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.
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 Gokscheit, 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
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CHILDREN’S HOSPITAL LOS ANGELES
RESEARCHCHLA
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, 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, 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.

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.

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.

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.
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.

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

By Candace Pearson

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
The Journey of a COVID-19 Test from Start to Finish

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.

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.

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Test Result Turnaround Time

<table>
<thead>
<tr>
<th>March 13, 2020</th>
<th>March 24, 2020</th>
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<tr>
<td>24 to 48 hours</td>
<td>6 hours</td>
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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.

“The team was in a fortunate position of being able to take advantage of 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 beginning 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 8 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.

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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.

**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.”

<table>
<thead>
<tr>
<th>COVID-19 TESTS PERFORMED MARCH 2020–MARCH 2021</th>
<th>80,000</th>
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<tr>
<td>COMMUNITY PEDIATRICIANS WITHIN CHLA’S CARE NETWORK OFFERED COVID-19 TESTING</td>
<td>200+</td>
</tr>
<tr>
<td>PEOPLE VACCINATED BY CHLA TEAM MEMBERS AS OF JUNE 2021</td>
<td>31,000+</td>
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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 put on hold, some science was not getting started.

Research that focused on SARS-CoV-2 and COVID-19 continued 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—posulating 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.

Elizabeth Sewell, 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 low risk for contracting COVID-19, also reported higher levels of stress than those from more underprivileged areas.


dr. g. a.

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 Sahan Research Institute, called the ABCD study, was already three years into monitoring social and emotional changes in adolescents. This is a national study, which follows 11,000 children at 21 sites around the U.S., was expanded to specifically monitor effects of the pandemic.

“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. Sewell. “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 Panraraj, MD, an infectious diseases 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. Panraraj. “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. Panraraj 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.

“Women were eager to have an opportunity to talk about it,” says Dr. Smith.

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

While the world was encountering a brand new virus, Xiaoru Gai, PhD, who leads bioinformatics at CHLA’s Center for Personalized Medicine, was creating a suite of informative 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 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.”

Research CHLA 2021
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 limiting 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.
2020 helped shape research activities. In addition to the pandemic, there were other occurrences that changed people’s lives and influenced the world view at our institution. The timeline depicts key events of 2020 that helped shape research activities.
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. (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 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.

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 patients’ 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 openness 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 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.’”

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.

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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.

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.
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.

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.

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 therapeutics 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.

**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.

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

Thanks to a pediatric cancer panel called OncoKids®, developed at CHLA, and participation in a national clinical trial, Michelle received treatment that shrank her tumor dramatically—and she went home within days.

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

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

Donate today at CHLA.org/FundResearch
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 those cancers, they often come with toxic and long-term health effects. And not all patients respond to them.

“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.

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

— James Amatruda, MD, PhD

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.

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.”
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 Charité 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.

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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, 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, 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.
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, 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.

The COVID-19 pandemic has caused a shortage in blood supply. But donating is safe, easy and helps so much. Donating blood especially helps kids with disorders like sickle cell disease, who need regular transfusions from donors who very closely match their own blood type.

Save a life, donate blood.

Visit CHLA.org/DonateBlood to make an appointment today.
JAMIEs 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.

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.

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.

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.

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.

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AWARDS AND HONORS

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.

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.

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.

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.
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.

WORK THAT MATTERS

Find your career today.

Children’s Hospital Los Angeles is one of the few freestanding pediatric hospitals in the country where scientific inquiry is combined with clinical care devoted exclusively to children.

Join a hospital where the work you do matters. Visit Jobs.CHLA.org and apply today!
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

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

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.

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

TO EXPLORE THE DIGITAL VERSION OF RESEARCHLA, VISIT CHLA.org/ResearCHLA