CHILDREN'S HOSPITAL LOS ANGELES

RESEARCHLA

2021

COVID-19 RESEARCH: FROM THE LAB TO THE PATIENT IN RECORD TIME

An early, proactive response by the Department of Pathology and Laboratory Medicine helped put Children's Hospital Los Angeles ahead of the SARS-CoV-2 curve—and advanced science to battle the virus.

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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 2021, CHLA received $43.7 million in National Institutes of Health (NIH) funding and $92.5 million in total extramural 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

The past year was full of lessons. Across the globe, every person was affected by the COVID-19 pandemic, if not directly by illness, then by job losses, school closures, business slowdowns or shortages of food and supplies.

Severe circumstances often present a choice. We did not ask for a pandemic, but we have a choice about how to respond to it.

At Children's Hospital Los Angeles, we are proud that our research enterprise—and the entire hospital—chose to stand up and live the mission we signed up for. While our research laboratories closed to comply with safety measures, the work did not stop. It did not stop because the need for lifesaving research didn't stop. In fact, the need became greater. In response, our team members developed new ways to safely continue—and thrive.

Our investigators continued to apply for and receive research grants, to publish their work in top-tier journals—and they developed entirely new lines of research. Our team members knew we needed to respond quickly to better understand the SARS-CoV-2 virus and the spread of COVID-19. And we did—because we know that research is the single best tool for advancing medicine and improving children's hope for a healthier future.

If there was a theme for this period, it has been our ability to rise up and meet challenges. In a year full of obstacles, our research enterprise overcame each one and forged ahead. There are many examples of how research advanced—including COVID-related studies and investigations into the other disorders that impact the lives of children. A few examples are:

- The Department of Pathology and Laboratory Medicine recognized the signs of a pandemic long before the virus reached our shores. The team had prepared in-house testing by the time California officially shut down, met seven days a week to stay on top of an evolving virus and conducted some of the largest pediatric COVID-19 studies in the world.

- Thomas Coates, MD, and his team are unraveling the biological mechanisms that trigger pain in people with sickle cell disease, by working to identify a biomarker that will allow patients to prevent rather than treat the debilitating pain associated with this condition.

- Tracy Grikscheit, MD, is working toward a clinical trial, scheduled to begin in 2022, testing stem cell therapies for children with severe digestive tract disorders. Her work and passion were fortified by the passing of a proposition granting $5.5 billion to stem cell research.

Though the threat of SARS-CoV-2 continues, we have learned that not even a pandemic can stop our efforts to conduct lifesaving research and to continue discovering ways to improve the lives of children, adolescents and young adults.

We hope you enjoy learning more about the work in this issue of ResearCHLA magazine.

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)

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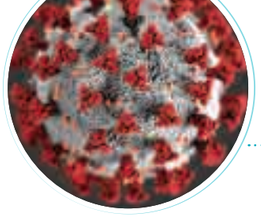

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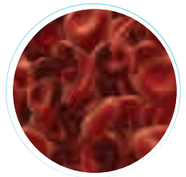
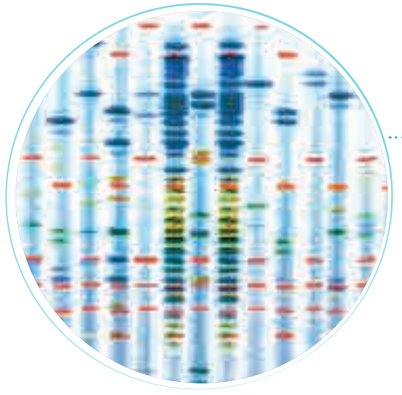




IN THE **NEWS**

XIAOWU **GAI**

Center for Personalized Medicine

JENNIFER **DIEN BARD**

Division of Laboratory Medicine

Multiple news outlets, including The Washington Post and The New York Times, featured the work of **Xiaowu Gai**, **PhD**, and **Jennifer Dien Bard**, **PhD**. Along with colleagues in the Department of Pathology and Laboratory Medicine, **Drs. Gai** and **Dien Bard** published a number of studies tracking the spread of SARS-CoV-2 through genomic testing, using genomics to track potentially dangerous variants and contributing their findings to national and international databases.

MICHAEL I. **GORAN**

Endocrinology, Diabetes and Metabolism

Michael I. Goran, **PhD**, led a study analyzing the effects of consuming sugary beverages while breastfeeding. Higher sugar consumption during nursing negatively impacted children's cognitive development at 2 years of age. The study was covered by multiple outlets across the United States and internationally.

JULIE **JAFFRAY**

Cancer and Blood Disease Institute

CLAUDIA **BORZUTZKY**

Adolescent and Young Adult Medicine

Julie Jaffray, **MD**, and **Claudia Borzutzky**, **MD**, spoke to The New York Times about their research on safe and effective ways to help teenagers whose heavy menstruation interferes with daily activities. Their study, published in JAMA Pediatrics, discusses the high prevalence of young girls with heavy menstrual bleeding, as well as best practices for diagnosing underlying causes and treatment.

DIANA **MOKE**

Cancer and Blood Disease Institute

ETAN **ORGEL**

Cancer and Blood Disease Institute

Etan Orgel, **MD**, **MS**, and **Diana Moke**, **MD**, **MS**, conducted the largest study to date characterizing hearing loss associated with the common chemotherapy agent cisplatin. This landmark study, published in The Lancet Child & Adolescent Health, provides new insights into which children are at risk for hearing loss and suggests future approaches to minimize hearing loss without compromising treatment.

Dr. Orgel also will lead a randomized phase 2 clinical trial through the Therapeutic Advances in Childhood Leukemia & Lymphoma (TACL) consortium, headquartered at Children's Hospital Los Angeles. The Associated Press reported on phase 1 of the IDEAL trial, which showed diet and exercise can improve the effectiveness of chemotherapy in children with leukemia.

SHAHAB **ASGHARZADEH**

Cancer and Blood Disease Institute

CAR T-cell therapy is a powerful agent against leukemia when traditional chemotherapies fail, but the therapy has not been successful in solid tumors and other cancers. **Shahab Asgharzadeh**, **MD**, and colleagues modified CAR T-cells to be more potent and selective using a technology called SynNotch gating. The preclinical study, published in Nature Communications, suggests a potential for more widespread use of CAR T-cell therapy.

ROHIT **KOHLI**

Gastroenterology, Hepatology and Nutrition

Sugar consumption can lead to obesity and fatty liver disease, including scarring of the liver. In a preclinical study published in Scientific Reports, a Nature journal, **Rohit Kohli**, **MBBS**, **MS**, showed that consumption of stevia extract, a natural noncaloric sweetener, can actually improve markers of fatty liver disease and prevent scarring. Other artificial sweeteners did not have this effect.

LORRAINE **KELLEY-QUON**

General Pediatric Surgery

Attending Surgeon **Lorraine Kelley-Quon**, **MD**, was the lead author on the first-ever set of guidelines for safely prescribing opioids to manage pain after children's surgery. The evidence-based guidelines, published in JAMA Surgery, were reported by The New York Times.

TEAMWORK

HOW **CHLA** STAYED AHEAD OF THE COVID-19 CURVE

Discoveries moved from the lab to the patient in record time.

By Candace Pearson

Britain's royal family led international news covered by U.S. news outlets on Jan. 9, 2020. Fortunately, a smaller story caught the attention of **Jennifer Dien Bard**, **PhD**. The World Health Organization issued a statement regarding a cluster of pneumonia cases in Wuhan, China. On that day, she began tracking the progression of the still unnamed novel coronavirus.

By February, the respiratory virus—now called SARS-CoV-2 for severe acute respiratory syndrome—had moved beyond China into Italy and Iran.

"We knew then we were facing a global crisis," recalls **Dr. Dien Bard**, Director of the Clinical Microbiology and Virology Laboratory at Children's Hospital Los Angeles. "It was only a matter of time before the virus would strike the United States."

Dr. Dien Bard reached out to **Alexander R. Judkins**, **MD**, Pathologist-in-Chief and Chair of the Department of Pathology and Laboratory Medicine at CHLA, and **Maurice O'Gorman**, **PhD**, **MSc**, Chief of Laboratory Medicine. Her urgent recommendation: The hospital should begin to increase in-house quantities of test supplies and materials.

Based on continuing international reports, she anticipated worldwide demand would outstrip supply. The team made calls. Reinforced supply chains. And took delivery of all types of testing materials—from swabs to reagents.

That early work and planning prompted by **Dr. Dien Bard** ensured CHLA was ready when COVID-19 hit the U.S. The hospital quickly launched an ambitious testing program and fast-tracked research to study the source of the virus's rapid growth.

"As an academic medical center, we were prepared with expertise and infrastructure to begin tackling this rapidly evolving situation from many directions at once," says **Dr. Judkins**. "Our team was among the first in the nation to develop and validate a highly specific test, make it available and fast-track results."

Over the next year, the hospital marshaled its resources to help ensure the continued delivery of care for children—and lead the scientific community's understanding of COVID-19 in pediatrics through the use of genomic epidemiology, a 21st century scientific technique. "We created bioinformatics tools to analyze the genetics of the virus and subsequent mutations," says **Dr. Judkins**. "Then we sequenced and tracked the spread of the virus both locally and nationally and established an ongoing effort among U.S. children's hospitals to catalog all variants of the virus that impact children."

MOVING FROM 'NO TEST' TO 'RESULTS IN FOUR HOURS'

In those early weeks of the pandemic, with no commercial test available, the team began developing a highly sensitive COVID-19 test to determine if an individual had been infected with the virus. Unlike a test kit that is ready to

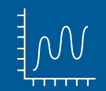
(continued on next page)

1 Swab collected from patient at CHLA testing site and sent to CHLA Virology Lab.

2 Sample is processed and genetic material is removed.

3 Genetic material is prepared for analysis.

4 A process called a polymerase chain reaction (PCR) amplifies viral genetic material, if present.



5 PCR data is analyzed.

6 Sample is determined to be COVID-19 positive or negative.

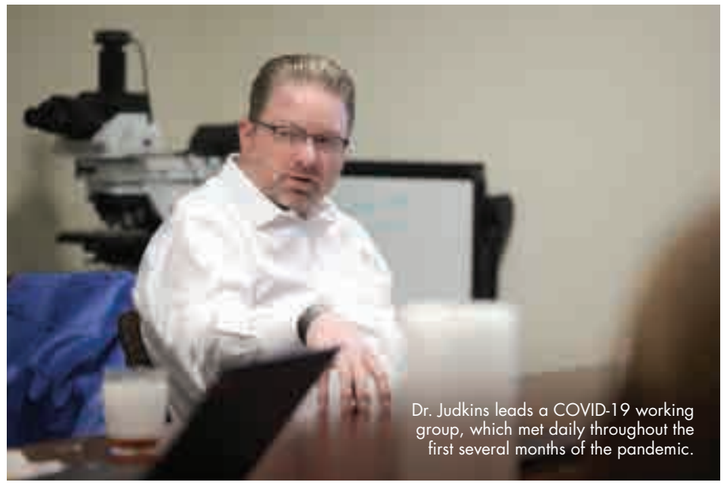
7 Patient is notified of COVID-19 status.

8 COVID-19 positive results reported to patient and public health databases.

9 Every COVID-19 positive sample is saved and sequenced.

10 Genomic data uploaded into international databases.

THE JOURNEY OF A COVID-19 TEST FROM START TO FINISH



Dr. Judkins leads a COVID-19 working group, which met daily throughout the first several months of the pandemic.

use, a lab-developed test requires design, development, validation, training and implementation. But those steps take time, one resource the team didn't have.

"At CHLA, we invest in people and equipment, and that put us in the fortunate position of being able to move quickly," says **Dr. Dien Bard**. "We developed a test prior to the shutdown in California. We moved ahead with offering the test, shortening the time for results to just hours and began developing a saliva test. All while many institutions were still waiting for test materials."

On March 1, 2020, the Centers for Disease Control and Prevention reported 23 confirmed COVID-19 cases in five major U.S. metropolitan areas. Experts now say the actual numbers then likely reached into the tens of thousands.

"No one knew what was going to happen in the coming months," says **Dr. Judkins**, "but we knew that communication and teamwork would be critical."

To meet that need, **Dr. Judkins** launched a COVID-19 working group, which convened seven days a week to strategize each move against the virus as the death toll rose. Daily participants included **Dr. Judkins**, **Dr. O'Gorman** and **Dr. Dien Bard**, along with key department administrators and laboratory leaders. Additional specialists rotated in as needed, including those with expertise in microbiology, pathology, immunology, genetics and bioinformatics. The assembled group members pooled their knowledge and ideas as they reviewed worldwide research and strategized questions they would strive to answer.

When the hospital's COVID-19 test became ready the first week of March—before schools and public places even began to shut down—**Dr. O'Gorman** took a leadership role in planning the actual testing at CHLA. That included interfacing the testing with the hospital's electronic medical record to provide an online patient portal where members of the public could easily check their results.

On March 13, CHLA received emergency use authorization for its COVID-19 test from the Food and Drug Administration. Three days later, the hospital's drive-through and walk-through COVID-19 testing site opened, one of the first in Southern California. (See page 11.)

Initially, the virology laboratory produced results in 24 to 48 hours. "Within two weeks, we achieved a six-hour turnaround," says **Dr. O'Gorman**. Shortly after, it added a four-hour rapid test to help clinicians in diagnosing and treating emergency cases.

It fell to **Jennifer Lee**, Administrative Director of the Department of Pathology and Laboratory Medicine, to staff a laboratory that suddenly went from one nine-hour shift a day to a 24/7 operation.

"Within two weeks, we achieved a six-hour turnaround," says Dr. O'Gorman. Shortly after, the virology laboratory added a four-hour rapid test to help clinicians in diagnosing and treating emergency cases.

TEST RESULT TURNAROUND TIMES

Lab technicians were redeployed to process the COVID-19 test, with more help coming from other areas of the hospital. "There was a lot of confusion at the onset of the pandemic, and the work was overwhelming at times," says **Ms. Lee**. "But we knew we had a critically important job to do, and everyone stepped up to do it."

From March 2020 to March 2021, the department performed more than 80,000 COVID-19 tests for employees, patients, patient families, neighboring hospitals and community physicians.

UNRAVELING THE VIRAL GENOME

In April 2020, **Xiaowu Gai, PhD**, Director of Bioinformatics in the Center for Personalized Medicine, led development of whole-genome sequencing and bioinformatics tools to analyze the evolution, spread and risk factors of COVID-19.

"We couldn't wait for information to come to us," he says. "As geneticists, we wanted to decode the genetics of the virus and discover what enabled it to become so infectious."

His team created a database of SARS-CoV-2 genomic sequences from every positive test result processed at Children's Hospital Los Angeles and, to fortify that resource, solicited test data from pediatric institutions around the globe.

The investigators knew they weren't tracking a single virus. "Every time a virus infects a person, it replicates and sometimes makes mistakes in copying its genes," says **Dr. Gai**. "These mutations were leading to different forms of the virus."

By October 2020, the team's analysis of COVID-19 transmission patterns, based on analysis of mutations, confirmed that early travel restrictions and other measures in the U.S. had helped limit spread between states and regions nationwide. A month later, they published the largest pediatric COVID-19 study to date, which identified a specific group of mutations more commonly seen in pediatric patients and—for the first time—linked them with the most severe COVID-19 symptoms.

The team also formed a sequencing consortium with eight other U.S. pediatric medical centers, which sent (and continue to send) their positive COVID-19 results to be sequenced and tracked at CHLA for ongoing research.

PROGRESS IN THE LAB, THE COMMUNITY AND THE WORLD

In an extraordinary year for science, researchers around the world pooled their findings and went from discovering the virus to creating a vaccine—an unprecedented event in scientific history. Children's Hospital Los Angeles began offering the vaccine to its team members in late December 2020 and soon after, to patients, patient families and members of the community.

Dr. Judkins confers with Jennifer Lee.

(continued on next page)

By spring 2021, the investigators had authored or co-authored 17 publications, with more on the way, and given 14 invited presentations—including an international webinar sponsored by the American Academy for the Advancement of Science that featured Dr. O'Gorman.

Dr. Gai and Dr. Dien Bard discuss an upcoming publication.

As the pandemic entered year two, the areas of study were multiplying. Clinicians at the Cancer and Blood Disease Institute noted that some patients with a compromised immune response continued to record positive COVID-19 results month after month. An interdisciplinary investigation led by **Dr. Dien Bard** showed that SARS-CoV-2 can produce a lingering infection, which helps viral mutations multiply—an important insight for treating children and adults with weakened immune systems.

By spring 2021, the investigators had authored or co-authored 17 publications, with more on the way, and given 14 invited presentations—including an international webinar sponsored by the American Academy for the Advancement of Science that featured **Dr. O'Gorman**.

From the start, the team focused on the science and used its skills to understand and track the virus, to help protect patients and families, and make Children's Hospital Los Angeles a leader in pediatric COVID-19 research. The group's work continues.

Moving forward, **Dr. Dien Bard** is eager to study a new method of school-based testing for COVID-19 and other respiratory viruses. **Dr. Gai** and his team are busy sequencing the virus present in children with multisystem inflammatory syndrome or MIS-C to find genetic clues into why some patients develop this more devastating form of infection.

"We've learned a great deal about this pandemic," says **Dr. Judkins**. "And now, we need to be ready for the next one."

WHAT IS MIS-C?

- Multisystem inflammatory syndrome in children (MIS-C) is a rare and serious condition affecting some children who were previously exposed to COVID-19.
- The risk of developing MIS-C remains very low for children.
- MIS-C causes severe inflammation to various parts of the body, including the heart, lungs, kidneys, brain, skin, eyes and gastrointestinal organs.
- MIS-C patients experience fever plus such symptoms as abdominal pain, vomiting, rash, diarrhea or bloodshot eyes.
- MIS-C can be serious, even deadly, but most children get better with medical care.
- Treatment includes immune-modifying therapies like intravenous immune globulin (IVIG) and steroids.
- Children's Hospital Los Angeles has a specialized multidisciplinary MIS-C clinical service that cares for more than half of all MIS-C cases in Los Angeles County.
- Investigators are participating in RECOVER, a National Institutes of Health initiative to study post-acute effects of COVID-19, including MIS-C.

A GOOD NEIGHBOR

From the first hint of a COVID-19 pandemic in early 2020, scientists in the Children's Hospital Los Angeles Department of Pathology and Laboratory Medicine knew testing would be crucial to controlling the virus.

In March 2020, the hospital developed health screenings for everyone entering its campus. That same month, it launched drive-through and walk-through COVID-19 testing at its Sunset Boulevard site for hospital team members and all children admitted to the hospital or undergoing procedures.

Access didn't end there. CHLA expanded its testing services to area hospitals, many of which had trouble securing test supplies. Among the first "customers" were Keck Medicine of USC, Huntington Hospital and USC Verdugo Hills Hospital, along with Shriners for Children Medical Center-Pasadena, Harbor-UCLA Medical Center, Adventist Health Glendale and others.

The hospital also made testing available to patients of more than 200 community pediatricians within the Children's Hospital Los Angeles Care Network.

As the first COVID-19 vaccines gained approval, CHLA began immunizing its staff and opened a free vaccine clinic for community members, teachers and parents. As of June 2021, hospital team members had vaccinated more than 31,000 people.

"In addition to keeping our hospital safe and open," says **Maurice O'Gorman, PhD, MSc**, Chief of Laboratory Medicine, "we wanted to provide our neighbors with access to both testing and vaccines."

80,000
COVID-19 TESTS PERFORMED MARCH 2020–MARCH 2021

200+
COMMUNITY PEDIATRICIANS WITHIN CHLA'S CARE NETWORK OFFERED COVID-19 TESTING

31,000+
PEOPLE VACCINATED BY CHLA TEAM MEMBERS AS OF JUNE 2021

5 THINGS TO KNOW ABOUT COVID-19 RESEARCH

The pandemic stopped the world in its tracks, forcing many industries to shut down. Research was affected, with labs closed and investigators asked to work remotely. But while many projects were placed on hold, some science was just getting started.

Research that focused on SARS-CoV-2 and COVID-19 flourished and continues to grow. Beyond development of vaccines and treatments, scientists began investigating how the pandemic affected us, from the level of specific cells in our bodies, to the health and well-being of our families, our communities and the world.

Here are five things you should know about COVID-19 research at Children's Hospital Los Angeles:

1

SARS-CoV-2 damages cells that produce insulin.

Endocrinologists at Children's Hospital Los Angeles noticed that more patients were presenting with new-onset Type 2 diabetes at an advanced stage—with a complication called diabetic ketoacidosis.

Senta Georgia, **PhD**, who researches diabetes and insulin-secreting pancreatic cells called beta cells, wanted to find out what was driving this trend. She was aware of the debate among her clinical colleagues—postulating whether it was a product of delayed diagnosis and treatment because of the pandemic, or if it was a real effect of SARS-CoV-2 on the beta cells.

Most laboratory studies reported on the effects of virus added to beta cells in a petri dish. **Dr. Georgia** wanted a model that would more accurately reflect how humans contract the virus.

Using preclinical models that encountered the virus by inhalation, she observed that SARS-CoV-2 was present in the pancreas—and the beta cells showed signs of metabolic stress, even when symptoms were no longer visible. Although these findings don't fully explain the trend, they shed some light on what might be occurring. According to **Dr. Georgia**, pancreatic cells do not regenerate quickly, so it is unknown how long the damage to the beta cells might persist.

"Our concern is that we may be impacting an entire generation, either to develop diabetes now or to increase their susceptibility to it later in life because of decreased beta cell capacity brought on by the stress of COVID-19," she says.

2

Some adolescents are dealing with the pandemic better than others.

A big concern throughout the pandemic has been about young people. How stressed are they, separated from their normal routines revolving around school and friends? Fortunately, an ongoing study at The Saban Research Institute, called the ABCD study, was already three years into monitoring social and emotional changes in adolescents. This national study, which follows 11,000 children at 21 sites around the U.S., was expanded to specifically monitor effects of the pandemic.

Elizabeth Sowell, **PhD**, Children's Hospital Site Principal Investigator who specializes in the neurodevelopment of children and adolescents, sent questionnaires to every parent and child enrolled at CHLA asking about stress.

From a national perspective, investigators found that children and parents in wealthy areas, at less risk for contracting COVID-19 since their parents were working from home and not risking infection each day, demonstrated a significant amount of stress. **Dr. Sowell** and her team predicted even higher levels for CHLA participants—many of whom have parents who were working outside the home and potentially increasing the family's risk for exposure to the virus.

"We were thrilled to discover that the families we follow appeared to talk to their kids more about the risk of COVID-19, and their kids demonstrated more risk-reduction behavior like handwashing and masking—allowing everyone in the family to worry less," says **Dr. Sowell**. "Parents in our study are doing an amazing job at buffering their kids against stress."

3

COVID-19 transmission in families varies—a lot.

What happens when one member of a household gets infected with SARS-CoV-2? According to **Pia Pannaraj**, **MD**, an infectious disease specialist who is leading a study that has enrolled 150 local households and more than 600 individuals, the chances of other family members developing COVID-19 are more than 70%.

"We were surprised by such a high transmission rate," says **Dr. Pannaraj**. "When we controlled for various aspects like income, family size and density in the home, we found that the strongest predictor of transmission was Hispanic ethnicity. We don't know if this is driven by cultural or genetic factors."

The study also found that children were the source of the virus being brought into the home nearly 50% of the time, despite school closures and other restrictions. The study continues for another year and will monitor trends that emerge as children return to school.

Dr. Pannaraj and her team are also considering immune response and whether protection against subsequent infection will differ for people who contracted and recovered from COVID-19 compared with children and adults who received the vaccine.

4

New moms are stressed and want to talk about it.

Plans for a national study on children's brain development from infancy until school age were being led by Principal Investigator **Pat Levitt**, **PhD**, Chief Scientific Officer, Director of The Saban Research Institute and Simms/Mann Chair in Developmental Neurogenetics. Then the pandemic intervened—causing the research team to pivot.

"We know that stress impacts early brain development," says **Beth Smith**, **PhD**, **DPT**, an infant neuromotor development specialist who led the Children's Hospital Los Angeles COVID-19 and Perinatal Experience (COPE) study. "Suddenly faced with this uniquely stressful experience, we wanted to see how mothers and their babies were managing."

Dr. Smith and her colleagues conducted an online survey for pregnant women or women who had recently given birth. If the new moms or moms-to-be chose to give their contact information, the research team followed up and asked if the women would be interested in further participation, including interactive assessments and providing noninvasive biological samples.

Women answered questions about their experiences, their own health and wellness, and the development of their child. Although data are still being collected and have not yet been analyzed, one thing is already clear.

"This was an unprecedented experience—being pregnant, delivering a baby and nurturing an infant during a time of tremendous stress and isolation," says **Dr. Smith**. "Women were eager to have an opportunity to talk about it."

5

The virus keeps changing (which is why getting vaccinated matters).

While the world was encountering a brand new virus, **Xiaowu Gai**, **PhD**, who leads bioinformatics at CHLA's Center for Personalized Medicine, was creating a suite of informatic tools to study it. These novel tools compare the genetic blueprints of the virus isolated from each patient, providing a mechanism for tracking the ever-changing virus. Using a type of 21st century science called genomic epidemiology, **Dr. Gai** continues the hunt.

"The virus is always evolving and so is the disease it causes," he says. "Our job is to monitor and report these conditions because they not only affect individual patients, but also present public health concerns for our country and the rest of the world."

As it moves from person to person, the virus acquires mutations, eventually producing a new variant. The more people that are infected, the higher the chances are that this will happen. **Dr. Gai** and his colleagues have discovered that certain variants are associated with more serious disease. They have also determined that acquiring certain mutations produces variants that are more easily transmitted. These accumulated mutations, like in the Delta variant, confer a competitive advantage resulting in a globally dominant version of the virus.

Although multiple vaccines are available and millions of people have received one, many have not. According to **Dr. Gai**, each unvaccinated person represents a vulnerability for the virus to exploit.

As the virus continues to mutate, producing new variants that are more easily transmitted and causing increasingly severe disease, it could cause the current vaccine to become ineffective.

"We are constantly on the lookout for new variants of concern and checking for their ability to produce breakthrough infections," says **Dr. Gai**. "If that happens, we will provide that information so that the vaccine can be updated."

2020:

LIFE AFFECTS RESEARCH

How national and international events influenced the work of The Saban Research Institute

Researchers spend their careers discovering information that benefits society. At an academic medical center like Children's Hospital Los Angeles, investigators are constantly working on ways to address patients' unmet medical needs observed by their clinical colleagues. Even discovery research—which is geared toward gaining a deeper understanding of basic biology—is conducted with the long view toward improving the lives of patients.

This year, scientists at The Saban Research Institute focused on needs that were both close and far reaching. These ranged from identifying and battling the effects of SARS-CoV-2, the virus behind COVID-19, to taking a leading role in tracing its spread and working to contain it. This work had both a local and global reach.

In addition to the pandemic, there were other occurrences that changed people's lives and influenced the work done at our institution. This timeline depicts how some major events of 2020 helped shape research activities.

2020

JANUARY

JAN 9
The World Health Organization (WHO) announces the first reports of a novel coronavirus causing severe pneumonia-like cases in Wuhan, China.

JAN 21
The U.S. Centers for Disease Control and Prevention (CDC) confirms the first case of COVID-19 in the United States.

JAN 23
China initiates lockdown in Wuhan.

JAN 31
WHO declares a global public health emergency.

FEBRUARY

FEB 11
The new virus is named SARS-CoV-2.

FEB 23
Italy sees its first major surge.

FEB 24
Iran emerges with a surge of cases.

Members of CHLA's Department of Pathology and Lab Medicine recognize the beginnings of a pandemic. They begin stocking up on test supplies and reagents and developing an in-house COVID-19 test.

See: Teamwork: How CHLA Stayed Ahead of the COVID-19 Curve. pg. 6

MARCH

MAR 11
The WHO declares COVID-19 a pandemic.

MAR 13
President Donald Trump declares a national emergency.

MAR 13
Los Angeles Unified School District announces that all schools will close.

MAR 13
The COVID-19 test developed by the Department of Pathology and Laboratory Medicine receives emergency use authorization (EUA) and is offered to hospital staff and patients.

See: Backstory on Genetic Sequencing pg. 40

MAR 17
The Centers for Medicare & Medicaid Services expands U.S. telehealth rules, setting the stage for quick, large-scale adoption of virtual visits.

MAR 19
California announces "Safer at Home" orders that mandate residents to stay home unless work or shopping is essential.

Work published by our Pathology and Laboratory Medicine team later showed that measures like these limited the spread of new viral variants.

MAR 26
The United States leads the world in confirmed COVID-19 cases.

MAR 20
The Saban Research Institute shuts down its laboratories to limit the spread of SARS-CoV-2. Amid a worldwide shortage of personal protective equipment, the research enterprise gives its supplies of masks, gloves and wipes to be used by staff for clinical care at Children's Hospital Los Angeles.

APRIL

APR 2
Total cumulative cases of COVID-19 pass 1 million across 171 countries and six continents. The virus's death toll passes 51,000 worldwide.

APR 5
The Department of Pathology and Laboratory Medicine begins offering SARS-CoV-2 wholegenome sequencing to Children's Hospital Los Angeles and eight other children's hospitals around the nation to help track the virus.

APR 10
The Department of Pathology and Laboratory Medicine begins offering SARS-CoV-2 antibody testing to CHLA team members if required.

APR 15
Clinical trials continue at CHLA, with some visits shifted to virtual meetings.

APR 16
Tracked global deaths from the virus exceed 200,000 people, with more than 2.9 million sickened.

MAY

MAY 9
The FDA grants an EUA to Rutgers Clinical Genomics Laboratory for a saliva-based test that can be used at home.

Our Pathology and Laboratory Medicine team conducted research to compare saliva versus nasal swab testing and began offering saliva-based tests in the fall.

MAY 13
CHLA holds a virtual press conference to discuss multisystem inflammatory syndrome in children (MIS-C), a rare but serious complication occurring in some children who have recovered from COVID-19.

MAY 15
U.S. launches Operation Warp Speed to develop a COVID-19 vaccine.

MAY 26
Large-scale Black Lives Matter demonstrations begin in the wake of George Floyd's murder, one of multiple high-profile killings of Black people that sparked the movement.

MAY 27
U.S. deaths from the virus pass 100,000, more than any other nation.

USA	101,567
UK	38,376
ITALY	33,340
SPAIN	29,043
FRANCE	28,717

JUNE

JUN 5
Medical professionals gather to protest racism as part of White Coats for Black Lives.

JUN 10
U.S. COVID-19 cases top 2 million.

JUN 24
The Saban Research Institute announces a phased recovery for the research enterprise, with some investigators returning to their labs.

JULY

JUL 2
California is among several states that postpone or reverse reopening plans.

Research conducted by Pathology and Laboratory Medicine shows that these safety measures limited spread of SARS-CoV-2 variants.

JUL 7
The United States surpasses 3 million cases.

JUL 9
WHO announces that SARS-CoV-2 can be transmitted by air and by asymptomatic people.

JUL 13
The Saban Research Institute officially reopens with masking, social distancing and other safety guidelines.

JUL 14
Phase 1 and 2 trial data from Moderna's vaccine show promise.

JUL 21
CHLA adds its ongoing commitment to the community and underserved populations to its mission statement.

JUL 22
U.S. Department of Health and Human Services and the Department of Defense announce a partnership with Pfizer and BioNTech for 100 million vaccine doses.

AUGUST

AUG 15
The FDA issues an EUA for a saliva COVID-19 test.

AUG 16
The CDC starts to develop a vaccine distribution plan.

AUG 17
COVID-19 becomes the third-leading cause of death in the United States, behind heart disease and cancer.

SEPTEMBER

SEP 3
With the largest pediatric COVID-19 study in the United States to date, the Pathology and Laboratory Medicine team publishes data showing that early safety measures and travel restrictions limited the initial spread of COVID-19 in states like California and Washington.

SEP 14
Pfizer and BioNTech announce the expansion of a phase 3 trial of their COVID-19 vaccine.

SEP 21
Johnson & Johnson begins a phase 3 trial of its one-dose COVID-19 vaccine.

SEP 23
A study in Texas finds a more contagious strain of the virus.

Consistent monitoring of viral genomics makes findings like this possible.

SEP 27
Armenian and Azerbaijani forces clash in Nagorno-Karabakh.

SEP 28
Global deaths from COVID-19 surpass 1 million.

Pathology and Laboratory Medicine continues to genetically sequence every COVID-19 positive sample from Children's Hospital Los Angeles and many from the greater Los Angeles community, and to contribute findings to national and international databases.

OCTOBER

OCT 2
President Trump and Melania Trump test positive for COVID-19. The President is hospitalized and returns to the White House Oct. 5.

OCT 15
The U.S. reports 60,000 new COVID-19 cases in a day.

OCT 19
Global cases top 40 million, with more than 1.1 million killed by the virus.

Map courtesy of Wikimedia Commons.

NOVEMBER

NOV 3
California voters approve Proposition 14, providing $5.5 billion for stem cell research.

See: Under the Microscope pg. 24

NOV 4
The U.S. hits a new record high of 100,000 new cases reported in one day.

NOV 16
Moderna announces that its vaccine reduces the risk of infection by 94.5%.

NOV 18
Pfizer and BioNTech release data demonstrating their vaccine is 95% effective.

NOV 20
Vigil for Peace for Armenia and Artsakh.

DECEMBER

DEC 8
The U.K. begins vaccinations.

DEC 11
FDA approves emergency use authorization for the Pfizer/BioNTech vaccine in the U.S.

DEC 17
The first CHLA team members begin receiving the COVID-19 vaccine.

DEC 18
FDA approves emergency use authorization for the Moderna vaccine in the U.S.

DEC 21
The U.K. announces a new variant of the virus, B.1.1.7, is spreading and more contagious.

Consistent monitoring of viral genomics makes findings like this possible.

"When people ask me, 'What is the conclusion of your $9.5 million research grant,'" says Dr. Coates, "I say, 'Well, you should listen to mothers.'"

MOM KNOWS BEST

Researchers at Children's Hospital Los Angeles are unraveling the biological mechanism that triggers pain in people with sickle cell disease—and confirming what mothers have been saying all along.

By Stephanie Cajigal

Over the course of more than three decades studying sickle cell disease and caring for patients, **Thomas Coates, MD**, has learned an important lesson: listen to the mothers. It is their detailed accounts of their children's pain that inspired his current research focus.

Supported by a five-year National Institutes of Health (NIH) award of $9.5 million, Dr. Coates and colleagues are studying how the autonomic nervous system—a network of cells that regulates processes we don't consciously think about (like breathing and blood vessel constriction)—plays a role in sickle cell disease.

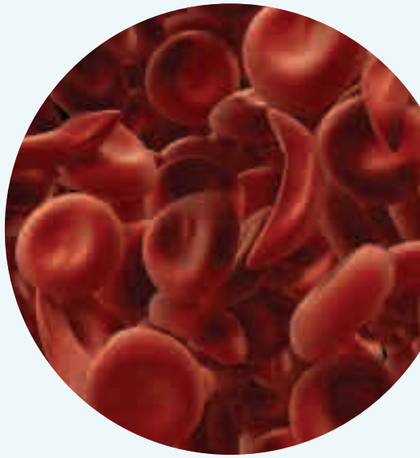
A life-threatening inherited blood disorder, sickle cell disease is most prevalent in parts of the world where malaria is or was common; the genetic mutation that can lead to the disease is thought to have a protective effect against malaria. In the United States, sickle cell disease is rare and most commonly found in people of African and Hispanic descent.

In treating children with sickle cell disease, Dr. Coates knows that parents are an important part of the medical team.

Normally, red blood cells carry hemoglobin, a protein that transports oxygen throughout the body. But in sickle cell disease, the hemoglobin molecules stick together, causing the red blood cells to become rigid and take on a crescent or sickle shape. These cells get stuck traveling through small blood vessels, preventing a healthy supply of oxygen to the tissues. When muscles and bones are deprived of oxygen, people with sickle cell disease can go through episodes of severe pain—similar to the pain of a bone fracture—that can last many days. The pain can be severe enough to require hospitalization.

The question of what causes the change from steady state to crisis has long stumped researchers and clinicians. The consensus from patients and their families is that pain crises most often occur after experiences involving mental stress, anxiety, exposure to extreme temperatures or pain itself.

"Mothers are always saying to their kids, 'Dress warmly, wear a hat, because if you get cold you are going to have a crisis,'" says Dr. Coates, Section Head of



Healthy red blood cells are round and move easily through arteries and veins. Sickle cells, which appear crescent in shape, can lodge in blood vessels and block blood flow, causing pain.

(continued on next page)

Hematology within the Cancer and Blood Disease Institute at Children's Hospital Los Angeles.

Through a series of studies with people who have sickle cell disease, Dr. Coates and his research team have shown that when exposed to cold, heat, a painful stimulus or when asked to do tasks that cause some degree of mental stress, these individuals experience a narrowing of their blood vessels called vasoconstriction. According to Dr. Coates, the reduction in blood flow may be what causes pain.

"In the lab, we showed that mental stress, pain and cold can cause an 80% reduction in blood flow, within seconds," he says.

Further investigation could change the way doctors, nurses—and patients themselves—track and manage this devastating disease.

MEASURING BLOOD FLOW

One way that researchers are working to better understand sickle cell disease is by directly measuring blood flow. This information could lead to the creation of a biomarker, an externally measurable substance or process that signals when a biological condition is occurring. For people with sickle cell disease, a biomarker could indicate when a pain crisis will happen.

Dr. Coates and colleagues use available technology—like the red-lighted fingertip oxygen sensor you commonly see in the hospital or the green light in a smart watch that measures heart rate—and mathematical modeling to estimate blood flow.

"We measured and quantified blood flow changes," Dr. Coates says, "and patients who have more vasoconstriction and low blood flow tend to have more pain crises."

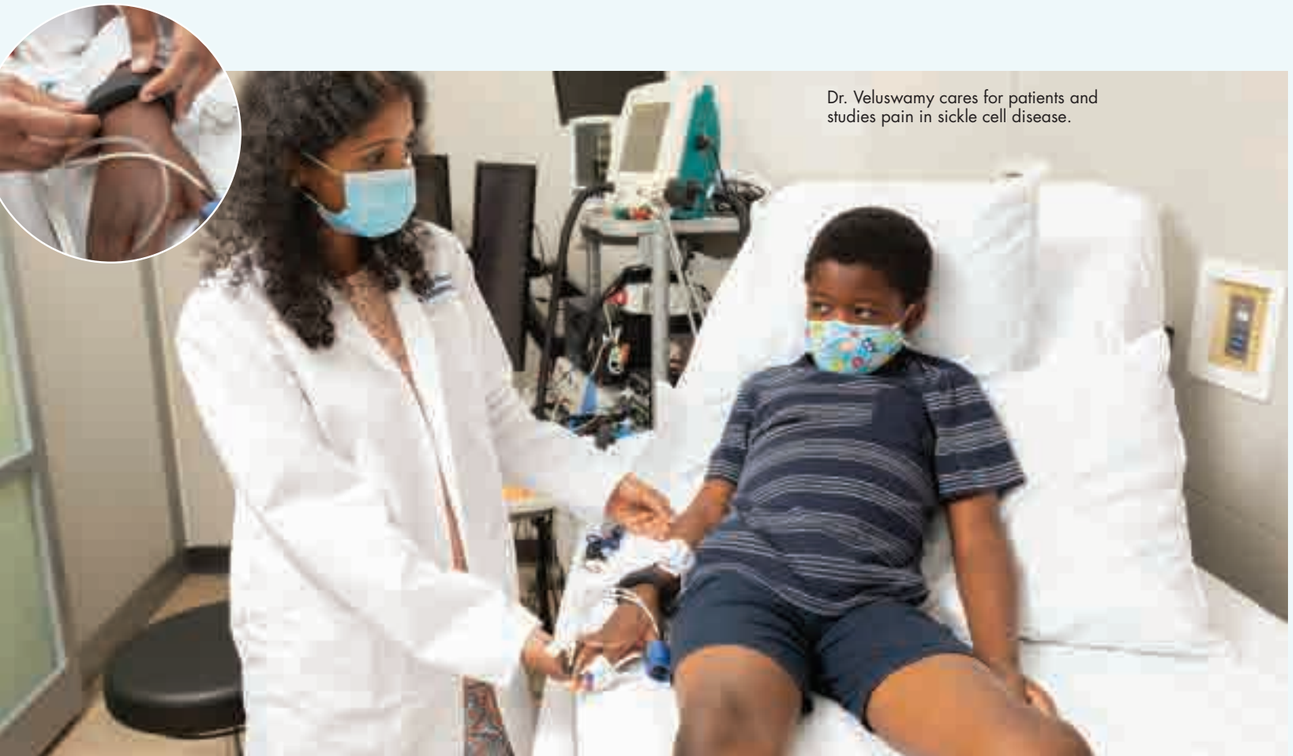
Payal Shah, MS, Senior Research Associate at Children's Hospital Los Angeles, says results from the team's experiments show stress reduces blood flow in people with sickle cell disease. These findings correlate with what patients report. In one study, people with sickle cell disease were asked to record their daily pain and stress symptoms

PAYAL SHAH, MS

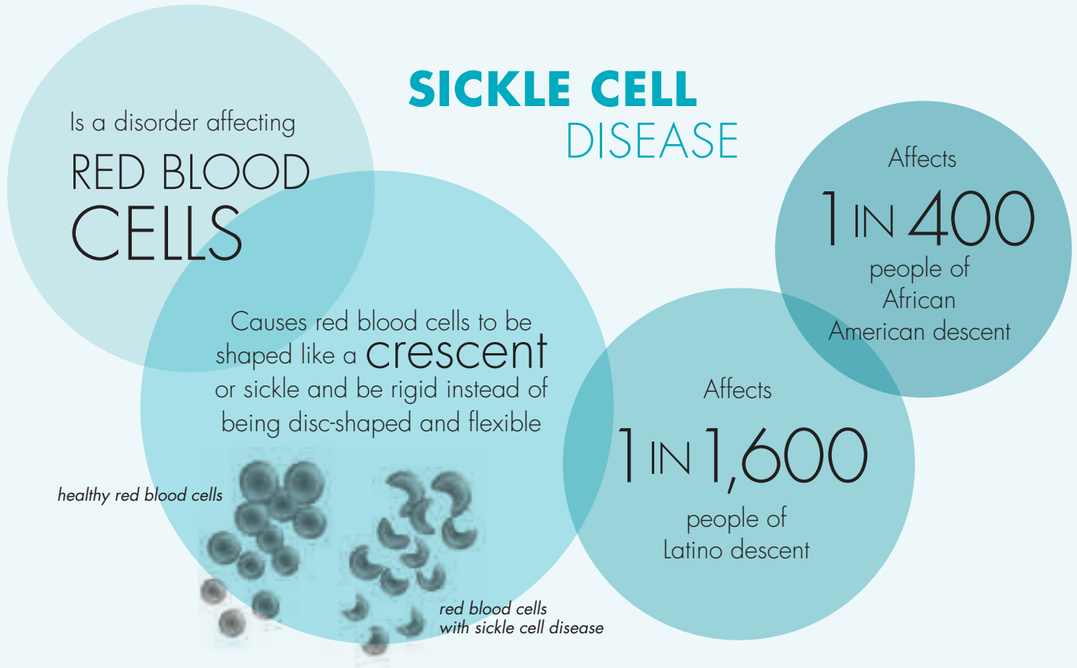
on a phone app. Researchers found that patients reported more pain during times of higher stress.

But there is still a lot to learn about why some people with sickle cell disease feel pain very often and some do not, according to **Saranya Veluswamy, MD**, an attending physician in the Cancer and Blood Disease Institute and a co-investigator on several sickle cell studies. "We are looking at whether it's due to differences in their autonomic nervous systems," she says. "Are people who have an autonomic nervous system imbalance more prone to pain?"

Understanding why people experience debilitating pain and finding ways to predict when it happens could lead to prevention strategies.



Dr. Veluswamy cares for patients and studies pain in sickle cell disease.



COGNITIVE-BASED THERAPIES

The team is studying whether cognitive-based interventions, which focus on teaching people with sickle cell disease how to calm their mind and body, could help them avoid a pain crisis.

"We definitely won't replace mainstream therapies, but if these cognitive-based therapies translate into patients having fewer hospitalizations or emergency room visits, and that they can continue with their day-to-day life, that is valuable," says Shah.

An earlier pilot study led by Dr. Coates and **Lonnie Zeltzer, MD**, Director of the Pediatric Pain Program at UCLA Mattel Children's Hospital, showed that a 30-minute hypnosis session increased blood flow in people with sickle cell disease. The team recently completed a larger study, led by Dr. Zeltzer's postdoctoral fellow, **Sarah R. Martin, PhD**, a clinical psychologist and now an Assistant Professor in the Department of Anesthesiology and Perioperative Care at the University of California, Irvine, School of Medicine's Center on Stress and Health.

Dr. Martin guided half of the participants through a hypnosis exercise in which they were asked to imagine creating a comforting medication for their own unique pain. The other half, the controls, listened as Dr. Martin read them stories. Before and after the hypnosis and stories, researchers placed a thermal metal device on participants' arms meant to cause some slight pain. Those who did the hypnosis exercise reported less pain and less reduction in blood flow compared with the control group that did not do the hypnosis.

"I always like to promote open-mindedness in terms of considering these other evidence-based and effective interventions for pain," Dr. Martin says.

MOVING FROM THE LAB TO HOME

The team is currently proposing a follow-up study that would monitor how hypnosis affects blood flow over time in teenagers with sickle cell disease. In addition to practicing self-hypnosis at home and using a cognitive-based therapy app, study participants would wear a device on their wrist, similar to a fitness tracker, that would optically measure vasoconstriction—allowing investigators to track and remotely measure the impact of hypnosis on blood flow.

According to Dr. Coates, the findings could have long-term effects on how sickle cell disease is managed. "It could be possible that by wearing a device on their wrist, a patient could monitor their blood flow, and if it is decreasing, they could take a medication that would reverse the process and, hopefully, prevent a crisis," he says.

Also, they can take steps to prevent vasoconstriction—such as practicing self-hypnosis and wearing warm clothing when it's cold.

"When people ask me, 'What is the conclusion of your $9.5 million research grant,'" says Dr. Coates, "I say, 'Well, you should listen to mothers.'"

UNDER THE MICROSCOPE

Tracy Grikscheit, MD, discusses her groundbreaking clinical trial, how optimism drives her and why she was made for pediatric surgery.

By Melinda Smith, PhD

In the operating room and clinic, **Tracy Grikscheit, MD**, treats children with disorders affecting the digestive tract. Sometimes, this means removing diseased or non-functioning sections of the intestines. If enough tissue is removed, children may require transplant surgeries or intravenous (IV) nutrition for the rest of their lives. As these treatments are incredibly challenging and have significant side effects, Dr. Grikscheit has developed a research program aimed at delivering better outcomes.

In her laboratory, she works in the realm of tissue engineering—the growth of new intestinal tissue to replace missing or diseased sections. Dr. Grikscheit's preclinical studies have culminated in a method to grow induced pluripotent stem cells, or IPSCs, into fully functional tissue. Her already overlapping worlds of pediatric surgery and discovery science are about to converge even more as she edges toward a clinical trial.

Now in her 15th year at Children's Hospital Los Angeles, Dr. Grikscheit talks about stem cell therapies, funding for research and why adding pictures to a wall means so much.

WHAT ARE YOUR ROLES AT CHILDREN'S HOSPITAL LOS ANGELES?

I came to CHLA right out of my fellowship, so I've been here 15 years. I recently became the Chief of the Division of Pediatric Surgery. Part of the time, I'm a surgeon taking care of children; part of the time, I'm leading my division. But I also run a research laboratory, working on stem cell therapies.

THAT'S A LOT OF ROLES. DOES IT FEEL LIKE A BALANCING ACT?

No, it's all very synergistic. At the end of the day, everything I do is about optimism. I think most pediatric surgeons are optimists. It's why we do what we do. We love seeing that we can fix a problem and then that baby thrives for the next 90 years. As a surgeon, when I see an unmet clinical need, I am very hopeful that, through science, I can make medicine better by finding a way to meet that need. And as a division chief, part of my job is to remove hurdles for those doing discovery or clinical work. It's all about optimism, making things better.

WHAT LED YOU TO BECOME A PEDIATRIC SURGEON?

I always loved to do technical things with my hands, so in medical school I realized that surgery was a natural fit. Then when I rotated into pediatric surgery, the world just came together.

Pediatric surgery allows me to be the kind of doctor I want to be—I get to participate from the very beginning. I have great dialogues with the families, where we work together to decide how to proceed. I feel like I'm part of a team that is championing each child. And that's how it should be.

DO YOU EVER GET THE CHANCE TO FOLLOW UP WITH YOUR FAMILIES DOWN THE ROAD?

Just today, actually. A dad brought in his little boy who I had treated a couple of years ago. If we didn't intervene, his son would have died. Today he brought the child into the clinic just to show him to me, as if to say, you did this. And if I can do that 100 times, and have 100 wonderful kids running around who otherwise wouldn't have been, then maybe I've earned my place in the world. We're all here to do something positive, make a mark. [Dr. Grikscheit points to a wall, where there's a corkboard covered with letters and pictures.] Here are some of my kids. These families are letting me know that they're out there enjoying the world, and that's really the whole reason we're here.

SHIFTING TO YOUR RESEARCH, WHAT ARE YOUR GOALS? WHAT NEEDS ARE YOU TRYING TO MEET?

Sometimes children are born with disorders where a large section of the intestine simply doesn't work. It could be that the tissue is diseased, or the digestive tract is missing the proper nervous system. Either way, we often have to remove sections of intestine.

If the condition is severe enough, the child will need an intestinal transplant or they'll have to get IV nutrition. But transplants aren't always successful, and IV nutrition keeps children alive but isn't really a permanent solution. We need better options for these kids. And that's where my lab work comes in.

HOW WILL RESEARCH PROVIDE BETTER OPTIONS?

If we could replace sections of tissue by helping the child regrow them, these kids could have a shot at eating normally and doing everything their peers are doing. Even though I run a discovery science lab, we will only pursue a research question if it's going to directly lead to a future human therapy.

SMALL BEGINNINGS LEAD TO GREAT THINGS

Dr. Grikscheit has many roles at CHLA, but her story can be distilled into one common theme: The biggest and most meaningful things can grow from the tiniest. A simple vision to support future research can evolve into billions of dollars of funding to develop much needed treatments. A stem cell, smaller than the period at the end of this sentence, can become a working part of a new organ for a child. That 6-pound baby can grow up to live a full life. And a picture on the wall can remind us of our purpose—to do the kind of work that matters.

Discovery science for the sake of discovery is very important, and we depend on that foundation for our work. But we have a specific goal to get stem cell therapies out and available to children in need. And because we have been so focused, we are getting close to testing our stem cell therapy in a clinical trial.

HOW CLOSE ARE YOU TO GETTING STEM CELL THERAPIES INTO THE CLINIC?

We are currently working with the Food and Drug Administration (FDA) to initiate a clinical trial in the next year or two to help children with severe enteric neuropathy. These are children who are missing some or all of the nerve tissue controlling their digestive tract. It's like having a roadway with no signs or traffic lights. The intestines are there, but there are no signals to get them to work.

In our experiments, we've been able to regrow the nerve cells and they're fully functional. The goal is to rebuild the nervous system in the digestive tract without having to remove or replace the child's intestines. After many, many years of experiments, we are ready to bring this therapy to our patients.

WHY STEM CELLS?

Stem cells are special because they are essentially waiting to be told what to do. With the right environment, they can become any kind of cell, and we've spent many years discovering the most effective ways to get them to grow into fully functional tissue.

WHAT ADVANTAGES WOULD YOUR STEM CELL THERAPY HAVE OVER CURRENT TREATMENTS?

Some babies with enteric neuropathy are so sick and they're just too small to undergo a surgical procedure like a transplant, even if donor tissue is available. We don't always know that a baby will be born with a poorly functioning digestive tract, so it would be a huge advantage to have a therapy ready immediately.

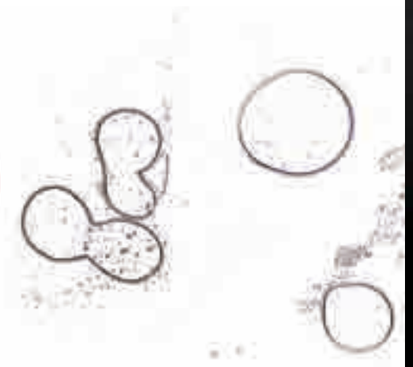
The stem cell therapy we are working on is essentially an "off-the-shelf" treatment, meaning that once the clinical trials are complete and it is FDA-approved, it would be ready to go for any baby who needs it. And if we can help a child regrow the missing tissue themselves, we would eliminate issues like donor tissue availability and the risk of transplant rejection.

LAST YEAR, PROPOSITION 14 PASSED, GIVING $5.5 BILLION TO THE CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE (CIRM). HOW HAS FUNDING LIKE THIS IMPACTED YOUR WORK?

The people of California have driven my ability to make stem cell therapies for babies. CIRM funding isn't just money. It's a mindset that has really caused this area of research to bloom; it has helped to cultivate an entire field and a generation of scientists.

We've had many CIRM-funded students in our lab, and they have gone on to get advanced degrees and are working with stem cells. An entire network of people and field of research have arisen from the vision that the people of California had to make their state a leader in developing stem cell therapies to fill unmet clinical needs.

When the proposition passed, I had a video call with some other scientists who also championed the initiative. We all just looked at each other in awe and said, "Let's do this. Let's fix people."



CAN A TINY FISH TRANSFORM TREATMENT FOR

CHILDHOOD CANCERS?

A physician-scientist is harnessing the power of zebrafish—and a new, state-of-the-art facility—to develop innovative treatments for solid tumors in children.

By Katie Sweeney

You might think you couldn't possibly have much in common with a fish—especially an inch-long member of the minnow family with colorful, zebra-like stripes. But **James Amatruda, MD, PhD**, begs to differ.

"Zebrafish are, in many ways, quite similar to humans in anatomy, physiology and disease susceptibility," says Dr. Amatruda, Head of Basic and Translational Research for the Cancer and Blood Disease Institute at Children's Hospital Los Angeles. "They're vertebrates, we share 70% of the same genes, and 80% of disease-causing genes in humans have a corresponding gene in zebrafish."

These traits make zebrafish an excellent model for studying human disease. To harness this potential, Dr. Amatruda is leading the new Alfred E. Mann Family Foundation Zebrafish Facility at Children's Hospital Los Angeles. The 3,000-square-foot lab will support scientists studying many pediatric conditions and house up to 120,000 zebrafish.

"We have big ambitions," he says. "We want to study all the cancer genes. We want to study thousands of drug treatments. And we want to do it all very quickly, on a large scale."

DEVELOPMENT GONE AWRY?

Dr. Amatruda, who holds the Dr. Kenneth O. Williams Chair in Cancer Research, studies solid tumor cancers in children, including liver and kidney cancers and sarcomas (cancers of the bone, muscle and connective tissue). Although treatments like surgery, chemotherapy and radiation have dramatically improved survival rates for these cancers, they often come with toxic and long-term health effects. And not all patients respond to them.

"Zebrafish are, in many ways, quite similar to humans in anatomy, physiology and disease susceptibility."

— James Amatruda, MD, PhD

"We're starting to hit a plateau," he says, slapping one face-down palm over another, mimicking a ceiling. "We need new approaches."

One focus for his team: the link between these cancers and early development. Normally, a child's primitive fetal cells grow and mature into organs, bones and muscles. Once this tissue is fully formed, the cells stop dividing. But in children with solid tumor cancers, the cells keep growing long after they're supposed to stop.

"Most adult cancers are due to aging and environmental effects," Dr. Amatruda notes. "In children, it's a different story. We think that it's during these key moments in development that the tumor process starts."

To understand this process at a deep biological level, researchers need a living model. That's where those tiny zebrafish come in. The fish grow quickly and are initially transparent—making it easy to observe both normal and tumor development.

NOVEL APPROACHES

Dr. Amatruda's team has developed a zebrafish model of rhabdomyosarcoma, a muscle cancer in children. The team found that a cancer-causing "fusion oncogene" called PAX3-FOXO1 disrupts muscle development in children, causing these cells to keep growing instead of maturing.

"With our zebrafish model and this beautiful new facility, these studies are now accessible to us."

— James Amatruda, MD, PhD

The team is now validating possible pathways for blocking this disruption. The approach would be highly targeted to tumor tissue—and potentially less toxic to normal cells. "It's always the dream to target the tumor and none of the normal tissue," he says. "It's imperfect, but there are some tantalizing hints that there's a real therapeutic avenue forward."

In Ewing sarcoma, a bone cancer in kids and young adults, the fusion oncogene involved is so toxic, it's impossible to study in other preclinical models. But Dr. Amatruda's team created a model in zebrafish.

Over just a few weeks, researchers can track a tumor's development, gaining insight into how normal cells in the tumor's "neighborhood" are coerced into promoting the tumor's growth.

"We're looking at the most specific way to target this interaction," he says. "With our zebrafish model and this beautiful new facility, these studies are now accessible to us."

As a physician-scientist, Dr. Amatruda is passionate about developing these new approaches for young patients—including his own.

"I never feel like progress is fast enough, because there are kids right now struggling with these cancers," he says. "Working with patients and families is a tremendous motivator. It's a continual reminder of what's at stake."

NEW **FACES**

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

MOHAMED **ABOU-EL-ENEIN**

Cell Therapy Program

Mohamed Abou-el-Enein, MBChB, PhD, MSPH, joined Children's Hospital Los Angeles and USC as the inaugural Executive Director of the Cell Therapy Program. Dr. Abou-el-Enein is trained as a physician and received a clinical research diploma from Harvard University, a doctorate from Charitè Medical University in Berlin and a Master of Science in public health from the London School of Hygiene & Tropical Medicine. He is working with researchers to accelerate promising scientific discoveries into clinical applications and to establish robust bio-manufacturing capabilities.

MATTHEW **DEARDORFF**

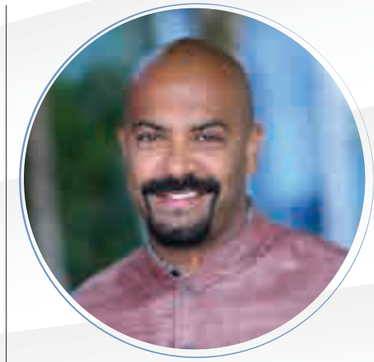
Center for Personalized Medicine

Matthew Deardorff, MD, PhD, joined the Department of Pathology and Laboratory Medicine as Director of Translational Genomics at the Center for Personalized Medicine. He earned his medical degree, completed his clinical training and began his career at the University of Pennsylvania and Children's Hospital of Philadelphia. Dr. Deardorff's expertise in genetics, genomics, rare diseases and electronic health record implementation guides him in his new role as the inaugural Director of the Personalized Care Program at Children's Hospital Los Angeles.

SABRINA **DERRINGTON**

Center for Pediatric Bioethics

Sabrina Derrington, MD, MA, HEC-C, joined Children's Hospital Los Angeles as the inaugural Director of the new Center for Pediatric Bioethics. She earned her medical degree from the University of California, Davis, School of Medicine and her master's in bioethics from Loyola University of Chicago. Dr. Derrington completed her residency and fellowship at Children's Hospital Los Angeles and most recently served as Associate Professor and Associate Director of Clinical Ethics and Education at Lurie Children's Hospital of Chicago.



BRIAN G. **DIAS**

Developmental Neuroscience and Neurogenetics Program

Brian G. Dias, PhD, joined the Developmental Neuroscience and Neurogenetics Program and is studying how stress and trauma affect genes, gametes (reproductive cells), physiology and neurobiology. He earned his doctorate from the University of Texas at Austin and came to Children's Hospital Los Angeles from Emory University, where he was an Assistant Professor in the Department of Psychiatry and Behavioral Sciences.

(continued on next page)

RAMON **DURAZO-ARVIZU**

Biostatistics and Data Analysis Core

Ramon Durazo-Arvizu, PhD, joined Children's Hospital Los Angeles as Faculty Director of the Biostatistics and Data Analysis Core. He provides analytical expertise to investigators and works on applying statistical methods to epidemiology and clinical research. Dr. Durazo-Arvizu received his doctorate in applied mathematics from the University of Arizona and came to Children's Hospital Los Angeles from Loyola Medical Center. His research background includes work to describe and understand racial and ethnic health disparities.

BRIDGET **FERNANDEZ**

Division of Medical Genetics

Bridget Fernandez, MD, MS, joined the Division of Medical Genetics and is using deep phenotyping approaches to better understand the genomic underpinnings of autism spectrum disorder. She is also Associate Director of Clinical Research at The Saban Research Institute. Dr. Fernandez received a bachelor's degree in human physiology from McGill University and her master's and medical degrees from Memorial University. Dr. Fernandez also completed a residency in medical genetics at the Hospital for Sick Children in Toronto.

MILLER **HUANG**

Cancer and Blood Disease Institute

Miller Huang, PhD, joined the Cancer and Blood Disease Institute. His research focuses on central nervous system cancers—seeking to find the genetic causes of medulloblastoma and neuroblastoma, as well as new therapeutic strategies to treat these diseases. Dr. Huang received a bachelor's degree in bioengineering from the University of California, Berkeley, and a doctorate in molecular pathology from the University of California, San Diego.

SHAFALI **SPURLING JESTE**

Neurological Institute

Shafali Spurling Jeste, MD, joined the Neurological Institute as Chief of the Division of Neurology and Co-Director of the Neurological Institute. She earned her medical degree from Harvard Medical School and completed her residency and fellowship at Boston Children's Hospital. Dr. Jeste is helping to grow the clinical, academic and training programs in Neurology and is collaborating with other specialties to develop clinical research programs of excellence in neurodevelopmental disorders. Her research includes developing methods to improve diagnoses and treatments for children with neurodevelopmental disorders.

JINSEOK **PARK**

Cancer and Blood Disease Institute

JinSeok Park, PhD, joined the Cancer and Blood Disease Institute with an interest in understanding the role of the tumor microenvironment in cancer development. He studies how cancer cells decode physical properties of their environment, regulating cancer-related signaling pathways to promote tumor development. Dr. Park obtained his bachelor's in chemical and biological engineering from Seoul National University in South Korea and his doctorate in biomedical engineering from Johns Hopkins University.

SARAH A. **RICHMAN**

Cancer and Blood Disease Institute

Sarah A. Richman, MD, PhD, joined the Cancer and Blood Disease Institute, where she is continuing her research into how to redirect T-cells to better recognize and target tumors. She also serves as an attending physician in the Transplantation and Cellular Therapy Section. Dr. Richman received her medical and doctorate degrees from the University of Illinois at Urbana-Champaign and completed a residency at Columbia University Irving Medical Center and a fellowship at Children's Hospital of Philadelphia.

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TAMARA D. **SIMON**

Hospital Medicine

Tamara D. Simon, MD, MSPH, joined the Division of Hospital Medicine as an attending physician and serves as Associate Director of Training and Education at The Saban Research Institute. She received her medical degree from the University of North Carolina at Chapel Hill School of Medicine and a Master of Science in public health from the University of Colorado, Denver. Dr. Simon's research involves improving the evidence base for inpatient care for children with complex medical needs, focusing on hydrocephalus.

BETH **SMITH**

Infant Neuromotor Control Laboratory

Beth Smith, PhD, DPT, PT, joined the Division of Research on Children, Youth and Families as Director of the Infant Neuromotor Control Laboratory. She studies the development of neural control of movement in infants with either typical development or developmental disabilities. Dr. Smith, who came to Children's Hospital Los Angeles from USC, earned a doctorate in physical therapy from Boston University and a doctorate in kinesiology from the University of Michigan.

JAMES **AMATRUDA**

James Amatruda, MD, PhD, was named the inaugural Dr. Kenneth O. Williams Chair in Cancer Research. Dr. Williams was a pillar of the Hematology-Oncology team at Children's Hospital Los Angeles for four decades; the chair is made possible thanks to a generous gift from longstanding hospital supporters Helen and Bill Close.

JESSE **BERRY**

Jesse Berry, MD, Associate Director of The Vision Center at Children's Hospital Los Angeles, received the highly selective 2021 USC Mentoring Award for Faculty Mentoring Graduate Students. The award recognizes Dr. Berry's efforts in going above and beyond what is expected and in fostering an engaging, supportive and inclusive academic environment.

PAT **LEVITT**

Pat Levitt, PhD, was named to the Governing Board of the California Institute for Regenerative Medicine (CIRM) for a six-year term. In the coming years, CIRM will include a new focus on brain disorders, which will be significantly advanced by Dr. Levitt's expertise in neuroscience.

MICHELE **KIPKE**

The National Institute on Drug Abuse of the National Institutes of Health (NIH) awarded **Michele Kipke, PhD**, $14.3 million to examine disparities among underrepresented youth in the prevention and treatment of HIV/AIDS.

BRADLEY **PETERSON**

Bradley Peterson, MD, received $6.1 million from the Patient-Centered Outcomes Research Institute (PCORI) to initiate a study in more than 400 youth with anxiety.

JOHANNA **OLSON-KENNEDY**

Spearheaded by Principal Investigator **Johanna Olson-Kennedy, MD**, the Division of Adolescent and Young Adult Medicine's Center for Transyouth Health and Development was awarded $4.9 million from the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the NIH to study the impact of early medical treatment in transgender youth.

CHINTAN **PAREKH**

Chintan Parekh, MD, received a $2.3 million grant from the National Institute of Allergy and Infectious Diseases of the NIH to study a specific gene in T-cells that may help researchers make immunotherapies like chimeric antigen receptor T-cell therapy (CAR-T) more effective.

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PIA **PANNARAJ**

Pia Pannaraj, MD, MPH, received $3.4 million from the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the NIH to study global disparities of the rotavirus vaccine. She was also awarded $1.3 million to study SARS-CoV-2 viral transmission and immunity within households. The SARS-CoV-2 funding is part of a larger, multicenter study enrolling over 250 families to better understand the behavior of the virus and why it affects some individuals more than others within the home.

LESLIE F. **CLARK**

The Department of Health and Human Services awarded **Leslie F. Clark, PhD, MPH**, of Adolescent and Young Adult Medicine, $2 million to examine the effects of school and neighborhood context on the effectiveness of teen pregnancy prevention programs. This research, using 11 longitudinal datasets of federally funded studies, will increase understanding of vulnerable populations still at greater risk of unplanned pregnancies and will identify needs to address.

PAT **LEVITT**

A research partnership between Children's Hospital Los Angeles and AltaMed has garnered a $2.4 million grant from the state of California to study the effects of adverse childhood experiences (ACEs). The lead principal investigator on the grant, **Pat Levitt, PhD**, hopes to develop ways to identify the impact of ACEs as early as possible to prevent toxic stress and health challenges in children. Funding comes from the California Initiative to Advance Precision Medicine.

AWARDS
AND HONORS

STEFANO **DA SACCO**

Stefano Da Sacco, PhD, received $1.9 million from the National Institute of Diabetes and Digestive and Kidney Diseases of the NIH to study the mechanisms of glomerular injury in an autoimmune disease called primary membranous nephropathy.

ELIZABETH **SOWELL**

The National Institute of Environmental Health Sciences of the NIH awarded **Elizabeth Sowell, PhD**, $1.8 million to continue her research into evaluating the effects of lead exposure on brain and cognitive development in children.

CHING-LING **LIEN**

Ching-Ling (Ellen) Lien, PhD, studies the ability of zebrafish to regenerate cardiac tissue after substantial injury to the heart. Dr. Lien has received $1.7 million from the National Heart, Lung and Blood Institute of the NIH to study how the lymphatic system of the heart may contribute to regeneration of damaged tissue, giving insight into congenital heart conditions.

BRIAN **DIAS**

Brian G. Dias, PhD, studies how stress and trauma affect not only individuals but also their offspring. The National Institutes of Health has awarded Dr. Dias $1.5 million to study how a brain region called the zona incerta influences dimensions of post-traumatic stress disorder.

GENETIC SEQUENCING

By Ellin Kavanagh

Research is rarely the work of a single individual. It is a complex and dynamic process that requires interacting within the scientific community and building upon the earlier work of others. Much of the testing and tracing performed during the pandemic has relied upon genetic sequencing, the origins of which date back more than half a century.

In the 1950s, scientists knew that deoxyribonucleic acid, or DNA, was the molecule that stored the genetic information of most organisms, including humans. After a period of intense and competitive research to learn more about it, discovery of the structure of DNA was credited to James D. Watson and Francis Crick, based on the crucial work of Rosalind Franklin in Cambridge, England, in 1953.

DNA and single-stranded ribonucleic acid, or RNA, are made of building blocks, called nucleotides, that create the genetic code for each organism. This information can also be "decoded" through genetic sequencing—a process that has revolutionized medicine by allowing scientists to uncover mutations, or changes in the genetic code, that can cause diseases ranging from cancer to heart disease to autism.

The first sequencing method—capable of sequencing both DNA and RNA—was developed in 1977 by Frederick Sanger and his colleagues and is still in use today. More widely employed is the next-generation sequencing (NGS) method, developed in 2007, which can run a large volume of samples at high speed. This technology has provided the foundation for personalized medicine.

Over the past year and a half, viral genetic sequencing has been crucial in the battle against COVID-19 and the virus that causes it, SARS-CoV-2. NGS sequencing enabled scientists to develop tests for COVID-19 and vaccines. It continues to be essential for monitoring mutations used to track the spread of the virus.

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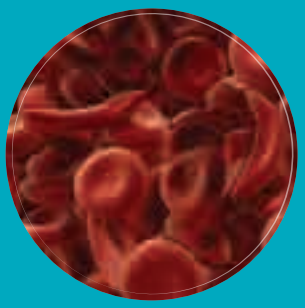
IN THIS **ISSUE**

UNDER THE MICROSCOPE
A conversation with a pediatric surgeon whose upcoming clinical trial could provide the first-ever treatment for babies with a rare intestinal disorder



MOMS KNOW BEST
Our doctors know that treating children with sickle cell disease means listening to one of the best resources on their well-being: their parents.

TEAMWORK: HOW CHLA STAYED AHEAD OF THE COVID-19 CURVE
The story of scientists who turned foresight and determination into action … fast

2020: LIFE AFFECTS RESEARCH
A timeline of a year that shaped our research, our hospital and our world

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