

RESEARCHLA

Summer 2014



Innovation

The Saban Research Institute of Children's Hospital Los Angeles

The Saban Research Institute is one of the few freestanding research centers in the U.S. where scientific inquiry is combined with clinical care and is devoted exclusively to children. Our goal is to improve the health and wellness of children through a combination of basic, clinical and translational studies. Research is performed at the lab bench, in the clinic and in the community.

The Institute's interdisciplinary research is organized around three synergistic areas of focus that together fully explore the developmental origins of health and disease while addressing the most pressing issues of children's health. These three areas are:

- The Institute for the Developing Mind
- Metabolism, Immunity, Infection and Inflammation
- Regenerative Medicine and Cellular Therapies

Originally established in 1992, The Children's Hospital Research Institute became The Saban Research Institute in 2003 following a \$40 million gift in support of pediatric research made by Cheryl Saban, PhD, Haim Saban and The Saban Family Foundation.

In fiscal year 2013, The Saban Research Institute received \$20.6 million in National Institutes of Health funding and \$65.5 million in total funding.

The Saban Research Institute maintains strong scientific and strategic affiliations with the University of Southern California (USC) and, in particular, the Keck School of Medicine of USC.

All of the Institute's principal investigators (clinical investigators, physician-scientists and PhD scientists) are USC faculty, and many have collaborative projects with scientists at the Keck School of Medicine and other departments at USC. The Institute's researchers also are involved in collaborative projects with academic institutions throughout the U.S. and abroad.



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On the Cover

With this issue we are introducing our new name. **To keep up with research news, visit our blog at ResearCHLABlog.org.**

RESEARCHCHLA  | Blog

What Drives Innovation?

Research drives leading-edge clinical care, and this relationship is at the very foundation of our reputation at The Saban Research Institute of Children's Hospital Los Angeles. Given the connection between innovation and success, it's worth considering—what drives innovation?

When we look at some of the recent advances in medical research, including genotyping, clinical diagnostics, proteomics, microarray technologies, imaging techniques and high-throughput screening, the answer is clear.

Technology—and the people who invent it, optimize it and employ it—creates the bridge to innovation.

The technologies I've mentioned have changed how we conduct basic research, how we diagnose and treat patients, and the ways in which we identify the most effective therapies. Technology enables research to advance to clinical applications for our patients.

In this issue of ResearCHLA, we focus on several areas within our institution where investigators are using technology to push the boundaries of their fields. Pat Levitt, PhD, employs neurogenetics, bioinformatics and other approaches to understand the interaction between genes and the environment in the etiology of autism and other neurodevelopmental disorders. To help determine the underlying physiology of sickle cell disease, Thomas Coates, MD, uses available technologies such as smartphones and cloud storage—with equipment needs so specialized that he and his team are building the instrumentation as they need it.

Perhaps nowhere is the use of technology as a driver of innovation more apparent than in the Translational Biomedical Imaging Lab. TBIL is a cross-institutional collaboration involving state-of-the-art laser scanning microscopes combined with an unparalleled intellectual infrastructure. The idea for this unique lab began with Rex Moats, PhD, who previously worked with Scott Fraser, PhD, at the California Institute of Technology. The two now share co-directing responsibilities for TBIL.

Once Dr. Moats began brainstorming with division heads about the project, it took on a life of its own, gaining enthusiasm and support as the concept traveled to Chief of Radiology Marvin Nelson Jr., MD, then to Deputy Director Richard Simerly, PhD, and, ultimately, to me. Joining forces with our colleagues at the University of Southern California, we have been able to take this great idea and turn it into an invaluable tool for research and clinical use. Instead of capturing one place and one moment in time, we can now witness biological processes in real time and in three dimensions. This kind of dynamic imaging promises to be a game-changing technology.

As we continue to innovate within our respective fields, The Saban Research Institute is growing to accommodate these changes. Because most adult diseases have their origins in childhood, pediatric medicine provides us with a unique opportunity to impact disease and affect the lives of children and the adults they will become. From our seven research priorities we have developed an encompassing research strategy—the Developmental Origins of Health and Disease—with three synergistic areas of focus:

- The Institute for the Developing Mind
- Metabolism, Immunity, Infection and Inflammation
- Regenerative Medicine and Cellular Therapies



The approach emphasizes how interconnected our research has become and how reliant our work is upon collaboration.

Along with our many research teams, I would like to acknowledge our longtime partners, Cheryl Saban, PhD, Haim Saban and The Saban Family Foundation, for their vision, generous contributions to biomedical research and continued support of innovation.

At The Saban Research Institute, we strive to innovate, educate, train and inspire. Thank you for joining us on this journey.

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

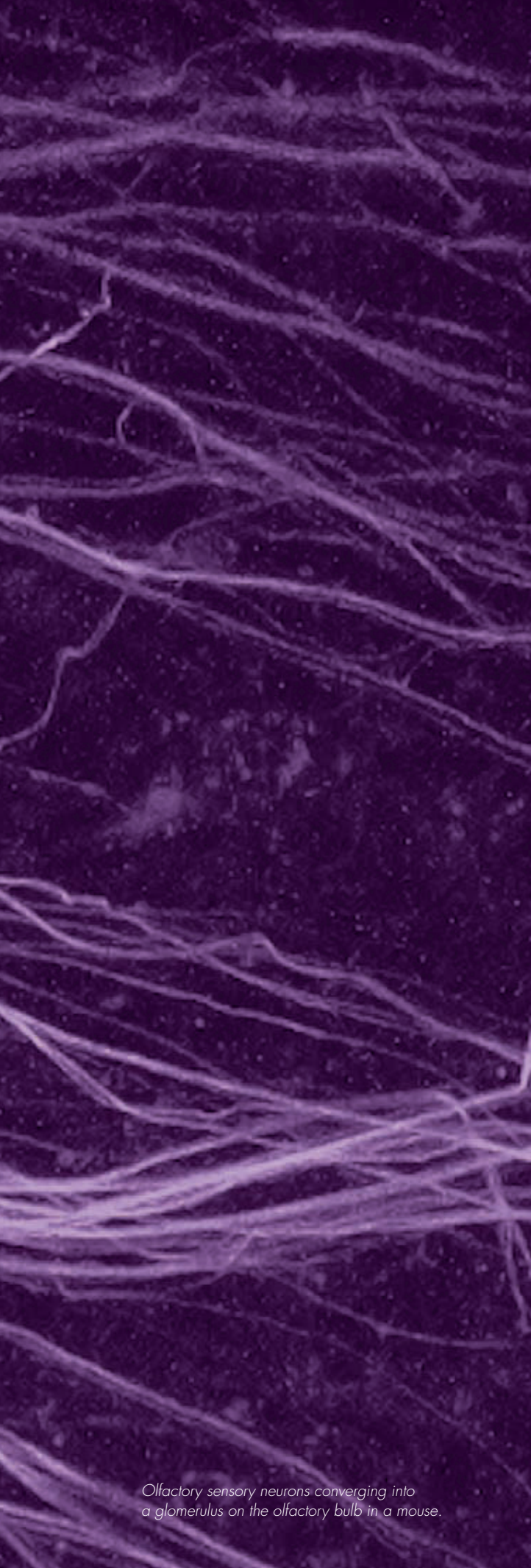
Vice Dean for Child Health,
University of Southern California





Showing the Way

New imaging capabilities bring clinicians and basic researchers together to view the origins of disease.



Olfactory sensory neurons converging into a glomerulus on the olfactory bulb in a mouse.

“Imaging has become the Rosetta Stone of research by allowing investigators access to disease at the most basic, molecular level,” says Scott Fraser, PhD, co-director of the new Translational Biomedical Imaging Lab (TBIL) at The Saban Research Institute of Children’s Hospital Los Angeles. “TBIL provides equipment and trained talent in order to accelerate the trajectory of scientific discovery from the bench, to the bassinet, to the bedside.”

Providing a unique, interdisciplinary environment, TBIL combines dynamic imaging equipment—including two state-of-the-art laser-scanning microscopes and a third in the process of being constructed—with an intellectual infrastructure consisting of optical physicists, computer scientists, translational researchers and clinicians.



Scott Fraser, PhD, provost professor of Biological Sciences, Biomedical Engineering and Pediatrics at the University of Southern California (USC) and co-director of TBIL

The confocal laser-scanning microscope provides optical sectioning to allow three-dimensional mapping of structures at the cellular level, making it an invaluable resource for a broad range of disciplines. Currently, TBIL is partnering on studies that include intestinal stem cell propagation, neuroblastoma and heart regeneration. Another study, on hypoplastic left heart syndrome, provides investigators the ability to follow the cells of a developing organ and see when and how a congenital defect occurs—allowing for an opportunity to intervene and change the outcome.

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Showing the Way (continued)



Scott Fraser, PhD (left), and Rex Moats, PhD

“Utilization of new imaging technologies has revolutionized the study of complex biological systems,” says Richard Simerly, PhD, deputy director of The Saban Research Institute and director of the Institute’s Developmental Neuroscience Program. “TBIL defines a novel collaboration space that will accelerate how visualization of both normal and disease processes impact diagnosis and delivery of advanced clinical care.”

The idea for this unique collaborative lab started with TBIL’s co-director, Rex Moats, PhD, of The Saban Research Institute. Moats, who uses *in vivo* imaging to study bone metastases, iron overload and cancer models, saw how other hospitals were building formidable platforms for technology transfer portfolios and were growing impressive lists of patents—all critical to accelerating the

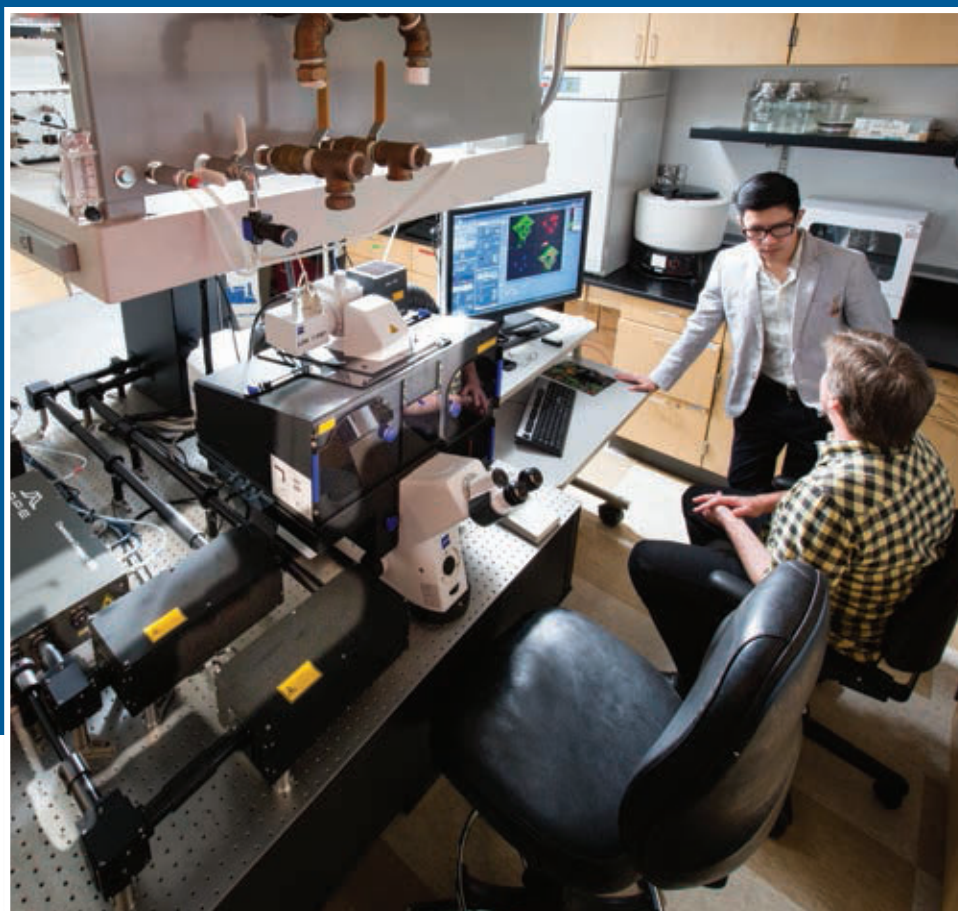
translation of new technologies, drugs and devices generated at those organizations. Indeed, such portfolios are crucial to attracting companies with the expertise for bringing new technologies to market and, therefore, closer to the patients who need special care.

“With Fraser’s unparalleled imaging expertise and Moats’ energetic drive to integrate clinical and basic research at Children’s Hospital and USC, we have been able to put this amazing imaging resource in place,” says Brent Polk, MD, director of The Saban Research Institute. “TBIL will help accelerate both the diagnosis and treatment of health issues that have a significant impact on children and the adults they will become.” ■

A Closer Look

Bioimaging includes powerful, innovative tools for the study of biological processes—such as confocal microscopes that can image virtually any specimen on a slide or culture dish, live-cell imaging and in vivo fluorescence imaging. Additionally, confocal laser scanning microscopy allows investigators to acquire in-focus images from selected depths, a process known as optical sectioning. Images are then acquired point by point and reconstructed with a computer, allowing three-dimensional reconstructions of topologically complex structures. All of these methods hold enormous potential for a wide variety of diagnostic and therapeutic applications.

With its broad array of advanced imaging microscopes and instrumentation resources on the third and fifth floors of The Saban Research Building, the Translational Biomedical Imaging Lab allows investigators from Children’s Hospital Los Angeles and their colleagues from the Keck School of Medicine of the University of Southern California to bring us closer to a day when disease can be treated before symptoms become apparent. ■



David Koos, PhD, technical director of TBIL, and a researcher using the laser scanning microscope.

A Better Fit

State-of-the-art medical devices are finally being customized for pediatric patients.

Technological innovations in health care can save lives and increase quality of life. Pacemakers restore rhythm to the heart, stents prop open weak arteries, and artificial knees and hips bring patients back to their feet.

But these devices aren't meant for children.

"For years, pediatric patients have dealt with ill-fitting medical devices that were made for the 5-foot-10-inch, 180-pound adult," says Yaniv Bar-Cohen, MD, co-director of the Southern California Center for Technology and Innovation in Pediatrics (CTIP). "Health care providers have been forced to adapt adult devices to children and infants. The resulting improvisations are often far from ideal, both in efficacy and safety."

In part to address the need for devices customized to a child's growing anatomy, CTIP was formed in 2011. This consortium between the University of Southern California (USC) and Children's Hospital Los Angeles brings together the best experts to accelerate the development of pediatric medical devices—a path that has not typically been easy or profitable to tread. These experts advise aspiring device developers on the manufacturing process, intellectual property protection, regulatory oversight, funding opportunities, clinical trial design and commercial partnerships.



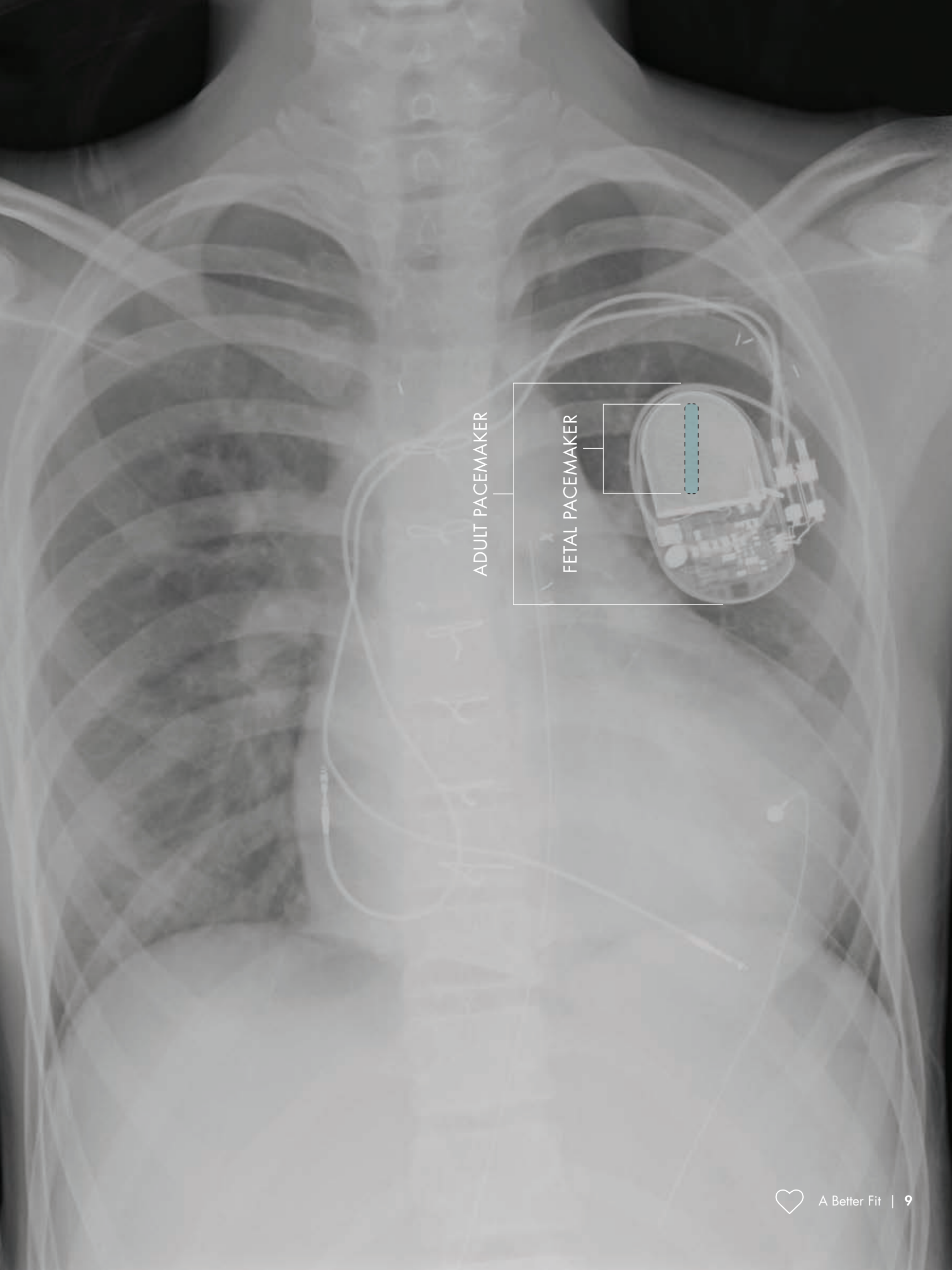
Jessica Rousset and Yaniv Bar-Cohen, MD, co-directors of the Southern California Center for Technology and Innovation in Pediatrics (CTIP)

"It is critical to surround ourselves with the best advisers because there are inherent challenges in commercializing products for pediatrics—a field that is characterized by small, and often vulnerable, patient populations," says Jessica Rousset, director of CHLA's Center for Innovation and co-director of CTIP. "Understanding these challenges and identifying a viable pathway to market is crucial, given that industry is less likely to support projects that offer a lower return on investment. Success requires out-of-the-box business models and the ability to broadly collaborate with others in the pediatric field."

In support of its work, CTIP recently received a five-year, \$1.5 million grant from the U.S. Food and Drug Administration (FDA). The award recognizes CTIP as a center of excellence and leadership in pediatric medical device development. Promoting the development and commercialization of novel devices conceived throughout Southern California, CTIP will also collaborate with six other FDA-funded consortia across the nation to develop strategies to improve device development and to help innovators navigate the laws, regulations and agency guidelines that protect the health and safety of children.

CTIP is currently guiding the advancement of several devices invented by Children's Hospital researchers and USC doctoral students, including a peripheral artery finder, which combines transillumination and ultrasound technologies to provide easy access to the arteries of newborns.

A team at Children's Hospital and USC is also developing the first-ever pacemaker for fetal use. As with other pediatric medical devices, physicians have modeled the fetal device after the adult pacemaker. However, the traditional design of a long leading wire, electrode and separate battery unit has never proven successful in utero. This new pacemaker is optimal for the growing child, as it can be safely implanted through minimally invasive surgery and will function for extended periods of time without being dislodged. ■



ADULT PACEMAKER

FETAL PACEMAKER





Engineering Options for Patients With Sickle Cell Disease

A variety of approaches—both high- and low-tech—have the potential to bring relief to sufferers of the disease.



Like most doctors, Thomas Coates, MD, tells his patients not to worry. Yet, unlike the gentle encouragement typically offered by clinicians, Coates' advice is prescriptive.

As a pediatric hematologist who treats one of the largest populations of patients with sickle cell disease (SCD) in California, Coates and his colleagues suspect that anxiety can affect the perception of pain—and that pain, in turn, affects blood flow. He knows that restricted blood flow can be devastating to his patients.

"We recently discovered something that hadn't been known before: Pain itself causes a decrease in blood flow. We anticipate that this decrease in flow will cause sickled cells to get stuck, obstructing circulation, which would then cause more pain," says Coates, section head of Hematology at Children's Hospital Los Angeles.



Thomas Coates, MD

"We recently discovered something that hadn't been known before: Pain itself causes a decrease in blood flow."

– Thomas Coates, MD

Sickle cell disease is a life-threatening genetic disorder of hemoglobin, the molecule in red blood cells that supplies oxygen to the body. Instead of rounded, flexible discs, the red blood cells in patients with SCD are stiff and crescent-shaped. These sickled cells become stuck in blood vessels, causing intense pain and eventual organ damage.

"No one suspected that dysregulation of the autonomic nervous system could be causing decreased blood flow, initiating this vicious cycle," says Coates, professor of Pediatrics and Pathology at the Keck School of Medicine of the University of Southern California (USC).

Earlier research identified that people with SCD have a more reactive autonomic nervous system (ANS). Part of the peripheral nervous system, the ANS controls involuntary functions such as breathing, heartbeat and blood flow. Patients with SCD lack these "checks and balances"—the work of the sympathetic and parasympathetic systems—that would typically modulate a response.

Coates has data demonstrating this difference. He compares the variation in blood flow in patients with SCD versus healthy individuals in response to a simple sigh. Eighty percent of patients with SCD experience vasoconstriction when they sigh, while only 20 percent of healthy individuals share this response.

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With a recent five-year, \$9.5 million award from the National Institutes of Health, Coates and his colleagues will standardize measurements and develop biomarkers that reflect a patient's "reactivity" and determine how ANS dysregulation affects vasoconstriction and frequency of sickle cell crises. Coates has assembled an unusual team—all but one of his co-principal investigators have a background in physics or engineering. They include Michael Khoo, PhD, and Herbert Meiselman, ScD, from the Biomedical Engineering and Physiology programs at USC; John Wood, MD, PhD, cardiologist and biomedical engineer at Children's Hospital Los Angeles; and Lonnie Zeltzer, MD, director of the Pain Program at the David Geffen School of Medicine at the University of California, Los Angeles.

Using high-tech tools like lasers, infrared light, magnetic resonance imaging and body sensors to capture the data, Coates' team employs a specialized computer system that can receive and coordinate these varied inputs. The researchers are also developing a smartphone app, so that patients can quantify and record their pain as it occurs and then relay that information to the cloud for storage. This compilation of patient information will allow the team to develop biomarkers that reflect ANS imbalance, pain-triggered constriction of blood vessels and brain perfusion. The goal is to test the theory that these biomarkers reflect underlying molecular and cellular pathologies resulting from the sickle cell gene mutation. "There is a lot of technology out there, and what we can't find we'll build ourselves," says Coates. "We'll be able to determine the fundamental processes of the disease and then begin evaluating specific interventions."

One intervention being considered is surprisingly low-tech. Zeltzer's area of expertise, cognitive behavioral therapy—which is used to treat anxiety, among other things—will be evaluated as a means of decreasing a patient's reactivity and, ultimately, reducing vasoconstriction, pain and sickling. Cognitive behavioral therapy could provide patients with SCD a way to effectively manage their disease by reducing the severity of their symptoms. Coates' patients would then have an easier time following his advice, because they'd have a lot less to worry about. ■

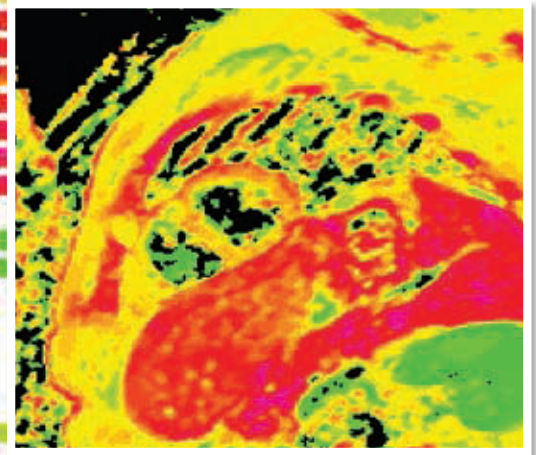
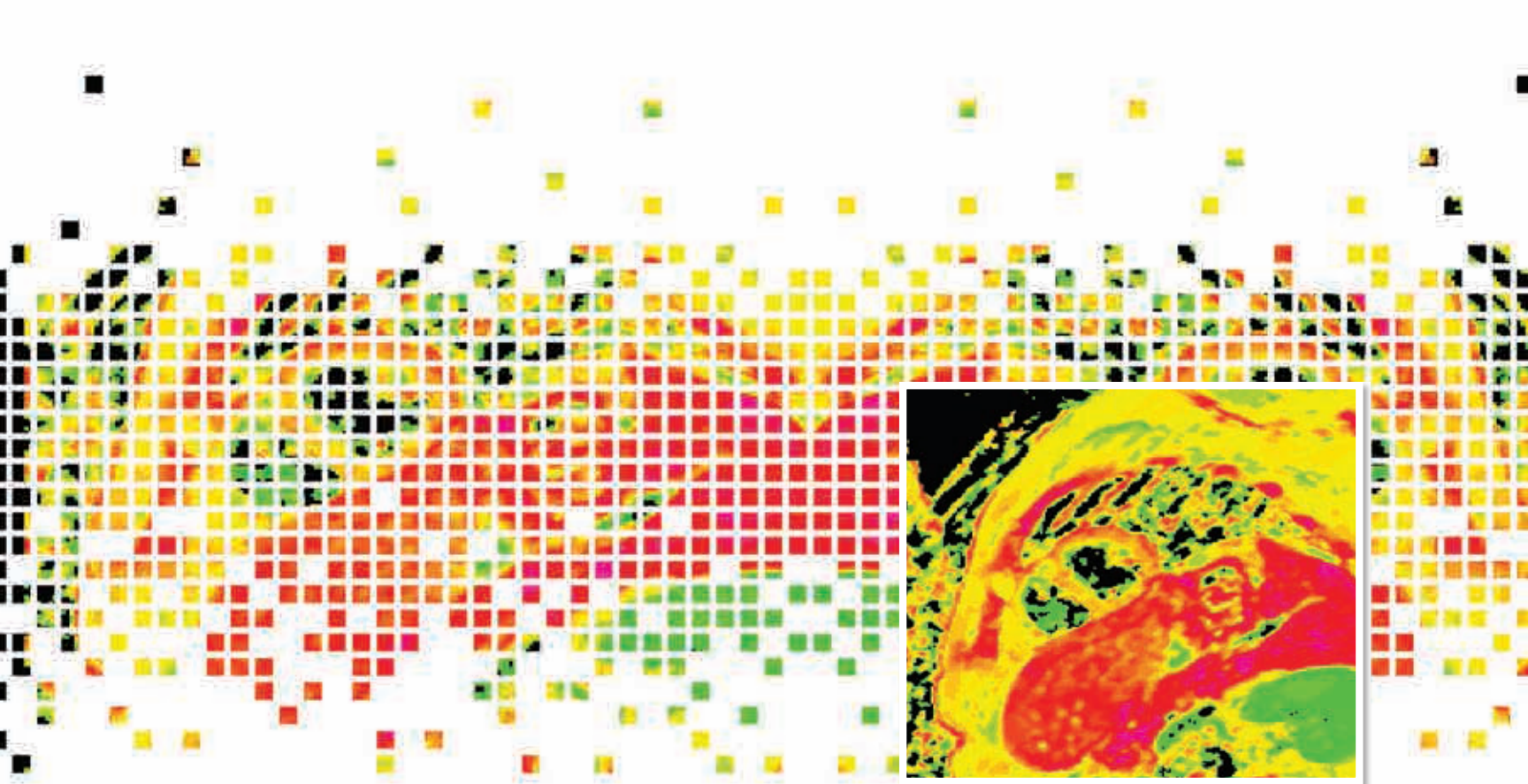
Inside Story

By 12 years of age, about 40 percent of children with sickle cell disease have small strokes, which result in a loss of cognitive function. John Wood, MD, PhD, is developing novel magnetic resonance imaging techniques to measure blood flow in the brain. He is also applying advanced math modeling to the effort to understand the relationship between abnormalities in blood flow, oxygenation and the physical properties of blood in sickle cell patients, as well as the impact of these abnormalities on cognitive function. ■



John Wood, MD, PhD





MRI of the heart. Green indicates no iron; yellow, orange and red demonstrate increasing severity of iron deposition.

Technology Takes On Thalassemia

A novel software tool is helping remote doctors manage the deadly disease.

Thalassemia is a family of inherited blood disorders characterized by too few healthy red blood cells with adequate hemoglobin, the protein necessary to transport oxygen. “Developing red blood cells don’t make it out of the bone marrow, and patients become horribly anemic,” says John Wood, MD, PhD, principal investigator at The Saban Research Institute of Children’s Hospital Los Angeles.

Treatment typically requires a blood transfusion every three weeks or so, but each transfusion also introduces a year’s worth of iron. “Iron is hard to come by, so the body hangs on to every molecule and recycles it,” says Wood. “Thalassemia patients are getting as much as 17 years of iron each year in transfusions. It’s too much. The liver stores it until the excess eventually spills into the endocrine glands and then into the heart.”

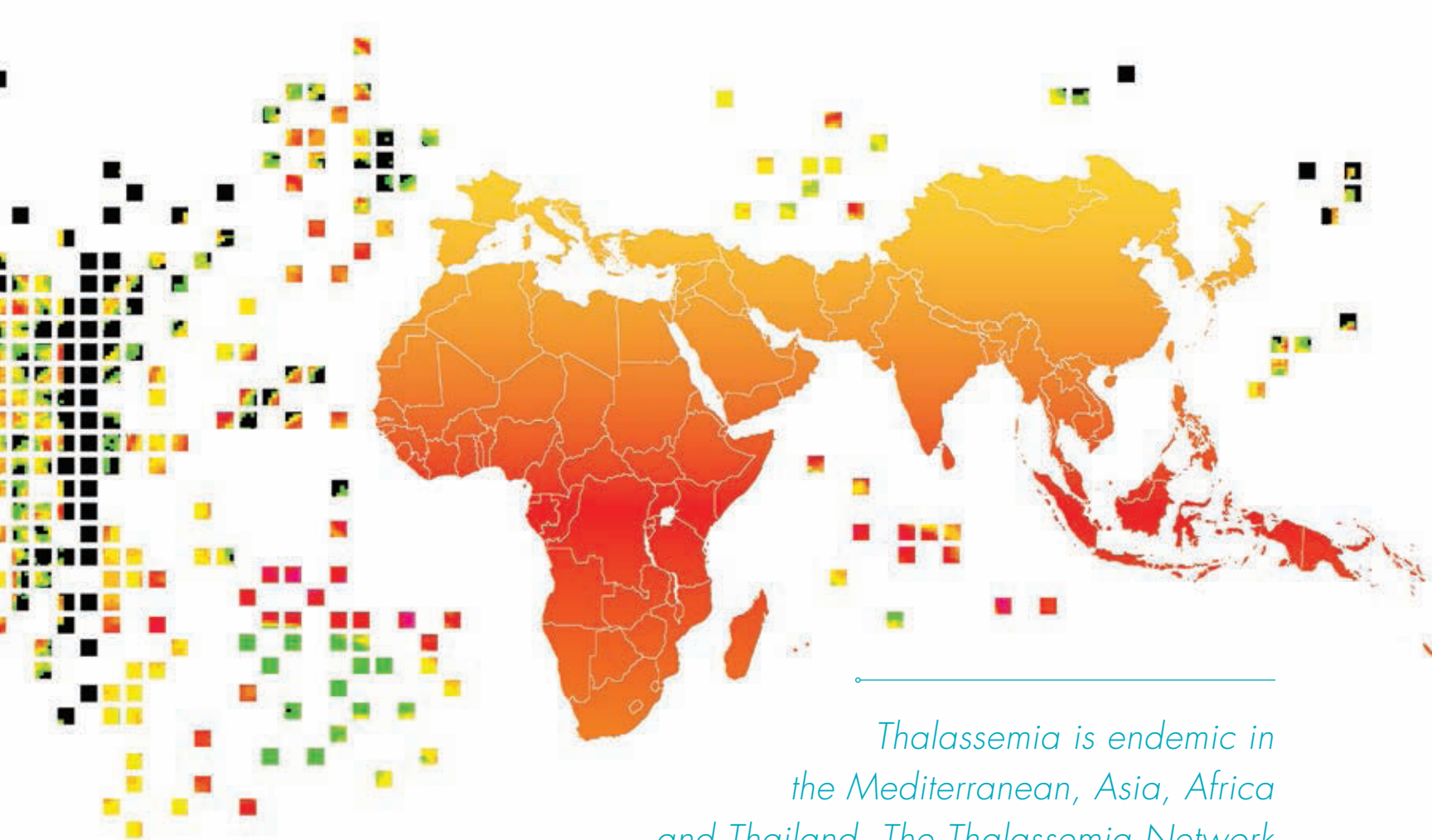
The heart is the breaking point. Until relatively recently, medical monitoring of patients with thalassemia involved conducting occasional, painful liver biopsies to assess levels of iron in

the organ. But liver biopsies tell doctors nothing about the heart, and heart biopsies are ineffective because iron deposits found there are too heterogeneous.

“You could miss them and think everything was perfectly normal,” says Wood. “By the time a patient saw a cardiologist, it was usually too late. They were likely dead in six months, no matter what we did.”

Wood, who has a doctorate in bioengineering, believed magnetic resonance imaging (MRI) of the heart was a diagnostic solution and came to Children’s Hospital Los Angeles in 2000 intent on proving it. By 2005, he had demonstrated the efficacy of noninvasive cardiac MRIs for patients with thalassemia.

Cardiac MRIs are now the standard of care for thalassemia in the United States, where the disease is relatively rare. Patients are typically scanned annually, with treatments to remove excess iron adjusted accordingly.



Thalassemia is endemic in the Mediterranean, Asia, Africa and Thailand. The Thalassemia Network “is telemedicine over thousands of miles.”

“Patients get a scan of their heart, liver and pancreas, which tells us a lot about where they are on the disease spectrum,” says Wood. “We’re able to stratify risk and decide how aggressively to treat.”

The bigger challenge is fighting thalassemia where the disease is endemic: in tropical regions and among people of Mediterranean, Asian and African descent. One such place is Thailand, where an estimated 37 percent of the indigenous population carries at least one defective gene for the disease, and approximately 300,000 babies are born with the disorder each year. It is a major public health dilemma, with significant adverse economic consequences.

Numbers, though, are just part of the problem. No less vexing is the lack of advanced technology and medical expertise. “Internationally, thalassemia is well-known, and people come to us asking for help,” says Stephan Erberich, PhD, director of Biomedical Informatics at The Saban Research Institute. “But a country like Thailand lacks the infrastructure and resources we have here. Teaching hospitals are scarce. There are

few experts capable of doing the necessary MRI analysis, and the technologies aren’t as developed.”

The solution, according to Wood and Erberich, both faculty members of the Keck School of Medicine of the University of Southern California, is to build the Thalassemia MRI Iron Load Network, allowing local Thai doctors to generate MRI images—a relatively simple thing to do—and transmit them to trained experts for analysis, a far more difficult thing to do.

“What is needed is to bring patients, physicians and imaging experts together—virtually—so they can jointly make the right treatment decisions based on all available data. That’s what the Thalassemia Network is about,” says Erberich. “It’s telemedicine over thousands of miles. We had to come up with a methodology to exchange large and complex images that fit into a dial-up scenario: low bandwidth, stable yet robust and as simple as email. That’s what ImageInbox provides.”

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ImagelInbox

This software app developed by Stephan Erberich, PhD, and members of the Department of Radiology at Children's Hospital Los Angeles, allows HIPAA-compliant transfer of medical images and diagnostic reports.

"ImagelInbox is the next generation of the award-winning Global MEDICUS software," says Marvin Nelson, MD, chairman of the Department of Radiology at Children's Hospital Los Angeles. "It is equally effective at sending images across town, to provide a second opinion, or across continents, to collaborate with researchers in far-off locations."



ImagelInbox on a mobile device

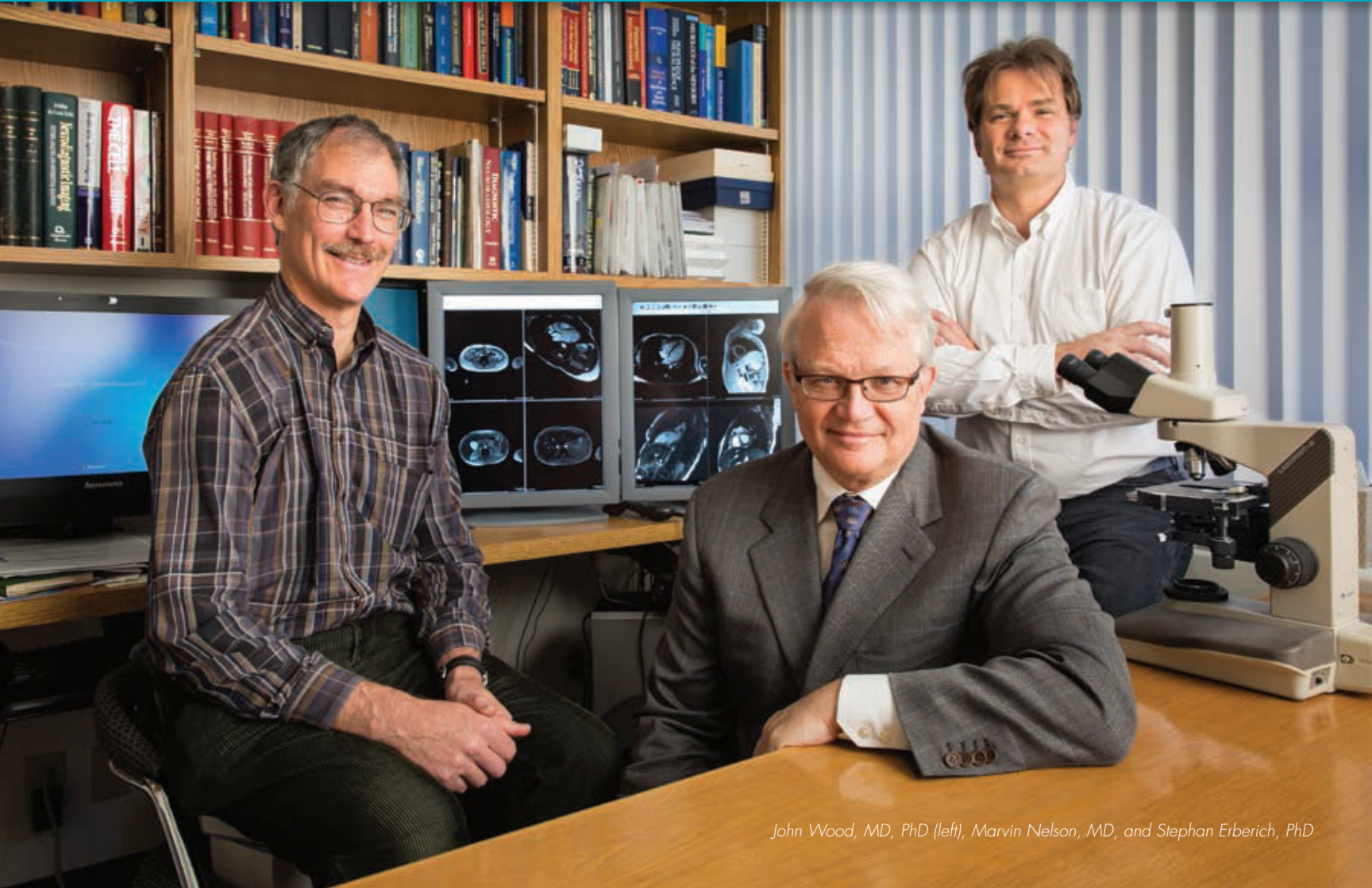
Erberich and colleagues developed this novel software program, which can be readily adapted to diverse medical systems far afield. "Doctors at remote sites can now send us an MRI via ImagelInbox from anywhere on the planet, with delivery guaranteed," he explains.

Another essential driver of the network is Vip Vipkrasit, MD, PhD, a pediatric hematologist and scientist at Mahidol University's Centre Siriraj Hospital in Bangkok. "Vip is the link to patients," Erberich adds. "He is the force behind trying to make cardiac MRIs available to everybody in the region."

The network is still in its infancy, with a dozen MRI centers scattered throughout Thailand beginning to feed images to Vipkrasit in Bangkok or to doctors



Vip Vipkrasit, MD, PhD, surrounded by his team at Centre Siriraj Hospital, Bangkok, Thailand



John Wood, MD, PhD (left), Marvin Nelson, MD, and Stephan Erberich, PhD

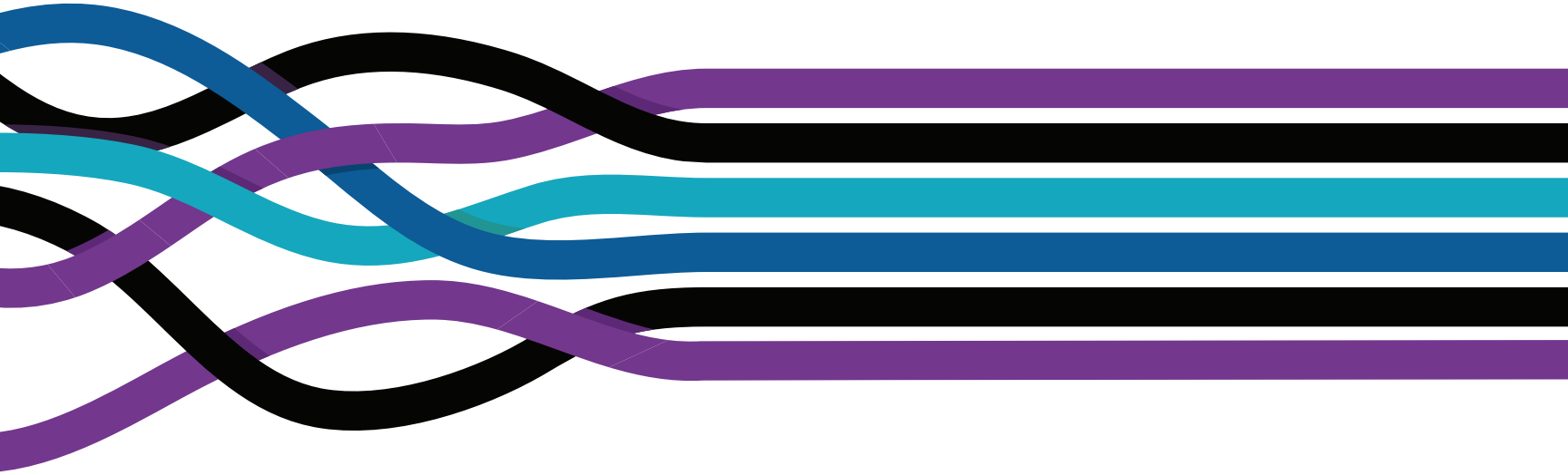
at Children's Hospital Los Angeles for analysis. The resulting data are not just benefiting individual patients, but they're also helping to create a deeper, fuller understanding of thalassemia. "The disease is different in different regions of the world," says Wood. "The only way to sort out the details is to create databases and compare clinical experiences."

Other parts of the world are already inquiring about establishing similar networks, including China, Malaysia, the Philippines, the Middle East and Latin America. "It's all about creating connections in these countries and allowing our partners to become self-sufficient—educating them on use of the imaging techniques, the network system and derived insights about the patient health data," says Erberich.

"We believe this technology represents the next frontier in medicine, where global experts and leaders in their field provide decision support based on rapid information sharing, not on geographic location of the patient," says Brent Polk, MD, director of The Saban Research Institute. "We are pioneering this new frontier." ■

How We Become What We Become

That, says Pat Levitt, is the big question at the core of his research into the roots of childhood brain disorders.



Neuroscientist Pat Levitt, PhD, has been chasing a soft, three-pound object for the past 40 years. Yet even as each new discovery brings him nearer to tracking it down, he knows the pursuit will go on.

“The brain is sort of infinity,” says Levitt, who holds the Simms/Mann Chair in Developmental Neurogenetics within the Institute for the Developing Mind (IDM) at Children’s Hospital Los Angeles. “I think that’s the problem. You’ve got trillions of connections, and they’re not soldered.

“Neurodevelopmental disorders, at their essence, are disorders of information processing,” he explains. “That’s fundamentally getting the wiring diagram right—brain cell A has to connect to brain cell B. There used to be question marks when you drew that diagram out, and now we have eliminated a lot of them.”

Levitt came to Children’s Hospital last July to try to cross off one more: How does the interplay of genes and environment increase the risk for disorders that disrupt memory, learning and social and emotional well-being?

“Right now we’re waiting until the person has the disorder, and then we try to treat it,” says Levitt, whose Developmental Neurogenetics program forms one of the IDM’s three spheres of research emphasis; behavioral neuroscience

and neuroimaging are the other two. His work is driving the IDM further toward its goals of understanding the origins of neurodevelopmental conditions, and then developing interventions that can moderate or even preempt them.

“That’s a big puzzle, but it’s critically important.”

Levitt is doing his part. His lab has made a trio of important discoveries in recent years, identifying a gene in 2006 that increases risk for autism spectrum disorder, and then following up in 2009 by showing that the gene exists more commonly in children who have both autism and gastrointestinal issues. This past year came the third breakthrough, when Levitt found a prevalence of high levels of oxidative stress in those same kids who have autism and GI problems. The findings have substantial clinical applications.

“You can treat the oxidative stress problems,” he says, “which may have an impact on brain function as well as GI function. Or if we can treat the GI problems, the child will become more compliant with the interventions they’re getting.”

The process of scientific discovery captivates Levitt—and has since he was first invited to join a research project as an undergraduate at the University of Chicago in the early 1970s. “I’m still excited and jazzed by it all,” he says.



Pat Levitt, PhD

But he also says the speed with which technology now allows researchers to obtain data has left neuroscience with a new problem. All that information, arriving in terabytes per hour, has to be sorted before anyone can pull more discoveries from it. He finds a useful analogy in his fascination with looking at flight patterns online.

“There are thousands of planes in the air—it looks like spaghetti! How can anybody make sense out of it? Let’s say all that information was related, and your goal was to find patterns in it that would relate disease to non-disease. How would you do it? That’s what we’re facing now.”

Much like Google and Amazon have, the IDM wants to hire informatics experts, Levitt says. “They don’t generate the data—they’re not biologists—but they know how to manage data and how to develop new models and algorithms to pull patterns out of something that seems impossible.”

Pulling patterns out of something that seems impossible could double as Levitt’s own job description, as he continues to try to decipher the body’s most inscrutable organ.

“I do a lot of public policy work,” says Levitt, who serves as the science director for the Harvard University-based National Scientific Council

“There are thousands of planes in the air—it looks like spaghetti! How can anybody make sense out of it? Let’s say all that information was related, and your goal was to find patterns in it that would relate disease to non-disease. How would you do it?”

— Pat Levitt, PhD

on the Developing Child. “I go out and talk to people all the time about the importance of early experience in building healthy brain architecture. I say, ‘Look, I love my heart. I can’t live without it. But the passion of trying to figure out who we are and how we develop, how we become what we become—that’s not about the four chambers of the heart. That’s about the brain.’ The brain is what the human condition is all about.” ■



Autism: A Hunt for Culprit Genes

Di Tian's investigations are part of an ambitious collaborative effort at Children's Hospital Los Angeles and the Keck School of Medicine of USC to uncover the origins of autism spectrum disorder—and the most effective interventions.

Scientists have linked literally hundreds of mutated genes with autism spectrum disorder (ASD), a success rate that could be viewed as both an important first step toward future interventions and an increasingly complex puzzle.

Di Tian, MD, PhD, an investigator in the Developmental Neuroscience program at The Saban Research Institute of Children's Hospital Los Angeles, has been studying a microdeletion—the loss of genetic material—from chromosome 16. He is zeroing in on clues that bring 30 possible genes in this region down to just five, or even fewer.

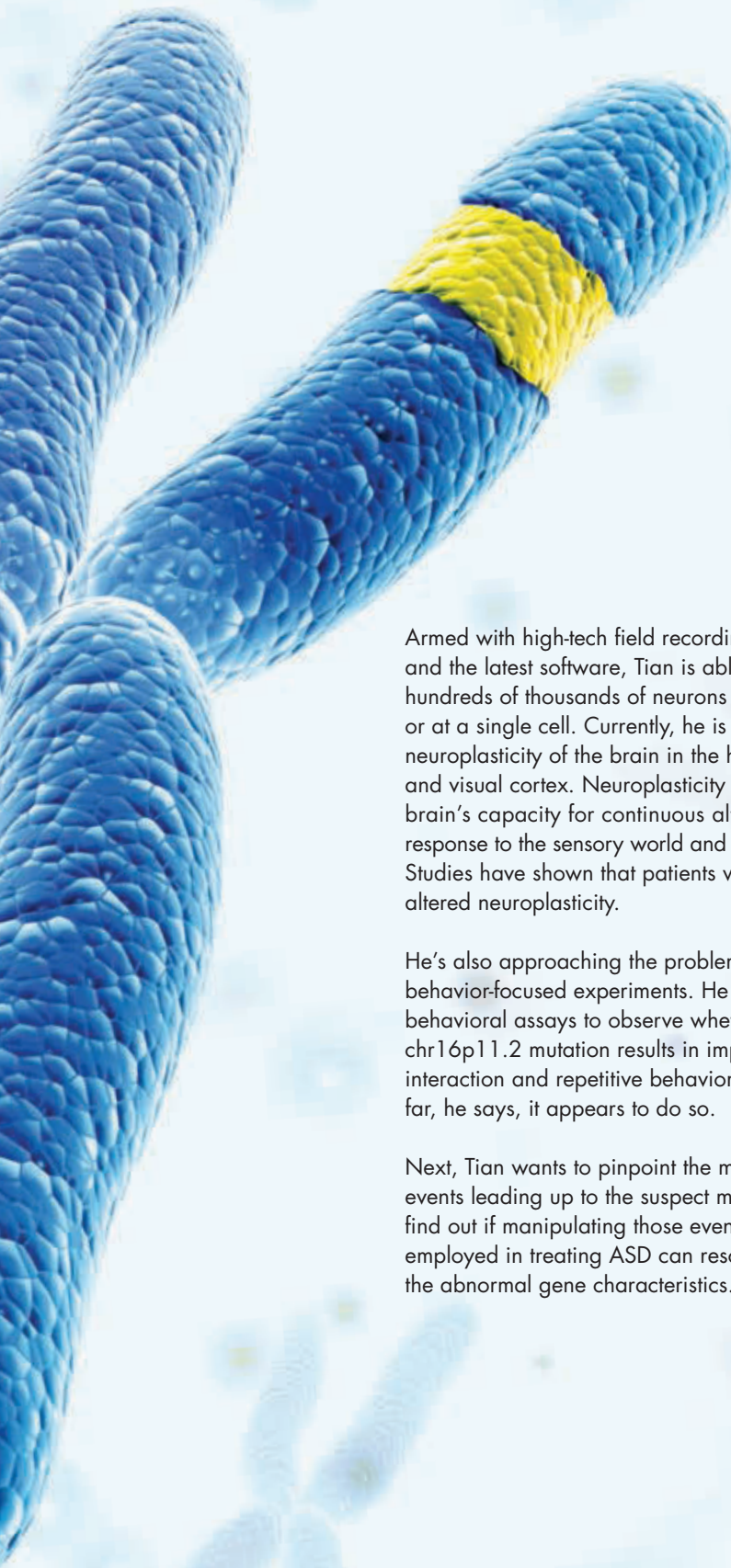
The microdeletion at chromosome 16, specifically, the region known as chr16p11.2, has been strongly associated with ASD. In fact, says Tian, assistant professor of Pathology at the Keck School of Medicine of the University of Southern California, "it is one of the most common genetic abnormalities associated with autism spectrum disorder."

Tian, a pediatric neuropathologist in the Department of Pathology and Laboratory Medicine at Children's Hospital, combines a passion for the developing brain with an expertise in creating in vivo models for autism and other neurological disorders. He employs a variety of experimental approaches, including electrophysiology,

biochemistry and behavioral studies. His ultimate goal is finding the causal gene or genes behind ASD, which affects approximately 1 in every 68 children in the United States.

"We need to be cautious," says Tian. "There may be no single gene responsible for this mutation. It might be multiple genes in combination."

About 30 percent of patients with the chr16p11.2 microdeletion display some of the most common symptoms of ASD, such as deficits in social interaction, language impairment and repetitive behavior.



Armed with high-tech field recording equipment and the latest software, Tian is able to look at hundreds of thousands of neurons at a time, or at a single cell. Currently, he is studying neuroplasticity of the brain in the hippocampus and visual cortex. Neuroplasticity refers to the brain's capacity for continuous alteration in response to the sensory world and life experience. Studies have shown that patients with ASD have altered neuroplasticity.

He's also approaching the problem of ASD using behavior-focused experiments. He has designed behavioral assays to observe whether the chr16p11.2 mutation results in impaired social interaction and repetitive behaviors in mice. So far, he says, it appears to do so.

Next, Tian wants to pinpoint the molecular events leading up to the suspect microdeletion to find out if manipulating those events with drugs employed in treating ASD can rescue or correct the abnormal gene characteristics.



Di Tian, MD, PhD

Using his translational in vivo models, Tian has already identified key synaptic dysfunctions in affected brain regions of patients with the chr16p11.2 mutation. Scientists believe that disruption in synapses—which allow neurons to pass signals to individual cells—is instrumental in ASD. Tian's studies connect those interrupted synapses to protein synthesis, the process by which cells generate new proteins.

The chromosome 16 mutation and faulty protein synthesis seem to go hand in hand, "which provides more clues to what might go wrong," he says, "and makes this puzzle very challenging and very interesting." ■

That'll Leave a Mark

Delving into what she calls “survivor biology,” Barbara Driscoll explores how early childhood ailments can affect future health.

Long after the aches and pains disappear, our bodies still remember the impact of illness. Barbara Driscoll, PhD, explores how cells use their first experiences with disease to influence future encounters, coining her area of interest “survivor biology.”

“We are imperfect at repair,” says Driscoll, an investigator in the Developmental Biology and Regenerative Medicine program at The Saban Research Institute of Children’s Hospital Los Angeles. “We survive, but we survive changed.”

These changes generally accumulate over decades. Each bout of flu, pneumonia or bronchitis leaves behind slightly altered cells that impact our overall health and rate of senescence, or the rate at which we age. The process begins during childhood, as some children experience serious stressors earlier than their healthy counterparts. This is especially true in premature infants. Born before their lungs are completely developed, preemies are at risk for such complications as irregular and shallow breathing, respiratory distress syndrome and bronchopulmonary dysplasia.

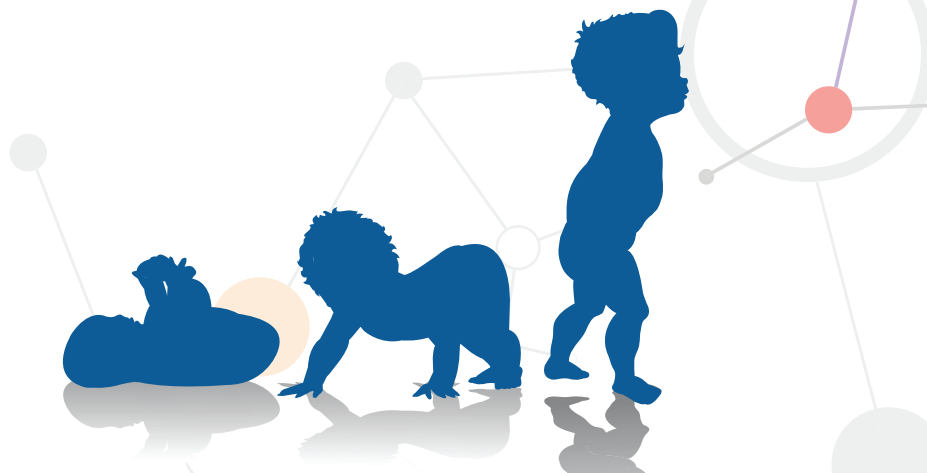
To study the long-term effects of early health complications, Driscoll utilized a “two-hit” approach in mouse models. The experiment allowed for the controlled observation of elicited respiratory stressors, or hits. Driscoll induced the first hit at 2 months of age—comparable to 25 years in humans—and the second hit seven months later. Now simulating a 40-year-old human organ, the mouse lung was predicted to be fully recovered from the first traumatic incidence. That was far from the truth.



Barbara Driscoll, PhD

“Scattered, abnormal cell masses, reminiscent of neoplasms, developed in the lungs after the second stressor,” says Driscoll, associate professor of Research at the Keck School of Medicine of the University of Southern California.

One hypothesis for the appearance of these masses suggests that surviving cells retain their memory of past injury. The first traumatic experience may alter mechanisms in the cell cycle, priming an overreaction to future encounters.



"These hits change the organism and the ability of the organism to respond to later hits," explains Driscoll. "Our goal now is to pinpoint exactly what is altered in these routine pathways and describe the changes as molecular events. Once we do this, we can better respond to these adverse effects and work to prevent them in the future."

Driscoll is already starting to isolate these changes. Since the regulatory processes disrupted by two hits are the same as those impacted by aging, Driscoll conducted a separate experiment aimed at halting these similarly damaging effects.

She designed a treatment involving an anti-aging drug to be administered to the senescing lungs in a second mouse population. By targeting specific mechanisms in the cell cycle, this therapy slowed

down the rate of lung aging and encouraged cell reproduction and vitality.

Driscoll hopes to mimic the condition of pediatric patients by eventually combining both experimental groups. After studying the two-hit approach on lungs that are rapidly aging, she can use the anti-aging treatment to see if it lessens the pathological response observed after a second hit.

"It's important to remember, especially in young children, that disease doesn't happen in a vacuum," says Driscoll. "We always knew that history and context affected disease development and outcome, but we're just starting to get a handle on how much." ■



Attacking Biliary Atresia

Supported by a host of researchers, surgeon Kasper Wang looks to uncover the sources of this life-threatening childhood liver disease.

Emmalani Johnson has rings of curly brown hair and matching brown eyes that melt your heart. Three years ago, days after she was born, her parents learned that she was headed toward liver failure.

Emmalani had been diagnosed with biliary atresia (BA), the most common cause of end-stage liver disease and the leading indication for liver transplantation in children.

As they rushed to Children's Hospital Los Angeles from San Diego to put their daughter in the arms of surgeon Kasper Wang, MD, Emmalani's mother, Roxanne, says it was the first time in weeks that she found relief.

"They told us that they had dedicated their lives to figuring out the mystery of biliary atresia," Roxanne says. "When a doctor looks you in the face and says that as you're handing over your little baby, it gives you a sense of trust. There's hope, and people who care."

At Children's Hospital Los Angeles, Wang—principal investigator for a National Institutes of Health-funded study within the Childhood Liver Disease Research and Education Network (CHILDRN)—is part of a team that performs highly successful surgical procedures on patients like Emmalani.

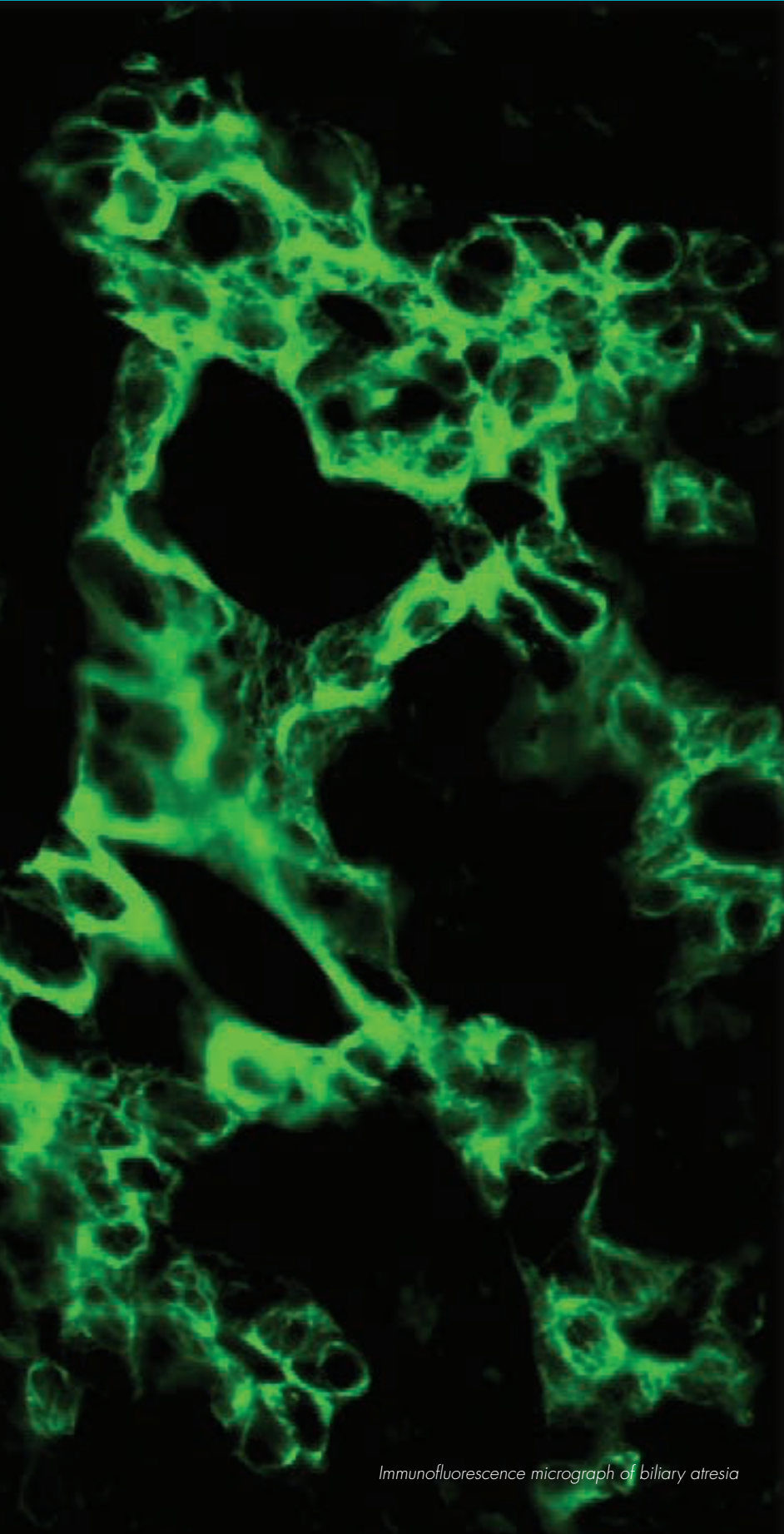
Biliary atresia is characterized by obstructed bile ducts. Bile is unable to flow from the liver, causing damage to the organ. While the progression of liver failure looms, a procedure—known as the Kasai—allows some patients to keep their own liver while permitting bile to drain. The hospital's 70 percent average for successful Kasai procedures exceeds the national average of 50 percent.

Kasper Wang, MD and Emmalani Johnson, 4 months old, three weeks after her operation

In his research lab, Wang is investigating what is unique about the liver cells in some patients with BA that results in fibrosis despite the fact that bile is no longer building up in their livers. He and his colleagues have identified cells that resemble stem cells and are most likely responsible for the scarring.

Alongside Wang are Gage Crump, PhD, a researcher at the Keck School of Medicine of the University of Southern California, and Nancy Spinner, PhD, a geneticist at The Children's Hospital of Philadelphia.





Immunofluorescence micrograph of biliary atresia



Emmalani Johnson, age 3

The trio is specifically looking into mutations in the Jagged 1 gene, which is associated with 10 percent of infants diagnosed with BA. The investigators are also incorporating a variety of research approaches, using a rotavirus model of the disease in mice, in order to find correlations in humans.

At Children’s Hospital Los Angeles, Wang works with study co-investigator Nanda Kerkar, MD, to manage and treat BA patients, and with research program manager Cat Goodhue, CPNP, who coordinates grant funding and the hospital’s annual Biliary Atresia Day. “We’ve got multiple pots boiling on the stove to figure out how to attack this disease and why it occurs,” Wang says. “Biliary atresia is as common as childhood leukemia. In terms of cost, patients diagnosed with this disease face a lifetime of immunosuppression therapy and, potentially, multiple liver transplants to survive.”

Researchers still don’t know why some children—like Emmalani, who has had the Kasai procedure and is thriving—grow to become healthy adults without the need for additional transplants, and others don’t.

“This is my professional passion, and what I have focused my clinical and research practice on for the last decade,” Wang says. “There are a lot of really smart people studying and attacking this disease, and I’m confident we’ll figure it out.” ■

Coming Together to Fight Obesity

The Diabetes and Obesity Program is working on all fronts—the lab, the clinic and the community—to stem the rising tide of childhood obesity and diabetes.

On the surface, the problem of childhood and adolescent obesity sounds simple to solve: Just eat less and exercise more.

But Steven Mittelman, MD, PhD, knows that the reality is more complex.

“As much as you can tell someone to eat less and exercise more, it doesn’t tend to happen,” says Mittelman, director of the Diabetes and Obesity program at Children’s Hospital Los Angeles. “We need to look at why kids are eating too much, why they aren’t exercising and why obesity causes so many problems, like diabetes and cancer.”

Mittelman is spearheading a major multidisciplinary effort to find the answers to those questions and more. The program’s goal: fight childhood obesity and diabetes on all fronts—the lab, the clinic and the community.

In the lab, researchers are taking a deeper look at several areas: how various genetic and environmental factors can cause obesity, why obesity creates so many health problems and how to develop new therapies to treat diabetes.

The program’s three bench scientists are each studying a different facet of the problem. Mittelman is focused on the relationship between obesity and cancer—investigating how fat tissue may help leukemia cells survive and resist chemotherapy.

Investigator Senta Georgia, PhD, is studying an entirely different issue: regenerating pancreatic beta cells. These are the cells that make and release insulin; patients with type 1 diabetes don’t have enough of them. Georgia’s lab is investigating myriad ways to make more, including reprogramming intestinal stem cells to make beta cells instead.

“Intestinal stem cells are highly related to the pancreas, and you literally have billions of them,” Georgia says. “If we could reprogram some of them to make beta cells, we’d have a potential therapy for patients that would allow them to make their own insulin.”

A third investigator, Lily Chao, MD, is researching the intricate mechanisms of muscle growth and metabolism. By investigating a nuclear receptor protein called Nur77, her lab is hoping to lay the groundwork for future therapies to improve glucose metabolism in diabetes patients.

Recently, Children’s Hospital launched the EMPOWER (Energy Management for Personalized Weight Reduction) Weight Management Clinic for overweight or obese children and teens. The clinic’s approach is highly personalized, with a team of specialists—a physician, dietitian, psychologist and physical therapist—working together to create a customized care plan for each patient and family.

The program is taking its expertise to the community, too. Its newest initiative, made possible through a grant from the California Community Foundation, is a faith-based pilot program offered in partnership with the New Mount Calvary Missionary Baptist Church in South Los Angeles.

In addition to bringing the hospital’s successful, evidence-based Kids N Fitness® program to the church, the pilot is providing health needs assessments, reaching out to local community clinics and working with church leaders to promote healthy lifestyle changes within their congregations. ■

the clinic

the lab



the community

Career Spotlight

Alan S. Wayne, MD

Director of the Children's Center for Cancer and Blood Diseases

The Children's Center for Cancer and Blood Diseases at Children's Hospital Los Angeles is one of the largest referral centers of its kind in the U.S., caring for more than 1,000 new patients from around the world each year. The Center, an innovative hub for translational research and treatment, turned to the nation's leading medical research institution in its search for a new director.

After serving 14 years as clinical director of the Pediatric Oncology branch of the National Cancer Institute at the National Institutes of Health (NIH), the renowned pediatric hematologist-oncologist, Alan S. Wayne, MD, joined Children's Hospital Los Angeles in July 2013.

While at the NIH, Wayne directed a leading-edge research program that worked to develop new treatments for blood cancers and conducted multiple clinical trials that achieved complete remissions for many study patients.

Wayne is leading efforts to accelerate the incorporation of innovative treatments, such as immunotherapy, into clinical practice.

Leading a large team of laboratory researchers, clinical investigators and staff, he directs a multisite clinical trials group, the Therapeutic Advances in Childhood Leukemia (TACL) Consortium, which is based at Children's Hospital Los Angeles. To facilitate scientific discovery in support of clinical advances, he is working to establish a tissue biorepository to house patient samples and data that can be accessed by scientists and laboratories around the globe.

"While our current research offers promising treatments for children with cancer and blood disorders, the process from discovery to implementation is hindered by numerous roadblocks," says Wayne, professor of Pediatrics at the Keck School of Medicine of the University of Southern California. "We are working to expedite the development of new therapies and to get the right treatment to the right patient." ■



"We are working to expedite the development of new therapies and to get the right treatment to the right patient."

– Alan S. Wayne, MD

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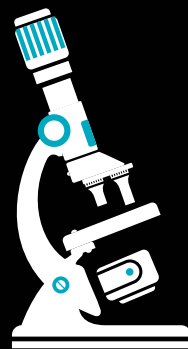
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140+ ACTIVE CLINICAL TRIALS WITH 1200+ ENROLLMENTS PER YEAR



\$10 million+ ANNUAL RESEARCH FUNDING (NIH=\$7M+)

Children's Hospital Los Angeles was ranked fifth in the nation for cancer care on the U.S. News & World Report Best Children's Hospitals rankings for 2014 – 2015.

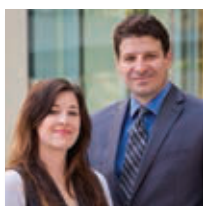


Major Awards



Grace Aldrovandi, MD, CM

Grace Aldrovandi, MD, CM, was awarded \$19 million by the National Institute of Allergy and Infectious Diseases and the Eunice Kennedy Shriver National Institute of Child Health and Human Development to provide scientific leadership and infrastructure for laboratory testing as part of the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network.



Jessica Rousset and Yaniv Bar-Cohen, MD

Yaniv Bar-Cohen, MD, and Jessica Rousset were awarded \$1.5 million from the U.S. Food and Drug Administration for the Southern California Center for Technology and Innovation in Pediatrics (CTIP), a consortium established by Children's Hospital Los Angeles and the University of Southern California for the development and commercialization of pediatric medical devices.



Thomas Coates, MD

A team led by Thomas Coates, MD, was awarded \$9.5 million from the National Heart, Lung, and Blood Institute to study the underlying physiology of sickle cell disease and to identify biomarkers that will aid in the development of new treatment options.



Yves DeClerck, MD

Yves DeClerck, MD, was awarded \$1.2 million from the National Cancer Institute to research the role of plasminogen activator inhibitor-1 (PAI-1) in tumor progression and metastasis.



Mark Frey, PhD

Mark Frey, PhD, was awarded \$1.7 million from the National Institute of Diabetes and Digestive and Kidney Diseases for his research on the regulation of colon epithelial cell survival.



Nora Heisterkamp, PhD

Nora Heisterkamp, PhD, received \$1.7 million from the National Cancer Institute to examine the role of Galectin-3 (Gal-3) as a communication molecule between acute lymphoblastic leukemia cells and their microenvironment.



Pat Levitt, PhD

Pat Levitt, PhD, has been named the Simms/Mann Chair in Developmental Neurogenetics, funded by a \$3 million endowment from the Simms/Mann Family Foundation.



Yong-Mi Kim, MD, PhD

Yong-Mi Kim, MD, PhD, was awarded \$1.7 million from the National Cancer Institute to research the chemoprotective mechanisms of acute lymphoblastic leukemia cells.



Takako Makita, PhD

Takako Makita, PhD, received \$1.7 million from the National Institute of Neurological Disorders and Stroke for her research on the interaction between endothelins and the sympathetic innervation of the heart. She was awarded an additional \$1.7 million to study the contribution of the placode to Hirschsprung's disease.



David Warburton, DSc, MD

David Warburton, DSc, MD, is the inaugural holder of the Pasadena Guild Chair in Developmental Biology and Regenerative Medicine, funded by a \$3 million endowment from the Pasadena Guild of Children's Hospital Los Angeles. Warburton also received \$1.25 million from the National Institutes of Health and the National Institute for Environmental Health Sciences to continue research on the effects of air pollution on the respiratory health of urban populations in Mongolia.

In the News



A study by Grace Aldrovandi, MD, CM, was reported on in the News and Comments section of Nature. The research examined HIV concentration in breast milk and found that virus concentration spikes when weaning begins. These findings emphasized the importance of taking antiretroviral drugs regularly throughout the breastfeeding and weaning periods.

Grace Aldrovandi, MD, CM

Fox News interviewed Parul Bhatia, MD, about the Baby Sound Check project. The three-year study showed the low cost and high benefit of postnatal hearing tests to identify deficits during children's language acquisition years. This study also determined that beneficial hearing screenings can be completed during routine doctor visits.



Parul Bhatia, MD



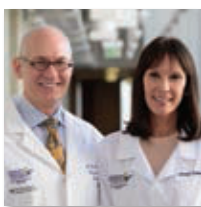
A research study using magnetic resonance spectroscopy revealed biochemical differences in the brains of preterm infants compared to their full-term counterparts. The premature infants showed earlier development of white matter, misaligning the growth with that of grey matter. It is unclear whether or not this difference is harmful. The study, presented by Stefan Bluml, PhD, received nationwide coverage.

Stefan Bluml, PhD

Reuters and other outlets covered the election of Pat Levitt, PhD, to the prestigious Institute of Medicine, part of the National Academy of Sciences. This honor recognizes Levitt's professional achievements in the study of the developing brain and his commitment to advancing the nation's health.



Pat Levitt, PhD



The Saban Research Institute hosted an event highlighting the growth of women in science, technology, engineering and math (STEM) careers. Attendees were invited to interact with female leaders in STEM fields and encouraged to continue on into these rigorous careers. KABC News interviewed Brent Polk, MD, and Cheryl Saban, PhD, about women in STEM.

Brent Polk, MD, and Cheryl Saban, PhD

The Los Angeles Times reported on an endowment from philanthropists Ted and Lori Samuels to fund CHLA's underrepresented minority high school science education program. Led by director Emil Bogenmann, PhD, EdD, the program begins with a summer biological research internship and offers continued guidance that prepares students for college and careers in science and medicine. The program is now named the Samuels Family Latino and African-American High School Internship Program.



Emil Bogenmann, PhD, EdD



Tracy Grikscheit, MD, received national attention for her work on successfully producing tissue-engineered small intestine from human cells, bringing the ability to grow healthy intestine in patients closer to reality. Grikscheit's achievement will help premature infants with congenital problems who need to have part of their intestine removed soon after birth, as well as other children with short-bowel syndrome.

Tracy Grikscheit, MD



Events and Initiatives



Edwin C. Jesudason, MD (left), David Warburton, DSc, MD, and Denise Al-Alam, PhD

The Saban Research Institute Annual Symposium serves as a forum to highlight the exciting strides researchers from Children’s Hospital Los Angeles and around the globe are making in understanding the developmental origins of health and disease. Each year, the theme of the event reflects a research priority area of The Saban Research Institute. In the past, the event served as an opportunity to launch the Institute for the Developing Mind by examining developmental neurogenetics, neuroimaging and behavioral neuroscience. This year’s symposium focused on “Regenerative Medicine and Cellular Therapies: Inventing the Future for Children.” Plans are already being made for the next annual symposium, which will focus on “Metabolism, Immunity, Inflammation and Infection.”



Workshop participants gain experience in partnering with industry.

The Saban Inspire Innovation Program (SIIP) is a unique, combined education and funding program designed to empower researchers to identify broader opportunities by leveraging the translational and commercial potential of their research. Developed in partnership with CHLA’s Center for Innovation at The Saban Research Institute, SIIP seeks to bridge the gap between basic research and the marketplace by offering participants workshops, connections to industry thought leaders and the opportunity for seed funding. Fifteen faculty and five postdoctoral fellows participated in the inaugural program in 2013. Four of the participants were awarded pilot funding for their projects, and others received additional mentoring to improve their chances of future funding.



Programming Committee, MUCMD 2013

The Saban Research Institute hosted the third annual **Meaningful Use of Complex Medical Data (MUCMD) Symposium** in August 2013. Organized by Randall Wetzel, MB, BS, FCCM, FAAP, chairman of the Department of Anesthesiology Critical Care Medicine, MUCMD is a forum that fosters communication between physicians and “big data” experts. By analyzing the continuous output from electronic health records, this interdisciplinary team works to develop innovative solutions that improve patient experiences and outcomes.



Marvin Nelson, MD (left), Rex Moats, PhD, Brent Polk, MD, Elizabeth Garrett, JD, Scott Fraser, PhD, and Carmen Puliafito, MD, MBA

At the November 2013 launch event for the **Translational Biomedical Imaging Lab (TBIL)**, cross-institutional collaboration was highlighted by the attendance of Brent Polk, MD, director of The Saban Research Institute; Elizabeth Garrett, JD, provost of the University of Southern California (USC); and Carmen Puliafito, MD, MBA, dean of the Keck School of Medicine of USC. The trio shared their support for TBIL and its potential to build and strengthen links between the Keck School of Medicine, Children’s Hospital Los Angeles and USC.

“Reaching across campuses, we continue to invest in the intellectual convergence of medicine, chemistry and engineering to improve clinical care for children in our community,” says Garrett. “USC and Children’s Hospital Los Angeles are committed to developing world-class research facilities such as TBIL, which provide flexibility for our faculty to collaborate as they bring interdisciplinary teams together to create solutions to complex health problems.”

New Faces

Kathie Eagleson, PhD, joined the hospital's Department of Pediatrics and the Developmental Neuroscience program at The Saban Research Institute. After earning her doctorate in neuroscience from the University of Sydney in Australia, Eagleson completed postdoctoral fellowships at the University of Southern California (USC) and the Medical College of Pennsylvania. Her research focuses on the development of circuits that modulate social and emotional behavior, and how these circuits adapt in the context of disrupted gene expression associated with various neurodevelopmental disorders, such as autism.

Laura Li, PhD, is now the associate director of Molecular Pathology and Genetics at Children's Hospital Los Angeles. In 2012, she graduated from the Medical Genetics Training Program at the University of California, Los Angeles, and she is Board-certified in clinical molecular genetics. She received her doctorate in molecular biology/genetics from Johns Hopkins University and completed postdoctoral training at the California Institute of Technology. Li's main research interest is bringing personalized medicine to patients using genomic tools to study the molecular mechanisms of genetic diseases and cancer.

David Parham, MD, is chief of Anatomic Pathology at Children's Hospital Los Angeles and professor of Pathology at the Keck School of Medicine of USC. Previously, Parham was the director of Pediatric Pathology at the University of Oklahoma Health Sciences Center, the director of Pediatric Pathology at Arkansas Children's Hospital and an associate member in Pathology at St. Jude Children's Research Hospital. His research interests include pediatric sarcomas, pediatric neoplasms and childhood infections.

Ajay Perumbeti, MD, FAAP, is the director of Transfusion Medicine at Children's Hospital Los Angeles and an assistant professor of Clinical Pathology at the Keck School of Medicine of USC. After a fellowship in the Division of Pediatric Hematology-Oncology at Cincinnati Children's Hospital, he completed a transfusion medicine fellowship at the Hoxworth Blood Center in Cincinnati. Perumbeti's research interests include pediatric transfusion medicine, development of personalized blood/cellular therapeutics and HLA-G in erythropoiesis and pediatric disease.



Kathie Eagleson, PhD



Laura Li, PhD



David Parham, MD



Ajay Perumbeti, MD, FAAP

Skorn Ponrartana, MD, MPH, has joined the hospital's Department of Radiology after two years as a Children's Hospital pediatric radiology fellow. Ponrartana received his master's degree in public health from Johns Hopkins University and his medical degree from the University of California, San Francisco. He then completed an internship in internal medicine and a diagnostic radiology residency at Cedars-Sinai Medical Center. Ponrartana is primarily interested in using magnetic resonance imaging to examine placental morphology and track the development of fetal characteristics through birth and infancy.

Tatiana Tatarinova, PhD, has joined the Division of Research on Children, Youth and Families at The Saban Research Institute. Her research focuses on the development of novel algorithms for efficient analysis of genomic and clinical data. Tatarinova received her doctorate in applied mathematics from USC and has worked at the biotechnology company Ceres, Loyola Marymount University and the Georgia Institute of Technology. Prior to joining Children's Hospital Los Angeles, Tatarinova established the Glamorgan Computational Biology research group (GlamCoBio) at the University of Glamorgan in the United Kingdom.

Hsiao-Huei (Juli) Wu, PhD, joined the hospital's Department of Pediatrics and the Developmental Neuroscience program at The Saban Research Institute. Wu received her doctorate from the Irell and Manella Graduate School at the Beckman Research Institute, City of Hope. She completed postdoctoral training at the University of California, Irvine, and at Vanderbilt University, after which she became a research instructor and assistant director of Vanderbilt's Beta Cell Biology Consortium. Her current research focuses on the role of the MET receptor tyrosine kinase, an autism risk gene, in the development and function of the autonomic nervous system.

Chadi Zeinati, MD, is now director of Interventional Radiology at Children's Hospital Los Angeles. After earning his medical degree from the American University of Beirut, Zeinati moved to Atlanta, where he completed two years of a general surgery residency prior to switching specialties and beginning a fellowship in interventional radiology at Emory University. Zeinati then attended the State University of New York Upstate Medical University, where he completed a residency in diagnostic radiology before joining the faculty of the Division of Interventional Radiology. He is interested in vascular malformations, trauma interventional radiology and interventional oncology.



Skorn Ponrartana, MD, MPH



Tatiana Tatarinova, PhD



Hsiao-Huei (Juli) Wu, PhD



Chadi Zeinati, MD

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We gratefully acknowledge the following donors, who made gifts of \$1,000 and above to Children's Hospital Los Angeles during the last fiscal year. We also extend a special thanks to Cheryl Saban, PhD, and Haim Saban, as well as our many Associate and Affiliate groups for their longstanding support of our investigators at The Saban Research Institute of Children's Hospital Los Angeles. Philanthropic support propels our research forward, bringing us closer to the happier, healthier future that all children deserve.

In spite of our best efforts, errors and omissions may occur. Please inform us of any inaccuracies by contacting Michele Phillips, associate director of Stewardship and Donor Relations, at 323-361-1788 or mphillips@chla.usc.edu. For more information on how you can provide philanthropic support, please contact Tina Johann, associate senior vice president of Development, at 323-361-5675 or tjohann@chla.usc.edu.

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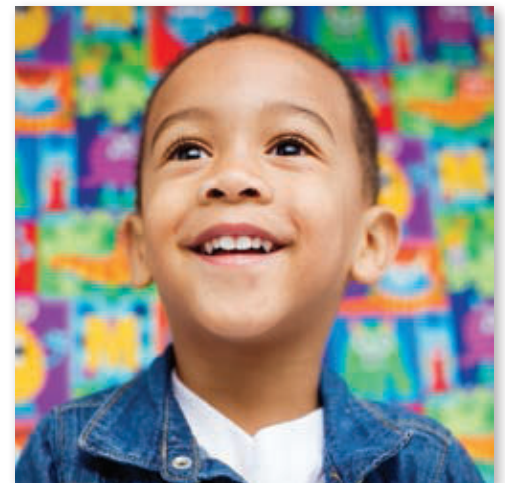
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31%

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\$4,266,024

7%

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\$14,661,861

22%

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\$626,794

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Intramural

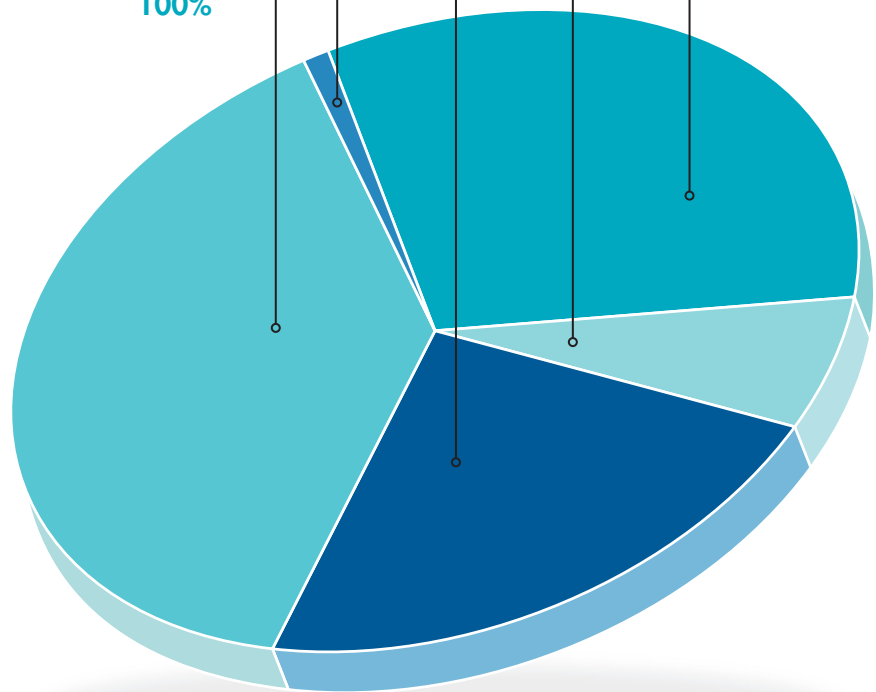
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