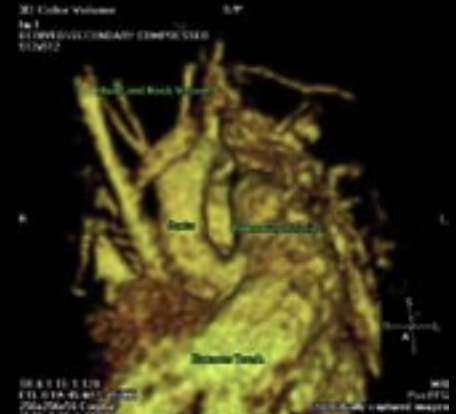
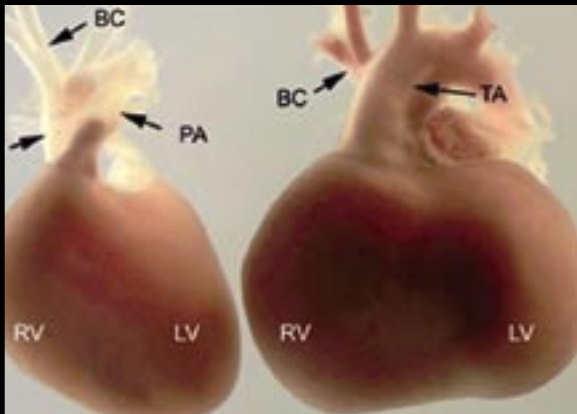
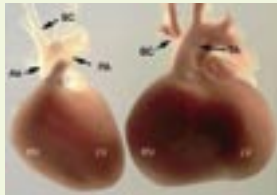


RESEARCH HIGHLIGHTS



Creating a Healthier Future for Children





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22.....The Saban Research Institute Committee

Welcome to the first edition of *Research Highlights*, designed to share with you some of the exciting investigations of the past year at The Saban Research Institute of Childrens Hospital Los Angeles.

On the cover: Childrens Hospital Los Angeles patient Isabel Morris with her mother, Jill

NOTE FROM THE DIRECTOR

CREATING A HEALTHIER FUTURE FOR CHILDREN

Investigators in The Saban Research Institute of Childrens Hospital Los Angeles are working to create a world where all children are healthy – where they are no longer threatened by such diseases as cancer, congenital heart defects, diabetes, sickle cell anemia, epilepsy, immune deficiencies and respiratory disorders.

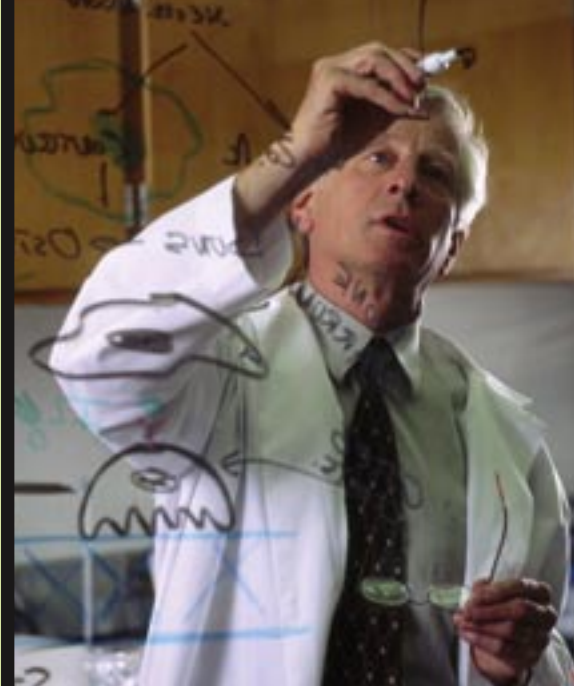
As we ask basic questions about human biology, find new ways to see inside the body, explore genetic mysteries, develop promising drug treatments and test preventive strategies, our scientific inquiries benefit both children and adults. We strive to move the discoveries we make at the laboratory bench as quickly as possible to the patient's bedside.

In this report, we highlight some of the achievements in fiscal year 2003-2004 of The Saban Research Institute, the leading pediatric research institution in the West and one of the top five institutions in the nation, in terms of funding from the National Institutes of Health (NIH). We're proud to note that NIH funding to support research at Childrens Hospital Los Angeles has increased for the sixth consecutive year. We are closer than ever to solving some of the vexing problems facing pediatric health and to creating a brighter tomorrow for children.

However, we face formidable challenges. Among them are establishing a premier program of clinical research that brings new knowledge even closer to useful fruition, along with the initiation of a major research program in Neuroscience. Both programs respond to pressing needs among the patients for whom we seek innovative treatments and cures.

Buoyed by the support of our friends and colleagues, we look to the future with great confidence and determination.

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



Dr. Yves A. DeClerck

The Saban Research Institute



ChildrensHospitalLosAngeles

International Leader in Pediatrics

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



OVERVIEW OF THE YEAR

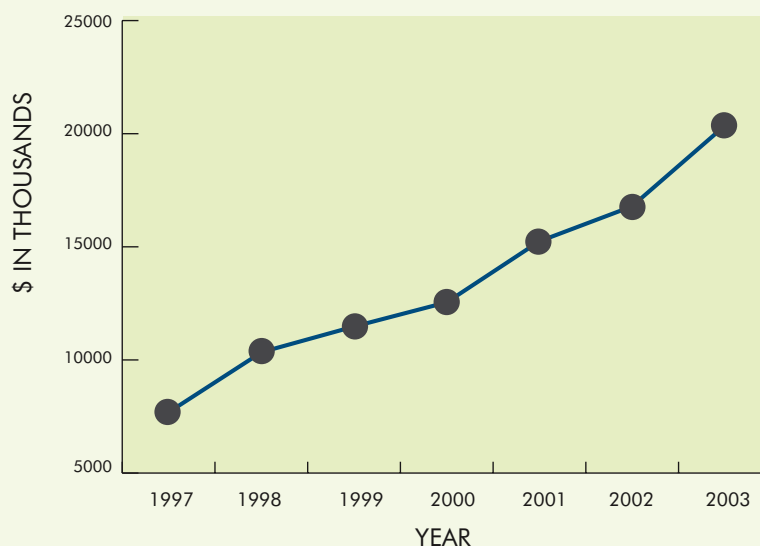
NEW KNOWLEDGE & NEW TOOLS

In 2003-2004, physician-scientists and researchers in The Saban Research Institute furthered the understanding of how cancer cells work and their possible deterrents, as well as defining the basic genetic function in cardiac and intestinal malformations and lung development.

Other far-reaching studies also:

- advanced the role of stem cells in diseases with pancreatic insufficiency, such as diabetes and cystic fibrosis, as well as the use of gene therapy to help children with AIDS and with such blood diseases as thalassemia and sickle cell anemia,
- developed breakthrough imaging techniques to measure iron overload in children with blood diseases,
- generated evidence for a new clinical trial in patients with severe combined immune deficiency disorder, and
- identified molecules by which bacteria affects the brain.

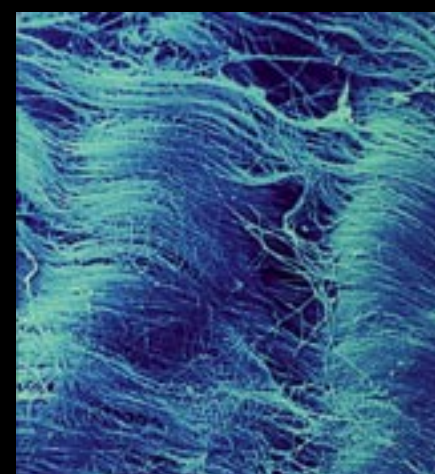
NATIONAL INSTITUTES OF HEALTH (NIH) FUNDING 1997-2003



Funding from the NIH for biomedical research at The Saban Research Institute of Childrens Hospital Los Angeles has been on a steady rise for several years.

**OUR RESEARCH
VOLUME
CONTINUES TO
GROW AT AN
IMPRESSIVE PACE,
WITH EXTERNAL
FUNDING
INCREASING FOR
THE SIXTH YEAR
IN A ROW –
TO \$34 MILLION
AT THE END OF
JUNE 2004.**





Last year, Saban Research Institute leaders predicted a modest annual funding increase of seven percent, given signs of a general tightening of government resources. Instead, external funding increased for the sixth year, this time by 17 percent, from \$29 million in 2003 to \$34 million at the end of June 2004.

Federal sources account for 83.5 percent of total funding, including the National Institutes of Health (NIH), Department of Defense, and Centers for Disease Control and Prevention.

NIH funding rose by 21 percent, from \$16.4 million in 2002 to \$20.4 million in the fiscal year ending 2004, and is expected to continue rising, with 10 new, individual NIH grants obtained this year. This brings the total NIH-funded projects to 84, with more projects ahead for 2005.

Twelve faculty members joined the Institute this past year, strengthening capabilities in such areas as cancer; cardiovascular research; gene, immune and stem cell therapy; community health outcomes; microbial pathogens; imaging research; bone and body composition; and biostatistics.

This expansion can be credited both to our planning as an institution – including the Childrens Hospital Los Angeles Board of Trustees' decision

to create new research space – and to the generosity of our donors.

We completed our move into The Saban Research Institute building, which houses programs in Developmental Biology and Cardiovascular Research, the Imaging Research Initiative, and will house the new Neuroscience Program. At the same time, renovations were undertaken in the H. Russell and Jeanne R. Smith Research Tower to accommodate the needs of other programs.

This past year, two core facilities in Biostatistics and Bioinformatics took shape. These will provide expertise to investigators in the design of experiments and the retrieval, analysis and interpretation of complex scientific data. A new office headed by an Administrative Director of Research will support investigators in managing corporate- and federally funded research.

At our Research Vision Retreat in February 2004, more than 130 faculty members, hospital leaders and members of The Saban Research Institute Committee explored ways in which we can build a clinical research program over the next decade commensurate with our renowned laboratory programs. Working together, we are developing a strategic plan that will chart our course.

The Saban Research Institute maintains a strong alliance with the Keck School of Medicine of the University of Southern California; all of our scientists hold faculty positions within the School. We benefit daily from this productive relationship, as we do from collaborations with pediatric scientists in a growing number of countries, who share our passion for research and service to children.

PROGRAMS & INITIATIVES

- Body and Bone Composition Initiative
- Cancer
- Cardiovascular Research
- Community Health Outcomes and Intervention Research
- Developmental Biology
- Gene, Immune and Stem Cell Therapy
- Imaging Research Initiative
- Microbial Pathogens Initiative

RESEARCH PROGRAMS



NEW DRUG COMBINATIONS UNDER DEVELOPMENT HAVE SHOWN AN INCREASED ABILITY TO DESTROY LEUKEMIA CELLS BY 100-FOLD.

Dr. Vicente Gilsanz

BONE AND BODY COMPOSITION INITIATIVE

Director: Vicente Gilsanz, MD, PhD*

Common adult diseases such as osteoporosis, type 2 diabetes and hypertension have their roots in childhood. Specific traits associated with these conditions in adults, including low bone density and high visceral fat, can be measured in children and lead to possible new solutions for people of all ages.

The Bone and Body Composition Initiative combines an interdisciplinary core of clinical research experts with the use of specialized imaging to identify biomarkers (biochemical measurements) that aid in the diagnosis, prevention and treatment of musculoskeletal and metabolic diseases.

Its scientists have developed solid evidence that bone mass measurements are helpful in determining which children are at risk for osteoporosis later in life and would benefit from early interventions. Among other 2003-2004 highlights, Vicente Gilsanz, MD, PhD,

initiative director, used sophisticated software analysis and computed tomography digital data to demonstrate a significant relation between coronary heart disease and osteoporosis, independent of the aging process. The study was conducted in collaboration with faculty at Loma Linda University.

In 2003, the NIH designated Childrens Hospital Los Angeles as one of five national Clinical Centers for the study of bone mineral density in childhood. In 2002, the agency awarded the hospital a five-year, \$2 million grant for this field of study.

Within this initiative, imaging is seen as a future tool for prevention as well as diagnosis. "There's no question that in years to come, imaging will play a tremendous role in identifying people at risk for certain diseases," says Dr. Gilsanz. "We will be able to predict which kids are predisposed to diseases that won't manifest until adulthood."



Dr. Anat Erdreich-Epstein (left) and Melissa Millard



Dr. Barry Maurer

CANCER PROGRAM

Director: Robert C. Seeger, MD*

Cancer Program researchers are exploring the biology of childhood cancers and devising inventive methods to attack the most aggressive pediatric cancers – such as neural tumors, acute leukemia and bone/soft tissue sarcomas – which often resist conventional treatments.

Physician-scientist Barry J. Maurer, MD, PhD*, has been developing a new type of chemotherapy based on an artificial vitamin A derivative, fenretinide. He has found that fenretinide causes leukemia blood cancer cells, but not normal blood cells, to make a large amount of ceramide, a wax-like substance that can cause cells to die – and that combining fenretinide with other drugs can increase the killing effect on leukemia cells by 100-fold. In 2004, Dr. Maurer received a four-year grant from the National Cancer Institute (NCI) to optimize these drug combinations.

He also received the Eurand Award Grand Prize for Novel Approaches in Oral Delivery for developing a powdered form of fenretinide. This

oral form, which tastes like cookie dough, can be mixed with food or drink, making it easier for children to take and absorb. “If we can get more of this drug into the body, we expect to increase the therapeutic effect,” he says.

Saban Research Institute investigator Anat Erdreich-Epstein, MD, PhD*, is looking to beat cancer from another angle – by inhibiting angiogenesis, the growth of new blood vessels, which is essential for tumor development.

In 2004, her laboratory received a five-year NCI grant to support studies into the molecular mechanisms that regulate the survival and death of endothelial cells, which line the small capillaries in the brain. “This will allow us to design drugs that will disrupt the capillary network that supplies tumors,” she explains. “We anticipate that such disruption, in combination with other medications, will improve the treatment of brain tumors.”



SCIENTISTS ARE TAKING AIM AT PEDIATRIC CARDIOVASCULAR DISEASE BY GROWING THE BUILDING BLOCKS OF NEW HEART VALVES THROUGH TISSUE ENGINEERING.

Dr. Ivan Vesely

CARDIOVASCULAR RESEARCH PROGRAM

Director: Ivan Vesely, PhD*

Both children and adults with heart disease someday could be beneficiaries of the innovative approaches to basic and applied research by investigators in the Cardiovascular Research Program.

In January 2004, Program Director Ivan Vesely, PhD, joined The Saban Research Institute, coming from The Cleveland Clinic Foundation in Ohio. The highly regarded bioengineer is the first to hold the H. Russell Smith Foundation Endowed Chair in Cardiothoracic Research at Childrens Hospital Los Angeles.

The program he heads focuses on heart valve biomechanics and tissue engineering; the molecular aspects of organ rejection; ways to minimize chronic rejection; and the possibilities of xenotransplantation (pig organs), in conjunction with gene therapy.

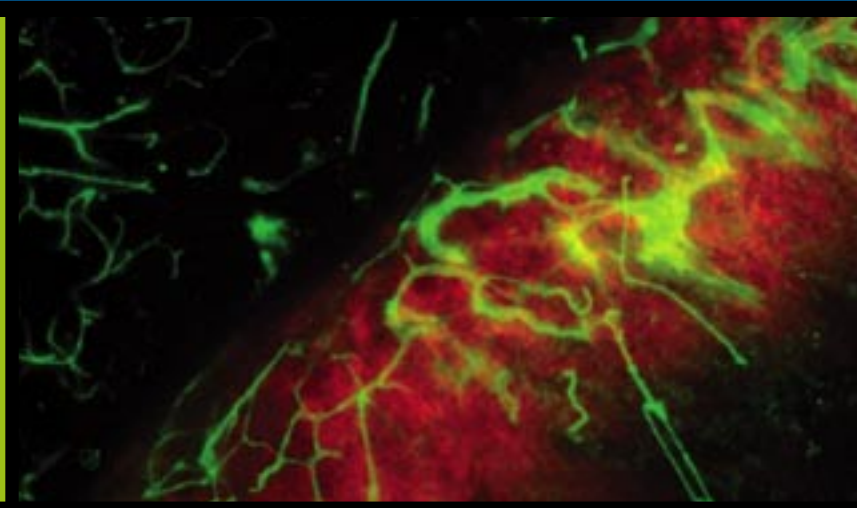
Dr. Vesely's NIH-funded tissue engineering research seeks to create the individual building blocks of living heart valves from collagen and elastin, fibrous proteins found in connective tissue, and from glycosaminoglycans, major structural components of cartilage.

These molecules can be synthesized by cells in culture or purified from tissues, then manipulated to mimic the normal structural framework of the aortic valve. Each of the heart's two mitral valves has a membrane suspended by strings called chordae, which can become diseased and break. Dr. Vesely and his colleagues have been pioneers in successfully fabricating tissue-engineered mitral valve chordae with a strength and stiffness 10 times greater than any other material produced using similar approaches.

The importance of this work is heightened by the fact that heart-valve alternatives for children are problematic. Mechanical valves can clot or induce strokes, while tissue valves fabricated from chemically preserved pig or calf tissues scar over and fail within five years. Moreover, neither valve can grow with the child.

"We want to give some of the technology we hope to develop to the surgeons so they can work with it and help children with valve disease," notes Dr. Vesely.





Dr. Michele D. Kipke

COMMUNITY HEALTH OUTCOMES AND INTERVENTION RESEARCH PROGRAM

Director: Michele D. Kipke, PhD*

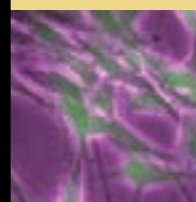
How can we prevent childhood and life-long health problems, promote healthy development and reduce disparities in children's health and access to care while ensuring delivery of quality care? What are the best ways to restore function and prevent disability among children with special needs? These are the pressing questions being addressed by the Community Health Outcomes and Intervention Research Program (CHOIR).

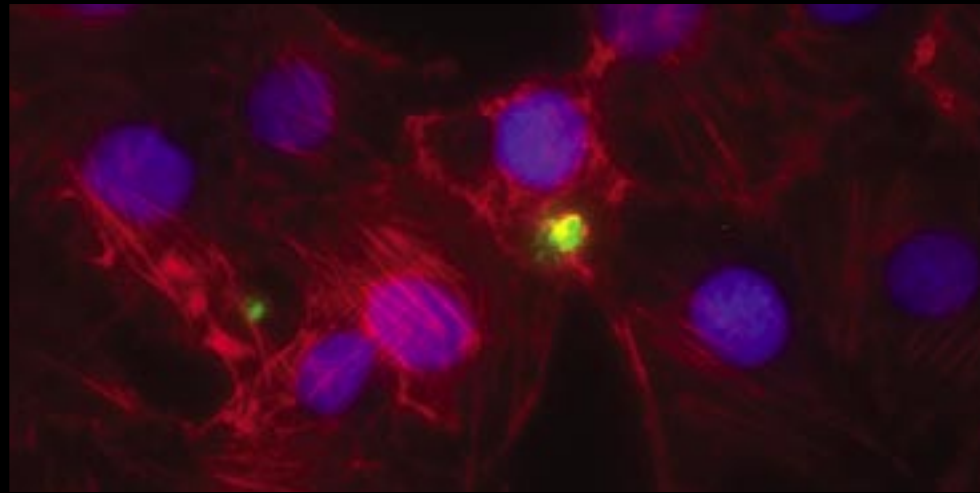
In 2003-2004, researchers received two career awards from the National Institute on Child Health and Human Development of the NIH. With one five-year grant, Alex Y. Chen, MD*, will identify the social and financial barriers that prevent children with chronic illnesses or special health needs from receiving access to health care. A second five-year grant to investigator Justeen Hyde, PhD*, supports ethnographic research examining the consequences of child abuse and neglect among adolescents in the Los Angeles foster care system.

A data collection system aimed at measuring patient safety indicators in five California hospitals was developed, pilot tested and implemented by the research team of Glenn S. Takata, MD*, Wilbert H. Mason, MD, MPH*, and Jordana Signer, PhD.

This multi-year project funded by the California HealthCare Foundation will develop a system to track medical errors, along with tools and strategies to reduce or eliminate these incidents. The data tracking system already has resulted in improved performance.

In the past year, CHOIR developed and implemented a new Biostatistical Core and Research Informatics Core to support investigations within The Saban Research Institute. Program faculty also conducted weekly research education and training seminars for fellows and junior faculty at Childrens Hospital, designed to nurture independent and collaborative research.





Dr. Vesa Kaartinen

DEVELOPMENTAL BIOLOGY PROGRAM

Director: David Warburton, DSc, MD, FRCP*

Developmental biologists are asking fundamental, often revolutionary questions to uncover the mysteries of how we grow at the cellular level. Their mission: to discover the basic mechanisms of human organ development, understand the impact of disease on the developing human and apply this knowledge to devising new therapies.

The Developmental Biology Program – which has grown tenfold in only five years in funding from the NIH – is internationally recognized for insights it has gained into the basic molecular and genetic processes underlying growth, regeneration and repair of body tissues. The program now occupies an entire floor in The Saban Research Institute building.

In 2003-2004, its scientists concentrated their attention on such issues as lung hypoplasia or injury caused by prematurity, cleft palate, congenital heart disease, scarless skin wounds, short gut

and intestinal atresia (lack of a normal opening), diabetes and breast cancer.

One breakthrough came in better understanding of the molecular basis of cardiac defects. Congenital heart defects are among the most common birth malfunctions in newborns, the reasons for which are often unknown despite intense studies. Research led by principal investigator Vesa Kaartinen, PhD*, identified a signaling pathway – a series of molecular signals – required for normal cardiac development, making it one of the many pathways that may be impaired in children suffering from this type of defect.

“Understanding the failure of this signaling mechanism opens the possibility of intervening and correcting this defect in the early stages of heart development,” says Dr. Kaartinen.

The study, which has received funding from the NIH, is the subject of an article published in the July 2004 issue of the journal *Development*.



MAJOR BREAKTHROUGHS IN UNDERSTANDING THE MOLECULAR BASIS OF RED BLOOD CELL PRODUCTION AND USING GENE THERAPY FOR THALASSEMIA AND SICKLE CELL OFFER HOPE TO CHILDREN WITH THESE CONDITIONS.



Dr. Punam Malik (right) with Dr. Azim Mohamedali

GENE, IMMUNE AND STEM CELL THERAPY PROGRAM

Director: Donald B. Kohn, MD*

Gene therapy may be a safer, more effective treatment for thalassemia, an inherited form of anemia, according to a study by Saban Research Institute physician-scientists to be published in the December 2004 issue of the journal *Blood*.

Patients with thalassemia major cannot make red blood cells, due to a defect in one gene responsible for the hemoglobin, a protein that picks up oxygen in the lungs and delivers it to peripheral tissues to maintain the viability of cells. As a result, such patients are dependent on lifelong transfusions, unless they receive a bone marrow transplant.

In 2003-2004, principal investigator Punam Malik, MD*, and her team were able to correct bone marrow stem cells from thalassemia major patients using gene transfer (incorporation of new DNA into an organism's cells). Specifically, they restored the ability of stem cells to make red blood cells, essentially identical to normal bone marrow, both in the test tube and on a long-term basis in immune-deficient mice. Pediatric fellow

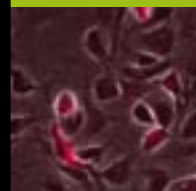
Geetha Puthenveetil, MD, performed the studies in Dr. Malik's laboratory.

"This represents a major step toward the development of gene therapy for thalassemia, as well as for other red blood cell diseases," reports Dr. Malik.

The Gene, Immune and Stem Cell Therapy Program is an interdisciplinary collaboration of scientists and physicians from Childrens Hospital's Divisions of Bone Marrow Transplant/Research Immunology, Allergy/Clinical Immunology and Hematology/Oncology, plus the Department of Cardiothoracic Surgery.

Investigators from these areas are working to improve treatments for children with blood disorders, leukemia and immune deficiencies, such as severe combined immunodeficiency disease (SCID) and AIDS.

Basic research laboratories focus on stem cell biology, immunology and gene therapy, while clinical research includes clinical trials in bone marrow transplantation and clinical immunology and hematology.





Dr. Marvin Nelson, Jr. (right) and Dr. Rex Moats



MR-compatible incubator

IMAGING RESEARCH INITIATIVE

Director: Marvin D. Nelson, Jr., MD, MBA*

With advanced imaging techniques, scientists participating in the Imaging Research Initiative are seeing inside the human body to measure its processes – from the chemistry of cells and growth of tumors to the brain’s electrical activity.

“In the past 10 years, imaging has changed perhaps more than any other science,” says Marvin Nelson, Jr., MD, MBA, initiative director and chair of the Department of Radiology at Childrens Hospital Los Angeles. As a result, physicians are better able to judge how fast a tumor is growing, where stem cells travel after transplantation or whether a new drug compound is effective.

The Imaging Research Initiative is unique in the nation for its breadth, expertise and focus on pediatric diseases in the laboratory and in clinical practice.

This past year was noteworthy for the opening of the state-of-the-art Small Animal Research Imaging Center in The Saban Research Institute building. This 1,200-square-foot facility has been designed to handle animal models from within The Saban Research Institute and from other institutions, expanding future research col-

laborations. The center’s director is Rex Moats, PhD*.

Its powerful imaging tools include a high-resolution magnetic resonance imaging (MRI) system, micro Computed Tomography (CT), real-time Doppler ultrasound unit, and multi-view bioluminescent/fluorescence imaging system, along with a combined CT/SPECT (single photon emission CT) instrument, which shows how blood flows to tissues and organs.

Also noteworthy this past year was the design and implementation of an MR-compatible incubator, with a specially designed head coil to produce high-resolution images of the smallest patients. As a result of this breakthrough, Childrens Hospital is the first in the world to perform functional MRI on even the tiniest babies.

Other highlights include advancement of MRI techniques to quantify iron buildup in the heart and liver of patients with certain blood diseases; new diffusion tensor imaging, which allows observation of the molecular organization of tissues; and other advanced imaging systems that will yield sharper, faster images of children in need of diagnosis and new treatments.

RESEARCHERS ARE STRIVING TO UNDERSTAND THE TYPE OF MATERNAL IMMUNE RESPONSES THAT HELP PREVENT MOTHER-TO-CHILD TRANSMISSION OF HIV-1.



Dr. Grace Aldrovandi and Don Decker

MICROBIAL PATHOGENS INITIATIVE

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

Grace M. Aldrovandi, MD*, wants to learn more about Human Immunodeficiency Virus (HIV) drug resistance and shine light on the origins of pediatric HIV infection, particularly its transmission from mother to child through breast milk.

She is motivated by an unfortunate statistic – each day, some 2,000 children worldwide are infected with HIV, the majority by breast feeding.

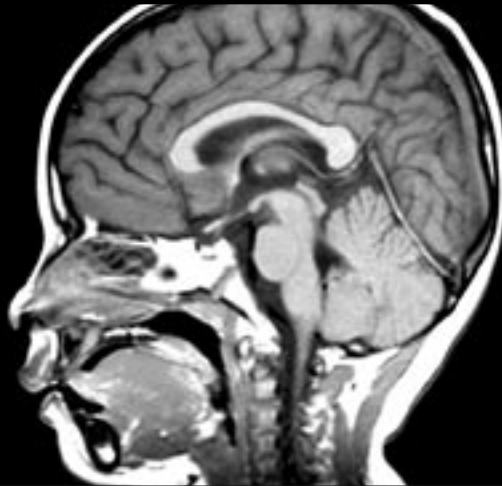
Dr. Aldrovandi, a physician-scientist in Childrens Hospital's Division of Infectious Diseases, received the 2004 Elizabeth Glaser Scientist Award, a five-year, \$700,000 grant given by the Elizabeth Glaser Pediatric AIDS Foundation. The award is designed to enable promising scientists/clinicians to focus their long-term efforts on issues specific to pediatric HIV/AIDS.

The funding will support Dr. Aldrovandi's studies aimed at better understanding of the types of maternal immune responses that help prevent mother-to-child transmission of HIV-1, the virus that causes AIDS. "Such knowledge is essential to our HIV vaccine efforts," she says.

In 2003, Dr. Aldrovandi and her colleagues used a novel method to measure the dynamics of HIV-1 recombination (a combination of genes different from what they were in the parents) – in specific target cells. Their research showed that a single round of HIV-1 replication generated recombination at an order of magnitude (tenfold) greater than previously recognized. These results have significant implications for understanding the rapid evolution and management of HIV-1 infection.

Researchers within the Microbial Pathogens Initiative are engaged in a range of investigations into the development, diagnosis and management of pathogens or disease-producing agents, in particular viruses or other microorganisms. Studies focus both on genomics, a branch of genetics that looks at organisms in terms of their full DNA sequences, and on proteomics or the study of gene-coded proteins. The mission: to translate innovative research into equally creative therapeutic tools and preventive strategies for viral or bacterial diseases affecting pediatric patients.

CLINICAL RESEARCH



Dr. Floyd Gilles

CLINICAL RESEARCH INVOLVING PATIENTS IS A VITAL ASPECT OF OUR WORK IN THE SABAN RESEARCH INSTITUTE, AS WE STRIVE TO TURN NEW SCIENCE INTO SOLUTIONS TO IMPROVE HEALTH CARE FOR CHILDREN.

CHILDRENS BRAIN CENTER

Director: Floyd H. Gilles, MD*

Understanding how the developing brain forms and functions may hold the key to treating a range of diseases in children and adults. Approximately 50 million people in the US suffer from a neurological disorder.

While scientists know much about the brain's gross and fine anatomy, they have much to learn about the genetic control of brain development.

Finding these answers is a priority for the Childrens Brain Center and a new Neuroscience Program (focused on developmental neurobiology) in The Saban Research Institute. Together, these research efforts encompass several areas of investigation: epilepsy, molecular and functional imaging, brain tumor prognosis, anti-epileptic drug studies, and childhood mood disorders and psychopharmacology.

In 2003-2004, a collaborative committee continued its search for a director for the Neuroscience Program, which will be housed in The Saban Research Institute building.

Major funding has been secured for the new program from The Saban Family Foundation, the University of Southern California and from The Associates, 24 community-based groups that provide significant support to Childrens Hospital. The Associates Endowment for Neuroscience and Imaging Research, announced in February 2004, will raise \$5 million for basic research in developmental neurobiology, as well as for clinical and animal imaging research.



Dr. Francine R. Kaufman

CLINICAL RESEARCH TAKES PLACE WITHIN THE CENTERS OF EXCELLENCE AT CHILDRENS HOSPITAL AND UNDER THE AUSPICES OF THE GENERAL CLINICAL RESEARCH CENTER, PART OF A FEDERALLY FUNDED NETWORK.



Dr. Jonathan Finlay (right)

CENTER FOR ENDOCRINOLOGY, DIABETES AND METABOLISM

Director: Francine R. Kaufman, MD*

Childrens Hospital Los Angeles is one of 12 centers taking part in the NIH-funded clinical study known as TODAY – Treatment Options for type 2 Diabetes in Adolescents and Youth. The study is the first nationwide clinical trial to examine the effects in youth of intensive lifestyle change in addition to medication. A total of 750 young people ages 10 to 18 will participate in helping to determine how well and for how long each of three treatment approaches controls blood glucose levels.

One group will receive metformin, the only approved oral medication to treat type 2 diabetes in children. A second group will receive a combination of metformin and rosiglitazone, an oral medication used in adults with type 2 diabetes. The third group will receive intensive lifestyle intervention therapy along with metformin.

With diabetes at epic proportions, time is critical. “What was once a disease of our grandparents is now a disease of our children,” says Francine R. Kaufman, MD, study chair for the TODAY trial, and head of Childrens Hospital’s Center for Endocrinology, Diabetes and Metabolism.

In 2004, the Center continued its type 1 diabetes prevention efforts with TrialNet, an international study funded by the NIH, along with studies funded by the American Diabetes Association to assess cardiovascular risk in youth ages 12 to 21 with type 1 diabetes.

CHILDRENS CENTER FOR CANCER AND BLOOD DISEASES

Director: Stuart E. Siegel, MD*

Co-director: Donald B. Kohn, MD*

Brain tumors are now the leading cause of cancer death in children under age 20, largely because many available treatments have proven ineffective. To encourage new, innovative approaches, the Childrens Center for Cancer and Blood Diseases has recruited Jonathan Finlay, MD*, as director of the Clinical Neural Tumors Program.

In 2004, Dr. Finlay documented that destructive doses of chemotherapy followed by autologous stem cell rescue (from a patient’s own stem cells) is effective therapy for both recurrent central nervous system germ cell tumors and for recurrent primitive neuroectodermal brain tumors.

This past year also saw expanded research in blood diseases. Two clinical trials seeking solutions for patients with sickle cell disease and thalassemia are led by Thomas D. Coates, MD,* section head of hematology at the Childrens Center for Cancer and Blood Diseases, and investigator John C. Wood, MD, PhD.* The scientists are employing new magnetic resonance imaging techniques (MRI) to accurately measure iron overload in patients who undergo chronic transfusions.

In addition, several clinical trials led by investigator Wing Yen Wong, MD*, focus on coagulation defects to treat hemophilia A and B, as well as protein C deficiency, an inherited disorder that causes abnormal blood clotting.



**RESEARCH HAS HELPED
SHAPE A PIONEERING PROGRAM
OF LIVING DONOR LUNG
TRANSPLANTS THAT OFFERS
HOPE FOR CHILDREN WITH
CYSTIC FIBROSIS AND SEVERE
LUNG DISEASES.**



Dr. Marlyn Woo (right)

GENERAL CLINICAL RESEARCH CENTER

Director: Kenneth I. Weinberg, MD*

Associate Director: John C. Wood, MD, PhD*

Funding clinical research is an ongoing challenge for non-profit institutions, with the health care system reluctant to pay for experimental studies. Scientists have found one solution in the General Clinical Research Center (GCRC) at Childrens Hospital, which serves as a source of financial support and other resources where innovative diagnostic or therapeutic modalities can be tested to determine if they are ready for general use.

The GCRC – established in 1995 as a satellite of the parent GCRC at the Keck School of Medicine – is one of about 75 centers nationwide funded by the NIH to provide infrastructure specifically for clinical research. Among other goals, it offers investigators certain types of support difficult to obtain in a conventional setting, such as research nursing and assistance in data recording and analysis.

In just one example, the Food and Drug Administration gave the go-ahead in 2003-2004 to two Childrens Hospital Los Angeles gene therapy studies for severe combined immunodeficiency disease. The treatment is so innovative, it couldn't be done without GCRC's support. Enrollment is expected to begin soon, with monitoring of study procedures carried out in the GCRC.

Other studies facilitated by the center ranged from advancements in blood diseases to exploring new ways to prevent diabetes.

The GCRC conducted an active educational program this past year to stimulate collaboration between researchers and clinicians, in coordination with The Saban Research Institute's Community Health Outcomes and Intervention Research Program.

THE HEART INSTITUTE

Director: Vaughn A. Starnes, MD*

A pioneering program of living donor lung transplants in The Heart Institute at Childrens Hospital is entering its second, successful decade with a multifaceted, clinical research initiative.

These transplants, in which a lung lobe is donated by a living person, are an important option for patients with cystic fibrosis, pulmonary hypertension or other progressive lung diseases, many of whom will not survive long enough for a cadaveric transplant.

"We're looking at some basic research questions to determine how well living lobar recipients fare," says Marlyn S. Woo, MD*, medical director of The Heart Institute's Cardiothoracic Transplant Program. The answer: very well. So far, research has shown:

- Recipients' post-transplant lungs have an exceptional ability to remodel their vessels to accept pulmonary pressure.
- Lung volume adapts with the recipient's growth, not by developing new tissue but by expanding old tissue so new lungs do not restrict activity.
- Living donor patients have a significantly lower incidence of acute and chronic rejection after transplant compared to cadaveric lung recipients.

Most patients who receive cadaveric lungs develop acute rejection within six months to a year after transplant. Living lobar patients had a much longer period before their first acute episode – sometimes two to four years – and some never had an acute episode.



Pre-surgical study done in John C. Wilson, Jr. Motion Analysis Laboratory

Dr. Tishya Wren

CHILDRENS ORTHOPAEDIC CENTER

Director: Vernon T. Tolo, MD*

The treatment of musculoskeletal disorders in children with cerebral palsy is the focus of two federal grants awarded in 2004 to Tishya Wren, PhD*, a scientist in the Childrens Orthopaedic Center and Department of Surgery at Childrens Hospital.

A \$1.5 million grant from the Agency for Healthcare Research and Quality will support a five-year study documenting how the results of multijoint surgery change when the surgeon has access to information provided by comprehensive gait analysis testing. This specialized diagnostic testing is performed at the John C. Wilson, Jr. Motion Analysis Laboratory in the Childrens Orthopaedic Center.

"We already have computerized models to show us a child's existing walk. Our pre-operative motion analysis results in changes to surgical plans in 90 percent of patients," reports Dr. Wren, director of research for the laboratory. "The next step is to build a system that will let us see the result of any combination of procedures, before they're done."

The new study will seek to determine the extent to which such changes translate into improved post-surgery outcomes and quality of life. If it can demonstrate a positive impact, the study could make a case for wider availability of the technology.

Dr. Wren also was awarded a two-year \$390,000 grant by the National Institute of Arthritis and Musculoskeletal and Skin Diseases for a study into whether low-level vibration can build bone and muscle strength in children with cerebral palsy.

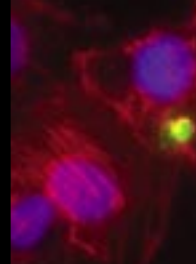
**AT THE SABAN
RESEARCH INSTITUTE,
WE CONTINUALLY SEEK
NEW KNOWLEDGE TO
BENEFIT CHILDREN
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PROGRAMS ARE
EXPANDING AS WE
LOOK TO THE FUTURE.
WE INVITE YOU TO JOIN
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*Postdoctoral fellow Stacy Townsend, PhD, (left) and Julie Badger, PhD**

**OUR THRIVING CAREER DEVELOPMENT PROGRAM SUPPORTS
RISING YOUNG SCIENTISTS AT A KEY STAGE IN THEIR CAREERS.**

EDUCATION



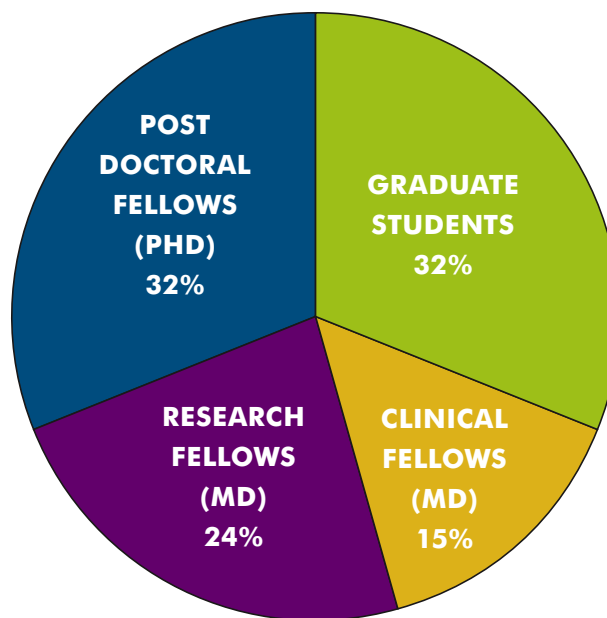
Encouraging new generations of scientists who will contribute to the fight against pediatric disease remains one of The Saban Research Institute's principal agendas.

Several years ago, aided by the Childrens Hospital Board of Trustees, the Institute established a career development program to support rising young scientists.

This year, significant resources from The Saban Family Foundation have been allocated toward this goal. In addition, a grant proposal has been submitted to the NIH to support the training of post-doctoral fellows (MDs and PhDs) in developing their research careers. The Saban Research Institute plans to make pilot awards in the coming year to establish the validity of this training model and, in doing so, attract the extramural support the program deserves.

This policy of nurturing scientific careers already has returned tangible rewards. Seven new NIH grants have been awarded for fiscal year 2005 to junior faculty members recruited and financially supported by The Saban Research Institute. This achievement highlights the value of investing in new faculty at an early or mid-stage point in their careers.

The first Saban Research Symposium in September 2003 focused on organogenesis



ACTIVE EDUCATIONAL PROGRAM

The Saban Research Institute provides new learning opportunities to both basic researchers and physician-scientists, with 103 postdoctoral fellows, graduate students, clinical and research fellows training here in the past fiscal year.

(the origin and development of organs). In 2003-2004, Institute members also organized conferences on infectious diseases; angiogenesis (the sprouting of new blood vessels in tumors); lung organogenesis, injury and repair; and neonatal hemodynamics (fluid flow principles or blood flow).

In sponsoring these scientific exchanges, as well as a Distinguished Lecturer Series, The Saban Research Institute is extending its resources to the larger community of physicians and scientists for the benefit of children everywhere.



Cheryl Saban, philanthropist, Childrens Hospital Trustee and The Saban Research Institute Committee member

Honor Roll of Donors, Fiscal Year 2004

The Saban Research Institute of Childrens Hospital Los Angeles

Our mission to provide better treatments and cures for children is advanced through private philanthropy. We acknowledge the following donors for their contributions of \$1,000 and above to The Saban Research Institute between July 1, 2003, and June 30, 2004.

We also wish to recognize donors who have established endowments that provide critical, ongoing support for research.

These donations are part of \$75 million in endowment and capital research initiatives we seek to raise through *Living Proof: The Campaign for Childrens Hospital Los Angeles*, a comprehensive \$500 million campaign to fund important new facilities, endowments and annual support.

Each gift has an impact beyond its own face value. Every philanthropic dollar invested in research leverages \$8 to \$10 in federal, corporate, and foundation support.

To join our cause, please contact Melany Duval, assistant vice president of major and planned gifts, at 323.671.1705 or mduval@chla.usc.edu, or Bethany Taylor, director of major and planned gifts, at 323.671.1708 or btaylor@chla.usc.edu.

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