



Research Highlights 2008

DISCOVERIES
HAPPEN HERE

The Saban Research Institute of
Childrens Hospital Los Angeles

The Saban Research Institute



ChildrensHospitalLosAngeles

International Leader in Pediatrics



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The microscopic and cellular images seen in this publication were produced by investigators in The Saban Research Institute of Childrens Hospital Los Angeles.

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1 Note from the Director

YVES A. DECLERCK, MD*

Director, The Saban Research Institute of Childrens Hospital Los Angeles
Vice President of Research, Childrens Hospital Los Angeles

Exciting conversation takes place each day at The Saban Research Institute of Childrens Hospital Los Angeles—a dialogue of ideas, observations and innovation. Within this creative environment, each person on a scientific team—whether graduate student, postdoctoral fellow, junior faculty, clinical researcher or senior investigator—may provide the spark that takes an idea to another level.

We are inspired by the possibility that the next experiment, or discovery, might well be the one that leads to a treatment or even a cure for the children who suffer from horrific childhood diseases, such as cancer, congenital heart defects, diabetes, sickle cell anemia, epilepsy, immune deficiencies, respiratory disorders and more.

We must continue to invest in this scientific inquiry to benefit children everywhere. Unfortunately, federal support for biomedical research has been in decline for some time; in fact, funding for vital research conducted under the auspices of the National Institutes of Health has not increased for the fourth consecutive year.

The impact is especially serious for investigators and junior faculty at the beginning of their scientific careers. The federal government doesn't provide "seed money" for a young investigator or new idea that shows promise, but hasn't yet produced results.

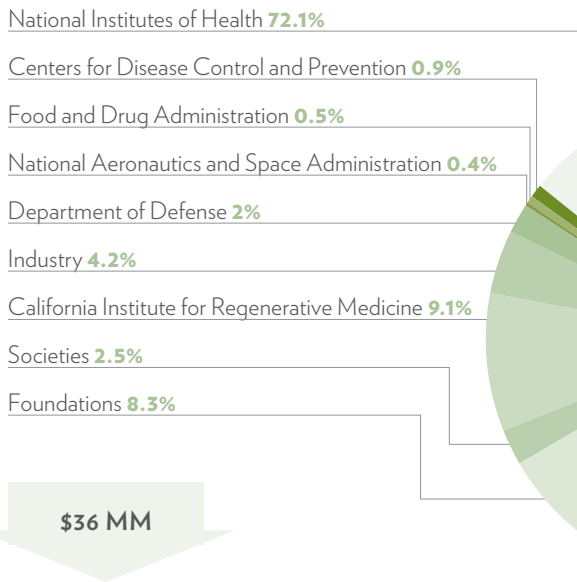
That's why The Saban Research Institute awards grants to selected investigators each year. And it is precisely why your support is increasingly vital. Our philanthropic partners provide the engine for our investigations. Thank you for furthering the pursuit of knowledge in this important cause.



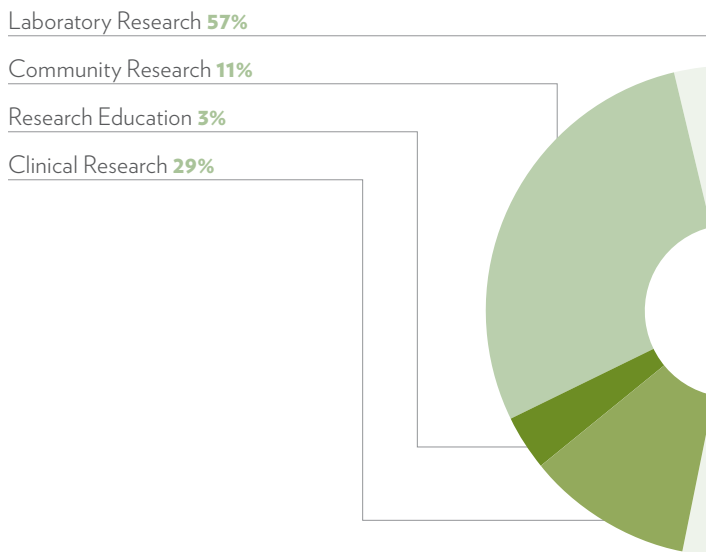
* Faculty member, the Keck School of Medicine of the University of Southern California



Funding sources



Funding uses



DISCOVERIES HAPPEN HERE

Every new medical treatment had its start in a single question: “What if?”

What if we understood cancer at the molecular level—could we stop it in its tracks? *What if* we could engineer intestinal stem cells or control cell growth in the retina—could we help children who suffer from intestinal failure or pediatric eye cancer? *What if* basic researchers, physician-scientists and communities joined forces—could we reverse the trend of childhood obesity and diabetes?

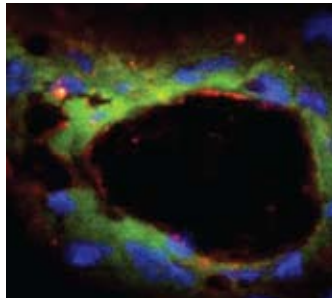
These are the kinds of questions we ask ourselves daily at The Saban Research Institute of Childrens Hospital Los Angeles.

We have 91 investigators engaged in 231 laboratory studies, clinical trials and community-based research and health services. In *Research Highlights 2008*, you will read about just a few of these investigations, which are looking for answers to cancer, cardiovascular disease, gastrointestinal disease, immune disorders, HIV prevention, spinal deformities, diabetes and neurodevelopmental disorders, among other diseases.

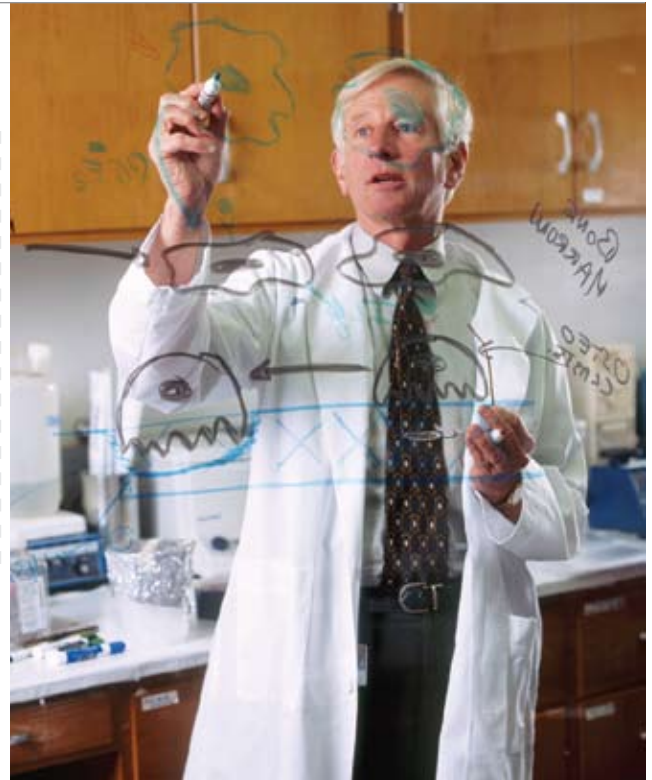
We are dedicated at The Saban Research Institute exclusively to pediatric research, yet our findings often impact adults as well. We are one of the nation’s few freestanding research centers to combine scientific inquiry with clinical care. Here, basic researchers and physician-scientists collaborate to integrate laboratory insights with clinical expertise, moving from “bench to bedside” to address difficult questions that others in pediatric medicine may never confront. This is where discoveries happen that change children’s lives forever.

In the one-year period ending June 30, 2008, Childrens Hospital Los Angeles received more than \$36 million in extramural funding for biomedical research. Funding came from a variety of government agencies, industry and philanthropic organizations. This funding supported 91 investigators conducting 231 laboratory, community and clinical research projects, along with research education.

Below: photomicrograph of a blood vessel in a neuroblastoma tumor. Seen in red are the endothelial cells that layer the inside of the blood vessel; in green is protein FasL, which is lethal for the cells in the absence of PAI-1.



Yves A. DeClerck, MD



CANCER PROGRAM

Director: **Robert C. Seeger, MD***

A cancer cell is like a seed, and the human body in which it grows is like the soil. This soil is called the tumor microenvironment. For more than three decades, Yves A. DeClerck, MD*, has been fascinated with that soil and its impact on cancer progression. “Today there is widespread acceptance that the growth of cancer is influenced by changes in the tumor microenvironment,” explains Dr. DeClerck, vice president for research and director of The Saban Research Institute of Childrens Hospital Los Angeles, and an active researcher in its Cancer Program.

The central theme of his laboratory’s work is understanding how malignant cells are affected by their surroundings on a molecular level. Of particular interest are proteases—

enzymes that break down proteins—and how they are controlled by specific inhibitors. Proteases are involved in cancer metastasis and angiogenesis, the formation of new blood vessels.

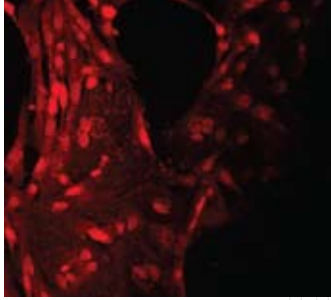
Several years ago, Dr. DeClerck and his team found that one particular inhibitor—plasminogen activator inhibitor-1 or PAI-1—was more abundantly expressed in aggressive forms of neuroblastoma. “This was a paradoxical observation,” says Dr. DeClerck. “We were anticipating the opposite: with more inhibitor, the cancer would be less aggressive.”

Their research led to the understanding that PAI-1, in fact, works on formation of blood vessels and actually protects them from dying. The results of this study, done

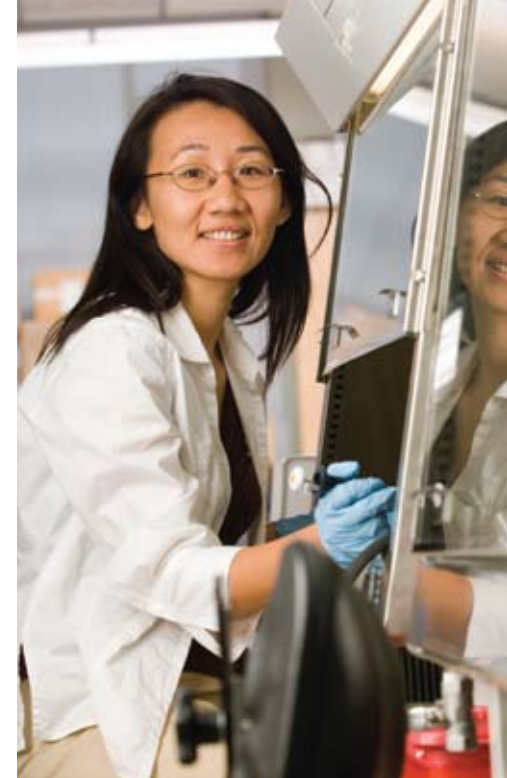
in collaboration with Walter E. Laug, MD**, and a research group at the University of Liège, Belgium, were published in October in the prestigious journal, *Cancer Cell*.

Now Dr. DeClerck is focused on another crucial question: If we can inhibit the inhibitor, can we prevent the growth of tumors?

This work was initially supported by a program project grant from the National Institutes of Health (NIH), led by Robert C. Seeger, MD*, and by an endowed chair from the Associates and Affiliates, community-based groups that support Childrens Hospital. In 2008, Dr. DeClerck was awarded a new, five-year, \$1.2 million grant from the NIH’s National Cancer Institute in support of this research.



Above: these zebrafish epicardial (heart) progenitor cells have the potential to form new coronary vessels.



Right: Cynthia S. Herrington, MD
Far Right: Ching-Ling (Ellen) Lien, PhD

CARDIOVASCULAR RESEARCH PROGRAM AND THE HEART INSTITUTE

Director: **Vaughn A. Starnes, MD***

Basic science and clinical care perpetually intersect and cross-pollinate. Limits to current therapy spur new research, while laboratory discoveries inspire clinical innovation. The Heart Institute at Childrens Hospital Los Angeles and the Cardiovascular Research Program work at both ends of this dynamic spectrum.

“We know what we can do today, and we do it very well,” explains Vaughn A. Starnes, MD*, director of the Heart Institute and its Division of Cardiothoracic Surgery, as well as the Cardiovascular Research Program. “We need research to help us see what we might be able to do tomorrow. That’s where progress lies.”

Driven by the need for more donor hearts, in 2007 the Heart Institute elected to offer ABO-incompatible heart transplantation. Studies done elsewhere have shown that young babies can tolerate the heart of an incompatible blood-type donor, because they haven’t yet begun producing antibodies that can cause organ rejection. Cynthia S. Herrington, MD*, recently recruited from the University of Minnesota Medical Center in Minneapolis, is leading the innovative effort. Dr. Herrington holds the Ryan Winston Family Chair in Transplant Cardiology in the Heart Institute.

Working in the laboratory at The Saban Research Institute, Ching-Ling (Ellen) Lien, PhD*, is uncovering basic information about tissue regeneration that someday

could help children with congenital heart defects—32,000 of whom are born annually in the United States.

The transparent embryos of the zebrafish offer Dr. Lien a window into prenatal heart development. Moreover, this aquatic creature has astounding regenerative ability. How, after even the most severe cardiac injury, can zebrafish re-grow healthy heart tissue? Dr. Lien recently discovered specific genes and growth factors that are central to this process.

They activate and protect stem cells as they mature to become heart muscle cells and blood vessels—all of which suggests that well-engineered stem cell activity may have future clinical applications.



Addressing the doctor-patient interaction in HIV prevention messaging is critical – “an opportunity we can’t afford to miss.”

– Ellen Iverson, MPH

Ellen F. Iverson, MPH

COMMUNITY, HEALTH OUTCOMES AND INTERVENTION RESEARCH PROGRAM

Director: **Michele D. Kipke, PhD***

An estimated 56,000 people in the United States became infected with HIV in 2007, according to the Centers for Disease Control and Prevention. Most of them were 18 to 25 years old.

To break the chain of transmission in this new generation, researchers have started prevention outreach to those already infected with HIV. Early results are encouraging. One University of Southern California (USC) study found, for example, that a five-minute, tailored HIV prevention message from a physician during each clinic visit reduces high-risk behavior among HIV-positive patients.

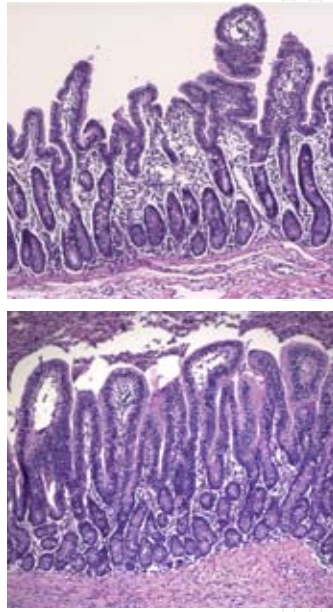
In 2007, Ellen F. Iverson, MPH*, conducted evaluation research for a similar

study funded by the Health Resources and Services Administration and the Los Angeles County Office of AIDS Programs and Policy. For two years, Ms. Iverson and her colleagues assessed the impact of the USC prevention model on physicians and patients from an HIV clinic that involved providers and patients selected from a control clinic. Doctors were asked to include a short prevention message at each clinic visit and give HIV patients written instructions on prevention measures.

Investigators wondered if integrating prevention messages into clinical practice would impact how doctors view their clinic role and if multiple exposures to messages would alter patient attitudes and behavior.

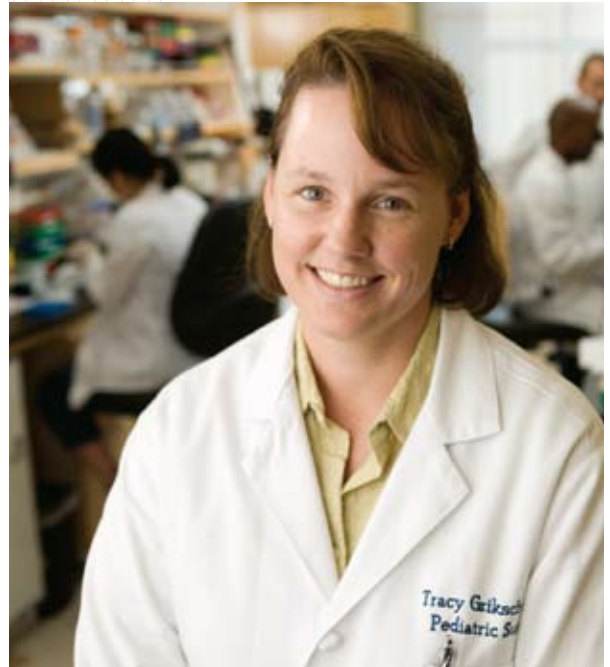
Among Ms. Iverson’s findings: even the most committed clinicians didn’t readily adopt a procedure that modified their tightly managed clinical routine and that they hadn’t helped design. Even so, incorporating the prevention message affected physician attitudes. At the conclusion, nearly 80 percent of test site providers reported that such messages are a vital part of their care. Only 40 percent of control site staff expressed comparable sentiments.

“Research shows the doctor-patient interaction is a uniquely promising setting for prevention messaging,” Ms. Iverson says. “We need to address any barriers to making it work, because this is an opportunity we can’t afford to miss.”



Above, top: intestinal stem cells.
 Bottom: After weeks of growth stimulation, the engineered intestine has multiplied in size.

Tracy C. Grikscheit, MD, PhD



DEVELOPMENTAL BIOLOGY AND REGENERATIVE MEDICINE PROGRAM

Director: **David Warburton, DSc, MD, FRCP, FRCS***

When congenital defects or acquired disease destroy too much of their intestines, babies can't absorb food and don't develop properly. Intravenous nutrition is a temporary solution, but many will need a small bowel transplant. Unfortunately, five years after transplant surgery, only 30 percent of these children are still alive.

"What if we could build new intestine using the regenerative potential of a baby's own intestinal cells?" asks Tracy C. Grikscheit, MD, PhD, a surgeon in the Division of Pediatric Surgery at Childrens Hospital Los Angeles and researcher in the Developmental Biology and Regenerative Medicine Program.

In animal model experiments, Dr. Grikscheit has done precisely that: surgically

removed intestine and harvested its stem cells, those rare cells that become many different cell types. She extracts the surrounding multi-cellular units the stem cells need to function, places them on a dissolvable polymer fabric and transplants them back, alongside the remaining intestine.

By four weeks, the engineered intestine has quadrupled in size. "After 40 days, every cell type arising from intestinal stem cells is present in the engineered tissue," says Dr. Grikscheit, who received a 2008 Career Development Award from The Saban Research Institute, along with support from the hospital's Department of Surgery, the Research Center for Liver Disease at the University of Southern

California and the California Institute for Regenerative Medicine.

In 2007, she replicated her work in mice engineered to produce large amounts of a human growth factor that stimulates intestinal growth, providing insights into how the process someday may be regulated in babies who receive engineered intestine.

Henri R. Ford, MD*, vice president and chief of surgery at Childrens Hospital Los Angeles, is an expert on necrotizing enterocolitis, a serious bacterial infection and the leading cause of gastrointestinal-related death in newborns. He says, "I'm excited that Dr. Grikscheit's novel and promising work may lead to new approaches in treating infants with intestinal failure."

* Faculty member, the Keck School of Medicine of the University of Southern California



“It’s one thing to see a clinical problem and accept it as an unknown. It’s another to ask, ‘What can I do about this?’”

—Joseph A. Church, MD

Joseph A. Church, MD

GENE, IMMUNE AND STEM CELL THERAPY PROGRAM

Director: **Donald B. Kohn, MD***

Joseph A. Church, MD*, is convinced that research which could lead to treatments for children flows in two directions—from the laboratory bench to patients’ bedsides and from the bedside back to the bench. “It’s one thing to see a clinical problem and accept it as an unknown. It’s another to ask, ‘What can I do about this?’” says Dr. Church, head of the Division of Clinical Immunology and Allergy at Childrens Hospital Los Angeles and a member of the Gene, Immune and Stem Cell Therapy Program.

One clinical problem on his radar is a life-threatening immunodeficiency called chronic granulomatous disease (CGD). In this inherited disorder, white blood cells lose their ability to destroy certain bacteria

and fungi. As a result, patients with CGD suffer frequent infections, including a form of inflammatory bowel disease (IBD) that resembles Crohn’s Disease, a chronic inflammation of the gastrointestinal tract.

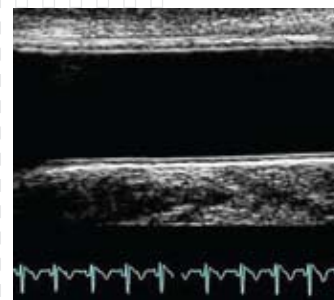
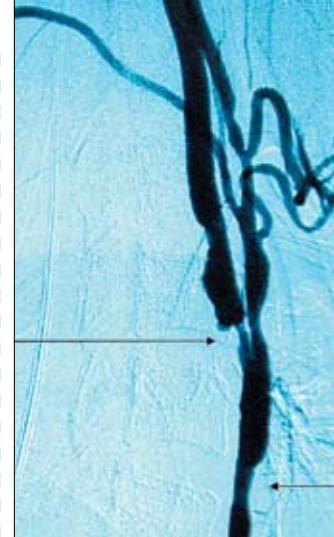
Dr. Church would like to be able to predict which children will get this complication. In 2008, he and his colleagues examined the usefulness of blood tests in identifying patients who will develop IBD. They discovered the tests could not differentiate between CGD patients with inflammatory bowel disease and those without. However, the investigators also found strong positive tests in all CGD subjects, suggesting that specific defects in the innate immune system predispose them to the disease.

“The results are more interesting than the ones I was looking for,” says Dr. Church. “This finding leads us back to more genetic research into immunodeficiencies like CGD to better understand the disease process.” He has turned the quest over to the basic scientists—a move back to the laboratory that eventually could open doors to new treatment approaches to IBD.

Also involved in the study are Thomas C. Coates, MD*, Division of Hematology/ Oncology; Rula Harb, MD*, Division of Gastroenterology and Nutrition; and Evelyn Baghdasraian, MD, Division of General Pediatrics.

*Right, top: Arrows indicate narrowing in the carotid artery.
Right, bottom: Advanced ultrasound technology was used to evaluate carotid vessels in childhood cancer survivors.*

Kathleen A. Meeske, RN, PhD



CHILDRENS IMAGING RESEARCH PROGRAM

Director: **Vicente Gilsanz, MD, PhD***

Kathleen A. Meeske, RN, PhD*, spent 20 years as an oncology nurse at Childrens Hospital Los Angeles before deciding to earn her doctorate in epidemiology. Today, her clinical experience combined with her research training inspires investigations into cancer survivorship. “With so many children surviving cancer today, our goal is to reduce health risks and to improve quality of life after cancer,” she says.

In 2007, Dr. Meeske served as principal investigator of a study to determine if neck irradiation for childhood cancer induces premature carotid artery disease (blockage of the major neck arteries supplying blood to the brain) and increases risk of stroke.

Seeds of the inquiry were planted over a decade ago, when a former cancer patient—by then in his 30s—was diagnosed with carotid artery disease on both sides of his neck and subsequently had a stroke. Five years later, a second patient presented with similar symptoms, and Dr. Meeske found the parallels more significant than coincidental.

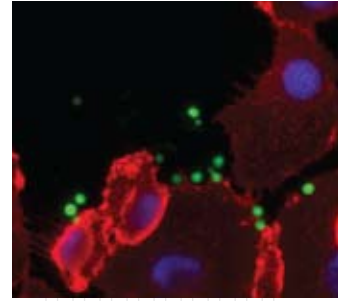
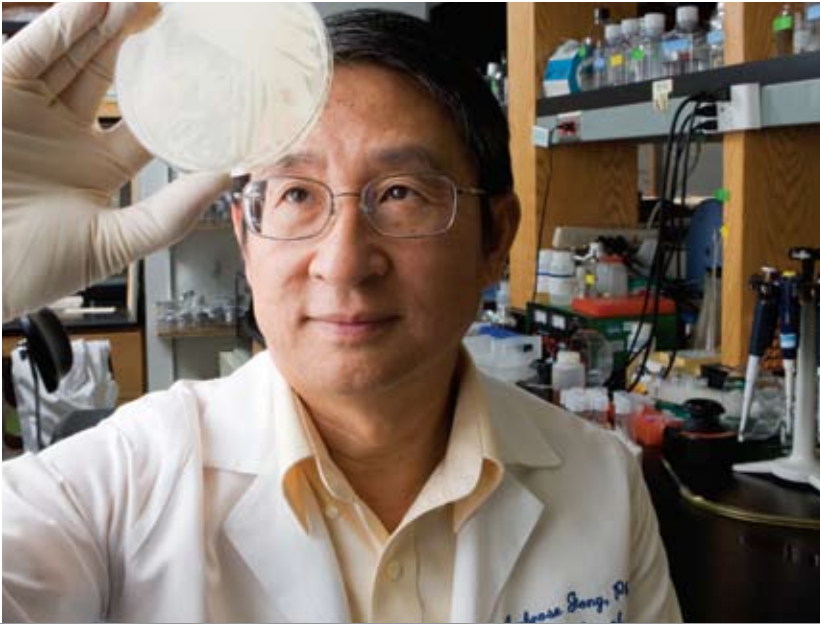
In collaboration with Vicente Gilsanz, MD, PhD*, director of the Childrens Imaging Research Program at The Saban Research Institute, Dr. Meeske used advanced ultrasound technology to evaluate carotid vessels in 30 asymptomatic childhood cancer survivors who had undergone neck irradiation. Results of this study, funded by

the National Institutes of Health, showed that the survivors had more disease than control participants; of the five subjects with severe disease, three already had experienced stroke.

Next, Dr. Meeske will conduct a cost-effectiveness study to show that this high-risk group should be regularly screened for carotid artery blockage. National guidelines currently don’t recommend such screening in young adults. “Early evaluation will alert doctors so they can be more aggressive in managing other factors correlated to stroke,” says Dr. Meeske. “Our long-range goal is to prevent strokes from occurring.”



Below: In a potentially deadly attraction, hyaluronic acid in a yeast-like fungus beckons a protein in the brain's endothelial cells, here stained green and red.



Ambrose Y. Jong, PhD



MICROBIAL PATHOGENS INITIATIVE

Director: **Wilbert H. Mason, Jr., MD, MPH***

Some microorganisms can enter the brain without causing damage. Others precipitate disaster—such as the yeast-like fungus *Cryptococcus neoformans*. “This pathogen is not a harmless tourist in the brain; it’s a terrorist,” explains Ambrose Y. Jong, PhD*, an investigator in the Microbial Pathogens Initiative.

Scientists have known for some time that after this fungus is inhaled, it lingers harmlessly in the lungs unless a weak immune system allows it to enter the bloodstream. When that happens, it travels to the brain, often causing life-threatening meningitis. More recently, researchers identified hyaluronic acid as the specific component of the fungus that lets it adhere to and

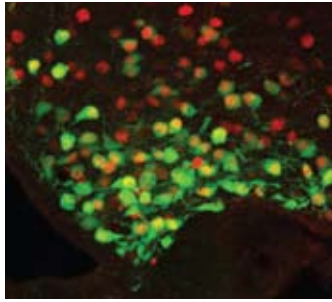
penetrate the human brain’s microvascular endothelial cells, which constitute the blood-brain barrier.

Beyond these rudimentary facts, however, investigators were uncertain how the pathogen functions. Then, in 2007, Dr. Jong and his laboratory team discovered that a specific gene, *CPS1*, triggers hyaluronic acid production and allows the fungus to stick to endothelial cells.

Speculating the brain must play a role in this dynamic, the investigators turned their attention to those endothelial cells. They found that a surface protein, CD44, not only interacts with hyaluronic acid, but is induced by the acid. Like a beckoning siren, hyaluronic acid calls out to CD44, luring it forward.

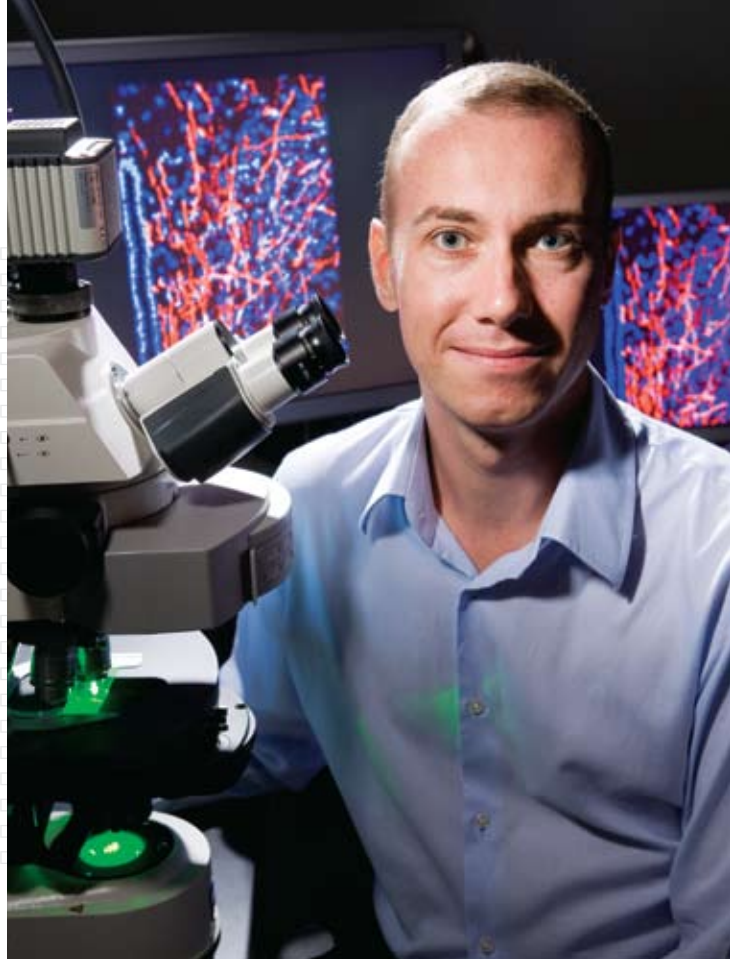
Dr. Jong and his team wondered why CD44 is so willing to ingest the fungus. The key, they found, is an enzyme in the brain that remains dormant most of the time. “We demonstrated that when the fungus arrives, this enzyme gets activated,” says Dr. Jong. “Once activated, it encourages CD44 to gather at the fungal entry site.”

If investigators can better understand the interaction between *Cryptococcus neoformans* and the brain, they can design therapies to protect youngsters from resulting brain infection. This is especially important for children with immune systems weakened by chemotherapy, AIDS or organ transplantation.



Above: The fat-derived hormone, leptin, is known to influence brain development. Here, neurons involved in the regulation of food intake are seen in green; the activation of those neurons by leptin is observed with red fluorescence.

Sebastien G. Bouret, PhD



NEUROSCIENCE PROGRAM

Director: **Richard B. Simerly, PhD***

Growing epidemiological evidence suggests that children born to diabetic mothers are at higher risk of developing obesity, diabetes and other metabolic syndromes. Sebastien G. Bouret, PhD*, is interested in biological evidence. “What we don’t know are the underlying mechanisms—why this happens,” he says.

Dr. Bouret and his team are trying to answer that question by examining the role of maternal diabetes on neuron development in the hypothalamus, a brain region controlling body weight and appetite regulation.

Investigators in the Neuroscience Program zeroed in on body weight changes, food intake and blood glucose levels in rats born to mothers with diabetes, compared with

a control group with non-diabetic mothers. Among their findings: the offspring of diabetic mothers had an increased body weight of 20 percent or more, even on normal diets. The weight gain occurred during lactation or a few days after—and was permanent—with the subjects still overweight as adults.

In addition, these offspring simply ate more than the control animals, suggesting a dysregulation of their energy balance. They showed impaired glucose regulation and an impaired response to a fat-derived hormone, leptin. Earlier studies by Dr. Bouret and Richard B. Simerly, PhD*, director of the Neuroscience Program, have shown that leptin influences brain development.

Dr. Bouret’s current investigations are supported by a 2007 Career Development Award from The Saban Research Institute, as well as funding from the Childhood Obesity Research Center at the University of Southern California and the March of Dimes.

Diabetes and obesity are critical problems in America and worldwide. “It’s only quite recent that people admit obesity and diabetes could be brain problems, too,” notes Dr. Bouret. The ultimate goal in studying neural systems during the perinatal period, he adds, is to develop therapies that may reverse this early programming by targeting the part of the brain involved in feeding.

* Faculty member, the Keck School of Medicine of the University of Southern California

4 The Obesity Epidemic

IN A VIGOROUS INTERDISCIPLINARY EFFORT, SCIENTISTS AND PHYSICIANS AT CHILDRENS HOSPITAL LOS ANGELES TAKE ON A COMMON ENEMY: CHILDHOOD OBESITY.



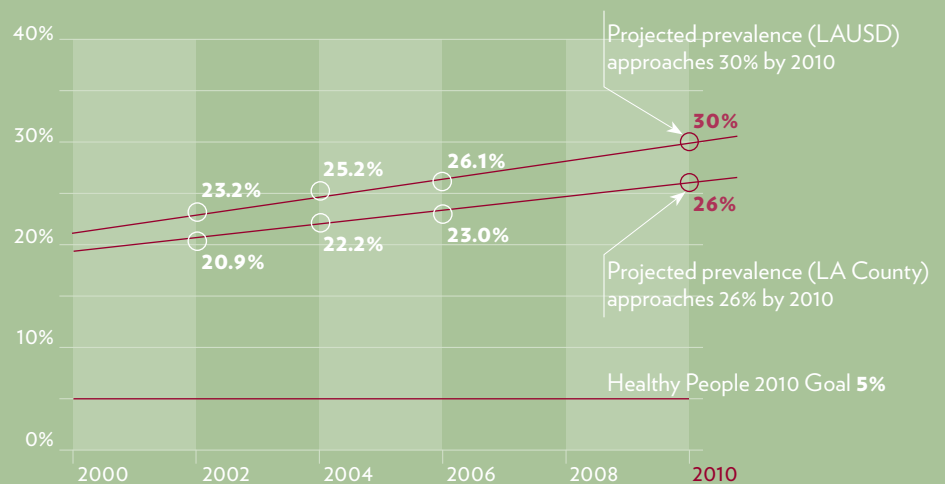
One-third of children in the United States—about 25 million kids—are now overweight or obese. The obesity rate in adolescents has nearly tripled over the past three decades, with minority communities at particular risk. As a result, this generation’s children are the first who may have a shorter lifespan than their parents.

“Thirty years ago, we rarely saw a child with type 2 diabetes. Now, 25 percent of our newly diagnosed patients have type 2 diabetes,” notes Francine R. Kaufman, MD*, head of the Center for Endocrinology, Diabetes and Metabolism at Childrens Hospital Los Angeles.

This alarming increase can be traced in part to sedentary lifestyles and high-fat foods. But basic research is showing that obesity and diabetes are a far more complex equation than eating less and exercising more. “It’s clear there are biological factors at play,” says Richard B. Simerly, PhD*, director of the Neuroscience Program in The Saban Research Institute of Childrens Hospital Los Angeles.

Scientists, clinicians and community health researchers at Childrens Hospital are confronting this problem from multiple angles, in collaboration with colleagues at the University of Southern California (USC). They’re looking inside the brain to see how hormones and the perinatal environment affect neurological connections, analyzing treatment alternatives, crafting intervention and prevention strategies, partnering with communities and advocating for change.

Andy Ascencio is helping to ensure his healthy future by participating in a nationwide clinical trial headquartered at Childrens Hospital Los Angeles: *Treatment Options for Type 2 Diabetes in Adolescents and Youth*.



About one-quarter of all school children in Los Angeles County are obese. An additional 19.4 percent are overweight. In the past two years, rates of obesity have been leveling off but are still unacceptably high. The federal government’s Healthy People 2010 has set a goal of five percent obesity among school children.

NEW INTERVENTIONS

Dr. Kaufman is study chair for TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth), a 15-center clinical trial funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health. TODAY is examining three treatment regimens for type 2 diabetes. "We can't assume therapies used in adults have the same safety and efficacy profiles for children," says Dr. Kaufman.

She chairs another NIDDK-funded study, the HEALTHY trial, the first national research consortium to investigate whether health-conscious changes in diet and exercise on middle school campuses can reduce diabetes risk. Now in its second year, the study is following 6,000 children for three years.

To get more kids moving, her Center expanded its Kids 'N Fitness after-school exercise programs in 2007 and 2008 to schools and parks in East and South Los Angeles, San Jose, Vacaville and other cities.

In July 2008, Dr. Kaufman testified on childhood obesity before the U.S. Senate Committee on Health, Education and Pensions. She also appeared before the Los Angeles Unified School District (LAUSD) on behalf of its resolution to enforce physical education laws for all students. This follows her successful effort a few years ago, when she urged the LAUSD to become America's first major district to ban soda machines on campus.

LISTENING TO COMMUNITIES

Last year, researchers in the Community, Health Outcomes and Intervention Research Program (CHOIR) at The Saban Research Institute analyzed neighborhood food environments in East and South Los Angeles. They found that both communities struggled with too few healthy food choices and inadequate park space. So, in partnership with Community Advisory Boards, the team began formulating solutions that worked for residents.

"This represents a new form of public health research related to childhood obesity," says Michele Kipke, PhD*, director of the CHOIR program. As a result of CHOIR's and others' efforts, East and South Los Angeles each have their own farmer's market, while the Los Angeles City Council banned new fast-food outlets for one year in South Los Angeles.

NEUROLOGICAL INSIGHTS

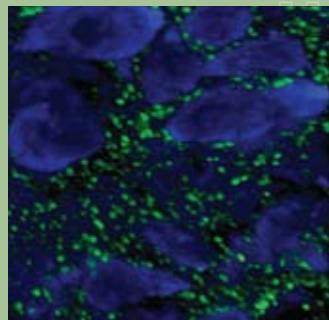
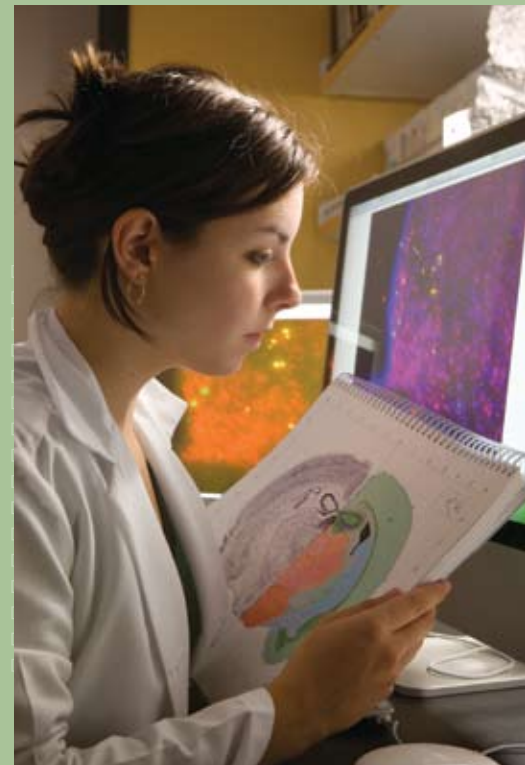
Dr. Simerly has studied the effect of hormones on brain development for 25 years and their link to obesity for the past decade. Working with Sebastien G. Bouret, PhD*, he recently identified a link between a genetic predisposition to obesity and formation of brain connections that regulate weight and appetite later in life. Their study, reported in the journal *Cell Metabolism* in February 2008, links changes in brain wiring to a reduced responsiveness of specific neurons to the hormone leptin.

Dr. Simerly serves as associate director of the Childhood Obesity Research Center (CORC) at USC, which is directed by Michael I. Goran, PhD. CORC's research efforts range from basic scientific explorations of the biological, genetic and developmental factors that contribute to childhood obesity to the development of novel, evidence-based individual, behavioral and community interventions.

Recent fitness data from LAUSD indicate 2004-2006 obesity rates are flat for the first time. "Our efforts may be having an impact at last," says Dr. Kaufman. Still, it could take years to reverse the trend. "Most of all, we need an environment in which the healthy choice is the easy one to make."

Below, left: 3-D reconstruction of stimulatory nerve endings (green) to nerve cells (blue) in the mouse brain. Experience, hormones and possibly other environmental factors can change the strength of such brain connections during key periods of brain development.

Below: Meredith Gibbons, PhD, compares microscope pictures of a brain with a brain atlas. Of particular interest is the hypothalamus, which controls feeding and metabolism.



For more on obesity-related research at The Saban Research Institute, please see page 11.

* Faculty member, the Keck School of Medicine of the University of Southern California

CHILDRENS CENTER FOR CANCER AND BLOOD DISEASES

Director: **Stuart E. Siegel, MD*** Co-director: **Donald B. Kohn, MD***

Sickle cell disease and thalassemia are inherited red blood cell disorders that lead to lifelong serious complications. The consequences, even in young patients, include chronic pain, growth retardation and high risk of stroke and cardiac failure. These genetic disorders can be treated with blood transfusions, but over time the therapy causes life-threatening iron overload.

Thomas D. Coates, MD*, section head of Hematology in the Childrens Center for Cancer and Blood Diseases, takes an interdisciplinary approach to hematology research, incorporating engineering and biophysics in the design of innovative diagnostic imaging technology.

For example, he has collaborated on the use of magnetic resonance imaging to quantify iron overload, with John C. Wood, MD, PhD*, a member of The Saban Research Institute's Imaging Research Program. This year, Dr. Coates received a four-year, \$2.48 million grant from the National Heart, Blood and Lung Institute of the National Institutes of Health to study the fundamental processes that cause damage in sickle cell anemia. This project represents a collaboration between Childrens Hospital Los Angeles and scientists at the University of Southern California in biomedical engineering, biophysics, cardiology and pulmonology.

Dr. Coates also received support from Novartis for research on a drug that removes excess iron from the body. Traditional chelating agents require all-night intravenous transfusion. This new drug is taken orally, once daily. "The results look fantastic," he says. Partnerships like this, between physician-scientists at Childrens Hospital and leading pharmaceutical companies, can expedite the journey from discovery to safe, effective therapies.

CHILDRENS CLINICAL INVESTIGATION CENTER

Director: **Edward D. Gomperts, MD***

Clinical research is active across all divisions at Childrens Hospital Los Angeles, with more than 200 studies funded by the National Institutes of Health (NIH) and 120 in partnership with industry.

The Childrens Clinical Investigation Center (CLIC) continued its support for clinical research in 2008 while opening new administrative offices. CLIC-sponsored research covers Phase I, II and III studies in a variety of areas, including new therapeutic agents, pain management,



Above: Thomas D. Coates, MD

neuropsychological issues for children with chronic diseases, iron overload syndromes and optic nerve hypoplasia.

This year marked CLIC's second annual Clinical Research Academic Career Development Award (see page 18). In addition, the Los Angeles Basin Clinical and Translational Science Institute (CTSI)—a collaborative effort of Childrens Hospital, City of Hope and the University of Southern California—awarded its first 10 grants for pilot research projects in July 2008. Five went to investigators based at Childrens Hospital.

"Our goal is to encourage innovative bench-to-bedside and bedside-to-community transfer of medical research with an emphasis on improving the health of urban, multicultural populations," says Edward D. Gomperts, MD*, director of clinical research at Childrens Hospital, associate director of The Saban Research Institute and chair of Novel Methods/Pilot Studies for the CTSI.

CLIC's new 8,120 square-foot administrative facility occupies the former site of the Childrens Hospital Thrift Shop on Sunset Boulevard, which was operated from 1917-2006 by the Associates and Affiliates, community groups that support Childrens Hospital. "Having the staff for clinical research in one place facilitates the sharing of ideas and resources at a time when regulatory requirements governing clinical research are increasingly complicated," notes Dr. Gomperts.

Occupying the offices are staff for the Biostatistics Core, the Committee on Clinical Investigations and the General Clinical Research Center at Childrens Hospital, among other programs.

INSTITUTE FOR THE DEVELOPING MIND

Director: **Roberta G. Williams, MD***

Autism Spectrum Disorders (ASD) affect one in 150 children—more than pediatric cancer, diabetes and AIDS combined—causing impairment in thinking, language and the ability to relate to others. In California, children receiving special services for autism tripled from 1987 to 1998 and doubled in the four years after that. Yet, services have been fragmented and the effectiveness of many interventions is in doubt.



“Studies have shown that children who are treated in the context of a research environment simply receive better care.”

—Michele Kipke, PhD

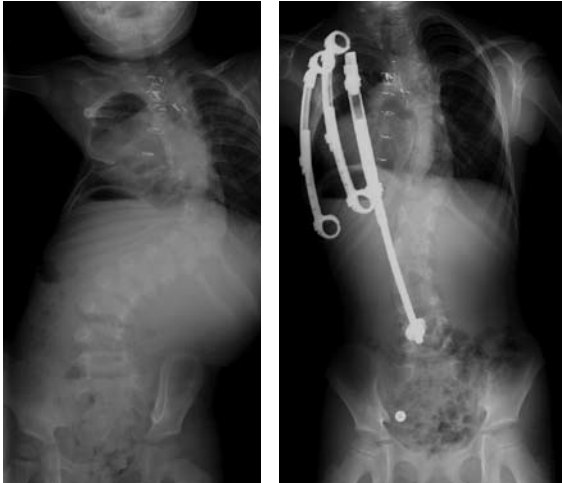
In 2008, Childrens Hospital Los Angeles launched the Institute for the Developing Mind (IDM), which will offer diagnostic and treatment services while advancing behavioral and diagnostic research. “Studies have shown that children who are treated in the context of a research environment simply receive better care,” says Michele Kipke, PhD*, director of the Community, Health Outcomes and Intervention Research Program in The Saban Research Institute.

In July 2008, the IDM’s Boone Fetter Clinic—funded by a \$1 million gift from the Boone Family Foundation—began offering interdisciplinary assessments for ASD. In early 2009, it will add follow-up medical services. Children and families meet with different specialists under one roof, including a developmental pediatrician, psychologist, nurse care manager, occupational therapist and speech/language therapist.

The \$5 million Las Madrinas Endowment for Autism Research, Interventions and Outcomes, awarded in 2007, is funding the IDM’s Research Diagnostic and Intervention Lab, which will develop tools and technologies to diagnose ASD earlier than ever before—and analyze intervention strategies.

Dr. Kipke has partnered with Maja J. Matarić, PhD, senior associate dean for research at the Viterbi School of Engineering at the University of Southern California, where the Robotics Lab is building and testing bubble-blowing robots as therapeutic partners for children with ASD. Recent research indicates these children may interact more easily with mechanical devices than with humans. Through a variety of strategies—including transitions from mechanical to more humanoid robots—the research team hopes to build social skills among children with ASD.

Left: A model of the human brain



CHILDRENS ORTHOPAEDIC CENTER

Director: **Vernon T. Tolo, MD***

Introducing an innovation in orthopaedic surgery is one thing—proving that it works to improve the lives of children is another. In 2002, David L. Skaggs, MD*, made headlines as the first orthopaedic surgeon in California to employ the vertical expandable prosthetic titanium rib (VEPTR). This surgery is designed to straighten the spine, which typically is curved from scoliosis, and allow the chest and lungs to grow.

Since then, demonstrating pulmonary improvement in patients with thoracic insufficiency syndrome following surgery has been elusive. So, in 2007, a study group led by Dr. Skaggs, associate director of the Childrens Orthopaedic Center, looked at nutritional outcomes in 79 children at seven orthopaedic centers nationwide.

Before VEPTR surgery, 78 percent of children in the study had “failure to thrive,” ranking at or below the fifth percentile in weight for their age. Those children gained a mean weight of nine percent after surgery. Children above the fifth percentile gained 17 percent. Participants gained weight over 48 months and continued to maintain it. The study was presented at the fall 2007 meeting of the Scoliosis Research Society.

Today, Dr. Skaggs is pioneering less invasive surgical techniques that avoid the chest, using spinal implants that can be extended as the child grows. He is collaborating with industry to develop new spinal instrumentation. “We’re constantly trying to innovate,” says Dr. Skaggs, who holds the Endowed Chair of Pediatric Spinal Disorders, funded by the Associates. “Children who had severe spinal deformities, which prohibited them from even taking a full breath, return months after surgery to show me their soccer trophies.”

THE VISION CENTER

Director: **Mark S. Borchert, MD***

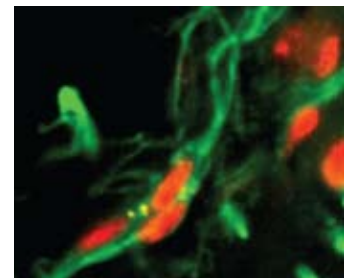
The “Jekyll and Hyde” personality of the oncogene called Bmi1—sometimes benevolent, sometimes nefarious—caught the attention of Thomas C. Lee, MD*, director of the Retina Institute in The Vision Center at Childrens Hospital Los Angeles. (An oncogene is capable of causing the transformation of normal cells into cancer cells.)

Bmi1 is expressed in the retina, that light-sensitive sensory membrane at the back of the eye. “We need to understand when it is and isn’t appropriate for Bmi1 to be active,” he says. “Ultimately, we want to figure out how to control the switch, so we can dictate when it’s on or off.”

Last year, Dr. Lee showed that Bmi1 was present in retinoblastoma tumors, a pediatric eye cancer, in studies done with Elizabeth R. Lawlor, MD, PhD*, an investigator in the Cancer Program of The Saban Research Institute. In retinoblastoma, retinal tumor cells multiply aggressively and uncontrollably. Dr. Lee thinks Bmi1 may play an important role in this renegade cell proliferation. “We also have evidence suggesting the gene may protect tumor cells from normal cell death,” he explains.

Now Dr. Lee and Dr. Lawlor are exploring the therapeutic potential of targeting Bmi1 pathways. In addition, they speculate that Bmi1 may be useful to enhance the growth of normal retina stem cells, which don’t normally grow well in laboratory culture. If these physician-scientists can learn to control Bmi1, they may be able to engineer more robust cell production and bring hope for one day replacing damaged retinal cells in children with vision loss and blindness.

Below: Retinal stem cells. Above: A patient with scoliosis, curvature of the spine, seen before and after surgery that implanted a vertical expandable prosthetic titanium rib.



Director: **Emil Bogenmann, PhD, EdD***

After Tove Berg, PhD, earned her doctorate in developmental biology at the Karolinska Institute in Stockholm, Sweden, she wanted to broaden her view of the field. She was drawn to The Saban Research Institute of Childrens Hospital Los Angeles by its stellar reputation. She found a unique, interactive and collaborative environment. “We can share ideas and learn from each other,” she says of her fellow investigators.

Dr. Berg is one of nearly 100 post-doctoral fellows and graduate students each year who conduct critical research studies at The

Saban Research Institute. The hospital also welcomes some 86 clinical fellows annually, who must pursue two years of research to earn board certification in their medical subspecialties.

“Our task is to attract outstanding, dedicated young people who wish to devote themselves to scientific careers. The competition for the best is enormous,” says Emil Bogenmann, PhD, EdD*, director of research education at The Saban Research Institute. The strategy: provide an excellent training environment for laboratory, clinical, translational and community health research in which investigators and physician-scientists feel they can excel in their careers and personal lives.

Tove Berg, PhD, left, with Kasper S. Wang, MD



Nurturing a new scientific career can be challenging, especially given declines in federal funding. This year, Dr. Berg received a Research Career Development Fellowship Award from The Saban Research Institute. It will help support her continuing investigations in the Developmental Biology and Regenerative Medicine Program into the role of a natural protein called Fibroblast Growth Factor 10 (FGF 10) in embryonic liver development and liver repair and regeneration.

Principal investigator on FGF 10 is Kasper S. Wang, MD*, a surgeon in the Division of Pediatric Surgery at Childrens Hospital. Being able to work with a physician-scientist who focuses on the clinical applications of laboratory research is a definite bonus in her training, says Dr. Berg. “You know the work you’re doing has even more meaning in the end.”



* Faculty member, the Keck School of Medicine of the University of Southern California

2008 INTRAMURAL RESEARCH AWARDS

Through these intramural research awards, The Saban Research Institute and Department of Pediatrics at Childrens Hospital Los Angeles nurture the development of new science and new scientific careers. The awards are reviewed by outside experts and are highly competitive.

Graduate Student Award

Eszter Pais, MD

Division of Immunology/Bone Marrow Transplantation (BMT)

Mentor: Donald B. Kohn, MD*

“Vector Constructs Designed to Induce the Controlled Proliferation of Pancreatic Beta Cells and Their Progenitors”

Steven Tsai, MD, PhD

Division of Immunology/BMT

Mentor: Carolyn Lutzko, PhD*

“The Role of OCT4 Isoforms in hESC Self-Renewal and Differentiation”

Career Development Fellowship Award

Tove Berg, PhD

Division of Surgery, Developmental Biology and Regenerative Medicine Program

Mentor: Kasper S. Wang, MD*

“The Role of FGF10 in Cell Fate Determination of Hepatic Progenitor Cells”

Yigit Guner, MD

Division of Surgery

Mentor: Henri R. Ford, MD*

“The Protective Role of P-Glycoprotein in Necrotizing Enterocolitis”

Frederic Sala, PhD

Developmental Biology and Regenerative Medicine Program

Mentor: Tracy Grikscheit, MD, PhD

“The Role of FGF10/FGFR2b Signaling in Tissue Engineered Colon Formation”

Career Development Award

Tracy Grikscheit, MD, PhD

Division of Surgery/Developmental Biology and Regenerative Medicine Program

Mentor: David Warburton, DSc, MD, FRCP, FRCS*

“Tissue Engineered Small Intestine Requires a Functional Intestinal Stem Cell Niche”

Ching-Ling (Ellen) Lien, PhD*

Division of Cardiothoracic Surgery

Mentor: Donald B. Kohn, MD*

“Characterization of Midkine Growth Factor During Zebrafish Heart Regeneration”

Carolyn Lutzko, PhD*

Division of Immunology/BMT

Mentor: Gay M. Crooks, MD*

“Characterizing the Role of NANOG in Human Embryonic Stem Cell Self-Renewal”

Clinical Research Academic Career Development Award

Brynie S. Collins, MD

Division of Gastroenterology and Nutrition

Mentors: Henry Lin, MD and Frank R. Sinatra, MD*

“Is Functional Dyspepsia in Children Related to Small Intestinal Bacterial Overgrowth?”

Patrick A. Ross, MD, FAAP*

Division of Anesthesiology Critical Care Medicine

Mentor: Christopher J.L. Newth, MB, ChB*

“Minimizing Work of Breathing in Infants and Children with Obstructed Airways Disease Being Weaned from Mechanical Ventilation”

Clinical and Translational Science Institute/ Pilot Projects Awards

Leslie F. Clark, PhD, MPH*

“Translating Science-based Intervention into Practice: Project AIM and High Risk Adolescents”

Donald B. Kohn, MD*

“In Utero Transplantation of Hematopoietic Stem Cells”

Maja Matarić, PhD

“Evaluating the Effectiveness of Social Robotics for Enhancing DIR/Floortime Therapy for Children with Autism Spectrum Disorder”

Steven D. Mittelman, MD, PhD*

“The Role of the Adipocyte in Leukemia Relapse”

Julie Wolfson, MD, FAAP

“Barriers to Care in Sickle Cell Disease in Los Angeles County”



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