and *IFL Science*.



Bradley Peterson, MD (left), and Jay Desai, MD



Jeffrey Gold, PhD

The *Wall Street Journal* interviewed **Jeffrey Gold, PhD**, about his studies on the use of virtual reality (VR) to manage pain and anxiety in some CHLA patients. Patients using VR while having blood drawn reported less pain and anxiety related to the procedure.



Leo Mascarenhas, MD, MS

Leo Mascarenhas, MD, MS, and colleagues reported on a phase 1/2 clinical trial of larotrectinib, a novel therapy that targets a type of genetic mutation known as TRK fusion, which accelerates cancer-cell growth. The studies, published in the *New England Journal of Medicine* and *Lancet Oncology*, found that the new therapy was highly selective in inhibiting the growth process in many types of cancer that harbored a TRK fusion, and that it had a favorable safety profile. The FDA granted larotrectinib breakthrough therapy designation and an expedited review for approval.

Research faculty participated in efforts to raise awareness for the March for Science to oppose proposed budget cuts to science and medical research. **Leo Mascarenhas, MD, MS**, was interviewed by CBS2 Los Angeles for a pre-march broadcast news feature, and **Diane Brown, MD, PhD**, who joined thousands in downtown Los Angeles to support the effort, was featured in the *Los Angeles Times'* coverage of the event.



Diane Brown, MD, PhD (left), and Leo Mascarenhas, MD, MS



Ram Kumar Subramanyan, MD, PhD

Ram Kumar Subramanyan, MD, PhD, discussed how hypoplastic left heart syndrome (HLHS) is surgically repaired and how a new study, conducted in conjunction with the Mayo Clinic, is investigating the use of regenerative medicine to help babies born with this severe heart defect. The story was carried by *CBS National News*.

An international team of hematologists that included **Guy Young, MD**, reported results of a multicenter phase 3 study called HAVEN 1 in the *New England Journal of Medicine* demonstrating that for patients with hemophilia A with inhibitors, a novel therapy called emicizumab decreases the incidence of bleeding episodes by 87 percent. The report received coverage from national media outlets such as *United Press International* and *U.S. News & World Report*. The drug was subsequently approved by the FDA based on this study.



Guy Young, MD

Awards and Honors



Denise Al Alam, PhD

The National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH) has awarded **Denise Al Alam, PhD**, \$2.6 million for her research into early fetal development of the human lung. Her research into these developmental processes has potential applications for premature babies and children with congenital pulmonary abnormalities.

Sebastien Bouret, PhD, was granted \$2.6 million by the National Institute of Diabetes and Digestive and Kidney Diseases of the NIH for his research into how leptin (a hormone that inhibits hunger) and nutritional programming impact the development of diabetes and obesity. This research will study the role of maternal obesity in the development of metabolic abnormalities in offspring.



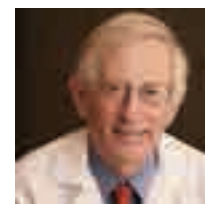
Sebastien Bouret, PhD



David Cobrinik, MD, PhD

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 NIH to support his research to improve understanding of how cone photoreceptors in the retina develop.

Yves DeClerck, MD, along with David C. Lyden, MD, PhD, from Weill Cornell Medicine, was awarded \$2.2 million from the National Cancer Institute of the NIH to study how exosomes released by tumor cells are taken in and modify the bone marrow, leading to cancer metastasis. Greater understanding of this process could lead to new strategies for reducing or preventing metastatic disease.



Yves DeClerck, MD



Mark R. Frey, PhD

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 and 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.



Lee J. Helman, MD

Lee J. Helman, MD, director of the Cancer and Blood Diseases Research Program at The Saban Research Institute of CHLA, has been named a vice-chair of the Stand Up To Cancer (SU2C) Scientific Advisory Committee. With SU2C's increased focus on pediatric cancer, Helman's expertise in this area will be beneficial to the organization's growing research portfolio.

Carla Hill, MPA, was awarded \$1 million by the California Department of Public Health Adolescent and Family Life Program to improve teen pregnancy outcomes, reduce the rate of repeat pregnancies, and assist with re-entry into school or continuation of education. The funding will support research to enable evidence-based interventions for expectant and parenting adolescents with a focus on increasing access to and utilization of services, including social and emotional support.



Carla Hill, MPA



Deborah Holder, MD

Deborah Holder, MD, was awarded \$1 million by the Ahmanson Foundation to acquire new electroencephalogram (EEG) machines critical to recording electrical signals of the brain to diagnose epilepsy. Ambulatory units will enable the monitoring of patients as they are transported to different areas of the hospital, providing physicians with the information needed to deliver more accurate and personalized treatment. The equipment will facilitate research initiatives, including one to determine the precise location of seizure onset.

A team of researchers led by **Michele Kipke, PhD**, at CHLA, and Thomas Buchanan, MD, and Steven Siegel, MD, PhD, of the Keck School of Medicine of USC, received a prestigious Clinical and Translational Science Award from the 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.



Michele Kipke, PhD



Natasha Leporé, PhD

Natasha Leporé, PhD, was awarded \$1.7 million from the National Institute of Biomedical Imaging and Bioengineering of the NIH to study the impact of prematurity on brain development. The goal of the research is to develop ways to detect cognitive problems and behavioral disorders in premature babies before the symptoms arise, improving physicians' ability to design early interventions and encourage healthy neurological development.

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Awards and Honors (continued)



Pat Levitt, PhD

Pat Levitt, PhD, received \$1.3 million from the JPB Research Network on Toxic Stress, a project of the Center on the Developing Child at Harvard University. This award will fund ongoing research into the development of biomarkers to detect toxic stress in early life.

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.



Ellen Lien, PhD



Miguel Martinez,
MSW, MPH

Miguel Martinez, MSW, MPH, was awarded \$2.5 million by the U.S. Department of Health and Human Services – Substance Abuse and Mental Health Services Administration to address disparities in access to youth-specific substance abuse treatment for gay and bisexual youth of color at risk for HIV/AIDS. The funding will support research to identify gaps in service and enable the enhancement of integrated programs for medical, behavioral health and HIV services for this population.

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, is 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

Brent Polk, MD, was awarded \$1.5 million from the National Institute of Diabetes and Digestive and Kidney Diseases of the NIH to study tumor necrosis factor and its role in IBD. This new research seeks to reveal important information about the cellular and molecular activity that triggers IBD and may point to new treatment approaches for patients who no longer respond to current treatments.



Brent Polk, MD



Michael Pulsipher, MD

Michael Pulsipher, MD, along with Sung-Yun Pai, MD, from Boston Children's Hospital, was awarded nearly \$9 million from the National Institute of Allergy and Infectious Diseases of the NIH to study a new treatment approach for babies born with severe combined immunodeficiency (SCID). The goal of the study is to determine the lowest dose of chemotherapy needed for babies with SCID undergoing bone marrow transplantation—to effectively restore the immune system with less toxicity than the higher-dose regimens currently in use.

Pulsipher and Michael Keller, MD, from Children's National Health System in Washington, DC, were awarded \$4.8 million by the California Institute for Regenerative Medicine (CIRM) to study the use of a new T-cell therapy to fight active viral infections in children with severe immune deficiencies. The research will test the feasibility of using "viral-specific" T-cells engineered to target three common and potentially toxic viruses—Epstein-Barr virus, cytomegalovirus and adenovirus—that can lead to severe organ damage or death in children with weakened immune systems.

In addition, Pulsipher was awarded \$1.3 million by the National Heart, Lung, and Blood Institute of the NIH to improve early immune-suppression-free survival for young patients with severe aplastic anemia. The funding represents a Clinical Trial Network Core Center Renewal for the Pediatric Blood and Marrow Transplantation Consortium headquartered at CHLA.

The Cancer Immunotherapy Trials Network (CITN) was funded by Congress at the request of former President Barack Obama as part of the Beau Biden Cancer Moonshot Initiative. Immunotherapy to treat pediatric cancer was designated one of 10 priority areas, leading to the development of the Pediatric CITN. As one of the original hospitals in the U.S. approved to treat patients using CAR T-cell immunotherapy, CHLA is now one of only 10 institutions in the Pediatric CITN. Pulsipher, of the Children's Center for Cancer and Blood Diseases, will serve on the steering committee, which prioritizes clinical trials for study through this consortium.

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Robert C. Seeger, MD

Robert C. Seeger, MD, of the Children's Center for Cancer and Blood Diseases, along with John M. Maris, MD, from Children's Hospital of Philadelphia, was awarded a grant of nearly \$11 million from the National Cancer Institute of the NIH to study new treatments for children with high-risk neuroblastoma while attempting to decrease treatment-related side effects. Collaborating with Seeger on this multisite study are CHLA's Shahab Asgharzadeh, MD; Yves DeClerck, MD; Araz Marachelian, MD; Richard Sposto, PhD; and Judith Villablanca, MD, and Susan Groshen, PhD, from the Keck School of Medicine of USC.

Wei Shi, MD, PhD, of the Developmental Biology and Regenerative Medicine research program at The Saban Research Institute, was awarded more than \$2.6 million by the National Heart, Lung, and Blood Institute of the NIH to study the molecular mechanisms of pulmonary disease in Birt-Hogg-Dubé (BHD) syndrome—a genetic condition associated with benign skin tumors, lung cysts and kidney cancer. His goal is to understand the disease mechanisms in order to provide a foundation for novel preventive and therapeutic strategies.



Wei Shi, MD, PhD



Elizabeth Sowell, PhD

Elizabeth Sowell, PhD, director of the Developmental Cognitive Neuroimaging Laboratory, part of CHLA's Institute for the Developing Mind, was awarded nearly \$2.8 million by the National Institute on Alcohol Abuse and Alcoholism of the NIH to study the impact of prenatal alcohol exposure on brain, cognition and facial morphology. The research will determine how maternal alcohol consumption patterns throughout pregnancy—including quantity, frequency and timing—impact the severity of fetal alcohol spectrum disorders.

David Warburton, MD, of the Developmental Biology and Regenerative Medicine Research Program, was elected as a fellow to the American Association for the Advancement of Science, in recognition of his contributions to innovation, education and scientific leadership in the section of Medical Sciences. Warburton also was named an inaugural fellow of the American Thoracic Society in honor of his pioneering discoveries in lung development, neonatology and global environmental sciences.



David Warburton, MD



Ashley Whitaker, PhD, ABPP-Cn

Ashley M. Whitaker, PhD, ABPP-Cn, of the Children's Center for Cancer and Blood Diseases, has completed American Board of Professional Psychology (ABPP) specialty board certification in clinical neuropsychology, as well as subspecialty board certification in pediatric neuropsychology. Whitaker is one of only about 1,000 neuropsychologists across the United States to achieve this professional milestone in clinical neuropsychology and one of about 100 to achieve it in pediatric clinical neuropsychology.

John Wood, MD, PhD, was awarded \$2.5 million by the National Institutes of Health to study the relationship between cerebrovascular reserve (CVR) and white matter disease in patients with anemia who are at risk for having silent, white matter strokes leading to significant cognitive dysfunction. The research aims to validate CVR as a biomarker for white matter vulnerability that can be used as a means of discovery for silent stroke prevention.



John Wood, MD, PhD



Larry Yin, MD

Larry Yin, MD, was awarded \$2.7 million from the U.S. Department of Health and Human Services Administration for Community Living to advance patient care for infants, children and adolescents with intellectual and developmental disabilities. The funding will support program development with emphasis on early intervention, health and quality assurance to strengthen the health and community services available at every stage of life for affected individuals.

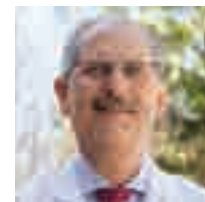
New Faces



Stefano Da Sacco, PhD, joined the Department of Urology. He earned his doctorate in tissue engineering while studying at the University of Padua and USC, and completed his postgraduate training at CHLA in the laboratory of Roger De Filippo, MD, FACS, FAAP, and Laura Perin, PhD. Da Sacco's research focuses on the relationship between the extracellular matrix and self-renewal, differentiation and specification of nephron progenitors.

Stefano Da Sacco, PhD

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.



Lee Helman, MD



Sonata Jodele, MD, joined the Children's Center for Cancer and Blood Diseases as medical director of the Blood and Marrow Transplantation Program (BMT). She will provide leadership for multidisciplinary BMT clinical programs and further development of clinical research efforts. Her research focus is on reducing organ toxicity after hematopoietic stem cell transplantation, with an emphasis on transplant-associated thrombotic microangiopathy. Jodele comes to Children's Hospital Los Angeles from Cincinnati Children's Hospital Medical Center.

Sonata Jodele, MD

Allison T. Knoll, PhD, joined the Division of Research on Children, Youth and Families. She earned her doctorate in neurobiology from Harvard University and began a postdoctoral fellowship at the Zilkha Neurogenetic Institute at the Keck School of Medicine of USC, and completed the program in the laboratory of Pat Levitt, PhD, at The Saban Research Institute. Knoll's research examines the genetic and environmental basis of individual differences in typical social behavior and in risk for neurodevelopmental disorders.



Allison T. Knoll, PhD



Omkar P. Kulkarni joined CHLA as the hospital's first chief innovation officer. He is responsible for fostering innovation across the clinical enterprise—including finding successful new methods of care, incubating new medical tools and software, and rallying communities in and out of the hospital to solve problems in the field of pediatrics. Kulkarni will also work with the Consortium for Technology and Innovation in Pediatrics (CTIP).

Omkar P. Kulkarni



John T. Li, MD, joined the Department of Anesthesiology and Critical Care Medicine and The Saban Research Institute of Children's Hospital Los Angeles. His research interests are focused on the immunology of acute respiratory distress syndrome (ARDS) and TGF- β signaling in lung diseases and cancer, with a goal toward understanding the adaptive immune response in ARDS and identifying pulmonary antigens that drive this process.

John T. Li, MD

Aaron Nagiel, MD, PhD, joined The Vision Center and The Saban Research Institute, where he leads an active clinical and translational research program aimed at developing better ways to treat pediatric retinal diseases through state-of-the-art imaging, advanced surgical devices and novel treatments, including gene therapy and stem cell-based therapy.



Aaron Nagiel, MD, PhD



Sargis Sedrakyan, PhD, joined the Department of Urology. He earned his doctorate in regenerative medicine from the University of Padua in Italy. Sedrakyan completed his postdoctoral fellowship in developmental biology and regenerative medicine at The Saban Research Institute. His research focuses on the role of endothelial injury and extracellular vesicles in kidney disease and amniotic fluid stem cell therapy in Alport syndrome.

Sargis Sedrakyan, PhD

Gianluca Turcatel, PhD, joined the Department of Pulmonology. He earned his Master of Science degree and doctorate from the University of Padua. Turcatel's research interests focus on embryonic and postnatal lung development, adult lung injury and repair, and tissue engineering.



Gianluca Turcatel, PhD

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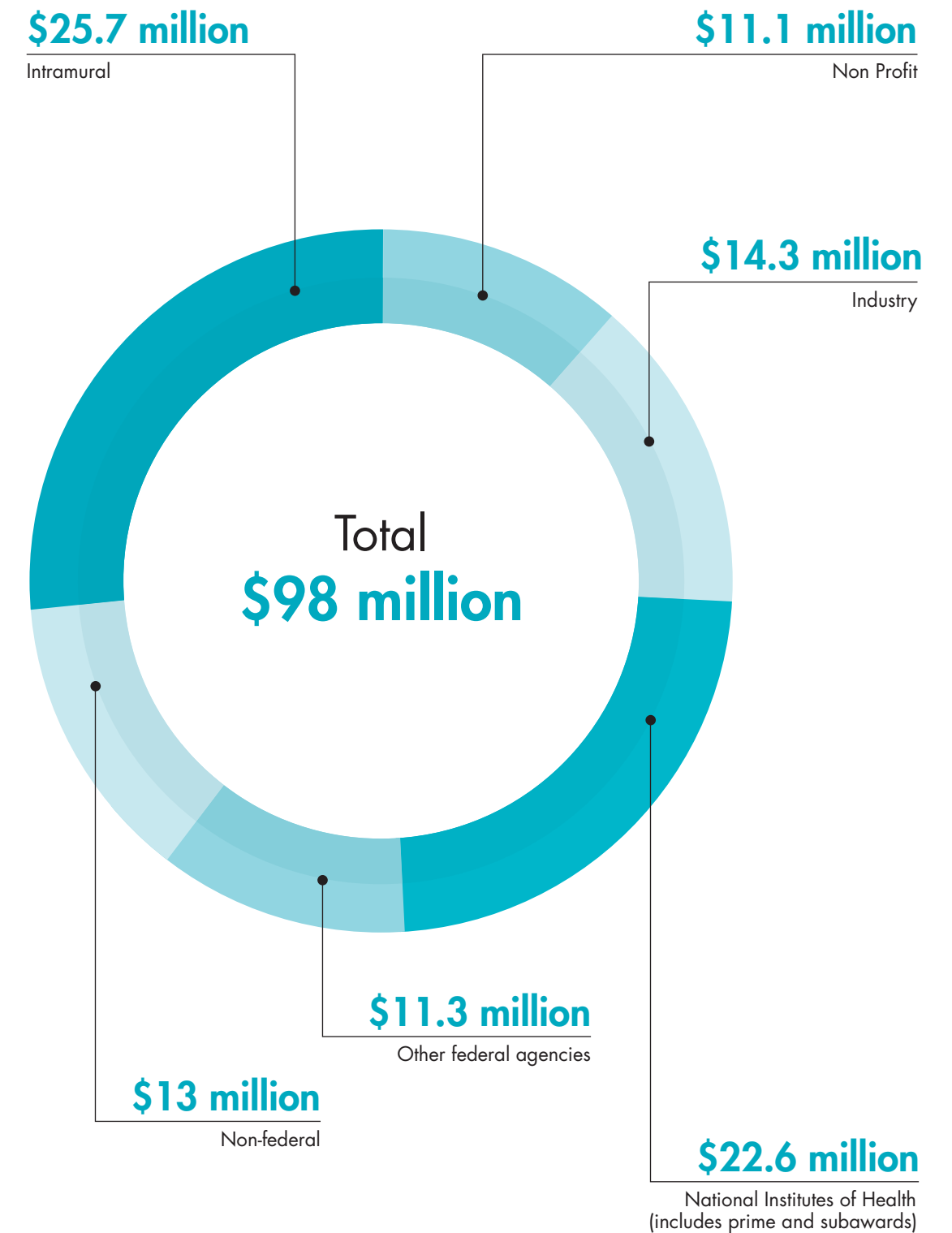
Christopher Del Vecchio

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Fiscal Year 2017-2018



In This Issue



ENGINEERING NEW ORGANS FROM LIVING CELLS

A novel, cell-based therapy for babies with intestinal disorders moves closer to a first-in-humans trial.



ZIPPY: THE VIRTUAL RESEARCH NAVIGATOR

Researcher Michele Kipke is hoping a kindly cartoon robot will help draw cautious, underrepresented minorities into clinical trials.



WHOLEHEARTED

Surgeons at CHLA are tapping into regenerative medicine to give newborns with a rare heart defect a better chance at a longer life.



WHAT A DIFFERENCE A DAY MAKES

A 2-year-old with a rare cancer benefits from a team of experts, personalized medicine and the right clinical trial.



TRANSFORMING THE LIVES OF PATIENTS WITH HEMOPHILIA A

For some patients, a new medication helps bleeding episodes decline from 30 each year – to zero.