CHILDRENS HOSPITAL LOS ANGELES

Research Highlights 2006

The Saban Research Institute of Childrens Hospital Los Angeles

Working Together to Improve Children's Futures

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

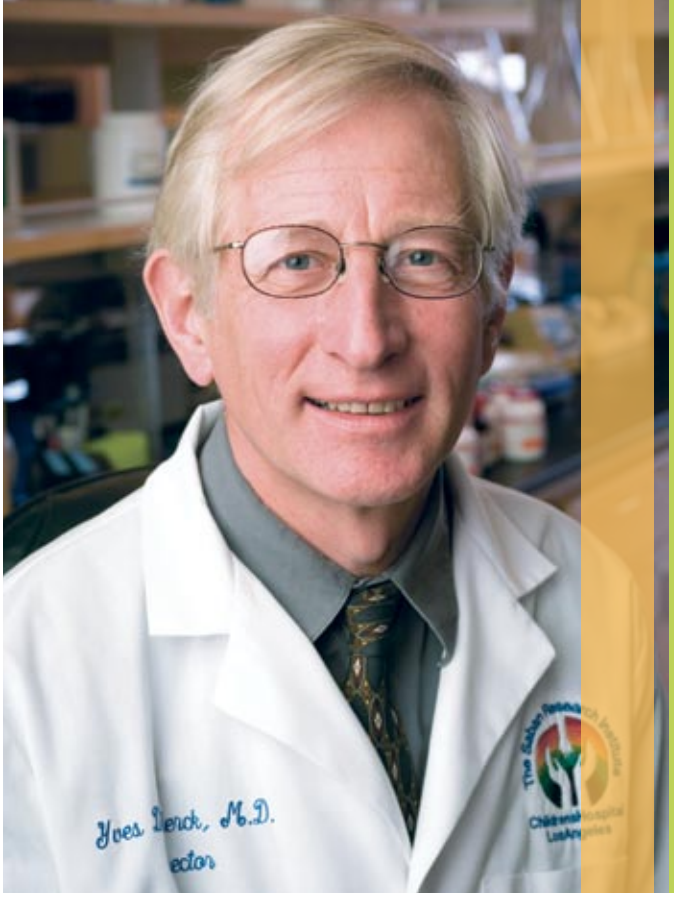
If you would like to know more about the programs at The Saban Research Institute, please visit www.ChildrensHospitalLA.org. Or use the convenient web addresses provided throughout this report.

The Saban Research Institute

ChildrensHospitalLosAngeles

International Leader in Pediatrics

KECK SCHOOL OF MEDICINE OF USC



Yves A. DeClerck, MD*
Director, The Saban Research Institute
Vice President of Research,
Childrens Hospital Los Angeles

Families Wait for Answers & Cures

How does a newborn child's brain develop the pathways that impact future health? Why, despite all our efforts, do some children develop a cancer that resists any known treatment? How can we help a child whose kidneys, lungs or heart are failing — for whom there is no available organ transplant?

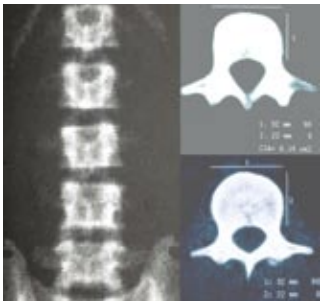
These questions, and others like them, fuel our investigations at The Saban Research Institute. Behind each scientific inquiry, each experiment, is a child waiting to be helped with a new treatment and new hope.

Welcome to this edition of Research Highlights, where we share some of the exciting developments of the past year, and honor the many supporters who further our mission. You will read about some inspired collaborations and investigations. This is only a sampling of what's going on at The Saban Research Institute.

Throughout time, major discoveries that led to medical breakthroughs have been made by scientists sharing their insights. Teamwork provides the foundation for innovation. Philanthropic partners are essential members of our team. With current economic trends, government support for biomedical research has become precarious at best. There is presently little funding for young investigators at the start of their careers or for an idea that needs time to grow. The donors listed in this report have helped make the difference. We look forward to more exciting work together.

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

A Year of Growth & Discovery



DEXA scans (above, left) give a two-dimensional view of three-dimensional structures such as the spine. CT images (above, right) can see the third dimension, revealing differences not apparent using DEXA, especially in assessing bone density in children. *(See page 15.)*

The Saban Research Institute of Childrens Hospital Los Angeles holds a distinction as one of the few freestanding pediatric research centers across the country to combine scientific inquiry with patient clinical care — dedicated exclusively to children. Here, some 100 investigators are engaged in more than 200 laboratory studies, clinical trials and community-based research.

In Fiscal Year (FY) 2006, we continued to make great progress in our search for new knowledge to help children, while at the same time, identifying challenges that will require a concerted, collaborative effort in the future.

Scientists at The Saban Research Institute published more than 200 scientific papers in FY 2006, extending their findings beyond our own boundaries. We successfully competed for more than $25.6 million in funding from the National Institutes of Health (NIH). As a result, we ranked fifth in NIH funding nationwide among 25 stand-alone pediatric institutions for the eighth consecutive year — and the leader in the Western United States.

You will read in these pages about some of the major discoveries made this year at The Saban Research Institute. Among other developments, you will learn how:

- Paula Cannon, PhD‡, obtains precious information that helps design better vectors to deliver genes into human cells by studying how the human immunodeficiency virus (HIV) penetrates and exits white blood cells;
- C. Patrick Reynolds, MD, PhD‡, and Barry Maurer, MD, PhD‡, have modified a synthetic vitamin (retinoic acid) to make it a potent anti-cancer drug that can be orally taken by children;
- John Wood, MD, PhD‡, and Thomas Coates, MD‡, are using the power of magnetic resonance imaging to accurately measure the amount of iron that accumulates in

the hearts of children with a life-threatening blood disease, such as thalassemia;

- Roger De Filippo, MD*, and Laura Perin, PhD, are instructing stem cells collected from the amniotic fluid to become kidney or bladder cells;

- Richard Simerly, PhD*, and Sebastien Bouret, PhD, are building on the discovery that leptin, a hormone that regulates obesity, is controlled during brain development;

- Tishya Wren, PhD*, and Vicente Gilsanz, MD, PhD*, have determined that CT (computed tomography) scans may be a superior bone density scanning tool in children.

Over the last two years, more than 20 scientists have joined The Saban Research Institute as faculty members, bringing new expertise and interests to our already large scientific community.

In FY 2006, we took a hard look at ourselves with two peer reviews. First, in December 2005, we underwent a complete evaluation of the use of our research space. In March 2006, a team of 13 scientists from some of the nation's leading academic and research institutions visited The Saban Research Institute, led by Thomas Boat, MD, chief of Pediatrics at Cincinnati Children's Hospital Medical Center.

This expert team acknowledged our admirable growth and leadership over the last five years, talented faculty and successful extramural funding of most of our priority programs — all within the context of our longstanding association with the University of Southern California (USC). At the same time, the scientists helped us to identify areas of potential growth.

We made significant progress in the area of clinical research in FY 2006, which we identified as a top priority in 2004. We recruited Edward Gomperts, MD*, a noted hematologist and clinical researcher, as associate director of The Saban Research Institute and director for clinical research. In addition, plans began to take shape for the Childrens Clinical Investigation Center (see page 14).

Critical Path: Teamwork

After five years of sustained growth, this year the NIH saw a reduction of its budget for the first time since 1982. It is increasingly clear that, in the future, successful research will be the result of the combined efforts of many different scientific disciplines.

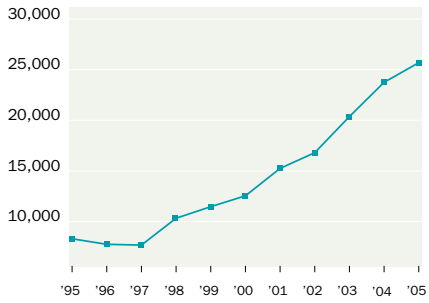
Our decision in 1996 to organize research into interdisciplinary programs is providing the best possible platform to promote interactive and collaborative investigations. We are forging strong partnerships with clinical investigators in the hospital's Centers of Excellence and with USC to bring discoveries made in the laboratory or the community to the children who need them.

It also is critically important to encourage young people to develop scientific careers. This year, The Saban Research Institute piloted a new high school outreach program that gave eight African American and Latino students the chance to conduct research in our laboratories (see page 16).

In November 2006, The Saban Research Institute will conduct a leadership retreat, with scientists and community advisors meeting together to discuss our challenges, strengths and goals. From this fertile exchange, we expect to set an ambitious agenda for the future of The Saban Research Institute.

National Institutes of Health (NIH) Funding 1995-2005

For biomedical research at The Saban Research Institute



In Fiscal Year 2005, funding from the NIH reached $25.6 million, an increase over 2004's $23.7 million. The Saban Research Institute ranks among the top five stand-alone pediatric research facilities in the nation in NIH funding — for the eighth consecutive year.

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

C. Patrick Reynolds, MD, PhD

Cancer Program

DIRECTOR: Robert C. Seeger, MD*
www.childrenshospitalla.org/cancer

"We study cancer cells to learn what makes them tick — especially the differences between cancer cells that chemotherapy can eliminate and those that manage to return."

–C. Patrick Reynolds, MD, PhD

Most new anti-cancer drugs are primarily developed for adults, and drug companies carry out little to no research in pediatrics. Researchers within the Cancer Program of The Saban Research Institute help fill this need.

"We study cancer cells to learn what makes them tick," says C. Patrick Reynolds, MD, PhD*, a member of the Cancer Program, and director of the Developmental Therapeutics Program in the USC-CHLA Institute for Pediatric Clinical Research. "We especially look at the differences between cancer cells that chemotherapy can eliminate and those that manage to return." The goal: match drug targets found in the deadliest cancer cells with novel therapeutic agents that may be able to destroy them.

One of the more promising drugs being developed at Childrens Hospital Los Angeles is fenretinide, a synthetic retinoid (Vitamin A) that Dr. Reynolds' team is investigating with support from the National Cancer Institute (NCI).

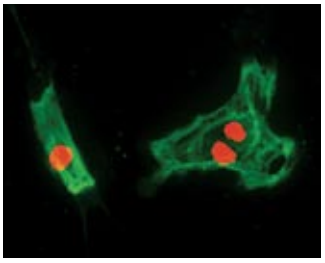
Fenretinide appears potentially effective against childhood cancers, such as neuroblastoma and leukemia, and selected adult cancers as well. During 2006, the unique oral formulation of fenretinide developed by Barry Maurer, MD, PhD*, investigator in the Cancer Program, entered a pediatric Phase I clinical trial that involves 13 institutions nationwide.

Fenretinide soon will be partnered with other drugs and tested in children. "Based on laboratory data, we have a number of novel drug combinations planned for clinical trials next year," says Dr. Reynolds. "We're optimistic that, together, these drugs will surpass the benefits any of them offer alone."

In addition to studying drugs developed at Childrens Hospital, the drug-testing laboratories of Dr. Reynolds, Nino Keshelava, MD*, and Min Kang, PharmD*, are a national resource lab for the NCI to test drugs for activity against cultured cells derived from childhood cancer (see page 15). Such data will guide clinical trials evaluating the new drugs in children.

Ching-Ling Lien, PhD

Cardiovascular Research Program



Researchers are exploring ways to activate the regenerative ability of heart tissues in patients by regenerating zebrafish heart cells. The red staining indicates the cells are multiplying.

DIRECTOR: Ivan Vesely, PhD*
www.childrenshospitalla.org/cardiovascular

Why does one in every hundred human hearts develop abnormally? Why do cardiac injuries heal with stiff scarring instead of fresh tissue that can contract and help pump fresh blood through the body? And can we repair and regenerate abnormal or injured heart tissue?

To try and resolve these questions, Ching-Ling (Ellen) Lien, PhD*, is investigating the molecular mechanisms of zebrafish heart development and regeneration. Dr. Lien, previously with Harvard Medical School, was recruited to The Saban Research Institute's Cardiovascular Research Program in August 2006 through support from the Heart Institute and Las Madrinas, a longtime volunteer support group of Childrens Hospital.

The zebrafish has proven an ideal model for cardiovascular investigations. This freshwater fish lays transparent eggs outside its body. Once fertilized, embryos remain transparent during development. With only a microscope, Dr. Lien can watch in real time as the tiny fish heart forms. By studying gene activity, she looks for clues to developmental errors that produce congenital human heart defects.

Dr. Lien is equally interested in the zebrafish's ability to regenerate tissues. For example, if the tail is cut off, a new one grows back. Amazingly, zebrafish hearts have a similar ability to regrow missing heart tissue. She has identified six gene clusters that change their activity after heart injury, and is examining the activity of proteins encoded by these genes. Already she has found that if one of them — a platelet-derived growth factor — is blocked, regeneration is impaired.

With help from a creature less than two-inches long, Dr. Lien is now investigating these regeneration genes to determine if they can improve heart repair after cardiac damage. "Our ultimate goal is to understand how these genes can activate tissue regeneration," says Dr. Lien, "and to work with our clinical colleagues to develop new therapeutic strategies for repairing defects to the heart."

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

Marizen Ramirez, MPH, PhD, with Natalia Ramirez

Community, Health Outcomes and Intervention Research Program

"When emergencies happen, how can schools balance conflicting priorities?"

–Marizen Ramirez, MPH, PhD

DIRECTOR: Michele D. Kipke, PhD*
www.childrenshospitalla.org/community

Keeping children safe at school from potential threats — ranging from earthquakes to gang violence and "soft-target" terrorist attacks — is a priority for families and the community. Marizen Ramirez, MPH, PhD*, is investigating emergency preparedness within the Compton and Lynwood Unified School Districts to better understand the issue, funded by a three-year career-development award from the Centers for Disease Control and Prevention. (In addition, the CHOIR program receives support from Cheryl Saban, PhD, Haim Saban and the Saban Family Foundation.)

In 2006, Dr. Ramirez reviewed existing practices in these high-need school systems, compiled incident reports from the Compton Unified's own private police force and the Lynwood Security Department, and interviewed administrators, teachers, students and parents about their perceptions of school safety.

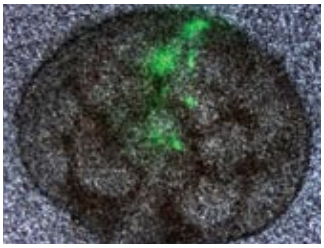
With a full year of analysis ahead, fundamental dilemmas have already risen to the surface. They include: Should schools try to develop specific response plans for every potential emergency? By expecting teachers to put aside personal responsibilities in favor of an obligation to students, are schools asking the impossible and, in effect, jeopardizing safety? How should schools respond when frightened parents arrive during an emergency? "In other words," says Dr. Ramirez, "when emergencies happen, how can schools balance conflicting priorities?"

These are perplexing questions. Childrens Hospital Los Angeles, designated as the pediatric Disaster Resource Center by the Los Angeles County Emergency Medical Services, is taking a leadership role in searching for answers.

Dr. Ramirez will soon begin working with parents in areas of significant need. All families deserve school preparedness, she says, but parents must learn to constructively make their expectations known. Simultaneously, schools must learn to export their preparedness to the homes of families they serve. "It increases our chances of keeping children safe."

Laura Perin, PhD, and Roger De Filippo, MD

Developmental Biology Program



Amniotic fluid stem cells are showing signs of versatility in laboratory studies. Here, the stem cells are marked with green fluorescent protein for easier tracking when injected directly into the kidney in vitro.

DIRECTOR: David Warburton, DSc, MD, FRCP*
www.childrenshospitalla.org/devbiol

More than 375,000 Americans are treated annually for end stage renal disease — 6,560 of those under the age of 19. These statistics fuel the work of Roger De Filippo, MD*, a surgeon in Pediatric Urology at Childrens Hospital Los Angeles.

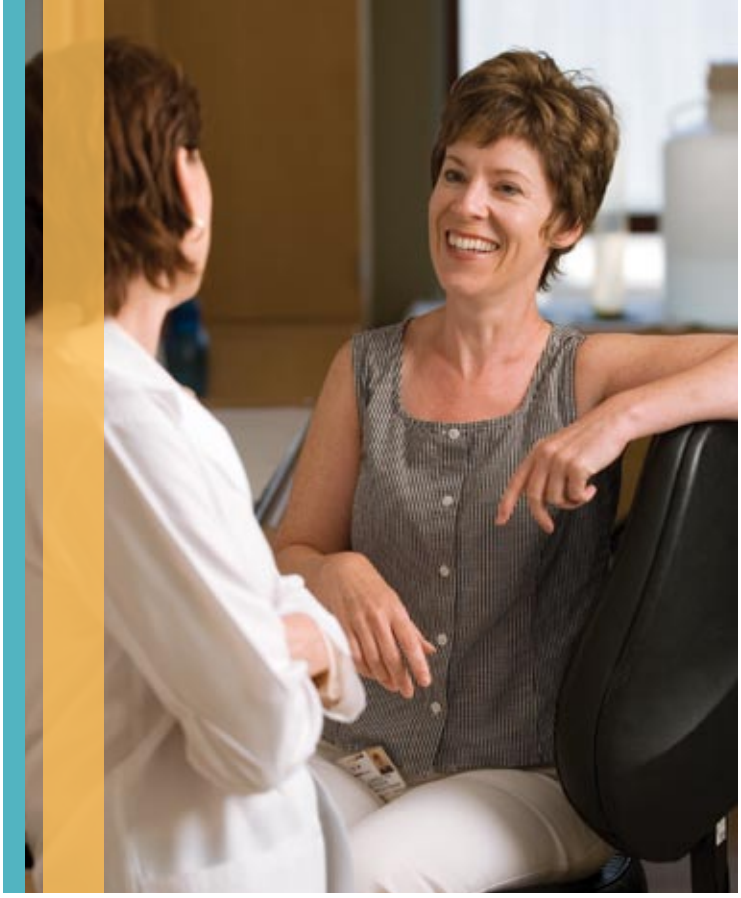
His laboratory in The Saban Research Institute is one of only two laboratories nationwide working with a novel stem cell population harvested from amniotic fluid. The goal: to rescue failing kidneys with cell therapy and, through tissue engineering, someday perhaps bypass the need for organ transplants or diminish the complications associated with these procedures. Dr. De Filippo was recruited through support from Cheryl Saban, PhD, Haim Saban and the Saban Family Foundation. He also received a five-year Career Development Award from the National Institutes of Health.

Compared to other stem cells, amniotic stem cells are easily retrieved, isolated and grown in the lab. Whether they prove to be as multipotential as embryonic stem cells still needs to be determined. In 2006, Dr. De Filippo's team, co-directed by Laura Perin, PhD, succeeded in using amniotic stem cells to regenerate kidney cells in a developing fetal animal kidney. They were able to deliver the stem cells to the kidney both through the blood stream and by direct injection. The second method showed better results for integrating cells into the developing organ.

During the experiments, a serendipitous finding revealed other possible benefits from this approach. Some amniotic stem cells lodged themselves in the lung and showed signs of differentiating into lung cells. Now, Dr. De Filippo's team is collaborating on studies with Dr. David Warburton to determine the potential of amniotic cells in helping the lung regenerate.

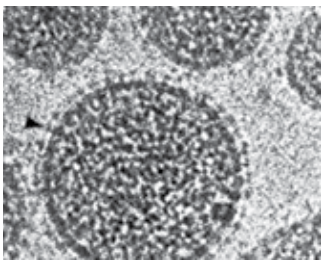
Dr. De Filippo says his team of researchers owes their success to the synergy between a surgeon-scientist and a basic scientist. "Everything starts with a clinical problem. Then the brainstorming in the laboratory begins."

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



Paula Cannon, PhD

Gene, Immune and Stem Cell Therapy Program



A highly pathogenic group of viruses called New World arenaviruses, like the one depicted here, can cause fatal fevers in humans — inspiring new investigations into how they work and how to thwart their power.

DIRECTOR: Donald B. Kohn, MD*
www.childrenshospitalla.org/gene

For many thousands of years, viruses have found ways to disguise themselves, enter cells and suppress their chosen target, developing and refining their strategies over time. Paula Cannon, PhD,* has made it her goal to outwit them.

Her particular focus: understanding how viruses enter and exit cells — both critical steps in the virus lifecycle — to devise methods to block them. This could give scientists critical information to better target the delivery of drug treatments or fine-tune gene therapy techniques.

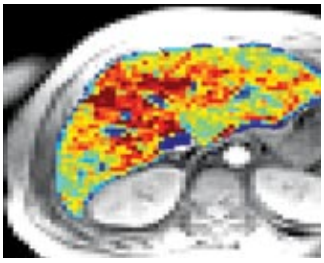
Dr. Cannon was recruited to The Saban Research Institute through the Las Madrinas Endowment for Gene, Immune and Stem Cell Therapy Research. In 2006, she received her first research grant from the National Institutes of Health for investigations into the basic strategies used by human immunodeficiency virus (HIV) to exit from infected human cells. She is concentrating on Vpu, one of nine proteins in HIV-1, which appears to give that virus the power to produce 10 times the offspring as an HIV-infected cell without Vpu.

Dr. Cannon also received a four-year $600,000 grant in 2005 from the Pacific-Southwest Regional Center of Excellence for Biodefense and Emerging Infectious Diseases to study a highly pathogenic group of viruses called New World arenaviruses, which are transmitted by rodents and can cause fatal hemorrhagic (bleeding) fevers in humans. These viruses are considered potential bioweapons.

She is collaborating with Donald B. Kohn, MD, on developing gene therapy vectors based on HIV. These so-called lentiviral vectors are extremely effective at delivering genetic information to human blood cells. To create a vector, she essentially “scoops out” the viral gene and replaces it with the therapeutic gene. “Ultimately,” says Dr. Cannon, “being able to harness a human pathogen such as HIV to develop tools to treat other human diseases is a sweet irony to me as a virologist.”

John Wood, MD, PhD

Childrens Imaging Research Program



In this liver "map," red areas indicate high concentrations of iron, while the blue shows low iron. Such variation in iron distribution makes liver biopsy an unreliable tool to monitor iron overload in some patients with thalassemia, especially compared to MRI.

DIRECTOR: Vicente Gilsanz, MD, PhD*
www.childrenshospitalla.org/imaging

Seven years ago, John Wood, MD, PhD,* was a fellow at Yale University, when two young patients he knew — both diagnosed with the genetic blood disorder, thalassemia major — died from cardiac disease due to excessive iron in the heart.

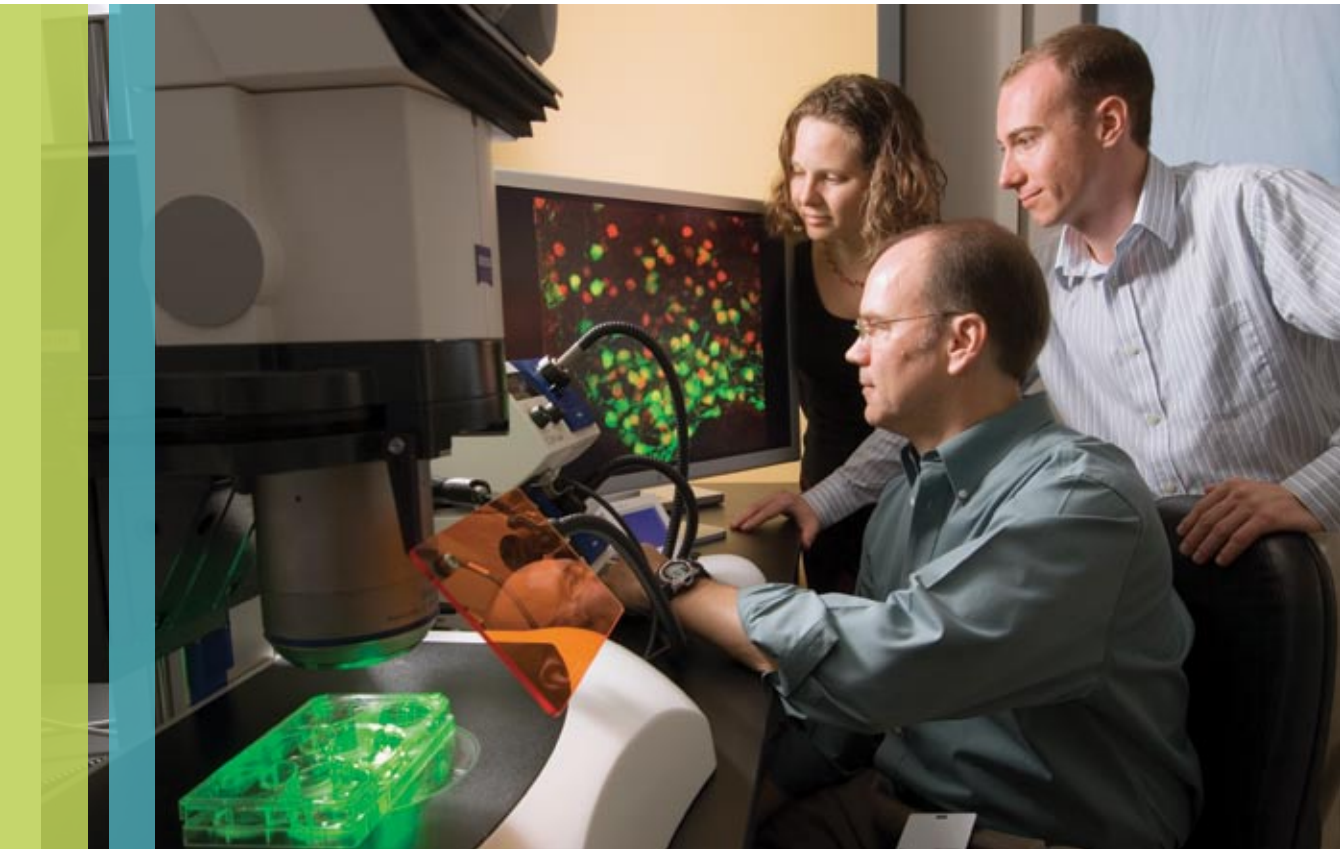
What bothered him most was the attitude many held that these deaths were inevitable. He started looking into the problem. "I felt certain our tests just weren't sensitive enough to tell us about the gradual period of iron buildup," he recalls. "There was enough evidence this was a treatable disease, but the problem was late diagnosis."

When Dr. Wood came to Childrens Hospital Los Angeles nearly six years ago, he found a community of support for his investigations. He began innovative collaborations with the Department of Radiology and with Thomas D. Coates, MD,* section head of Hematology in the Childrens Center for Cancer and Blood Diseases, who oversees one of the nation's largest thalassemia centers.

Today, Dr. Wood has proven the viability of a magnetic resonance imaging (MRI) technique called T2* which accurately determines iron levels in the liver and heart. Previously, thalassemia patients had to endure much riskier liver and cardiac biopsies.

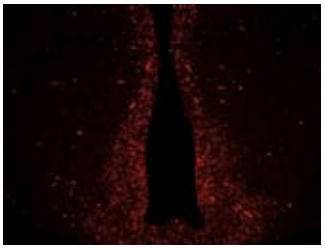
Dr. Wood, director of Cardiovascular MRI for the Heart Institute at Childrens Hospital, received a $2.2 million, four-year grant in 2005 from the National Heart, Lung and Blood Institute of the National Institutes of Health. So far, his studies have shown that measurements with MRI scans are as reliable as liver biopsy in monitoring patient response to iron removal therapy — and are non-invasive and painless for the patient. Similar results have been achieved for heart iron estimation. "This technology is changing the way people think about management of this disorder worldwide," notes Dr. Coates. "Thanks to Dr. Wood's inspiration and hard work, we are improving children's lives."

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



Richard Simerly, PhD, seated, with Christine Burt-Solorzano, MD, and Sebastien Bouret, PhD

Neuroscience Program/Childrens Brain Center



This cellular image of neurons in action reveals brain regions that control food intake and body weight — a shared focus for both basic and clinical investigators at Childrens Hospital Los Angeles.

DIRECTOR: Richard B. Simerly, PhD*
CHILDRENS BRAIN CENTER DIRECTOR:
Floyd H. Gilles, MD*
www.childrenshospitalla.org/neuroscience

Weighing in at around three pounds, the human brain is home to an estimated 100 billion neurons — a complex system of electrochemical impulses that control memory, thought, vision and such basic functions as heartbeat, digestion and respiration. This extremely intricate organ defies understanding by a single scientific discipline.

"Biomedical research has become increasingly complicated, particularly in neuroscience. We must take a multidisciplinary approach to progress," says Richard Simerly, PhD*, director of the Neuroscience Program in The Saban Research Institute. "Some of the biggest payoffs result when groups of investigators with complementary expertise come together to tackle tough questions."

Those investigators come from Dr. Simerly's area of expertise — developmental neurobiology — as well as from biochemistry, cell biology, anatomy, behavioral neuroscience, molecular genetics and imaging. "This is how we will make real advances in understanding the relationship between brain development and disease," he says.

"Together, we want to cure kids. We want to cure adults. Interacting with clinicians enables us to think differently about the problems."

–Sebastien Bouret, PhD

In its first full year in 2006, the Neuroscience Program laid the groundwork for new discoveries through broad-based collaborations with colleagues in the Childrens Brain Center at Childrens Hospital Los Angeles, at the University of Southern California (USC) and elsewhere.

Dr. Simerly's team won competitive renewal of a five-year grant from the National Institutes of Health (NIH) — "a definite sign we're on the right track, since only about 10 percent of renewal applications win approval in the current environment," he notes.

The Neuroscience Program also gained the expertise of Sebastien Bouret, PhD, an expert in hormones and brain development, who previously worked with Dr. Simerly at the Oregon National Primate Research Center, Oregon Health & Science University, and is now establishing his own laboratory within The Saban Research Institute.

Throughout 2006, the Neuroscience Program at Childrens Hospital emerged as a key player in the new USC Neuroscience Initiative. This far-reaching initiative, supported by the Office of the Provost at USC, is unifying various, internationally recognized efforts in the Neuroscience Research Institute on the University Park Campus and the Zilka Neurogenetics Institute at the USC Keck School of Medicine under one umbrella. Its goal: to provide the support to encourage USC scientists to organize novel, interdisciplinary research and training programs.

The Developing Brain

The Neuroscience Program at The Saban Research Institute contributes to the USC Neuroscience Initiative a core focus in developmental neurobiology — the cellular and molecular mechanisms of brain growth — with the goal to identify developmental events that can go awry. "Many of the most devastating disorders that can afflict a child's nervous system have their basis in development," says Dr. Simerly. "An added bonus is that if we can understand how neurocircuit formation goes wrong at the beginning, we can better understand how those same neurocircuits begin to fail during aging."

Interdisciplinary collaboration also formed the theme for investigations within the Neuroscience Program in 2006. Drs. Simerly and Bouret are collaborating with Christine Burt-Solorzano, MD, from the Division of Endocrinology, Diabetes and Metabolism, on issues of brain pathways and glucose metabolism. As Dr. Bouret explains, "Together, we want to cure kids. We want to cure adults. Interacting with clinicians enables us to think differently about the problems."

Working on Dr. Simerly's team in Oregon, Dr. Bouret discovered that a hormone called leptin can promote, during development, the formation of brain circuits that regulate feeding, which has long-term implications for obesity and diabetes. Now, his studies at The Saban Research Institute are exploring whether diet during lactation — a critical period for a newborn's developing brain — can impact and alter these same brain pathways.

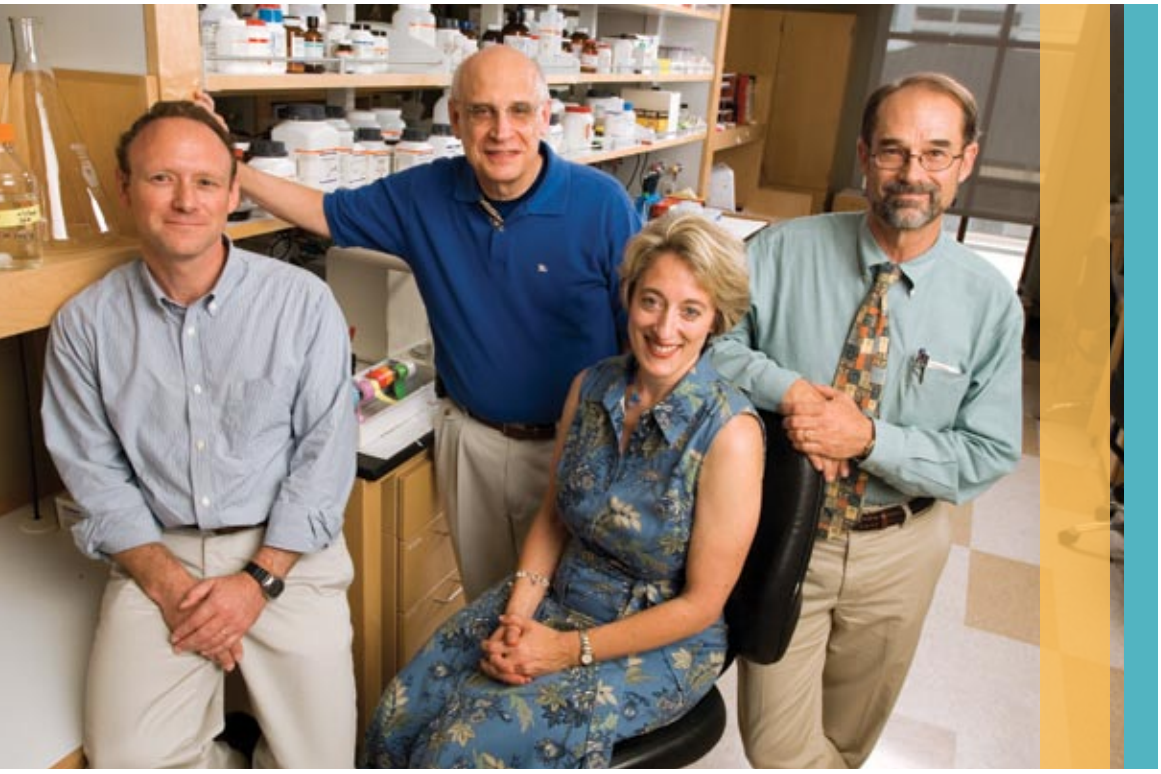
Dr. Bouret enjoys a tenured faculty position in his native France but has chosen to pursue his research in the United States. He is excited by the interaction between neurology, endocrinology and imaging research at The Saban Research Institute. "This is an amazing place to do research," he says.

Building on Strengths

Dr. Simerly is working to recruit other talented developmental neurobiologists, capitalizing on The Saban Research Institute's strengths in molecular genetics, cell biology and small animal imaging. He is supported in his efforts by funding received from the Associates Endowment for Neuroscience and Imaging Research, the Saban Family Foundation and the USC Office of the Provost.

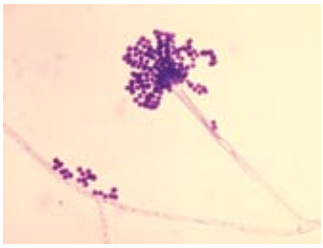
Building a new research program is a lot like trying to discover what makes the brain tick — it takes patience and determination. Dr. Simerly hadn't worked in a pediatric setting before joining The Saban Research Institute in 2005. "One of the most enjoyable things I've discovered this year is how energizing it is to be in an environment where scientific progress leads to clinical insights that influence the life and health of a child."

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



Left to right: Kevin Nash, PhD; Clark Inderlied, PhD; Jill Hoffman, MD, and Wilbert Mason, Jr., MD.

Microbial Pathogens Initiative



Aspergillus fumigatus conidiophore. *This spore-forming fungus can cause serious medical consequences for individuals who are immune compromised. Image provided courtesy of Centers for Disease Control and Prevention.*

DIRECTOR: Wilbert H. Mason, Jr., MD, MPH*
www.childrenshospitalla.org/microbial

Aspergillus, a family of common molds, enters everyone's lungs, everyday. In most youngsters, the airborne mold is harmless, but for those with an immune system compromised by chemotherapy or a bone marrow or lung transplant, it can be deadly. In fact, the mortality rate for pediatric Invasive Aspergillus (IA) is upwards of 40 percent.

Unfortunately, IA is difficult to diagnose. The first symptom may be fever. If IA is diagnosed or suspected, anti-fungal drugs are prescribed and computed tomography (CT) scans ordered. If CT scans reveal an infection, a lung biopsy is needed to confirm diagnosis. All these tests are invasive or potentially toxic.

Led by Jill Hoffman, MD*, clinical and basic investigators in the Microbial Pathogens Initiative are investigating innovative, non-invasive blood tests for IA. One detects galactomannan, a signature molecule produced by the mold. Others detect Aspergillus DNA or proteins. "We want to detect this disease before fever occurs," says Dr. Hoffman. "Initiated early, drug therapy is more likely to be effective."

Clark Inderlied, PhD*, and Kevin Nash, PhD*, are members of the research team. "Data indicates the galactomannan test may identify adults with early stage IA," explains Dr. Nash. "But infectious diseases progress differently in youngsters. Until we validate those results, we could miss youngsters who need therapy." The team began enrolling study participants in 2006. Twice a week, participants have their blood drawn and tested. The results are correlated with clinical data, to determine if the blood test can replace current invasive diagnostic techniques.

Only 20 percent of children treated for IA actually have the disease. Thus, a more reliable test would not only mean earlier therapy for those who need it, but avoid unnecessary interventions for children without IA. "Newer therapies make earlier diagnosis even more compelling," says Dr. Hoffman, "because of their promise of better outcomes."

Center for Endocrinology, Diabetes and Metabolism

DIRECTOR: Francine R. Kaufman, MD*
www.childrenshospitalla.org/diabetes

Only two to four percent of children diagnosed with diabetes at Childrens Hospital Los Angeles 15 years ago had type 2, a disease linked to obesity and inactivity. Today, that figure is 20 percent.

In 2004, 12 research centers launched a six-year investigation into this epidemic. Funded by the National Institutes of Health, TODAY (Treatment Options for type 2 Diabetes in Adolescents and Youth) is examining the effects of lifestyle change on patients with diabetes ages 10 to 18. By 2008, 750 participants will have signed on. All subjects receive medication. One-third also receive exercise and nutrition guidance. "We'll watch everyone until 2010, with the hypothesis that lifestyle changes will prove beneficial," explains Francine R. Kaufman, MD, director of the Center for Endocrinology, Diabetes and Metabolism, and TODAY's national chair.

The TODAY team presented some early findings at the 2006 American Diabetes Association meeting. In addition to analyzing participant characteristics upon enrollment, they examined the study's economic feasibility. "If we're correct, people will want to know the cost of replicating our protocol," says Mitchell Geffner, MD*, TODAY's principal investigator at Childrens Hospital.

Also in 2006, Dr. Kaufman was elected to the prestigious Institute of Medicine, which provides health and science information to policymakers and the public.

Mitchell Geffner, MD

Childrens Center for Cancer and Blood Diseases

Markus Müschen, MD

DIRECTOR: Stuart E. Siegel, MD*
CO-DIRECTOR: Donald B. Kohn, MD*
www.childrenshospitalla.org/cancercenter

Cancer cells are notoriously self-sufficient — a characteristic that scientists are determined to overcome. While normal cells depend on the continuous presence of growth and survival signals, cancer cells become progressively independent from their environment and proliferate.

Markus Müschen, MD*, leader of the Leukemia Section of the Cancer Program of The Saban Research Institute, recently showed that aberrant signaling molecules (chemicals involved in transmitting information within a cell and between cells) play a key role in the development and progression of leukemia, the most common childhood cancer.

The main questions driving his research include: How does leukemia originate and how can that process be prevented or interrupted? Pinpointing the survival strategies of leukemia cells is an essential first step. He and his colleagues recently identified one strategy as "molecular piracy" — in which aberrant signaling molecules in leukemia cells take control of other healthy molecules to feed in an oncogenic signaling pathway.

Dr. Müschen joined Childrens Hospital in August 2006 from the Heinrich-Heine Universität Düsseldorf, Germany. He is excited by the possibilities of collaborating with other scientists in The Saban Research Institute. "This is a fertile research environment," he says, "where basic research, pre-clinical testing and clinical applications are all being done at the highest possible level."

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

Childrens Clinical Investigation Center

DIRECTOR: Edward D. Gomperts, MD*
www.childrenshospitalla.org/CLIC

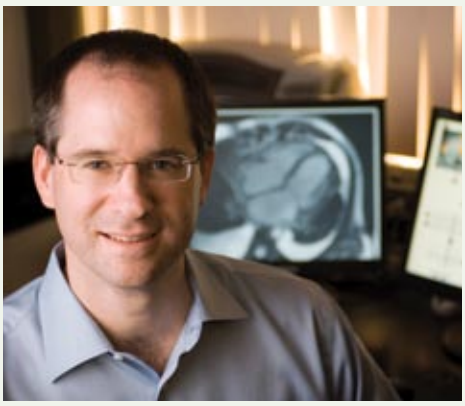
Clinical research is gaining added emphasis at Childrens Hospital Los Angeles — a commitment that reflects the recent strategic plan of The Saban Research Institute and a heightened priority for the federal government. "The leadership of the National Institutes of Health (NIH) believes that laboratory research needs to be interpreted or translated into clinical benefit — something we have always emphasized at Childrens Hospital Los Angeles," notes Edward D. Gomperts, MD, who was appointed director of clinical research at the hospital and associate director of The Saban Research Institute in 2006.

Dr. Gomperts is the principal investigator of the General Clinical Research Center (GCRC) at Childrens Hospital, which supports some 30 clinical research studies at the pediatric facility and serves as the pediatric satellite of the GCRC at the Keck School of Medicine of the University of Southern California.

Together with colleagues at the Keck School of Medicine, Childrens Hospital is preparing to apply for a Clinical Translational Science Award (CTSA) from the NIH. If approved, the CTSA will support clinical research studies, investigator training and facility expansion, informatics (the application of statistical techniques to data collection and management), and collaborative efforts with other disciplines, such as preventive medicine, bioengineering and imaging technologies.

Edward Gomperts, MD, left, with Liz and Daniel LaBianca and their son, Hayden

The Heart Institute



Jondavid Menteer, MD

DIRECTOR: Vaughn A. Starnes, MD*
www.childrenshospitalla.org/heart

Many children with heart failure have no congenital defect. Instead, their cardiomyopathy results from an infection or a metabolic error. In the short term, their bodies try to compensate — the autonomic nervous system and the adrenaline system kick into overdrive to keep blood pressure up and infuse tissues with oxygenated blood.

What happens if a child stays in this state for too long? Jondavid Menteer, MD*, thinks the result is brain damage. In a pioneering investigation, he's looking at the complex interplay between specific areas of a child's developing brain and serious pediatric heart problems. In 2006, Dr. Menteer studied the cases of several hundred cardiomyopathy patients at Childrens Hospital Los Angeles, and found that 60 percent to 80 percent displayed symptoms of autonomic dysfunction. Studies of current patients also are revealing warning signs. "Damage to centers of the brain that control autonomic function may eventually destroy the child's ability to keep compensating," he says.

With initial funding from the hospital's General Clinical Research Center, Dr. Menteer is using magnetic resonance imaging scans to look for such brain damage in study participants. "If we can actually observe severe brain damage, and know it signals eminent danger, we can better identify children who need immediate intervention."

Childrens Orthopaedic Center

DIRECTOR: Vernon T. Tolo, MD*
www.childrenshospitalla.org/ortho

Working together in inspired collaborations, basic and clinical researchers are uncovering important new knowledge about the effectiveness of bone density scanning techniques for pediatric patients. Tishya Wren, PhD*, a biomedical engineer, and Vicente Gilsanz, MD, PhD*, a radiologist, are comparing the value of measurements using DEXA (dual energy X-ray absorptiometry) scans against CT (computed tomography) scans.

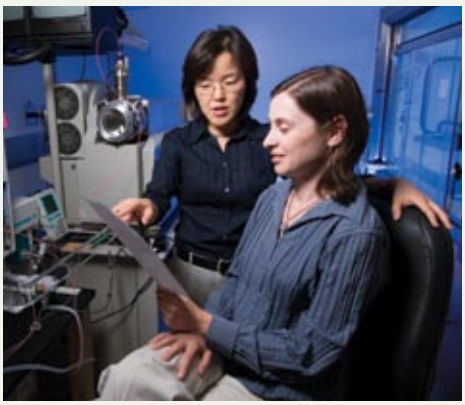
Although DEXA has been a standard body imaging technique to determine bone loss for adults and kids, side-by-side studies in 2005 by the Childrens Hospital researchers found that it tends to over diagnose osteoporosis in children, which can result in unnecessary treatments. Now in its second year, the study funded by the National Institutes of Health (NIH) eventually will collect data on more than 600 children.

The two-dimensional view provided by DEXA may be adequate when imaging adults, but it's proving far less so in growing children. "It can't reveal the size and shape of bone growth, and as a result, doesn't give very accurate measurements," says Dr. Wren, director of research for the John C. Wilson, Jr., Motion Analysis Lab in the Childrens Orthopaedic Center. By comparison, CT scans provide three-dimensional images. Using CT, the researchers have determined that children with cerebral palsy have smaller bones and lower bone density than children without cerebral palsy.

Dr. Wren's research is supported by The Associates Endowment in Motion Analysis Research and the NIH.

Tishya Wren, PhD

USC-CHLA Institute for Pediatric Clinical Research



Min Kang, PharmD, left, and Nino Keshelava, MD

PRINCIPAL INVESTIGATORS: Roberta G. Williams, MD*, and Stuart E. Siegel, MD*
www.ipcr.us

The USC-CHLA Institute for Pediatric Clinical Research (IPCR) is focused on identifying and developing new effective therapies against childhood diseases, beginning with cancer, the leading cause of death by disease for children in the United States.

Nino Keshelava, MD*, a member of the IPCR's Developmental Therapeutics Program, directs preclinical testing for the New Approaches to Neuroblastoma Therapy consortium funded by the National Cancer Institute (NCI). She is co-principal investigator, with Principal Investigator C. Patrick Reynolds, MD, PhD*, of the In Vitro Laboratory within the Pediatric Preclinical Testing Program. This NCI-initiated program involves six pediatric institutions in testing new agents in leukemia, lymphoma, neuroblastoma, sarcomas and brain tumors. Presently, Dr. Keshelava is investigating histone deacetylase inhibitors — drugs designed to make DNA accessible for new therapies, an approach that may better destroy the tumor.

Min Kang, PharmD*, heads the Leukemia Preclinical Testing Lab, which serves as reference laboratory for the Therapeutic Advances in Childhood Leukemia (TACL) consortium. "We believe many of the drugs we study at the IPCR ultimately will benefit adults as well as children," says Dr. Kang, also a member of the Developmental Therapeutics Program. In 2006, TACL launched a Phase I clinical trial into an experimental therapy for acute lymphoblastic lymphoma.

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

On the rooftop of The Saban Research Institute, left to right: Carlos Ramos, Perla Martinez, Brandon Bell, Lizet Gallardo, Linda Antonioli, Alex Marquez, Vanessa Guzman, Vanessa Lopez and Jessica Sanchez.

High School Summer Research Internships

"Seeing the students' passion, poise and knowledge was inspiring."

–Ted Samuels, chair of The Saban Research Institute Committee

The statement by a nervous applicant during final interviews said it all: "We don't get many opportunities like this in my neighborhood." With two years of private funding and permanent funding as its goal, The Saban Research Institute established a paid six-week summer internship program in 2006 for qualified African American and Latino public school students entering the 12th grade.

Interns were matched with investigators from The Saban Research Institute and given the chance to conduct pediatric studies in building better heart valves, developing organs immune to rejection, understanding bacterial development and the brain barrier, maintaining stem cells, stemming HIV transmission through breast milk, and identifying more effective surgical techniques.

Jessica Sanchez from Fremont High School in South Los Angeles was selected from among 32 applicants as one of eight students and five Latinas participating. "As with all the interns, Jessica grew so much, not only in the laboratory, but in her ability to present her research findings to scientists and lay people," says Linda Antonioli, the program's community liaison. "These incredible young people took advantage of the opportunities we gave them, ready for the next exciting step of applying to colleges with this experience on their applications."

"We want to show them the world of bench research," explains Emil Bogenmann, PhD*, program director. "In turn, they become messengers about the importance of medical science to their families, schools and communities."

Funding was provided this year and next by Lori and Ted Samuels. "Seeing the students' passion, poise and knowledge was inspiring," says Mr. Samuels, chair of The Saban Research Institute Committee. The Leonetti/O'Connell Foundation provided important educational funding, including support for weekly, interactive Research Roundtables with renowned researchers, health care role models and a college admissions officer. Richard Cordova, Childrens Hospital's president and chief executive officer, set an inspirational tone as the first speaker.

The H. Russell Smith Award was established in 1988 to recognize individuals who have made outstanding contributions in pediatric research during their careers at Childrens Hospital Los Angeles.

H. Russell Smith Awards

The award is named for honorary trustee and former chairman of the Childrens Hospital Board of Directors. Mr. Smith and his wife, Jeanne, have been actively involved in the hospital's growth and are strong advocates for research. The 2006 winners are:

Joseph A. Church, MD*
Dr. Church, head of the Division of Clinical Immunology and Allergy at Childrens Hospital Los Angeles, is considered a role model for clinical investigators. He is recognized as being among the first to identify pediatric HIV/AIDS in the mid-1980s and to initiate clinical investigations on this disease process.

Vesa M. Kaartinen, PhD*
Dr. Kaartinen is a principal investigator in the Developmental Biology Program of The Saban Research Institute. Dr. Kaartinen is an internationally recognized developmental geneticist, who has made major discoveries over several years in the fundamental mechanisms leading to craniofacial malformations and heart development.

2006 Intramural Awards

From The Saban Research Institute and the Department of Pediatrics

Pre-Doctoral Award

Nilesh Ghugre, MS
Department of Pediatrics/Division of Cardiology
Program: Imaging Research
Mentor: John Wood, MD, PhD*
Project: "Calibration of Iron-Mediated Relaxivity Using Monte Carlo Modeling"

Dennis To, MS
Department of Pathology
Program: Microbial Pathogens Initiative
Mentor: Kevin Nash, PhD*
Project: "The Role of the pknG and ppb2 Genes in the Physiology of Mycobacteria, Including Mycobacterium Tuberculosis"

Career Development Fellowship Award

Nikoo Saber, PhD
Division of Cardiothoracic Surgery
Program: Cardiovascular Research
Mentor: Ivan Vesely, PhD*
Project: "Development of Catheter-Implantable Artificial Valve for Neonatal Pulmonary Stenosis via Computational Modeling Methods"

Stijn De Langhe, PhD
Department of Surgery
Program: Developmental Biology
Mentor: Saverio Bellusci, PhD*
Project: "Role of Mesenchymal FGF Signaling in Lung Development"

Janet M. Yoon, MD
Department of Pediatrics/Division of Hematology/Oncology
Program: Cancer
Mentor: Yves A. DeClerck, MD*
Project: "Matrix Metalloproteinase-9 in Neuroblastoma Angiogenesis"

Research Faculty Career Development Award

Steve Mittelman, MD, PhD* **
Department of Pediatrics, Division of Endocrinology, Diabetes & Metabolism
Program: Cancer
Mentor: Nora Heisterkamp, PhD*
Project: "Exploring the Link Between Obesity and Poor Prognosis of Childhood Acute Lymphoblastic Leukemia Using a Murine Model"

Shahab Asgharzadeh, MD* **
Department of Pediatrics/Division of Hematology/Oncology
Program: Cancer
Mentor: Robert Seeger, MD
Project: "Correlative Genomics Studies of Neuroblastoma Lacking MYCN Amplification"

Jacqueline M. Evans, MD, PhD*
Department of Anesthesiology Critical Care Medicine
Program: Gene, Immune and Stem Cell Therapy
Mentors: Donald Kohn, MD*, and Mary Kearns-Jonker, PhD*
Project: "Tissue-Directed Gene Therapy with a Recombinant Adeno-associated Pseudotype Vector Encoding Heme Oxygenase-1 to Induce Tolerance after Cardiac Transplantation"

** Received a K12 Child Health Research Career Development Award from the National Institutes of Health
* Faculty member, the Keck School of Medicine of the University of Southern California

Honor Roll of Donors from July 1, 2005 to June 30, 2006

This Honor Roll of Donors recognizes individuals, foundations and corporations that have invested in research at Childrens Hospital Los Angeles with gifts of $1,000 and above.

Every dollar given to our research program and investigators reaffirms the donor's vision of a world without pediatric disease. Your support is paying life-saving dividends. Survival rates and treatments continue to improve for children living with severe illnesses that can sideline them from being carefree children with big dreams and bright futures. However, the fight is far from over.

Private funding works in tandem with federal funding. Both are essential to foster the most promising ideas, and move them from the laboratory bench to the patient's bedside in the form of new therapies. This essential philanthropic partnership keeps Childrens Hospital Los Angeles at the research forefront, helping to drive our mutual interest in the good health of children. For more information, please contact Melany Duval, associate vice president of major and planned gifts, at 323-671-1705 or mduval@chla.usc.edu.

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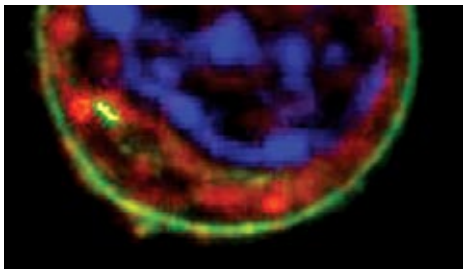

Cancer cells, such as this leukemia cell, become progressively independent from their environment and proliferate, driven by growth signals. Scientists in The Saban Research Institute are seeking ways to interrupt this signaling process. *(See page 13.)*

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The member investigators of The Saban Research Institute of Childrens Hospital Los Angeles hold faculty appointments at the Keck School of Medicine of the University of Southern California. Also supporting the work of The Saban Research Institute is a staff of post-doctoral fellows, graduate students and research associates, along with administrative staff.

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