CHILDREN'S HOSPITAL LOS ANGELES

RESEARCHLA

2023

THE FUTURE OF AUTISM TREATMENT

See how Children's Hospital Los Angeles is paving the way for diversity in autism research.

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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 2022, CHLA received $51 million in National Institutes of Health (NIH) funding and $154.1 million in total research 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.

CHLA.org/research

Health equity is one of the principles upon which Children's Hospital Los Angeles was built. From our earliest beginnings over a century ago, providing every child access to the highest level of care has always been central to the hospital's purpose. CHLA's statement of purpose makes this absolutely clear—"We fulfill our mission by *supporting our communities, especially underserved populations*."

This commitment to health equity extends beyond clinical care to CHLA's research enterprise. Driving The Saban Research Institute of CHLA is a belief that diversity in research is essential to truly achieving health equity. And the key to accomplishing this is inclusivity at every stage—from the researchers posing fundamental questions to the study participants themselves.

One approach to increasing equity in research is to identify and study what drives diseases that disproportionately affect underserved populations. In this issue you will read about the Southern California Center for Latino Health, led by Michael I. Goran, PhD. With a $24.5 million award from the National Institutes of Health, Dr. Goran and his team have created an interdisciplinary consortium across the region that aims to prevent development of chronic diseases—such as fatty liver disease, obesity and Type 2 diabetes—in Latino adults by addressing health disparities in young children.

Some of the barriers to families participating in research studies are pragmatic, and investigators are creatively addressing them. Most participants in autism studies are high-income white families, which, according to Shafali Spurling Jeste, MD, Las Madrinas Chair, Chief of Neurology, creates bias in the studies. She and her team are working to find a biomarker for autism that could be used to measure the effectiveness of new interventions. For this research to be inclusive, she is removing very real barriers to family participation—from paying for transportation to the clinic, providing childcare for siblings, and even having evening and weekend appointments.

CHLA investigators want all children to benefit from research, especially since new therapies will likely be based on genomics. Bridget Fernandez, MD, MS, is also working toward health equity in autism research. She is leading a study with the goal of conducting whole genome sequencing of 1,000 Hispanic children to build an ethnically representative database. Dr. Fernandez wants to be sure that when biological therapies are available, they will benefit all children.

Finally, one question CHLA scientists hear a lot: Why is it important to do research at a *children's* hospital? In the following pages, be prepared to be awed by the depth and breadth of our response.

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

Thank you for your support of CHLA's groundbreaking and transformative research initiatives.

Warmest regards,

PAUL S. VIVIANO
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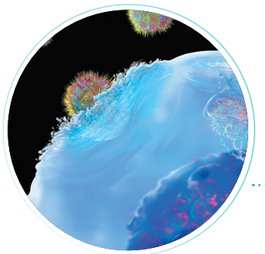

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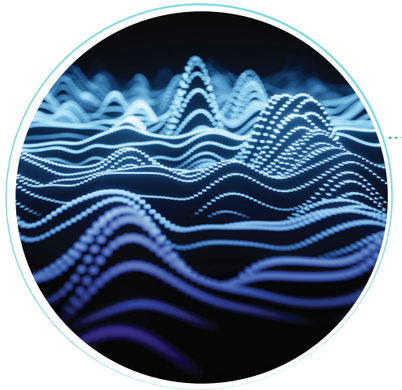


IN THE **NEWS**

RECOVER
Researching COVID to Enhance Recovery

An Initiative Funded by the National Institutes of Health

SINDHU **MOHANDAS**

Division of Infectious Diseases

Multiple outlets, including ABC7 News, interviewed **Sindhu Mohandas, MD**, about CHLA's Long COVID Recovery Care service. CHLA is part of the NIH-funded nationwide COVID RECOVER study enrolling 20,000 long COVID patients under age 25. An estimated 5%-15% of youth infected with COVID-19 experience long-term symptoms.

LORRAINE **KELLEY-QUON**

Division of General Pediatric Surgery

HealthDay covered a study led by **Lorraine Kelley-Quon, MD, MSHS**, on a quality improvement intervention that significantly reduced opioids prescribed at time of discharge for children who had undergone appendectomies. The study was published in the Journal of the American College of Surgeons.

DAVID R. **FREYER**

Cancer and Blood Disease Institute

MedPage Today featured **David R. Freyer, DO, MS**, in a story about sodium thiosulfate, the first treatment to reduce the risk of hearing loss in children given cisplatin, a common chemotherapy agent. Dr. Freyer headed up a pivotal clinical trial that led to FDA approval of the drug—which reduces the incidence of cisplatin-induced hearing loss by more than 50%.

PIA **PANNARAJ**

Division of Infectious Diseases

WFYI, the NPR affiliate in Indianapolis, interviewed **Pia Pannaraj, MD, MPH**, co-author of a nationwide study finding that mothers vaccinated against COVID-19 during pregnancy generated antibodies that protected infants up to 6 months of age. While protection for infants was greatest with mothers vaccinated after 20 weeks of gestation, maternal vaccination earlier in pregnancy was also beneficial.

Dr. Pannaraj also spoke to CBS News and multiple other media outlets about preventing COVID-19 transmission at home if a family member tests positive. Her team's 2020 study of Los Angeles families found that lower income levels and more people sharing a bedroom were significant factors in predicting the risk of disease spread.

MICHAEL I. **GORAN**

Center for Endocrinology, Diabetes and Metabolism

The Los Angeles Times and other outlets interviewed **Michael I. Goran, PhD**, about the launch of the Southern California Center for Latino Health. The Center supports studies and community engagement initiatives by CHLA and partners to reduce childhood health care disparities that lead to adult chronic illnesses.

JAMES **AMATRUDA**

Cancer and Blood Disease Institute

KCBS-TV interviewed **James Amatruda, MD, PhD**, Dr. Kenneth O. Williams Chair in Cancer Research, about his research using zebrafish to find more effective, less toxic cancer therapies. Employing zebrafish as experimental models to test research approaches, a team led by Dr. Amatruda in the Alfred E. Mann Family Foundation Zebrafish Laboratory can efficiently track tumor growth from a few cells and reduce the time to clinical trials and the development of treatments.

THE FUTURE OF **AUTISM TREATMENT**

Identifying biomarkers and studying children of all ethnicities are essential.

By Ellin Kavanagh

Each year in the U.S. the incidence of autism spectrum disorder increases, yet the number of medications to treat the core features of autism remains stuck at zero. Therapies and medications that address related symptoms like sleep, focus and behavioral issues are the current "gold standard" for autism treatment. But what's next?

WHY IS THERE NO MEDICATION TO TREAT AUTISM?

Although at any given time there are hundreds of ongoing clinical trials testing drugs to treat autism, there are many reasons why none have been proven effective. Autism is a heterogeneous disorder. It isn't caused by a single factor like a bacteria or even a single gene. It's a complex condition that has been linked to myriad genetic changes, as well as a variety of environmental factors. In addition, symptoms and the degree of their impact vary widely, giving rise to the now-famous quote, "If you've met one person with autism, you've met one person with autism."

Given all this variability, how can a study definitively show that a medication is working?

"Even with a viable therapeutic, the heterogeneity of autism makes clinical trials difficult," says **Shafali Spurling Jeste, MD**, Chief of Neurology, Co-Director of the Neurological Institute and Las Madrinas Chair at Children's Hospital Los Angeles. "Maybe you didn't measure the right thing or wait long enough to see a change."

According to Dr. Jeste, a validated biomarker for autism is necessary to make real progress. She explains that biomarkers are measurable, biological features that provide information about a clinical condition—like insulin levels for diabetes or temperature for infection.

Dr. Jeste is site principal investigator for the Autism Biomarkers Consortium for Clinical Trials (ABC-CT)—one of the largest initiatives ever undertaken by the National Institutes of Health focused on autism research. She is six years into the search to identify, quantify and validate biomarkers and clinical endpoints relevant for autism.

(continued on next page)

Autism is a heterogeneous disorder. It isn't caused by a single factor like a bacteria or even a single gene.

"We want all children to benefit from research, and as the nation's largest safety net children's hospital, CHLA should be the leader in increasing diversity in this area." – Shafali Spurling Jeste, MD

HOW WILL BIOMARKERS BE USEFUL IN TREATING AUTISM?

For this study, children come to the clinic for a comprehensive set of assessments. The biomarker testing includes electroencephalography (EEG) to measure brain function, eye tracking to determine visual attention, and recordings for studying behavior and speech. The same assessments are done again at six weeks and six months later. The objective is to determine if the potential biomarkers are stable over time in a growing child. The measurements will also be compared with those of typically developing children.

"Biomarkers would give us a way to meaningfully group children with common characteristics with the goal of eventually testing a medication in less heterogenous groups," says Dr. Jeste. "Changes in a stable biomarker also would provide an objective way to determine if a medication was affecting the brain and, as a result, could improve a core feature of autism."

Two years ago, Dr. Jeste moved her Kids with Neurogenetic and Developmental Disabilities (KiNDD) lab to Children's Hospital Los Angeles, in part because of CHLA's patient population. She explains that most participants in autism studies are high-income white families. This creates bias in the studies.

"Families of other ethnicities and socioeconomic status typically don't participate in research—including many of our families at CHLA," she says. "As a field, we have done a poor job of introducing these studies to families from underrepresented minority groups and those with low incomes, and as a result there is a lack of knowledge about the benefits of research. There are also some very real barriers to participation in studies, especially cost and time." Dr. Jeste's team has tried to remove some of those barriers by paying for transportation to the clinic for assessments, providing child care for siblings and having evening and weekend appointments.

Recent research indicates that 40% to 80% of autism risk is genetic, with more than 200 specific genes linked to the disorder.

WHY DOES DIVERSITY MATTER?

Recent research indicates that 40% to 80% of autism risk is genetic, with more than 200 specific genes linked to the disorder. Increasingly, clinicians are using advanced genetic testing to identify the cause of a person's autism. Interpretation of this genetic data relies upon large databases that, unfortunately, lack diversity.

Bridget Fernandez, MD, MS, a medical geneticist at CHLA, explains that most of what we know about genomic changes underlying particular medical conditions, including autism, comes from looking at individuals from families of European ancestry. Databases for people of other ancestral origins are needed to effectively interpret their genetic data.

"At CHLA, we are working to establish a basis for evaluating Hispanic children in the way that children of European ancestry have been studied," says Dr. Fernandez, who is also Associate Director of Clinical Research at The Saban Research Institute of Children's Hospital Los Angeles.

In her study, Dr. Jeste uses tools like EEG caps, which measure the brain's electrical activity.

IS PERSONALIZED MEDICINE THE ANSWER?

Dr. Fernandez is leading a study with the goal of conducting whole genome sequencing of 1,000 Hispanic children to build an ethnically appropriate database. She is also using "deep phenotyping" to better inform genetic studies of these kids. This involves gathering a lot of clinical information to pair with the genomic sequencing data to develop a more complete picture of the child's condition.

(continued on next page)

"Our hope is that we will eventually be able to provide families with therapeutic options—like medications—that are targeted to the specific genetic profile of their child." – Bridget Fernandez, MD, MS

These treatments can have significant benefits. "A child, who even with intense behavioral therapy remains nonverbal, may benefit from a medication that takes into account their specific genetic makeup," says Dr. Fernandez. "What if these future therapies helped this child develop expressive language? It would be life-changing."

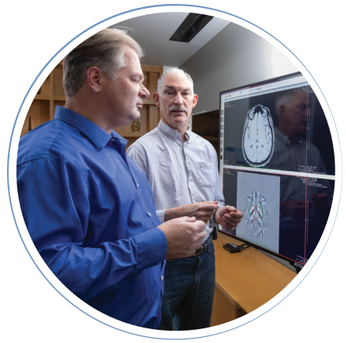
Dr. Fernandez is leading a study with the goal of conducting whole genome sequencing of 1,000 Hispanic children.

She is concerned that if clinical trials are only enrolling children of European ancestry because those are the ones volunteering, other children may be left behind in the development of biologically based therapies. Dr. Fernandez, Dr. Jeste and other investigators at CHLA are working to address this imbalance and are actively recruiting children from underserved populations.

"While this particular study is not focused on producing a therapy, unless we do this kind of work, treatments informed by genomics may only be available to children of European ancestry," says Dr. Fernandez. "In the future when there are biological therapies, we want all children to be able to benefit."

EARLY RESEARCH: USING AI TO FIND A BIOMARKER FOR AUTISM

Stephan Erberich, PhD, Chief Data Officer, and **John Wood, MD, PhD,** an expert on pediatric iron overload, have teamed up to use artificial intelligence (AI) and data science advanced analytics on MRI scans of children's brains. The goal: to identify "low-intensity" areas that indicate decreased iron content. They hypothesize that lack of normal brain iron uptake disrupts brain metabolic function in developing children—and has the potential to be a biomarker for autism.



THE INTERSECTION OF **AUTISM AND VISION DISORDERS**

There is a lot of research on the use of eye tracking to study visual attention in children with autism. Some studies indicate that when looking at pictures of people, individuals with autism focus on non-social aspects of the picture rather than social aspects such as looking at people's eyes. Yet many children with autism have issues with ocular motility and have an increased incidence of strabismus and amblyopia—creating problems with binocular vision.

"There haven't been any studies looking at whether visual disorders could affect eye tracking or visual attention in kids with autism," says **Melinda Chang, MD,** a pediatric neuro-ophthalmologist in The Vision Center. Her research interest is in the intersection between visual disorders and neurodevelopment.

Dr. Chang is beginning a pilot study to find out if vision problems could be affecting visual attention and behavior in kids with autism. She plans to enroll 25 children with autism and visual disorders and 25 with autism but without visual disorders.

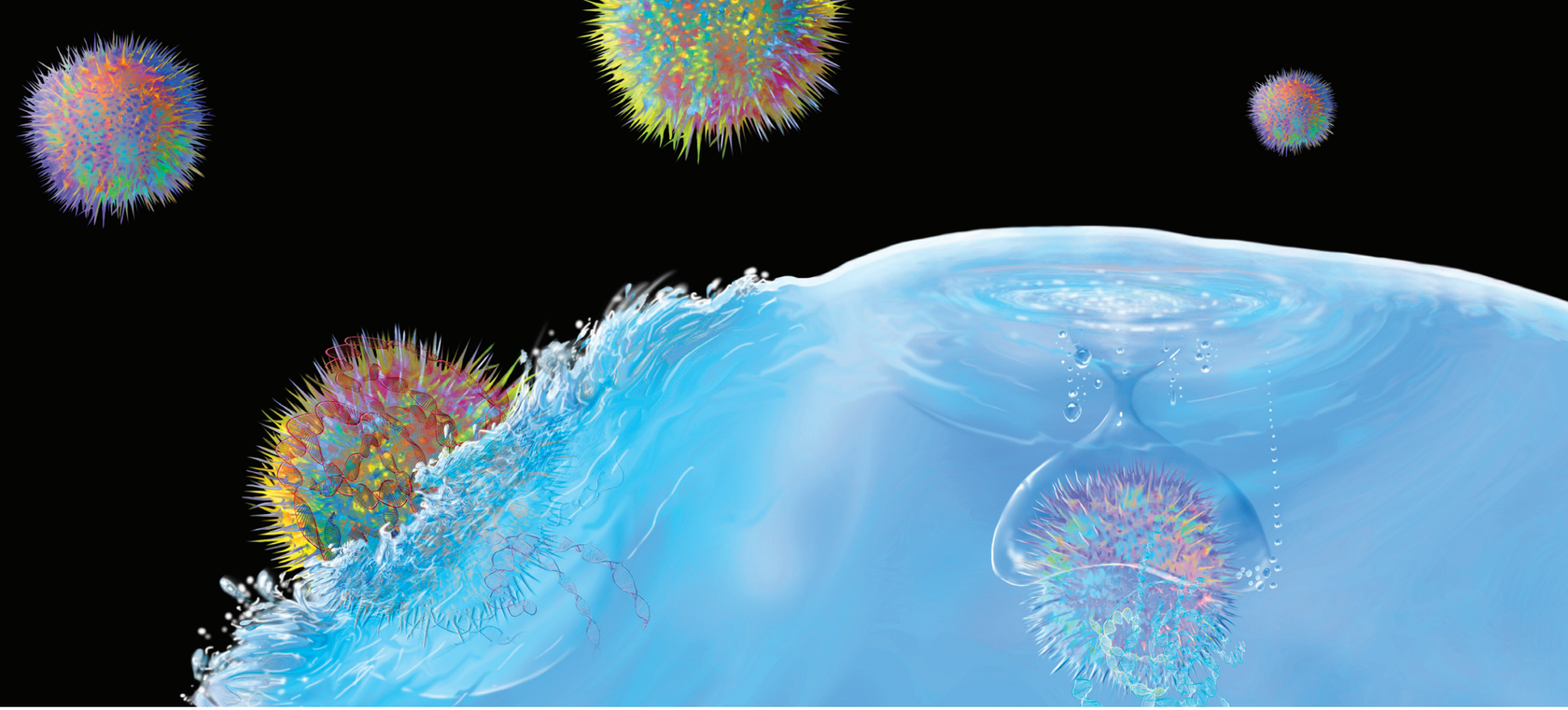
The objective is to determine if treating the visual disorder reduces symptoms of autism. Another goal is to help screen for vision problems in kids with autism because they tend to be underdiagnosed.

"Often, they can't tell us that they can't see," says Dr. Chang.

Dr. Chang performs eye tracking on a young child.

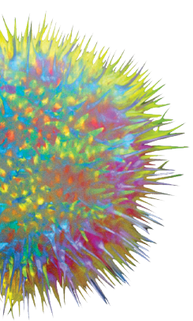
5 THINGS TO KNOW ABOUT **ADVANCES IN CANCER RESEARCH**

By Sara Jones



Dramatic advances in cancer research and treatment over the past two decades have made it possible for more children to survive a cancer diagnosis. Experts in the Cancer and Blood Disease Institute at Children's Hospital Los Angeles are investigating ways to make CAR T-cells more effective—a sort of CAR-T 2.0—as well as genetic and structural approaches for treating various types of cancer.

Here are five things to know about advances in cancer research at Children's Hospital Los Angeles:



1 CAR T-cells can be made more effective.

Chintan Parekh, MD, is studying whether increasing the activity of a T-cell gene called BCL 11B can improve immune recovery after bone marrow transplantation and make CAR T-cells more effective at destroying cancer cells.

"We have generated a roadmap for how T-cells—a type of white blood cell involved in immune response—develop in humans," says Dr. Parekh. "We are now applying this knowledge in the lab to develop approaches to kick-start immune recovery after bone marrow transplantation and design CAR T-cells against cancer that are more powerful."

2 CAR T-cells are showing promise against neuroblastoma.

It is no exaggeration to say that CAR T-cell therapy has revolutionized leukemia treatment; however, its application in treating other cancers, including neuroblastoma, has been limited due to safety concerns. A group of scientists at Children's Hospital Los Angeles has developed a modified version of CAR T-cell therapy that shows promise in treating neuroblastoma.

"CAR T-cell therapy is incredibly powerful, but for uses beyond leukemia it has significant barriers," says **Babak Moghimi, MD**. "We needed a way to boost the CAR T-cells to make them fight harder and smarter against neuroblastoma. But we also want to avoid injury to brain cells and other healthy tissue."

3 CAR T-cells are showing activity against solid tumors.

Sarah Richman, MD, PhD, is working to find ways to make immunotherapy—including CAR T-cell therapy—an effective, safe treatment for children with solid tumors.

"T-cells have evolved elegant ways to automatically shut themselves down following intense activation in order to prevent autoimmunity," says Dr. Richman. "However, when we are engineering these cells to fight cancer, those auto shut-off programs may be working against us—especially in solid tumors where CAR T-cells may need an extra boost. We aim to better understand these inherent auto shut-off programs in CAR T-cells in order to engineer them with that extra boost needed to eradicate a solid tumor."

4 Human stem cell models can be used to identify the underlying causes of pediatric cancers.

Miller Huang, PhD, focuses on finding genetic changes that cause healthy cells to become pediatric tumors. Using human stem cell models developed by his lab, Dr. Huang recently identified chromosomal changes as a potential cause of tumor formation in children.

"Unlike in adult cancers, pediatric tumors have few genetic mutations," says Dr. Huang. "Instead, we believe the cause of pediatric tumors comes from changes in large DNA segments called chromosomes, which mimic the effect of numerous mutations typically found in adult cancers."

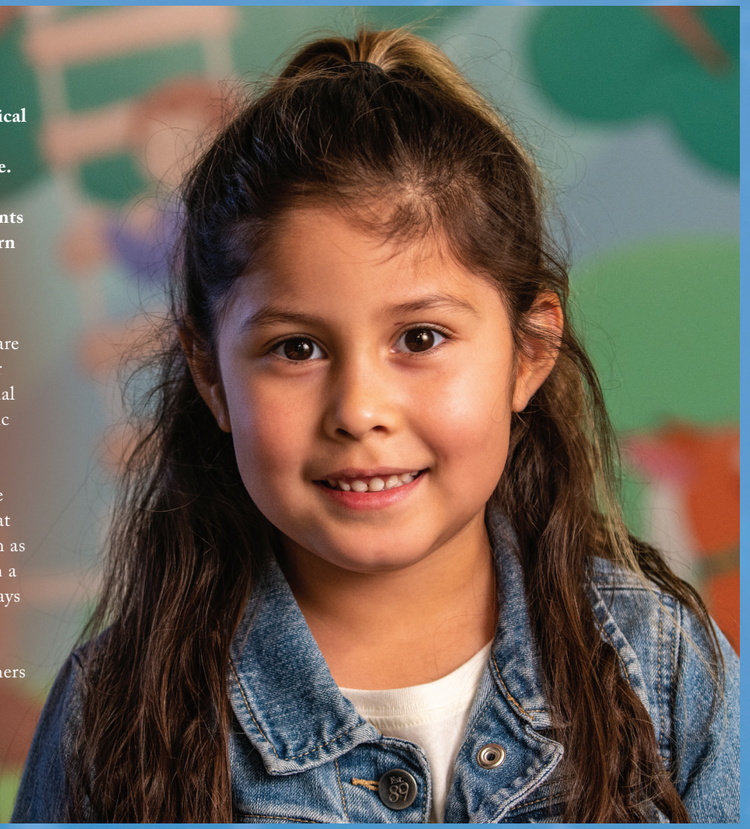
5 The physical properties of cancer cells may offer new treatment opportunities.

JinSeok Park, PhD, is applying multidisciplinary approaches to investigate how the "extracellular matrix"—the scaffolding that surrounds cells within tissues—provides the cells with physical support, regulating cancer cell behavior and affecting metastasis of solid tumors such as neuroblastoma and rhabdomyosarcoma.

"My lab aims to understand how this physical interaction between cancer cells and their environment may be cancer promoting—potentially offering therapeutic targets to improve outcomes," says Dr. Park.

WHY IS RESEARCH ESSENTIAL AT A CHILDREN'S HOSPITAL?

By Melinda A. Smith, PhD



Medicine is an ever-changing field. Treatments evolve from basic and translational research, advance to clinical trials and if successful, are introduced into the clinic. But it doesn't stop there. It can't. There's always the potential to get diagnoses sooner, to make treatments more effective and to turn what we learn into a more personalized approach for individual patients.

The ambitions of pediatric researchers are global in scale: Beyond patients at their own hospital, they look to shape national and international standards for pediatric care. These goals are best achieved through the very special relationship between research and clinical care. True change comes from an environment that fosters thought and innovation as much as it values treating disease. It comes from a culture of constantly questioning—always searching for better ways to do things.

The following stories showcase researchers who are changing the landscape of pediatric medicine and answering the question: *Why is research essential at a children's hospital?*

Laura Perin, PhD, and Stefano Da Sacco, PhD

BECAUSE DISCOVERY CAN BE FAST-TRACKED TO THE KIDS WHO NEED IT.

The next big medical breakthrough might be taking place right this very minute. But here's the thing: It may not look anything like a medical breakthrough. That's because discovery starts with basic research that investigates the mechanisms of pediatric diseases. It can take years before these discoveries lead to therapeutics and more years before these advances make their way into the clinic. That's why research at a children's hospital is so crucial. Here, investigators are steeped in a research environment that's directly informed by patient need. And in this environment, discoveries can benefit patients more quickly.

Meet **Laura Perin**, **PhD**, and **Stefano Da Sacco**, **PhD**, two scientists in the GOFARR Laboratory for Organ Regenerative Research and Cell Therapeutics in Urology. Drs. Perin and Da Sacco study diseases of the kidney, the body's main filter for toxins and wastes. "Learning exactly how renal filtration occurs has been difficult," says Dr. Perin, "because we don't have a good laboratory model." This is no small point. Accurate modeling of how human cells work in the body is critical to studying any disease.

Recently, Drs. Perin and Da Sacco developed a revolutionary model in which healthy human kidney cells grow into a filtration barrier, just as they do in the human body. This tool—which fits in the palm of your hand—is much more powerful than the sum of its parts. The device mimics the filtering action of the kidneys. The model has many potential uses, like testing the safety of new medications prior to clinical trials.

An individual patient's disease progression can even be monitored by running serum samples through the device, allowing researchers to see how certain factors circulating in the blood affect kidney function. This, in turn, can set the stage for more personalized care.

"Doing this research at a children's hospital is critical," says Dr. Da Sacco. There are many reasons for this, including access to healthy and diseased tissue samples for research. But there's something about being in a pediatric hospital that doesn't translate to any other lab. "We're in this environment where people are working on so many different levels to help these kids live longer, healthier lives," he says. "What better motivation to work hard could there be?"

EXISTING TREATMENTS CAN BE MADE BETTER WHEN THE PEOPLE WHO TREAT PATIENTS ALSO DO RESEARCH.

Leukemia—specifically acute lymphoblastic leukemia, or ALL—has one of the highest survival rates of any cancer. Up to 90% of children are in remission at their five-year follow-up appointment. So why do doctors like **Etan Orgel, MD, MS**, choose to work on improving therapies for cancers like this? For one thing, 90% isn't 100%. "Even though this is the best success rate we've ever had in treating leukemia, not every child beats the disease," says Dr. Orgel. If existing chemotherapies could be made more effective, more patients could go into remission.

Basic and translational research shows that the body's fat cells can actually get in the way of treatments by shielding cancer cells and making chemotherapy less effective. Based on this knowledge, Dr. Orgel and his team initiated the IDEAL study (Improving Diet and Exercise in ALL). Patients reduce their calorie intake and participate in light exercise during the first phase of chemotherapy. This change alone reduced the risk of detectible cancer cells—known as minimal residual disease—at the end of the first phase of chemotherapy.

What's more, this reduced risk involves no additional medications or treatments. "These kids are already going through so much during chemotherapy," says Dr. Orgel. "The goal is to improve their chances without adding in more pills, more side effects and more stress on the body."

Based on the success of the first phase of the IDEAL study, Dr. Orgel and his team have initiated IDEAL 2, which is currently enrolling patients across the United States.

When asked why it's important to conduct research at a children's hospital, he says that there would be no other way. "Children aren't just small adults, and we can't treat their cancers the same way," he says. Pediatric cancers are often very different from adult cancers, and treatments required are different, too. This necessitates special research. "Unfortunately, because pediatric cancer is relatively rare, it is underfunded and under-resourced," says Dr. Orgel. "Children's hospitals play a crucial role in bridging this gap."

"The goal is to improve their chances without adding in more pills, more side effects and more stress on the body."

— Etan Orgel, MD, MS

BECAUSE

SOMETIMES, THE CLINIC IS WHERE THE MOST PRESSING RESEARCH QUESTIONS—AND SOLUTIONS—ARE BORN.

Jesse Berry, MD, didn't set out to do research. She went to medical school so she could help children in need. After all, she says doctors were quite impactful in her own upbringing. But help comes in many forms, and in Dr. Berry's case, help turned out to be discovering a better way to diagnose retinoblastoma. This cancer—which develops at the back of the eye and can lead to blindness—has always been a problem to diagnose.

"You can't biopsy it like other cancer," she explains. "Performing the biopsy can help the cancer spread." Instead, doctors must rely on imaging to diagnose the disease. When it comes to retinoblastoma, arriving at a definitive diagnosis sooner could mean saving a child's vision.

Enter Dr. Berry, the A. Linn Murphree, MD, Chair in Ocular Oncology, whose drive and curiosity led her to think outside the box. She uncovered a way to find genetic material from the tumor in the aqueous humor, the fluid available at the front of the eye. This method (the liquid biopsy) allows clinicians to diagnose retinoblastoma more quickly and more accurately—on the molecular level. Dr. Berry's research shows that the genetic information coming from the aqueous humor can actually help doctors predict which treatment a child might best respond to. Personalized medicine like this leads to better, more individualized care.

Dr. Berry's discovery will have an impact beyond the patients she sees. The National Cancer Institute's Pediatric Match program aims to better understand genetic alterations in all known pediatric cancers. Retinoblastoma—being rare and poorly understood on the genetic level—is not in this data repository. But that will likely change very soon.

This discovery wouldn't exist if Dr. Berry wasn't at Children's Hospital Los Angeles, which is one of the largest referral centers for pediatric eye cancers in the western United States. As a clinician, she grew frustrated with the limitations in diagnosis. This led her to study the problem and work toward a solution. "If I wasn't seeing patients every day who needed something better," she says, "this research would not have happened."

BECAUSE

WHO BETTER THAN A PEDIATRIC SURGEON TO MAKE CARE AFTER SURGERY SAFER AND MORE EFFECTIVE?

"Being at a children's hospital means thinking about one patient at a time, focusing on each family with everything I have."

— Lorraine Kelley-Quon, MD, MSHS

If **Lorraine Kelley-Quon, MD, MSHS**, were a chess player, she'd be the type to think multiple moves ahead. Although she's a pediatric surgeon, she not only focuses on the immediate medical needs of her patients, but she also thinks about how to improve children's recovery after surgery.

"My work extends beyond surgery to the child or adolescent healing at home," she says. Dr. Kelley-Quon is making sure pain management is not only effective, but also safe.

While people don't tend to think the opioid epidemic affects children and adolescents, it absolutely does, she says. Prescription opioid misuse and abuse in teens continues, due in part to the frequent prescribing of opioids after surgery. A few decades ago, opioids were rarely given to children for pain. Fast forward to 2018, when a staggering 1 in 10 adolescents were prescribed opioids. Along with continued sharing and recreational use of prescription opioids, there is an upward trend of teen deaths due to opioid-related overdose. To call today's opioid problem a crisis is not hyperbolic.

It's understandable that potential risks of pain meds are upstaged when families are managing something as big as their child's surgery. Although opioids can help a child safely recover after surgery, they should be prescribed judiciously and not necessarily as the default when managing a patient's pain. This is why Dr. Kelley-Quon led a team of health care providers and community advocates to establish the first-ever guidelines on the safe use of opioids in children.

"It's not that opioids should never be prescribed," she says. "We just want it to be done in a thoughtful and consistent way to minimize risks and maximize recovery."

Eventually, we may see policy changes regarding prescription of opioids. For now, Dr. Kelley-Quon is laying the groundwork. And it wouldn't be possible anywhere else.

"Being at a children's hospital means thinking about one patient at a time," she says, "focusing on each family with everything I have. But sometimes it also means thinking bigger—not only for the safety of our patients but for the safety of a child's community, and for children across the country and beyond. It's up to us and that's why we work here."

SOUTHERN CALIFORNIA
Center for Latino Health
A regional consortium based at Children's Hospital Los Angeles

TO REDUCE HEALTH DISPARITIES, **THE SOUTHERN CALIFORNIA CENTER FOR LATINO HEALTH** FOCUSES ON CHILDREN AND FAMILIES

The largest grant in CHLA history funds research to foster long-term community health equity by preventing chronic disease early in life.

By Wendy Wolfson

The roots of chronic diseases can start surprisingly early in life, especially for certain populations who may experience limited access to healthy food and medical care. Latinos living in Southern California have a disproportionately high risk of heart disease, nonalcoholic fatty liver disease, obesity and Type 2 diabetes, compared with other Californians. These chronic diseases, linked to social and economic disparities, are rooted in childhood.

An ambitious consortium led by investigator **Michael I. Goran, PhD**, aims to prevent the development of chronic diseases in Latino adults by addressing health disparities in families and young children. The economic and social stakes are high for Southern California, where 10.8 million Latinos represent 45.2% of the population.

To help children grow up in healthier communities, Children's Hospital Los Angeles launched the Southern California Center for Latino Health in 2021 with a $24.5 million award from the National Institute on Minority Health and Health Disparities (NIMHD). The Center, which is a partnership with the Keck School of Medicine of USC as well as other universities, hospitals and dozens of community groups across the region, is one of 11 NIMHD regional centers funded by a Congressional mandate to address health disparities in chronic diseases in different populations across the nation. **Lourdes Baezconde-Garbanati, PhD, MPH**, Professor of Preventive Medicine at the Keck School of Medicine of USC and an expert in community engagement, is Co-Investigator and Associate Director of the Center.

The Center investigates how chronic disease disparities develop in Latinos across their lives and seeks to create and evaluate culturally sensitive, evidence-based solutions that families can use in their communities to create healthier lives for their children.

"We are studying the impact of social determinants of disease—how a combination of social, environmental and nutritional factors in early life, such as lack of access to healthy food, affects Latinos in Southern California," says Dr. Goran, Program Director for Nutrition and Obesity at The Saban Research Institute of CHLA and Principal Investigator of the grant.

(continued on next page)

STUDYING THE IMPACTS OF INTERCONNECTED EXPOSURES

To provide parents and community groups with effective research-based tools and education so they can help their children grow up healthier, the Center has started by sponsoring three clinical studies in Latino children and families: a longitudinal study on impacts of early life factors on young children, a study on telehealth parent-based treatment and a study that prescribes food as medicine to families.

Early Life Factors

A longitudinal study based at CHLA, "Early Life Social, Environmental and Nutritional Determinants of Disease" (EL SENDERO), tracks nutrition in early life, environmental factors such as air pollution, and social determinants such as cultural assimilation as well as access to health care and healthy foods. The goal is to measure how these factors affect risk markers for development of chronic diseases like obesity, Type 2 diabetes, fatty liver disease and heart disease in early life.

"From a residential address history, we can determine things like air pollution or green space exposure or healthy food access," says Dr. Goran, Director of the Center.

The Center's researchers are scrutinizing the impact that early life nutrition, such as breastfeeding or different types of infant formula, has on risks for chronic disease. "We already know that early weight trajectory—how rapidly an infant gains weight in the first six months of life—is an important marker for the later development of chronic diseases," says Dr. Goran. "We will look at how those early life measures relate to current disease risk at 6 years of age."

He notes that previous studies had found distinct changes in the microbiome—the bacteria that live in the gut—of children who were fed formula that was high in milk sugars, compared with children who received breast milk. These changes, detectable as early as 6 to 12 months of age, can signal an increased risk for obesity or chronic disease.

Parent-based Treatment

The second study, led by **Kerri Boutelle, PhD**, and a team of researchers from the University of California, San Diego, will investigate the effectiveness of telehealth parent-based treatment in helping both parents and kids lose weight and lower their risk for chronic diseases associated with obesity, including Type 2 diabetes, liver disease and heart disease. The study will include 160 Latino families. Family members will be randomized into either six months of telehealth parent-based treatment or a control group that receives health education without the telehealth component. Both groups will be followed for 12 months.

Food as Medicine

The third study in the Center is led by **Deborah Cohen, MD, MPH**, at Kaiser Permanente Research, and will be a randomized trial to test food as medicine to tackle obesity and chronic disease risk. The study prescribes six months of medically curated food, culturally sensitive meal planning and affordable grocery delivery for 180 Latino Kaiser Permanente member families, with 12 months of follow-up.

The food prescriptions will be designed to cost under $680 per month—the CalFresh (California's Supplemental Nutrition Assistance Program) budget for a family of four. Each family is expected to contribute $100 per week to their food budget, with the amount above this subsidized. "At least from the pilot studies, we're seeing big improvements in the overall quality of food these families eat and a reduction in body weight in both men and women who are participating," says Dr. Goran.

ENGAGING THE COMMUNITY

As the Center covers communities sprawling from Ventura County to the Mexican border, **Michele Kipke, PhD**, in the Department of Pediatrics at CHLA, and **Dr. Baezconde-Garbanati** at USC are leading a community engagement core that will build a regional coalition of academic institutions, health care providers, community leaders and organizations, policymakers and public health departments.

"These are big problems, and we really want to engage a whole range of stakeholders in thinking through strategies that might help us move the dial," says Dr. Kipke, who is also Associate Vice President for Strategic Health Initiatives at USC. "I think the most important partner in all this is the community itself."

For several months, the team has been running a series of "listening sessions" in different communities—hearing concerns about unhealthy food in schools, or that people don't know how to cook healthy food for their families.

Dr. Kipke is strategizing how to work with school districts to serve healthier lunches and partnering with a network of 4,000 Spanish-speaking health workers, known as promotoras, to run popular online workshops on healthy meal preparation. Responding to community requests, Dr. Kipke's team led seminars about the research process, after which attendees expressed interest in participating in clinical studies. "You're exposing someone to new information, and if you can offer little bite-size suggestions with the right person delivering it, suddenly you can really turn a lot of things around," says Dr. Kipke.

BY THE **NUMBERS**

10.8
million Latinos represent
45.2%
of the population
in Southern California

50%
of all Latinos will develop
diabetes
in their lifetime

Latino children are almost
200%
more likely to be
obese
than white children by age 2

DRAWING ON CHLA RESEARCH EXPERTISE

The Center draws on the collective expertise and community ties of multiple CHLA researchers. **Rohit Kohli, MBBS, MS**, Chief of the Division of Gastroenterology, Hepatology and Nutrition, and Associates Chair in Liver and Intestinal Research, is a co-investigator on the EL SENDERO study with **Alaina Vidmar, MD**, a pediatric endocrinologist and obesity specialist at CHLA. The two are researching conditions such as nonalcoholic fatty liver disease, which is now appearing at alarming rates in Latino children with obesity.

The Center also includes an investigator development core that grants up to $400,000 in annual awards across the region to fund promising projects and train young investigators. Dr. Vidmar is the recipient of one of these awards. She is conducting a study of the effect of meal timing on the blood sugar of Latino adolescents with obesity.

Data researchers including **Ramon Durazo-Arvizu, PhD**, Faculty Director, Biostatistics and Data Analysis Core at The Saban Research Institute, and **Mahsa Babaei, PhD**, Postdoctoral Research Fellow, will manage the massive amounts of information that will be generated by the different studies.

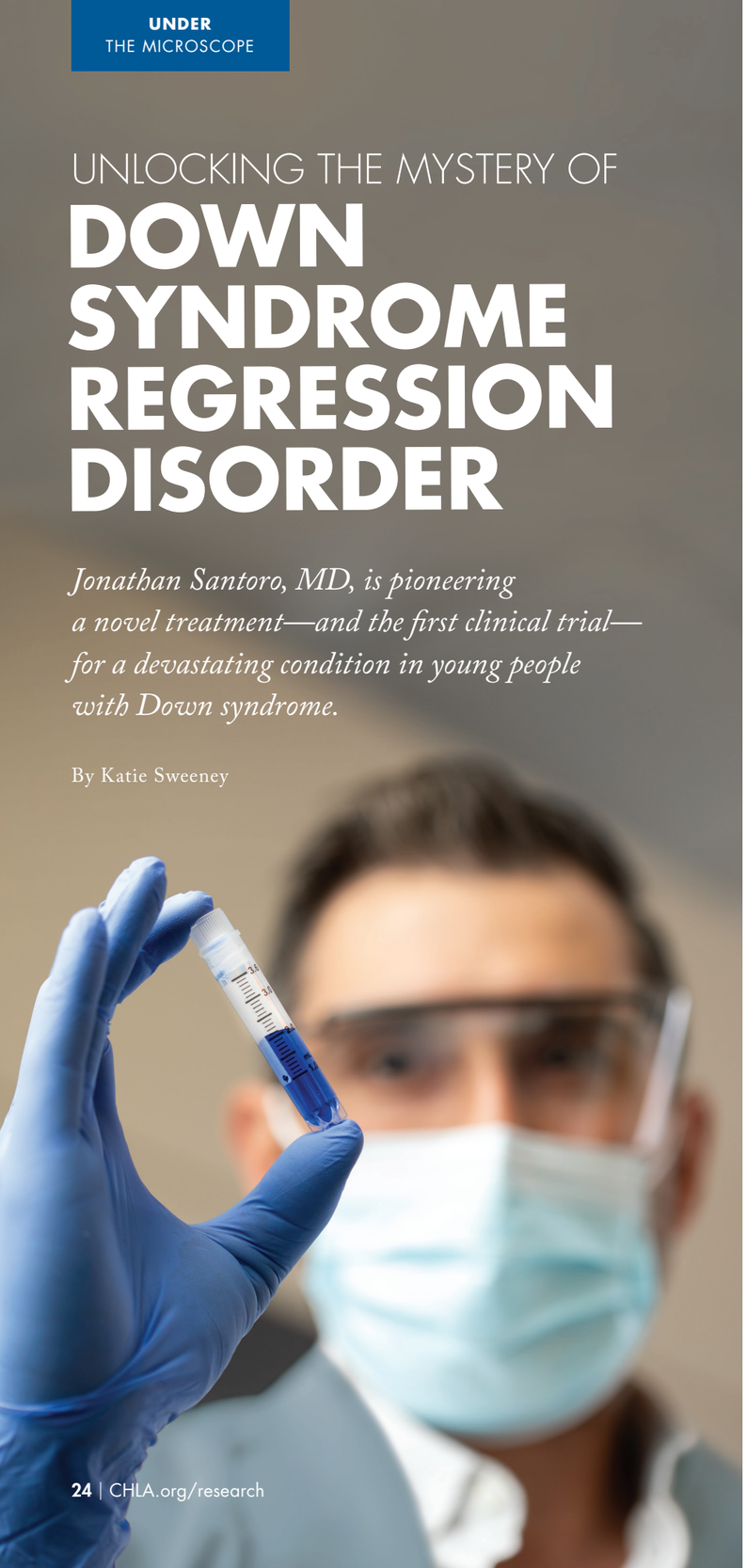
"This is a big interdisciplinary team effort," says Dr. Goran. "We want to know how these interventions might work effectively in different populations. But accomplishing this means working with the community to make sure we are doing research that's relevant and developing interventions that are culturally tailored and appropriate for Latinos in Southern California."

UNLOCKING THE MYSTERY OF

DOWN SYNDROME REGRESSION DISORDER

Jonathan Santoro, MD, is pioneering a novel treatment—and the first clinical trial—for a devastating condition in young people with Down syndrome.

By Katie Sweeney



“It’s like living with a ghost.”

“There’s a stranger in my house.”

“My child died and another child replaced them.”

That’s how families describe their experience with Down syndrome regression disorder (DSRD)—a rare condition that causes previously high-functioning young people with Down syndrome to suddenly lose their ability to communicate, dress or feed themselves, use the bathroom or even sleep. Long assumed to be a psychiatric condition, or even early-onset Alzheimer’s disease, DSRD has been the subject of virtually no research—until now.

Since 2019, **Jonathan Santoro, MD,** a pediatric neuroimmunologist at Children’s Hospital Los Angeles, has been developing a novel treatment protocol for this devastating disorder. Recently, he launched the first clinical trial in DSRD—a National Institutes of Health-funded collaboration between CHLA and the University of Colorado.

Dr. Santoro talks about how his research came about, what this new trial means for patients and why he’s in a race to find answers.

WHAT IS THE NEED FOR RESEARCH IN DSRD?

It’s critical. This is a condition that was first described in 1946, in a paper on 26 patients with what was called catatonic psychosis. But after that, there was essentially no research on it for 70-plus years. Patients have been misdiagnosed with schizophrenia, early-onset Alzheimer’s disease or late-onset autism. Basically, families have been told, “This is just part of Down syndrome.”

HOW DID YOU START STUDYING THIS CONDITION?

When I began seeing patients with this severe, unexplained regression, my question was: If these patients didn’t have Down syndrome, what would we be doing? Because of my training in neuroimmunology, my natural reaction was to perform a comprehensive workup for inflammatory conditions affecting the brain.

And when we did that, we found inflammatory markers in the cerebrospinal fluid. We then treated those patients with high-dose steroids and an immune therapy called intravenous immunoglobin (IVIG). Since 2019, we’ve seen 200 patients from 32 states at CHLA—by far the most in the country.

YOUR FIRST PATIENT HAD A DRAMATIC RESPONSE TO TREATMENT. WHAT HAPPENED?

This was a previously high-functioning young man who had been in a lot of mainstream classes at school. And then, out of the blue, he completely regressed over a few weeks. By the time I met him, he hadn’t spoken or moved in two years. The family had been flying all over the country to see Down syndrome specialists but had come away with no answers.

We treated him, and three weeks after his first IVIG infusion, he was talking and running down the hallway. It was really striking. Seeing him after treatment was like meeting a different person.

WHAT HAVE YOUR STUDIES FOUND SO FAR?

We’ve discovered that about 20% of patients have standard inflammatory markers in their spinal fluid, and 85% of those patients respond to treatment, particularly IVIG. Interestingly, individuals without those classic inflammation markers also respond to IVIG, at a rate of 70% to 75%.

What we’re doing in our research now is examining the spinal fluid on a deeper level—a protein level. We’ve found that the spinal fluid proteins in individuals with Down syndrome regression disorder are the same proteins we see in patients with inflammatory conditions like multiple sclerosis. In other words, the types of inflammatory proteins that can exist in the spinal fluid are actually there—even in patients who test negative on standard commercial tests.

DOES THAT MEAN THAT DSRD IS AN INFLAMMATORY DISEASE?

We don’t know yet. But there is mounting evidence that this is an inflammatory disorder that is potentially treatable. We also know that individuals with Down syndrome are already predisposed to other autoimmune conditions, such as Type 1 diabetes, and it makes sense that the brain could be predisposed toward autoimmune disease as well.

I think it’s complicated, though. Not every patient has a dramatic response to treatment. In neuroimmunology, it’s not one-size-fits-all. We don’t want to say everyone should get immune therapy because these treatments have side effects. That’s why we need research.

WHAT ARE YOU HOPING TO LEARN IN THIS CLINICAL TRIAL?

The goal is to better understand the role of the immune system in this disorder as well as compare different treatments. Patients will be randomized into three groups. One group will be treated with lorazepam, which is an anti-anxiety medication that treats catatonia and other symptoms. A second group will receive IVIG. And the third will receive a drug called tofacitinib, which directly suppresses the immune system.

The premise behind tofacitinib is that we already know this drug works well in people with Down syndrome who have other autoimmune diseases. It inhibits inflammation via a specific pathway known to be dysregulated in Down syndrome. Our hope is that this could be a more targeted treatment for DSRD.

WHAT IS MOST EXCITING TO YOU ABOUT THIS FIRST TRIAL?

First, it’s a very cool collaboration with the University of Colorado. This is a dual-center effort, and it’s also multidisciplinary—we’re working with experts in genetics, molecular biology, psychology, psychiatry and more.

But the most exciting thing is that we’re doing something. This is a disease that has been brushed under the rug for 75 years. No one has intentionally ignored it, but the fact is that individuals with Down syndrome have historically been underrepresented in research studies overall. When we tell families that we’re opening a clinical trial, I hear these sighs of relief. They appreciate that we are running and not walking in our search to find a treatment for people with this condition.

WHAT HAS BEEN MOST REWARDING FOR YOU?

I’ve seen patients who have had these symptoms for 10 years. You can tell they’re suffering—it’s like they’re locked inside, and they can’t get anything out. To watch them turn around, to see their personalities emerge, is incredibly rewarding.

That said, we’re still working in real time to understand this disease and learn what the best therapies are going to be. We’ve made a lot of progress in a short amount of time, but I still feel like I’m in a race. We have to continue to be very scientific in our approach, while also moving as quickly as possible. Families want their children back.

CHECK OUT THE **NEWEST FACES IN RESEARCH AT CHLA**

CALEB **CORNABY**

Department of Pathology and Laboratory Medicine

Caleb Cornaby, PhD, joined the Department of Pathology and Laboratory Medicine as Assistant Director of the HLA and Diagnostic Immunology and Flow Cytometry labs. He received his doctorate from Brigham Young University, followed by a postdoctoral immunology research training fellowship at the University of Florida. He also completed a postdoctoral clinical immunology and HLA laboratory fellowship at UNC Medical Center. Dr. Cornaby's research focuses on histocompatibility disease association, systemic lupus erythematosus, and immunodiagnostic test development and optimization. He came to Children's Hospital Los Angeles from the University of North Carolina at Chapel Hill.

MOLLY **EASTERLIN**

Fetal and Neonatal Institute

Molly Easterlin, MD, MS, joined the Fetal and Neonatal Institute as an attending neonatologist after completing a fellowship in neonatal-perinatal medicine at LAC+USC/CHLA. Dr. Easterlin received her medical degree from the University of California, San Diego. She completed a pediatrics residency at the University of California, Los Angeles, which she followed with a fellowship in health services research and a master's degree in health policy and management at UCLA. Dr. Easterlin's research is focused on neonatal health services.

REBECCA **ELIAS**

Division of Psychiatry

Rebecca Elias, PhD, received her doctorate in clinical psychology from Virginia Polytechnic Institute and State University. She then completed an internship in clinical psychology at the Indiana University School of Medicine and a postdoctoral fellowship in clinical psychology at the University of California, Los Angeles, before arriving at the Division of Psychiatry, Children's Hospital Los Angeles. Her research now focuses on understanding core processes associated with autism across the lifespan, and the influence that these processes have on treatment response and adult clinical outcomes.

KAMEELAH **GATEAU**

Fetal and Neonatal Institute

Kameelah Gateau, MD, MS, joined the Fetal and Neonatal Institute as an attending neonatologist. She earned her medical degree at the University of California San Diego School of Medicine, completed her residency at CHLA and a fellowship in neonatal-perinatal medicine at LAC+USC/CHLA. Dr. Gateau's research interests include the ecobiodevelopmental model of childhood health and its interaction with the toxic stress response in the perinatal/neonatal period. She is currently conducting a study on identifying the measures and predictors of toxic stress response.

ASHLEY N. **GRAY**

Cancer and Blood Disease Institute

Ashley N. Gray, MD, MS, joined the Cancer and Blood Disease Institute as an attending physician. She earned her Master of Science in integrative biology and physiology from the University of California, Los Angeles, and her medical degree from St. George's University School of Medicine in Grenada, West Indies. She completed general pediatrics residency training at the University of California, San Francisco Fresno campus, and a pediatric hematology-oncology fellowship at UCLA, where she served as Chief Fellow. She recently completed training as an advanced fellow in pediatric bone marrow transplantation/immunotherapy at Seattle Children's Hospital and as a postdoctoral research associate at the Fred Hutchinson Cancer Center. Dr. Gray's research is focused on improving the morbidity and mortality of pediatric patients with graft-versus-host disease (GVHD) by exploring the interaction between the gut microbiota and GVHD.

(continued on next page)

EMILY **HSIEH**

Cancer and Blood Disease Institute

Emily Hsieh, MD, joined the Cancer and Blood Disease Institute as an attending physician. Dr. Hsieh received her medical degree from the Duke-National University of Singapore Medical School. She went on to complete a pediatric hematology-oncology fellowship and bone marrow transplant/immunotherapy advanced fellowship at Texas Children's Hospital. Her research interests include developing cellular therapies for relapsed hematologic malignancies and identifying late toxicities related to CAR T-cell therapies.

AHLEE **KIM**

Center for Endocrinology, Diabetes and Metabolism

Ahlee Kim, MD, joined the Center for Endocrinology, Diabetes and Metabolism as an attending physician. She received her medical degree from Ewha Womans University in Seoul, South Korea, and worked for the University of Tennessee Health Science Center in Memphis. Dr. Kim's clinical and research interests lie in childhood obesity and its metabolic complications. Her goal is to advance the understanding of how these conditions develop over time and to find effective ways to prevent adverse health outcomes.

BIRAJ **MAHATO**

The Vision Center

Biraj Mahato, PhD, MS, came to Children's Hospital Los Angeles after working at Nanoscope Technologies in Bedford, Texas. He received his doctorate from the CSIR-Indian Institute of Chemical Biology in Kolkata, West Bengal, India. His major research interests lie in the field of stem cell biology and regenerative medicine. Dr. Mahato's lab focuses on developing novel cell-based therapies for retinal neurodegenerative diseases—such as glaucoma and optic nerve hypoplasia—by using a combination of cellular reprogramming, next-generation sequencing and preclinical models.

KARIN **MILLER**

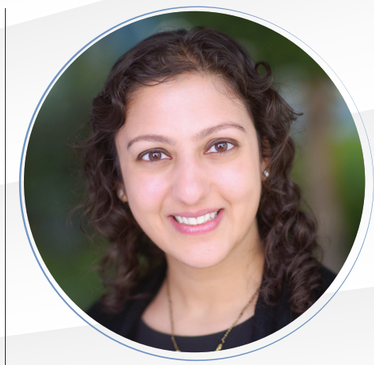
Department of Pathology and Laboratory Medicine

Karin Miller, MD, joined the Department of Pathology and Laboratory Medicine as a staff hematopathologist and molecular genetic pathologist. She completed fellowships in hematopathology and molecular genetic pathology at the Johns Hopkins University School of Medicine, where she also completed her residency in anatomic and clinical pathology and served as Chief Resident in her final year. Dr. Miller received her medical degree from The Ohio State University College of Medicine. Her research focuses on the morphologic, immunophenotypic, and molecular characterization and tracking of hematopoietic neoplasms.

MICHAEL **SCHUMACHER**

Division of Gastroenterology, Hepatology and Nutrition

Michael Schumacher, PhD, joined the Division of Gastroenterology, Hepatology and Nutrition after completing a postdoctoral fellowship at CHLA. He obtained his doctorate at the University of Cincinnati College of Medicine. Dr. Schumacher's National Institutes of Health-funded research focuses on understanding the drivers of tissue and cellular remodeling in intestinal inflammatory diseases—like Crohn's disease and ulcerative colitis—and how to harness these pathways to protect against injury and disease.



JESSICA **SHETH BHUTADA**

Cancer and Blood Disease Institute

Jessica Sheth Bhutada, MD, MS, joined the Cancer and Blood Disease Institute as an attending physician. She received her medical degree from the University of Kansas School of Medicine and completed a pediatrics residency at the Ann & Robert H. Lurie Children's Hospital of Chicago. She then completed a fellowship in pediatric hematology-oncology and an advanced fellowship in adolescent and young adult oncology at CHLA. Her research focuses on identifying and addressing health disparities in adolescents and young adults with cancer.

AWARDS **AND HONORS**

MARVIN **BELZER**

The National Institute of Allergy and Infectious Diseases at the National Institutes of Health (NIH) awarded $2.5 million to **Marvin Belzer, MD,** Director of the Division of Adolescent and Young Adult Medicine at Children's Hospital Los Angeles. In collaboration with researchers at UCLA and Lurie Children's Hospital of Chicago, Dr. Belzer will conduct a randomized clinical trial to evaluate a mobile adaptation of LifeSkills, a Centers for Disease Control and Prevention evidence-based intervention designed to reduce the risk of young transgender women acquiring HIV.

MICHAEL I. **GORAN**

Michael I. Goran, PhD, Director of the Nutrition and Obesity Program at The Saban Research Institute of CHLA, received $24.5 million from the NIH's National Institute on Minority Health and Health Disparities. Dr. Goran will lead the Southern California Center for Latino Health to address the many factors that contribute to chronic health disparities in Latino/a/x children and families.

MICHAEL I. **GORAN** & BRADLEY **PETERSON**

Michael I. Goran, PhD, and **Bradley Peterson, MD,** were awarded $2.8 million from the National Institute of Diabetes and Digestive and Kidney Diseases at the NIH to study the role of early nutrition on brain development. Their project will examine how early life diet affects obesity, appetite regulation, brain structure and function, and cognitive outcomes during early childhood.

AWARDS
AND HONORS

SHAFALI SPURLING **JESTE**

The National Institute of Mental Health at the NIH granted **Shafali Spurling Jeste, MD,** Chief of Neurology and Las Madrinas Chair, $2.3 million to help lead the Autism Biomarkers Consortium for Clinical Trials, one of the largest autism research projects in the country. In this study of children ages 6 to 11, investigators at five institutions are aiming to establish biomarkers in autism that can help determine the effectiveness of new treatments in future clinical trials.

LORRAINE **KELLEY-QUON**

Lorraine Kelley-Quon, MD, MSHS, received over $3 million from the Eunice Kennedy Shriver National Institute of Child Health and Human Development at the NIH to lead a study on the long-term impact of opioid use in hospitalized infants. The goal of Dr. Kelley-Quon's research is to determine how doctors can help critically ill infants tolerate surgery and life-sustaining interventions while minimizing the long-term risks of prolonged or excess opioid use.

NATASHA **LEPORÉ**

Natasha Leporé, PhD, and her collaborator at Children's National Hospital were granted $3.5 million from the NIH's National Institute of Dental and Craniofacial Research to study brain and cranium development in children. The project will use cranial phenotyping tools in MRI scans to better understand how the brain and cranium interact and grow together, with the goal of benefiting infants with cranial deformities.

(continued on next page)

JESSICA L. **WISNOWSKI** BETH A. **SMITH** & PAT **LEVITT**

Jessica L. Wisnowski, PhD, Beth A. Smith, DPT, PhD, and **Pat Levitt, PhD (left to right),** were awarded $6.8 million from the NIH's National Institute on Drug Abuse to help lead the HEALthy Brain and Child Development Study. This national research program will follow approximately 7,500 pregnant women and their infants to determine how a child's environment affects their brain development. The study seeks to identify the environmental factors that pose the greatest risk, as well as those that build resilience.

CHING-LING (ELLEN) **LIEN**

The California Institute for Regenerative Medicine granted **Ching-Ling (Ellen) Lien, PhD,** $5 million to create a five-year training program for promising young scientists in stem cell and regenerative medicine. Participants will receive research project support, education, mentorship and career development. The program aims to support regenerative medicine research that will ultimately lead to new treatments for patients.

ETAN **ORGEL**

The National Cancer Institute at the NIH awarded $3.2 million to **Etan Orgel, MD, MS,** of CHLA's Cancer and Blood Disease Institute, to investigate benefits of nutrition and exercise during treatment for acute lymphoblastic leukemia. In a national trial conducted by the Therapeutic Advances in Childhood Leukemia & Lymphoma (TACL) consortium, Dr. Orgel is studying how changes in diet and activity can reprogram leukemia cells to be more susceptible to chemotherapy and reduce leukemia relapse.

BETH A. **SMITH**

The NIH's Eunice Kennedy Shriver National Institute of Child Health and Human Development awarded $3.1 million to **Beth A. Smith, DPT, PhD,** to study the emergence of cortical lateralization of motor function in infancy. Her project examines how the infant brain refines and specializes its function as an infant learns to reach.

DOUGLAS **VANDERBILT**

Douglas Vanderbilt, MD, MS, CHLA's Division Chief of Developmental-Behavioral Pediatrics, was awarded $3.9 million by the Health Resources and Services Administration's Maternal and Child Health Bureau to conduct the California Leadership Education in Neurodevelopmental Disabilities Program. This grant seeks to train the next generation of interdisciplinary leaders in research, policy, education and clinical care for those with or at risk of developmental and behavioral problems.

LARRY **YIN**

The USC University Center for Excellence in Developmental Disabilities at CHLA received $3 million from the U.S. Department of Health and Human Services to continue interdisciplinary work in support of children, youth and young adults with disabilities—including early intervention, health care, community-based services, education, transition assistance, employment, research, policy and technical assistance. The research project, led by **Larry Yin, MD, MSPH,** Chief of the Division of General Pediatrics, is aimed at helping these individuals and their families live independently in their communities.

AN 18-YEAR JOURNEY

FROM IDEA TO FDA-APPROVED THERAPY

By Amy Schleunes

For decades, parents of children with several types of cancer treated with cisplatin have faced a difficult reality—knowing that this lifesaving form of chemotherapy comes with a high risk for causing permanent, life-altering hearing loss. **David R. Freyer, DO, MS,** Director of the Survivorship and Supportive Care Program at Children's Hospital Los Angeles, felt like there should be better options for these patients and their families, so he led a key study to test a medication that could protect against hearing loss without compromising the lifesaving effects of the chemotherapy. After two randomized clinical trials and 18 years of collaboration, that medication, sodium thiosulfate, has now been approved by the FDA for this use.

"It's an ambitious, complex, multiyear effort that succeeded only because many essential people were behind it," Dr. Freyer says.

Back in 2004, Dr. Freyer first heard about using sodium thiosulfate to treat cisplatin-induced hearing loss from Edward Neuwelt, MD, a neurosurgeon at Oregon Health and Science University, who had shown that the medication prevented cisplatin-induced hearing loss in animal models. That preclinical work provided the foundation for the Phase 3 randomized, controlled clinical trial that began in North America in 2008 and included pediatric participants at CHLA and over 30 other hospitals. The study was sponsored by the Children's Oncology Group and funded principally by the National Cancer Institute of the National Institutes of Health.

The trial showed that the incidence of hearing loss in patients treated with cisplatin alone was 56.4%, while the incidence dropped to 28.6% in patients treated with both cisplatin and sodium thiosulfate. In children who received sodium thiosulfate, the risk for developing hearing loss was reduced by 70%. This finding is clinically important because sodium thiosulfate offers the hope of preventing the downstream consequences of childhood hearing loss, including speech, learning and behavioral difficulties.

DAVID R. FREYER, DO, MS

This step is key for enabling sodium thiosulfate to be covered by insurance and become more widely available to patients nationwide.

"If we're able to protect their hearing, these children will experience many decades of improved quality of life."

— David R. Freyer, DO, MS

"Most of the cancers treated with cisplatin are curable, and as a result, most of those children become long-term survivors," says Dr. Freyer. "If we're able to protect their hearing, these children will experience many decades of improved quality of life."

The results from the North American trial and a separate, concurrent one conducted in the United Kingdom were published in 2018, after which the drug manufacturer applied for FDA approval.

The nearly two decades-long process fundamentally changed the way pediatric oncologists think about cisplatin-induced hearing loss, according to Dr. Freyer. Instead of accepting hearing loss as a necessary consequence of curative treatment with cisplatin, doctors are able to offer the hope of preventing this problem for the majority of patients.

"As a cancer survivorship specialist, I've personally taken care of many children, teens and young adults who have had to live with hearing loss," Dr. Freyer says. "Knowing there will be fewer of those patients is really meaningful."

Jennifer Dien Bard, PhD,
Director of the Clinical Microbiology
and Virology Laboratory

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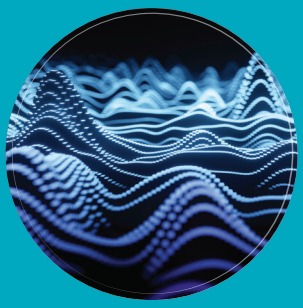
IN THIS **ISSUE**

UNDER THE MICROSCOPE
An experimental treatment that taps the immune system could reverse the devastating effects of Down syndrome regression disorder.

SOUTHERN CALIFORNIA CENTER FOR LATINO HEALTH
Reducing health disparities and obesity risk for Latino children could be the most effective way of preventing chronic diseases in adults.

THE FUTURE OF AUTISM TREATMENT
Diversity in autism research studies is essential so that new therapies will benefit children of all ethnicities.



BACKSTORY
The 18 year journey from a good idea to an FDA-approved medication that prevents hearing loss associated with chemotherapy

TO LEARN MORE ABOUT RESEARCH VISIT
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