

CHILDREN'S HOSPITAL LOS ANGELES

RESEARCHLA



2016



The Saban Research Institute

The Saban Research Institute comprises 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 is organized around areas that fully explore the developmental origins of health and disease and address the most pressing national child health issues.

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 2015, The Saban Research Institute received \$32.7 million (prime and subawards) in National Institutes of Health (NIH) funding and \$74.8 million in total funding. The Saban Research Institute ranks eighth in the nation among children's hospitals in 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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A Message From the Director





You've probably heard friends say, "If I lost my cell phone, I'd lose half my brain." Not only do they mean it, they're right—at least metaphorically. Technology has become a virtual extension of our brain and an essential tool for managing our increasingly complex world. Both of these topics, technology and the brain, are actively being investigated at The Saban Research Institute of Children's Hospital Los Angeles.

In this issue of ResearCHLA, "Digital Natives Go to the Doctor" explores the use of technology with young people who are growing up in the digital age—and the implications it has for their health care. Another story, "Game Boy"—about a generation raised with video games—shows how Todd Chang, MD, is using serious gaming techniques to help train future emergency room physicians.

As technology transforms the practice of medicine, new and more effective medical devices are being designed for and tested on adults. Similar to what happens in drug development, the use of new and better treatment options for children often lags behind. In "There's a Hack for That," read how Bibiana Jin Reiser, MD, of The Vision Center, is challenging the status quo. Applying leading-edge technology marketed for adult eye surgery, she is optimizing it for use in children while working toward her goal of lowering the incidence of pediatric blindness.

"Wake-up Call" is a story about a family who had to deal with the unthinkable—a child being diagnosed with a spinal tumor—and how they are investing in research in order to change the odds for other families in that situation. The Kort Family Foundation's gift of \$2 million will help develop noninvasive diagnostic techniques and more effective personalized treatments for brain and spinal cord tumors.

There are other ways that a child's brain can be impacted that may not be as obvious as a tumor. Current estimates suggest that 1 in 5 children have learning or behavioral disorders. Genetics contribute, but research by Brad Peterson, MD, Pat Levitt, PhD, and Elizabeth Sowell, PhD—all part of our Institute for the Developing Mind—shows that environmental conditions also play a significant role. In the article "Why Does He Do That?" the investigators discuss opportunities to intervene and influence a child's development—helping the child realize his fullest potential.

Also in this issue, Paul Viviano, the new CEO of Children's Hospital Los Angeles, shares his commitment to research as a critical component of an academic medical center like CHLA. Paul brings an extensive background in health care to his new role, and a dedication to the children whose care and treatment we are privileged to provide.

Please enjoy the magazine and thank you for your continuing support.

Sincerely,



Brent Polk, MD

Director, The Saban Research Institute of Children's Hospital Los Angeles

Physician in Chief; Vice President, Academic Affairs; Chair, Department of Pediatrics, Children's Hospital Los Angeles

Professor of Pediatrics and Vice Dean for Child Health, Keck School of Medicine of the University of Southern California



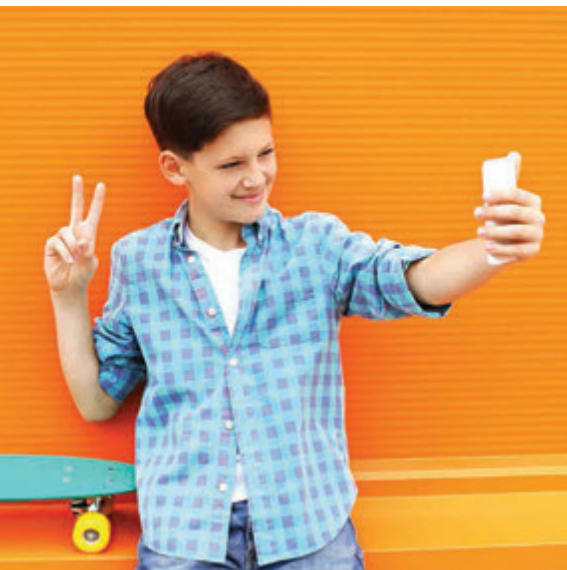
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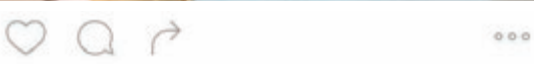
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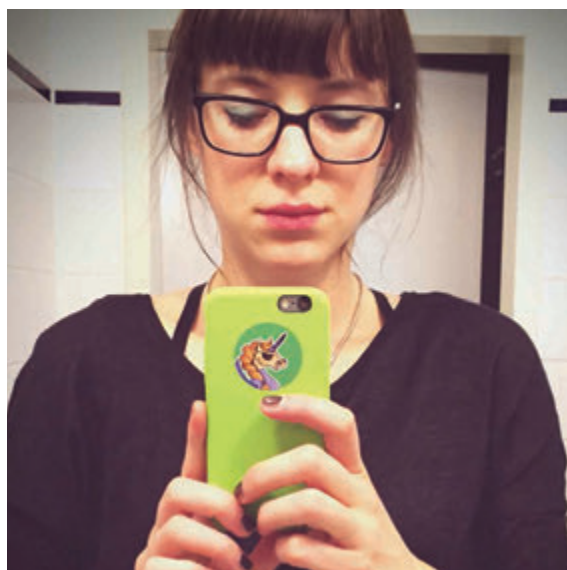
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Digital Natives

Go to the Doctor

How kids' intuitive use of technology advances care at CHLA

Sometimes it seems like today's kids were born with a cell phone in hand, intuitively searching the Web and sharing selfies on Instagram. These "digital natives" have been immersed in technology since early childhood, their lives fully integrated with devices that make them digitally fluent and often the envy of older generations—the "digital immigrants" who may find such technology less than intuitive.

Parents—who ultimately must choose to allow or deny their kids access to technology—are also the ones who worry about its effects. Until recently adopting a more nuanced approach, the American Academy of Pediatrics had recommended no screen time for children younger than 2 years of age. That confirms technology is harmful for kids, right?

Not always.



Margaret Trost, MD

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“At a pediatric hospital, sometimes we have to get kids to buy in to doing something they’re reluctant to do,” says Margaret Trost, MD, a hospitalist at Children’s Hospital Los Angeles. “That’s when kids’ innate attraction to technology comes in handy.” Trost is testing whether the use of socially assistive robotics reduces pain and anxiety during placement of intravenous lines in children prior to undergoing MRI.

Collaborators Maja Matarić, PhD, and Jillian Greczek, PhD student, of the USC Viterbi School of Engineering designed the digital humanoids to be autonomous—there is no one “off-stage” telling the robots what to say. The robots are preprogrammed with an array of responses to fit a variety of scenarios. In fact, the study is designed to determine what sorts of communication help patients most.

Previous research has indicated that robots with more empathetic speech tend to have a greater effect on patients. So in one arm of this study, the robot is simply a distraction—talking about the weather, sports or vacation plans. In another arm of the study, the robot talks about its role as a helper to CHLA’s Child Life Program, describing how it has seen other kids get IVs and that the procedure might hurt a little or be a little bit frightening. The third arm of the study is the Child Life specialist only, talking to the child.

“The goal is not to have the robot replace a human, but rather to work with the Child Life specialist to explain the process and make it a little more appealing for the child,” says Trost, who is also an assistant professor of Clinical Pediatrics at the Keck School of Medicine of the University of Southern California (USC). “Kids like robots, so we anticipate that their stress level—along with their pain—will be lessened when the robot talks them through their feelings.”



Socially assistive robots



Rebecca Dahl, PhD

There's an app for that

With technology being incorporated into clinical trials throughout the hospital, it isn't surprising that this type of innovation has also found its way to one of the earliest stages of a study—patient assent. Rebecca Dahl, PhD, director of the Human Subjects Protection Program, explains that federal regulations have always required that even young patients agree to participate in a study. Although parents need to give consent for their young children, Dahl says that at about age 7 kids gain the maturity to assent for themselves and need to have the clinical trial explained in language they can understand.

"There is just no way a child at 7 years old can understand risks as well as we adults understand them—or benefits, for that matter," says Dahl. "But we still need to find a way to really reach kids, not just in terms of the type of information but also how we provide it."

Dahl's initial idea was a board game. The prototype is similar to the game Candyland, but set at CHLA. Responses from her colleagues were positive, but they were unanimous on one point—switch out the cardboard for the cloud.

rebecca dahl "We still need to find a way to really reach kids, not just in terms of the type of information but also how we provide it." #DigitalNatives

♥ Add a comment...

Just a few months later, ConsentQuest became a software application, making CHLA the first hospital to develop an app for assent. "Kids migrate toward technology," says Dahl. "This will fit right into their area of interest."



Terence Sanger, MD, PhD



Wearables

With 1 in 5 Americans already using wearable technologies, pediatricians have been quick to see their potential in many areas of the hospital, like on the wrist of a rehab patient cared for by Terence Sanger, MD, PhD. Sanger is a pediatric neurologist with a doctorate in engineering. In addition to seeing patients, he spends his time in the lab inventing devices for children with movement disorders.

"The great thing is that you don't have to give kids instructions about how to use a device," says Sanger. "You can put it on a 1-year-old and they'll figure it out."

He is currently heading up a clinical trial on the use of surface electromyography. Sanger, a provost associate professor of Biomedical Engineering, Neurology and Biokinesiology at the USC Viterbi School of Engineering, designed the device, the software and the algorithm. The small, oval unit is placed on a muscle group to monitor electrical current. The device is very sensitive and can pick up muscle activity that is too weak to result in movement. Yet the buzzing sound provides biofeedback that the muscle is working.

Sanger tells the child, "Don't worry about raising your wrist, just make it buzz." Kids practice all day because they like the sound; it's reminiscent of a video game. After a while, all that practice pays off and the muscle gets stronger. Sanger gets the necessary result, but in a way that's more interesting—even fun—for the child.

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Terence Sanger, MD, PhD, and Jesus Munoz

Activity trackers

The most popular form of wearable tech is probably the activity tracker. Typically used during the day, these devices can also provide clinicians with information about their patients at night. Clinical Research Coordinator Beth Osterbauer, MPH, who works with Debra Don, MD, a pediatric otolaryngologist at CHLA, is using the Fitbit to study sleep-disordered breathing. “The kids love it—they actually remind their parents to put the device on them at night.”

A snoring toddler might seem cute until behavioral disorders, poor progress in school and even physiological problems develop due to obstructed breathing and sleep deprivation. Currently, sleep-

disordered breathing can only be diagnosed by an overnight sleep study that is expensive and can be frightening for young patients.

The Fitbit records movement, and clinicians believe that kids who snore and have upper airway obstruction tend to move around a lot at night. Don’s hypothesis is that results from the device will correlate with the sleep study findings. “We think the Fitbit could be useful for identifying which kids have more movement and disturbed sleep due to airway obstruction,” says Don, who is also an assistant professor of Clinical Otolaryngology at the Keck School of Medicine of USC. “This may help us determine which kids need to be treated and are more likely to benefit from treatment without performing a sleep study.”



Beth Osterbauer, MPH



Debra Don, MD



Juan Espinoza, MD



Pediatricians are realizing that wearable medical tech can help form a bridge to reluctant patients. “I think that using tools that they are familiar with, that they are excited about, is potentially the way in, especially for those who have been resistant to treatment,” says Juan Espinoza, MD, an attending physician in General Pediatrics.

He and his colleagues are using Fitbit as part of a randomized, controlled trial studying weight loss in children. The literature is clear that interventional programs must include nutrition, behavioral changes and physical activity. Until now, patients would complete a journal or be asked about their daily athletics and physical play. However, when clinicians compared reported activity to what they could objectively assess, the discrepancy was huge.

“You can’t hand them a brochure,” says Espinoza. “When you’re dealing with digital natives, asking them to step outside their ecosystem is a step backward. They’re not going to do it.” As a result, the motivational piece of the weight-loss program may have been lacking.

Espinoza, who is also an assistant professor of Pediatrics at the Keck School of Medicine of USC, plans to find out if Fitbits can provide that necessary motivation. Half of the patients and their parents enrolled in this study will wear one, and the other half will rely on traditional reporting techniques.

Data showing the activity levels of the children and adults wearing the device will be sent directly to Espinoza and his colleagues. When a patient comes in for a weekly appointment, the provider can look at the information and see how much time the patient spent doing moderate exercise.

“Then we can say, ‘Hey, you did great!’” says Espinoza. “We won’t have to rely on the patient remembering correctly or reporting accurately. We can see what they really did.”

He anticipates that the Fitbit group will have increased motivation to exercise and will lose more weight. Why? Because, as Espinoza explains, the appeal of wearable tech is that it’s familiar to teens, it’s current. “The device blends into the ecosystem where these kids live. It’s an extension of what they’re already doing.”

juan espinoza “When you’re dealing with digital natives, asking them to step outside their ecosystem is a step backward. They’re not going to do it.” #DigitalNatives

♥ Add a comment... ...

To stay current and keep up with what kids are doing, the big question is: What’s next?

You will soon be hearing about “medical selfies.” As the name implies, these are patient-generated digital photos and videos sent to doctors to assist in the diagnosis of conditions ranging from autism to an ear infection. To deal with privacy issues, companies are currently developing strategies to ensure secure transmission of these images.

“But the real challenge,” warns Espinoza, “will be working with teens to figure out what are reasonable limits to sharing personal health information on social media.”

In other words, keep it off Instagram. ■

GAME BOY



Physician Todd Chang is using serious gaming as a tool to train young doctors.

Activity in the emergency department (ED) in a pediatric hospital is fast-paced, and the most precious resource is time. With more than 80,000 patients to attend to every year for trauma, rare diseases and complex conditions, physicians and residents at Children's Hospital Los Angeles have to manage resources accurately and efficiently.

Residents rotating into a pediatric ED can have difficulty adjusting to the sharp difference in tempo, after training in departments that function at a steady pace, enabling watchful observation and measured assessment. In an instant, Todd Chang, MD, an attending physician in the Emergency Department at CHLA, can spot a novice resident in the midst of seasoned emergency physicians.

Because teaching and assessing patient care one patient at a time is the current norm in medical education, students often graduate with inadequate experience in providing care to multiple patients at the same time, while prioritizing resources in a crowded ED.

"The transition to a busy ward, clinic or operating room requires a critical set of management skills that is not taught in medical school," says Chang, who is also associate professor of Clinical Pediatrics at the Keck School of Medicine of the University of Southern California. "Additional training is needed to help residents feel ready for the emergency room setting and to perform time-sensitive, multipatient care."

Chang works with medical students, residents and fellows every day, utilizing the most current educational technologies and techniques, including distance learning and e-learning. His expertise has earned him the role of director of technology within the International Network for Simulation-based Pediatric Innovation, Research, & Education (INSPIRE).

Combining a passion for game design and resource management, he set out to develop a game with the goal of teaching and assessing cost- and time-effective patient care using serious gaming strategies.

"I've always liked video games, but the type I particularly enjoy are called 'resource management games,'" Chang says. "Farmville is an example, where you manage certain types of resources including your time; performance and scores are based on how well you manage the resources to accomplish whatever goal the game provides."

Whether asking players to build cities, create a civilization or run a restaurant, resource management games can be extremely realistic. Entire worlds can be created, with every layer of reality familiar to that setting. This burgeoning field, known as "serious gaming," allows players to build certain skills in addition to having fun.

"A few years ago," Chang says, "I came across a superhero game online where you could pick a hero based on his or her superpower. Some were traditional superhero-type powers, but others were very subtle. For example, there was one character who could instantly heal certain injuries, but not others. So when faced with a dilemma where several people are hurt, the player had to decide which superhero to send to which person, depending on their injuries. I found this very interesting. It was literally a resource management game, but with superheroes wearing spandex costumes." Chang immediately saw the analogy to medicine.

"I imagined each of us working in our ED. Currently, there are about 17 full-time faculty and

"Additional training is needed to help residents feel ready for the emergency room setting and to perform time-sensitive, multipatient care."

– Todd Chang, MD

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Todd Chang, MD

I knew exactly which superpower each one of us would have. Originally, I wondered if we could make a video game of just us.”

In this whimsical idea Chang saw the potential for a unique training tool. He set out to develop and validate a serious game platform using a virtual pediatric emergency department to assess and improve multipatient care skills for residents rotating through the department.

This year, the Stemmler Fund of the National Board of Medical Examiners awarded Chang a multiyear grant to develop his game, called VitalSigns. Using best practices in game development, the game is being designed to encourage repeated use and practice that may improve multipatient management in the hospital.

“The fund allows us to study real patient management and correlate it with in-game patient management. It’s our hope that we can use the game both as an assessment tool and as a training tool, since we will be using actual patient metrics within the game to maximize fidelity,” explains Chang.

Initially, 16 separate medical emergency scenarios will be developed with variations in the patients’ age, appearance and gender for a total of four permutations per case. This provides a total of 64 distinct cases. Ultimately, the game will provide three to five cases per gameplay, lasting 15 minutes per session. Each scenario will include graded levels of difficulty, emphasizing clinical decision-making, efficiency and multitasking abilities. The incremental levels of difficulty will provide challenging motivation to improve management skills and the ability to deliver multipatient care while prioritizing tasks within a given timeframe.

“In the ED, you can’t simply see patients in the order that they arrive. Some of them are sicker than others and you have to figure out who needs to be seen first,” says Chang.

Time is precious in pediatric emergency medicine. With specialized training tools like VitalSigns, Chang and his team are making sure that doctors can maximize their impact in order to make every moment count. ■

VitalSigns

GAME STATS



4

VARIATIONS
PER CASE



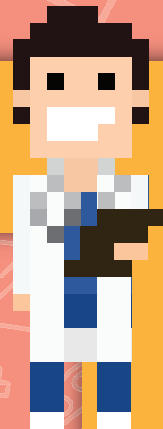
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EMERGENCY
SCENARIOS



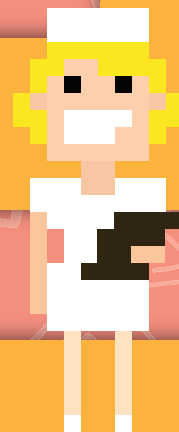
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CASES PER
GAMEPLAY



64

DISTINCT
CASES



1UP

3

AREAS OF
SKILL BUILDING



15

MINUTE
GAMEPLAY



THERE'S
A

HACK
FOR THAT

*Optimizing existing technology to treat
glaucoma and cataracts in kids*

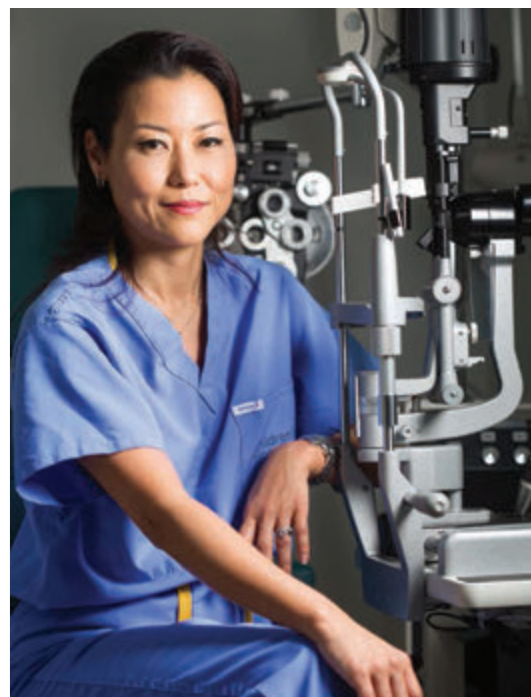
"My goal is to decrease childhood blindness by treating pediatric eye disease in an innovative way," says Bibiana Jin Reiser, MD, MS, director of the Cornea and Glaucoma Institute at The Vision Center at Children's Hospital Los Angeles. Using technology developed for adults, she is modifying or "hacking" it to treat children.

Ophthalmologists who treat adults have access to high-tech, ultraprecise equipment. Yet the transfer of that technology to pediatric ophthalmology has been slow. Reiser explains that one of the reasons for this lag is that many ophthalmologists are very conservative in how they treat children. Although "conservative" might sound like the best and safest approach where children's vision is concerned, that supposition isn't always true.

"The disease process is totally different in adults and kids, and so is their anatomy," says Reiser, who is one of the few doctors in the United States who treats pediatric patients with cataracts. She explains that unlike adults, a baby or young child with an untreated cataract may be slowly going blind. The cloudy lens that distinguishes a cataract blocks light from reaching the retina, affecting the ability of the retina to relay visual information to the brain. The eyes and brain must work together for a baby to learn to see. If surgery is done too late, even if the cataract is removed, the child may never be able to see well.

Reiser was instrumental in The Vision Center's acquisition of a Trabectome, a minimally invasive device marketed for the treatment of adult-onset glaucoma. CHLA is the first children's hospital to have a dedicated device for its pediatric patients. "I would not have been able to get this device and use it on kids anywhere but at CHLA," she says.

Instead of leaving raw edges typical of an incision that can scar and result in a failed surgery, the Trabectome is equipped with an electrocautery device that can minimize scar tissue and ultimately increase success rates. Surgery done with this device can also eliminate the need for an invasive implant. Reiser is



Bibiana Jin Reiser, MD, MS

currently using the Trabectome on children 8 years of age and older while beginning a clinical trial to study its use in babies and young children.

She's also employing a laser, marketed for refractive laser surgery (LASIK), and an imaging device used in a procedure called anterior segment optical coherence tomography (AS-OCT), developed for adults, to achieve high-resolution corneal imaging at a microscopic level to make surgeries safer and more precise. Because of The Vision Center's worldwide reputation, which draws a large number of patients requiring complex corneal surgery, CHLA has a dedicated AS-OCT in its operating room—a prototype developed specifically for CHLA. This setup allows Reiser to image the eye while the child is under general anesthesia, then immediately use that information to perform the most precise surgery possible.

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"Kids are not the same as adults. That's why at CHLA, everything we do and every instrument we use is specifically chosen for children."

— Bibiana Jin Reiser, MD, MS

At CHLA, a significant number of pediatric corneal transplants are performed. This complex surgery can restore vision to a child following a trauma to the eye or a serious infection. Reiser explains that corneal transplants in children are quite complex, and successful outcomes lag behind those in adults.

Luckily, Reiser has a hack for that, too.

Taking an unconventional approach to imaging technology she's optimized for pediatric use, Reiser can precisely image a scar, excise it, and puzzle-piece a section of donor cornea ordered from an eye bank. By placing the piece that fits precisely where the corneal scar used to be, she can ultimately restore the child's vision.

Reiser and her colleagues at The Vision Center know that kids deserve the best that medicine has to offer, but since the anatomy and the disease processes of children and adults are so different, high-tech devices need to be optimized in order to deliver precision ophthalmic surgery for children.

"Kids are not the same as adults," Reiser says. "That's why at CHLA, everything we do and every instrument we use is specifically chosen for children." ■

Laser's Edge

Soon after birth, Nick Moreno was diagnosed with persistent hyperplastic primary vitreous, a rare condition that results in cataracts. His family was immediately referred to Children's Hospital Los Angeles, where Nick had his first of many eye surgeries—this one to remove the cataract—when he was just 12 weeks old.

At age 7, he developed glaucoma—a condition that occurs secondary to cataract surgery in 5 to 30 percent of cases. With glaucoma, intraocular pressure increases, resulting in damage to the optic nerve and loss of vision. Treatment involves draining fluid from the eye to decrease the pressure. Nick had a shunt, a type of drainage device, placed in his eye when he was 12. He also required three types of eye drops each day.

"The recovery time was significant," says Vivien Moreno, Nick's mom. "Following the surgery, he had to spend two weeks flat on his back. Then, he needed to stay home for another month. When he was finally able to return to school, I had to go to the school every day to give him eye drops—three sets, each separated by five minutes."

Vivien explains that she and Nick gladly complied, but she felt it was a lot to ask of a child.

Eventually, the shunt stopped working. When Nick was 15, his intraocular pressure was significantly above the normal range. His family was also concerned about the quantity of eye drops—they were damaging Nick's cornea. In fact, he was being considered for a corneal transplant.

Bibiana Jin Reiser, MD, MS, was now Nick's doctor. She confirmed what Nick and his mom already knew—something had to be done. She could replace the shunt in Nick's eye or his family could consider an experimental option.



Reiser and Nick Moreno

"Dr. Reiser was doing a study on the Trabectome—a device licensed for eye surgery in adults—only she was testing its use in kids," says Nick. The Trabectome uses a laser to cut and cauterize an opening in the eye to allow drainage and reduce pressure.

Vivien was concerned about her son's quality of life—she wanted something that worked better than the shunt and wouldn't require him to miss so much school. "Dr. Reiser told me the post-op recovery would be much easier, probably just one week."

In fact, Nick returned to school in three days.

"Before, my pressure just kept going up," says Nick. "After the Trabectome surgery, it dropped." As a self-proclaimed nerd, Nick created a scatterplot to monitor his daily pressure. Now it's consistently within the normal range. Nick also needs fewer eye drops, so his cornea has healed and he no longer needs a transplant.

"All because of a single procedure," says Vivien. "It's pretty amazing." ■

CEO With a Vision

“Research informs the excellent care that we provide to our young patients every day.”

– Paul S. Viviano



Paul Viviano joined Children's Hospital Los Angeles as president and CEO in fall of 2015. He has enjoyed three decades of success leading academic medical centers, for-profit health care organizations and nonprofit community hospitals. Most recently, he served as CEO of UC San Diego Health and associate vice chancellor of UC San Diego Health Sciences. There he oversaw the entire \$1.7 billion UC San Diego health care enterprise, which includes leading-edge medical care; training of medical students, residents and fellows; responsibility for the faculty practice plan; and patient care delivery for two teaching hospitals.

Q: How do you view the role of research at Children's Hospital Los Angeles?

A: As an academic medical center, CHLA is more than just a pediatric hospital. Along with serving the health care needs of our community—including complex, specialized pediatric care—we teach generations of future pediatric health care providers, and we develop new therapies and technology that improve the lives of our young patients. I view these three roles—patient care, teaching and research—to be equally essential in ensuring that CHLA remains among the top children's hospitals in the nation.

Q: What is your vision for the future of research here?

A: Research informs the excellent care that we provide our young patients every day, and I am committed to improving and expanding research efforts of The Saban Research Institute. To this end, in late 2015, we commenced an exciting and collaborative strategic planning process to set the course for research over the next five years and beyond.

We know that we want to build on an already excellent reputation for leading-edge pediatric research. This interdisciplinary planning process—involving leadership, physicians, researchers, postdoctoral fellows and staff



Paul Viviano (left); Lynda Boone Fetter, co-chair of the Board of Trustees; Pat Leviitt, PhD; and Arnold Kleiner, co-chair of the Board of Trustees

from across the hospital—will help us build the necessary momentum to leverage CHLA's talent and resources and build our research profile.

This is such an exciting time for Children's Hospital Los Angeles, and for me personally, as we embark on the strategic planning process that is designed to assess where we are today and where we want to be in the future, and develop a plan for how to get there.

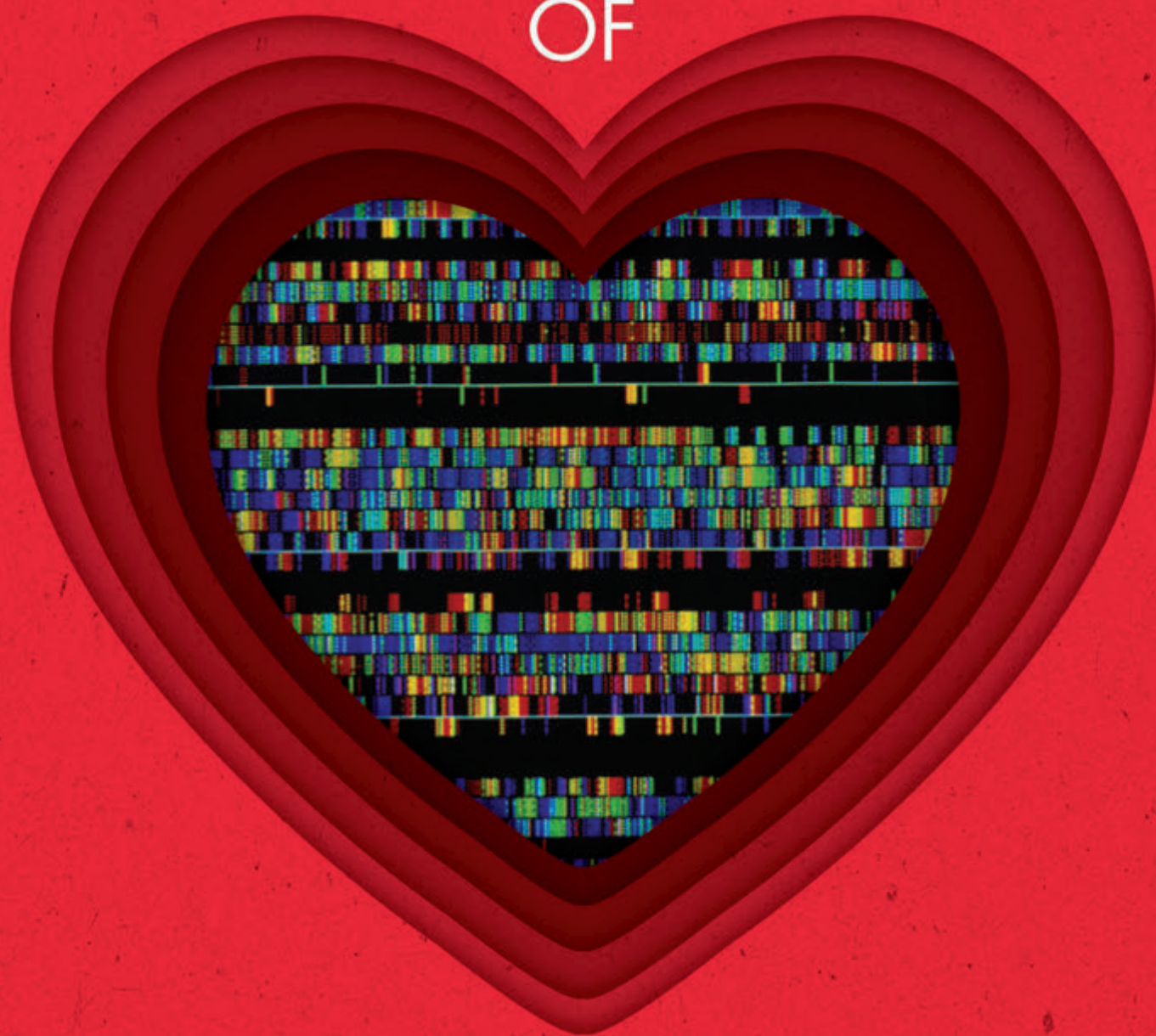
Q: What do you see as the key strengths and opportunities for research at CHLA?

A: I believe that, together, we will define the next big ideas for The Saban Research Institute and ensure an environment in which innovation and discovery thrive. Just a few of the obvious strengths on which to build are our excellent faculty researchers and their close affiliation with the Keck School of Medicine of the University of Southern California, and the unique diversity of the patient population we serve in Greater Los Angeles. As the site of hundreds of clinical trials, we are able to bring discoveries from the lab to our patients' bedsides, and then learn from our patients themselves what therapies are most beneficial. I am confident that we can provide the tools, infrastructure and support necessary to continue our leadership in this area—offering clinical trials that truly change the face of patient care here and throughout the world. ■



Robert Adler, MD (left), Alan Wayne, MD, Marlon Duarte and Paul Viviano at the 2015 Nautica Malibu Triathlon

AT THE HEART OF



THE MATTER

A study looks at the reasons behind congenital heart defects.

Cardiothoracic surgeon Richard Kim, MD, is interested in doing more than basic research alone. "I want to do research that has a real impact on our patients," he says, "with results that I can see in my lifetime."

Since 2010, Kim has been an integral part of a multicenter research team funded by the National Institutes of Health to investigate the genetic causes of congenital heart disease (CHD). Called Bench to Bassinet: Pediatric Cardiac Genomics Consortium, the group has enrolled more than 9,500 individuals with CHD as well as nearly 13,000 family members to study the role of genes in the development of babies with CHD.

"We're really trying to focus on how genetic mutations affect clinical outcomes," Kim says. He explains that understanding how changes in complex development pathways that lead to heart malformations may provide a target for therapies to slow down progression of CHD or even stop its development in the first place.

One of 11 national centers participating in the genomics consortium, Children's Hospital Los Angeles has contributed nearly 15 percent of the whole-genome sequencing completed to date as part of the study, representing the largest percentage of young children of any site. In addition, Kim, who is also an assistant professor of Cardiothoracic Surgery at the Keck School of Medicine of the University of Southern California, is the only surgeon in the study and has provided tissue samples from about 500 patients.

Congenital heart disease is a complex, multigene birth defect occurring in just 1 percent of newborns. Research conducted by consortium scientists suggests that about 20 percent of individuals with severe CHD have missing or extra genetic material that differs from their parents'.

Although genetics plays a significant role, the specific mutation is unknown in most cases. But the studies by Kim and his colleagues have



Richard Kim, MD

CONGENITAL HEART DISEASE OCCURS IN JUST 1% OF NEWBORNS



20% OF INDIVIDUALS WITH SEVERE CHD HAVE MISSING OR EXTRA GENETIC MATERIAL THAT DIFFERS FROM THEIR PARENTS'



Human DNA genome sequence (left)

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Richard Kim, MD (standing), flanked by Omar Toubat, BS (left), and Michael Krainock, MD

“I want to do research that has a real impact on our patients, with results that I can see in my lifetime.”

– Richard Kim, MD

shown that de novo mutations—new mutations that occur when a gene in the DNA is damaged or changed in a way that alters the message carried by that gene—may be responsible. Even though these new mutations aren’t inherited from either parent, they can be passed down from the person who has them to the next generation.

The information gained from these studies will help families determine the risk of having another child with congenital heart disease. It also provides a reason for the heart defect; parents don’t have to continue wondering why it happened in their child.

“While we know that genetic mutation plays a critical role in the development of some forms of congenital heart disease, what we have discovered since the advent of the human sequencing project is that most babies and parents of babies with heart defects actually do

not seem to harbor causative gene mutations,” Kim explains. In other words, despite what is commonly believed, when you look at the gene sequences of otherwise healthy children with heart disease and compare them to those of their parents, there are not likely to be significant differences.

Last year, however, consortium scientists made the landmark discovery that certain DNA-modifying mechanisms called epigenetic changes are critical to the development of CHD. These are a modification of the genome, as opposed to being part of the genome itself.

Kim’s laboratory at CHLA is currently focused on understanding one contributing factor to CHD—a type of epigenetic marker, which cells use to modify the function of DNA, called H3K4me3. He and his team discovered that this marker is initially found in surprisingly low levels in the epicardium, or the outer layer of the heart, but needs to be acquired in order for epicardial cells to mature into other types of heart cells. Patients with mutations in this H3K4me3 developmental pathway may be born with heart defects, because without these epicardial cells, coronary vessels and heart valves cannot develop normally.

The reason this is an especially important finding is that epigenetic problems are, by definition, potentially reversible. “We normally think that genetic problems can’t be changed, but here is a situation in which we can potentially intervene with the problem without the need to change the underlying DNA,” Kim says.

This discovery has introduced a new therapeutic target for adult heart disease as well. Although the cells of the epicardium become dormant after development, they reactivate after a heart attack, and the acquisition of H3K4me3 in adult epicardial cells may play a critical role in how the adult heart heals after injury.

“We hope that by targeting these important regulators during heart development, we will take critical steps toward our goal of treating CHD before children are born, and improving the outcome of patients who harbor genetic mutations affecting this pathway,” Kim concludes. ■

BENCH TO BASSINET



NATIONWIDE, MORE THAN

9,500

KIDS WITH CHD ENROLLED



NATIONAL CENTERS PARTICIPATING IN THE
GENOMICS CONSORTIUM



CHLA HAS CONTRIBUTED
NEARLY 15% OF THE WHOLE-GENOME SEQUENCING COMPLETED TO DATE AS PART OF THE STUDY



"WHY DOES HE DO THAT?"

*How early adversity can
shape behavior*

What happens in early childhood can matter for a lifetime.

Pediatricians are growing increasingly alarmed about the dangers of so-called “toxic stress”—chronic activation of a young child’s stress response systems due to repeated, uncontrollable adverse events, which can alter brain chemistry and hurt a child’s ability to thrive.

“When bad things happen early in life, whether you remember them or not, the brain doesn’t forget,” says Jack Shonkoff, MD, professor of Pediatrics at Harvard Medical School and Boston Children’s Hospital, and founding director of the Center on the Developing Child at Harvard University. Shonkoff was the keynote speaker at The Saban Research Institute 2016 Symposium, “Toxic Stress, Resiliency and Development.”

The brain develops from a combination of information from a genetic blueprint and experiences, both before and after birth. From the prenatal period through the first years of life, the brain undergoes rapid development. As it matures, neurological circuits that support higher-level functions like memory, emotional and behavioral regulation, and language are strengthened through positive reinforcement. But repeated adverse experiences, such as neglect or abuse, increase the likelihood that a child will fall behind developmentally.

“One remarkable aspect of the human brain is that it is actually designed to use experiences to continue its own development,” says Pat Levitt, PhD, Simms/Mann Chair in Developmental Neurogenetics at Children’s Hospital Los Angeles.

The basic blueprint—genetics—is sort of like the plans to a house, Levitt says. Some wiring is done prenatally, so when infants are born, their senses develop rapidly. They hear, see, smell, touch—using all their senses to take information from the outside world. They take it all in and, over time, begin to make sense of it. If patterns are repeated over and over, and the sensory experiences coincide with positive outcomes, they are reinforced. The same is true, however, with negative experiences.

“One remarkable aspect of the human brain is that it is actually designed to use experiences to continue its own development.”

– Pat Levitt, PhD

“In cases of neglect, a child may receive very little sensory stimulation in the course of a day,” says Levitt, who is also provost professor of Pediatrics, Neuroscience, Psychiatry and Pharmacy at the Keck School of Medicine of the University of Southern California. For example, when a baby isn’t observing different facial expressions and linking them to moods or feelings, that child might have difficulty later differentiating between various emotions. “This is the way a child develops; by interacting with people, she distinguishes between emotions and learns to navigate the social world. This is why the absence of such input is so powerful.”

While learning how to cope with adversity is an important part of healthy early-child development, it requires stable and supportive relationships with parents, siblings, teachers or caregivers.

“There exists a delicate balance between a child’s inherent constitution or ‘hard wiring’ and the environmental support that allows her or him to achieve well-being in thought, emotion and behavior,” says Brad Peterson, MD, director of the Institute for the Developing Mind (IDM) at Children’s Hospital Los Angeles. He states that parental influence is tremendously important, providing support at the “leading developmental edge” of the child’s experience.

(continued on next page)



Pat Levitt, PhD (left), Elizabeth Sowell, PhD, and Bradley Peterson, MD

“There exists a delicate balance between a child’s inherent constitution or ‘hard wiring’ and the environmental support that allows her or him to achieve well-being in thought, emotion and behavior.”

— Bradley Peterson, MD

Peterson gives the example of a 9-month-old toddler just learning to walk: She can pull herself up and stand on wobbly legs with a parent holding her hands, or perhaps just a finger, until the moment she lets go and takes her first steps. “This is a beautiful, iconic encapsulation of parental love,” he says.

“Picture this type of scenario at 9, or 19, or 29 years—the tasks are different, but the parent’s role is the same: to allow their child to develop and master what they can do on their own, and help them to the next step of development through subtle, nonintrusive but authoritative support,” says Peterson, who is also professor of Psychiatry at the Keck School of Medicine of USC.

This requires what he terms “emphatic attunement” to the child’s trial-and-error efforts, which allows the child to struggle in an attempt to master a new skill and even fail occasionally.

“Every interaction a child has with the world affects the brain, and how the brain is wired and morphs as it changes and adapts to the environment.”

– Elizabeth Sowell, PhD

If the parent remains attuned—knowing just when and how much support to provide—the child eventually achieves mastery and independence in that skill.

Peterson, Levitt and Elizabeth Sowell, PhD—all part of the IDM—share the common goal of applying information about social, emotional and cognitive development and the environment to ensure that every child reaches his or her highest potential.

“Every interaction a child has with the world affects the brain, and how the brain is wired and morphs as it changes and adapts to the environment,” echoes Sowell, who is also professor of Pediatrics at the Keck School of Medicine of USC. She notes a huge variability in kids—in both the function of their brains and their cognitive abilities. “I wonder how kids who function very highly do that—what makes them tick? Even a typically developing child needs clean air, parks to play in, books read to them. The same is true of a child with a neurocognitive disorder. We must learn to help that child improve through the efforts of family, schools and health care resources.”

Sowell adds that kids with cognitive issues have different experiences when they are acting out and getting in trouble—electrical signals aren’t being sent between the parts of the brain that act on emotions and those parts that hold back and help them understand consequences. “We have to use the part of our brain that tells us what is a good decision and what is a bad decision by practicing behavior over long periods of time.” The researchers all say that it’s possible that intervention can help develop wiring in the brain, even after the most critical early years of development.

“We don’t know a lot about the critical periods in which changing a child’s experience can change brain function,” says Levitt. “For example, if a child has attention problems or emotional outbursts, which interventions are going to work? If so, are these interventions less effective as the child grows older? We don’t really know.”

Researchers know, for example, that executive function—the bringing together of skills for controlling emotions and impulses, working memory and decision-making—does continue to develop in adolescence. Levitt says that mindfulness training, exercise and martial arts may all be good activities to help an older child develop impulse control and emotional regulation.

It is estimated that as many as 1 in 5 kids may have a learning or behavioral disorder that results in trouble concentrating, paying attention, staying organized and remembering details. Some disorders may be due to the individual’s genetic makeup; others the effect of adverse events in early childhood.

“Resilience in the face of adversity has its basis in the constitution of a person, such as genes for vulnerability or anxiety,” says Peterson. “But there are still ways to change and influence a child’s development through the role of mature and loving adults who help them realize their fullest potential.” ■

To learn more about how you can support scientific research into the developing mind at CHLA, please contact us at foundation@chla.usc.edu or 323-361-2308.

WAKE-UP CALL

One family's health scare leads to new hope for children with brain and spinal cord tumors.

MRI of a healthy spine

Erika Kort had just finished dance class when her legs started to feel numb. Thinking she probably just pulled a muscle, the 16-year-old wasn't concerned until the sensation began spreading. Just a few days later, it reached her abdominal area. "It felt like my muscles were freezing," she recalls.

Alarmed, her parents made an appointment with her pediatrician, who within minutes of seeing Erika's symptoms told the family to immediately go to Children's Hospital Los Angeles. An MRI scan revealed something the seemingly healthy teen never expected: a tumor on her spine.

"I was pretty terrified," says Erika, "because I didn't think anything was wrong with me."

After receiving the shocking news, Erika underwent surgery. The mass pressing on her spinal cord was a cavernous angioma—an abnormal tangle of blood vessels—that had been bleeding little by little in an extremely sensitive area of the body where even small hemorrhages can trigger significant problems.

"When I first saw the scan of this abnormal lesion in Erika's spinal cord, it was hard to tell what it was going to be: whether a tumor or vascular lesion, malignant or benign," says Division Chief Mark Krieger, MD, Billy and Audrey L. Wilder Endowed Chair in Neurosurgery. "Because the spinal cord is so small in diameter, when you have this angioma that is bleeding, it gradually eats away at the tracks that carry strength and sensation to different parts of the body. If we had left it alone, even if benign, it would most likely have just kept bleeding, eventually causing Erika to lose all function below that location on her spine."

Krieger delicately removed the tumor, which was found to be benign, and the surgery was a success. Today, despite some residual numbness in her left hand, Erika is otherwise fully recovered, healthy and eager to get back into the dance studio.

"What happened to us was a wake-up call, a realization that health issues have no boundaries," says Erika's mother, Jill. "We had



Erika Kort

a wonderful outcome, and we witnessed such professionalism and such care at Children's Hospital Los Angeles—making an experience that was so scary a little easier to handle from start to finish."

The Korts' life-changing event led them to fund an endowment to support The Kort Family Foundation Brain and Spinal Cord Tumor Research Program in the Division of Neurosurgery at Children's Hospital Los Angeles. Their \$2 million gift will enable CHLA neurosurgeons to continue to provide optimal outcomes for children with brain and spinal cord tumors—by addressing the underlying cause and genetic profile of each tumor, and through accurate, noninvasive diagnosis and more effective personalized treatments.

"Erika's case brought up questions that we want to be capable of answering prior to surgery," says Krieger. "How could we have known exactly what this tumor was before we operated, lessening the risk? How can we screen earlier for people who may develop a tumor due

(continued on next page)



Mark Krieger, MD

to a genetic mutation? The hope is to develop a genetic biomarker for such a tumor and, hopefully, develop a treatment that's targeted to these abnormal blood vessels."

For example, creation of a genetic tumor bank would allow CHLA researchers to develop and sustain a database of tissue samples, DNA data, MRI scans and other state-of-the-art technologies. "Ultimately, such modern, molecular-based research will allow CHLA to bring genomic discoveries into the clinical setting, where they impact our patients," says Krieger.

The Division is uniquely positioned for this lifesaving endeavor: As one of the largest pediatric neurosurgery programs in the country, it has unparalleled access to a high volume of common and rare cases, providing valuable data to fuel the discovery of the most effective, personalized treatments.

As the Korts got to know Krieger well, Jill and husband Lee decided that they wanted to give

back. "Our concept for giving to CHLA is twofold: We want to feel that our gift will have an impact, and we want to be involved with the institution, to get a sense of what is happening and how our dollars are affecting the future," Lee explains, adding that it was an opportunity to set an example for their two daughters, Erika and Alexa, and "pay it forward."

Krieger agrees. "For us, the most exciting thing is partnership. The Korts went through this crisis as a family, so they understand the challenges—both the things we go through as caregivers and what our patients go through. I think it really shows the strength of this family to be able to turn what was such a difficult time for them into something positive that will benefit the community of Los Angeles and children everywhere." ■

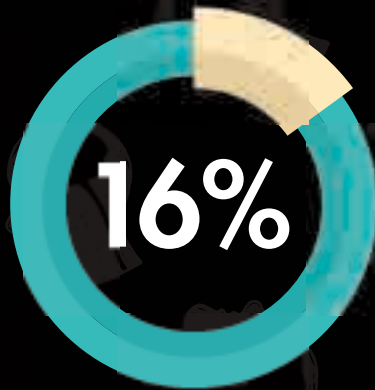
To learn more about how you can support neurosurgery at CHLA, please contact us at foundation@chla.usc.edu or 323-361-2308.

LEADERS IN CARE

THE DIVISION OF NEUROSURGERY AT CHLA



750
SURGERIES
PERFORMED
EACH YEAR



OF SURGERIES
ARE FOR BRAIN
OR SPINAL
TUMORS



LONG-TERM THERAPY MAY INCLUDE



CHEMOTHERAPY
AND/OR **RADIATION**



THESE THERAPIES ARE PROVIDED BY CHLA'S
CHILDREN'S CENTER FOR CANCER AND BLOOD DISEASES

PATIENTS RANGE FROM **NEWBORNS**
TO **YOUNG ADULTS**



Innovation in Whole-Patient Care

The Institute for Nursing and Interprofessional Research looks beyond biology to improve care.

Mary Dee Hacker, MBA, RN, was a young nursing student in Minnesota in the 1970s when she came upon innovative research being done by nurses at CHLA—work that would draw her to Los Angeles to visit and, ultimately, to stay.

At the time, the predominant policy across pediatric hospitals and wards was that parents were not allowed to stay with their children. Visits were sometimes limited to only one day a week. Reasons given were that the children would misbehave or that having parents around was disruptive to administering medical care. More than anything, it was just how things had always been done.

But nurses at CHLA saw that having parents stay with their kids at the hospital was not only beneficial to their young patients, but actually contributed to more positive outcomes.

“This is a profession that requires us to challenge the status quo, to become better educated and to protect,” says Hacker, now vice president of Patient Care Services at Children’s Hospital Los Angeles.

Mary Dee Hacker, MBA, RN

“We have a passion to be better tomorrow than we are today. Based on data and based on evidence, we will make it better.”

– Mary Dee Hacker, MBA, RN

These nurses not only observed the negative effects of parental absence on the spirit, and ultimately the health, of children in the hospital, but eventually changed the established paradigm.

“Kids had vivid memories of being abandoned,” explains Hacker. “If we’ve cured the disease but we’ve hurt the spirit of a child, we have not done our very best work.” The findings of these nurses led to the adoption of a family-centered model of care at CHLA, where parents would be allowed substantial time at the bedsides of their children—a practice that is now commonplace and encouraged in pediatric hospitals everywhere.

It is this spirit of challenging the status quo that has driven the creation of CHLA’s new Institute for Nursing and Interprofessional Research (INIR), which will support nurses and other care providers—from nutritionists and pharmacists to social workers and Child Life specialists—interested in conducting research that will look beyond biology to improve care.

“We are ready as a research institution to allow all of us, nurses and other care providers, to ask the questions necessary to improve pediatric care,” says Hacker, who will serve as inaugural director of the Institute.

In bringing together nursing and interprofessional research, the Institute will provide a unique framework to support researchers by fostering new inquiry, funding discoveries and helping publish results. The Institute is seeking a \$10 million endowment, which will be the largest investment of any nursing research institute of its kind in the nation. Half of the endowment will directly fund research efforts at CHLA. Novice

researchers will receive smaller innovation grants, while more experienced researchers will receive larger awards. Studies to be funded are required to have researchers from at least two different disciplines: nursing and pharmacy, or nursing and emergency medicine, for example.

There are several projects currently in the works through the INIR. Nancy Pike, RN, PhD, of the Heart Institute, is researching cognitive development of children who have received repairs in the heart’s left ventricle. Mary Nelson, RN, PhD, who also serves on the faculty of the Keck School of Medicine of the University of Southern California, is looking at the effects of chemotherapy on long-term development and learning abilities in children treated for brain tumors. And working with pharmacists and oncologists, Rita Secola, RN, PhD, is studying line management for intravenous infusions, hoping to better understand risk of infections and determine the best way to administer IV lines for children receiving chemotherapy and other potentially toxic treatments.

The Institute will be affiliated with the School of Nursing at the University of California, Los Angeles, which will help provide mentorship to researchers. The Institute will also assist researchers in obtaining government and private grant funding.

Hacker says the INIR will challenge the status quo by involving the entire care team to help provide better and more holistic care to patients.

“We have a passion to be better tomorrow than we are today. Based on data and based on evidence, we will make it better.” ■

A Long Line of Successes

40 years at the forefront of pediatric cancer research

Cell lines, or populations of identical cells maintained in a laboratory, are fundamental to even the most basic of biomedical research. With a thriving cell line, researchers do not have to rely on precious, and often rare, patient samples.

"You can be doing some research this week, but then you might wait six weeks to get another sample. So with cell lines, if you had the energy, you could crank things out 24/7," says Robert C. Seeger, MD, who in 1977 established two new neuroblastoma cell lines; only three had existed previously. What started as a way to foster basic research into neuroblastoma, a pediatric cancer of the sympathetic nervous system, would eventually lead to the creation of the first-ever immunotherapy drug (dinutuximab) approved by the Food and Drug Administration (FDA) to treat pediatric cancer.

In fact, few have had as much of an impact on the understanding and treatment of a single disease as Seeger has had on neuroblastoma, which affects roughly 700 children annually in the United States alone. Seeger, who has served as director of the Cancer Research Program in The Saban Research Institute of Children's Hospital Los Angeles since 1995, has been at the forefront of cancer immunotherapy and genetics for decades. From his contributions to the creation of dinutuximab, to his work on genetically based risk stratification for neuroblastoma patients, to identifying and treating patients with residual neuroblastoma post-treatment, Seeger has changed the game.

Basics and beyond

In 1986, Seeger discovered that neuroblastoma cells have increased amounts of a molecule called GD2 on their surface, making it a prime target for drug development. Using the cell lines Seeger developed, Ralph Reisfeld, PhD, of the Scripps Research Institute produced what are called monoclonal antibodies, proteins that specifically bind a single substance, in this case GD2. After further development and a multitude of clinical trials, including one conducted by Seeger here at CHLA, the antibody now known as dinutuximab, was approved by the FDA in March 2015 for treatment of neuroblastoma.

"It's actually quite interesting to go back in the history of the cell lines and see how they contributed to an FDA-approved product," observes Seeger, who is also a professor of Pediatrics at the Keck School of Medicine of the University of Southern California. "It takes patience. With basic science, you never know where it's going to go."

(continued on page 36)



1995

Named director of the Cancer Research Program at The Saban Research Institute

1989

Recruited to CHLA



Few have had as much of an impact on the understanding and treatment of a single disease as Seeger has had on neuroblastoma.

1977

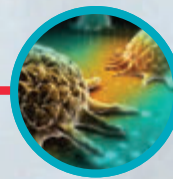
Established two new neuroblastoma (NB) cell lines

1985

Linked the presence of excess copies of the oncogene MYCN to outcomes in patients with NB

1986

Discovered molecule GD2 is increased on NB cells, making it a prime target for drug development



Seeger would go far beyond the basics and delve deep into the genetics of neuroblastoma. In 1985, he and Garrett Brodeur, MD, now at The Children's Hospital of Philadelphia, linked the presence of excess copies of the gene MYCN, common for neuroblastoma tumors, to patient outcomes. Seeger's findings were translated into a test now used worldwide as a means of identifying and predicting which patients are at high risk for relapse and prioritizing the management of their care. This marked the first time a cancer gene had ever been related to outcome in patients, either for children or adults.

"This was at the dawn of the cancer gene, the oncogene era," says Seeger. "It's hard to believe that was 30 years ago." Seeger would continue to work on the genetics of neuroblastoma with other CHLA researchers, including Shahab Asgharzadeh, MD, with whom he demonstrated the efficacy of analyzing multiple genes, rather than just one, in risk stratification for neuroblastoma patients.

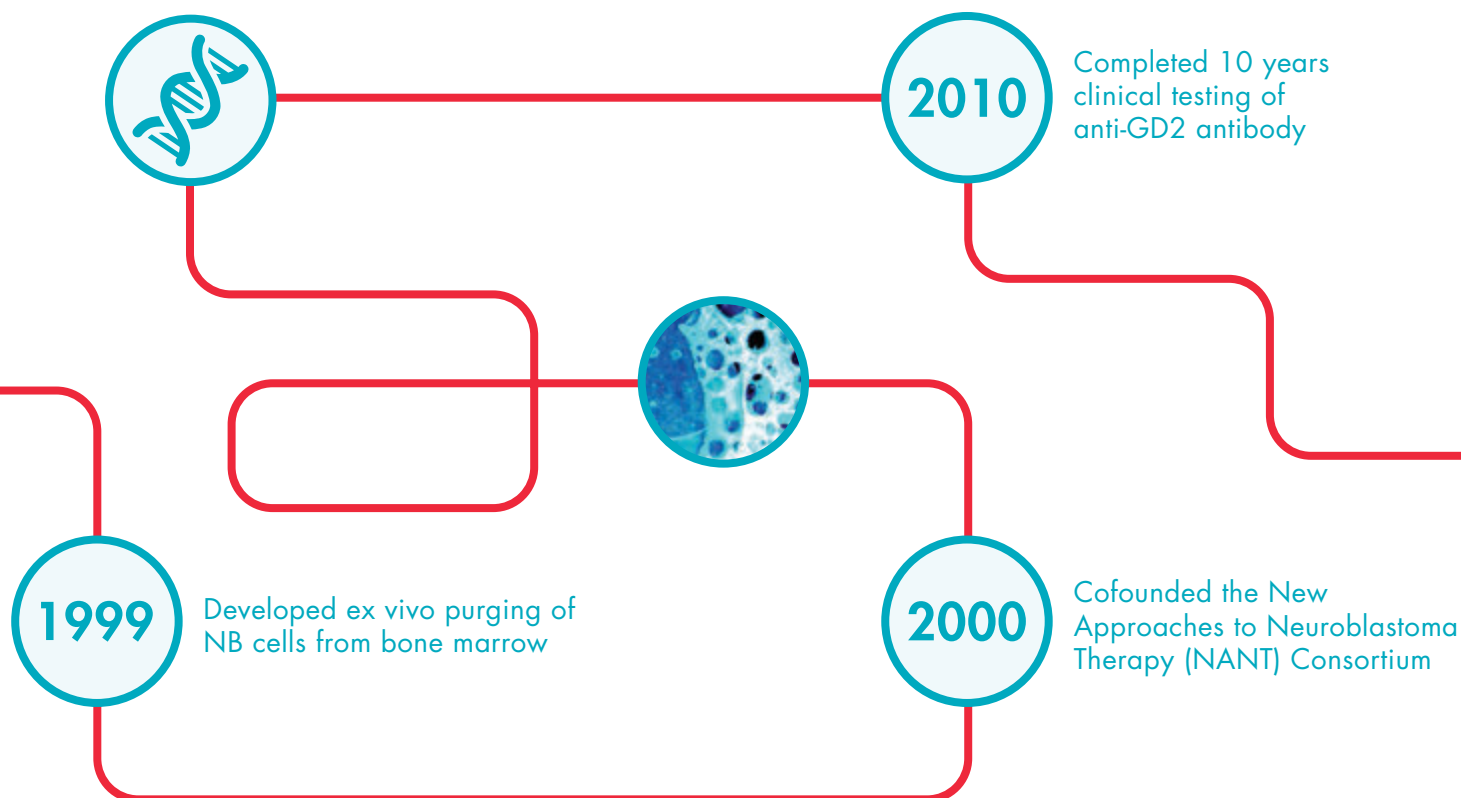
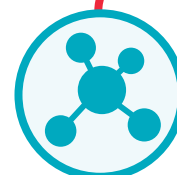
"We're now in an era where you have to look at the genetic signature, or fingerprint, of a tumor to

most accurately predict how the patient's going to do," explains Seeger.

One in a million

Stratifying newly diagnosed neuroblastoma patients according to their level of risk helps physicians coordinate a better, more personalized treatment plan. But what about patients at risk for relapse? Standard treatments can knock down cancers so they are no longer detected by typical scans like bone marrow biopsies, which detect roughly one cancerous cell among 100 normal cells.

But identifying patients with minimal residual disease (MRD) not detectable through standard tests is incredibly important, as nearly 40 percent of patients relapse due to MRD. This was the goal when Seeger teamed with Asgharzadeh, Richard Sposto, PhD, and Cathy Liu in his laboratory, to develop a far more sensitive test for relapse known as NB5, which allows physicians to identify patients with MRD—even those with just one cancer cell per million cells.



2015

Anti-GD2 antibody (dinutuximab) approved by the FDA



2016

Lifetime Achievement Award from the Pediatric Blood and Marrow Transplant Consortium



With funding from the National Cancer Institute and several foundations, Seeger and his laboratory are currently investigating how to improve immunotherapy—treatments that utilize or boost the body’s immune response—for patients with MRD. This work involves researching the tumor microenvironment, which includes the cellular and molecular environment of tumors in the body. Tumor cells will often recruit some of the body’s normal cells to promote a better environment for cancer proliferation and suppression of potential immune responses, which could hamper immunotherapies administered to patients. Understanding the nature of the tumor microenvironment is critical to improving immunotherapy.

“It’s essentially the ‘seed and soil’ idea: If you have really fertile soil, the plants are going to grow well. If you don’t, they’re not going to grow. Cancer is very similar to that,” Seeger explains.

Investigating new therapies

In 2000, as part of his effort to expand therapeutic possibilities for neuroblastoma patients, Seeger cofounded the New Approaches to Neuroblastoma Therapy (NANT) Consortium with Katherine Matthay, MD, of the University of California, San Francisco. The Operations Center for the NANT consortium, directed by Araz Marachelian, MD, is here at CHLA. To date, NANT, which takes lab-based research into phase 1 and 2 clinical trials, has treated more than 500 patients with relapsed neuroblastoma using novel therapies targeted to neuroblastoma cells.



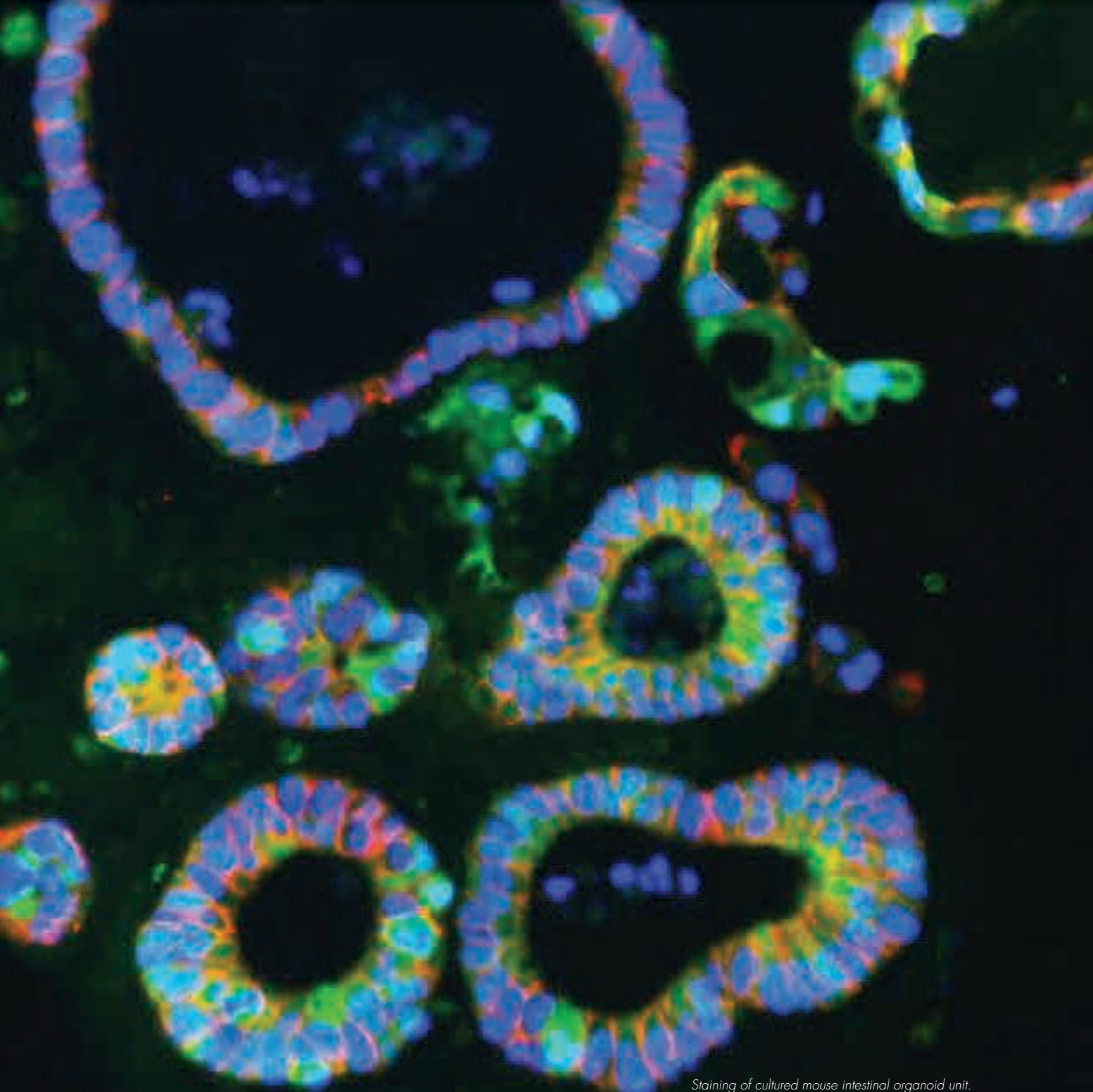
Robert C. Seeger, MD, in 1991

It has been 38 years since Seeger established those first cell lines, but he shows no signs of slowing down. His laboratory currently receives \$1.8 million in direct costs for research from the National Cancer Institute and various foundations to investigate biomarkers and immunotherapy for neuroblastoma.

“With each new therapy, we keep moving closer to our goal of 100 percent survival,” says Seeger. ■



Highlights



*Staining of cultured mouse intestinal organoid unit.
Green: GFP; Red: E-cadherin. Image courtesy of
Xiaogang Hou, PhD, and Tracy C. Grikscheit, MD*

Michael Allen Pulsipher, MD, joined the Children’s Center for Cancer and Blood Diseases as section head of Blood and Marrow Transplantation (BMT) and BMT clinical research chair. He is also current group chair of the Pediatric Blood and Marrow Transplant Consortium—an 80-member international clinical trials group recognized as a leading influence in the field of pediatric BMT.



Michael Allen Pulsipher, MD

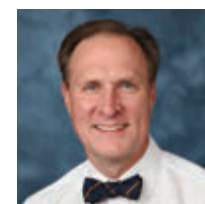


Elizabeth Sowell, PhD, was awarded nearly \$8 million from the National Institutes of Health as part of a landmark study about the effects of substance use on the developing brain.

In a study published in *Nature Neuroscience*, Sowell also reported that family income and parental education are linked to changes in the brain structure of children and adolescents. These findings received wide national coverage including feature stories in the *Los Angeles Times* and the *San Diego Union-Tribune*.

Elizabeth Sowell, PhD

Douglas Nordli Jr., MD, joined CHLA as chief of the Division of Neurology and co-director of the newly announced Neurosciences Center. Previously, he was division head of the Epilepsy Center at Lurie Children’s Hospital of Chicago.



Douglas Nordli Jr., MD



Jodi Ogden joined CHLA as vice president of Research Administration. She oversees all business, financial and compliance operations pertaining to research and sponsored research activities at The Saban Research Institute.

Jodi Ogden

Brent Polk, MD, received over \$1.8 million from the National Institute of Diabetes and Digestive and Kidney Disorders to study how stem cells in the colon respond to injury and inflammation.



Brent Polk, MD

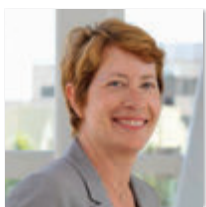
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Highlights (continued)

Bradley Peterson, MD, reported that prenatal exposure to common air pollutants is linked to cognitive and behavioral impairment. The findings, published in the Journal of the American Medical Association, were reported in The New York Times and the Los Angeles Times. He was also included in a separate feature in The New York Times Sunday Magazine about brain scanning and Freudian psychoanalysis.



Bradley Peterson, MD



Michele Kipke, PhD, has been awarded \$8.4 million from the National Institute on Drug Abuse to conduct research to improve HIV care and prevention in a study focusing on black, Latino and multiracial gay and bisexual young men—the group at highest risk for contracting HIV.

Michele Kipke, PhD

Johanna Olson-Kennedy, MD, received \$5.7 million from the National Institutes of Health for the first multisite study of transgender youth in the U.S. The study will evaluate the long-term outcomes of medical treatment for transgender youth and will provide essential, evidence-based information on the physiological and psychosocial impact, as well as safety, of hormone blockers and cross-sex hormone use in this population.



Johanna Olson-Kennedy, MD



A \$2 million gift from Jill and Lee Kort will fund an endowment to support The Kort Family Foundation Brain and Spinal Cord Tumor Research Program, headed by **Mark Krieger, MD**, Division of Neurosurgery.

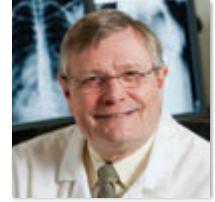
Mark Krieger, MD

A \$5 million gift from Tom and Holly Gores will establish The Gores Family Allergy Center to expand treatment and research into life-threatening allergies in children. The Center is the first of its kind in Los Angeles, specializing in more effective treatments for severe food allergies. **Jonathan Tam, MD**, serves as medical director.



Jonathan Tam, MD

Using magnetic resonance imaging, **Vicente Gilsanz, MD, PhD**, found that the spines of boys and girls differ at birth. While the difference aids in childbearing, it likely results in older women being more susceptible to scoliosis and osteoporosis. The report was featured in The New York Times.



Vicente Gilsanz, MD, PhD



Sebastien Bouret, PhD, was awarded more than \$1.2 million from the National Institute of Diabetes and Digestive and Kidney Diseases to study neurodevelopmental pathways and molecular mechanisms involved in the development of metabolic diseases such as obesity and diabetes.

Sebastien Bouret, PhD

Pat Levitt, PhD, was interviewed by The New Yorker magazine about the effects of poverty on the developing brain. Additionally, ABC TV News interviewed Levitt on how parents can more effectively support their child's neurodevelopment.



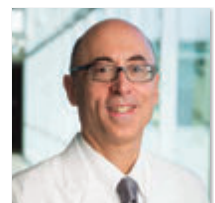
Pat Levitt, PhD



A \$2 million gift from the Larry & Celia Moh Foundation to The Vision Center will help establish the **A. Linn Murphree** Retinoblastoma Program Chair. CHLA ophthalmologist Murphree himself has pledged an additional \$2 million toward the endowment for the chair. The inaugural chair is Jonathan W. Kim, MD, director of the Retinoblastoma Center.

A. Linn Murphree, MD

The Children's Center for Cancer and Blood Diseases (CCCBD) at Children's Hospital Los Angeles is one of the first sites in the world to offer a promising new therapy to treat pediatric acute lymphoblastic leukemia (ALL). **Alan S. Wayne, MD**, director of the CCCBD, is the lead principal investigator for the ZUMA 4 trial that is now open to patients with ALL whose disease is resistant to, or has relapsed following, standard chemotherapy or stem cell transplant.



Alan S. Wayne, MD

Honor Roll of Donors

From July 1, 2014 to June 30, 2015

It is with heartfelt gratitude and pride that we recognize the following donors who made gifts of \$1,000 and above during the last fiscal year 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.

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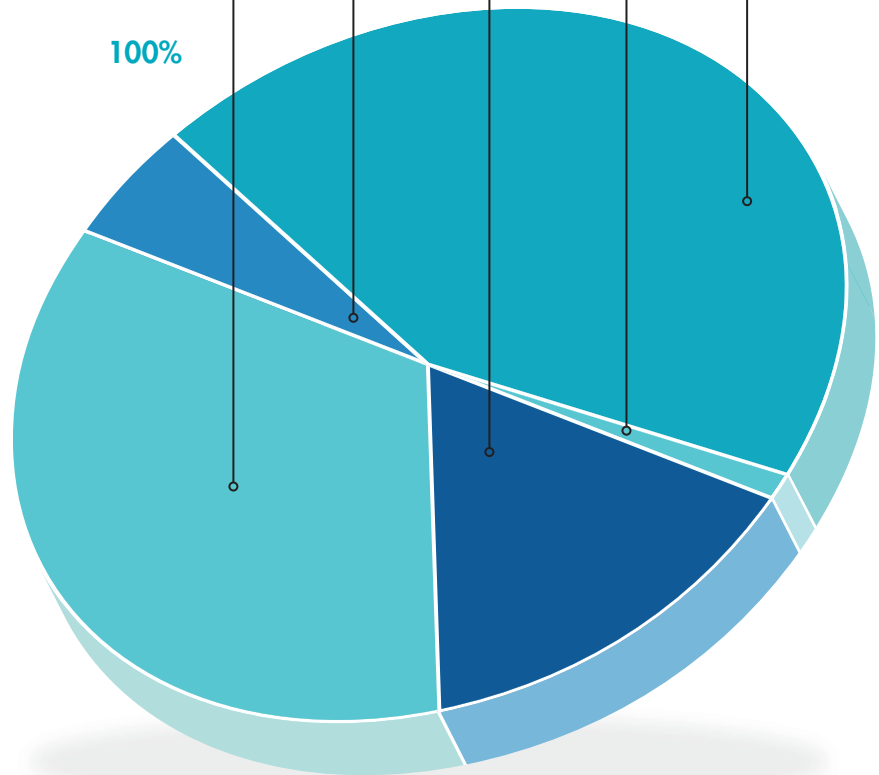
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Associate Vice President,
Content Development

Ellin Kavanagh
Executive Editor

Writers

Debra Kain
Ellin Kavanagh
Jennifer Marcus
Eunice Oh
Shanika Pelpola

Design

Jessica Kucinkas

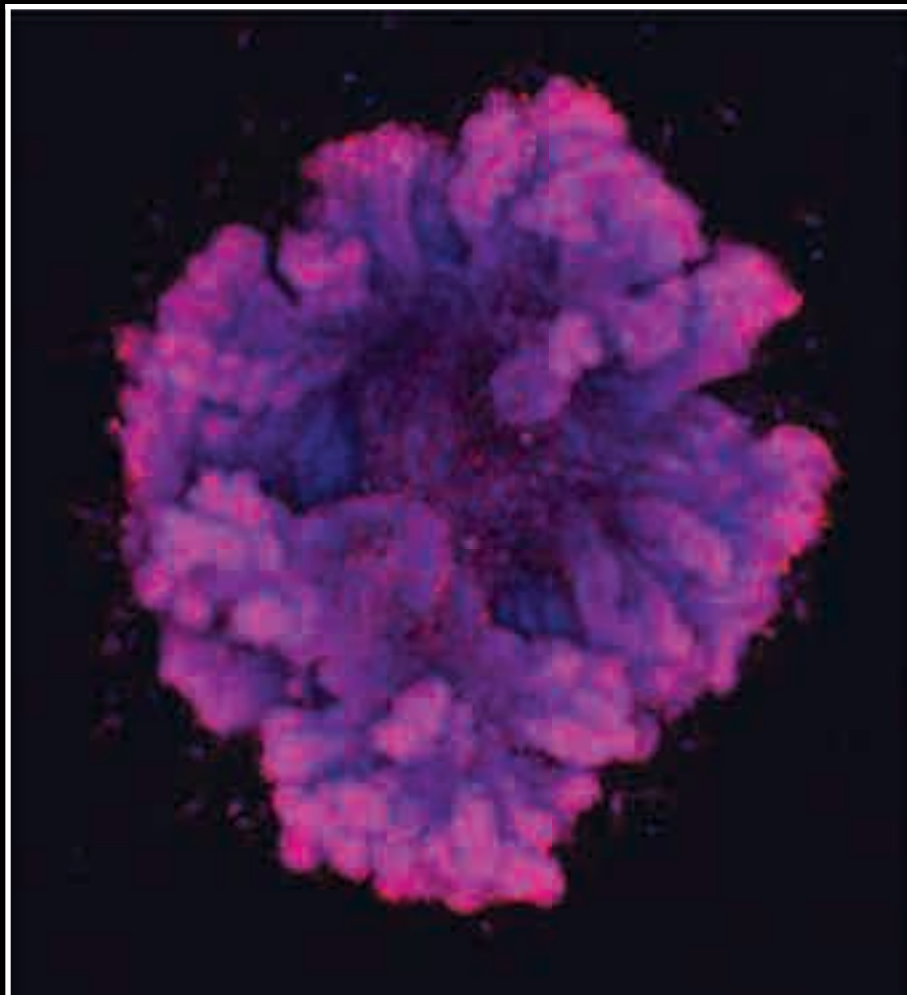
Project Managers

Sarah T. Brown
Mallory Car
Jennifer Duerksen

Photography

Keats Elliott
Vern Evans
Jessica Kucinkas
Karine Simon
Walter Urie
Alex Vaz

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*Epithelial tips occurring as part of normal branching in the lung.
Image courtesy of Sonia Navarro, The Saban Research Institute*

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