



Summer 2013

# RESEARCH HIGHLIGHTS

Team Science

Children's  
Hospital  
LOS ANGELES®

THE SABAN RESEARCH  
INSTITUTE

# The Saban Research Institute of Children's Hospital Los Angeles

The Saban Research Institute is one of the few freestanding research centers in the U.S. where scientific inquiry is combined with clinical care and is devoted exclusively to children. Our goal is to improve the health and wellness of children through a combination of basic, clinical and translational studies. Research is performed at the lab bench, in the clinic and in the community.

The Institute's interdisciplinary research is organized around three thematic areas that together fully explore the developmental origins of health and disease:

- The developing mind
- Metabolism, immunity, infection and inflammation
- Regenerative medicine and cellular therapies

Originally established in 1992, The Children's Hospital Los Angeles 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 2012, The Saban Research Institute received \$16.6 million in National Institutes of Health (NIH) funding and \$37 million in total funding.

The Saban Research Institute maintains strong scientific and strategic affiliations with the University of Southern California (USC) and, in particular, the Keck School of Medicine of USC.

All of the Institute's principal investigators (clinical investigators, physician-scientists and PhD-scientists) are USC faculty, and many have collaborative projects with scientists at the Keck School of Medicine and other departments at USC. The Institute's researchers also are involved in collaborative projects with academic institutions throughout the U.S. and abroad.



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# Team Science

*"It took an ex-physicist and a former ornithology student to crack the secret of life."*

— Robert Wright, Time magazine

In one of the most significant scientific discoveries of all time, James Watson and Francis Crick first reported the structure of DNA in 1953. This revolutionary breakthrough was the result of an unlikely partnership between an ex-physicist (Crick) and a former ornithologist (Watson)—and it won them the Nobel Prize. Collaboration and diversity had paid off in ways that hierarchy and homogeneity had not.

And team science was born.

Counter to the model of a single scientist in his or her lab coordinating the efforts of a small group of subordinates on an independent research project, team science involves two or more investigators with a shared vision and uses diversity—of discipline, location or stage of career—to its advantage. Assembling a research team is like planting a garden. Alone, each plant may be beautiful, but only together can they achieve the unique synergy that moves the soul.

At Children's Hospital Los Angeles, we work to unravel the complicated disorders of childhood that continue to manifest throughout a lifetime. These disorders cannot be traced to one single gene or a single organism, but rather emerge from a constellation of genetics, nutrition, physiology, socioeconomics and environment. We believe that changing the outcome for child health and well-being will be equally complex—requiring the insights of a multidisciplinary team.

At The Saban Research Institute of Children's Hospital Los Angeles, our "dream teams" coalesce around three thematic areas that together fully explore the developmental origins of health and disease:

- The developing mind
- Metabolism, immunity, infection and inflammation
- Regenerative medicine and cellular therapies

Interdisciplinary teams within our institution provide a multitude of complementary skills and expertise. Vicente Gilsanz, MD, PhD, an expert in imaging and body composition, has joined forces with Houchun (Harry) Hu, PhD, an engineer developing techniques to image fat without radiation exposure. Together they are working with endocrinologists to investigate the therapeutic potential of brown fat.



Jim Kim Soh, PhD, (left), Mark Frey, PhD, and Brent Polk, MD

Our collaborations also reach across the city and combine our talents with the best scientists from neighboring institutions. Our own Rex Moats, PhD, is working with City of Hope's Karen Aboody, MD, on translational research benefiting patients with glioma.

International collaborations are the ultimate examples of teamwork. Across time zones, cultures, languages, institutions and specialties, the global nature of our research is illustrated in work being done by investigators like Grace Aldrovandi, MD, CM, and her efforts to reduce maternal-infant transmission of HIV, literally changing the outcome for these infants, their families and society.

At the heart of any collaboration is an effective partnership, and there have been no stronger partners than Cheryl and Haim Saban. I would like to take this opportunity to acknowledge them, along with The Saban Family Foundation, for their vision and generous contributions to scientific research on this 10<sup>th</sup> anniversary of their transformative gift. Their philanthropy has supported many of our programs and projects, including the design and construction of The Saban Research Building, which provides an open, creative space to foster

interactions and collaborations between our researchers and those visiting our campus.

Childhood stands out as the single best time to maximize our human potential. As we have come to realize that the origins of adult diseases have their roots in childhood, pediatric medicine provides a unique opportunity to produce the best return for investments in research and health care. At The Saban Research Institute and Children's Hospital Los Angeles, we are working to improve outcomes through prevention, early detection and interventions that are specifically targeted to the individual patient. At the same time, we continue to push the frontiers of understanding to reduce inflammatory conditions that can increase cancer and contribute to obesity and diabetes, while pursuing regenerative medicine and cellular therapies to promote the body's own abilities to heal. Finally, we remain ever mindful of the particular care that must be exercised to protect and nourish the developing minds of children and adolescents.

By working together and leveraging the strengths of many, we will advance the health of children—and ultimately adults—in Los Angeles, the United States and around the world.

As you read the following stories, please know how much we appreciate your continued commitment and support.

Sincerely,

Brent Polk, MD  
Director, The Saban Research Institute  
Physician in Chief; Vice President, Academic Affairs;  
Chair of the Department of Pediatrics,  
Children's Hospital Los Angeles  
Vice Dean for Child Health,  
University of Southern California

# In the News



Tracy Grikscheit, MD

Tracy Grikscheit, MD, scientist in Developmental Biology and Regenerative Medicine and attending surgeon at Children's Hospital Los Angeles, was profiled on the front page of The New York Times for her care of infants with intestinal failure. Grikscheit is funded by the California Institute of Regenerative Medicine (CIRM) for her investigations in tissue-engineering the gastrointestinal tract as a future cure for premature infants with intestinal deficits.



Mitchell Geffner, MD

Mitchell Geffner, MD, division chief for the Center for Endocrinology, Diabetes and Metabolism, was interviewed by the Associated Press for his work on the TODAY (Treatment Options for type 2 Diabetes in Adolescents and Youth) study, a nationwide clinical trial that enrolled 699 teenagers with type 2 diabetes and followed them for nearly four years. The interview was carried by Time magazine, the Los Angeles Times, CBS, MSNBC and The Huffington Post. Results of the study were published in the New England Journal of Medicine.



Brent Polk, MD

Brent Polk, MD, director of The Saban Research Institute, and his collaborator and former postdoctoral fellow Fang Yan, MD, PhD, of Vanderbilt University, published their findings on the effects of probiotic bacteria on inflammatory bowel disorders in the Journal of Clinical Investigation. The study was subsequently reported on by Science Daily.



Larry Yin, MD

Larry Yin, MD, medical director of the Boone Fetter Clinic, spoke about the increasing incidence of autism—now 1 in 88 children. Following release of these revised statistics by the Centers for Disease Control and Prevention, interviews with Yin and his colleagues were carried on NBC, ABC, Fox, CBS, Univision, KTLA and KPCC.



Emil Bogenmann, PhD, EdD

Emil Bogenmann, PhD, EdD, and his students in the Samuels Family Latino and African-American High School Internship Program (LA-HIP) were profiled in the Los Angeles Times and on ABC News, and Cheryl Saban, PhD, and the students were interviewed by Univision. This program begins with a rigorous science internship followed by assistance with college applications and acceptance, encouraging minority students to pursue careers in science and medicine.



Pia Pannaraj, MD, MPH

A research study on the flu vaccine presented by Pia Pannaraj, MD, MPH, received both national and international media coverage. The study showed that school vaccination was particularly effective at preventing spread of the disease at school, as well as in the community.

# Major Grants Awarded



Fatih Uckun, MD, PhD

Fatih Uckun, MD, PhD, received an award of \$536,000 from the National Cancer Institute for his research on amplifying radiation potency against leukemic stem cells.



Tai-Lan Tuan, PhD

Tai-Lan Tuan, PhD, received \$1.2 million from the National Institutes for General Medical Sciences for her work on therapeutic approaches to keloid fibrosis using siRNA inhibition and fibrin matrix skin equivalent mouse models.



Tracy Grikscheit, MD

Tracy Grikscheit, MD, was awarded \$3.4 million from the California Institute for Regenerative Medicine to continue her work on tissue-engineered intestine.



Wei Shi, MD, PhD

Wei Shi, MD, PhD, was awarded \$1.6 million from the National Heart, Lung and Blood Institute to study the molecular mechanisms of lung development.



Yong-Mi Kim, MD, MPH, (left), Steven Mittelman, MD, PhD, and Nora Heisterkamp, PhD

Nora Heisterkamp, PhD, Steven Mittelman, MD, PhD, and Yong-Mi Kim, MD, MPH, received a \$600,000 Translational Research Grant from The V Foundation for Cancer Research to investigate strategies to inhibit interactions between leukemia and bone marrow cells in order to improve treatment outcomes.



Emil Bogenmann, PhD, EdD

Emil Bogenmann, PhD, EdD, received renewal of the \$890,000 National Institute of Diabetes and Digestive and Kidney Diseases grant for the Short-Term Education Program for Underrepresented Persons (STEP-UP) to provide biomedical research training to disadvantaged college undergraduates.



Randall Wetzel, MB, BS

Randall Wetzel, MB, BS, received \$3.1 million for development of the Laura P. and Leland K. Whittier Virtual Pediatric Intensive Care Unit (VPICU) 2.0 Program, a network that will provide decision support to pediatric intensive care units throughout the U.S. and improve quality and patient outcomes through knowledge sharing.



Mitchell Geffner, MD

Mitchell Geffner, MD, was awarded \$1 million from the National Institute of Diabetes and Digestive and Kidney Diseases for the next phase of the TODAY study, examining the long-term health of patients who were enrolled in the original treatment study of youth with type 2 diabetes.



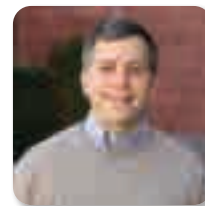
# New Faces

Lily Chao, MD, joined the Division of Endocrinology at Children's Hospital Los Angeles and the Obesity Program at The Saban Research Institute, where she studies the actions of nuclear receptors on skeletal muscle growth and metabolism. After completing medical school and her pediatric residency at the University of California, Los Angeles (UCLA), Chao did her clinical endocrinology training at Children's Hospital Los Angeles and her research training at the Howard Hughes Medical Institute at UCLA, both under the auspices of the Association of Medical School Pediatric Department Chairs' Pediatric Scientist Development Program.



Lily Chao, MD

David Cobrinik, MD, PhD, has joined the Division of Ophthalmology and Department of Surgery and is a member of the Developmental Neuroscience and Cancer Research programs at The Saban Research Institute. Before joining Children's Hospital as associate professor of Research Ophthalmology at the Keck School of Medicine of the University of Southern California (USC), Cobrinik was a visiting investigator and senior research scientist at Sloan-Kettering Institute for Cancer Research. His research focuses on the development of retinoblastoma, a retinal tumor that occurs in very young children.



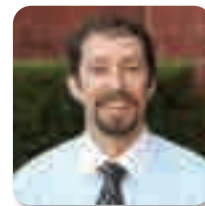
David Cobrinik, MD, PhD

Muller Fabbri, MD, PhD, is now a member of the Children's Center for Cancer and Blood Diseases. Fabbri attended medical school in Italy and continued his postdoctoral training at Thomas Jefferson University in Philadelphia and then at Ohio State University, where he worked in the lab of Carlo Croce, MD. He is investigating the role of microRNAs and other non-coding RNAs in cancer growth and dissemination, and in the development of cancer resistance to therapy, the main cause of cancer-related mortality.



Muller Fabbri, MD, PhD

Christopher Gayer, MD, PhD, has joined the hospital's Department of Surgery and the Developmental Neuroscience Program at The Saban Research Institute. Gayer received both his doctorate and medical degree from Wayne State University, where he completed a general surgery residency, followed by a fellowship in pediatric surgery. His areas of research include gastrointestinal mucosal wound healing and necrotizing enterocolitis.



Christopher Gayer, MD, PhD

Senta Georgia, PhD, has joined the hospital's Division of Endocrinology and the Developmental Biology and Regenerative Medicine Program at The Saban Research Institute, where she studies the regeneration of insulin-producing pancreatic beta cells as a potential therapy for patients with type 1 diabetes. After receiving a doctorate in molecular biology from UCLA, Georgia served as a postdoctoral fellow and assistant adjunct professor at the university's Hillblom Islet Research Center.



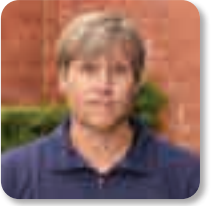
Senta Georgia, PhD

Frank Ing, MD, joins the Department of Cardiology as associate chief and is serving as director of the Cardiac Catheterization Laboratory. Ing was previously director of the Cardiac Catheterization Laboratory and professor of Pediatrics at Baylor College of Medicine, where he established his research focus in therapeutic catheterizations and the development of transcatheter techniques and cardiovascular devices. He received his medical degree from Stony Brook University School of Medicine and completed his residency and chief residency in the Department of Pediatrics at New York University.



Frank Ing, MD

Rusty Lansford, PhD, has joined the hospital's Department of Radiology and the Developmental Neuroscience Program at The Saban Research Institute. Lansford received his doctorate in immunology from the Columbia University College of Physicians and Surgeons. He completed a postdoctoral fellowship in Scott Fraser's lab at the California Institute of Technology, where he subsequently became a senior scientist. Using dynamic four-dimensional imaging, he studies the role of embryonic development on pathogenesis.



Rusty Lansford, PhD

Pat Levitt, PhD, joins the Department of Pediatrics as the inaugural director of the Developmental Neurogenetics Program at the Institute for the Developing Mind. Arriving from USC, Levitt will continue to direct the university's Neuroscience Graduate Program and will spearhead an initiative to develop and lead an interdisciplinary autism center, bringing together experts from Children's Hospital and USC. Levitt earned a doctorate in neuroscience from the University of California, San Diego, and completed a post-doctoral fellowship in neuroanatomy at Yale University School of Medicine.



Pat Levitt, PhD

Michael Neely, MD, has joined the Division of Pediatric Infectious Diseases as director of the Laboratory of Applied Pharmacokinetics and Bioinformatics. His research and clinical interests involve anti-bacterial, anti-viral and anti-fungal pharmacology, as well as clinical pharmacometrics that apply modeling and simulation techniques to the optimization of dosing in individual patients. He completed medical school at University of California, Davis, and recently received a Master of Science degree in clinical and biomedical investigations at USC.



Michael Neely, MD

Chintan Parekh, MBBS, has joined the hospital's Division of Hematology-Oncology and The Saban Research Institute, where he studies normal T-cell development and T-cell leukemias. Parekh received his medical degree from Seth GS Medical College, Mumbai, India. After doing a fellowship in Pediatric Hematology-Oncology at Children's Hospital Los Angeles, he served as a clinical instructor at UCLA.



Chintan Parekh, MBBS

Di Tian, MD, PhD, accepted an appointment as a neuropathologist with the hospital's Department of Pathology and Laboratory Medicine and the Developmental Neuroscience Program at The Saban Research Institute. Tian received his medical degree from Beijing Medical University and a doctorate in neuroscience from Northwestern University. He completed his residency in anatomical pathology and a fellowship in neuropathology at Massachusetts General Hospital (MGH). Tian conducted postdoctoral research at MGH and the Massachusetts Institute of Technology. He combines expertise in genetics with the ability to develop and characterize in vivo models for autism and other neurodevelopmental disorders.



Di Tian, MD, PhD

Alan Wayne, MD, is now director of the Children's Center for Cancer and Blood Diseases and division head of Hematology-Oncology and Bone Marrow Transplantation in the Department of Pediatrics. He previously served for 14 years as clinical director of the Pediatric Oncology Branch of the National Cancer Institute at the National Institutes of Health. He holds a medical degree from Northwestern University and completed his internship, residency and chief residency at Boston Children's Hospital and the Dana-Farber Cancer Institute.



Alan Wayne, MD

Yaling Yang, PhD, is now a member of the hospital's Department of Pediatrics and the Developmental Neuroscience Program at The Saban Research Institute. After receiving her doctorate from the University of Southern California, Yang was a postdoctoral scholar in the Department of Neurology at UCLA. Yang's expertise is in structural brain imaging as a technique for investigating the pathophysiological mechanisms associated with the development of antisocial personality disorder, schizophrenia, substance abuse and other psychiatric and neurodevelopmental disorders.



Yaling Yang, PhD



# CAREER SPOTLIGHT

## Jonathan Finlay, MD, Endowed Chair and Director of the Neuro-Oncology Program

Jonathan Finlay, MD, is director of the hospital's newly established, interdepartmental Neuro-Oncology Program and was recently named to an endowed chair funded by The Wilder Family Trust. He will work in collaboration with colleagues in neurology, neuropathology, neurosurgery and neuroradiology to research new diagnostic and therapeutic strategies to treat brain cancer in children.



Jonathan Finlay, MD, with patient Alicia Chu, age 2.

One of the overall goals of the endowed chair is to develop translational research in these different areas and incorporate the scientific findings into clinical practice. Finlay, a professor of Pediatrics, Neurology and Neurological Surgery at the Keck School of Medicine of the University of Southern California, has been conducting pioneering research throughout his career.

Recently, Finlay was a co-principal investigator in a cancer study that connected an otherwise rare childhood malignant brain tumor, choroid plexus carcinoma, with a mutation of the P53 gene responsible for Li-Fraumeni Syndrome. The findings concluded that children with this rare brain tumor should be tested for the P53 mutation, and if possible, family members should also be tested. Finlay's group has shown that implementing appropriate cancer screening strategies improves the cure rates for patients with cancers diagnosed early through such surveillance screening.

In addition to directing one of the largest brain tumor treatment programs in the country, Finlay is also leading two multinational consortia: the "Head Start" Consortium, to improve the cure rate and quality of survival for young children with newly diagnosed malignant brain tumors through avoidance or minimization of radiotherapy; and the International CNS Germ Cell Tumor Consortium, to develop innovative treatment strategies for children, adolescents and young adults with rare germ cell tumors of the brain. Finlay also is leading an international effort to develop management strategies to improve outcomes in low-income, developing countries previously unable to combat otherwise curable childhood brain cancers. ■



Jonathan Finlay, MD, reviews a brain scan.



# Brown Fat, Brown Fat, What Do You See?

I see your future looking at me.

The newest weapon being studied to battle the worldwide epidemic of obesity might surprise you—it's fat.

The fat we associate with weight gain is white fat, a substance that stores excess calories. There is another kind of fat, however, usually associated with babies and hibernating mammals, called brown fat. Brown fat is full of blood vessels and mitochondria, making it efficient at burning calories instead of storing them. Could brown fat have a role in the treatment of obesity and the prevention of associated chronic diseases—like cardiovascular disease and diabetes?

Vicente Gilsanz, MD, PhD, and Houchun (Harry) Hu, PhD, researchers at The Saban Research Institute of Children's Hospital Los Angeles, are working to find out.



Vicente Gilsanz, MD, PhD, and Houchun (Harry) Hu, PhD

"Young people who are obese tend to become adults who are obese," says Gilsanz, director of Clinical Imaging at Children's Hospital and professor of Radiology and Pediatrics at the Keck School of Medicine of the University of Southern California. "The objective should be to intervene early and reduce the risk of chronic disease while increasing quality of life. A leaner body could come from a change in metabolism, rather than medication or a change in diet."

That's great news for the millions of children and adults who struggle with obesity, including many for whom lifestyle changes and medication simply don't work. Yet research on brown fat is still in its infancy. There is some information available on brown fat in adults, but few studies have been done in children.

Why has work on this potentially promising area taken so long? "Until quite recently, we didn't know that brown fat existed in humans past infancy," explains Hu. "There has been a lot of research done by cell biologists on the thermogenic effects of brown fat in rodents and hibernating mammals, but there was little awareness of its potential relevance in humans."

Recent studies that identified brown fat in patients undergoing positron emission and computed tomography (PET/CT) scans for medical conditions renewed interest in deciphering the relevance of this tissue in humans. "When we first scanned these pediatric patients with cancer, they typically didn't have brown fat," says Hu. "Yet on follow-up, most of these same kids now had brown fat—and it was metabolically active."

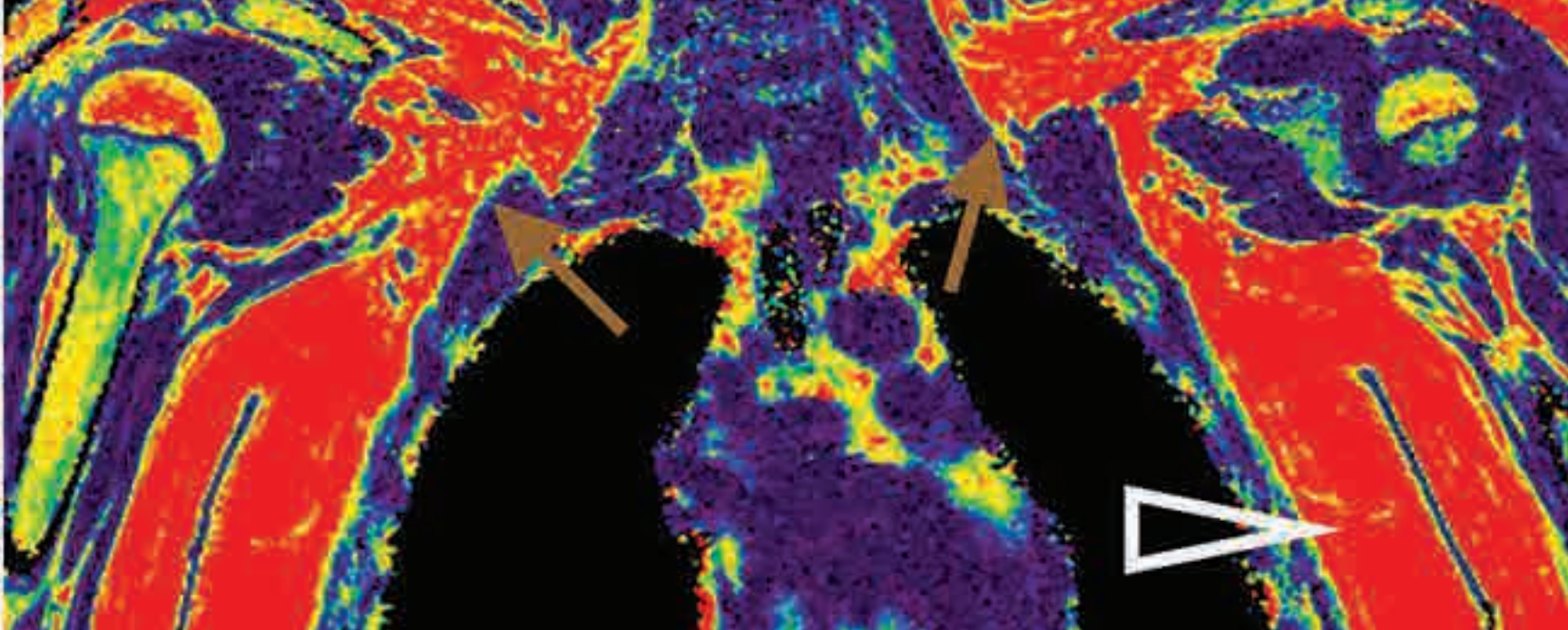
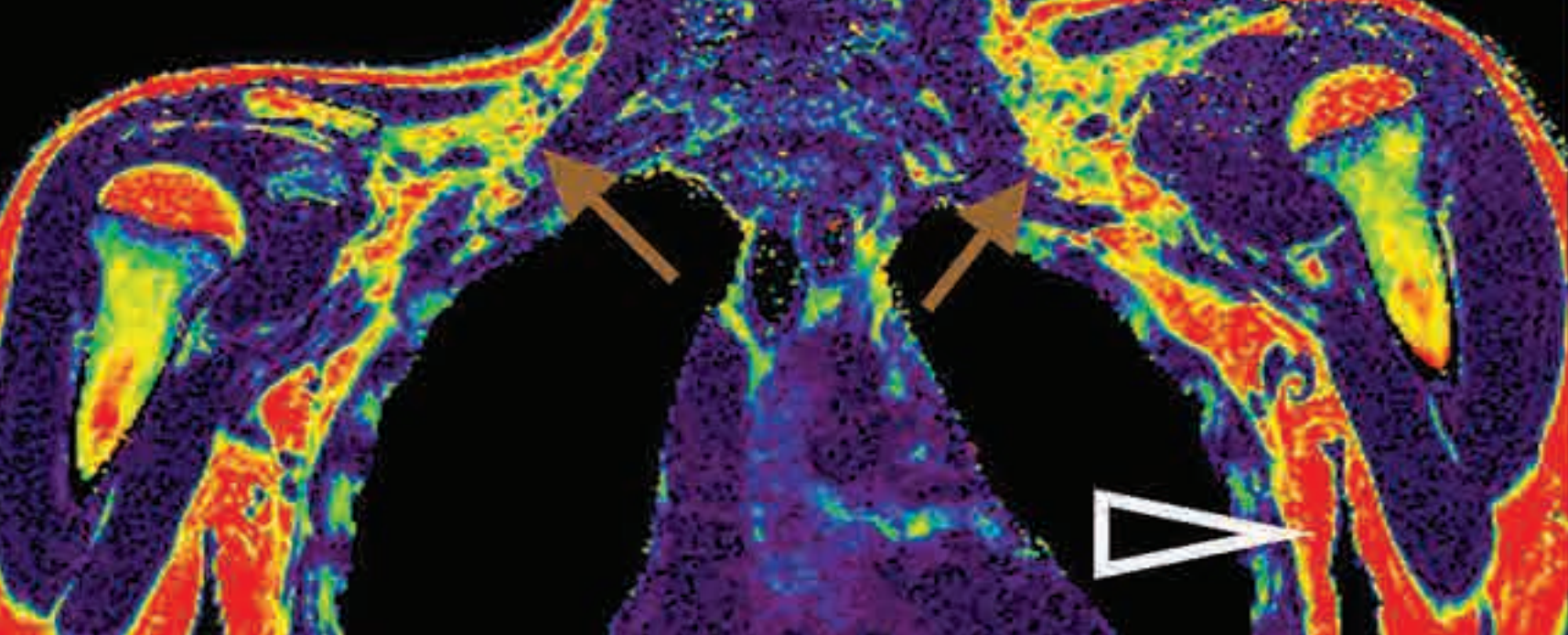
Gilsanz explains, "The significance of this finding could be striking. Children without active brown fat gained three times more weight and subcutaneous fat than children with active brown fat." These observations are consistent with what has previously been reported: Overweight children and adults have less brown fat than their lean peers, suggesting an inverse relationship between brown fat and white fat.

The finding also suggested that it might be possible to "turn on" brown fat, revealing additional possibilities for the tissue's therapeutic potential. Unfortunately, the significant amount of radiation exposure associated with PET/CT scans made them unsuitable for studying healthy patients, particularly children.

Until now.

*continued on page 12*





Brown arrows point to brown fat (shown in yellow) and white arrow indicates minimal amount of subcutaneous white fat (shown in red) in an MRI of a lean 12-year-old boy. On the adjacent page in an MRI of an overweight 11-year-old boy, brown arrows point to the area where brown fat would be located. The white arrow points to significant amounts of white fat (shown in red). The visual similarity between the brown fat and white fat deposits suggests that the brown fat is metabolically inactive and has been infiltrated by white fat.

Gilsanz saw the opportunity in this area and searched for a collaborator who could work with him to safely and accurately measure brown fat. He found Hu, an assistant professor at the Viterbi School of Engineering at USC, who was developing techniques for using magnetic resonance imaging (MRI) as a radiation-free method for identifying and quantifying brown fat. A cross-disciplinary partnership began.

“Research needs to exist across disciplines and across institutions,” says Gilsanz. “Even with outstanding individual scientists, the group is always stronger and can accomplish more than the sum of each individual. Indeed, the imaging program is currently collaborating on several studies with the divisions of Endocrinology, General Pediatrics, Hematology-Oncology, Neonatology and Orthopaedics.”

The team also now includes Shingo Kajimura, PhD, a cell biologist from the University of California, San Francisco, who can provide genetic confirmation of what Gilsanz and Hu are observing clinically. Additional technical expertise is provided by industry—Philips Healthcare makes the MRI device and helps optimize the newly developed scanning protocols.

The ability to safely and repetitively image brown fat using MRI will allow the team to do longitudinal studies, following individuals from birth to puberty. “Some people say you become obese because you lack brown fat,” says Gilsanz. “The corollary is that there are people who can eat anything without gaining weight. Why is that? We don’t know, but we can now examine whether brown fat has a role.”

The investigators also hope to discover a mechanism for “activating” the obese child’s brown fat. Then they can begin developing therapeutic applications for the tissue—to fight fat with fat. ■

*“Research needs to exist across disciplines and across institutions. Even with outstanding individual scientists, the group is always stronger and can accomplish more than the sum of each individual.”*

— Vicente Gilsanz, MD, PhD

## Innovation Incubator

A multidisciplinary group of researchers at The Saban Research Institute of Children’s Hospital Los Angeles recently came together to create a new, safe way to study brown fat in children with unique hormone problems—using a novel MRI technique instead of PET/CT scans. The project received the first-ever award from The Saban Research Institute Innovative Pilot Project Grant, a new intramural funding program aimed at expanding multidisciplinary research.

“The big issues of pediatric medicine require new approaches,” says Brent Polk, MD, director of The Saban Research Institute. “We believe that this new program will create an innovation incubator for teams committed to addressing child health and well-being.”

The brown fat project is a collaboration between four faculty members in three disciplines: Mimi Kim, MD, and Mitchell Geffner, MD, in Endocrinology;

Vicente Gilsanz, MD, PhD, in Radiology; and Houchun (Harry) Hu, PhD, in Radiology and the Viterbi School of Engineering at the University of Southern California (USC). Gilsanz and Hu developed the specialized MRI technique.

“We needed each person’s expertise to make this study possible,” says Kim, the project’s principal investigator. “It’s a perfect example of how team science can push innovative research forward.”

Driving innovation is precisely the goal of the Innovative Pilot Project Grant. The Saban Research Institute has allocated \$100,000 per year to fund the program, which will provide an avenue for more cross-competency teamwork and encourage new collaborations between researchers in different disciplines.

This kind of pilot funding is key to supporting those non-traditional collaborations that can lead to novel discoveries. It is also essential when competing for federal grants. “This funding is crucial to generating proof-of-principle data that we can use to apply for larger NIH funding,” says Kim.

The brown fat study, for example, has the potential to greatly impact the understanding of brown fat’s link to metabolism and obesity in children.

“This grant really will help to jump-start our research,” explains Kim, assistant professor of Clinical Pediatrics at the Keck School of Medicine of USC. “The internal support frees our team to focus more on collaborating and problem solving. It makes a huge difference.” ■



Houchun (Harry) Hu, PhD, (left), Mitchell Geffner, MD, Vicente Gilsanz, MD, PhD, and Mimi Kim, MD



# The Changing Face of Type 2 Diabetes

Mitchell Geffner, MD, and his colleagues found that type 2 diabetes affects children differently than adults. In the face of rising diagnoses of the disease in pediatric patients, he hopes to find better treatment methods.

Mitchell Geffner, MD, recently saw an 80-pound 3-year-old in his clinic.

Geffner, who serves as division chief of the Center for Endocrinology, Diabetes and Metabolism at Children's Hospital Los Angeles, fears the worst for obese children, who are on the fast track to a type 2 diabetes diagnosis.

He should know. As principal investigator of the TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth) and TODAY 2 studies, Geffner and his colleagues at The Saban Research Institute of Children's Hospital Los Angeles have found that the disease takes on a much more dangerous, virulent form in children.

Their findings were recently published in the *New England Journal of Medicine*.

"When I was a fellow, type 2 diabetes was a disease of adults," says Geffner, professor of Pediatrics at the Keck School of Medicine of the University of Southern California. "Over the last 15 to 20 years in this country and in others, the disease is occurring much more frequently in children. Our own data show that over the last 10-plus years, 20 percent of newly diagnosed pediatric diabetes cases are type 2.

"That's 1 in 5 children in a little more than a decade," he says. "Twenty to 30 years ago, this was unheard of."

Those rising diagnosis rates, coupled with the growing obesity epidemic throughout the world, spurred the creation of the national TODAY study, which focused on finding the most effective treatment for type 2 diabetes in children and



Patrice Yasuda, PhD, (left); Mitchell Geffner, MD; Debra Miller, RN, TODAY-VELKid Study nurse coordinator; Lynda Fisher, MD; and Nancy Chang, FNP

adolescents ages 10 to 17. It was also the first aimed at determining the effects of intensive lifestyle changes in this population.

Nationwide, 699 participants enrolled in the five-year multi-institutional study, which began in 2002. Ten percent of those were from Children's Hospital; in fact, the hospital was the only research center west of Denver to participate.

Geffner worked with a team of Children's Hospital experts, including Nancy Chang, FNP, Patrice Yasuda, PhD, and Lynda Fisher, MD. The group's top goal was to determine the most effective method for treating type 2 diabetes in children, using metformin, the only drug approved to treat youth, and in some subjects, metformin and rosiglitazone, a drug typically only used in adults. The study also integrated diet and exercise, a proven treatment in adults.

Specifically the study compared:

- Metformin alone, versus metformin plus intensive lifestyle changes
- Metformin alone, versus metformin plus rosiglitazone
- Metformin plus intensive lifestyle changes, versus metformin plus rosiglitazone

*"As a children's hospital, we **have** to do something. It would be wrong not to."*

*— Mitchell Geffner, MD*



"We assumed, as in adults, that diet and exercise was going to be the best option for kids," Geffner says. "But the best overall group was the double-med group."

However, during the study, rosiglitazone was found to have cardiac risk for adult patients and was given a black box warning by the Food and Drug Administration.

"In a way, it was the worst outcome," Geffner says. "The best treatment involved a drug we couldn't use. Perhaps the most important lesson learned is that the disease will likely require multiple drugs to achieve the best control."

Geffner and his colleagues also learned that lifestyle still played an important role in the health of children in the study, particularly over the long run. What's more, they walked away with a better understanding of just how aggressive the disease is in youth.

Children with type 2 diabetes face more hypertension, abnormal lipid counts and overall more co-morbidities of disease.

Now in the second phase of the study with TODAY 2, researchers hope to continue tracking study participants and the effect their randomized treatments have had on their long-term health, even after subjects have stopped that therapy. Based on the results of the TODAY study, researchers anticipate conducting additional studies of multi-drug treatments to optimize insulin control in youth.

The thinking is that the kids who did the best at the beginning might enjoy a carryover effect down the road, Geffner says. Many are now in their 20s, and some participants are as old as 28.

"We have one of the highest retention rates of the participating institutions," Geffner says. "That really speaks to the relationship our subjects have with our phenomenal team, particularly within the context of such a difficult study population in terms of their education and socio-economics."

He feels that the virulence of the disease may have a serious effect on quality of life and lifespan.



Lynda Fisher, MD, with patient Angel Dominguez

"Compare the future health of a 16-year-old with type 2 diabetes to a 50-year-old diagnosed with the same disease over time," Geffner says. "Long-term complications—like heart disease, stroke and high blood pressure—that have been associated with advanced age may now appear much earlier, resulting in a loss of human potential and a huge increase in health care costs. It's mind-boggling that the prevalence and the severity of this disease is so high."

So what's next? Geffner and his colleagues believe it's imperative to find better treatment paradigms.

Ongoing efforts at the Center and at Children's Hospital include:

- Offering referred patients access to physicians, nutritionists, psychologists and social workers to assist with weight management goals
- Working with community sites using the Kids N Fitness® weight management program developed at Children's Hospital
- Offering an obesity clinic within the AltaMed General Pediatrics Clinic
- Offering nutritional services within the Adolescent Medicine Program

The hospital has also established a prevention-focused, multidisciplinary diabetes and obesity program with clinical and research components, as well as medical and surgical connections.

"As a children's hospital, we have to do something," Geffner says. "It would be wrong not to." ■

"It's mind-boggling that the prevalence and the severity of this disease is so high."  
- Mitchell Geffner, MD

## TYPE 2 DIABETES IN KIDS

A GROWING PROBLEM

### YESTERDAY

Type 2 diabetes was rare; formerly known as adult-onset diabetes.

### TODAY

One in every 400 kids and adolescents have diabetes.

### TOMORROW

Total deaths from diabetes are projected to rise more than 50% in the next 10 years.



OBESITY IS THE LEADING RISK FACTOR FOR TYPE 2 DIABETES

1 IN 3

AMERICAN KIDS ARE OVERWEIGHT OR OBESE

\$245 BILLION IN ANNUAL SPENDING ON DIABETES



TYPE 2 DIABETES CAN BE PREVENTED



DIABETES KILLS MORE AMERICANS THAN AIDS + BREAST CANCER

### ONGOING EFFORTS AT CHILDREN'S HOSPITAL LOS ANGELES:



Weight management and nutritional services



Obesity Clinic at the AltaMed General Pediatrics Clinic



Prevention-focused, multidisciplinary diabetes and obesity program



# One Step at a Time in the Fight Against Obesity

When it comes to obesity, Steven Mittelman, MD, PhD, has found that there is no one simple answer.

In response to the toll obesity and diabetes have taken on the country's health and health care system, Mittelman, who was recently named director of the newly established diabetes and obesity program, has partnered with colleagues throughout Children's Hospital Los Angeles. He and Mitchell Geffner, MD, chief of the Center for Endocrinology, Diabetes and Metabolism at Children's Hospital, have been collaborating with others to address several areas of potential impact, including community outreach and research.

"As we laid the groundwork for that larger vision, we also wanted to figure out what we could do now to effect change," Mittelman says.



## Community Outreach

To get the conversation started, the hospital held screenings of HBO's "Weight of the Nation," offering those interested in the topic of obesity the opportunity to come together. The series was shown at The Saban Research Institute.

"We found that a lot of people—from various divisions and departments—care about this, and there was a will to move forward," Mittelman says.

That led to researching the possibilities of opening a farmers market at the hospital, starting a visual public awareness campaign on sugar-sweetened beverages and establishing a multidisciplinary obesity clinic. All these ideas are currently being pursued.

## Research

With the newly formed program, researchers focusing their laboratory efforts on diabetes and obesity will now have a central location, which will facilitate collaboration. The Saban Research Institute has also recruited Lily Chao, MD, an investigator who is studying insulin signaling in muscle tissue.

Another junior investigator, Senta Georgia, PhD, will also join Mittelman and his team to study the potential therapeutic use of stem cell transplantation to establish new beta-cells for patients with diabetes.

In conjunction with the University of Southern California Diabetes and Obesity Research Institute (DORI), the hospital is jointly recruiting an adipose biology expert as well. This expanding group of researchers will be a valuable asset to the team of clinical and translational researchers at Children's Hospital.

As he and his colleagues continue with their efforts, Mittelman looks forward to changing the future of many children for the better.

"Like in 'Weight of a Nation,' it's a huge mountain that we have to move," he says, "but everything we do will make a difference." ■



Lily Chao, MD, (left) and Steven Mittelman, MD, PhD

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*"We found that a lot of people—from various divisions and departments—care about this, and there was a will to move forward."*

*— Steven Mittelman, MD, PhD*

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## New View on Autism

Is America experiencing an autism epidemic? Experts disagree, but all say that early diagnosis is critical. Mark Borchert, MD, thinks he's found a new approach to achieving early diagnosis by studying a rare eye disorder.

The parallels between autism spectrum disorders (ASDs) and optic nerve hypoplasia (ONH) are striking, with one dramatic exception: their prevalence.

ASDs now impact 1 in 88 children and 1.5 million Americans, according to the Centers for Disease Control and Prevention. ONH, meanwhile, affects fewer than 200,000 people in the U.S., yet it is the leading ocular cause of blindness and visual impairment in young children.

ONH is characterized by underdeveloped optic nerves, neurological impairment, endocrine abnormalities and developmental delays. Its effects have a broad range, from little or no impairment to near-total blindness. That makes ONH a spectrum disorder, much like autism, says Borchert, director of the Eye Birth Defects Institute and Eye Technology Institute in The Vision Center at Children's Hospital Los Angeles.

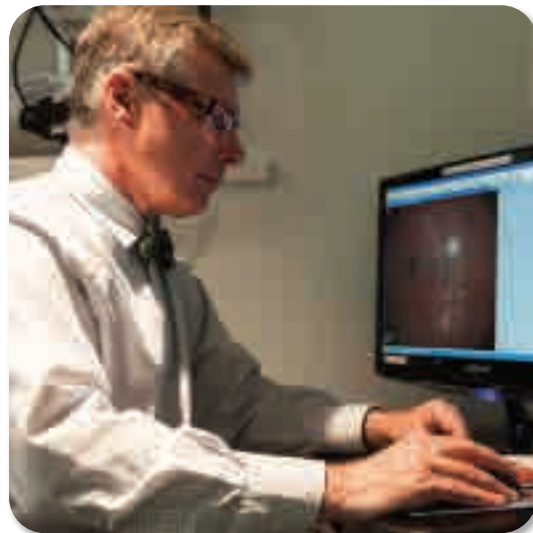
Children with ONH and ASDs typically have gastrointestinal and sleep disorders. The two conditions also show impairment in central nervous system connectivity—in ONH's case, a kind of global mis-wiring. And ONH and ASD share a similar trajectory in their increasing numbers.

"With the similarities between the two conditions, we have an opportunity to achieve new understanding and solutions for both ONH and autism spectrum disorders," says Borchert.



He estimates that nearly a third of children with ONH also have ASD. Proper assessment can be difficult. Many behaviors in visually impaired children resemble ASD symptoms—such as repetitive speech, pronoun reversal, singsong language and ritualistic movements. Often these behaviors are termed “blindisms” and attributed solely to diminished sight.

Complicating the diagnosis is the fact that many screening methods for autism rely on visual cues such as making eye contact—problematic for children with poor vision.



Mark Borchert, MD

Borchert’s solution: a vision-independent diagnostic tool. “Accurate diagnosis will enable us to identify ASD risk factors that were present in the first year of life in children with ONH, since we already have detailed first-year data from these children,” he says.

If these early-onset risk factors are the same for sighted children, they may set the stage for testing new intervention therapies to prevent or impact ASD earlier than is now possible.

The added advantage of focusing on children with ONH is that researchers can study far fewer children—versus thousands in the general population—to pinpoint those crucial risk factors for ASD.

In a pilot study in 2012, Borchert and his colleagues modified existing screening instruments for evaluating autism to eliminate visually dependent tests. This included replacing small toys with larger or lighted toys, as well as finding non-visual responses, such as turning toward a person’s voice instead of pointing.

So far, the modified test has proven effective in predicting ASD in a limited number of children with ONH. The next logical step is conducting a large-scale, multi-center trial to validate the tool in more children with different levels of visual impairment, not just ONH. That will take additional funding, says Borchert.

Right now, a diagnosis of autism relies largely on signs and symptoms. There are no biological markers—yet. Borchert has turned to advanced imaging technologies for clues.

About 40 percent of children with ONH have brain abnormalities that can be visualized with magnetic resonance imaging (MRI). Working with neurological and imaging experts at Children’s Hospital, Borchert is trying to determine if subtle features of the brain can be seen in MRIs that correlate with a diagnosis of ASD.

He is accustomed to such cross-disciplinary collaborations, which also include colleagues in Endocrinology, Pediatrics and Psychology. Uncovering the link between ONH and ASD has broadened his partnerships to embrace the USC University Center for Excellence in Developmental Disabilities (UCEDD) at Children’s Hospital and the Southern California Clinical and Translational Science Institute.



Mark Borchert, MD, with patient Abrar Z. Kazi, age 9

“When you have a multi-system condition such as this, you need to know which of the issues are related to each other and how. Collaboration is essential,” notes Borchert, associate professor of clinical ophthalmology and neurology at the Keck School of Medicine of the University of Southern California.

Michele Kipke, PhD, principal investigator of the Autism Speaks Autism Treatment Network Center of Clinical Excellence at Children’s Hospital and vice chair of Research in the department of Pediatrics, concurs. “As we learn more about the incredible complexity of ASD, it is clear that we need more effective screening and diagnostic tools to help reduce the misdiagnosis rate, particularly for children who also have complex medical needs,” she says. “Dr. Borchert’s work is a great example of an innovative new strategy that will help children receive a diagnosis sooner and enable them to get the care that they need.”

Borchert is working toward that goal. “It will make a huge difference in the lives of all children, including those with a visual impairment,” he says. ■



Michele Kipke, PhD



# The Power of Partnership



An enduring, cross-disciplinary investigation is improving the outlook for children with neuroblastoma. Collaboration takes place at all levels—from clinicians and lab scientists to support staff and families.

Araz Marachelian, MD,  
and Robert C. Seeger, MD

Thirty-eight years ago, when Robert C. Seeger, MD, began studying neuroblastoma—the second-most common solid cancer in children—the survival rate for the widespread, high-risk form of the disease was an abysmal 5 percent.

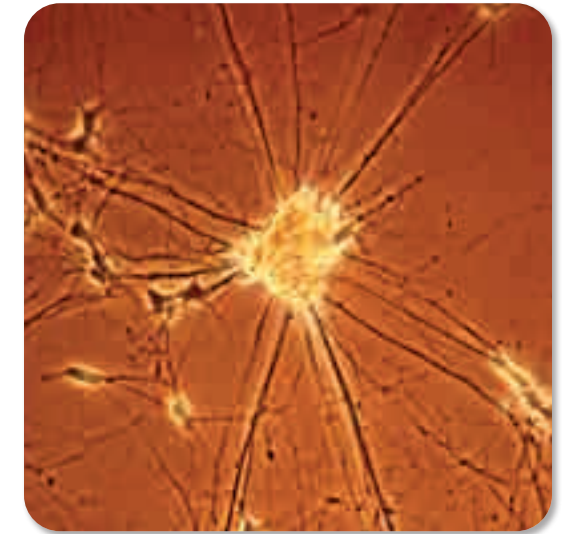
Today, 45 percent of children with high-risk neuroblastoma are cured, as are essentially all children with low-to-medium disease risk. This steady improvement over decades represents a triumph of the collaborative determination, expertise and teamwork of clinicians, scientists and support personnel across North America.

“Teamwork will always get you a lot further than one individual can achieve. You can’t be as innovative or make as much progress otherwise,” says Seeger, director of the Cancer Research Program at The Saban Research Institute, division head for Basic and Translational Research in the Children’s Center for Cancer and Blood Diseases and professor of Pediatrics at the Keck School of Medicine of the University of Southern California (USC).

Seeger has been involved in nearly every major advance in understanding the biology and treatment of neuroblastoma, which strikes mainly infants and toddlers. But he hasn’t been alone.

In 2000, the National Cancer Institute (NCI), after peer review, approved a Program Project Grant (PPG), with Seeger as principal investigator. That led to the creation of the New Approaches to Neuroblastoma Therapy (NANT) Consortium, which now includes 15 universities and children’s cancer centers in the U.S. and Canada.

Working together in a consortium is indispensable in cancer research—particularly in pediatric cancer, where any one center may not have enough patients to optimize a clinical trial and bring a new treatment from laboratory to clinic. NANT is a particularly successful example, with funding



High-risk neuroblastoma cultured tumor cells

renewed twice, most recently in 2010, when the NCI awarded \$11 million for another five years of support.

NANT’s focus: early Phase I and II clinical trials that target tumor cells, as well as normal cells around them that promote tumor growth. The PPG and NANT partnership includes experts in developing and running clinical trials and identifying tumor cell and pro-tumor normal cell targets for therapy, as well as experts in immunotherapy, molecular biomarkers for evaluating treatments, pathology and biostatistics.

“We’re always moving forward; it’s like a river flowing,” says Araz Marachelian, MD, NANT medical director and assistant professor of Clinical Pediatrics at the Keck School of Medicine of USC.

Promising new treatments from the NANT Consortium travel to the even larger proving ground of the Children’s Oncology Group (COG), which unites more than 200 institutions globally. Several treatments developed by NANT investigators have become standards of care for children with high-risk or relapsed neuroblastoma.





Members of the NANT Consortium

Among their current strategies, NANT teams are looking at targeted radiation therapy; immune therapy that employs anti-tumor natural killer cells in combination with a protein antibody and a potent immune-modulating drug; and a molecular biomarker test that can detect one tumor cell per million normal cells in blood and bone marrow.

NANT's success can be attributed in large part to the collaborative spirit that extends beyond its investigators and scientists. All NANT studies are supported by the NANT Operations Center team, located at Children's Hospital Los Angeles. Woosa Visatpaliphol serves as administrative director, and Scarlett Czarnecki, research nurse, coordinates study protocols with nurses across the country. Sabrina Young, data manager, maintains an extensive body of clinical study databases. The team also includes Diamond Martin, protocol/regulatory coordinator, and Jean Meadows, program coordinator.

Other key partners include NANT's Parent Advisory Committee, whose members help assess clinical trial protocols and offer assistance and education to families.

"We're all collaborating on different levels," says Marachelian. "You need the whole team to make things happen for these kids."

You also need patience. Translational research takes a long-term commitment. A Phase I study chaired by Marachelian, which opened for enrollment of patients in December 2012, will test a new immunotherapy for relapsed neuroblastoma. It combines three drugs for the first time: lenalidomide, approved for use in other cancers; an anti-cancer monoclonal antibody; and retinoic acid, a form of vitamin A. The study builds on an earlier clinical trial.

Marachelian and Seeger are optimistic they're on the track toward a new gold standard treatment. "We know this antibody therapy is good, and we think we will make it better," Seeger says. "We're always aiming for 100 percent survival."

For more on the NANT Consortium, visit [NANT.org](http://NANT.org). ■

*"Teamwork will always get you a lot further than one individual can achieve."*

— Robert C. Seeger, MD

## NEUROBLASTOMA

Cancer that arises in immature nerve cells and affects mostly infants and children  
-National Cancer Institute

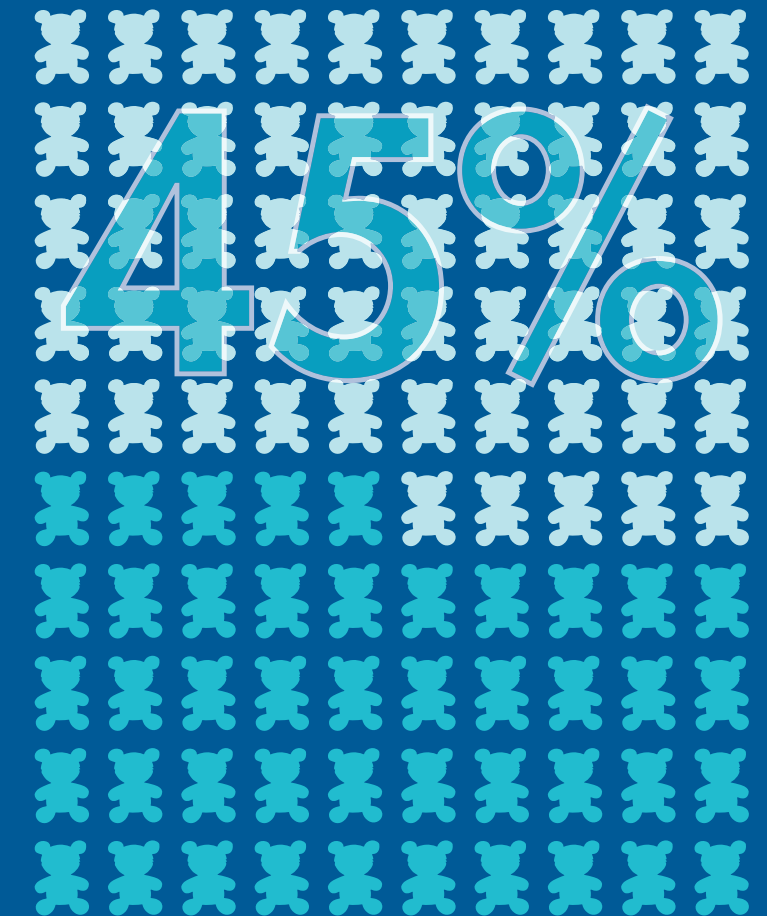
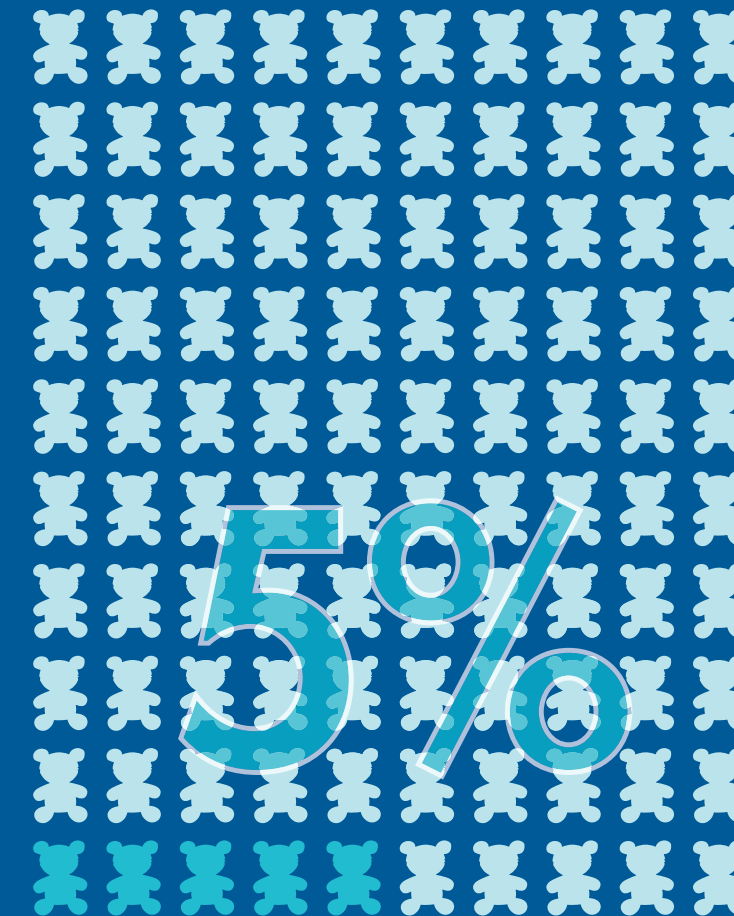
Second-most common solid cancer in infants and children

# 1975

Survival rate of high-risk patients

# 2013

Survival rate of high-risk patients



Today, essentially all children with **low- to medium-risk** neuroblastoma are cured.



# Personalized Medicine: One Patient at a Time

In a lab overlooking the Hollywood Hills, Timothy Triche, MD, PhD, and a team of physicians, scientists and staff in the Department of Pathology and Laboratory Medicine's Center for Personalized Medicine are on the verge of something big: creating a new test that will identify all changes related to the retinoblastoma gene (RB1) in eye cancer patients, using leading-edge genomic sequencing technology and bioinformatics.

"Retinoblastoma occurs early in life, from infancy to 2 years, and the sporadic, or non-inherited, form of retinoblastoma can be cured with the removal of the affected eye," says Alexander R. Judkins, MD, pathologist in chief at Children's Hospital Los Angeles. "However, that is not enough for patients who have the inherited form of the disease. For them, and for most children with cancer, it is critical to identify all the disease-causing genetic alterations. That is why I have worked with Tim to develop the Center for Personalized Medicine here at Children's Hospital and have made this kind of innovation a key priority for the Department of Pathology and Laboratory Medicine."

Triche and the Center for Personalized Medicine team are working closely with ocular oncologists A. Linn Murphree, MD, and Jonathan Kim, MD, of the Retinoblastoma Program in The Vision Center at Children's Hospital Los Angeles. Their goal is to develop a test that can help physicians identify previously unrecognized cases of germline RB1 mutations.

Murphree and others have found that almost 1 in 5 "sporadic" retinoblastoma patients—those with no family history of the disease and tumor in only one eye—in fact have germline RB1 gene mutations. The mutated RB1 gene lurks undetected in these "sporadic" retinoblastoma patients, preventing the body from fending off cancerous cells. Patients can go for years until cancer strikes again, sometimes even passing along the RB1 gene defect to their children.

"We now know the defect is present in all the tissues of their body, which often results in cancers elsewhere. In fact, these 'second malignancies' are far more likely to be lethal than the original retinoblastoma," Triche explains.

Triche and the Center for Personalized Medicine team are developing a rapid, less-costly test based on new genomic technology that was recently made available at Children's Hospital through a grant from the Department of Defense. This genomic technology has made it possible for the Center to develop a test based on sequencing the entire RB1 gene, one of the largest genes in humans. As a result, soon it will be possible for Murphree and Kim to offer a comprehensive genetic test for RB1 to patients and their families.



Timothy Triche, MD, PhD, (left) and Alexander R. Judkins, MD

Because Murphree and Kim treat a fifth of the retinoblastoma patients in North America, this day can't come soon enough. There are hundreds of patients and families who travel to Children's Hospital from all over the western United States who will immediately benefit from this new test. Doctors will be able to identify patients at risk for a second malignancy and closely monitor them so they can act early if it occurs.

"We are on the verge of a revolution in medicine," says Judkins. "It is fitting that at Children's Hospital, where Dr. Murphree led the team that first cloned the RB1 gene and introduced key innovations in the treatment of retinoblastoma, we are poised to again redefine the standard of diagnosis and care for this devastating disease. What is even more exciting is that this work is opening the door to an era of personalized medicine for all of pediatric cancer." ■

*"This work is opening the door to an era of personalized medicine for all of pediatric cancer."*

— Alexander R. Judkins, MD



# Helping Premature Infants Breathe Easy

Of the myriad challenges that a premature baby faces upon entering the world, simply breathing can be the most difficult.



Alba Vega with her son, Sebastian Ochoa, in the Newborn and Infant Critical Care Unit

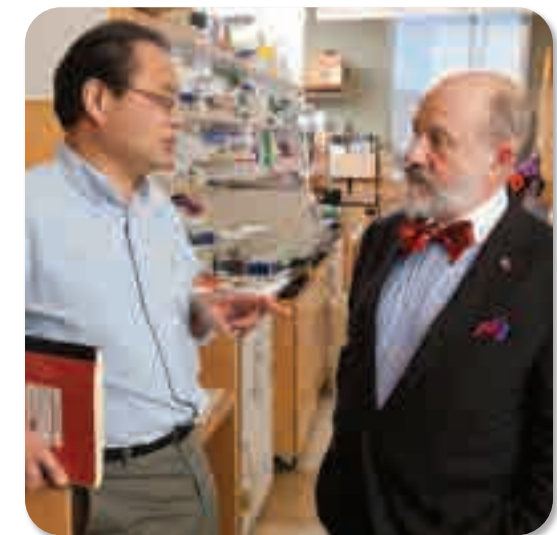
Neonatal respiratory distress is the leading cause of death among premature infants in the United States, and even when cured, it often has lifelong side effects. Wei Shi, MD, PhD, of the Developmental Biology and Regenerative Medicine Program at The Saban Research Institute, aims to develop new therapies for preventing and treating neonatal respiratory distress that avoid these debilitating side effects.

Neonatal respiratory distress can be caused by either transient tachypnea, in which there is excessive fluid in the lungs, or respiratory distress syndrome (RDS), in which there is too much surface tension for the lungs to expand. While transient tachypnea generally affects full-term infants delivered by cesarean section and often resolves itself, RDS incidence is higher in premature babies and can be fatal without intervention.

Premature infants are at higher risk for RDS because their lungs cannot yet produce surfactant, a soap-like substance that reduces surface tension in the alveoli so the lungs can expand. RDS affects 10 percent of all premature babies in the United States, and the risk rises with increasing prematurity. Infants born prior to 29 weeks have a 60 percent chance of developing the condition.

Treatments for RDS—such as surfactant replacement, oxygen therapy, steroids and mechanical ventilation—have drastically reduced premature infant mortality due to RDS, from almost 100 percent to just 10 percent. However, RDS can still have lasting effects. Affected neonates are more likely to develop chronic lung disease or neurological disorders, and some of the therapies that initially save lives can add to that risk.

“The goal of this project is to identify the molecular pathways responsible for the fetal lung transition from the amniotic fluid environment to postnatal air breathing, and to use these basic biological findings to develop a better treatment option for infant respiratory distress,” explains Shi, associate

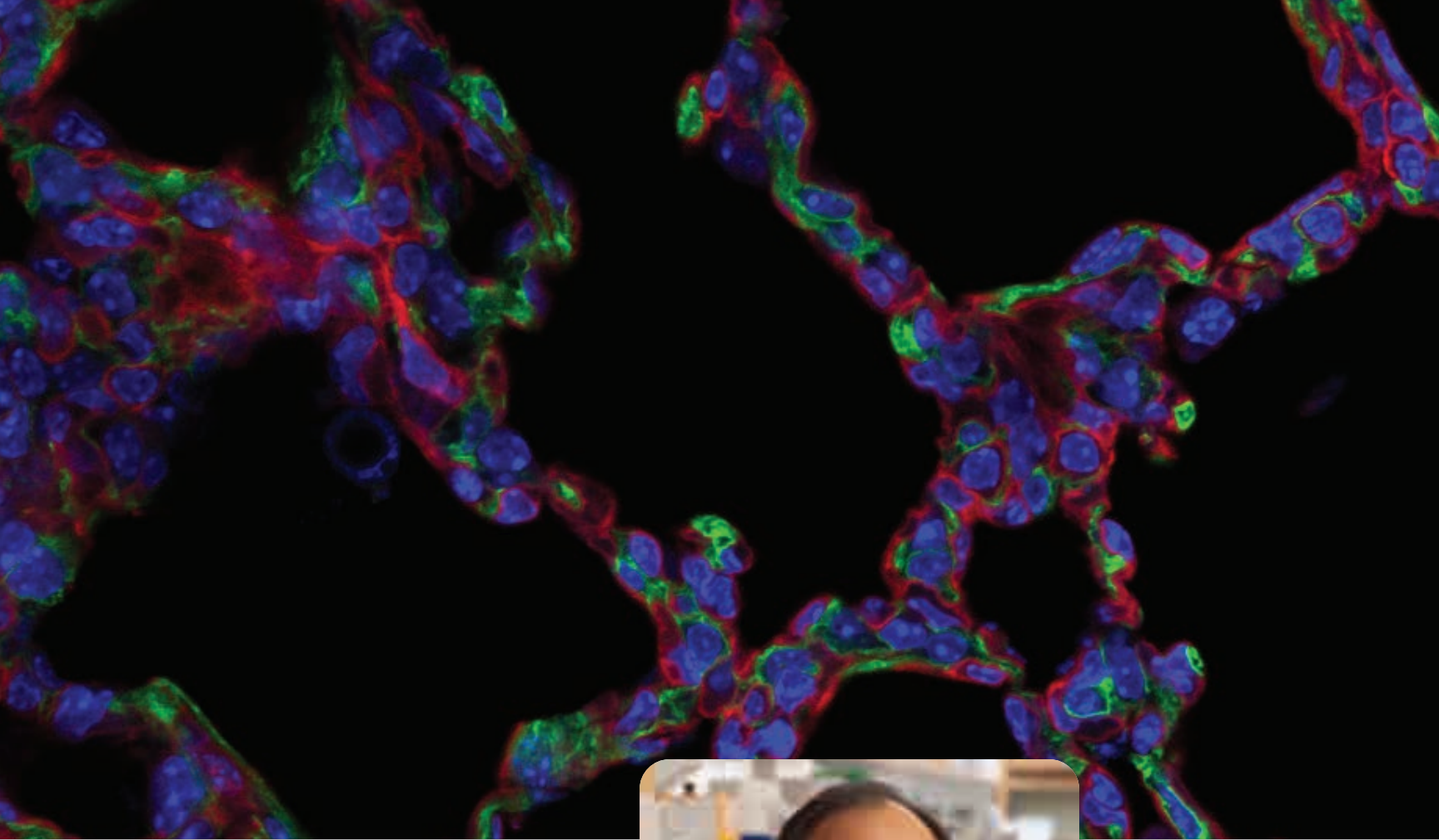


Wei Shi, MD, PhD, (left), and David Warburton, MD

professor of Surgery at the Keck School of Medicine of the University of Southern California. “We think that bone morphogenic protein may be a key player in the process of neonatal respiratory adaptation. We hope that it will lead us to a target for clinical translation.”

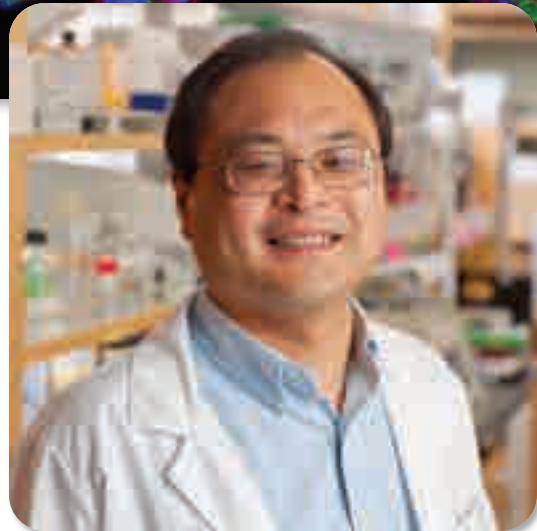
Bone morphogenic protein (BMP) functions in the development of many organs, including the earlier branching stages of lung formation. Shi has found that an increase in BMP activity is required for neonatal lung adaptation. Now, he is working to discover why BMP is so crucial to this process. His lab is unique in that few groups are studying this phase of lung development—most focus on earlier stages when branching morphogenesis takes place. This choice in direction is a result of both experimental data and collaborations with colleagues at Children’s Hospital Los Angeles.





Lung mesenchymal cells (shown in green) with epithelial and endothelial cells (shown in red)

"I came to Children's Hospital to work with Dr. David Warburton. Although I now run my own laboratory, his insights continue to be useful; we still collaborate and have written papers together," says Shi. "I also benefit from casual conversations with my colleagues in the hallway outside our offices."



Wei Shi, MD, PhD

Beyond Children's Hospital, Shi is working toward international collaborations with researchers in Canada and China. These partnerships will help make the goal of developing better treatments for respiratory diseases a reality.

"Our international collaboration provides the translational piece," he says. "These researchers are already testing stem cell therapy in adult lung diseases. Our next step is clinical trials in children. Our collaborators can help us get there."

Shi also recently received an NIH Exploratory/Developmental Research Grant Award (R21) to study lung mesenchymal stem cell function in lung development and repair. His laboratory is working to develop innovative molecular tools that will allow continued advancement in this field.

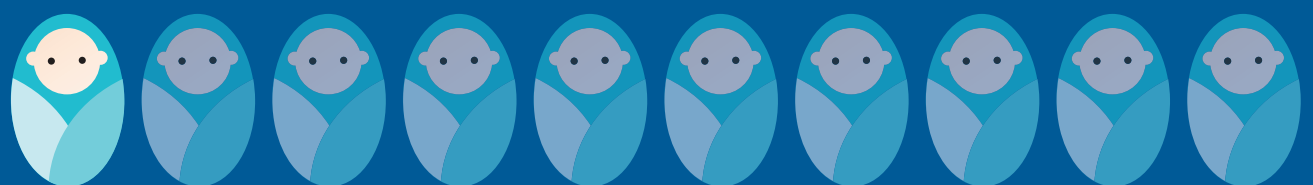
"Although improving treatment of respiratory diseases is an important goal, eventually we want to understand lung development well enough to be able to prevent the disease entirely," says Shi. "This will take time, but we are determined to succeed." ■

*"Our next step is clinical trials in children. Our collaborators can help us get there."*

— Wei Shi, MD, PhD

# RESPIRATORY DISTRESS SYNDROME (RDS)

A syndrome of respiratory difficulty in newborn infants caused by a deficiency of a molecule called surfactant



AFFECTS **10%** of **PREEMIES** IN THE U.S.

INFANTS BORN PRIOR TO 29 WEEKS HAVE A



CHANCE OF DEVELOPING **RDS**



**TREATMENTS** HAVE REDUCED MORTALITY FROM **100%** TO **10%**

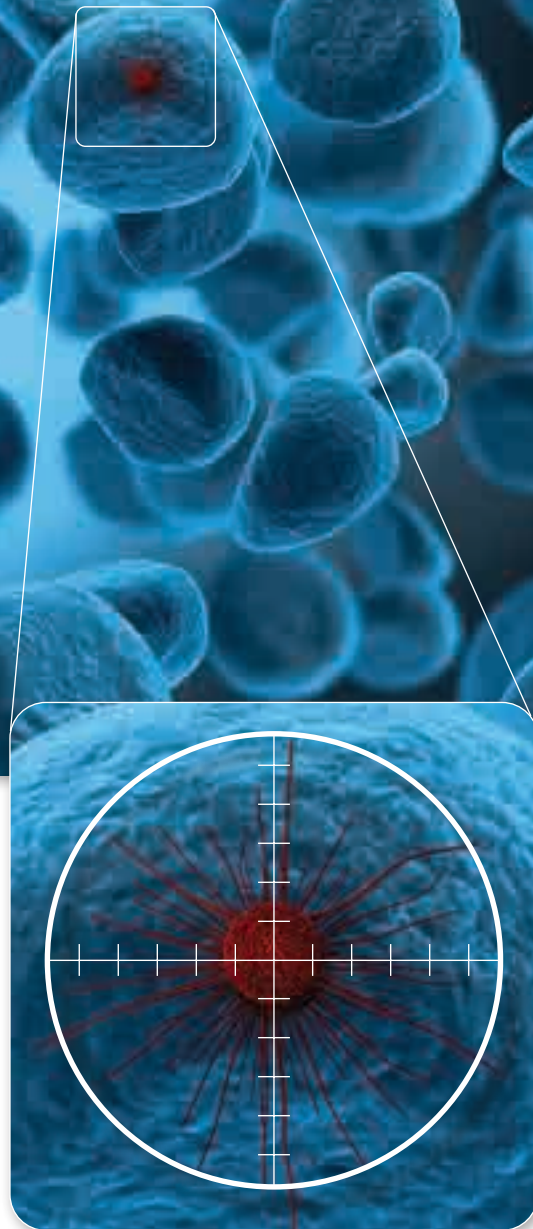


# Seek and Destroy

Neural stem cells specifically target cancer cells, reducing impact to the brain.

Neural stem cells possess a remarkable talent for seeking out invasive tumor cells, even migrating across the brain or through the blood-brain barrier to reach them. A team of researchers that includes Rex Moats, PhD, of The Saban Research Institute, is trying to exploit this singular ability by using neural stem cells to deliver anti-cancer drugs to hard-to-reach and even harder-to-treat brain tumors.

Every year, more than 22,000 Americans are diagnosed with malignant tumors of the brain or nervous system; a subset of these are gliomas. These tumors are frequently deadly, sometimes killing with appalling swiftness. The mean survival rate for glioblastoma—the most common type of malignant primary brain tumor in adults—is a mere 15 months.



Current glioma treatments have produced mixed, modest results. Tumor cells typically develop resistance to standard radiation and chemotherapies, leaving patients with no options or hope. In 2010, the California Institute for Regenerative Medicine (CIRM) approved an \$18 million grant to a multi-institution disease team to develop a neural stem cell-based glioma treatment that would be in the clinic within four years. A first-in-humans trial is already underway for an early version of the therapy.

CIRM's disease team model is momentous, both in scale and timetable. "This is a huge effort that's very translational and milestone-driven," says Moats, an assistant professor of Research at the Keck School of Medicine of the University of Southern California. "It involves scientists at multiple institutions working elbow-to-elbow. We share a common goal, and that's to improve outcomes for brain tumor patients within a relatively short time span."

The disease team is headed by Karen S. Aboody, MD, associate professor at City of Hope's Department of Neuroscience, and includes Joseph A. Frank, MD, MS, from the National Institutes of Health.

Moats, who has collaborated with Aboody on glioma research for more than a decade, is tasked with tracking the movement of neural stem cells injected into the brains of patients in the clinical trial. The cells are tagged with iron molecules that are visible in magnetic resonance imaging examinations. "Once injected, neural stem cells are basically on their own," Moats says. "One question we want to answer is just how close they get to satellite tumors. Recently, the Food and Drug Administration approved our methodology for tracking the neural stem cells."

Proximity is critical. The closer the neural cells get to their target, the less likely the treatment will impact nearby healthy tissues. In addition to the iron tag, injected stem cells carry a special enzyme. After the stem cells have had time to find their target, patients receive a relatively non-toxic drug. The enzyme excreted by the stem cells in the area of the tumor cells then converts the non-toxic drug to the active chemotherapeutic agent. All of the action takes place within the immediate area of the stem cell, reducing the chances of adverse side effects.



Joseph A. Frank, MD, MS, (left) of the National Institutes of Health; Karen S. Aboody, MD, from City of Hope; and Rex Moats, PhD, of The Saban Research Institute

The neural stem cells, which are grown in culture and are pre-immunogenic—meaning they can be used in most people—never fully mature. In fact, their lifespan is a mere month, after which they are resorbed by the body.

"Right now, this approach is a last resort," says Moats, "but it has the potential to be an early-stage treatment, where the novel neural stem cell-based therapy could be used to reduce tumors and save neurons." Saving neurons is priority one in pediatric patients.

Moats is confident the researchers will reach their target—just like the neural stem cells. ■

*"This is a huge effort that's very translational and milestone-driven. It involves scientists at multiple institutions and departments working elbow-to-elbow."*

— Rex Moats, PhD



# One Virus, All of Medicine

Grace Aldrovandi, MD, CM, has spent her career studying HIV. Working with an international team of scientists, she discovered that infected women in Africa could still breastfeed their babies.

As a medical student, Grace Aldrovandi, MD, CM—now an internationally known physician-scientist with the Division of Infectious Diseases at Children’s Hospital Los Angeles—spent hours at the bedsides of children and adults dying of AIDS.

In fact, her first faculty position entailed analyzing protease inhibitors, the class of drugs used to treat the virus.

“The flower girl at my wedding had HIV,” Aldrovandi says. “She died six months before the drugs became available.”

Looking back on a career spent studying the disease around the world, Aldrovandi, also a professor of Pediatrics and of Pathology, Molecular Microbiology and Immunology at the Keck School of Medicine of the University of Southern California, describes understanding HIV/AIDS as akin to unlocking the secrets of medicine.



Grace Aldrovandi, MD, CM



A breastfeeding clinic in Zambia, Africa, where Aldrovandi is studying breast milk transmission of HIV

She likens it to a famous quote by Sir William Osler, MD. “He who knows syphilis knows medicine,” the well-known pathologist, who is considered the father of modern medicine, has been quoted as saying.

“But in this case,” Aldrovandi says, “if you know HIV, you know all of medicine and a good part of science.”

This past year, Aldrovandi’s recent work as principal investigator was published in the American Journal of Clinical Nutrition. Collaborating with an international team of researchers in Zambia, she found that bioactive components in human breast milk were associated with a reduced risk of HIV transmission from infected mothers to breastfed infants.

Specifically, women whose milk contained high concentrations of human milk oligosaccharides, one component of breast milk, were less than half as likely to transmit HIV to their babies.



Aldrovandi’s recent work as principal investigator found that women whose milk contained high concentrations of human milk oligosaccharides, one component of breast milk, were less than half as likely to transmit HIV to their babies.

Despite previous thought, the significant public health finding indicates that many women on drug therapy in resource-strapped countries can safely breastfeed. This provides their babies with essential nutrition and crucial immunological support, which can mean the difference between life and death.

“There are 1,000 children infected with HIV each day,” Aldrovandi says. “And children progress to AIDS much faster. How are we going to change that? We have to.”

In collaboration with investigators throughout the U.S. and in Africa, India, China, Thailand and many other countries, Aldrovandi will head the laboratory efforts of the National Institutes of Health-funded global network that aims to decrease the morbidity and mortality associated with HIV disease in children, adolescents and pregnant women.

Aldrovandi admits that coordinating among so many different groups and types of people can be challenging. From physicians and virologists focused on the biological implications of their specimens, to public health policy colleagues concerned with the World Health Organization and changing practice, to community activists who want answers now, the potential for friction is endless.

“It’s difficult because we all speak different languages,” Aldrovandi says, “but we can be really powerful once we learn to communicate.”

Over the years, that power has kept her working tirelessly to find better treatments for the disease.

“That’s why I believe in research,” she says. “It can change lives; it can change the world.” ■

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*“It’s difficult because we all speak different languages. But we can be really powerful once we learn to communicate.”*

— Grace Aldrovandi, MD, CM

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# Out Cold

## Using therapeutic hypothermia to treat pediatric cardiac arrest

When a person suffers cardiac arrest, blood flow is interrupted, causing a lack of oxygenation to the brain and an inflammatory response. The brain swells, cells become disorganized, and the body heats up to dangerous levels. This can cause serious brain damage or death. Therapeutic hypothermia—the intentional cooling of the body—has become a popular treatment for the aftermath of cardiac arrest. But how successful is it in children? And what are the long-term effects on children’s neurological development, since their brains are growing and changing every day?

Christopher J. L. Newth, MD, and his colleagues around the nation plan to find out. Research director for the Department of Anesthesiology Critical Care Medicine (ACCM) at Children’s Hospital Los Angeles, Newth is principal investigator for the Los Angeles-area arm of a 37-center trial examining the long-term effectiveness of therapeutic hypothermia. It is the single largest study the National Heart, Lung and Blood Institute has ever funded.

The study is unique in that it does not simply track the survival of children treated with therapeutic hypothermia; it also tracks their long-term development.

“It’s not just a matter of whether a child survives,” says Newth. “It’s a matter of how their long-term development is affected. It’s about survival and quality of life.”

Parents are given an in-depth survey at the time of the treatment, establishing a baseline for their child’s neurodevelopmental status. Then the research team follows up with them over the next year to assess the child’s continuing development post-treatment.



Christopher J. L. Newth, MD

In a study this size, collaboration is key. Newth is overseeing the study at Children’s Hospital Los Angeles and Mattel Children’s Hospital at the University of California, Los Angeles. His counterpart at Mattel is Rick Harrison, MD, and the two organizations share research staff for data gathering. With the help of the nursing staff, as well as Robinder Khemani, MD, Patrick Ross, MD, and numerous other faculty members in the ACCM Department, subjects are recruited for the study from the Children’s Hospital Los Angeles patient population.

Clinicians have a six-hour window in which to enroll patients who have gone into cardiac arrest either inside or outside the hospital. They are then treated with either hypothermia—in which the body is cooled for 48 hours to 33 degrees Celsius, followed by strict normothermia, keeping the body at a constant normal temperature of 36.8 degrees Celsius, for three more days—or with normothermia for the entire five-day period. Body temperature is regulated by cooling mattresses placed above and below the child.

The six-year study began in 2009, and when complete it will involve 700 kids across the country. The results could have far-reaching effects for the more than 15,000 children who suffer from cardiac arrest in the U.S. each year. ■



Patrick Ross, MD, (left), Robinder Khemani, MD, and Christopher J. L. Newth, MD

*“It’s about survival and quality of life.”*

— Christopher Newth, MD



# Changing the World, Starting at Home

Ten years ago, Cheryl Saban, PhD, Haim Saban and The Saban Family Foundation united their philanthropy and passion with the longstanding and distinguished research enterprise at Children's Hospital Los Angeles. Their transformative \$40 million gift resulted in naming The Saban Research Institute of Children's Hospital Los Angeles, one of the few freestanding research centers in the U.S. where scientific inquiry is combined with clinical care and devoted exclusively to children.

"The Sabans enjoy a worldwide reputation for their commitment to improving health and well-being for children and families," says Brent Polk, MD, director of The Saban Research Institute.

"This year, Cheryl Saban furthered that mission when she accepted the presidential appointment to become a public delegate to the United Nations General Assembly as an advocate for women and children. She and Haim continue to partner with investigators at The Saban Research Institute to

tackle the most significant challenges to the health of children throughout the world—conditions such as autism, obesity, diabetes and cancer."

A decade ago, the collaboration began with a focus on infrastructure—The Saban Research Building was constructed so that the labs had an open floor plan to encourage discussion and interaction among scientists. Today, the partnership continues to evolve as new projects and goals are envisioned.

"Having a building in which to conduct research is crucial, but putting the right people together is even more important," says Cheryl. "That's where we are investing our commitment and resources now—enhancing education, building out research programs and achieving transformative recruitment. We are excited about the future—working with Dr. Polk and colleagues at Children's Hospital Los Angeles—to accelerate innovation into prevention, early and more precise diagnosis and individualized treatment of disease for the benefit of children everywhere." ■



Cheryl Saban, PhD, with First Lady Michelle Obama and President Barack Obama

*"Having a building in which to conduct research is crucial, but putting the right people together is even more important."*

*— Cheryl Saban, PhD*



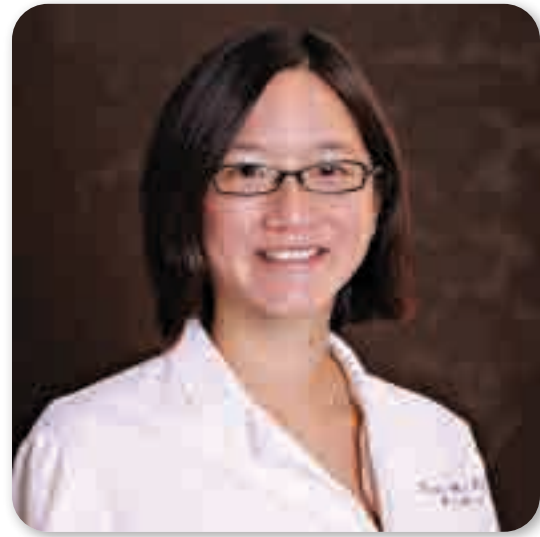


# Moving Best Practices into Current Practice

When research establishes new best practices and guidelines, that's not the end of the story. Those new guidelines still need to be adopted at the community level, by the frontline physicians providing care.

The average lag time between discovery and adoption? Fifteen years.

"So much research is published every day, it's impossible for a physician to keep up with it," says Susan Wu, MD, associate division head for Clinical Programs for the Division of Hospital Medicine at Children's Hospital Los Angeles. "Even then, there are many barriers to change, from insurance issues to limited resources."



Susan Wu, MD

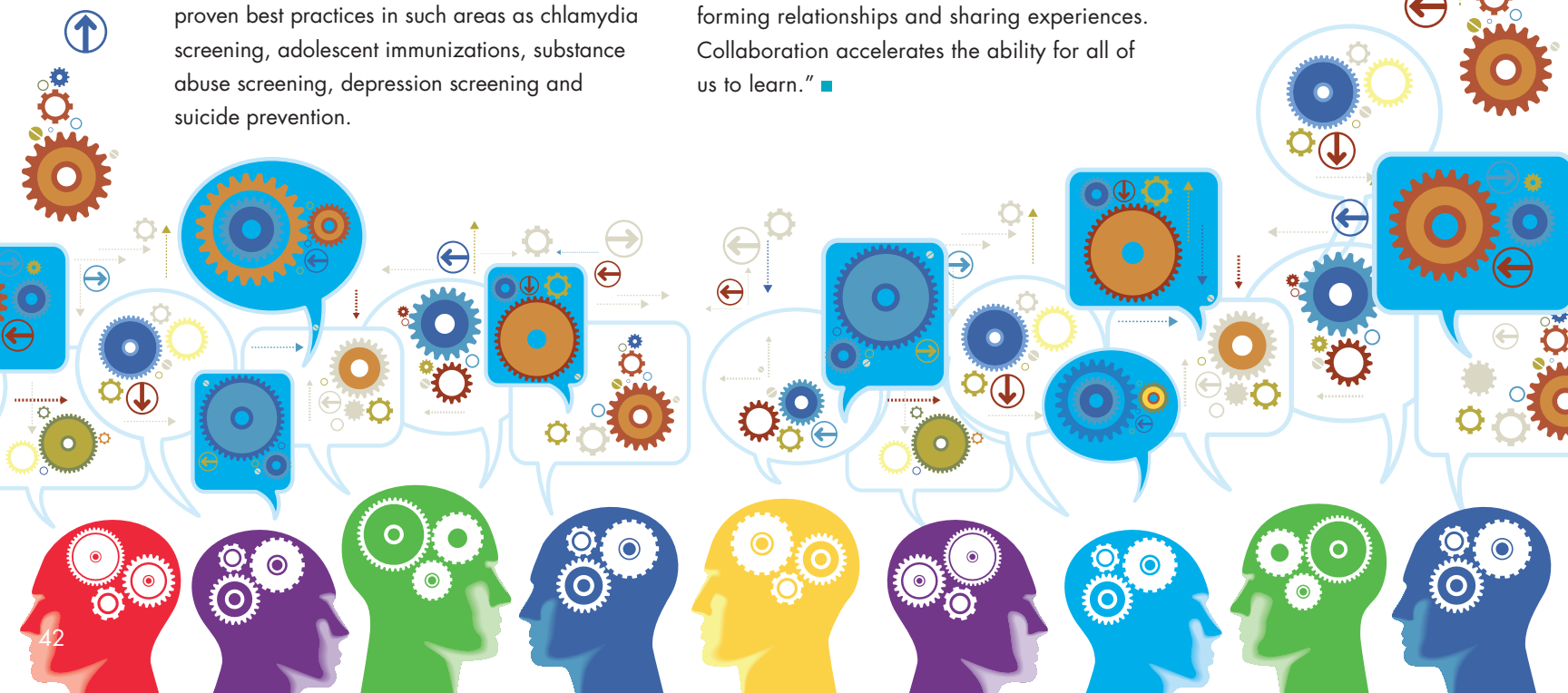
To help speed adoption of evidence-based guidelines, Wu is leading a new pilot project, the Southern California Children's Health Improvement Collaborative. Supported by the Southern California Clinical and Translational Science Institute, the project is focused on improving adolescent preventive health care and will bring together six to eight Los Angeles-area primary care practices from academic, community clinic and private practice settings.

During the nine-month pilot, these practitioners and office staff will receive comprehensive tools and support for implementing and measuring proven best practices in such areas as chlamydia screening, adolescent immunizations, substance abuse screening, depression screening and suicide prevention.

The project also features group conference calls and in-person and virtual learning sessions with adolescent health experts from Children's Hospital, the American Academy of Pediatrics and school and community clinics.

After the initial pilot, the plan is to expand the number of participants and form new collaborations in other areas of pediatric health.


"The strength of this model is that it's not about one-way information," says Wu, assistant professor of Clinical Pediatrics at the Keck School of Medicine of the University of Southern California. "It's about forming relationships and sharing experiences. Collaboration accelerates the ability for all of us to learn." ■



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The Saban Research Institute of Children's Hospital Los Angeles is one of the few freestanding research centers in the U.S. where scientific inquiry is combined with clinical care and devoted exclusively to children.





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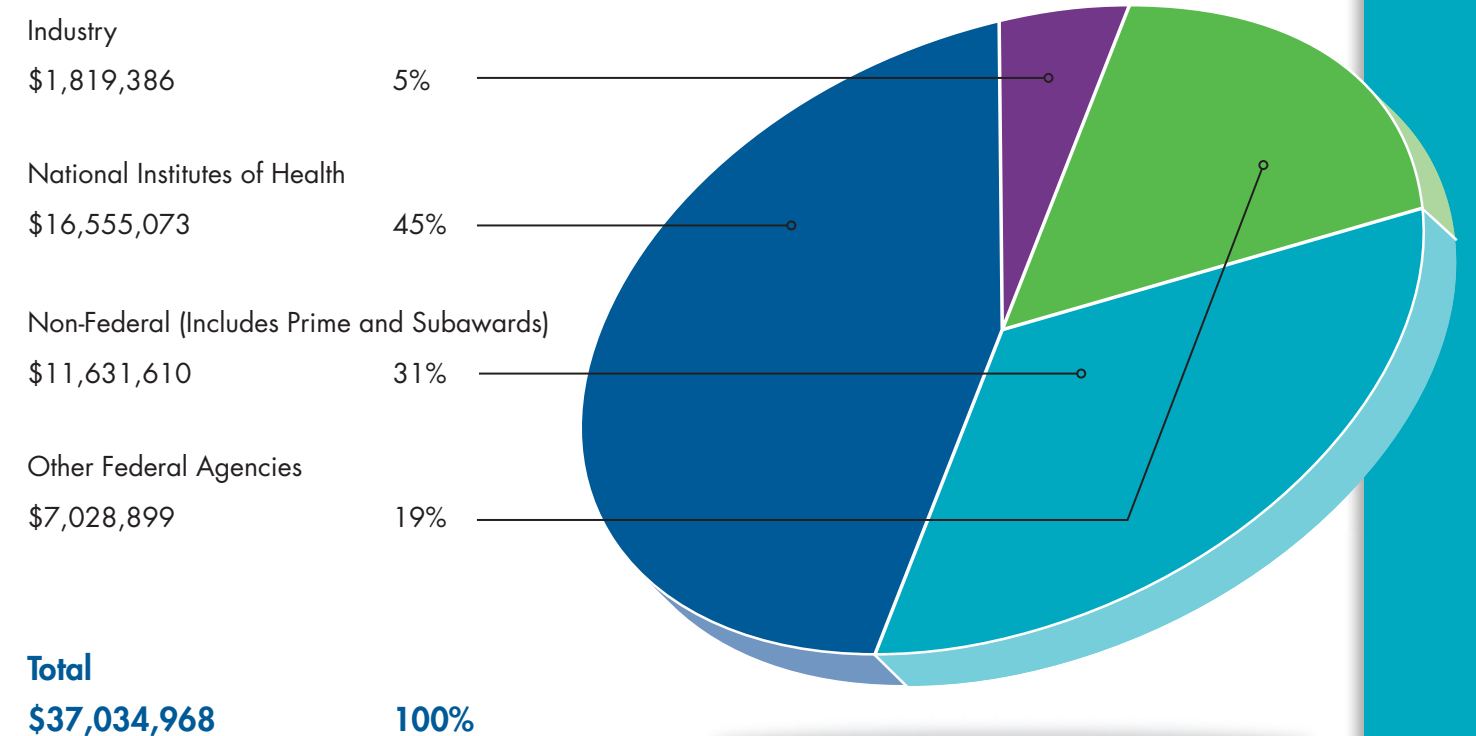
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