

CHILDREN'S HOSPITAL LOS ANGELES

RESEARCHLA

2020

ANYTHING BUT BASIC

Researchers are tapping into basic science as a launchpad for discovery at Children's Hospital Los Angeles.



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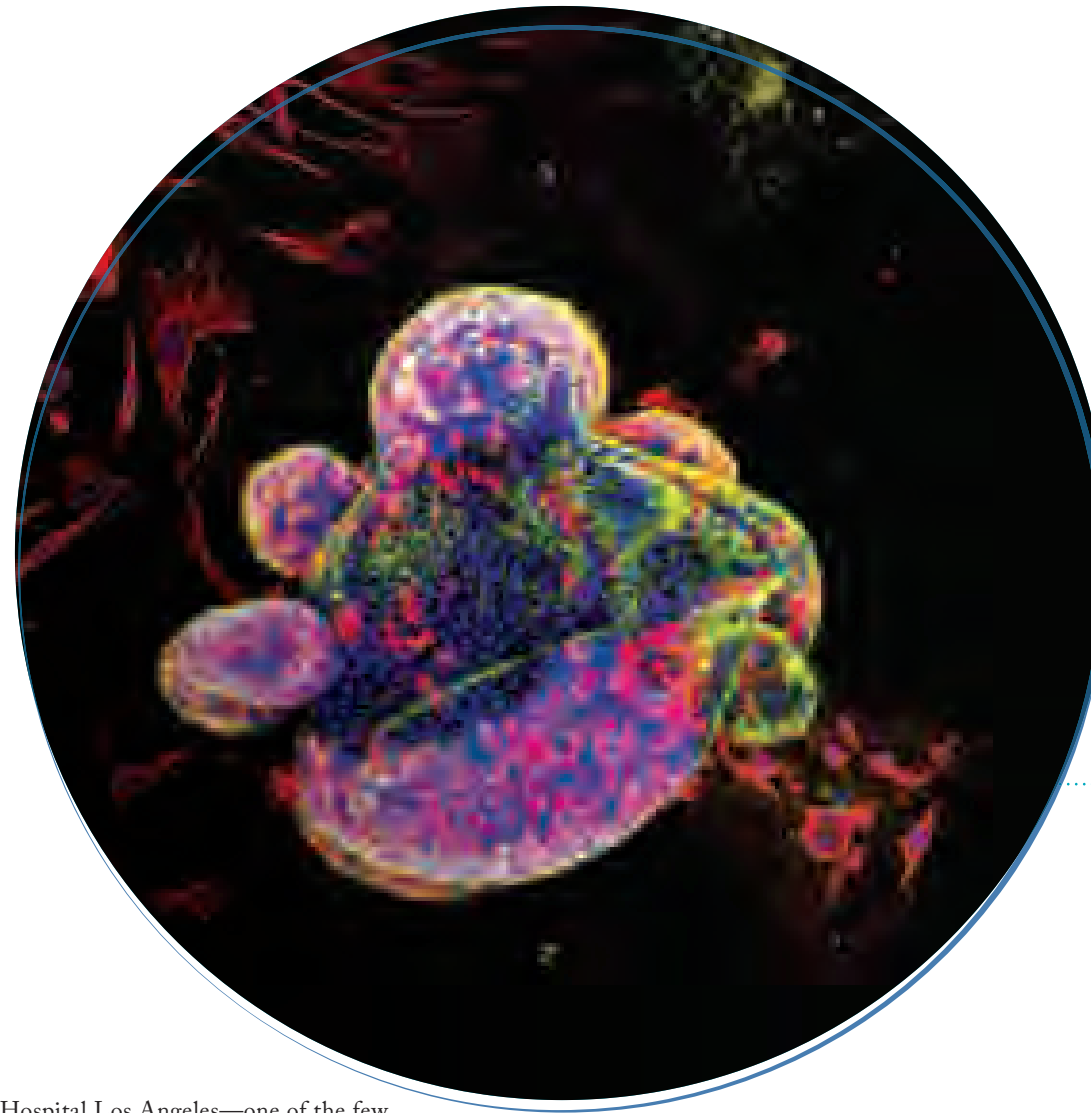
ABOUT THE SABAN RESEARCH INSTITUTE

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

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

Originally established in 1992, the Children's Hospital Research Institute became The Saban Research Institute in 2003 following a transformative gift in support of pediatric research made by Cheryl Saban, PhD, Haim Saban and The Saban Family Foundation. In fiscal year 2019, The Saban Research Institute received \$32.4 million in National Institutes of Health (NIH) funding and \$85 million in total extramural funding. The Saban Research Institute ranks eighth in the nation among children's hospitals for NIH funding.

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



CHILDREN'S HOSPITAL LOS ANGELES
RESEARCHCHLA

A MESSAGE FROM LEADERSHIP
2

IN THE NEWS
6

MENTORING MATTERS
8

DECODING THE EPILEPSY PUZZLE
14

NEW FACES
18

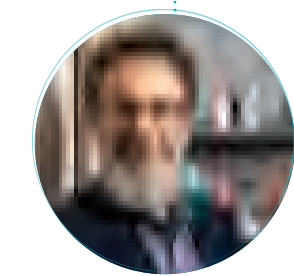
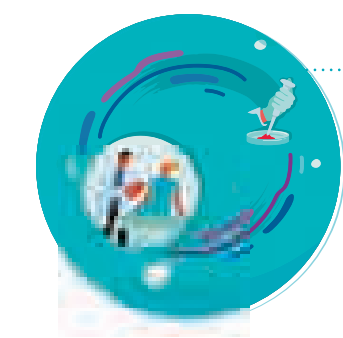


WHAT IS A RESEARCH CORE?
24

ANYTHING BUT BASIC
31

BITTERSWEET
42

AWARDS AND HONORS
46



PAUL S. VIVIANO



At The Saban Research Institute of Children's Hospital Los Angeles, we are driven by a desire to accelerate life-changing discoveries for children. Ranked one of the top five pediatric medical centers in the nation by U.S. News & World Report, we draw upon the expertise and commitment of investigators doing research in the lab, the clinic and the community to achieve this vision. Driven by our objective to translate scientific advances into improved patient care, we recently completed a strategic plan for our research enterprise.

As we begin implementation of the plan, we will strengthen the connections between basic and clinical investigators, encourage a culture that advances research, and provide invaluable infrastructure through core facilities and operational support structures.

To increase opportunities for collaboration while enhancing grant opportunities, we have aligned our diverse enterprise into four inclusive research themes. These themes, illustrated on the next page, are also articulated throughout the stories in this issue of ResearCHLA. Here, you will read about our efforts and successes in the many aspects of research that make a pediatric academic medical center like ours such an important contributor to the futures of children everywhere.

This research takes senior, experienced faculty members devoting themselves to the success of junior researchers through mentorship. It takes investments in core research facilities that can look deep within cells to view their DNA, search for mutations that drive disease and help inform leading-edge, clinical care. It takes an organization that is committed to focused investigation and innovation in basic, translational and clinical research. And it takes strong alignment across a complex enterprise to ensure that the dedication of researchers pays off in new treatments for patients in Los Angeles and throughout the nation.

Because we serve one of the most diverse patient populations in the nation, treatments and insights developed here—emanating from our research enterprise—will build healthier futures for children everywhere.

This important research and subsequent clinical applications could not have progressed without the vision, generosity and support of our donors. Thank you.

We are now at an inspiring moment as we begin inventing the future of pediatric medicine. Please join us on this journey of transformation—for children in Los Angeles, in California and around the world.

Warmest regards,

PAUL S. VIVIANO
President and Chief Executive Officer
Children's Hospital Los Angeles

PAT LEVITT, PhD
Vice President, Chief Scientific Officer and
Director of The Saban Research Institute

Simms/Mann Chair in Developmental
Neurogenetics (CHLA)

W.M. Keck Provost Professor of
Neurogenetics (USC)

THEMATIC AREAS OF RESEARCH

BEST STARTS TO LIFE

Identify early risk factors and interventions, from fetal development to early childhood, to improve the lives of all children

FROM DISCOVERY TO PEDIATRIC CARE INNOVATION

Transform knowledge gleaned from clinical care provided today into the new and innovative approaches of tomorrow

PIONEER DISCOVERIES TO PROMOTE HEALTHY FUTURES FOR ALL CHILDREN

PERSONALIZED PREVENTION AND CARE

Develop an understanding of each patient down to the cellular level to intervene early and effectively for a lifetime

PEDIATRIC DISEASE MODELS AND MECHANISMS

Discover the underlying causes of pediatric disease to drive development of new interventions and cures

One of CHLA's many strengths is the breadth and depth of its research.

To optimize the connections between research and clinical care, enhance opportunities for collaborations and further facilitate funding opportunities, we have aligned our diverse research efforts into these four inclusive research themes.

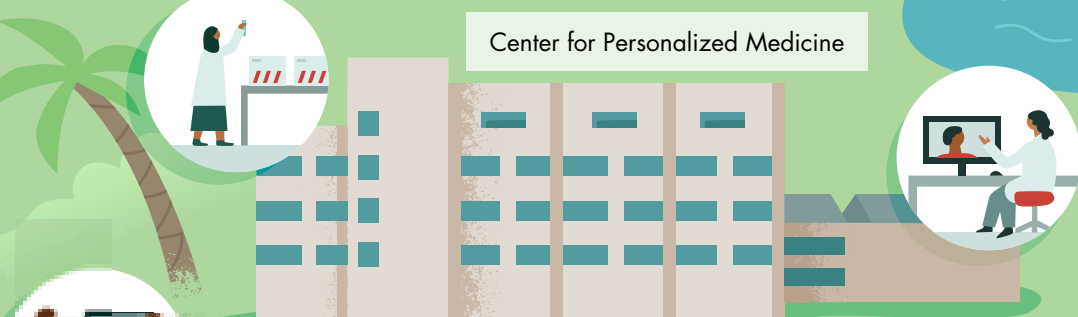
The four research themes encompass the breadth and diversity represented in CHLA's research portfolio. Every research program fits into at least one theme, while researchers in some programs fit into multiple themes. These themes will help the institution focus its recruitment, investment and future growth.

"At Children's Hospital Los Angeles, research is in our DNA."

— Pat Levitt, PhD, Chief Scientific Officer

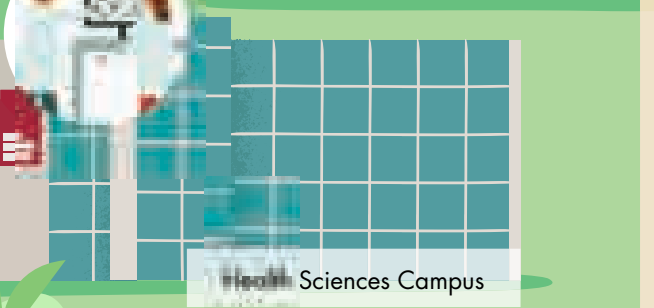
Center for Personalized Medicine

Institute for Creative Technologies



Innovation Studio

USC Information Sciences Institute



University Center for Excellence in Developmental Disabilities

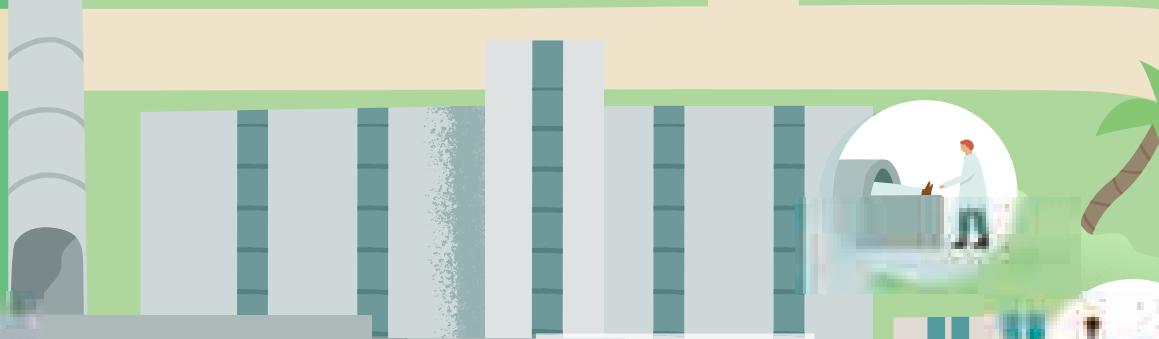
Sciences Campus

Outpatient Tower

Boone Fetter Clinic



Marion and John E. Anderson Pavilion



Mary Duque Building



Adolescent and Young Adult Medicine



University Park Campus



H. Russell and Jeanne R. Smith Research Tower



Gateway Building

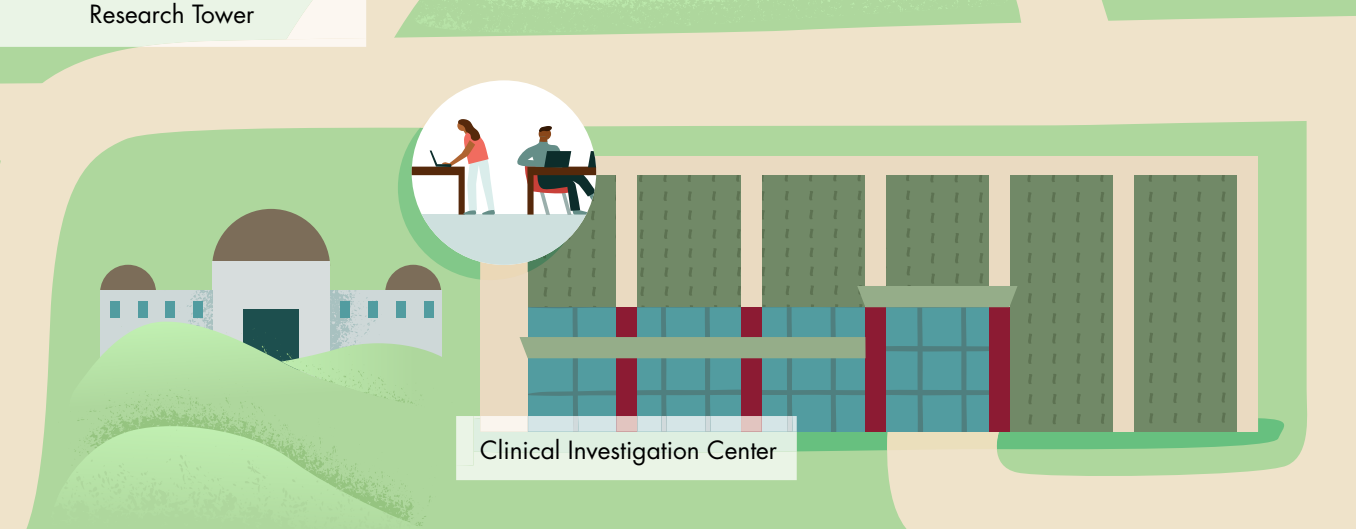


George C. Page Building

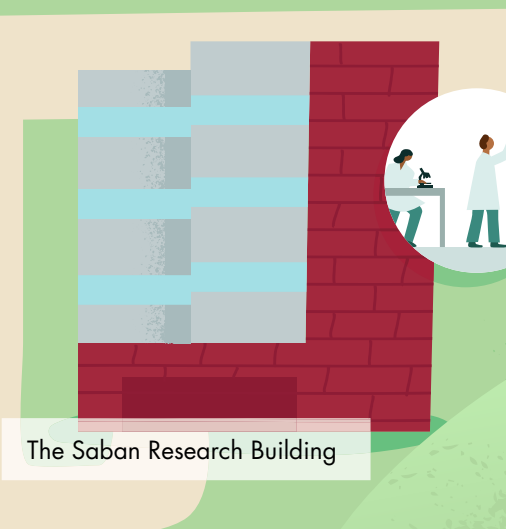
McAlister Building



Research Operations



Clinical Investigation Center



The Saban Research Building

HOLLYWOOD

MORE THAN A BUILDING

Research at Children's Hospital Los Angeles is wide-ranging—from basic and translational science to clinical studies and trials. The Saban Research Institute fosters investigators working at the main hospital campus and across L.A. Check out the many locations where life-changing discoveries are made.



JEFFREY GOLD, PhD

Jeffrey Gold, PhD, was interviewed by The New York Times about his research on the use of virtual reality to mitigate pain in children receiving medical care.

Scientific American and various national news outlets reported on the research findings of Michael Goran, PhD, and clinical observations of Rohit Kohli, MBBS, MS, regarding the increase of fatty liver disease in Latino youth.



MICHAEL GORAN, PhD



ROHIT KOHLI, MBBS, MS



LEO MASCARENHAS, MD, MS



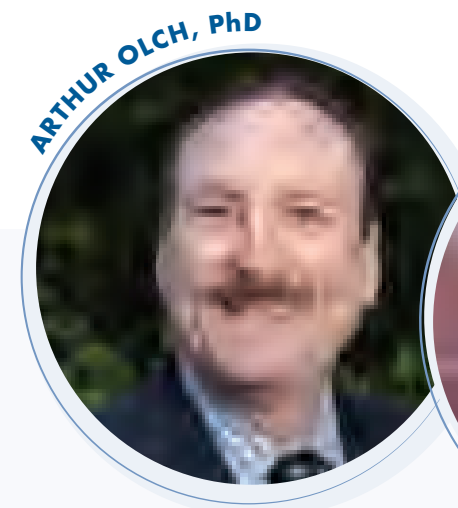
RACHANA SHAH, MD

The Wall Street Journal carried the story, reported on in the 2018 issue of this magazine, of patient Michelle Lowry and her battle against a life-threatening tumor using a targeted cancer therapy called larotrectinib. The treatment was administered as part of a phase 1 trial by Leo Mascarenhas, MD, MS, and Rachana Shah, MD, of the Cancer and Blood Disease Institute.

Aaron Nagiel, MD, PhD, of The Vision Center, was interviewed on ABC's Nightline about his treatment of two patients with an inherited form of vision loss. Using this revolutionary FDA-approved gene therapy, Dr. Nagiel was able to successfully deliver the treatment and significantly improve the vision of his patients.



AARON NAGIEL, MD, PhD



ARTHUR OLCH, PhD



KENNETH WONG, MD

Associated Press reported on research by Arthur Olch, PhD, and Kenneth Wong, MD, about the use of specialized software that could advance treatment accuracy for pediatric cancer patients.

Research conducted by Laura Perin, PhD, Stefano Da Sacco, PhD, and Roger De Filippo, MD, in the GOFARR Laboratory led to development of a new scientific model that was described in Nature Communications. The model, which filters blood just like human kidneys do, represents a significant step forward in kidney disease research. Their work will support a personalized medicine approach to chronic kidney disease and could aid in testing of new drugs prior to clinical use.



LEFT TO RIGHT: ROGER DE FILIPPO, MD; STEFANO DA SACCO, PhD; AND LAURA PERIN, PhD



GUY YOUNG, MD

London's Financial Times quoted Guy Young, MD, on his use of emicizumab to successfully treat children with hemophilia A with factor VIII inhibitors.

TO DEVELOP THE NEXT GENERATION OF SCIENTISTS— MENTORING MATTERS

Guiding early-career investigators to become world-class scientists

By Ellin Kavanagh

Pick up a scientific journal and you'll find articles showing a clear trajectory from hypothesis to conclusion. Missing is the years-long odyssey that the investigator and team have taken to reach their destination and how many individuals contributed along the way.

Those researchers who completed their own journeys are in a unique position to train others. A select few serve as

mentors—earning their name from Mentor, the teacher of Greek lore. They are essential to the success of those who are still finding their way.

Mentors at The Saban Research Institute of Children's Hospital Los Angeles help develop innovative, paradigm-shifting scientists dedicated to accelerating discoveries into leading-edge pediatric care. Fortunately, the institution is home

to many MDs and PhDs who have traveled this path and are dedicated to helping the next generation of researchers access the resources necessary to achieve transformative careers.

RESEARCH TAKES TIME

Much as he'd like to, **Pat Levitt, PhD**, Chief Scientific Officer, Director of The Saban Research Institute and Simms/Mann Chair in Developmental Neurogenetics at CHLA, can't increase the number of hours in a day. But by leveraging time through mentorship, he can make it feel like his time is more abundant.

Dr. Levitt believes that time is a crucial component for successful mentorship. But it's also a resource in short supply for principal investigators like himself, who already manage a burgeoning portfolio of grants, manuscripts and speaking engagements, as well as a full lab with many trainees. "It's about making the effort to truly understand each of your mentee's goals, and that takes dedicated, predictable, one-on-one time," he says.

One of his mentees, **Alexandra Lanjewar, BS**, entered USC's Neuroscience Graduate Program immediately after completing her bachelor's degree, so she did not have a lot of lab experience. The goal of her research project is to define the biological mechanisms regulating neural circuit growth and maturation that leads to the onset of executive function. She needed access to someone who could teach her lab skills. She also needed time to make mistakes and learn from them. "Alexandra has taken full advantage of the available resources," says Dr. Levitt. "She's already a co-author of two research manuscripts in less than two years."

In addition to providing one-on-one time, Dr. Levitt has been able to create more time for trainees to learn and experiment by establishing a culture of mentorship in his lab. The lab is set



up to ensure that an experienced member of the lab is always available to offer instruction on techniques to anyone who needs it.

Dr. Levitt's commitment arises from the belief that mentorship is foundational to conducting research. His longstanding dedication was recognized when he received the USC Mellon Mentoring Award for Postdoctoral Fellows. "In my lab, mentoring is front and center and begins with high school students," he says.

Trainees who are awarded fellowships at CHLA are now asked to become mentors to students in the Samuels Family Latino and African American High School Internship Program—known as LA-HIP. Now in its 14th year, LA-HIP provides hands-on training in laboratory-based research to public high school students preparing for future careers in science. "It's effective in so many ways—the mentee learns to model behavior, to teach techniques and to communicate science," says Dr. Levitt.

Lanjewar agrees. She says that Dr. Levitt is a great mentor, so she tries to follow his lead in working with her own mentee.

"Mentoring an LA-HIP student has helped with my science communications skills," Lanjewar says. "Being able to talk about science in a way that is accessible to people who are early in the process of becoming scientists is really important. Our job also is to convince the public of the need, the larger purpose of our work and how it can be applied to improve people's lives. I'm getting better at it by working with my LA-HIP student."

Now in her third year of a five-year doctoral program, Lanjewar looks forward to taking her place in this continuum of mentorship when she has a lab of her own. From her perspective, the key element is to allow people the time and freedom to make mistakes. "My advice is don't get frustrated. Start again. Just keep working."

"It's about making the effort to truly understand each of your mentee's goals, and that takes dedicated, predictable, one-on-one time."

— Pat Levitt, PhD



MAKE THINGS HAPPEN

John Wood, MD, PhD, breaks things. More from training than temperament, the engineer in him likes to take things apart and put them back together in a new way that allows him to “make things happen.”

“Our work is driven by unsolved clinical problems,” says Dr. Wood, whose lab is focused on the cardiovascular consequences of red blood cell disorders. “We develop robust tools and then ask interesting questions about the basic physiology of disease.” Often the technology Dr. Wood and his team need to study a clinical problem does not yet exist, so he takes available technology and changes it. “I take the ‘toy’ and break it and figure out how to make it fit our current needs,” he says. “I’ve had a lot of luck with doing this—it really appeals to the engineer in me.”

This desire to make things happen is also a vital aspect of Dr. Wood’s approach to mentoring. **Jon Detterich, MD**, a pediatric cardiologist at CHLA, first met Dr. Wood when he was a resident. Dr. Detterich waited until he was a clinical fellow before approaching his potential mentor.

“I wanted to do a prospective study on pulmonary hypertension in patients with sickle cell disease,” says Dr. Detterich.

“John challenged me [to take a different approach]. Since a prospective study is difficult to complete during a three-year fellowship, he worked with me on a separate project that allowed me to explore a complex data set, similar to what I was planning for the prospective project.” Dr. Detterich wrote an abstract about his research for the American Society of Hematology conference. The abstract was accepted and he was offered a travel award so he could attend the meeting and present his work.

“After that success, I started the prospective study, even though I was still a fellow. I learned a lot about research design and planning, methodology, data collection and analysis—in large part due to John’s mentoring.

“I think he was surprised—given the demands of the fellowship program—that I got the study off the ground and started enrolling patients. John says, ‘Ideas are cheap and making things happen is hard.’ Thanks to him, I was able to make something happen.”

Dr. Detterich is continuing to make things happen—he has received several National Institutes of Health grants in support of his research on the biomechanics of red blood cells and vasoconstriction in patients with sickle cell disease.

“Our work is driven by unsolved clinical problems.”

— John Wood, MD, PhD



BIG DREAMS NEED FINANCIAL SUPPORT

Ashwini Lakshmanan, MD, MPH, was encouraged to dream big, yet her current project can be stored in your pocket. Her big dream was to reduce the barriers to care through mobile health by developing a cell phone app. She needed guidance about funding to turn this dream into a reality.

Her mentor, **Michele Kipke, PhD**, has helped guide a lot of scientific careers. From her vantage point as Vice Chair of Research in the Department of Pediatrics and Head of the Division of Research on Children, Youth and Families, she describes the relationship between mentor and mentee as crucial.

“The young scientist needs to figure out where he or she wants to be in their career in five years and start on a path to get there,” says Dr. Kipke. “It’s my job to figure out how to help them reach their goal.”

“When I was figuring out my path, Michele asked me, ‘If you could do anything, what would you do?’” says Dr. Lakshmanan. “She encouraged me to think broad and wide. She also challenged me to consider implementation right from the start.”

As an attending neonatologist in the Fetal and Neonatal Institute, Dr. Lakshmanan was particularly interested in high-risk infants and

“It’s my job to figure out how to help [the mentee] reach their goal.”

— Michele Kipke, PhD

their transition from the hospital to home. Existing follow-up care programs demonstrated improved outcomes and significant cost savings—but their reach was limited. She hypothesized that a way to broaden the scope of these programs was to integrate a free cell phone app, called Baby Steps LA, into discharge planning.

Both mentor and mentee agree on a crucial component of mentoring: guidance around financial support to protect Dr. Lakshmanan’s time so it can be devoted to research. Under Dr. Kipke’s leadership, Dr. Lakshmanan obtained a Southern California Clinical and Translational Science Institute KL2 Career Development Award, and also was able to participate in her mentor’s grant from a private foundation.

“We wouldn’t have been able to develop or pilot-test the app without Michele’s support,” says Dr. Lakshmanan.

Dr. Lakshmanan and the team have spent the past year developing Baby Steps LA, a virtual transition program available in English and Spanish that provides medical information, family resources and access to a moderated online support group. The Baby Steps LA app was recently awarded third place in the national American Hospital Association’s Innovation Challenge.





RECOGNIZE POTENTIAL

Jesse Berry, MD, an ophthalmic surgeon and ocular oncologist, was in the operating room preparing to treat a child with retinoblastoma, a pediatric eye cancer. As she removed a small amount of fluid from the child's eye in preparation for giving chemotherapy, she had an idea. Later when she shared the idea, many people discouraged her from pursuing it. Her mentor wasn't one of them.

Thomas Lee, MD, Director of The Vision Center, knows a thing or two about career development, having recently been honored with the USC Faculty Mentoring Award for paying his expertise forward. From his perspective, the most important part of mentoring is understanding your mentees well enough to recognize their potential and help them realize it.

"Several years ago, I selected Jesse Berry from a number of residents interested in training at CHLA," says Dr. Lee. "Jesse grew up in a rural area and was raised by her grandmother. She went on to Harvard for college and medical school on scholarships. I could tell she knew a lot about risk and making the most of an opportunity."

The opportunity Dr. Lee had in mind for Dr. Berry was research on retinoblastoma.

Retinoblastoma was the first human cancer to have its underlying genetic mutation identified—the Rosetta stone of cancer genetics. Three key physicians made



this discovery—one at Massachusetts General Hospital, one at SickKids in Toronto, and A. Linn Murphree, MD, at CHLA. They had each reached the culmination of their life's work and were nearing retirement.

Dr. Lee spoke to Dr. Berry about the institution's role in retinoblastoma research and about the need for new expertise. "We were losing the key people in the field, and there were no ophthalmologists preparing to step in and fill that gap," says Dr. Lee.

He suggested that if Dr. Berry had any interest in basic science, she should consider this an area where she could make a tremendous impact, both in the field and in patients' lives. At that time, Dr. Berry wanted to focus on surgery and clinical work.

"I spoke to her about it in 2011," says Dr. Lee. "Then again in 2012 and 2013. In 2014, she said to me, 'I have this idea ...' After that conversation, she went on to change the field of retinoblastoma research."

Unlike most tumors, retinoblastoma is unique in that it cannot be biopsied because of the risk of spreading cancer cells outside of the eye. Diagnosis is

"CHLA can grow high-impact scientists. We know we can because we've done it."

— Thomas Lee, MD



made clinically, and the only time that tumor tissue is available is if the eye needs to be removed to stop the spread of disease. For this reason, clinicians are unable to use any tumor-specific genetic information or markers to aid in diagnosis or to inform treatment recommendations or prognosis.


Since 2014, Dr. Berry has been making steady progress on proof-of-concept research for a safe way to gather genetic information about the retinoblastoma tumor. It began that day in the operating room when she paused before discarding the small amount of fluid—called aqueous humor. She found that the fluid contained tumor DNA—allowing it to function as a "liquid biopsy."

Dr. Berry says that her mentor's most significant influence was allowing her to figure things out. "If he had just given me a project, I probably wouldn't have been driven to figure out how to do something so impactful," she says. "Now there's potential that this may one day change the treatment paradigm for retinoblastoma."

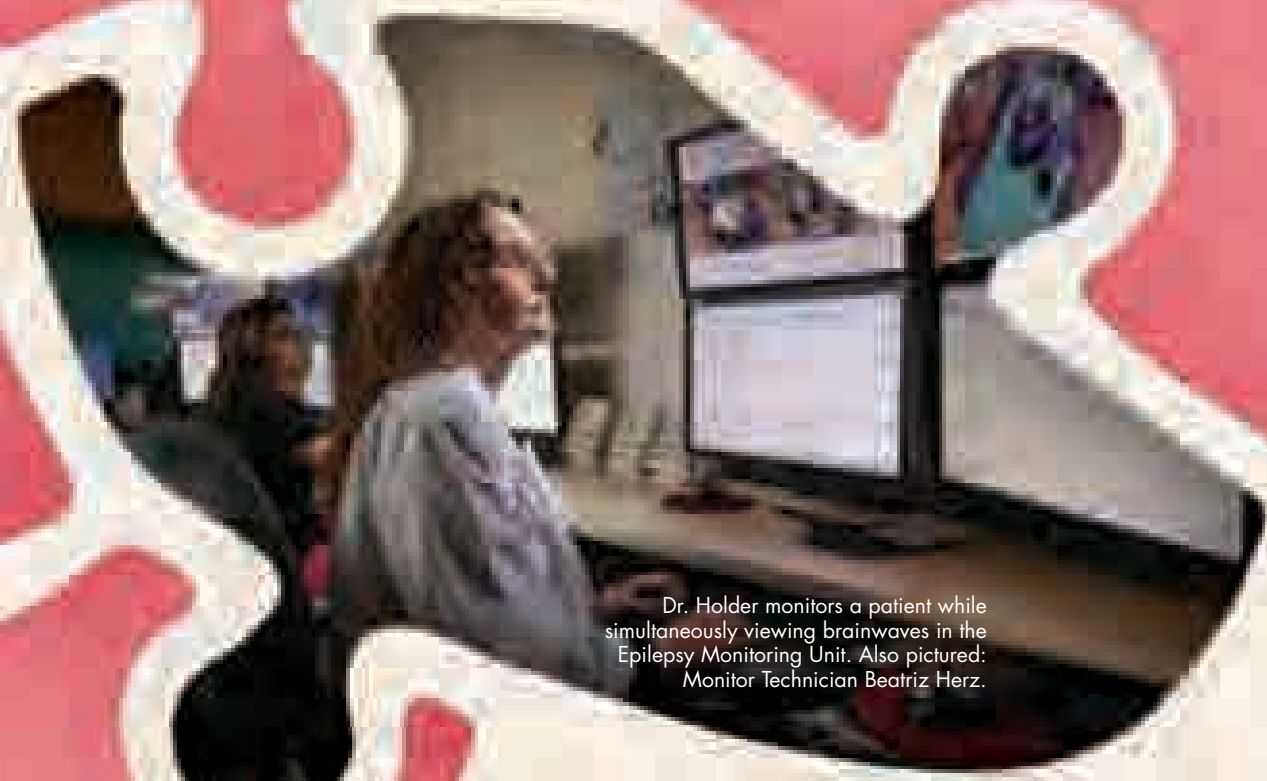
For Dr. Berry, the right environment and Dr. Lee's support and encouragement made all the difference. "He created an atmosphere where it was OK to be wrong," says Dr. Berry. "I might not have mentioned the liquid biopsy idea to him unless I felt like it was OK to make a mistake. Even if he thought it was crazy—and some people did—it would be alright."

The National Cancer Institute recently awarded Dr. Berry \$1.14 million to study the development of an aqueous humor liquid biopsy to more effectively diagnose and treat retinoblastoma.

According to Dr. Lee, the important takeaway is that CHLA can develop world-class scientists. "Dr. Berry started her career here without a scientific

background and has become a thought leader who has created a new field of research. She is proof of concept that CHLA can grow high-impact scientists. We know we can because we've done it." 

DECODING THE EPILEPSY PUZZLE



Dr. Holder monitors a patient while simultaneously viewing brainwaves in the Epilepsy Monitoring Unit. Also pictured: Monitor Technician Beatriz Herz.

Using game-changing genetic testing to develop personalized treatments for kids

By Candace Pearson

It is early Christmas morning, and 7-year-old Gracie and her twin brother, Jonah, are happily opening presents when their parents notice something odd. Gracie's head shakes side-to-side and, for a few moments, she stares off into the distance, as if she has gone somewhere far away.

When her mother, Cynthia, asks Gracie what happened, she says, "Nothing, I was just being silly." Only she wasn't.

Almost immediately, the episodes started happening more often, as Gracie shook and "spaced out" for longer periods of time. "That's when we realized something was really wrong," says Cynthia.

The diagnosis came quickly, and the news was serious. Gracie had epilepsy—and the electrical storms in her brain that came with it. One of the most common neurological conditions, epilepsy affects some 50 million people worldwide; 1 in 26 people in the U.S. will develop epilepsy in their lifetime.

Finding the right treatment would take longer, as the family saw a round of doctors and Gracie started a cycle of medications. Not only did the drugs fail to stem her seizures, "the side effects were astronomical," recalls her father, Geoff.

Gracie—distracted, sobbing—would often hide in her closet. "My brain hurts," she told her parents. Her grades at school slipped and she sometimes lashed out. Then a physician shared with her parents, "I don't think I can help you, but I know someone who can."

That someone was **Deborah Holder, MD**, Director of the Comprehensive Epilepsy Center at Children's Hospital Los Angeles—where a revolution in the treatment of childhood epilepsy is underway, thanks to genetic research.



The Center, part of CHLA's highly regarded Neurological Institute, holds level 4 certification—the highest possible—from the National Association of Epilepsy Centers. Its five pediatric epileptologists are double Board-certified in adult and pediatric neurology, with specialty training in pediatric seizure disorders.

"If you can stop seizures in a child, you can change their whole life."

— Deborah Holder, MD

A CRUCIAL TIME

The multidisciplinary team takes an aggressive approach to treating epilepsy because children's brains are still developing. "This is the time when you learn how to learn," says Dr. Holder. "If you can stop seizures in a child, you change their whole life."

"The brain is very plastic and adaptable in children, which gives us the opportunity to intervene early and make a difference," notes **Mark Krieger, MD**, Surgeon-in-Chief, Senior Vice President, Director of the Neurological Institute and the Billy and Audrey L. Wilder Endowed Chair in Neurosurgery.



The explosion in genetic science is just one of the reasons for the tremendous growth of the Institute, which is ranked in the top 10 in the nation by U.S. News and World Report.

The Institute's guiding principle is a commitment "to ensure all children can achieve their full neurological potential," says Dr. Krieger.

(continued on next page)

By the time the family arrived at CHLA, Gracie was having 60 to 65 seizures a day. About two-thirds of people with epilepsy can control it with medication. Gracie fell into the one-third who are drug-resistant.

The first step: video electroencephalographic monitoring (EEG). At CHLA, children being tested for epilepsy can wear portable battery packs and leave their hospital beds for a special “wired” playroom where their brain waves and seizures are continually monitored.

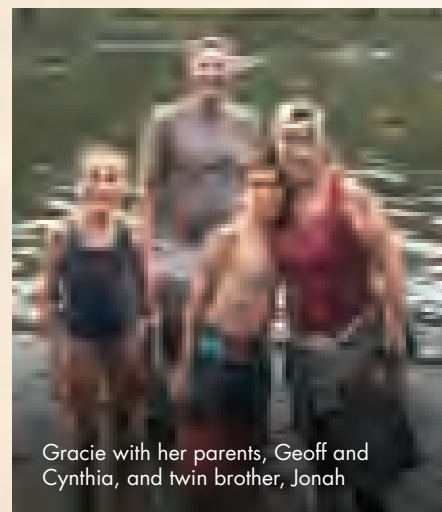
Gracie’s EEG showed an abnormality in her brain and a possible seizure source. The end game, at that point, was brain surgery. But before taking that route, Dr. Holder decided to delve into Gracie’s genes.

This involved collaborating with the Center for Personalized Medicine (CPM) for high-level genetic testing. The CPM rapidly initiated testing to analyze Gracie’s DNA with a panel of nearly 200 genes discovered through research to be associated with epilepsy.

The disease is complex in part because it has many potential causes—including prenatal injury, infection, head trauma, brain tumors and developmental disorders—but in up to 70% of cases, the cause is unknown. Dr. Holder thinks most, if not all of those, have a genetic basis.

CHANGING THE OUTCOME

Testing can tell the doctors a great deal, including which medicine may work and which won’t. “Genetics is a game changer,”



Gracie with her parents, Geoff and Cynthia, and twin brother, Jonah



Dr. Holder discusses EEG activity with her team, pictured behind her, left to right: Justine Camarco, Tanya Gidish, Mari Lemus, Beatriz Herz and Mike Pena.

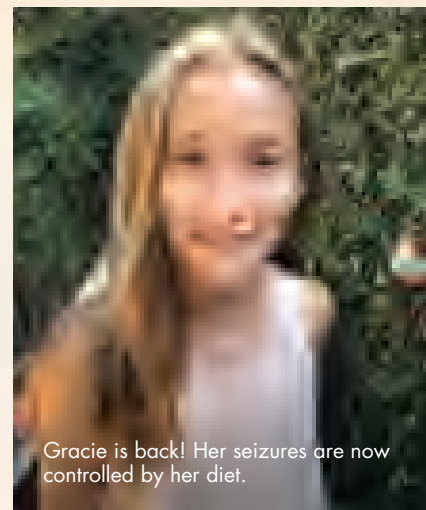
says Dr. Holder. “It is transforming how we care for our patients. Instead of treating based on EEG or seizure type, whenever possible we treat based on genetics, allowing us to personalize the care.”

So far, the Comprehensive Epilepsy Center has diagnosed hundreds of children like Gracie using an epilepsy genetic panel developed at the CPM. In Gracie’s case, DNA told the story. She had a genetic condition called glucose transporter type 1 deficiency (GLUT1), in which sugar can’t get from the blood to the brain. Her brain essentially was starving for energy.

More testing revealed that her dad had the same gene mutation. While he never developed epilepsy, he had coped with lifelong migraines. (Gracie’s twin, Jonah, does not have the disorder.)

There is no cure. Fortunately, for some people with GLUT1, a strict ketogenic (high-fat, very low-carbohydrate) diet will help control symptoms. Putting babies on the keto diet can eliminate the disease, says Dr. Holder. Under the guidance of a CHLA dietitian, Gracie began a restricted diet of 30 grams of carbohydrates per day. Within days, her seizures dropped by 90%. Adhering to a more severe 20 grams of carbs a day brought even fewer seizures.

The diet isn’t easy to follow, especially for a 12-year-old. Gracie wants to be like her friends, who can eat cookies, chips and birthday cake. Cynthia is always on the hunt for new ketogenic recipes, and she’s gone on the diet with Gracie.



Gracie is back! Her seizures are now controlled by her diet.

“We were so close to having brain surgery on our daughter,” says Geoff. “This may be hard, but it’s so much better.”

Research will find the answer for the treatment of GLUT1. The ultimate goal is to fix the abnormality with gene replacement. Gracie may still need surgery someday. For now, her diet is her primary medicine, and the treatment is lifelong.

Best of all, Gracie is smiling again. She lost her brain fog and her grades shot up. “It makes a big difference in school,” says Gracie, “and in being with my friends.” She has returned to playing soccer. And she can enjoy reading without constantly losing her place because of seizures.

“It’s like the real Gracie woke up,” says her mother, “and came back to us.”

A NEW STANDARD OF CARE

Inside the Center for Personalized Medicine (CPM) at Children’s Hospital Los Angeles, the mission is clear: capitalize on sophisticated genetic information to develop personalized solutions for sick kids, based on their DNA. Forty percent of patients have an underlying genetic cause for epilepsy. For these patients, genetic testing can often reveal the best approach for treatment.

“Genetic testing is rapidly becoming the standard of care,” says **Jaclyn Biegel, PhD, FACMG**, Chief of the Division of Genomic Medicine and Director of CHLA’s Center for Personalized Medicine.

She and her colleagues at the CPM had debilitating diseases like epilepsy in their sights as they and their collaborators brought together a powerful triumvirate of genetic sequencing, bioinformatics, and clinical and diagnostic expertise.

“We wanted to build a comprehensive foundation and approach to genetic testing,” says Dr. Biegel of the 4-year-old Center.

That foundation includes whole-exome sequencing, where laboratory scientists analyze the protein-coding sections of DNA contained in genes; this is where the majority of DNA changes that may cause a genetic disorder are found. The revolution in next-generation sequencing enables the sequencing of thousands to millions of DNA molecules simultaneously. Ten years ago, scientists had to decode one gene at a time.

This leading-edge technology enables genetic scientists to capture and analyze all the known genes that may be responsible for a condition like epilepsy. Genetic testing is not as simple as one gene or gene variation and one disease, notes Dr. Biegel.

Two people with the same genetic variation in the same family can be affected in dramatically different ways—from a mild set of symptoms to severe effects. One gene can play a role in multiple disorders, or multiple genes may contribute to one condition. “One of the major trends we’re seeing is a focus on polygenic conditions, caused by the combined activities of more than one gene,” she says.

That complexity adds to the urgency for scientists to identify which mutation (or combination) is most influential in every case.

The genetics of epilepsy are constantly changing. Every month, research links another gene or variation to the disease. Dr. Biegel says, “We use these tools and evolving data to find new ways to treat each individual child.”

DR. BIEGEL IN HER LABORATORY. ALSO PICTURED: YUXIA ZHAN AND CINDY FONG.

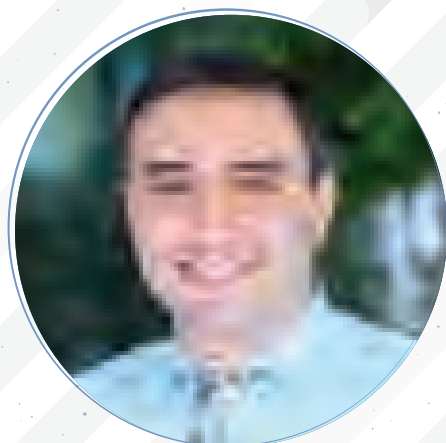


1 IN 26
AMERICANS
DEVELOP EPILEPSY



25,000 – 45,000
KIDS EXPERIENCE A
SEIZURE EVERY YEAR

CHECK OUT THE NEWEST FACES IN RESEARCH AT CHLA



OUSSAMA ABOUSAMRA
Children's Orthopaedic Center

Oussama Abousamra, MD, joined the Children's Orthopaedic Center. He earned his doctorate from the University of Damascus in Syria before completing three fellowships in pediatric orthopaedic surgery at Nationwide Children's Hospital in Ohio, Nemours/Alfred I. duPont Hospital for Children in Delaware, and Johns Hopkins University in Maryland. Dr. Abousamra's clinical and research expertise is in the areas of pediatric neuromuscular and gait disorders, skeletal dysplasia and pediatric limb deformity reconstruction.



JAMES AMATRUDA
Cancer and Blood Disease Institute

James Amatruda, MD, PhD, joined the Cancer and Blood Disease Institute as Endowed Chair of Sarcoma Research and Director of the Alfred E. Mann Family Foundation Zebrafish Facility. He earned his medical degree and doctorate of philosophy in cell biology through the Medical Scientist Training Program at Washington University School of Medicine in St. Louis. Dr. Amatruda's primary research and clinical focus is on pediatric solid tumors; his lab developed zebrafish models of genetic subtypes of pediatric solid tumors to help identify and validate novel therapies.



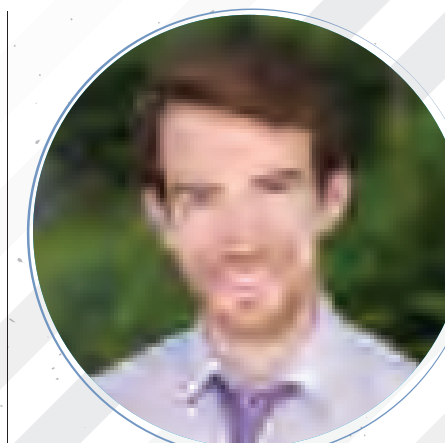
BETH A. CARTER
Division of Gastroenterology, Hepatology and Nutrition

Beth A. Carter, MD, joined the Division of Gastroenterology, Hepatology and Nutrition as Medical Director of Liver Transplant and Intestinal Rehabilitation. She provides leadership for the multidisciplinary liver transplant and TPN (total parenteral nutrition) programs. Her research focuses on pediatric liver disease and novel therapeutics for short bowel syndrome patients who are dependent on home TPN. Dr. Carter came to Children's Hospital Los Angeles from Texas Children's Hospital in Houston.



MALLORY CHAVANNES
Division of Gastroenterology, Hepatology and Nutrition

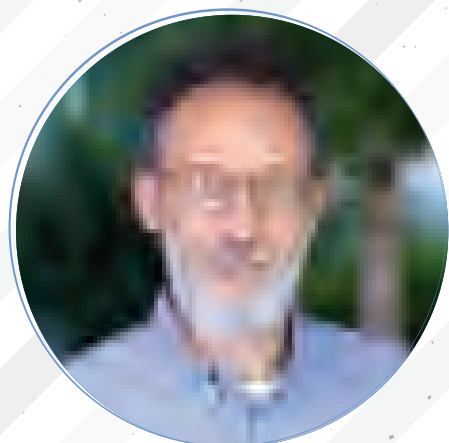
Mallory Chavannes, MD, MHSc, joined the Division of Gastroenterology, Hepatology and Nutrition as an attending physician. She earned her doctorate from McGill University in Montreal and completed an advanced fellowship in inflammatory bowel disease (IBD) at the University of British Columbia. Dr. Chavannes' research focuses on evaluating IBD therapies and finding noninvasive ways of monitoring disease activity in children with IBD.



CHRISTOPHER DENTON
Cancer and Blood Disease Institute

Christopher Denton, MD, joined the Cancer and Blood Disease Institute as an attending physician specializing in hematological disorders. A recipient of the Hoag Foundation Fellowship Training Grant, his research concentrates on the effect of alpha-globin gene expression on small-vessel blood flow. He earned his doctorate from Oregon Health & Science University before completing his pediatric residency at Seattle Children's Hospital and his hematology-oncology fellowship at Children's Hospital Los Angeles.

(continued on next page)

**MICHAEL GORAN**

Center for Endocrinology, Diabetes and Metabolism

Michael Goran, PhD, joined the Center for Endocrinology, Diabetes and Metabolism as Director of the Diabetes and Obesity Program. He previously served as Director of the USC Childhood Obesity Research Center. Dr. Goran's research is focused on dietary treatment of fatty liver disease in the Hispanic pediatric population. He also is investigating how breast milk composition impacts development of the infant gut microbiome as well as weight gain and cognitive outcomes in the first years of life.

**MARCO A. HIDALGO**

*Division of Adolescent and Young Adult Medicine
Center for Transyouth Health and Development*

Marco A. Hidalgo, PhD, joined the Division of Adolescent and Young Adult Medicine and the Center for Transyouth Health and Development, where he conducts psychotherapy and research. He came from Lurie Children's Hospital of Chicago, where he co-established the nationally renowned Gender and Sex Development Program for transgender/gender-expansive youth and their families. Dr. Hidalgo's National Institutes of Health-funded research focuses on identity development and mental health among transgender and gender-nonconforming youth, as well as HIV prevention among sexual and gender minority adolescents.

**KENNETH ILLINGWORTH**

Children's Orthopaedic Center

Kenneth Illingworth, MD, joined the Children's Orthopaedic Center as a pediatric spine surgeon and Director of the Orthopaedic Trauma Program. He earned his doctorate from the University of Tennessee and completed his advanced training in pediatrics and pediatric spinal deformity at Children's Hospital Los Angeles. Dr. Illingworth specializes in pediatric spinal deformities and has a special interest in pediatric skeletal trauma in patients who have reached or are near skeletal maturity.

**TANIA MITSINIKOS**

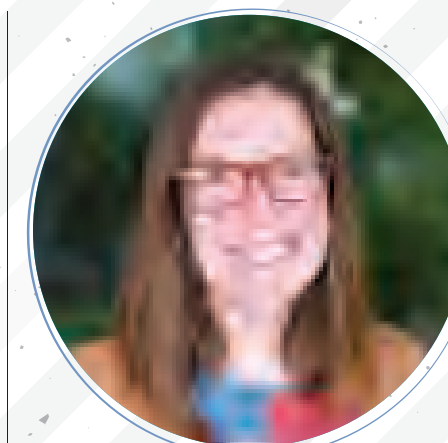
Division of Gastroenterology, Hepatology and Nutrition

Tania Mitsinikos, MD, joined the Division of Gastroenterology, Hepatology and Nutrition. She earned her doctorate at the Keck School of Medicine of USC before completing her internship, residency and fellowship at Children's Hospital Los Angeles. As Medical Director of the Fatty Liver Clinic, she helps coordinate multidisciplinary research and care for patients with obesity-related nonalcoholic fatty liver disease (NAFLD). Dr. Mitsinikos' research involves identifying noninvasive biomarkers for children with NAFLD and using nutritional interventions to improve and potentially reverse the disease.

**BABAK MOGHIMI**

Cancer and Blood Disease Institute

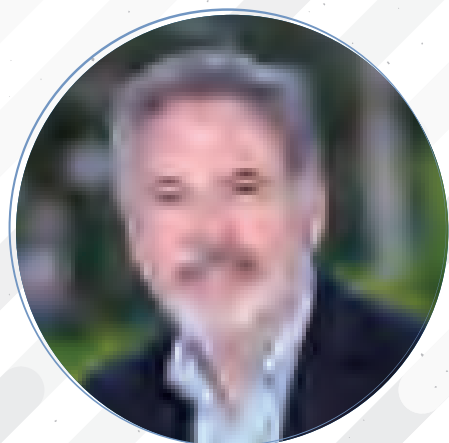
Babak Moghimi, MD, joined the Cancer and Blood Disease Institute after completing his second year of an advanced fellowship in blood and marrow transplantation and immunotherapy at Children's Hospital Los Angeles. He earned his doctorate at Tehran University of Medical Sciences in Iran, followed by postdoctoral training in cell therapy and a clinical residency in pediatrics at the University of Florida, and a pediatric hematology-oncology fellowship at Children's Hospital of Philadelphia. Dr. Moghimi conducts leading-edge research in the field of chimeric antigen receptor (CAR) T-cell therapy for neuroblastoma and other childhood cancers.

**DIANA MOKE**

Cancer and Blood Disease Institute

Diana Moke, MD, MS, joined the Cancer and Blood Disease Institute after conducting a third year of research as a recipient of the National Cancer Institute Ruth L. Kirschstein National Research Service Award Institutional Research Training Grant. She earned her doctorate from the Warren Alpert Medical School at Brown University and conducted her internship and residency training in internal medicine/pediatrics at the University of California, San Diego, before completing her hematology-oncology fellowship training at Children's Hospital Los Angeles. In her research, Dr. Moke is examining survival trends and related outcomes of adolescents and young adults with cancer.

(continued on next page)

**BRUCE R. PAWEL**

Department of Pathology and Laboratory Medicine

Bruce R. Pawel, MD, joined the Department of Pathology and Laboratory Medicine as Division Chief of Anatomic Pathology. He has 35 years of clinical, academic and research experience, including the last two decades at Children's Hospital of Philadelphia, where he most recently served as Pathology Director of the Center for Childhood Cancer Research Biorepository. Dr. Pawel is an internationally renowned expert on the pathology of sarcomas, neuroblastoma and other solid tumors, and his research focuses on identifying potential targets for treating these cancers in children.

**JOSE PINEDA**

Division of Critical Care Medicine

Jose Pineda, MD, MSCI, joined Children's Hospital Los Angeles as Chief of the Division of Critical Care Medicine. He previously served as an Associate Professor of Pediatrics and Neurology at Washington University in St. Louis, Missouri, and as Director of the Neurocritical Care Program at St. Louis Children's Hospital. Internationally recognized for his research in pediatric neurocritical care, Dr. Pineda is committed to improving treatment and outcomes for children with traumatic brain injuries.

**CAITLIN SAYEGH**

*Division of General Pediatrics
Division of Adolescent and Young Adult Medicine*

Caitlin Sayegh, PhD, joined the divisions of General Pediatrics and Adolescent and Young Adult Medicine as a psychologist specializing in treating adolescents. She earned her doctorate in clinical psychology at the USC Dana and David Dornsife College of Letters, Arts and Sciences before completing her postdoctoral fellowship at Children's Hospital Los Angeles. Dr. Sayegh's research focuses on psychotherapy change processes and mobile health interventions to improve medication adherence among youth with chronic medical conditions.

**SARANYA VELUSWAMY**

Cancer and Blood Disease Institute

Saranya Veluswamy, MD, joined the Cancer and Blood Disease Institute as an attending physician after completing her third year of hematology-oncology training as a recipient of the Hoag Foundation Fellowship Training Grant. She earned her doctorate from the The Tamil Nadu Dr.M.G.R. Medical University in India. Her research focuses on the relationship between blood flow, pain and nervous system regulation in children with sickle cell disease.

**ALAINA VIDMAR**

Center for Endocrinology, Diabetes and Metabolism

Alaina Vidmar, MD, joined the Center for Endocrinology, Diabetes and Metabolism after completing her fellowship in pediatric endocrinology at Children's Hospital Los Angeles. She did her medical training and completed her residency in pediatrics at Children's Hospital of Wisconsin. Dr. Vidmar is investigating the clinical and cost efficacy of mobile health interventions compared with traditional multidisciplinary in-clinic models for pediatric obesity management.

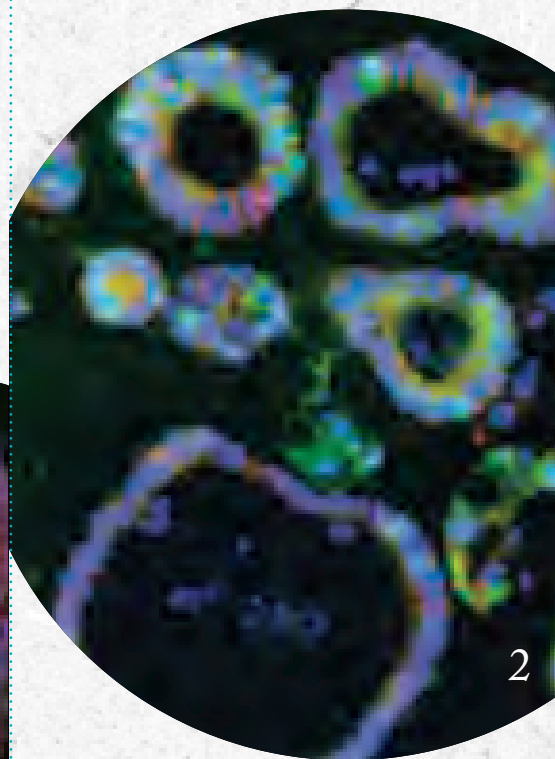
**RONGFU WANG**

Cancer and Blood Disease Institute

Rongfu Wang, PhD, joined the Cancer and Blood Disease Institute as Co-Leader of the Tumor Microenvironment Program and Director of the Cell Immunotherapy Program. He holds the Endowed Chair in Cell Therapy Research at CHLA. Dr. Wang earned his doctorate from the University of Georgia and most recently served as Director of the Center for Inflammation and Epigenetics at Houston Methodist Research Institute. His research interests include cancer antigen discovery, cancer immunotherapy, innate immune signaling and epigenetic reprogramming.

WHAT IS A RESEARCH CORE?

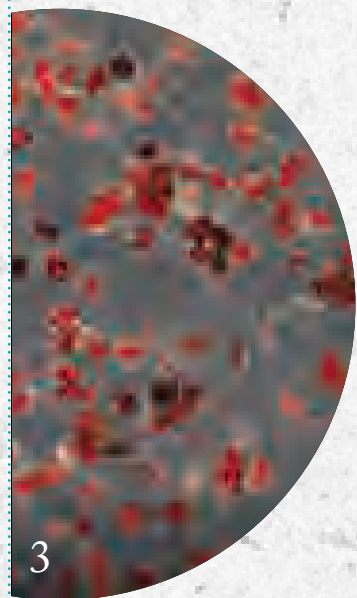
By Melinda Smith, PhD



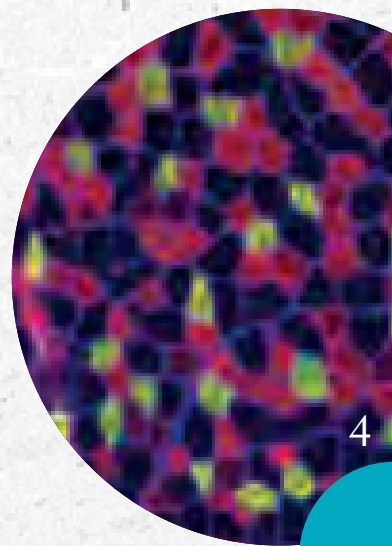
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Look inside to learn more about our research cores

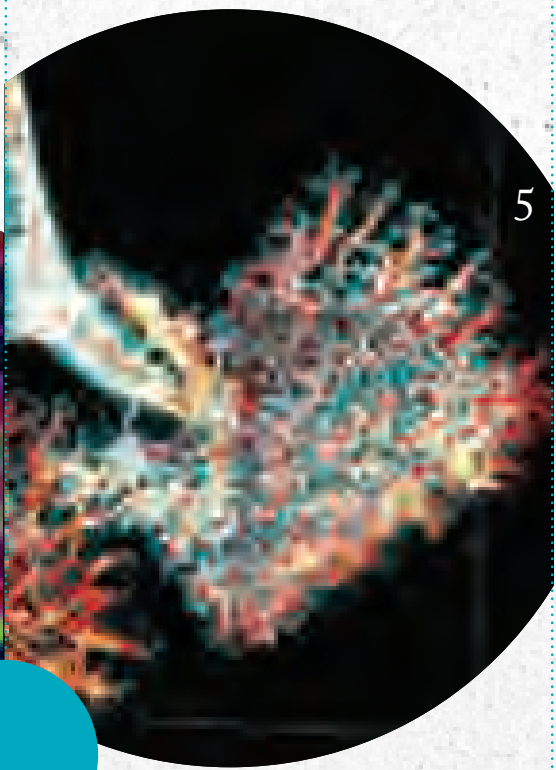
No scientist is an island. Research thrives on collaboration. Investigators depend on each other to share ideas, equipment and expertise. That's where The Saban Research Institute's cores come in. Not only do core facilities have the latest, most advanced technology, but they are also run by experts who help scientists plan and execute their experiments. Scientists turn to the cores for images, data analysis and much more.



3

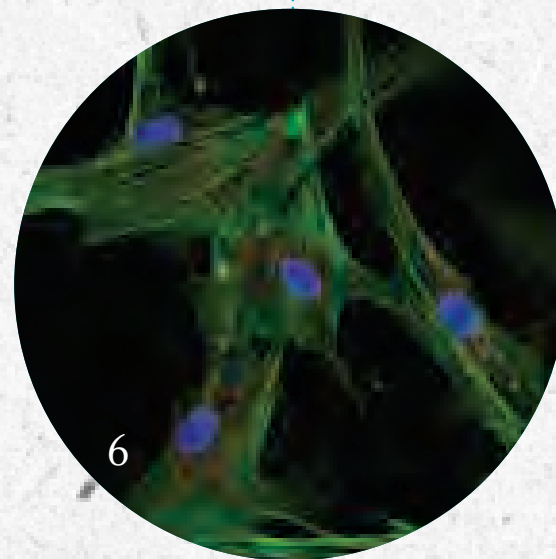


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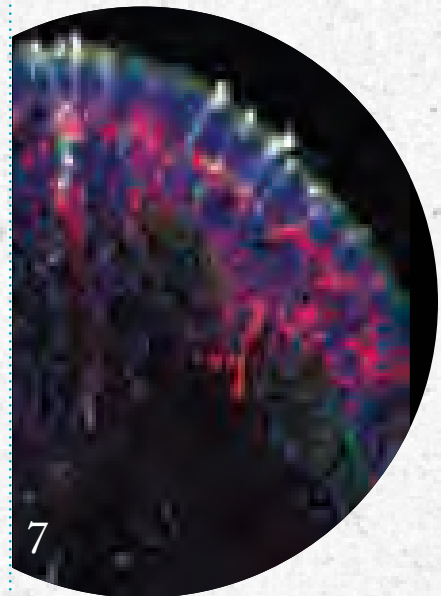


5

1. **Zebrafish heart**
Michael Harrison, PhD
Ellen Lien's lab
2. **Intestinal cells**
Xiaogang Hou, PhD
Tracy Grikscheit's lab



6



7

3. **Differentiating cells**
Laurence Sarte, PhD
Yves DeClerck's lab
4. **Muscle tissue**
Omar Cortez
Lily Chao's lab
5. **Lung tissue**
Soula Danopoulos, PhD
Denise Al Alam's lab
6. **Stem cells**
G. Esteban Fernandez, PhD
Cellular Imaging Core
7. **Mini-retina**
Sumitha Bharathan, PhD
Aaron Nagiel's lab

(continued on next page)

A SINGLE CELL, MANY ANSWERS

SHAHAB ASGHARZADEH, MD



JEFFREY BENDER, MD

If barcoding individual cells and attaching heavy metals to antibodies sounds like science fiction, then you haven't visited the Single Cell Sequencing Core at Children's Hospital Los Angeles. Here, it's part of a typical workday for Co-Directors Shahab Asgharzadeh, MD, and Jeffrey Bender, MD.

"The vision of the Core is to bring the latest research technologies together to really focus on single cells," says Dr. Asgharzadeh. "We want to know what is happening in each one and use this information to fuel discovery."

Acquiring information from single cells is like having a higher-resolution image. This allows clinicians to take a personalized approach to medicine. For example, given a tumor sample, the Core can get information about tens of thousands of cells—one cell at a time. This allows investigators to identify clusters of cell types within a tumor that could respond to specific, targeted treatments. It's also possible to test a patient's blood sample to predict how the patient will respond to certain therapies.

The Core also helps researchers advance their discovery science. Remember those heavy metal antibodies? They are used in

a technique that allows investigators to examine up to 40 different proteins in a single cell simultaneously. This means a higher resolution of data, which could lead to more rapid discoveries. But the Core is more than the sum of its technology.

"We are not just a place to send samples," says Dr. Bender. "We pride ourselves on supporting the researchers throughout the process—from planning experiments, to getting answers, to sharing results with the rest of the world."

"We want to know what is happening in each cell and use this information to fuel discovery."

— Shahab Asgharzadeh, MD

G. ESTEBAN FERNANDEZ, PhD



LASER-FOCUSED PASSION

"I love microscopy. It was my passion long before it was my job."

— G. Esteban Fernandez, PhD

What do you get when you cross lasers, powerful microscopes and an enthusiastic, highly trained imaging scientist? You get the Cellular Imaging Core.

G. Esteban Fernandez, PhD, is CHLA's resident imaging guru. As Director of the Core, he delights in helping investigators capture the perfect research image, even if they don't know exactly what they want. In addition to securing images for investigators, Dr. Fernandez also trains them to acquire their own images. And he has a passion for it. "I love microscopy," he says. "It was my passion long before it was my job. Even my kids know I don't just come to work. I come to play."

This may be true, but make no mistake, Dr. Fernandez takes imaging seriously. He speaks with pride of the many ways his core facility can deliver the stunning images CHLA investigators have come to expect.

"We have so many ways to capture data," he says. "Our confocal microscopes take 3D images. We also do live imaging—taking pictures over time as cells move and grow."

Dr. Fernandez may offer researchers many options, but only one promise: If you have a sample, he will find the best way to image it.

The old adage about a picture being worth 1,000 words may be true, but in Dr. Fernandez's case, it should be amended. Words just aren't adequate for describing his images. ✨

"Mini-gut" by Safina Gadeock, PhD, a postdoctoral researcher in the lab of Brent Polk, MD. Dr. Gadeock's image, featuring cells from the large intestine, won the inaugural Cellular Imaging Core Image Contest.



MEET MICHELLE.

Michelle came to the Children's Hospital Los Angeles Emergency Department on a Friday morning. Her doctors were afraid she might not live through the weekend because she had an aggressive tumor on her neck that was growing so rapidly, it threatened to block her ability to breathe.

Thanks to a pediatric cancer panel called OncoKids®, developed at CHLA, and participation in a national clinical trial, Michelle received treatment that shrank her tumor dramatically—and she went home within days. That was two years ago. Today, Michelle is cancer-free.

Innovative, lifesaving research requires brilliant ideas, time to develop those ideas and funding.

Will you support the next lifesaving therapy and save kids like Michelle?

Donate today at [CHLA.org/FundResearch](https://www.chla.org/fundresearch)



From discovery science to clinical studies, research at Children's Hospital Los Angeles is —

ANYTHING BUT BASIC

By Melinda Smith, PhD

On the surface, the term basic science isn't exactly compelling. But investigators at The Saban Research Institute of Children's Hospital Los Angeles couldn't be more excited about basic or "discovery" science. Each level of biomedical research—basic, translational and clinical—plays a crucial role in the development of lifesaving treatments. Researchers at CHLA are doing all three types of research, while changing the way scientists think about discovery altogether.

Instead of thinking of science as a one-way street that proceeds from basic to translational to clinical research, investigators at The Saban Research Institute think of it as a loop. The pipeline does not end at the child's bedside, because each scientific discovery comes with the opportunity to do even better. This close tie between scientific investigation and clinical practice accelerates life-changing discoveries. Ideas for new research studies, even those at the basic level, stem from a clinical need—a need our researchers see every day.

This unique relationship between clinical care and research fosters investigators who are driven to discover and are informed by an intimate understanding of the greatest unmet needs in pediatric medicine. In other words, the kids shape the research.

CHLA investigators are influencing the future of patient care in unexpected ways. Here, meet a medical doctor who learned the importance and beauty of benchwork; a nurse who studies brain scans to give children better lives; an investigator who takes a discovery approach to clinical management of at-risk babies; a laboratory director helping more families get the answers they seek; and a scientist whose drive to understand pediatric cancer is in her bones.

Their paths to discovery are anything but a straight line, and they are most certainly anything but basic.



(continued on next page)



“Babies need answers now.”

— Jessica Wisnowski, PhD

THE SCIENTIST AND THE 24-HOUR COUNTDOWN

An investigator looks deep inside the infant brain to improve outcomes for babies who have suffered ischemic brain injury.

The phone rings. There was a difficult birth. A critically ill newborn infant is being transported to Children’s Hospital Los Angeles for neuroprotective therapy.

Jessica Wisnowski, PhD, is an investigator in the Department of Radiology and Division of Neonatology at CHLA. She works to develop therapies for newborns with hypoxic ischemic injury—brain damage caused by lack of oxygen at or around the time of birth. Many babies suffering this injury do not survive, or they develop severe neurological conditions like cerebral palsy. Dr. Wisnowski and her colleagues in the Steven & Alexandra Cohen Foundation Newborn and Infant Critical Care Unit have implemented a hypothermia treatment to prevent brain damage—lowering a baby’s body temperature from 98.6 F to 92.3 F—and it works.

The use of cooling, which is now the standard of care at CHLA, has nearly doubled the chance of a healthy outcome. But there is more work to do. Dr. Wisnowski’s line of research investigates why cooling works and how that knowledge can be used to make it work even better.

“Cooling is just the beginning,” she explains. “There are more than two dozen new therapies for brain injury, and we are working on getting the next generation of therapies into the neonatal intensive care unit.”

But she has to work fast. Her urgency is driven by two needs.

“Brain cells—neurons—don’t die when they’re injured; they die later,” she says. “There’s a 24-hour period after injury before the brain crosses a point of no return. This offers a window of opportunity.”

But then there is her other battle with time. The one that is less immediate but just as critical. The one that she wages to bring treatments to babies more swiftly. As it is now, clinical trials can take almost a decade due to all the planning and analysis they require.

“We need to identify which therapies are working, and we need to identify them earlier and faster,” she says. “Babies need answers now.”



Fortunately, her current research may soon deliver these answers. Using magnetic resonance imaging (MRI), Dr. Wisnowski maps out what biological processes are happening in the brain and precisely when they are happening.

To get answers, scientists need to have an appropriate marker that tracks how brain cells respond to lack of oxygen over time. Using a biomarker like this is common in clinical practice. In a patient who has suffered heart damage, doctors can measure blood levels of a protein that acts as a proxy for how extensive the injury is. Ideally, a marker for brain damage could tell clinicians which brain cells are at risk before they die.

Dr. Wisnowski’s team has identified candidate biomarkers that could do just that. These markers are measured using MRI brain scans during and after hypothermia therapy. This, she hopes, will reduce the time it takes to get critical answers. The National Institutes of Health has awarded Dr. Wisnowski \$725,000 to study these biomarkers.

“Working at CHLA affords us an incredible opportunity,” she says. “Here we have the ability to study these questions and immediately implement what works.”

Dr. Wisnowski is not battle-shy. She will keep fighting the clock. “To get to the forefront of medicine,” she says, “we need to ask, ‘Why is this therapy working? What is driving it?’ We want to work out the whys and hows. And soon, those will become the next we can do.”

LOWERING A BABY’S
BODY TEMPERATURE FROM

98.6 F



92.3 F

CAN PREVENT
BRAIN DAMAGE

THE MICROBIOLOGIST AND THE NEXT GENERATION

This laboratory director is reshaping patient care by revolutionizing diagnostics.

She has never met your child, but she might be able to tell you the genetic makeup of the virus that is making him sick.

Jennifer Dien Bard, PhD, is board-certified in medical microbiology and the Director of the Clinical Microbiology and Virology Laboratory at CHLA. From a patient perspective, she functions behind the scenes. But she leads a team that gets the results clinicians depend upon to make that patient's diagnosis.

Dr. Dien Bard's lab in the Department of Pathology and Laboratory Medicine functions 24 hours a day and has dozens of different diagnostic assays. Most clinical testing for CHLA patients can be conducted on-site.

In addition to running this facility, Dr. Dien Bard is interested in understanding the clinical impact of new testing technologies. "We want kids getting the right treatments sooner, we want to reduce their length of stay in the hospital, and we want their outcomes to be better," she says.

Our understanding of the genome—the entire library of an organism's genes—has changed the face of research and how clinicians treat patients. Genomes have been decoded for many organisms—not only humans, but also infectious agents such as viruses and bacteria. This gives scientists a template for diagnosing infections.

Recently, Dr. Dien Bard collaborated with colleagues to evaluate the use of metagenomic next-generation sequencing, or mNGS, in clinical settings. This advanced technology was

developed for research and was adapted quickly to compare a patient's sample, which includes genetic information from the infection, to a database of hundreds of known sequences of pathogens.

The ability to quickly test for hundreds of possible infections ultimately translates to faster diagnosis and treatment. In the past, this identification could take weeks, and each round meant more waiting for families to get answers. Today, it is a matter of a few days.

Dr. Dien Bard and her team are currently pursuing the development of new NGS assays at CHLA to detect pathogens that cannot be recovered by conventional methods. Her research findings show that molecular testing is not only quicker, but it can often reveal infections that would otherwise have been missed.

"Findings from these broad-spectrum molecular assays are promising and improving patient diagnosis and management," she says. "More families are getting answers and they're getting them faster."

Clinical laboratories like Dr. Dien Bard's play a crucial role in health care. They also represent an important bridge between discovery science and clinical research. "These technologies are the product of basic science," she explains. "My goal is to evaluate them with clinical research trials and determine how they can translate into better care for our patients."



15,000

SAMPLES ARE PROCESSED BY THE CLINICAL MICROBIOLOGY AND VIROLOGY LABORATORY EACH MONTH



"We want kids getting the right treatments sooner, we want to reduce their length of stay in the hospital, and we want their outcomes to be better."

—Jennifer Dien Bard, PhD

THE CLINICIAN IMPROVING HEALTH FROM THE LABORATORY BENCH

How one clinician-scientist tackles liver disease from multiple directions



“Here in the lab—this is where it all starts.”

—Rohit Kohli, MBBS, MS

It’s difficult to imagine that Rohit Kohli, MBBS, MS, came into research almost by accident. He went to medical school in India to learn how to help children. But it was in a basic science laboratory where he found the tools to do even more.

After medical school, Dr. Kohli moved to the United States, where he volunteered in a neonatology laboratory before beginning his career in pediatrics. What was supposed to be a brief research experience turned into an epiphany that altered his career trajectory. The work involved basic research into retinopathy of prematurity, a disease that causes blindness in babies—a disease Dr. Kohli had seen in his clinical training.

“Maybe it wouldn’t have been such a distinct moment of truth if I had been exposed to research first. But I came from the clinic, where I spent time caring for kids with this very disease,” he says. “It really hit me. We can find a fix for these things!”

This was the turning point. Dr. Kohli became invested in research and gained an appreciation for addressing medical concerns from a discovery science perspective.

Flash forward to nearly two decades later, when Dr. Kohli—now CHLA’s Chief of the Division of Gastroenterology, Hepatology and Nutrition and the Associates Chair in Liver and Intestinal Research—has published dozens of peer-reviewed scientific articles. His work integrates multiple levels of research to address pediatric health. “My work comes from a clinical need,” he says, “but it starts in the lab.”

This current clinical need is a condition known as fatty liver disease, a complication of obesity. When the body accumulates too much fat, some of it begins to collect in the liver, resulting in nonalcoholic fatty liver disease (NAFLD). Nearly 1 in 10 children in the United States have this condition,

and given the rise of obesity in American youth, the number is likely to increase. The more severe form of fatty liver, called NASH (nonalcoholic steatohepatitis), produces scar tissue and can lead to cirrhosis or liver cancer.

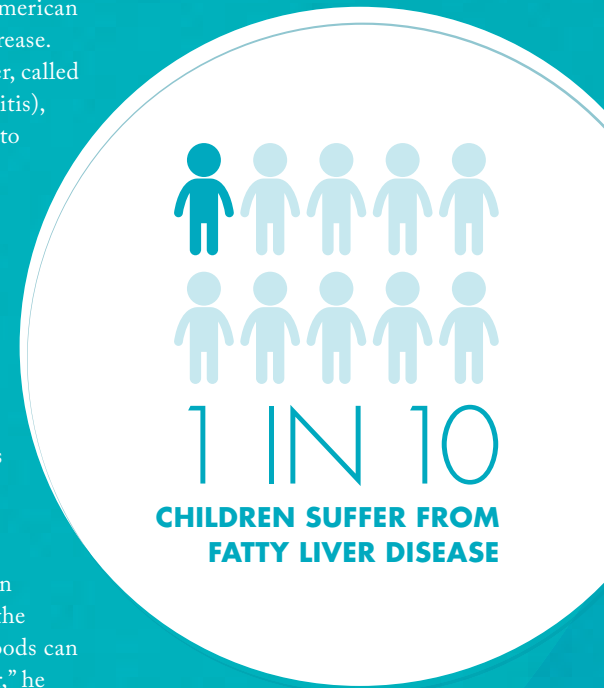
Dr. Kohli researches the mechanisms of fatty liver disease while also working to change outcomes of patients at a clinical level. His research is geared toward understanding cellular mechanisms that result in weight loss. This could lead to treatments or even prevention of NAFLD and NASH.

His research also has shed light on the negative effects sugar has on the liver. “Fructose found in sugary foods can actually cause scarring in the liver,” he says. Not only do findings like these help shape his research, but they also inform his patient interactions.

“It’s not easy to make changes,” he says. “We are wired to eat. I try to start with simple steps, like encouraging patients to reduce sugary drinks.”

Based upon his laboratory findings, Dr. Kohli will soon begin a clinical trial to examine potential benefits of natural sugar substitutes. He will continue to study pediatric disease from many perspectives, but his epiphany about basic research still drives him. “Here in the lab,” he says, “this is where it all starts.”

Read more about nonalcoholic fatty liver disease on page 43.



When your patient's brain cancer goes into remission, it's a turning point. But it's only part of the journey for nurses like **Mary Baron Nelson, PhD, RN, CPNP**.

A nurse practitioner for much of her career, Dr. Baron Nelson cared for many pediatric patients with neurological disorders and brain tumors. She then worked with many of these children in the clinic as survivors.

After noticing a pattern in the long-term health of these patients, she realized there was more work to do. So she went back to school, earned a PhD and began looking for answers. The cure wasn't the only objective.

THE NURSE LOOKING BEYOND THE CURE

After years of caring for patients, this nurse got an advanced degree to do the research that will change their lives.

"I was seeing kids who I had known since they were really tiny, who had gone through cancer therapy," she says. "They were cured of their disease, but they grew up to have lives that were not necessarily of the quality that their parents would have hoped for."

Dr. Baron Nelson is referring to a wide spectrum of cognitive disabilities that can affect children who have undergone chemotherapy or radiation for the treatment of brain tumors. These children don't necessarily lose skills that they've already gained, but they may have trouble learning new skills. She wanted to know why, but there was little research on the effects of cancer treatments on healthy brain tissue. So, she began the research herself.

She had many questions. Does having a brain tumor itself cause certain delays? Or do chemo and radiation therapies cause different types of irreversible damage? Is there a critical time in development during which children are most vulnerable to these treatments?

"Of course, we can't change treatment markedly because we don't want to interfere with their cure," she explains, "but if we know what is happening neurologically and when, we can start to think about interventions to prevent long-term effects."

Dr. Baron Nelson examined brain imaging data from patients after treatment. She observed damage to parts of the brain far from the tumor site. Some of these areas—such as the hippocampus and the thalamus—are directly involved in learning new skills and processing information. This could explain some of the deficits Dr. Baron Nelson and others observed in children after cancer treatment.

Her current study examines the effects of cancer treatment on the trajectory of brain growth by comparing brain



"If we know what is happening neurologically and when, we can start to think about interventions to prevent long-term effects."

—Mary Baron Nelson, PhD, RN, CPNP

images from children before and after tumor removal operations, after cancer treatments, and at one-, two- and four-year visits after treatment. This data set will give clinicians an unprecedented look at how therapies affect the developing brain.

"This will help us understand when any cognitive effects start to occur," she says.

The study's findings could shape the way patients are treated outside of their cancer therapies. Because children are missing months or even a year of school

during critical periods of development, Dr. Baron Nelson suggests that there could be a focus on educational activities between treatments, during times when children feel well.

This hypothesis-driven research is the spirit of outside-of-the-box basic science. It embodies what CHLA is all about—conducting research that not only saves lives but can also alter the trajectory of health, producing benefits that last a lifetime.

> 11,000
SCHOOL-AGE KIDS
ARE DIAGNOSED WITH
CANCER EACH YEAR

THE DOCTOR WHO FIGHTS FOR THE LAST 10%

This investigator is looking to improve outcomes for drug-resistant leukemia using discovery science.

Why would a scientist study a disease that most children beat? If you ask **Yong-Mi Kim, MD, PhD**, she'll tell you that it's because most is not good enough.

Acute lymphoblastic leukemia (ALL) is one of the most treatable childhood cancers. Thanks to advances in science and medicine, most pediatric patients are cancer-free for the long term. Of the roughly 3,000 children who will be diagnosed with ALL this year, nearly 2,700 of them will be cured. What drives Dr. Kim are the remaining 300.

This subset of patients with ALL—about 10%—don't respond to current



CHILDREN DIAGNOSED WITH ACUTE LYMPHOBLASTIC LEUKEMIA THIS YEAR



“Without basic science we would not have the tools and knowledge to study, understand and cure diseases.”

—Yong-Mi Kim, MD, PhD

treatments. Her research is aimed at uncovering potential new treatment targets. She also believes that newer treatments could reduce drug-resistance side effects and toxicity for the majority of children who do respond to therapy.

“With ALL, we have two problems,” says Dr. Kim. “We need to find a way to cure all children. But we also need to help these children survive better.”

She says we are not out of the woods once a child is in remission. Leukemia treatments are highly toxic, and many survivors suffer from late-term side effects.

A clinician-scientist in the Cancer and Blood Disease Institute, Dr. Kim has taken a discovery science approach to ALL. Paradoxically, she studies ALL by not focusing on the cancer. Instead, she studies its microenvironment—the area immediately surrounding the cancer cells. ALL is a type of cancer that affects blood cells, but Dr. Kim’s work is buried deep inside the bones.

“Relapse typically occurs in the bone marrow,” she explains. “Here, the tissue provides a safe environment that shields cancer cells from the chemotherapy.” Research has shown that cells in the bone, called marrow stromal cells, are

responsible for shielding the cancer, but scientists still don’t know how they do it.

One major area of study in Dr. Kim’s laboratory involves proteins called integrins. Found on the surfaces of cells, integrins act like glue to fix cells in certain spots. Her laboratory discovered that one of these proteins, integrin alpha 4, anchors leukemia cells in the bone marrow. This allows the cancer to hide in a safe haven and resist treatment.

Dr. Kim’s current research focuses on other adhesion molecules that likely work with integrin alpha 4 to aid cancer cells. The development of newer therapies depends on findings like these that provide critical targets for translational and pharmaceutical research.

Questions begin with basic research that provides initial answers, even long before medications or treatments are developed. “This takes time,” she concedes, “and it may seem far away from clinical research and applications. But the truth is, without basic science we would not have the tools and knowledge to study, understand and cure diseases.”



Dr. Goran in front of a cabinet full of beverages he uses to show the sugar content of popular drinks

There's a simple reason why kids love sugar so much, says Michael Goran, PhD. They were literally born that way.

"It's protective," he explains. "It was designed to encourage consumption of breast milk, which is sweet, and prevent the eating of poisonous berries from the forest floor."

Today, though, that evolutionary advantage has been turned upside down. Most children don't frequent forests, let alone crawl around in one. Instead of bitter berries, the threat to their health is deceptively sweet: sugar.

"Sugar is everywhere. We're basically being bombarded," says Dr. Goran, Program Director for Diabetes and Obesity at The Saban Research Institute of Children's Hospital Los Angeles. "The types of sugars we're consuming are also different than in past generations. It's a perfect storm."

That storm may be hitting children the hardest. In their research at CHLA, Dr. Goran and his team are finding that excess sugars can disrupt a child's growth and development, including cognitive development.

And those disruptions can start early in life—even before a baby is born.

CRITICAL WINDOWS

Not all sugars are created equal. One type is particularly troublesome: fructose.

Unlike other sugars, fructose is metabolized entirely in the liver, where it's converted to fat. Give the body too much fructose, and over time that fat can build up in the liver and even lead to nonalcoholic fatty liver disease—a life-threatening condition. Other times, extra fat is pushed back into the bloodstream, where it can wreak havoc on metabolism.

"The problem is not so much the calories," says Dr. Goran. "Fructose is just not as well-regulated in the body."

BITTER SWEET

How the tastiest of treats—sugar—may be wreaking havoc on children's growth and development, as early as in the womb

By Katie Sweeney

(continued on next page)

Sweet Stats

Amount of sugar consumed in one year

1 cube = 2 pounds of sugar

200 YEARS AGO

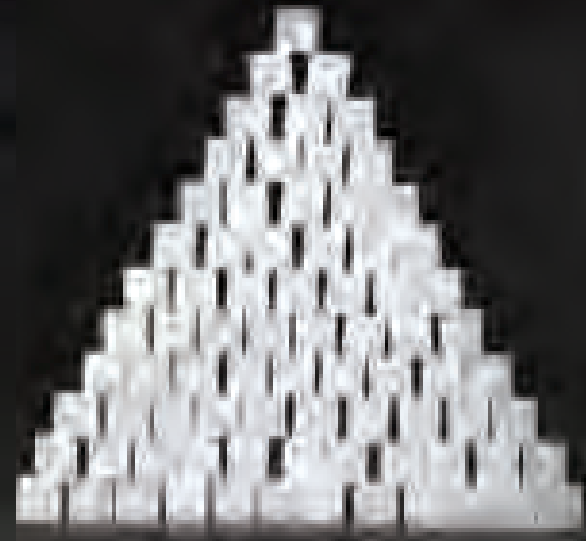
TODAY

WATER

APPLE JUICE

SODA

ICE BLENDED COFFEE



0g

32g

65g

38g

And yet, it's found in abundance in processed foods—everything from cereal to bread to yogurt—and in beverages like sodas and fruit juices. Often, it takes the form of high-fructose corn syrup or “fruit sugar.”

Fructose is found in fruit, too. But when you eat an apple, the amount of fructose is too small to do any harm. Each glass of apple juice, meanwhile, delivers a much more concentrated dose.

“It's the higher doses and rapid consumption in liquid form that become problematic,” Dr. Goran says.

He and his team have already identified sugar-sweetened beverages as the main nutritional factor explaining obesity in 2-year-olds and diabetes in teens. Now evidence is also mounting that sugar impacts the developing brain.

“Several studies have found that maternal consumption of sugars or artificial

sweeteners during pregnancy contributes to disruptions in a child's cognitive development, including lowering of memory,” he adds. “The same goes for sugar consumption in infancy and early childhood.”

In addition, Dr. Goran's collaborators at USC found that high fructose consumption caused memory problems and brain inflammation in rats—but only when fructose was consumed during adolescence. Most alarming of all: Even after switching to a normal diet, the rats' brain damage was irreversible.

“What we're learning is that sugars may have an effect during critical windows of development,” he says. “That's another part of the perfect storm.”

SECONDHAND SUGARS

One of those critical windows Dr. Goran is studying is early life. Currently, his team is following 200 babies and their moms from birth to age 2 in a clinical study called “Mother's Milk.”

Researchers conduct detailed surveys on what moms and babies are eating and drinking. They also collect breast milk and stool samples. The goal: See how early nutrition affects the development of a baby's microbiome (healthy gut bacteria), as well as body fat composition and cognitive health, by age 2.

The group is looking not only at a baby's direct intake of sugar, but also a phenomenon Dr. Goran has coined “secondhand sugars.”

The team has found that when moms drink a large sugary beverage, some of the fructose from that drink is transmitted into their breast milk—where it can remain for up to five hours. In other words, many babies are getting their first taste of fructose, which is not part of the usual sugars in breast milk, when they're just days old.

The group's newest study, called Sweet PEA, is tracing the effects of

secondhand sugars back even further, to early pregnancy. Researchers are examining how nutrition during pregnancy impacts infant growth and development, including a baby's body fat and brain structure.

Investigators are paying particular attention to pregnant moms' consumption of sugars and low-calorie sweeteners. And yes, artificial sweeteners appear to be just as damaging as sugar—if not more so.

“Evidence shows that consuming sugars in pregnancy contributes to obesity development in newborns. But when pregnant women consume diet sodas, the effect may be more pronounced and at an earlier age,” Dr. Goran notes. “We're trying to verify those findings and, most importantly, understand why this happens.”

Both studies are also focused on the potential protective power of

breastfeeding. In earlier research, Dr. Goran's team found that breastfeeding for longer than 12 months “obliterated” the obesity risk from sugar-sweetened beverages.

“We know that breastfeeding can be protective, but we don't really know why,” he adds. “The idea is to identify specific components in breast milk that protect the baby.”

FINDING A BALANCE

A father of two teenagers, Dr. Goran understands that eliminating all sugar is unrealistic—and probably not necessary.

“You don't have to be the parent who puts out celery sticks from the Easter Bunny,” he says. “It's important to find a balance.”

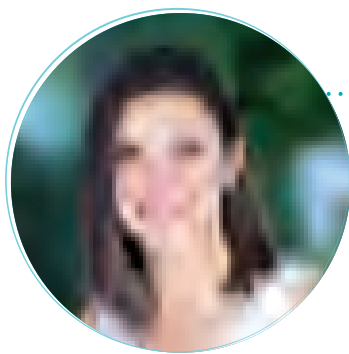
His advice to families? Keep sugars out of the house as much as possible, reserve sweets for special treats, avoid sugary beverages (including fruit juices) and

reduce processed foods. For pregnant women, he recommends limiting sugars and avoiding “fake sugars” altogether.

Educating parents is a key part of his efforts. His team's research includes an intervention program designed to get new moms off of sugar and avoid introducing it to their children during the first two years of life. Dr. Goran is the author of a forthcoming book called “Sugarproof,” which aims to spread the word about the dangers of too much sugar during childhood and provide families with strategies to reduce it from their diet.

“We need to translate our scientific data into practical tools and information,” he says. “We're doing all this research, but it won't have much impact until we get major shifts in diet in the population. That's what I want to see.”

Read more about nonalcoholic fatty liver disease on page 36.



DENISE AL ALAM

Denise Al Alam, PhD, was recognized by the National Heart, Lung, and Blood Institute—part of the National Institutes of Health (NIH)—and the American Thoracic Society as an investigator who exemplifies the future of the field. Dr. Al Alam was honored for her innovative research of childhood lung diseases such as pulmonary hypoplasia and bronchopulmonary dysplasia.



JESSE BERRY

The NIH's National Cancer Institute has granted **Jesse Berry, MD**, \$1.14 million to develop a safe method of biopsy for retinoblastoma. Unlike most cancers, traditional tumor biopsy in retinoblastoma is prohibited, as it can spread tumor cells outside the eye. Dr. Berry's work shows that tumor-specific genetic markers can be found in fluid removed from the front of the eye prior to administering localized chemotherapy. This biofluid can be used as a "surrogate" or liquid biopsy for retinoblastoma. (See page 12 to read more about Dr. Berry's research.)

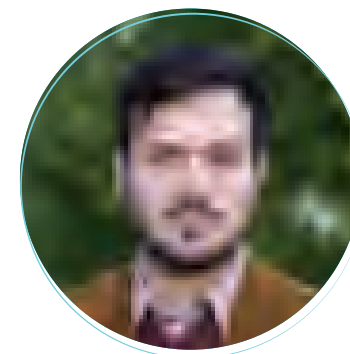
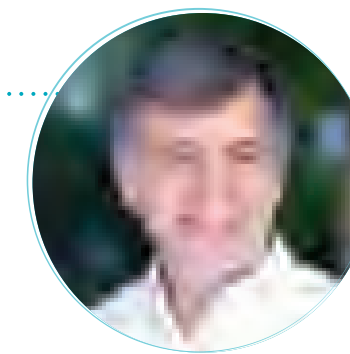


TODD P. CHANG

The Maurice Marciano Family Foundation Emergency Department and Trauma Center has been named a Pediatric Emergency Care Applied Research Network site, the first federally funded pediatric emergency medicine research network in the United States. Children's Hospital Los Angeles is one of only 18 hospitals to receive this designation. **Todd P. Chang, MD, MAcM**, is the site principal investigator on this multiyear infrastructure grant, which provides immediate access to federally funded studies for acutely ill or injured children at CHLA.

DAVID COBRINIK

The NIH's National Cancer Institute awarded \$1.7 million to **David Cobrinik, MD, PhD**. Dr. Cobrinik is studying how mutations in the RB1 gene cause cone cells in the retina to proliferate and form retinoblastoma tumors in children.



JUAN ESPINOZA

CHLA's West Coast Consortium for Technology and Innovation in Pediatrics (CTIP), a pediatric medical device accelerator, was awarded \$6.6 million from the Food and Drug Administration. One of CTIP's projects, led by **Juan Espinoza, MD, FAAP**, is a real-time, prospective data platform that collects clinical data, device data and patient-reported outcomes for pediatric patients with type 1 diabetes. This data platform will then be used for clinical, research and regulatory activities.

MARK FREY

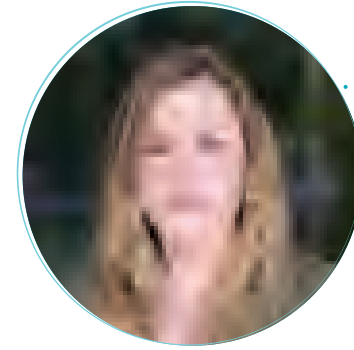
Mark Frey, PhD, was awarded \$1.7 million from the NIH's National Institute of Diabetes and Digestive and Kidney Diseases for his study, which will investigate the role that receptor tyrosine kinases ErbB4 and ErbB3 play in the repair and regeneration of the lining of the intestine. The intestinal epithelium is often injured as a side effect of radiation or chemotherapy, or by conditions such as inflammatory bowel disease.



(continued on next page)

MICHAEL GORAN

The NIH's National Institute of Diabetes and Digestive and Kidney Diseases granted \$1.7 million to **Michael Goran, PhD**, Director of CHLA's Diabetes and Obesity Program, to examine how human milk oligosaccharides affect development of the infant gut microbiome—and how this in turn might predispose children to a wide variety of diseases, such as obesity, and affect cognitive development. He also will explore how extended breastfeeding may protect against obesity in infants. (See page 42 to learn more about Dr. Goran's research.)



MIA HUMPHREYS

Mia Humphreys, MSW, was awarded \$1.45 million from the Centers for Disease Control and Prevention for her project, which will establish and maintain safe and supportive environments in schools—especially for youth at highest risk of HIV infection and other sexually transmitted diseases (STDs). The project intends to improve the health and well-being of our nation's youth by reducing HIV, STDs, teen pregnancy and related risk behaviors among middle and high school students.



TRACY GRIKSCHAIT

Tracy Grikscheit, MD, was awarded nearly \$1.3 million by the California Institute for Regenerative Medicine for her project, which will determine whether using universal pluripotent stem cells derived from adult cells can successfully treat liver failure resulting from metabolic diseases. If successful, this would be a viable alternate option to organ transplant, which is the only currently available treatment for metabolic liver disease.

YONG-MI KIM

Yong-Mi Kim, MD, PhD, MPH, received \$1.2 million from the NIH's National Cancer Institute to study drug resistance in leukemia. Dr. Kim was the first to discover that integrin alpha 4 anchors leukemia cells in the bone marrow, allowing them to become resistant to treatment. Her project aims to uncover other integrins that work in concert to shield leukemia cells from chemotherapy, with the eventual goal of devising treatments that can impede this activity and make leukemia cells more sensitive to treatment. (See page 40 to read more about Dr. Kim's research.)



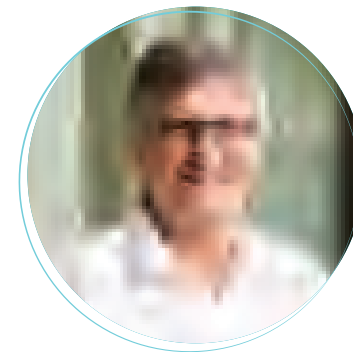
PAT LEVITT

The NIH's National Institute of Mental Health awarded \$3.7 million to Children's Hospital Los Angeles Chief Scientific Officer **Pat Levitt, PhD**, to study the role of the MET receptor in the development of neural circuits. He is studying how the wiring of the brain regions that underlie cognition and social and emotional behavior is built over time.



MARCO HIDALGO

The NIH's Eunice Kennedy Shriver National Institute of Child Health and Human Development has awarded **Marco A. Hidalgo, PhD**, a grant of \$3.4 million to longitudinally examine gender identity and mental health among prepubescent children who are transgender or gender nonconforming (TGNC). This is the first federally funded study to establish a large cohort of prepubescent TGNC youth (and their parents). Using surveys, data will be collected at renowned multidisciplinary gender clinics housed within four of the nation's leading children's hospitals, including Children's Hospital Los Angeles.

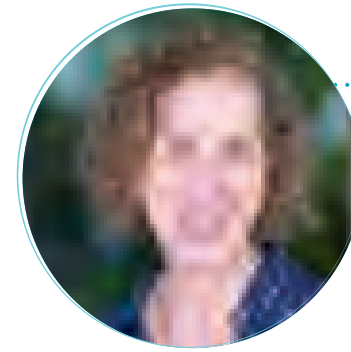


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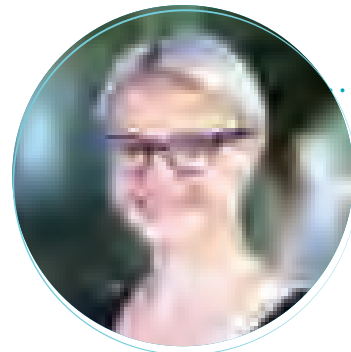
IRENE LIM

Irene Lim, LCSW, was granted \$2.7 million from the Substance Abuse and Mental Health Services Administration. Her project will expand and enhance comprehensive treatment, early intervention and recovery support services for adolescents and emerging adults with substance abuse who are identified through local high schools and CHLA's Emergency Department.



ARLENE SCHNEIR

The California Community Foundation granted \$1.2 million to **Arlene Schneir, MPH**, Division Administrator for Adolescent and Young Adult Medicine, to promote standardized substance use screening at five Los Angeles Unified School District Wellness Centers located in South Los Angeles. This grant is a partnership between Children's Hospital Los Angeles, the L.A. Trust for Children's Health and four federally qualified health centers operating Wellness Centers on these school campuses.



JENNIFER RAYMOND

Jennifer Raymond, MD, MCR, developed Team Clinic, a shared medical appointment model for adolescents with type 1 diabetes. CHLA received a \$1.3 million grant from the Leona M. and Harry B. Helmsley Charitable Trust. In Team Clinic, adolescents meet with their providers one-on-one before attending a patient-driven, shared medical appointment with their peers that allows them to ask questions and receive information in a way they feel is more supportive. The grant will include the development of a virtual toolkit to allow for replication of the model at other institutions.



WEI SHI

Wei Shi, MD, PhD, was awarded \$2.6 million from the NIH's National Heart, Lung, and Blood Institute for his study on the disease mechanisms of lymphangioliomyomatosis (LAM), a rare lung disease. He developed the first genetically engineered mouse with spontaneous LAM-like lung pathology, providing a novel platform for preclinical therapeutic investigation.

DAVID WARBURTON

David Warburton, OBE, DSc, MD, MMM, FRCP, FRCS, FRCPC, Director of the Developmental Biology and Regenerative Medicine Program, has been awarded the rank of Fellow of the American Physiological Society. He is honored for his leadership and pioneering research in the basic and clinical physiology of child health and human developmental biology.

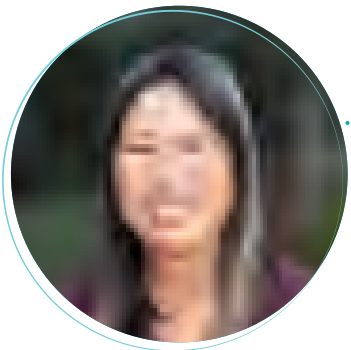


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JAMES AMATRUDA ALAN S. WAYNE



The Alfred E. Mann Family Foundation has dedicated \$6 million in support of leading-edge research and clinical care in the fight against childhood cancers and other diseases. Half of this generous gift established the Alfred E. Mann Family Foundation Chair in Cancer Research, and **Alan S. Wayne, MD**, Director of the Cancer and Blood Disease Institute, is the inaugural chairholder. The additional \$3 million supports a new zebrafish research facility led by **James Amatruda, MD, PhD**, a physician-scientist renowned for developing zebrafish models to discover and test novel therapies for cancer and other diseases.



TISHYA WREN

The NIH's Eunice Kennedy Shriver National Institute of Child Health and Human Development awarded **Tishya Wren, PhD**, a \$2.3 million grant to study bone loss associated with cerebral palsy (CP) in ambulatory children and adults. Study results will help determine who is at highest risk for developing osteoporosis, and will guide the future design of interventions aimed at maximizing and maintaining bone strength in people with CP.

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IN THIS ISSUE



MENTORING MATTERS

Guiding early-career investigators to become world-class scientists



DECODING THE EPILEPSY PUZZLE

Using game-changing genetic testing to develop personalized treatments for kids



ANYTHING BUT BASIC

Developing lifesaving therapies through discovery science



BITTERSWEET

The effect of sugar on children's growth and development—beginning in the womb