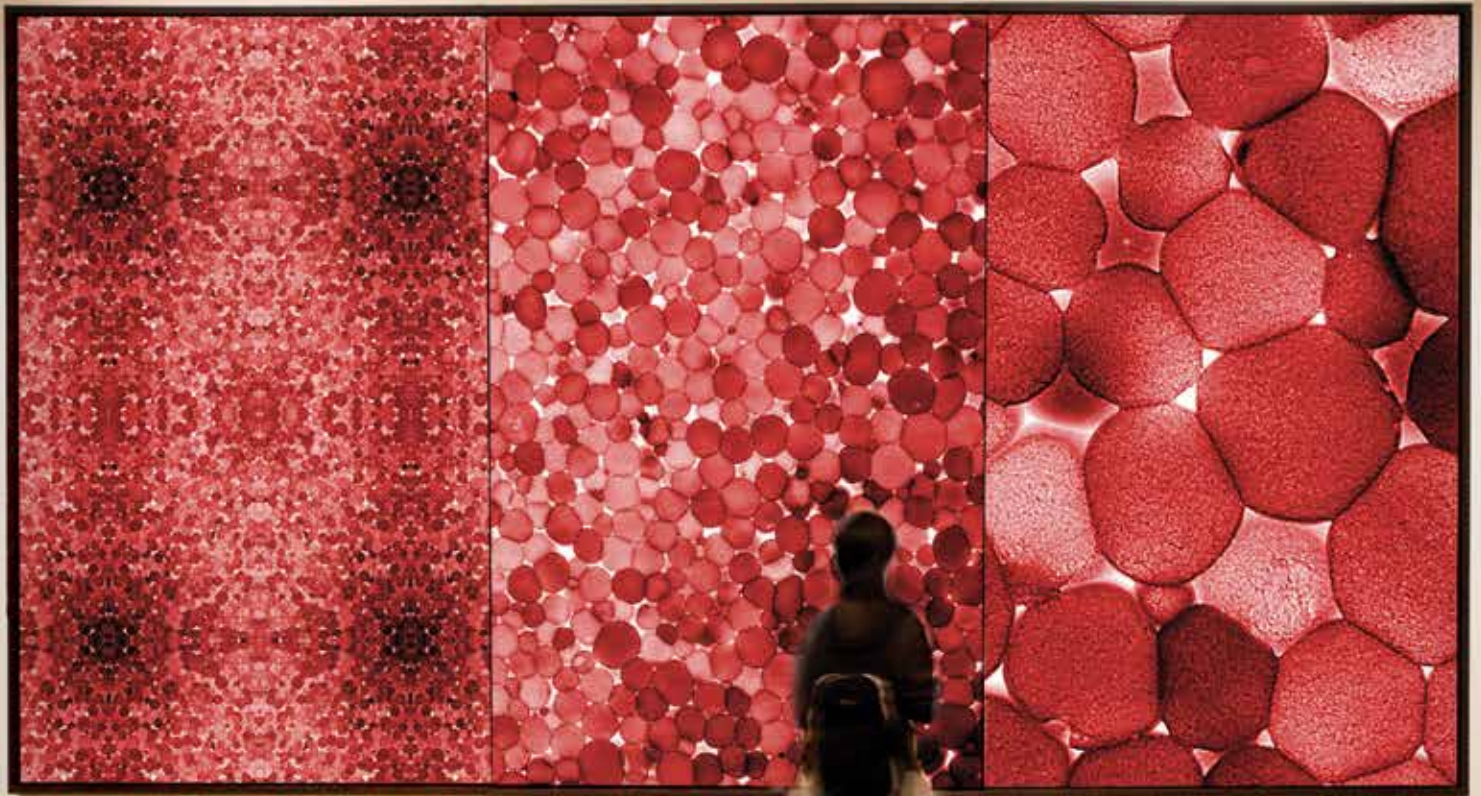


RESEARCHLA

2015



The Saban Research Institute of Children's Hospital Los Angeles

The Saban Research Institute comprises 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 and devoted exclusively to children.

The Institute's interdisciplinary research is organized around three synergistic areas of focus that together fully explore the developmental origins of health and disease and address the most pressing national child health issues:

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

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

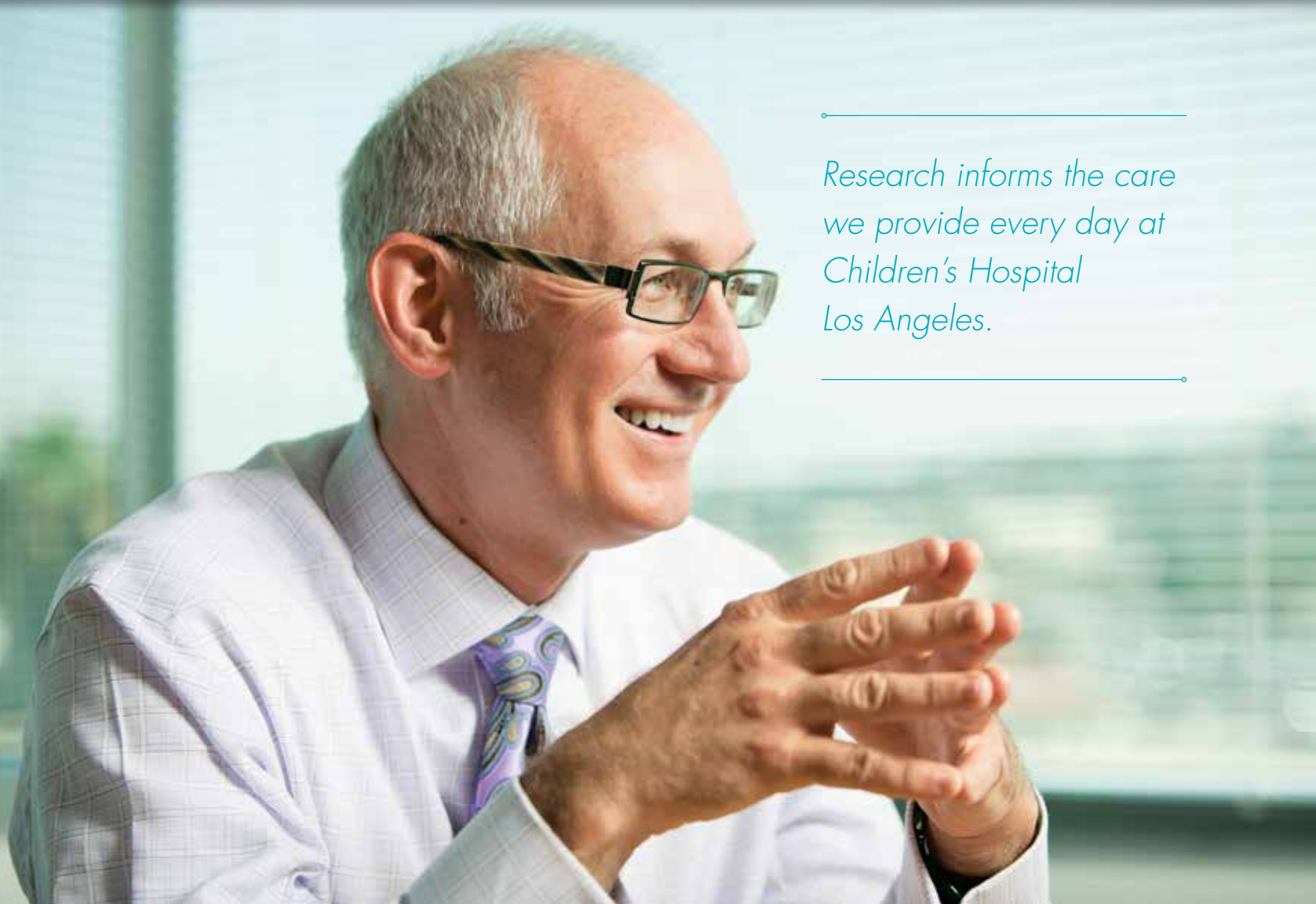
In fiscal year 2014, The Saban Research Institute received \$26.5 million (prime and subawards) in National Institutes of Health (NIH) funding and \$77.4 million in total funding. The Saban Research Institute ranks eighth in the nation among children's hospitals in NIH funding.

The Saban Research Institute and CHLA maintain strong scientific and strategic affiliations with the University of Southern California (USC) 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.

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A Message From the Director



Research informs the care we provide every day at Children's Hospital Los Angeles.

We know that kids are not just small adults. They require unique medical care—the kind best provided by a pediatric academic medical center like Children's Hospital Los Angeles.

Children require different therapies for diseases such as diabetes and cancer—disorders that often originate in early childhood or are the result of genetic or congenital conditions. They may also need specialized medical devices like child-sized blood pressure cuffs, miniature heart valves or even fetal pacemakers.

Given the fundamental differences in the health care of kids and adults, the best place to discover and develop the safest, most effective therapies and devices for children is a hospital dedicated exclusively to children.

Research informs the care we provide every day at Children's Hospital Los Angeles. At The Saban Research Institute of CHLA, research is conducted by investigators embedded in the process of children's care, with faculty and staff who possess a depth and breadth of expertise that exists in few other places. The stories in this issue of ResearCHLA illustrate the continuum of basic, translational and clinical research throughout our institution, and explain the pivotal role research plays at a pediatric academic medical center.

The story about interventional cardiologist Frank Ing, MD, highlights research that would likely not be done in any setting other than a children's hospital. Since the number of children and babies who require medical devices such as cardiac stents is relatively small, device manufacturers are often reluctant to undertake the costly development process. Pediatric specialists like Dr. Ing are therefore challenged to optimize existing devices for their young patients.

At CHLA, we have a unique opportunity to perform translational research that specifically benefits the young patients in our care.

You will read how surgeons Henri Ford, MD, Christopher Gayer, MD, and Tracy Grikscheit, MD, observed an unmet need and moved from the surgery suite to the lab to collaborate with basic scientists Mark Frey, PhD, and Anatoly Grishin, PhD, to battle necrotizing enterocolitis, a devastating intestinal disease associated with prematurity.

Our long tradition of translational research in cancer is illustrated in the story of a former patient, Darren Russell, whose cancer was treated with an experimental therapy developed by CHLA researchers more than a decade ago. Fast-forward to 2014, when Darren was married in the presence of family and friends—including the doctors who treated him at Children's Hospital Los Angeles. Soon after the wedding, Darren graduated from medical school and became a doctor himself.

Two other articles describe innovative neuroimaging research done by Stefan Bluml, PhD, and Bradley Peterson, MD, of our Institute for the Developing Mind. These studies are advancing our understanding of the origins of pediatric neurological disorders, and how to more effectively diagnose and treat them.

Because the origins of many adult diseases have their roots in childhood, pediatric medicine provides a unique opportunity to produce the best return on investment for research dollars. I am pleased to share with you that in fiscal year 2014, funding from the National Institutes of Health totaled nearly \$27 million, up more than 25 percent from the previous year—especially good news during these times of shrinking federal budgets. But more research dollars and continued philanthropic support are needed to continue this important work.

As you enjoy this issue of ResearCHLA, I know you will come to share my appreciation for the physician-scientists and investigators who are inspired each day by our young patients and their families. Working side by side at Children's Hospital Los Angeles, our investigators and clinicians are creating hope and building healthier futures for children everywhere.

Sincerely,

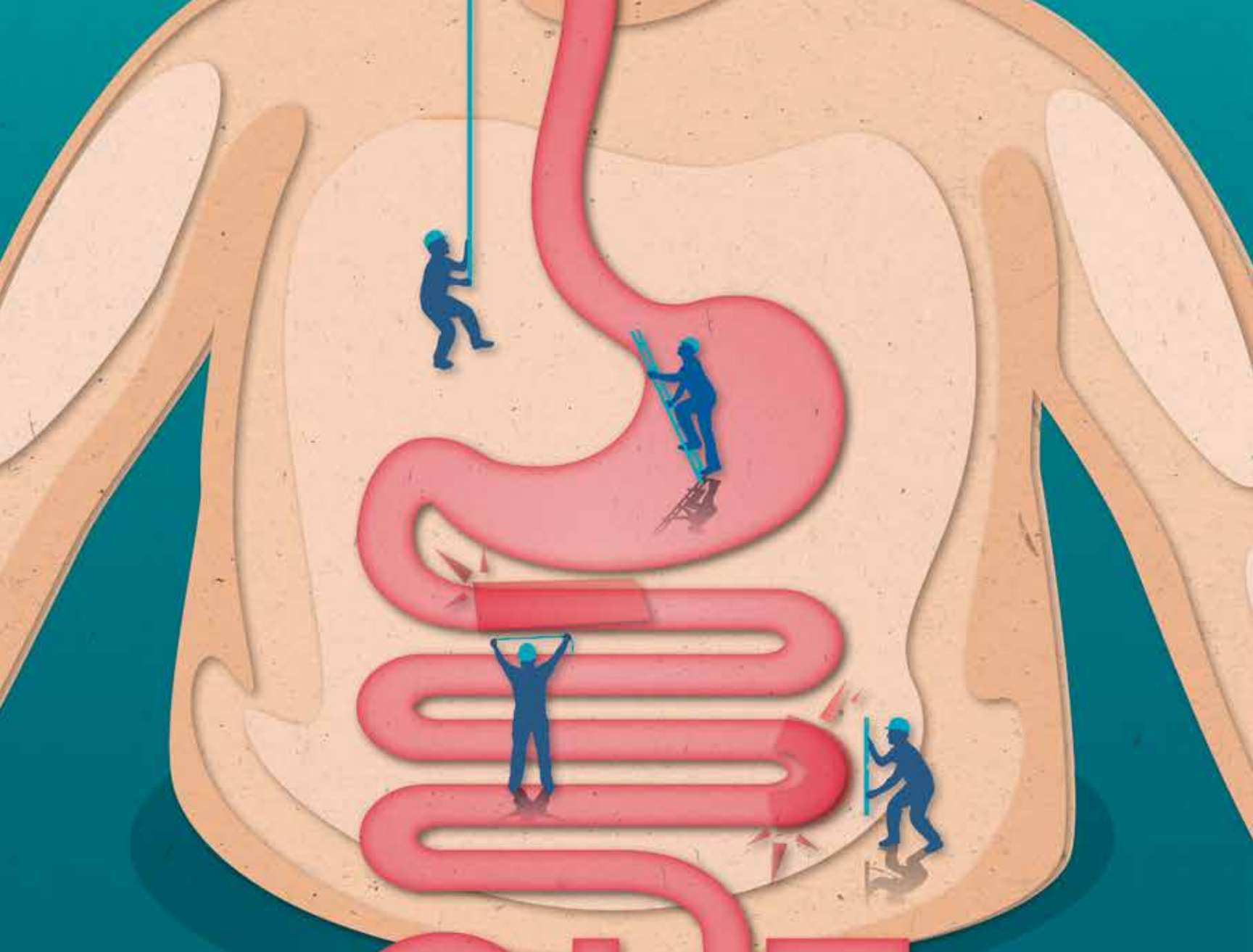


Brent Polk, MD

Director, The Saban Research Institute of Children's Hospital Los Angeles

Physician in Chief; Vice President, Academic Affairs; Chair, Department of Pediatrics,
Children's Hospital Los Angeles

Professor of Pediatrics and Vice Dean for Child Health,
Keck School of Medicine of the University of Southern California



GUT CHECK TIME



Investigators at The Saban Research Institute take a full-circle approach to a life-threatening intestinal disease that targets newborns.



Henri Ford, MD, MHA (center)

As a young surgical fellow at the University of Pittsburgh in the late 1980s, Henri Ford, MD, MHA, vowed he would try to unlock the mysteries of a terrible disease he saw all too often in the operating room—necrotizing enterocolitis, or NEC, which damages and even destroys the intestinal tissue of newborns.

“Too many babies were dying. We just didn’t have enough answers,” recalls Ford, vice president and surgeon in chief at Children’s Hospital Los Angeles.

Now, thanks to a 360-degree offensive by multiple investigators at The Saban Research Institute of Children’s Hospital Los Angeles, more clues are surfacing about some likely culprits for NEC, along with possible future intervention and prevention strategies. In addition to Ford, two of the leading investigators are also surgeons; like him, they have been inspired to look beyond their surgical training to biology. They are joined by basic researchers who are equally determined to defeat the most common and serious gastrointestinal disorder among newborns.

This impressive brain trust is good news for families dealing with NEC, which most often targets preemies, whose organs are still developing at birth. About 30 percent of babies who develop NEC will die. Survivors face life-changing consequences such as removal of part of their intestine—resulting in long-term dependence on intravenous nutrition and possible liver damage—or a bowel transplant. Either spells an uncertain future.

“It’s imperative we come up with a means of preventing this disease,” says Ford, who is also vice dean of medical education and professor and vice chair for clinical affairs in the Department of Surgery at the Keck School of Medicine of the University of Southern California (USC). “If we can understand what pathogen or injury triggers the cascade of events that lead to the inflammation characterized by NEC, perhaps we can prevent it.”

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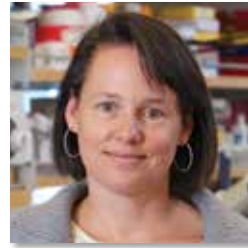
Anatoly Grishin, PhD



Christopher Gayer, MD, PhD



Mark Frey, PhD



Tracy Grikscheit, MD



Zeroing in on bacteria

Bacterial colonization starts immediately after birth, but so-called “good” bacteria don’t emerge until weeks 2 to 4, giving time for NEC to enter

the equation. Normally, the intestinal epithelium, or lining, is tight, so no bacteria can cross over. As NEC begins its attack, the intestine becomes inflamed and openings can appear in the lining, allowing viruses and bacteria to enter.

In Ford’s lab at The Saban Research Institute, research led by Anatoly Grishin, PhD, focuses on a bacterial species called *Cronobacter sakazakii*, associated with NEC and neonatal meningitis. Researchers believe that *Cronobacter sakazakii* is just one example of a broad group of opportunistic pathogens in babies with weakened immune systems. “If we can identify which bacteria are the harmful ones, and which protective, we hope to also identify babies at high risk for NEC and intervene with targeted therapies aimed at specific pathogens,” says Grishin.

Also important, he adds, is “finding the defining event that causes the gut barrier to break down the first time.” CHLA researchers were the first to discover that abnormally high levels of nitric oxide, a molecule that aids in cellular signaling, induces cell and tissue death in the intestinal lining. They also found that it is not nitric oxide itself, but rather short-lived compounds resulting from its reaction with oxygen, that damage cellular proteins and kill cells.

An investigational anti-inflammatory drug called semapimod appears to block nitric oxide synthesis, a finding that led the Ford team to apply for a patent on its use in NEC.



Finding a biomarker

Christopher Gayer, MD, PhD, a surgeon at CHLA, is curious about another player in our digestive tract, bile acids, which facilitate the movement

and absorption of fats and cholesterol. As they enter the small intestine, bile acids are “changed into about 100-plus different forms, depending on the bacteria there,” says Gayer, an assistant professor of Surgery at the Keck School of Medicine of USC, whose postgraduate work focused on intestinal wound healing.

His hypothesis: Certain bacteria interacting with bile acids will inhibit the ability of the intestine to heal and may be one mechanism behind NEC—something Ford calls “an exciting new avenue of investigation.”

In addition to studying the molecular signals that govern bile acid migration, Gayer is measuring bile acids and bacteria in stool specimens of babies with NEC to determine which bacteria are in highest concentrations. Ultimately, he suspects he won’t find a single type of bacteria behind NEC but a combination of them, all sharing the ability to create toxic bile acids.

He’d like to identify a biomarker—a biological predictor of disease—that could indicate whether a newborn is likely to develop NEC even before symptoms manifest. “We often can’t diagnose NEC until it’s very advanced and the baby is already sick,” Gayer explains.



Protective factors

Mark Frey, PhD, is principal investigator on a study at The Saban Research Institute that recently showed that a protein called neuregulin-4 (NRG4)—present in breast milk but missing in infant formula—may help guard against intestinal damage caused by NEC.

During NEC’s inflammatory assault, specialized intestinal cells called Paneth cells, which protect the intestine from microbial damage, are lost. NRG4 binds with a receptor found in the intestine, ErbB4, to block that damage. When mice were given a chemical that damages Paneth cells, NRG4 protected the animals from developing NEC. NRG4 also provided protection when newborn, formula-fed rats and cultured intestinal cells were given bacteria related to strains that may induce NEC in humans. Ford was among the contributors to Frey’s study, published in the American Journal of Pathology.

“Given that NEC is a significant clinical problem without an effective treatment, we plan to evaluate NRG4 for its therapeutic potential,” says Frey, who is also an assistant professor of Pediatrics and Biochemistry and Molecular Biology at the Keck School of Medicine of USC.



Tissue engineering

Tracy Grikscheit, MD, a researcher and surgeon at CHLA, wants to help babies who have surgery to remove diseased or dead intestinal tissue and subsequently develop short-bowel syndrome, for which there is no cure except transplant.

In January, Grikscheit, who is also an assistant professor of Surgery at the Keck School of Medicine of USC, received her second five-year, \$3.1 million grant from the California Institute for Regenerative Medicine to continue her efforts to engineer intestinal tissue from stem cells. So far, her team has succeeded in growing pieces of large and small intestine in the lab, using stem cells from intestinal tissue discarded during surgery.

The good news: All the necessary cell types are present in the engineered tissue and, adds Grikscheit, “as the cells grow, the new intestine is able to perform all the functions of a healthy organ—absorbing nutrients and providing a barrier against infection.” Along the way, she and her team have found that their stem cell-growing techniques seem to support tissue engineering of other organs as well.

Now they’re focused on another task—finalizing a device that can help standardize the process of tissue engineering. The machine under development will cryopreserve the stem cells, maintaining their viability, and then thaw them without damage to the cells. Grikscheit envisions a day when such a device may be used in an operating room, enabling parents to save their baby’s stem cells for later use if, for example, a tissue-engineered small intestine is needed. As for what drives her and other investigators, she says, “I get to take care of these babies and families, and I want to be able to tell them that we have more options.”

With so many dedicated investigators in one place, CHLA is “poised to emerge as the leading center in the U.S., if not the world, studying this disease.”

– Henri Ford, MD, MHA

In a powerful synchronicity, the inquiries of these NEC-focused surgeon-scientists and researchers complement other current CHLA studies of intestinal conditions such as inflammatory bowel disease. With so many dedicated investigators in one place, says Ford, Children’s Hospital Los Angeles is “poised to emerge as the leading center in the U.S., if not the world, studying this disease.” ■

A man with short, graying hair, wearing a dark blue button-down shirt, is sitting at a green poker table. He is looking directly at the camera with a slight smile. In front of him are several stacks of colorful poker chips (red, green, blue, white) and some playing cards. The background is a blurred casino setting with warm lighting and other tables.

HE'S ALL IN

Facing the bleakest odds, Andreas Reiff, MD, helped launch a new age in the treatment of autoimmune diseases.



Andreas Reiff, MD, examines a young patient.

The popular metaphor for a strategic leader is someone who “plays chess, not checkers.” Andreas Reiff, MD, plays neither. His game is poker. He knows advances in medicine come from playing probabilities—where bluffs and bets are crucial aspects of strategy.

Now head of the Division of Rheumatology at Children’s Hospital Los Angeles, Reiff has seen his career parallel the biopharmaceutical revolution, and its game-changing technology that forever altered treatment of autoimmune diseases.

“We changed the odds for a lot of patients,” says Reiff, who is also a professor of Pediatrics at the Keck School of Medicine of the University of Southern California.

He began his career at CHLA as a fellow, studying signaling of autoimmune T-cells. When the immune system is activated and destroys a pathogen, the T-cells send a message to call off the battle. If signaling is impaired, the immune system continues to fight—attacking the body and causing autoimmune disease.

During his fellowship, Reiff and others at CHLA helped discover the inflammatory signaling pathways of a substance called tumor necrosis

factor (TNF); excess levels of TNF had been associated with autoimmune disease. This work validated TNF as a therapeutic target and initiated a worldwide effort to develop a medication that would block it.

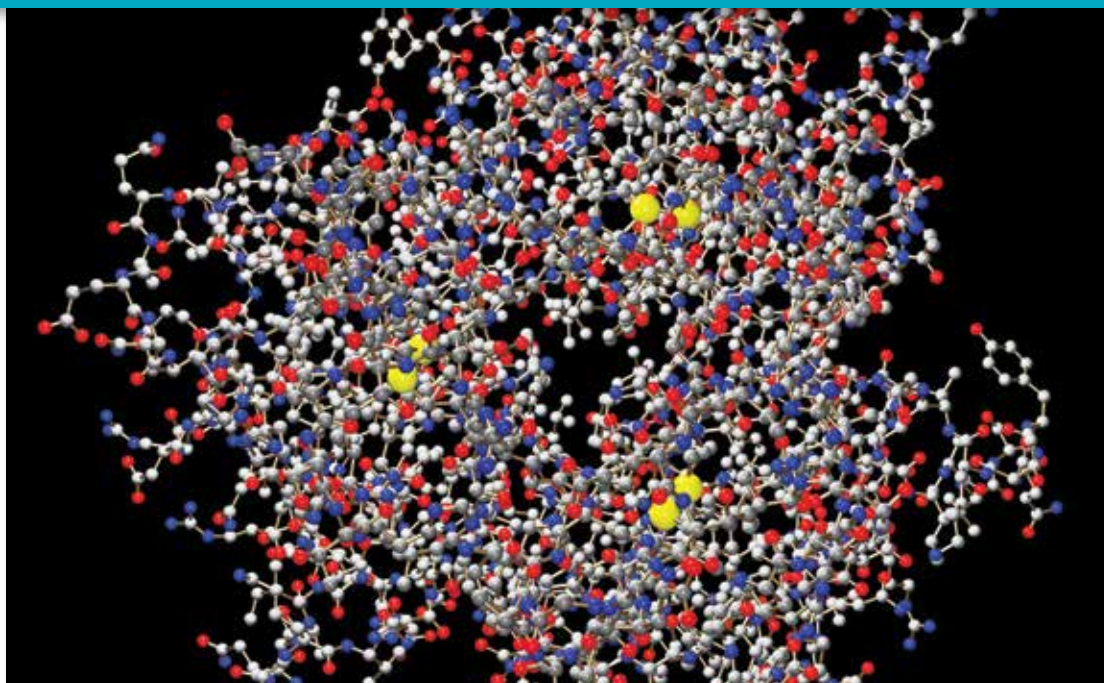
Reiff returned to the University of Freiburg in Germany, where he had received his medical degree, to lead the rheumatology program there, but was recruited back to CHLA in 1996. During his first day back on the job, a call came in about a new drug called Enbrel, a TNF inhibitor. Was he interested in starting a clinical trial?

At that time, the standard treatment for juvenile inflammatory arthritis was corticosteroids and chemotherapy, but the therapy didn’t work for some patients and had long-term side effects. The children were incapacitated and in pain; their parents were willing to try anything.

“This was in 1997,” Reiff says. “The drug wasn’t licensed and there was no phase 3 data proving it worked in adults.”

With odds this bleak, the conventional play would have been to fold. Reiff decided to gamble.

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Tumor necrosis factor-alpha

With odds this bleak, the conventional play would have been to fold. Reiff decided to gamble.

“When we spoke to the parents we said, ‘We have something brand new. We don’t know how it works. We don’t even know that it will work. All we do know is that it has an effect in adults.’”

Reiff and his team opened the trial for kids with inflammatory arthritis. The rest became medical history.

Lives changed. Kids who had never been to school were now able to go every day. Teenagers who had never had friends because they couldn’t leave the house became popular. One girl who had been unable to participate in activities became a swimmer and, eventually, a coach.

The age of treating autoimmune disorders with biopharmaceuticals—drugs produced by recombinant DNA—had begun.

During the second year of the trial in 1999, Reiff started thinking about other autoimmune diseases. If Enbrel could be life-changing for arthritis patients, maybe it would be effective in other disorders. As many of his patients were going blind from autoimmune eye diseases, he studied the scientific literature and knew that TNF was involved.

“I wanted to try it on kids who were going blind,” says Reiff. “Just like with the arthritis patients—we had nothing else to offer them.”

With no cards left to play, Reiff went all in.

“I had 20 patients, so I wrote 20 letters to insurance companies saying that, if they didn’t cover the cost of this drug, their insured patients would go blind,” Reiff recalls. “I didn’t know what would happen. Probably nothing.”

Ten companies wrote back—they would pay for the drug. The hospital provided the drug for the other 10 children. Treating these patients provided the first evidence of Enbrel’s effect on inflammatory eye disease. Had these patients been treated with the standard therapy, they would have lost their vision.

In 2000, Reiff was invited to speak at the International Conference of Inflammatory Eye Diseases at the University of California, Los Angeles. Reiff explained why TNF inhibitor worked for these diseases. At the time, the standard of care was to treat the condition symptomatically, with steroid eye drops. The concept of treating the underlying cause of the disease this way seemed so futuristic, one attendee raised his hand and said, “Captain Kirk, I have a question.”

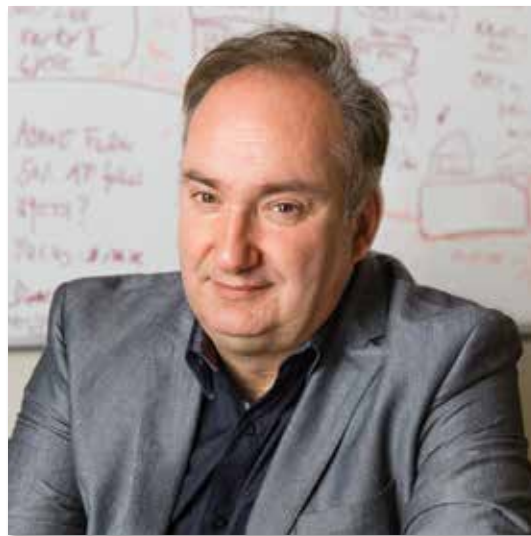
“This treatment that I was describing—using infused antibodies to block TNF—is how we now treat inflammatory eye disease,” says Reiff. “We developed the standard of care right here at CHLA.”

These medications, developed in Rheumatology, changed the lives of children with chronic diseases treated in other areas of the hospital, including Ophthalmology, Neurology, Gastroenterology and Nephrology.

After years of playing against long odds, Reiff now has the cards in his favor. CHLA cares for the largest population of children with autoimmune diseases in the country, so biotech and pharmaceutical companies clamor to test their new therapies here, where they can treat the most patients. Reiff’s team currently has 16 open clinical trials evaluating third-generation biopharmaceuticals.

But the biggest benefit is to his patients, who now have a much better chance at a winning hand. ■

To learn more about Andreas Reiff’s research, visit [CHLA.org/ReiffResearch](https://www.chla.org/ReiffResearch).



Reiff is head of CHLA’s Division of Rheumatology.



$\frac{20}{200}$

RB

$\frac{200}{61}$ 1

$\frac{20}{100}$

Or Not RB

$\frac{100}{30.5}$ 2

$\frac{20}{70}$

CHLA is a world leader

$\frac{70}{21.3}$ 3

$\frac{20}{50}$

in the research and treatment

$\frac{50}{15.2}$ 4

$\frac{20}{40}$

of retinoblastoma, the No. 1

$\frac{40}{12.2}$ 5

$\frac{20}{30}$

malignant eye tumor in children.

$\frac{30}{9.14}$ 6

$\frac{20}{25}$

$\frac{25}{7.62}$ 7

Retinoblastoma (or RB) is a childhood retinal tumor usually affecting children 1 to 2 years of age. Although rare, it is the most common malignant tumor of the eye in children.

A common sign of this cancer is a white glow or glint in the pupil of one or both eyes. Parents may first notice the condition when looking at their child in a photograph. The child's pupil does not have the normal red appearance that a flash photo creates. Instead, the pupil is white.

Left untreated, retinoblastoma can be fatal or result in blindness. It also plays a special role in explaining cancer; retinoblastomas have been

found to grow in response to the mutation of a single gene, the RB1 gene, demonstrating that some cells are only a step away from developing into a life-threatening malignancy.

David E. Cobrinik, MD, PhD, of The Vision Center at Children's Hospital Los Angeles, together with colleagues at Memorial Sloan-Kettering Cancer Center in New York City, has answered the longstanding question of why mutations to the RB1 gene primarily cause tumors of the retina and not other cell types. His study could reveal new cellular signaling pathways relevant to retinal development, cancer development and, ultimately, the discovery of novel therapies.

(continued on page 14)



Retinoblastoma is sometimes discovered when a white reflection, rather than the typical "red eye," appears in the pupil in a flash photograph.

Researchers at CHLA were among the first to isolate and clone the RB1 gene. The Vision Center at CHLA, one of the largest clinical programs in the U.S. for the treatment of retinoblastoma, was among the first sites in the nation to offer gene testing for all retinoblastoma patients and the first to offer a prenatal diagnosis for the disease.



David E. Cobrinik, MD, PhD

(continued from page 12)

“Finding the single genetic change that causes these retinal tumors in young children advances our understanding of cancer, not only because it solves the RB riddle, but because the discovery more generally implies that cancers can develop through the collaboration between a cancer-causing mutation—in this case, inactivation of the RB1 gene—and cell type-specific circuitry,” says Cobrinik, who is also an investigator with The Saban Research Institute of CHLA and associate professor of Ophthalmology at the USC Eye Institute in the Keck School of Medicine of the University of Southern California.

RB1 gene

Photo Credit: David E. Cobrinik, MD, PhD

The RB1 gene encodes a tumor suppressor protein, referred to as Rb, which prevents excessive cell growth by regulating cell division. If both alleles of the RB1 gene are mutated early in life, the Rb protein is inactivated, resulting in development of retinoblastoma cancers.

The scientists found that retinoblastomas originate in a particular type of cell in the eye called cone photoreceptor precursors. Cone cells, or cones, are one of the two types of photoreceptor cells in the retina and are responsible for color vision. A cone precursor is an immature cone cell that is not yet fully differentiated.

“We found that loss of the RB1 gene results in abnormal proliferation because the cone precursor cells lack a self-monitoring ‘surveillance system,’ which would normally cause aberrantly proliferating cells to undergo cell death. Instead, cells are able to divide uncontrollably and eventually become cancerous,” Cobrinik explains.



Thomas Lee, MD, with a patient

Researchers at CHLA were also among the first to isolate and clone the RB1 gene. The Vision Center at CHLA, one of the largest clinical programs in the U.S. for the treatment of retinoblastoma, was among the first sites in the nation to offer gene testing for all retinoblastoma patients and the first to offer a prenatal diagnosis for the disease.

In June 2014, a team of CHLA physicians and scientists announced development of a retinoblastoma next-generation (RB1 NextGen) sequencing panel. The hospital became the first to offer this whole-gene sequencing to patients and family members who may also have inherited the gene mutation, placing them at high risk.

In germ-line cases—where a lineage of cells passes down genetic information from one generation to the next—the disease-causing mutation is inherited and is present in cells throughout the body. This can result in tumors in both eyes, as well as in other locations. Therefore, early detection and accurate diagnosis are critical to determining the best course of treatment.

“We used to think that if a child had a tumor in one eye and not in the other eye, it was a result of a somatic mutation, meaning that it wasn’t inherited. So we believed removal of the tumor stopped the cancer,” says Thomas Lee, MD, director of The Vision Center. “But now we know

that 10 to 15 percent of those children who had an apparent somatic mutation are actually carrying a germ-line mutation, putting them at risk of developing subsequent tumors during adolescence or early adulthood.”

Lee adds that the ability to determine the existence of RB1 germ-line mutations early has significant implications—not only for the prognosis of a new patient with retinoblastoma, but for siblings who could also be at risk and, eventually, for a patient’s own children.

With a legacy of treating hundreds of children with retinoblastoma, CHLA now has the ability to also offer this unique and comprehensive screening test to survivors of the disease and their family members, as well as to patients at other cancer centers.

“We believe that siblings and children of carriers of the germ line should be tested immediately after birth,” says Lee, “because by detecting the gene mutations early, we can save a patient’s vision.” ■

To learn more about how to support innovative research at The Vision Center, please call **323-361-2308**.

Personalized Medicine Across the Hospital

Genetic information offers physicians a powerful tool to individualize patient care.

“Personalized medicine is a revolutionary way of practicing medicine in which a person’s biological profile—his or her very own genes—helps guide individualized, lifelong health care,” says Alexander Judkins, MD, pathologist in chief at Children’s Hospital Los Angeles and executive director of the Center for Personalized Medicine.

This powerful new approach has the potential to reduce the risk of developing diseases for which patients are genetically predisposed—such as obesity, diabetes or brain disorders—and guide treatment plans for patients with cancer or neurological disorders like schizophrenia or depression. In the future, it may well become common to sequence a newborn’s genome, setting the stage for a lifetime of personalized health care that focuses on preventing, rather than reacting to, illness.



Instead of using a one-size-fits-all approach, physicians will be able to identify the genetic origins of diseases and use targeted therapies to reduce side effects of treatments while increasing the likelihood of successful outcomes.

“Using an individual’s genetic information, we have the potential to tailor cancer therapy more specifically to that patient, with the goal of increasing the effectiveness of treatment while reducing its risks,” says Alan Wayne, MD, director of the Children’s Center for Cancer and Blood Diseases.

Next-generation sequencing panels like the one developed at CHLA for RB1 allow physician-researchers to determine the best treatment strategy, predict which patients are at the highest risk for recurrence of the disease, and measure risks to future generations.



Alexander Judkins, MD

Judkins, recognized for his diagnostic expertise and research in pediatric brain tumor markers, is also a leader in the digital transformation of pathology. He is working to develop an integrated diagnostics system to link genomic information and diagnostic imaging directly to patient electronic medical records—an innovative step toward integrating personalized medicine into daily clinical practice.

“With one of the most diverse patient populations in the world and a shared commitment to better outcomes in the future, CHLA is in a position to pioneer research that will help answer the question of why diseases strike particular individuals and use this knowledge in the development of new therapies,” says Brent Polk, MD, director of The Saban Research Institute. “Using a personalized approach, we could set the standard of care for treating children.” ■

To learn more about how you can help define the future of personalized medicine, please call **323-361-2308**.







Out of Step

Why does one part of the premature infant's brain develop out of step with the other? New studies may have the answer—and show the way to early intervention.

What does brain development have in common with a dance performance?

"Both are carefully choreographed," explains Stefan Bluml, PhD, an investigator at The Saban Research Institute. "I can point to an area of the brain and know exactly where it falls in the program. I can say, 'This area matures before this one and after this one.'"

This predictability is shattered when the period of fetal development is cut short, as it is in premature infants. Born before reaching 37 weeks in utero, "preemies" experience life outside the womb before they are ready. This puts them at a higher risk for brain abnormalities, often resulting in motor deficits, cognitive disorders and behavioral problems.

Recently, researchers found that with the use of magnetic resonance imaging (MRI), they were able to identify specific structural injuries that cause these adverse neurological effects. While this discovery allows for earlier diagnosis and treatment, it's estimated that up to 40 percent of children who show no overt injury to the brain's structure will still develop long-term neurological problems.

"This is why we need to look beyond the surface and turn our attention to the compounds that influence brain growth and functionality," says Bluml, who is also associate professor of Research Radiology at the Viterbi School of Engineering at the University of Southern California (USC).

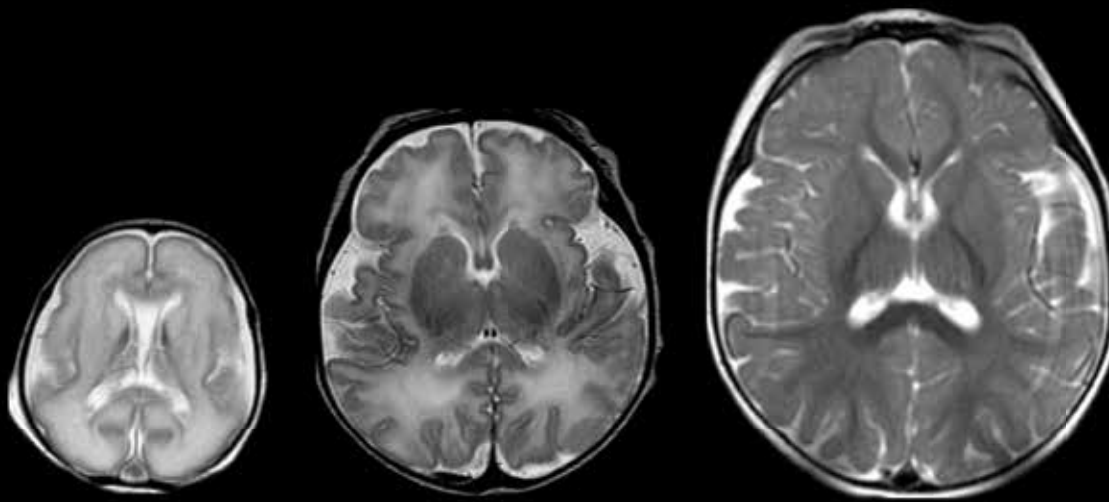
To do this, Bluml and colleagues use a technique called magnetic resonance spectroscopy (MRS). MRS takes the imaging capabilities of MRI one step further by measuring the chemical components in specific areas of the brain.

Among the numerous biochemical measurements, Bluml is primarily interested in those of N-acetylaspartate (NAA) and creatine. NAA is a marker for the development of neurons and axons—long projections from the nerve cells that send out signals. High levels of NAA mean there are more brain cells and more connections between them. Creatine measures energy metabolism, which is an indication of how effectively brain cells are creating and using energy from the nutrients in their surrounding environment. Both substances give researchers valuable insight into what functional areas of the brain are maturing, and when.

(continued on page 21)

The *Rapidly* Changing Human Brain

MR images show dramatic changes as the brain develops.



15 WEEKS PREMATURE

The cerebral cortex has a mostly smooth surface.

TERM

The characteristic “folded” appearance of the brain has started to develop. Myelination of white matter begins.

1 YEAR

The further differentiation of white and grey matter occurs as myelination of nerve fibers continues.

“Modern imaging modalities, such as MR, provide a wealth of information that we can use to better manage the health of small babies at the most crucial time of their development.”

– Stefan Bluml, PhD

(continued from page 19)

In a recent study, Bluml used MRS to examine the levels of NAA and creatine in premature and full-term infants. Specifically, he compared the biochemical levels of white matter (the area of the brain that contains axons and transmits signals) with those of gray matter (the area with the most neurons, which create and process information). In his study, Bluml wanted to find out whether prematurity affects brain development and, if so, whether white matter and gray matter are affected differently.

The results suggest that both are true.

“We found that the development of axons and energy metabolism, marked by the levels of NAA and creatine, both begin earlier in the white matter of preemies,” notes Bluml. “This development initially precedes that of term-born infants, but then progresses at a slower pace. On the other hand, the data suggested that gray matter was not, or was to a much lesser extent, affected by premature birth. Essentially, the maturation of the white matter is out of sync with that of the gray matter in premature infants.”

Bluml believes that the white matter’s false start is triggered by the events that take place after birth.

Regardless of the gestational age of the newborn, the physical process of birth triggers significant physiological changes. In the womb, the fetal brain is developing in its ideal, low-oxygen environment. The birthing events immediately expose the infant to a high-oxygen environment that it may not be prepared to breathe. If the lungs are not fully developed, as in preemies, this can lead to respiratory distress and increased sensitivity to infectious pathogens and stimuli. In addition, the maternal-fetal blood supply is terminated when the umbilical cord is cut. When this happens too early in development, it may prevent key materials, including hormones, from being delivered from mother to baby.

“All of these changes after birth may explain the altered trajectory of brain maturation in premature infants,” says Bluml. “These processes may contribute to preemies’



Stefan Bluml, PhD

increased risk of developing long-term neurodevelopmental disorders.”

While the risks for neurological challenges are greater in preemies, noninvasive imaging techniques like MRS mean that changes to the brain can be observed, diagnosed and possibly treated within months. By comparison, it can take years for changes in cognition or behavior to be seen under traditional observation.

This reduced timeframe between diagnosis and therapy is crucial because of the brain’s ability to adapt and “rewire” itself. This “plasticity” enables the newborn brain to take in and process a wealth of information and establish crucial connections. Plasticity may also make the child’s brain more responsive to therapeutic interventions, says Bluml, noting that a child learns more in the first three months than over the rest of his or her entire life. Because the brain’s flexibility decreases as we age, observing and treating brain abnormalities immediately after birth will result in the most successful outcomes.

“Modern imaging modalities, such as MR,” says Bluml, “provide a wealth of information that we can use to better manage the health of small babies at the most crucial time of their development.” ■



A REASON TO HOPE

Clinical trials offer cancer patients and their families access to potentially lifesaving alternatives when standard therapies haven't helped.



Weili Sun, MD, PhD (left), Leo Mascarenhas, MD, Alan Wayne, MD, and Deepa Bhojwani, MD, new director of the Leukemia/Lymphoma Program

“All hospitals deliver the standard of care. We are working to create the new standard through our translational research programs.”

– Alan Wayne, MD

(continued from page 23)

Claire was being treated at another hospital in Southern California. Her doctors and her parents knew that standard chemotherapy wasn't going to help her. They needed to find alternatives; that's when her family made the decision to travel to CHLA.

CHLA had just begun an early-phase immunotherapy trial for patients with ALL whose leukemia had become resistant to chemotherapy. While chemotherapy kills rapidly dividing cells—both cancerous and healthy—immunotherapy more specifically targets cancer cells. In this case, the new drug being tested was the product of an antibody fused to a bacterial toxin. When the antibody binds to the cancer cell, the toxin enters the cell and kills it. Wayne led the development of the drug for children with ALL and headed up the phase 1 trial while at the National Cancer Institute; when he was recruited to CHLA, he brought the study with him.

“Many centers offer clinical trials,” says Leo Mascarenhas, MD, section head of Oncology at Children's Hospital. “Here at CHLA, families have access to clinical trials, in addition to having their child treated by a national or international expert in the field.”

Claire's parents chose to have their daughter treated at CHLA.

Weili Sun, MD, PhD, a physician specializing in leukemia, treated Claire with the novel immunotherapy. “Immunotherapy provided the turning point for Claire's disease,” says Sun. “Her blood counts normalized, and there was only a very low level of leukemia cells in her body after two doses of the new drug.”

Claire subsequently received additional immunotherapy at her local hospital. In a follow-up bone marrow test, leukemia cells were no longer detected. “Considering how resistant Claire's disease was, her response to immunotherapy has been truly remarkable,” Sun says.

Claire is back home. She's continuing treatment at her local hospital and has returned to school. Only time will tell what the future holds for her, but for now her parents treasure each day.

“We are incredibly grateful to Claire's parents, and to all our patient families, for their participation in these studies,” says Wayne. “Sadly, not all children with cancer will survive, but by participating in a clinical trial, patients and their families are helping us develop new therapies that will offer hope to children in the future.” ■

To learn more about how to support innovative cancer research at CHLA, please call **323-361-2308**.

From Cancer Patient to Med School Grad

The recurrence of his cancer changed Darren Russell's life—in more ways than one.

Fourteen years ago, Darren Russell was treated at Children's Hospital Los Angeles for Ewing sarcoma, a rare bone cancer that primarily occurs in children and adolescents. Darren's medical team, led by Stuart E. Siegel, MD, treated his disease aggressively—as part of an international Children's Oncology Group protocol—with surgery, chemotherapy, radiation and a bone marrow transplant. The treatment was successful. Darren's disease went into remission and his life returned to normal.

Then two years later the unthinkable happened. The cancer not only returned but it had spread. Having developed metastatic disease, Darren faced a poor prognosis. He received additional chemotherapy and radiotherapy, but his parents worried it was not enough to cure their son.

With one of the largest pediatric hematology-oncology programs in the United States, CHLA is home to more major, multicenter clinical trials and research consortia than any other pediatric cancer program in the country. But in addition to those large trials, CHLA can offer parents something many hospitals cannot—leading-edge studies providing access to early-stage, novel therapies.

"What sets us apart from many pediatric hospitals is that we have scientists who work to translate discoveries made in our labs into clinical trials for our patients," says Robert C. Seeger, MD, director of the Cancer Research Program at The Saban Research Institute of Children's Hospital Los Angeles. "This capability allowed us to provide Darren and his family with another option."

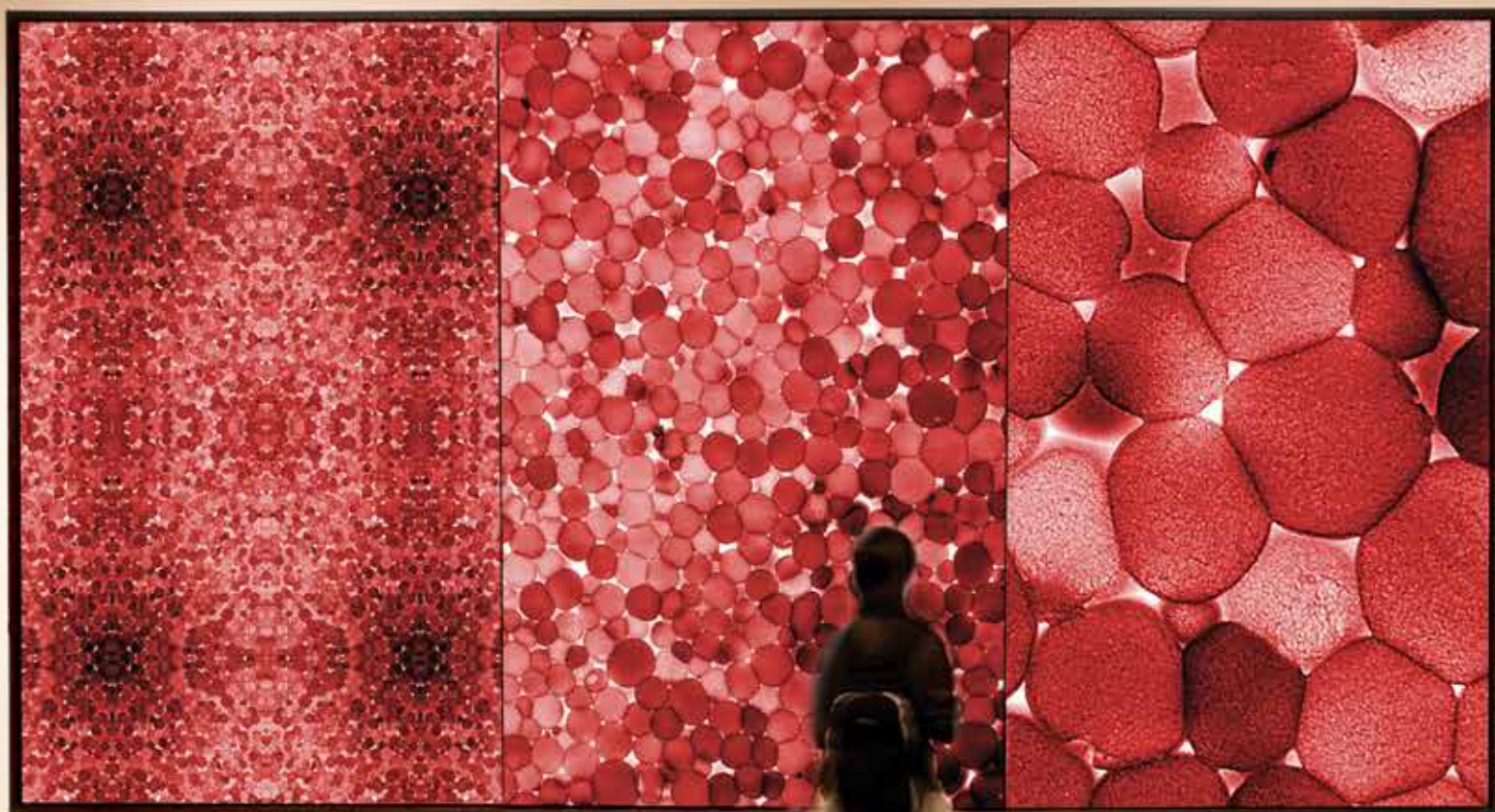
Siegel and Seeger approached the family about a clinical trial for an oral medication that had few side effects and a lot of potential. The experimental medication, fenretinide, had been developed by investigators at CHLA. Darren would be one of the first pediatric patients to receive the therapy.



With one of the largest pediatric hematology-oncology programs in the United States, CHLA is home to more major, multicenter clinical trials and research consortia than any other pediatric cancer program in the country.

The Smallest Part of the Big Picture

Sickle cell disease symptoms all begin with the red blood cell.



Magnifications of healthy red blood cells

“Often, you have to understand the minute details before you can make sense of the bigger picture,” muses Jon Detterich, MD. This mentality fuels his research at Children’s Hospital Los Angeles, where he looks to the smallest component of human life, the cell, to understand the complex symptoms of sickle cell disease.

Affecting more than 80,000 individuals in the United States, sickle cell disease is a lifelong condition characterized by crescent-shaped, or sickled, red blood cells. Because of their abnormal shape, these cells can become stuck in blood vessels, blocking blood flow to muscles and organs. This, in turn, can cause a variety of symptoms and complications, ranging from episodes of extreme pain to pulmonary hypertension and stroke.

“The problem with sickle cell disease is that doctors can treat these secondary effects, but they aren’t getting to the root of the problem—the red blood cell,” notes Detterich, a pediatric cardiologist at CHLA, as well as an assistant professor of Clinical Pediatrics, Physiology and Biophysics at the Keck School of Medicine of University of Southern California (USC).

Detterich first began exploring the fundamental makeup of sickle cell disease in 2008. His initial research, funded by a Sickle Cell Scholar Award from the National Institutes of Health (NIH), examined the fluid dynamics and unique properties of transfused blood.

All sickle cell patients will undergo at least one blood transfusion during their treatment, making it essential to understand the relationship between transfused blood and blood vessels. After studying these interactions, Detterich then turned his focus to the red blood cell itself.

“I wanted to see exactly how the process of cell sickling is impacted by molecules in the bloodstream, specifically nitric oxide,” says Detterich. “Furthermore, how does the cell then act on the blood vessel?”

Nitric oxide (NO) controls vessel constriction and dilation—a process that regulates blood flow to various tissues in the body. Dysregulation of the process is harmful to the blood vessels, potentially triggering them to narrow and leading to complications in sickle cell patients.



Jon Detterich, MD

“Often, you have to understand the minute details before you can make sense of the bigger picture.”

— Jon Detterich, MD

While NO is usually released by the inner lining of the blood vessels, Detterich believes that red blood cells may also be able to release NO of their own, resulting in dysregulation of NO in the bloodstream. Detterich recently received funding from the NIH to study his hypothesis, which could lead to novel treatments.

“It’s important that we look to understand the very foundation of the disease in order to successfully manage the complications and develop new therapies,” says Detterich. ■



He Hasn't Missed a Beat



Frank Ing sets a fast pace in his push to establish CHLA as a frontrunner in pediatric cardiology.

Two minutes, Frank Ing, MD, tells a visitor, with all the best intentions. He flashes a pair of fingers as reinforcement. “Two minutes.”

Then he’s off on what he might call a mission of eminence, seeing Children’s Hospital Los Angeles through the final moments of a year-long effort to become the first hospital on the West Coast accredited as a Pediatric Heart Failure Institute by The Healthcare Colloquium. Representatives from the Colloquium, an alliance of organizations recognized for their excellence in treating heart failure, have been on-site all day evaluating CHLA’s Heart Institute. Ing has one last obligation: They need him for a picture.

“You’ll hear about this at some point if we get the accreditation,” he says. “This is a big deal.”

These kinds of undertakings are now Ing’s concern. One of the country’s top pediatric interventional cardiologists, he was elevated last July to co-director of the Heart Institute and chief of the hospital’s Cardiology Division. Planning, motivating, rolling strategies over in his head, being jolted by an inspiration—they’re all now part of Ing’s extended workday.

“I think about what I need to do for the program as an organization—I think about that 24/7,” he says. “I’ll wake up or I’ll be driving and I’ll have this idea, and I’ll say, ‘Hey, maybe we can do this!’ I find myself at the end of the day very mentally tired.”

(continued on next page)

All of that activity points toward one goal. “I want to take CHLA from a position of excellence to a position of eminence.”

How long a trip is that? Ing says it amounts to merely a single stride—from having a reputation for topnotch patient care and excellent outcomes, to having one’s name entrenched in the public’s awareness as a pacesetter and an authority. In plain terms, it may just mean a nod from a noted independent observer.

“We’re number 7 and that’s great,” Ing says, referring to Cardiology’s current national ranking from U.S. News & World Report. “But I’d love for us to get into the top five.”

“We have all the different services in place,” he says, noting the presence of The Saban Research Institute as a source of wide-ranging expertise that can help move an idea forward, and a progressive Institutional Review Board to greenlight pioneering clinical trials. “If you want to be eminent you have to be willing to get on the edge. You have to be willing to innovate and create and follow through.”

Ing’s own research into designing tools and devices made to fit his patients with congenital heart disease is one example. With companies profiting more from manufacturing adult devices, nothing exists that’s shaped and sized for the smallest of patients, from fetuses to newborns to 1-year-olds.

“There’s a wide range of sizes in that age group,” Ing says. “We innovate as we go along.” He calls on an old pop-culture reference to characterize the improvising he has to do. “MacGyver,” he says with a grin. “Remember him?”

That amount of clever resourcefulness gets to be a burden, so Ing is working to develop tools suited for littler cardiac patients. His particular focus is stents—tubes placed in the arteries to keep them open and allow proper blood flow.

To learn more about how to support innovative cardiology research at CHLA, please call **323-361-2308**.



Frank Ing, MD, is also a professor of Clinical Pediatrics at the Keck School of Medicine of USC.

"You need a stent that can be further dilated to match the growth of the child," he explains. He's also gathering data for a paper he has titled "Tailoring the Stent to Fit the Anatomy," the play on words openly intentional. "You can picture a tailor making something to fit a baby," he says.

The precision of Ing's clinical work—he remains the director of CHLA's Cardiac Catheterization Lab—is in contrast to the big-picture thinking that preoccupies him as the division head. "I'm constantly planning for the next stage—what are we going to do and how are we going to do it, what's the best thing, and so forth.

"I'm looking forward to next year at this time saying, 'What have we done? How far have we gone?' I have never failed in my career. If everything goes according to plan, next year at this time a lot of this stuff that I have in my head should be in place or in process."

Later in the evening, he'll be able to notch today's meet-and-greet as a success, when word comes that the Colloquium has selected CHLA for accreditation, an honor conferred on only six children's hospitals in the nation. Those two minutes he promised became 30, but it's forgivable. Eminence cannot be rushed. ■



3-D printed models of a patient's heart

Putting Their Heads Together

Bradley Peterson, MD, answers questions about how CHLA intends to revolutionize the study of the young, developing mind.

Bradley Peterson, MD, was named the inaugural director of the Institute for the Developing Mind (IDM) at The Saban Research Institute of Children's Hospital Los Angeles in July 2014. He joined CHLA after spending 13 years at Columbia University, most recently as the director of the Center for Developmental Neuropsychiatry at the Columbia University Medical Center. Peterson's vast experience as a scientist, physician, teacher and mentor provides the Institute with the transformative leadership necessary to establish a comprehensive program of interdisciplinary research, education, training and clinical services for childhood neurodevelopmental problems at CHLA.

Peterson's own research has used brain-imaging technologies to understand the origins of neurodevelopmental disorders, and to map the complex pathways between the genetic and environmental influences that can trigger their onset or progression. We talked with him about his vision for the IDM.

Brad Peterson, MD, is also professor of Psychiatry at the Keck School of Medicine of USC.

Q: Why did you decide to come to The Saban Research Institute of CHLA?

A: I came to CHLA because of the prospect that the IDM will redefine the process for scientific discovery in childhood neuropsychiatric disorders. This new process will involve scientists and clinicians with diverse backgrounds and expertise—geneticists, molecular and cellular biologists, systems neuroscientists and brain imaging specialists, behavioral and cognitive neuroscientists, clinical trial specialists and expert clinicians—all coming together to tackle highly focused questions in a coordinated way. This integration of scientific questions and expertise will allow us to understand the causes of these devastating illnesses much more deeply and more quickly than would be possible with the old way of doing science, in which investigators work in the relative isolation of their own laboratories. Many institutions talk about conducting science in this new way, but they don't really do it. It was the institutional commitment to this revolutionary process of scientific discovery that ultimately convinced me to make the move.

Q: Why is this important?

A: To understand how a deeper understanding of the mind, brain and behavior comes from a collective understanding at different levels of investigation, it may help to consider what we have learned over many decades about one of the most important capacities of mind and brain: learning itself. At the level of observable behavior, for example, we know a lot about reinforcement processes—reward, punishment, incentive and motivation—that create and sustain patterns of learned behavior. At this level of investigation, scientists understand in a fairly sophisticated way why people do things—even things we aren't fully aware of doing, like when we act out of unconscious habit.

Researchers can then use brain imaging to identify the changes in neural activity and brain structure that support such learned behaviors. In turn, these changes can be understood at other levels by basic scientists who study the changes in the structure and function of neurons; and at still other levels by scientists who study the molecules that induce those neuronal changes.

The result—a more comprehensive understanding of the cause of neuropsychiatric illnesses—will speed the development of truly rational preventions and therapeutic interventions, reducing the suffering of millions of children and their families.

Q: Most of the brain-imaging studies published to date are interpretations based on correlations, but demonstrate flimsy causal relationships.

A: That's correct. Just because two things are correlated doesn't mean that either one of those things causes the other. We must work to design and implement imaging studies that allow us to identify what is truly causing a disorder and how treatments are actually working in the brain—what is placing us at risk for getting sick and what is protecting us from illness. How do we prove that these things are either making us vulnerable to becoming ill or conferring resilience?

A major component of my own work uses imaging to help identify features of the brain that diagnose illness more accurately, in order to better plan treatments and monitor treatment results. These were the promises of brain imaging when the field first began, and now is the time to fulfill those promises. That ability is within our reach.

We have the potential to use cutting-edge MRI technology to identify disorders that are very difficult to diagnose definitively, particularly early in the course of illness. If we can realize that potential, bring it into clinical practice and then disseminate that ability, my professional life will have been worth living. ■

To learn more about how you can support scientific research into childhood neuropsychiatric disorders, please call **323-361-2308**.

The New Digital Frontier

Bioinformatics will harness the data pool so researchers across Los Angeles can more easily translate information into discoveries.

In efforts to formulate—and answer—the next big scientific questions, academic medical centers are looking for ways to become increasingly nimble in their ability to tap into the wealth of medical information being generated in today’s digital age. With physicians in more than 350 subspecialty programs and clinical services treating 107,000 pediatric patients each year, Children’s Hospital Los Angeles and its diverse patient population provide a valuable resource for medical research.

Supported in part by \$8.4 million in funding from the University of Southern California (USC), plans are underway for a joint CHLA/USC clinical research data warehouse. It will combine elements of the hospital’s electronic medical records system (KIDS) with the National Institutes of Health-funded software tool i2b2 (Informatics for Integrating Biology and the Bedside), which allows researchers to search and sort data such as patient demographics, diagnoses, code procedures and lab test results.

“A centralized system will significantly reduce the amount of time it takes to query and analyze data,” says Michele Kipke, PhD, vice chair of Research for the Department of Pediatrics at CHLA. “Researchers will be able to use the system for cohort discovery in clinical trials research, as well as conduct analyses for health outcomes and quality research.”

The project is known as DEWARS (Data Exploration, Warehousing and Archiving for Researchers). It is led by Daniella Meeker, PhD, director of the Clinical Research Informatics program within the Southern California Clinical and Translational Science Institute and a leader in the emerging field of clinical research informatics.

DEWARS will integrate patient records across CHLA and USC health systems into a common, protected database. Sophisticated query functions will enable a broad range of research options—from testing hypotheses to identifying potential

What’s the BIG deal about BIG data?

CHLA began digitizing clinical data in 2004, creating the KIDS database. In the 10 years since, we’ve accumulated 6.3 terabytes of data.

For comparison: Printed collection of the U.S. Library of Congress = 10 terabytes



With physicians in more than 350 subspecialty programs and clinical services treating 107,000 pediatric patients each year, Children's Hospital Los Angeles and its diverse patient population provide a valuable resource for medical research.

participants for clinical trials. In addition to ensuring that protected information can be pooled and accessed by CHLA and USC physician-scientists, sharing data will open up opportunities for new research partnerships with other institutes. Discussions have also begun for phase two—formation of a Los Angeles Data Resource that will potentially include other local hospitals, further expanding research opportunities.

"The vision is to integrate our research data management systems with other operational and compliance systems, creating applications that accelerate research and enable scientists to focus on the creative and intellectual aspects of their work," says Meeker. ■

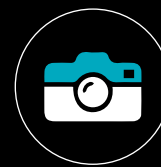
The amount of data in 1 terabyte:



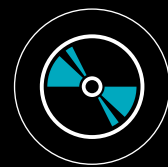
> 900 million pages of text



> 4.5 million books



> 350,000 digital photos



> 230 DVDs

Since 2004, the KIDS database has stored info from:



Nearly 10 million lab tests



> 4 million patient visits



> 8 million pharmacy orders



> 1 million radiology tests

Major Awards



Shahab Asgharzadeh, MD (right), and Robert Seeger, MD

Shahab Asgharzadeh, MD, and Robert Seeger, MD, received \$2 million from the National Cancer Institute to develop and test immunotherapies as part of the New Approaches to Neuroblastoma Therapy (NANT) consortium.



Steven Mittelman, MD, PhD

Steven Mittelman, MD, PhD, received \$1.5 million from the UniHealth Foundation to fund the EMPOWER (Energy Management for Personalized Weight Reduction) Weight Management Clinic. This multidisciplinary clinic offers resources for patients and families struggling with significant weight issues.



Tracy Grikscheit, MD

Tracy Grikscheit, MD, was awarded \$3.1 million by the California Institute for Regenerative Medicine for her research into developing tissue-engineered small intestine as a functional replacement for patients with short bowel syndrome.



Robert Seeger, MD

Robert Seeger, MD, was awarded \$800,000 by the St. Baldrick's Foundation for his continued work testing and developing new cancer treatments as part of the NANT consortium.



Pat Levitt, PhD

Pat Levitt, PhD, received over \$1 million from the National Institute of Mental Health to study the function and structural adaptations in the development of the forebrain.



Kasper Wang, MD

Kasper Wang, MD, received \$1.5 million from the National Institute of Diabetes and Digestive and Kidney Diseases to continue funding the Childhood Liver Disease Research and Education Network (ChILDREN) Liver Research Center at CHLA.



Brent Polk, MD

Brent Polk, MD, was awarded more than \$1 million from the National Institute of Diabetes and Digestive and Kidney Diseases to test tumor necrosis factor signaling and find a potentially novel therapeutic target for inflammatory bowel disease.



David Warburton, DSc, MD

David Warburton, DSc, MD, was awarded \$4 million from the National Heart, Lung, and Blood Institute for the LungMAP project, which uses detailed imaging techniques to map the cellular development of the lung.



Miguel Martinez, MSW, MPH

Miguel Martinez, MSW, MPH, was awarded over \$1 million by the U.S. Department of Health and Human Services to establish a comprehensive HIV prevention and care center that will address the unmet needs of minority men.

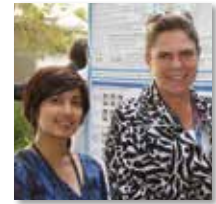
In the News



Steven Mittelman, MD, PhD, Hisham Abdel-Azim, MD, and Etan Orgel, MD, reported that obese youths with leukemia are more than twice as likely to show persistent signs of cancer after initial chemotherapy, possibly explaining why these patients have worse outcomes than their lean counterparts. This was one of the most-viewed articles ever published in the journal *Blood*, and was covered by national news outlets including Science Daily and U.S. News & World Report.

Steven Mittelman, MD, PhD, (right), Hisham Abdel-Azim, MD, (not pictured: Etan Orgel, MD)

A study by **Prapti Gautam, PhD, and Elizabeth Sowell, PhD,** found that alcohol exposure in the womb alters the development of brain function during childhood and adolescence. These results demonstrated the long-term effects of fetal alcohol spectrum disorders and received wide national and international coverage.



Prapti Gautam, PhD, (left) and Elizabeth Sowell, PhD



Reuters, Bloomberg Businessweek and other outlets reported on the discovery that a patient's own natural killer cells can be used to destroy cancer cells. This study, presented by **Nora Heisterkamp, PhD, and Hisham Abdel-Azim, MD,** may lead to a less toxic and more effective way to battle acute lymphoblastic leukemia in children.

Nora Heisterkamp, PhD (left), and Hisham Abdel-Azim, MD

Premature infants are at an increased risk for a potentially lethal gastrointestinal disease called necrotizing enterocolitis (NEC). In a study covered by Yahoo!, WebMD and U.S. News & World Report, **Mark R. Frey, PhD,** discovered that a protein in breast milk may protect against the intestinal destruction caused by NEC.



Mark R. Frey, PhD



David Cobrinik, MD, PhD, discovered why the mutation of the RB1 gene causes tumors in the retina, and not in other cell types. His study, published in the journal *Nature*, could reveal new pathways of retinal and cancer development and ultimately lead to novel therapies. The study received broad national coverage.

David Cobrinik, MD, PhD

Tracy Grikscheit, MD, received national and international coverage for her work successfully growing esophageal tissue from human cells. This tissue-engineered esophagus may eventually help children who are born with missing or damaged esophageal portions, as well as repair the tissue in adults who have had esophageal cancer.



Tracy Grikscheit, MD



KCBS, KCAL and KABC interviewed **Megan Lipton, MA,** on "Health and Wellness Sunday," a day celebrating the partnership between the Kids N Fitness® Program at Children's Hospital Los Angeles and New Mount Calvary Baptist Church. Former boxer Sugar Ray Leonard, a longtime supporter of the Kids N Fitness Program, attended the event and spoke about the importance of a healthy lifestyle.

Megan Lipton, MA

New Faces



Deepa Bhojwani, MD

Deepa Bhojwani, MD, is the new director of the Leukemia/Lymphoma Program within the Children's Center for Cancer and Blood Diseases, joining CHLA after eight years at St. Jude Children's Research Hospital. An internationally renowned clinical investigator, Bhojwani is focused on developing therapeutics for leukemias and lymphomas. She specifically studies risk factors for toxicity from therapy for childhood acute lymphoblastic leukemia, and is strongly invested in outreach efforts to improve the care of children with cancer in countries with limited resources.



David Geller, MD, PhD

David Geller, MD, PhD, recently joined the Division of Endocrinology and Metabolism after directing the Pediatric Endocrine service at Cedars-Sinai Medical Center for the past 16 years. He earned both his medical and doctoral degrees in biochemistry and molecular biology from the University of Chicago. After graduation, Geller completed a pediatric residency at the University of California, Los Angeles, and a pediatric endocrinology fellowship at the University of California, San Francisco, where he also conducted postdoctoral research in molecular steroidogenesis.



Hunter Hardy, MD

Hunter Hardy, MD, serves as director of Pathology Informatics in the Department of Pathology and Laboratory Medicine. In this position, Hardy pairs his lifelong interest in computer science with an active career in medicine. He is specifically focused on developing new information technologies for quality improvement and error reduction within the health care setting. Hardy received his medical degree from the University of Arkansas, and completed a residency in pathology and a fellowship in pathology informatics at Emory University.



Eugene Kim, MD

Eugene Kim, MD, has joined the Division of Pediatric Surgery at CHLA after nine years at Texas Children's Hospital. Kim earned his medical degree from Columbia University College of Physicians & Surgeons, and completed his residency in general surgery at Columbia University Medical Center and a fellowship in pediatric surgery at Cincinnati Children's Hospital. In addition to his clinical expertise in pediatric surgical oncology and the management of chest wall deformities and anorectal malformations, Kim is also a principal investigator working to develop novel therapeutics for neuroblastoma.



Ashley Margol, MD, MS

Ashley Margol, MD, MS, has joined the Children's Center for Cancer and Blood Diseases. She earned her medical degree from the Keck School of Medicine of the University of Southern California (USC) and recently completed her pediatric hematology-oncology fellowship at CHLA, which included an additional year of training dedicated solely to pediatric brain tumors. Margol's research focuses on biomarkers of the microenvironment of these tumors, specifically medulloblastoma and atypical teratoid rhabdoid tumors. Margol holds a master's degree in clinical, biomedical and translational research from the Keck School of Medicine of USC.



*Kanokporn
Mongkolrattanothai, MD*

Kanokporn Mongkolrattanothai, MD, has joined the Division of Infectious Diseases following seven years at the University of Illinois College of Medicine. After earning her medical degree from Chulalongkorn University School of Medicine in Bangkok, Thailand, Mongkolrattanothai completed her pediatric residency and pediatric infectious diseases fellowship at the Mahidol University in Bangkok and the University of Chicago Children's Hospital. Her primary research interests include antimicrobial stewardship and molecular epidemiology of *S. aureus*.



*Erika Shin-
Kashiyama, JD*

Erika Shin-Kashiyama, JD, was recently named administrative director of the Therapeutic Advances in Childhood Leukemia & Lymphoma (TACL) Operations Center and Children's Center for Cancer and Blood Diseases Regulatory Affairs. She received her law degree from the University of the Pacific McGeorge School with a concentration in intellectual property law, and has more than 16 years of experience in the biotechnology and life-science industry.



Honor Roll of Donors

From July 1, 2013, to June 30, 2014

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

In spite of our best efforts, errors and omissions may occur. Please inform us of any inaccuracies by contacting Christian Nelson, assistant vice president of Stewardship and Donor Relations, at cnelson@chla.usc.edu or 323-361-1779. For more information on how you can provide philanthropic support, please contact Kerri Seibly, associate vice president, Foundation, at kseibly@chla.usc.edu or 323-361-1705.

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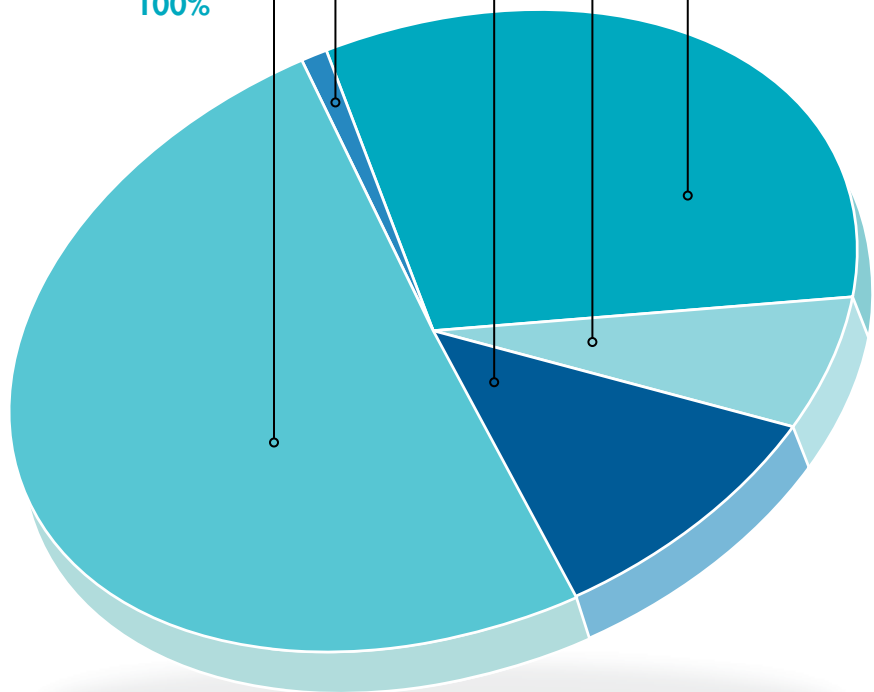
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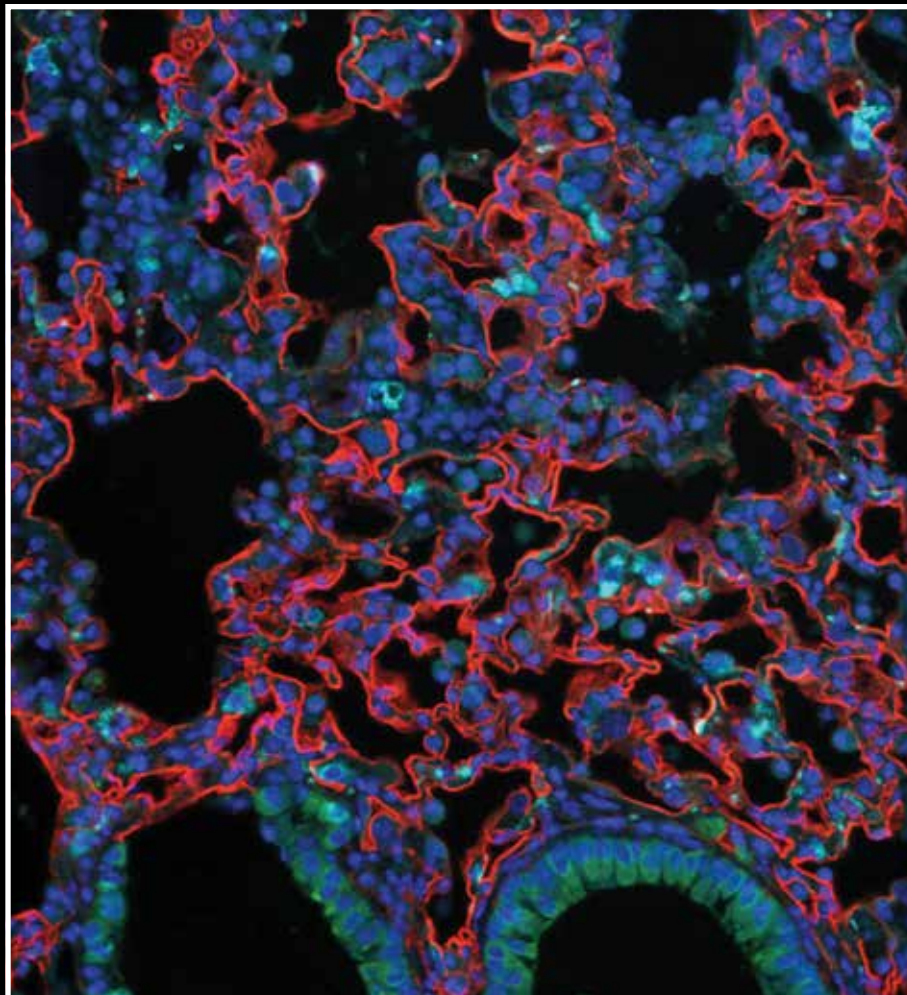
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This image features collapsed, immune cell-infiltrated alveoli composed of alveolar epithelial type 1 cells (red) and alveolar epithelial type 2 cells (aqua). Uninjured small airways are lined with club cells (green).

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