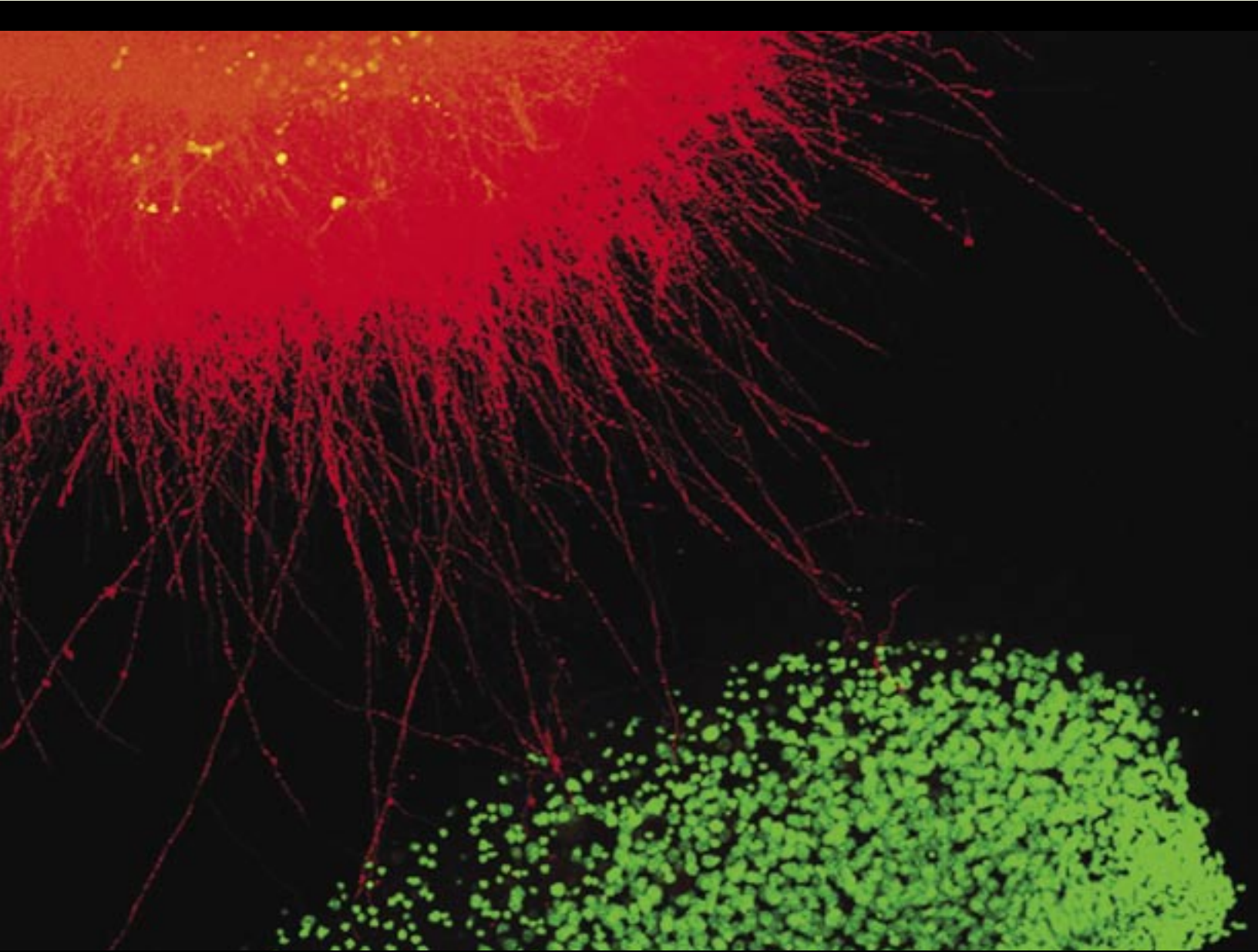


Research Highlights 2005

The Saban Research Institute of Childrens Hospital Los Angeles



Breakthrough Science, Brighter Futures

KECK
SCHOOL OF MEDICINE **USC**

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 of The Saban Research Institute of Childrens Hospital Los Angeles.

On the cover: This microscopic image illustrates how nerve fibers find their targets in the brain. Here, neural axons from the forebrain (labeled with red dye) reach out to tissue from the hypothalamus, in green. The goal: to weigh the influence of genetic background, age and environmental factors on the development of neural connections.

For more on the Neuroscience Program, see page 12.



Dr. Yves A. DeClerck

Note from the Director

A PLACE WHERE IDEAS GROW

On behalf of The Saban Research Institute, I am pleased to share with you the second issue of *Research Highlights*, which provides our constituents with an annual update on some of the most significant and exciting scientific developments of the past year. At the same time, we recognize the community of committed donors who help to make our pediatric research mission possible.

In this year of discoveries, I am proud to note that we have grown in our research talent, our extramural funding and our philanthropic support. A recurring theme has been the intrinsic value of collaboration.

When you meet the gaze of a child suffering from life-threatening illness, you want to give him or her every opportunity to prevail and thrive. As a physician for more than 25 years, I experience this feeling with each of my young cancer patients. As an oncology researcher, I recognize that many of the most promising treatments are the result of strong collaborations among talented investigators.

As scientists, we do not – cannot – work alone. Within The Saban Research Institute, our investigators work as teams, across disciplines and with colleagues at the University of Southern California and other institutions across the country. In this way, ideas spark and fuel each other.

Another vital collaboration is with our philanthropic partners. To you, we are sincerely grateful. Working together, we can ensure that lifesaving breakthroughs continue. For this is a place where ideas grow, so that children can grow.

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

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

Overview of the Year

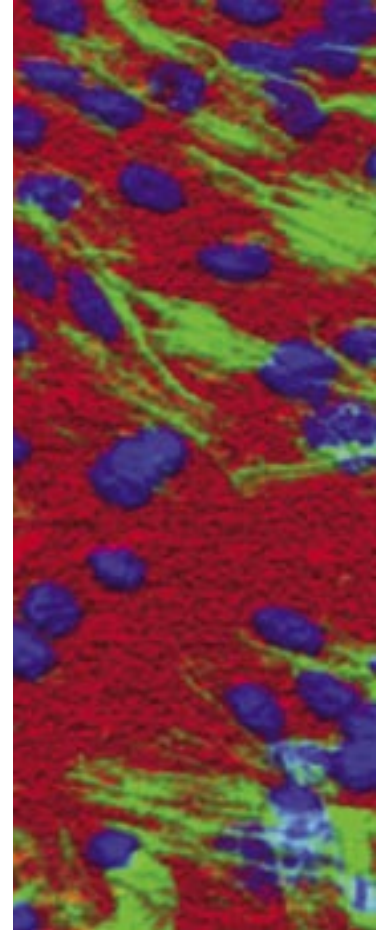


To gain significant ground in the hard-won fight against disease, scientists must be willing to ask difficult questions, test paths never taken and defy previously accepted wisdom. In 2005, researchers at The Saban Research Institute advanced our understanding of cancer, deadly blood and immune deficiency diseases, diabetes, bacterial meningitis, life-threatening respiratory problems and many other conditions.

These dedicated investigators explored the potential power of human stem cells and tissue engineering. They employed inventive imaging technologies, whether to track development of brain tumor cells, follow stem cells in action or measure so-called “bad fat” in the body.

AMONG THE TOP BREAKTHROUGHS OF THE YEAR:

- The first-ever study to demonstrate that a small gene-silencing particle wrapped in nano-sized sugar polymers can inhibit tumor cells. The study, published in the October 2005 issue of the journal *Cancer Research*, has broad implications for all cancers. It involved a collaboration of Saban Research Institute scientists Timothy J. Triche, MD, PhD*, and Siwen Hu, MD, PhD, with chemical engineering experts from the California Institute of Technology. (See page 5.)
- The discovery of new molecules and pathways that govern the development of the lung during embryonic life, by a team of researchers in the Developmental Biology Program that included David Warburton, DSc, MD, FRCP*; Saverio Bellusci, PhD*; and Stijn De Langhe, PhD. The findings recently appeared in two issues of the journal *Developmental Biology*. (See page 8.)
- The unraveling of a mechanism by which tumor cells in neuroblastoma, a nerve-cell cancer, escape surveillance of the immune system. Robert C. Seeger, MD*, and Leonid S. Metelitsa, MD, PhD*, found that an oncogene (a gene associated with cancer) called MYCN prevents the entrance of Natural Killer immune cells into the tumor. The study, published in the journal *Experimental Medicine*, is part of a five-year, \$8 million federal grant led by Dr. Seeger to develop new therapies for neuroblastoma. Also involved are Yves A. DeClerck, MD*; Barry J. Maurer, MD, PhD*; C. Patrick Reynolds, MD, PhD*; Judith G. Villablanca, MD*; Hiro Shimada, MD, PhD*; and K.K. Matthay, MD, University of California, San Francisco.
- Development of a non-invasive Magnetic Resonance Imaging (MRI) technique to measure iron in the liver of patients with



Each blue dot in this microscopic image represents an adult stem cell. Scientists at The Saban Research Institute are collaborating to discover and unleash the potential healing power of stem cells.

thalassemia, which may lead to new therapies. The findings of John C. Wood, MD, PhD*, and Thomas D. Coates, MD*, were reported in a recent issue of the journal *Blood*. (See page 17.)

- Employment of innovative MRI techniques to obtain accurate measures of fat accumulation in certain “deep” organs such as the pancreas and muscle, which are associated with insulin resistance in type 2 diabetes. The study led by Arzu Kovanlikaya, MD*; Vicente Gilsanz, MD, PhD*; and Steven Mittelman, MD, PhD, appeared in the journals *Pediatric Radiology* and *Academic Radiology* in 2005. (See page 4.)

NATIONAL INSTITUTES OF HEALTH (NIH) FUNDING 1999-2005

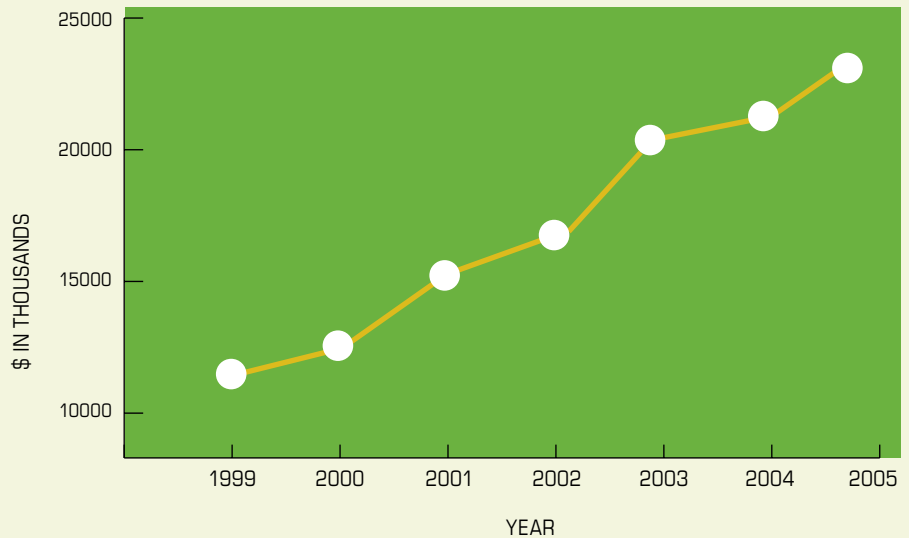
For biomedical research at The Saban Research Institute

FUNDING NEW KNOWLEDGE

Our scientists continue to succeed in attracting key research grants. In 2005, external research funding to Childrens Hospital Los Angeles increased for the fifth consecutive year, from \$33.9 million to \$36.6 million. Major grants were obtained in the areas of cancer, genomics, neuroblastoma, lung injury and stem cells.

Donald B. Kohn, MD*, recently was awarded a three-year, \$2.4 million training grant from the California Institute for Regenerative Medicine, established in early 2005 with the passage of Proposition 71, the California Stem Cell Research and Cures Initiative. We were the only pediatric institution to receive such a grant. In addition, many junior faculty members obtained their first federal grants in 2005. (See page 17.)

Philanthropic donors share our commitment to improve the health of children. In 2005, The Saban Research Institute received a new \$1.5 million endowed chair program from The Saban Family Foundation. The support of the volunteer Associate and Affiliate Groups has been invaluable. The Pasadena Guild raised \$3 million for the Developmental Biology Program, while Las Madrinas completed a \$2.4 million endowment for the Gene, Immune and Stem Cell Therapy Program. In addition, the 25 Associate groups raised \$5 million for the Neuroscience Program and Imaging Research Initiative.



In Fiscal Year 2005, funding from the NIH reached \$23.7 million, a 16.2 percent jump over 2004's \$20.4 million. The number of NIH-funded projects increased to 59 from 49 in Fiscal Year 2004. The Saban Research Institute ranks among the top five research facilities in the nation in NIH funding.

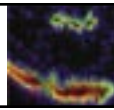
AN ENERGIZING FUTURE

As we go forward, we continue to develop interdisciplinary programs within our own Institute and with other major institutions to attract funding and spur new discoveries.

Our close relationship with the University of Southern California (USC) – another great strength – was reinforced in 2005, with joint ventures in neuroscience and genomics and the advent of the USC-CHLA Institute for Pediatric Clinical Research. Our collaboration with USC's Norris Comprehensive Cancer Center earned renewal of a five-year core grant from the National Cancer Institute.

Nine new faculty members joined our ranks in 2005. Among them is Richard Simerly, PhD*, who leads a new research program in Neuroscience. (See page 12.) In addition, Sylvester "Sac" Carreathers, who has extensive experience in management of federal grants, became The Saban Research Institute's administrative director.

Clinical research remains a key priority at Childrens Hospital Los Angeles. We have identified additional space for this effort and are currently recruiting a director of clinical research. With the synergy from this initiative, we will more rapidly turn fundamental discoveries into vitally needed treatments.



Left to right: Vicente Gilsanz, MD, PhD; Steven Mittelman, MD, PhD; Mitchell Geffner, MD; and Arzu Kovanlikaya, MD

BONE AND BODY COMPOSITION INITIATIVE

DIRECTOR: VICENTE GILSANZ, MD, PHD*

The escalating rate of obesity and its accompanying medical complications in children are leading scientists to explore the biology of adipose (fat tissue) and the significance of its distribution in the different regions of the body.

Using novel magnetic resonance imaging (MRI) techniques, Arzu Kovanlikaya, MD*, and Vicente Gilsanz, MD, PhD, in the Department of Radiology, compared the distribution and volume of fatty tissue in the liver, pancreas and muscle of 15 healthy lean and obese teenagers between the ages of 14 and 17. The researchers found a strong correlation between obesity and increased levels of “bad fat” – called that because of its destructive effect on organ function. “On average, obese teenagers stored 50 to 150 percent more fat than lean subjects,” notes Dr. Kovanlikaya.

The researchers employed advanced MRI technology known as a three-point Dixon technique to obtain accurate quantitative



Cutting-edge magnetic resonance imaging techniques are helping to reveal fat deposits in such organs as the liver, which can't be seen with standard imaging methods.

measures of fat accumulation in the intra-abdominal organs – areas not accessible by standard imaging methods.

Further studies are planned to establish the degree to which fat accumulation in the pancreas is associated with decreased insulin secretion. This noninvasive assessment could eventually become a tool for diagnosis and prevention of type 2 diabetes, which develops when the body becomes resistant to insulin produced by the pancreas.

Drs. Kovanlikaya and Gilsanz are working in close collaboration with two physicians in the Center for Endocrinology, Diabetes and Metabolism: Mitchell Geffner, MD*, principal investigator on the TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth) clinical research study; and Steven Mittelman, MD, PhD, an endocrinology fellow who has authored several publications on insulin metabolism. The team's findings appeared this year in the journals *Pediatric Radiology* and *Academic Radiology*.



Timothy J. Triche, MD, PhD, with Sitara Waidyaratne, research specialist

CANCER PROGRAM

DIRECTOR: ROBERT C. SEEGER, MD*

A groundbreaking collaboration in 2005 resulted in a novel, Trojan Horse-style delivery system that transports gene-silencing nanoparticles into tumor cells and could help pave the way for individualized cancer therapies.

The innovative experiment combined the skills of a cancer biology group and a team of chemical engineers. The two teams were led by Timothy J. Triche, MD, PhD*, chief of the Department of Pathology and Laboratory Medicine at Childrens Hospital Los Angeles; Siwen Hu, MD, PhD, a postdoctoral fellow in Dr. Triche's lab at The Saban Research Institute; and Mark E. Davis, PhD, at the California Institute of Technology.

In the pioneering study, recently published in the journal, *Cancer Research*, a protein called transferrin that normally delivers iron into cells was attached to the surface of nanoparticles to smuggle siRNA (short interfering RNA) into tumor cells in mice with Ewing's Sarcoma. This rare, often deadly bone cancer strikes children and young adults.

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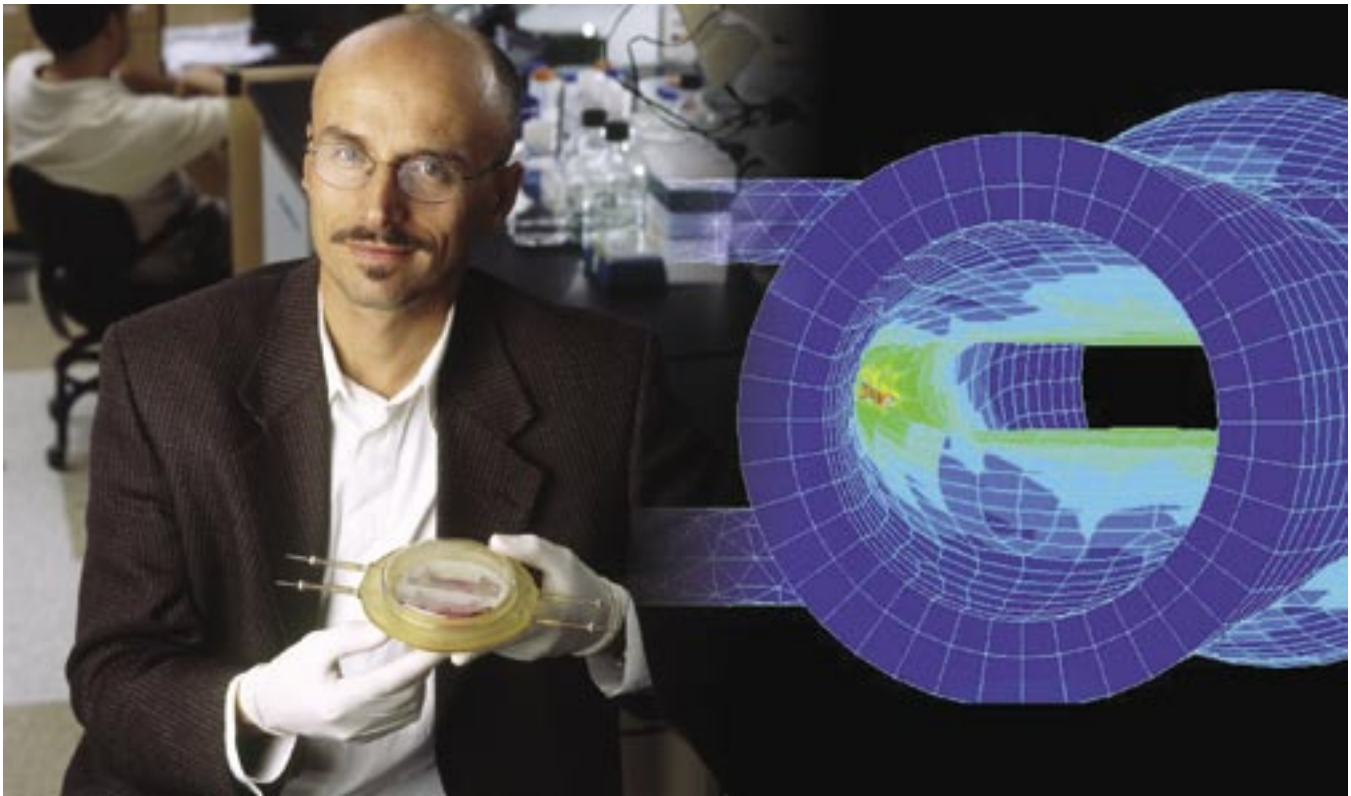
— Dr. Robert Seeger

The siRNA was encased in nanoparticles composed of cyclodextrin (similar to the sugar dextrose). The nanoparticle “vehicle” is essential because within minutes of exposure to the blood stream, all “naked” RNA is destroyed.

The target was a growth-promoting gene in Ewing's Sarcoma called EWS-FLI1. Once the siRNA reached the EWS-FLI1 inside the cells, it effectively shut down the genetic machinery of the tumor cell proliferation, preventing further growth and leading to tumor cell death.

“Our goal is to establish a generalizable model of targeted cancer therapy,” notes Dr. Triche, who received a five-year, \$15 million grant from the National Institutes of Health for this research. “The benefits for children and adults are obvious.”

Now, The Saban Research Institute researchers are exploring another technology with Lawrence Berkeley National Laboratory that will enable them to create “cocktails” of molecules and siRNAs, maximizing the dose effect and targeting. Early data are encouraging.



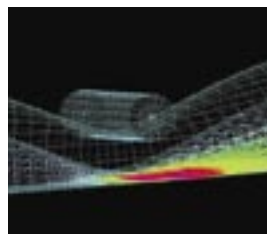
Ivan Vesely, PhD. Right: A computer simulation of an artery being pinched

CARDIOVASCULAR RESEARCH PROGRAM

DIRECTOR: IVAN VESELY, PHD*

Surgeons at Childrens Hospital Los Angeles often treat newborn children with hypoplastic left heart syndrome (HLHS), a condition in which the left side of the heart fails to develop during pregnancy – the most common lethal condition in congenital heart disease. With the left ventricle either missing or too small to function after birth, it cannot pump blood through the body. Without effective intervention, the child dies shortly after birth.

The answer is surgical reconnection of the various veins and arteries that flow between the heart, lungs and remainder of the body. Fabricating such connections properly requires considerable judgment. The flow between the lungs and the rest of the body must be properly divided and balanced to prevent pressure overload in the lungs, for example, which can lead to death from related complications within a few years. To make this division, cardiovascular surgeons rely on shunts, artificially created passageways between two parts of the heart.

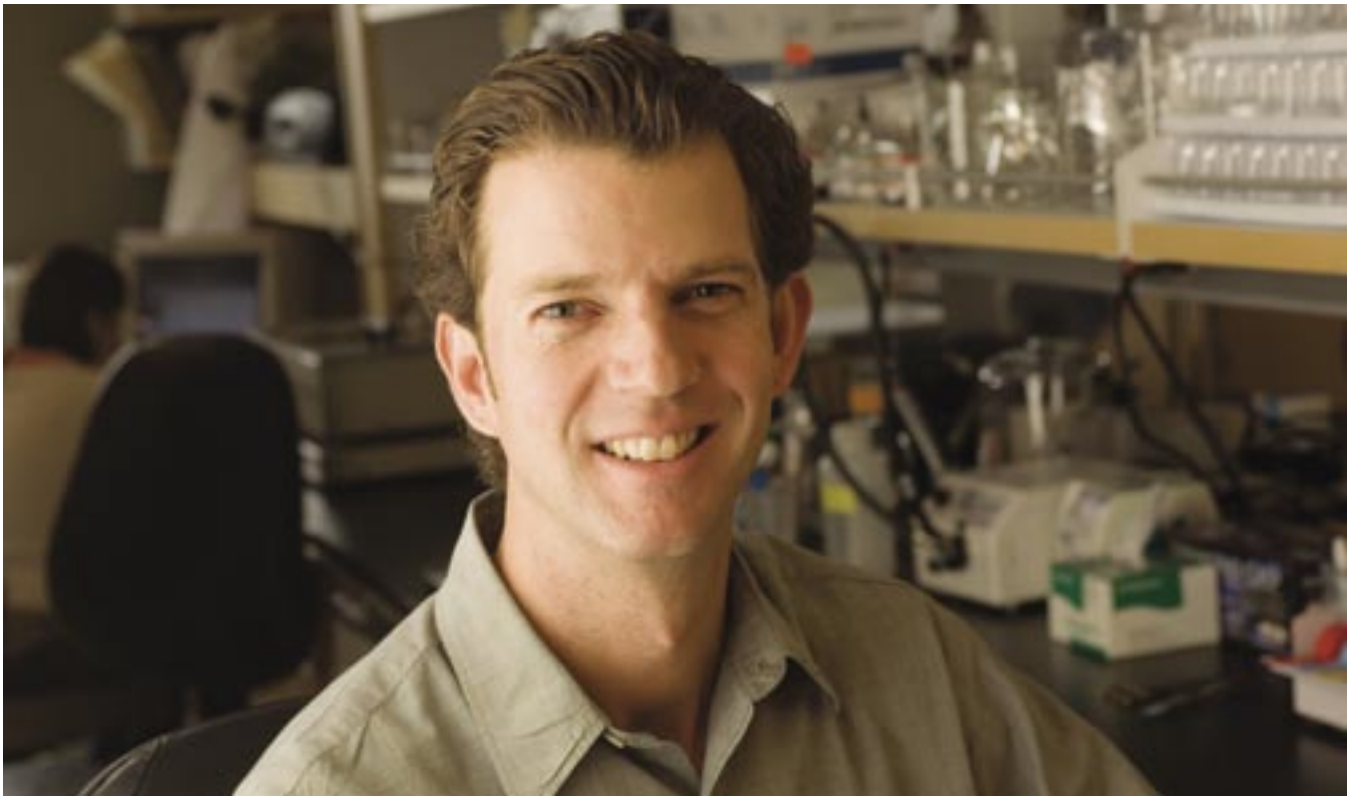


A computer simulation of the blood flow velocities through a constricted artery – another tool for surgeons in visualizing an optimal surgical plan.

The difficulty has been that surgeons have no quantitative methods, measurements or simulations on which to base their decision on sizing of the shunts and balancing the flow.

To fill this need, investigators in the Cardiovascular Research Program currently are setting up a computer modeling infrastructure to enable mathematical modeling of the complex flow patterns through the reconstructed hearts of HLHS patients.

“A great deal of computational modeling involves running ‘what-if’ simulations to determine the relative merit of design modifications,” notes Ivan Vesely, PhD, program director, and the H. Russell Smith Foundation Endowed Chair in Cardiothoracic Research. “By having such a modeling system, surgeons and engineers can work together to simulate a particular surgical approach, optimize the procedure on the computer and then do the surgery.” This will lead to better fluid dynamics in the neonatal heart, which ultimately will mean greater survival of these very delicate patients.



Stephen E. Lankenau, PhD

COMMUNITY, HEALTH OUTCOMES, AND INTERVENTION RESEARCH PROGRAM

DIRECTOR: MICHELE D. KIPKE, PHD*

In the 1960s, the drug ketamine debuted as a new anesthetic. By the 1980s, it evolved into a recreational drug known as “Special K”, fueled by an emerging dance and rave culture among urban youth. While ketamine is commonly administered intra-nasally, in the last decade injecting it has gained popularity among underground users. Yet little is known about ketamine injection practices or the people who are using it. Stephen E. Lankenau, PhD*, wants to find out.

Dr. Lankenau, a member of the Community, Health Outcomes, and Intervention Research Program, is principal investigator on a four-year project to examine ketamine injection and its unanticipated medical consequences such as infectious diseases, drug dependence, overdose and cognitive impairment. The ethnographic research, funded by the National Institute on Drug Abuse, focuses on high-risk, out-of-treatment populations, including homeless youth and injection drug users in Los Angeles,

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— Dr. Stephen Lankenau

New York and New Orleans (interviews done pre-Hurricane Katrina). Co-investigator is Michael Clatts, PhD, of the National Development and Research Institutes, Inc., in New York.

The study’s first phase, which includes interviews in each city with 50 drug users between the ages of 16 and 25, will be completed by the end of 2005. Interviewers have gathered data about ketamine injection, history of drug use, presence of infectious disease such as HIV and hepatitis, social networks and demographic background.

The second phase will involve a two-year study in Los Angeles of drug use patterns and associated medical risks, including how ketamine injection impacts users’ relationships with family, friends and school.

“By studying three cities, we are able to understand local differences in drug markets and practices,” says Dr. Lankenau. “By following one group over time, we begin to gain a more complete picture of each person.”



Left to right: John Groffen, PhD; David Warburton, DSc, MD, FRCP; and Nora Heisterkamp, PhD*

DEVELOPMENTAL BIOLOGY PROGRAM

DIRECTOR: DAVID WARBURTON, DSc, MD, FRCP*

A multi-institution effort to unravel the causes of chronic lung disease in premature infants is demonstrating the value of collaboration. “We work together in a synergistic manner to accelerate our rate of knowledge of this important disease,” says David Warburton, DSc, MD, FRCP, principal investigator, and director of the Developmental Biology Program in The Saban Research Institute.

In 2005, the National Heart, Lung, and Blood Institute of the National Institutes of Health renewed the original five-year, \$8 million Program Project grant to investigate human lung development, injury and therapeutic intervention.

“Over the last five years, we have made tremendous progress in understanding premature lung development and the fundamentals of lung disease,” says Dr. Warburton.

Investigators have discovered that premature infants, whose lungs are unprepared to handle the challenge of normal breathing, have excessive amounts of a growth factor

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— Dr. David Warburton

called “TGF- β (beta)” in their airways which interferes with normal lung function. The researchers were able to reproduce this effect in animal studies. Over the next five years, they hope to identify the mechanisms that create this excess growth factor and develop ways to correct it.

The investigators bring various skills to the collaborative process.

Dr. Warburton has nearly 20 years of experience in understanding how the lung grows and the impact of premature delivery on lung development. He is joined by John Groffen, PhD*, from The Saban Research Institute, who has a background in cancer research and brings insights into how the body regulates inflammation; Parviz Minoo, PhD*, who has made major discoveries in chronic pediatric lung disease; Rik Derynck, PhD, University of California, San Francisco, who has extensively researched fundamental mechanisms of TGF- β ; and Jack Gauldie, PhD, McMaster University in Canada, an expert on the effects of TGF- β on adult lung disease.



Carolyn Lutzko, PhD, left, and Gay Crooks, MD

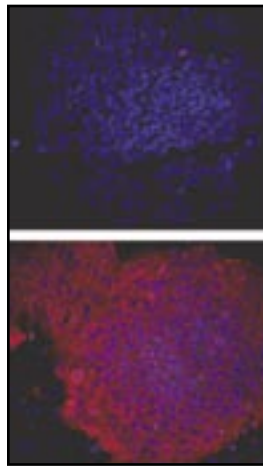
GENE, IMMUNE AND STEM CELL THERAPY PROGRAM

DIRECTOR: DONALD B. KOHN, MD*

Embryonic stem cells have the potential to become all the cells in the body. The problem: scientists don't yet know how to control that process. One researcher who is trying to unlock that mystery is Carolyn Lutzko, PhD*, a stem cell biologist in the Gene, Immune and Stem Cell Therapy Program. It is one aspect of the Childrens Hospital Los Angeles Stem Cell Project, established in 2005 at The Saban Research Institute and led by Gay Crooks, MD*.

The interdisciplinary, collaborative project involves more than 30 researchers within The Saban Research Institute, giving it a unique advantage in California to apply embryonic and adult stem cell technologies as therapies for many childhood and adult diseases.

Dr. Lutzko began studying bone marrow stem cells as a graduate student in Dr. Kohn's laboratory. "I found them fascinating because they regenerate new blood cells throughout our lives, even following serious injuries."



In the top photo, these human embryonic stem cells have yet to acquire specialized features of other cells. In bottom photo, red staining indicates the stem cells are positive for a marker of stem cells.

Over the past three years, her lab in The Saban Research Institute has gained invaluable experience working with two federally approved stem cell lines. Her research focuses on determining exactly how a stem cell copies itself and which processes signal its decision to differentiate or specialize into another type of cell. In particular, Dr. Lutzko is interested in two cell types: blood and lung. So far, experiments into creating blood cells have shown promise.

She finds motivation at Childrens Hospital for her painstaking work. "The focus of our research isn't the experiment itself," she says. "Behind every experiment is a child waiting to be treated."

Stem cells have to be increased in numbers in the laboratory before therapeutic applications may be possible. Serious clinical trials or an embryonic stem cell-based therapy may be more than a decade away. However, notes Dr. Crooks, "The potential of stem cells may be even greater than thought a decade ago."



Michael Rosol, PhD

IMAGING RESEARCH INITIATIVE

DIRECTOR: MARVIN D. NELSON, JR., MD, MBA*

A gene from the firefly or the sea pansy, a soft coral, is helping researchers to employ an innovative imaging technique known as “in vivo bioluminescence.” Scientists tag human cells with the “glowing” gene to observe them under various conditions in living organisms. Michael Rosol, PhD*, associate director of the Small Animal Imaging Research Core in The Saban Research Institute, is using this cutting-edge tool to follow brain tumor cells over time and study their development and response to different types of treatments.

Once the tagged human tumor cells are infused into mice, the light produced by the cells makes them easier to observe. This highly sensitive imaging is useful for early detection of very small tumors or subtle changes within a tumor.

In 2005, Dr. Rosol and his team began testing the effectiveness of a new compound that selectively targets tumor tissue and increases the leakiness of the blood

“**Imaging is about answering questions. This non-invasive tool supports and accelerates cancer therapy in the clinic.**”

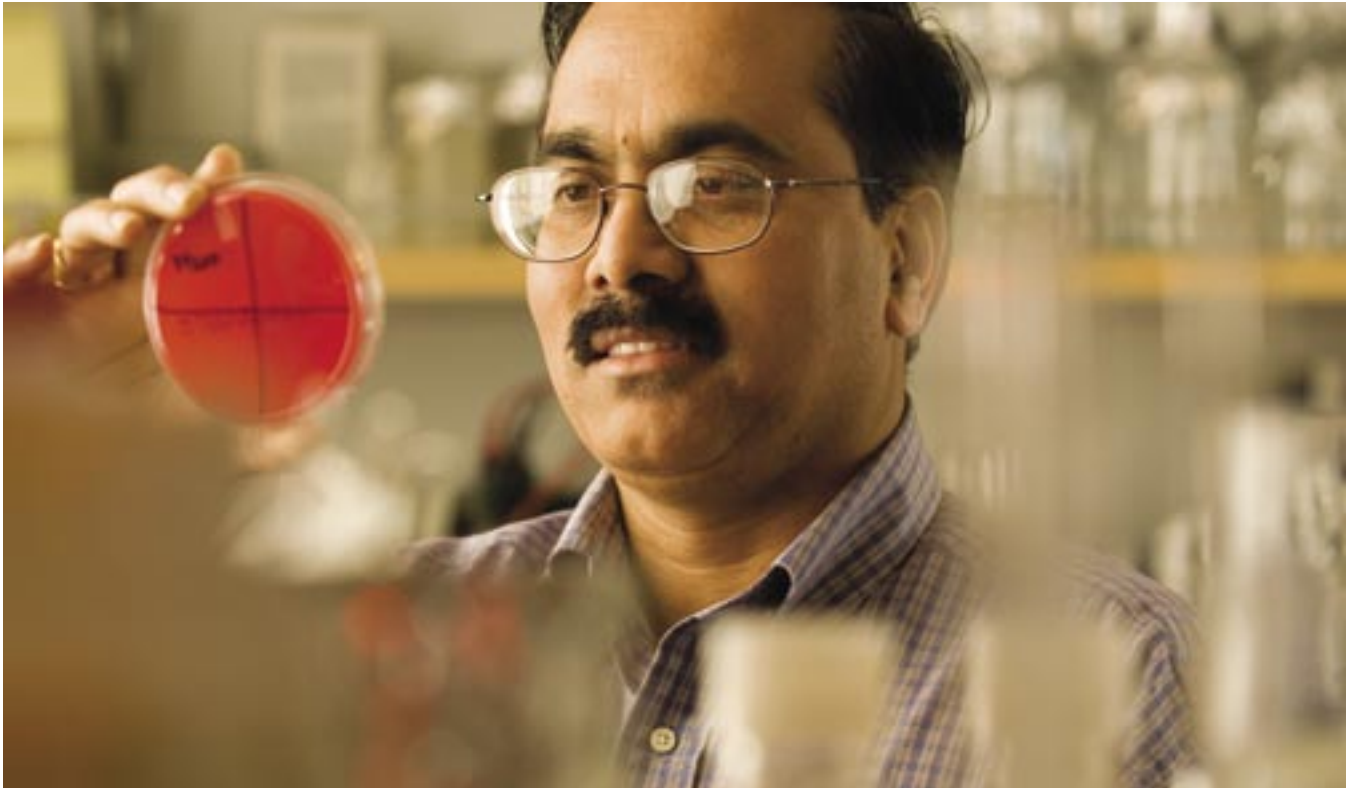
— Dr. Michael Rosol

vessels within tumors, which enhances the effectiveness of therapies.

“Imaging is about answering questions,” says Dr. Rosol. “This noninvasive tool acts to support and accelerate cancer therapy in the clinic.”

In addition to brain tumor research, Dr. Rosol has been awarded a grant by the Radiological Society of North America Research and Education Foundation for developing methods to study how human stem cells graft and grow in the bone marrow after they are transplanted. He is working in collaboration with Gay Crooks, MD*, and Marvin D. Nelson, Jr., MD, MBA, head of the Department of Radiology.

Together they published a groundbreaking study in the prestigious journal *Blood* in 2003 showing how bioluminescence imaging can be used to track stem cells throughout the body. The study was the first to show how stem cells behave in the bone marrow following transplantation.



Prasad Rao Nemani, PhD

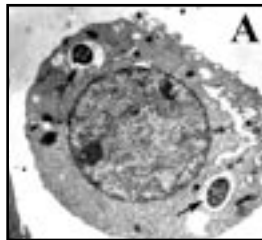
MICROBIAL PATHOGENS INITIATIVE

DIRECTOR: WILBERT H. MASON, JR., MD, MPH*

Watching infectious diseases take the lives of many children in his native India led Prasad Rao Nemani, PhD*, to his passion for investigating ways to prevent bacterial meningitis in newborns. “I want to do something for society, for children everywhere,” he says.

Bacterial meningitis in newborns is the most common serious infection of the brain, causing 50 to 60 percent of survivors to suffer from mental retardation and hearing loss. Several pathogens are responsible for meningitis, such as *E. coli* K1, Group B streptococcus and *Listeria monocytogenes*. However, a recent surge of *E. coli* infections in the United States is putting an increasing number of newborns at risk. Once these disease-producing microorganisms enter the blood, they multiply and cross the blood-brain barrier into the central nervous system.

Treatment remains a challenge because diagnosing the disease is difficult until it reaches the final stage of infection. Antibiotics are not always successful due to the release of toxins from dead bacteria, which cause

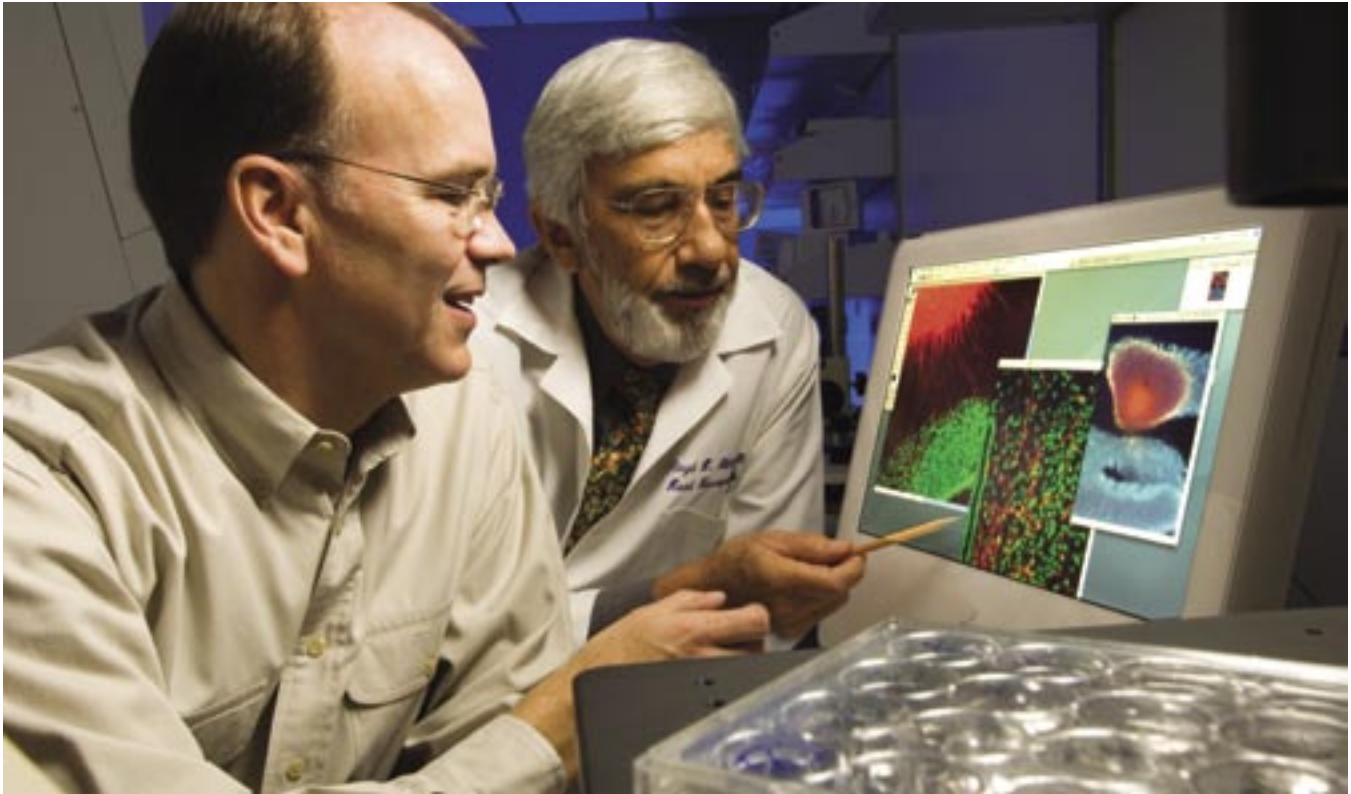


Research is seeking answers to infectious diseases in newborns. These slides show immune cells invaded by the pathogen *E. coli* K1, one hour after incubation with bacteria (A) and 24 hours after (B), when bacteria have multiplied.

adverse reactions in the body. Compounding the problem is the newborn’s underdeveloped immune system, which cannot efficiently battle the infection.

In an attempt to circumvent these issues, Dr. Nemani is focusing his research on preventing bacterial meningitis from ever developing in newborns. He and his team have studied the *E. coli* interactions with brain cells and the immune system for several years. They have identified a protein on the surface of the bacteria called “OmpA” that plays a key role in development of meningitis in newborn rats, which has several important similarities to the human disease.

The researchers recently found that *E. coli* can enter, survive and multiply in “macrophages” – cells that normally protect the body from invading bacteria. “Understanding how the bacteria subvert our defenses will provide clues to eventually develop preventive strategies,” says Dr. Nemani. These may include immunizing mothers carrying the *E. coli* bacteria.



Richard B. Simerly, PhD, left, with Floyd H. Gilles, MD

NEUROSCIENCE PROGRAM

DIRECTOR: RICHARD B. SIMERLY, PHD*

CHILDRENS BRAIN CENTER DIRECTOR: FLOYD H. GILLES, MD*

The Neuroscience Program, a new program at The Saban Research Institute, began to take shape in 2005 with the recruitment of its director: Richard B. Simerly, PhD, formerly a senior scientist at the Oregon National Primate Research Center and Oregon Health & Science University.

The laboratories Dr. Simerly is establishing in The Saban Research Institute will provide a nucleus of basic science in developmental neurobiology, which will feed a wide range of research projects within the Childrens Brain Center, directed by Floyd H. Gilles, MD, head of the Division of Neurology at Childrens Hospital Los Angeles.

Dr. Simerly was recruited in a nationwide search by a multi-institution committee with representatives from the California Institute of Technology and from the University of Southern California's University Park Campus and Keck School of Medicine.

"It's wonderful to collaborate with a new group of researchers interested in brain development," he says. "By working with



Neuroscientists are exploring brain development in a variety of ways. In this image, two sections of a forebrain are combined to study how neural connections form between the regions.

neurobiologists at the University Park Campus and at the Keck School of Medicine, we will be well-positioned to make significant progress."

Dr. Simerly currently has three grants from the National Institutes of Health for research centered on the development of neurocircuits in the forebrain, responsible for controlling basic homeostatic functions such as feeding and reproduction.

His newest focus – an appetite-suppressing hormone known as leptin – is causing excitement in the field of obesity. Experiments in Dr. Simerly's lab recently found that leptin acts as a kind of developmental signal which molds neural circuits, then impacts them later in life – early evidence the brain may be programmed from birth for obesity.

"If we could identify a way to extend the brain's plasticity period, it may be possible to rescue damaged circuits at any time of life," says Dr. Simerly, referring to the early period when the brain is organizing itself. "Although only a dream at present, this exciting prospect motivates our current research efforts."



Francine R. Kaufman, MD, with patient Bekah Echeverria, 9

CENTER FOR ENDOCRINOLOGY, DIABETES AND METABOLISM

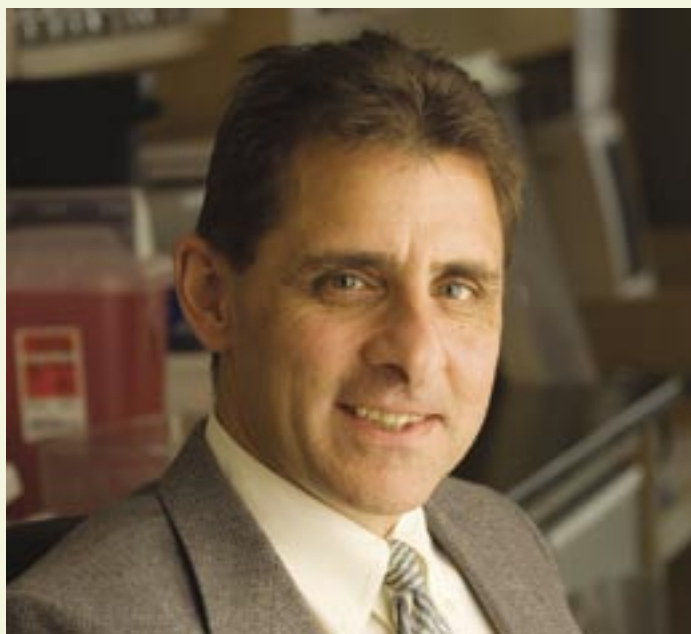
DIRECTOR: FRANCINE R. KAUFMAN, MD*

America is in the midst of an epidemic, with soaring rates of obesity and type 2 diabetes. “What was once a disease of our grandparents is now a disease of our children,” says Francine R. Kaufman, MD, head of Childrens Hospital’s Center for Endocrinology, Diabetes and Metabolism.

Dr. Kaufman details the issues in her new book, published in 2005: *Diabesity: The Obesity-Diabetes Epidemic That Threatens America – and What We Must Do to Stop It*. In its review, *Publishers Weekly* said this “first-rate, important book . . . is a call to arms for policymakers and those in the health-care industry.”

Dr. Kaufman, past president of the American Diabetes Association (2002-2003), was first inspired to join the fight against the disease at age nine when her grandmother developed type 2 diabetes.

Now, she is study chair of the first nationwide clinical trial into lifestyle changes and type 2 diabetes funded by the National Institutes of Health, called TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth), launched in 2004. Unless current trends are stemmed, experts predict more than 10 percent of Americans will have diabetes in a few years, Dr. Kaufman warns. In the multifaceted solution, individuals, families, schools, corporations, communities and government all play a role.



Richard Sposto, PhD

CHILDRENS CENTER FOR CANCER AND BLOOD DISEASES

DIRECTOR: STUART E. SIEGEL, MD*

CO-DIRECTOR: DONALD B. KOHN, MD*

Statistical science may seem to be all about the numbers. But Richard Sposto, PhD*, says it’s really about helping sick children get better.

An expert in designing clinical studies, Dr. Sposto joined Childrens Hospital Los Angeles in 2005, coming from a respected career as senior statistician with the Children’s Oncology Group (and its predecessor, the Children’s Cancer Group), a national consortium of pediatric hospitals that promotes clinical research.

Now, as director of Biostatistics/Bioinformatics in the Childrens Center for Cancer and Blood Diseases, his expertise serves to support research efforts in The Saban Research Institute and within the USC-CHLA Institute for Pediatric Clinical Research, where he is a member of the Therapeutic Advances in Childhood Leukemia consortium.

Innovative statistical methods for analyzing clinical and biological data, coupled with advanced technologies for storing and retrieving information, enhance the ability of researchers to determine the safety, activity and benefits of new drugs and new drug combinations, while protecting patients in clinical trials.

“I’m working closely with outstanding scientists in clinical oncology,” notes Dr. Sposto. “Together, we hope to accelerate our progress in developing new treatments for children with cancer by asking the right questions and using quality data.”



Punam Malik, MD, left, and Thomas D. Coates, MD

GENERAL CLINICAL RESEARCH CENTER

DIRECTORS: KENNETH WEINBERG, MD*
AND JOHN C. WOOD, MD, PHD*

The General Clinical Research Center (GCRC) supports a broad spectrum of clinical research, including projects from endocrinology, ophthalmology, gene therapy, neurology and oncology. A recently sponsored project by Punam Malik, MD*, examines possible indicators for onset of a deadly syndrome called Acute Chest Syndrome, which develops without warning in people with sickle cell disease, causing chest pain, coughing, fever and difficulty in breathing. The syndrome is responsible for 25 percent of deaths among patients afflicted with the inherited chronic red blood cell disorder.

Under investigation is a correlation between “placental growth factor,” a protein found in red blood cells, and Acute Chest Syndrome. Dr. Malik is working in collaboration with Thomas D. Coates, MD*, section head of Hematology at the Childrens Center for Cancer and Blood Diseases, and Thomas G. Keens, MD*, division of Pulmonology.

The higher the growth factor, the researchers have observed, the more likely a patient will suffer a “sickle crisis” marked by severe pain in arms, legs, chest or abdomen. Within three days of hospital admission for sickle crisis, 50 percent of patients developed the pneumonia-like illness. “My hope is that one day we will have an antibody to block this syndrome’s devastating effect,” says Dr. Malik.



Mark S. Sklansky, MD

THE HEART INSTITUTE

DIRECTOR: VAUGHN A. STARNES, MD*

Congenital heart disease (CHD) remains the most common major anomaly to affect children at birth. Prenatal screening requires time and expertise not available in local obstetricians’ offices, where such tests typically take place. As a result, most CHD goes undetected until after birth.

The Fetal Cardiology Program, under the direction of Mark S. Sklansky, MD*, combines state-of-the-art clinical practice and academic leadership in prenatal detection and diagnosis of CHD. With rapid advances in fetal cardiology, screening methods are now useful in the first trimester (10 to 14 weeks), thanks to improvements in image resolution and the discovery of nuchal translucency thickness (fluid behind the neck of a fetus) as an indicator for CHD.

For the past decade, Dr. Sklansky has been developing 3D approaches to fetal cardiac imaging. Collaborative research by the Fetal Cardiology Program and the Institute for Maternal and Fetal Health, led by Istvan Seri, MD*, an alliance between Childrens Hospital Los Angeles and the Keck School of Medicine, has demonstrated the feasibility of using 3D fetal echocardiography as a screening tool for CHD. “With such interdisciplinary efforts, we can offer our patients a unique and seamless transition between prenatal and postnatal care,” says Dr. Sklansky.



David L. Skaggs, MD, with patient Alex Ito, 3

CHILDRENS ORTHOPAEDIC CENTER

DIRECTOR: VERNON T. TOLO, MD*

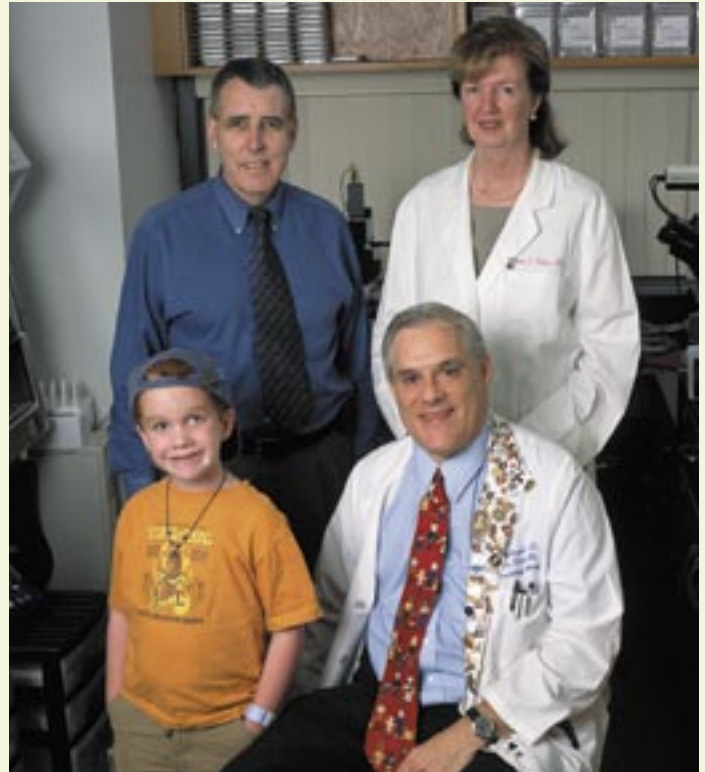
An innovative surgical treatment being advanced in the Childrens Orthopaedic Center is giving children with congenital spine and thoracic deformities a chance to breathe easier.

By implanting a titanium rib prosthesis in a child's rib cage, orthopaedic surgeon David L. Skaggs, MD*, is able to widen the chest cavity and lung capacity for children with such life-threatening respiratory problems as asphyxiating thoracic dystrophy (a condition where the chest does not grow), congenital scoliosis (curved spine) and small chests or fused ribs. As the child grows, the device is expanded with a small incision.

Dr. Skaggs was selected to learn the breakthrough procedure after winning the international Young Investigator Award from the Pediatric Orthopaedic Society of North America. Childrens Hospital is one of only seven hospitals in America that participated in the Administration's U.S. Food and Drug Administration's clinical trials of this device.

Dr. Skaggs and co-surgeon James Stein, MD*, made headlines in 2002 as the first in California to perform titanium rib implantation. Since then, Dr. Skaggs has performed more than 30 such groundbreaking surgeries, most recently on a patient who came from Hawaii.

"This is probably the single greatest advance I've seen," says Dr. Skaggs. "Kids who were otherwise going to die are now out playing soccer."



From upper left: C. Patrick Reynolds, MD, PhD; Roberta G. Williams, MD; Stuart E. Siegel, MD; and patient Zachary Marks, 7.

USC-CHLA INSTITUTE FOR PEDIATRIC CLINICAL RESEARCH

PRINCIPAL INVESTIGATORS: ROBERTA G.
WILLIAMS, MD*, AND STUART E. SIEGEL, MD*

A \$15 million gift from an anonymous donor in 2004 created the USC-CHLA Institute for Pediatric Clinical Research (IPCR), currently housed at The Saban Research Institute. "The IPCR's focus is to conduct translational and clinical research leading to new therapies for serious childhood illnesses," says Stuart E. Siegel, MD, co-principal investigator of the IPCR.

In 2005, the National Cancer Institute awarded three IPCR investigators – C. Patrick Reynolds, MD, PhD*; Nino Keshelava, MD*; and Barry J. Maurer, MD, PhD* – with a contract for the sole cell culture testing component of its new Pediatric Preclinical Testing Program, which will determine if laboratory activity on new drugs warrants clinical studies. "It is particularly exciting that one of the agents developed in our laboratories recently has entered clinical trials," says Dr. Reynolds, head of the IPCR's Developmental Therapeutics Program.

With childhood cancers attacking relatively few youngsters, pharmaceutical companies often are reluctant to invest in new drug development. "We intend to have a worldwide impact on treatment of pediatric diseases by bringing new cures and preventive measures from concept to reality," says Roberta G. Williams, MD, co-principal investigator of the IPCR.

“
Our
strategy
to identify,
engage and
educate
motivated
students
with an
aptitude for
research
is working.”

— Dr. Emil Bogenmann



Left to right: Traci Kuratomi, Sandi Soderstrom, Maral DerSarkissian and Paola Guevara, students from La Crescenta Valley High School who took part in The Saban Research Institute's High School Research Education Program in 2004. Participating but not pictured: Jessica Friedland and Stephanie Dusaban.

SCIENCE EDUCATION

In a troubling nationwide trend, the number of young investigators and physician-scientists with doctoral and medical degrees interested in pursuing medical research careers has declined over the past decade. The Saban Research Institute has been working to help reverse this development.

In 2001, the American Academy of Pediatrics issued a paper recommending that research education and training begin before medical school. Four years earlier, in 1997, The Saban Research Institute launched its High School Research Education Program in collaboration with Marlborough School, a private girls' high school, with support from The Saban Research Institute Committee; Ken Mitsuhashi, MBA, administrator for The Saban Research Institute; and Arleen Forsheit, PhD, of the Marlborough School.

Faculty mentors within The Saban Research Institute provide talented and motivated students with lab-based opportunities that often encourage them to consider careers in biomedical research.

Participants have the chance to work for an entire academic year on a research project, gaining direct exposure to research methodologies, experimentation and data analysis. Of the more than 25 girls who have received training to date, nearly 50 percent are now furthering their interest in science or research, including some who have entered medical or graduate schools.

In 2004, the High School Research Education Program, under direction of Emil Bogenmann, PhD*, expanded to La Crescenta Valley High School in the Glendale Unified School District. So far, eight students have participated. “We believe our strategy to identify, engage and educate motivated high school students with an aptitude for patient-based research is working,” says Dr. Bogenmann.

Future goals include increasing the number of participating schools and disadvantaged and under-represented minority students, as well as developing an administrative infrastructure to facilitate program expansion.

Faculty Awards

Nurturing the scientists of tomorrow is central to The Saban Research Institute's mission. In 2005, eight junior faculty members were awarded their first grant from the National Institutes of Health (NIH) and other organizations – the result of their own dedication and of The Saban Research Institute's early investment in promising research.



Saverio Bellusci, PhD*:

A five-year \$1.5 million grant from the National Heart, Lung, and Blood Institute to focus on the role of Fgf-10, a growth factor, in the establishment of smooth muscle cells. These cells are known to over-proliferate in diseases such as asthma and bronchopulmonary dysplasia, one of the most common chronic lung diseases in infants in the United States.



Alex Chen, MD, MSHS*:

A five-year, \$600,000 grant from the National Institute of Child Health and Human Development to identify social and financial barriers that prevent children with chronic illnesses access to health care, in collaboration with investigators at the RAND Institute and The Saban Research Institute.



Barry J. Maurer, MD, PhD*:

A four-year, \$980,000 National Cancer Institute grant for his efforts to optimize combinations of fenretinide (an artificial vitamin A derivative) with other drugs for the development of new chemotherapy agents that can attack leukemia cancer cells.



John C. Wood, MD, PhD*:

A four-year, \$2.2 million grant from the National Heart, Lung, and Blood Institute for further development of a Magnetic Resonance Imaging technique that accurately measures iron overload in patients who undergo chronic blood transfusions, which can damage the liver and heart.



Paula Cannon, PhD*:

A four-year \$600,000 grant from the new Pacific-Southwest Regional Center of Excellence for Biodefense and Emerging Infectious Diseases based at the University of California, Irvine. Dr. Cannon's research concerns a highly pathogenic group of viruses called arenaviruses, which cause fatal hemorrhagic (bleeding) fevers in humans.



Anat Erdreich-Epstein, MD, PhD*:

A five-year, \$1.5 million grant from the National Cancer Institute to study the mechanisms that increase levels of ceramide, a wax-like molecule that can cause cell death. This knowledge could eventually lead to clinical trials in children with deadly brain tumors.



Leonid S. Metelitsa, MD, PhD*:

A five-year, \$1.23 million grant from the National Cancer Institute for a study that seeks to understand the molecular basis for ways in which tumors "escape" from immune responses affected by Natural Killer T cells. This research would lead to new strategies for neuroblastoma and other cancers.

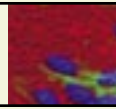


Tishya Wren, PhD*:

A two-year, \$390,000 grant from the National Institute of Arthritis and Musculoskeletal and Skin Diseases to study how changes made in surgical plans based on motion analysis study impact outcomes and quality of life in children with neuromuscular diseases such as cerebral palsy.

Honor Roll of Donors

Fiscal Year 2005



The Saban Research Institute of Childrens Hospital Los Angeles

Our friends in the community play a crucially important role in furthering the cause of biomedical research. Every gift is valuable in itself – and carries powerful echoes. Each philanthropic dollar invested in research leverages \$8 to \$10 in federal, corporate and foundation support. Philanthropy also serves to fund new ideas in their earliest stages, allowing scientists the time to prove the validity of their theories.

In this Honor Roll of Donors, we acknowledge our thoughtful benefactors for their contributions of \$1,000 and above to The Saban Research Institute between July 1, 2004, and June 30, 2005. We also are grateful to those donors who have created endowments that bring essential, ongoing support.

These gifts are part of \$75 million in endowment and capital research initiatives that we are endeavoring to raise through *Living Proof: The Campaign for Childrens Hospital Los Angeles*, a comprehensive campaign to fund new facilities and generate endowment, program and annual support.

To join our cause, 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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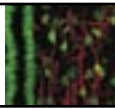


Haim and Dr. Cheryl Saban

The Saban family's unique and precious contribution is generously gifted to address the most perplexing medical issues affecting children and adolescents. Childrens Hospital Los Angeles is proud to recognize Haim and Dr. Cheryl Saban for their great generosity and love of mankind.

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Yves A. DeClerck, MD, left, with Theodore R. Samuels, chair of The Saban Research Institute Committee for 2005

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The faculty and staff of The Saban Research Institute wish to thank the members of The Saban Research Institute Committee for their continuing guidance and leadership. Committee members help to shape strategic planning for research at Childrens Hospital Los Angeles, as well as raise vitally needed funds and awareness of the work we do.

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