The Saban Research Institute of Children’s Hospital Los Angeles is among the largest, most productive pediatric research facilities in the United States, with 100 investigators engaged in 186 laboratory studies, clinical trials and community-based research and health services.

It is one of the few freestanding research centers in the nation that combines scientific inquiry with patient clinical care and is dedicated exclusively to children. This year, The Saban Research Institute received $23 million in National Institutes of Health (NIH) funding and $37 million in total funding.

Originally established in 1992, The Children’s Hospital Los Angeles Research Institute became The Saban Research Institute in 2003 following a $40 million gift in support of pediatric research made by Cheryl Saban, PhD, Haim Saban and the Saban Family Foundation.

The Saban Research Institute maintains strong scientific and strategic affiliations with the University of Southern California (USC) and, in particular, the Keck School of Medicine of USC. All of the Institute’s principal investigators (clinical investigators, physician-scientists and PhD-scientists) are USC faculty and many have collaborative projects with scientists at the Keck School of Medicine and other departments at USC. The Institute’s researchers also are involved in collaborative projects with academic institutions in other cities in the U.S. and abroad.
The Greek philosopher Plato said the beginning is the most important part of the work.

With that in mind, I would like to welcome you to my inaugural issue of Research Highlights. As the new chair of the Department of Pediatrics and director of The Saban Research Institute of Children’s Hospital Los Angeles, I want to share with you just some of the scientific advances our investigators have made over the past year.

At The Saban Research Institute, our research clusters around seven key priority areas:

- Cancer
- Childhood Obesity
- Community, Health Outcomes and Intervention Research
- Developmental Biology and Regenerative Medicine
- Imaging and Human Physiology
- Immunology and Pathogens
- Neurodevelopment

These multidisciplinary areas serve as the focus for research emanating from The Saban Research Institute. Our investigators collectively share the goal of improving the diagnosis, treatment and overall management of these diseases in children. As such, all faculty recruitment and programmatic development are focused on supporting these core areas.

Much of our work this year has been concentrated on the origin of disease. Heather Volk, PhD, MPH, found evidence that in utero exposure to freeway pollutants led to an increased risk for developing autism. Sebastien Bouret, PhD, explored the relationship between perinatal nutrition and a lifelong risk for developing obesity and diabetes. And Vicente Gilsanz, MD, PhD, discovered a link between puberty and the onset of osteoporosis. These findings confirm that, while health is produced over a lifetime, childhood stands out as an especially critical period.

At The Saban Research Institute, we are continuing our mission to improve the health and wellness of children through a combination of basic, clinical and translational studies. Located in the second-largest city in the U.S., our hospital caters to one of the largest and most diverse populations of children in the world.
This unique population and the opportunity it provides for studying a wide range of patient outcomes were recognized by the National Institutes of Health when we were awarded—along with our academic partner, the University of Southern California (USC)—a Clinical and Translational Science Institute (CTSI) grant. Michele Kipke, PhD, vice chair of Research for the Department of Pediatrics, serves as associate CTSI director for Community Engagement.

Children’s Hospital Los Angeles already is ranked eighth in pediatric research program funding by the National Institutes of Health. In this issue, I invite you to read about the many significant innovations unique to our hospital.

At Children’s Hospital Los Angeles, we are in the business of providing great beginnings. We aim to treat kids better through researching the origins of disease, educating the next generation of caregivers and providing exemplary care to our patients and their families.

Please join me in our journey to develop leaders in pediatrics, integrate interdisciplinary research programs and transform clinical programs into innovations of 21st century child, adolescent and young adult health and well-being.

In closing, I would like to extend a gracious thank you to Cheryl Saban, PhD, and Haim Saban, for without their generous gift to The Saban Research Institute, many of these advances would not be possible.

Sincerely,

D. Brent Polk, MD
Chair, Department of Pediatrics
Director, The Saban Research Institute,
Children’s Hospital Los Angeles
The American Recovery and Reinvestment Act of 2009 was passed to help stimulate the U.S. economy by providing significant funding to the National Institutes of Health (NIH). Eight Children’s Hospital investigators were awarded a total of $2.8 million:

- Saverio Bellusci, PhD
- Emil Bogenmann, PhD, EdD
- Jeffrey I. Gold, PhD
- Anatoly V. Grishin, PhD
- Mary Kearns-Jonker, PhD
- Stephen E. Lankenau, PhD
- Robert C. Seeger, MD
- Lingtao Wu, MD

Randall Wetzel, MD, was awarded a $989,855 Challenge Grant in Health and Science Research by the NIH-National Library of Medicine for his project on decision-support software for the management of critically ill children.

Prasadarao V. Nemani, PhD, was awarded $1.65 million from the NIH-National Institute of Neurological Disorders and Stroke to study the role of the macrophage in the molecular mechanism that allows the buildup of E. coli and its eventual invasion of the brain, resulting in meningitis.

Tishya Wren, PhD, received $2.5 million from the NIH-National Institute of Child Health and Human Development to study bone development in children with myelomeningocele, the most severe type of spina bifida.

Children’s Hospital Los Angeles has been named to the prestigious U.S. News & World Report Honor Roll for being among the best in the nation for clinical excellence, and is the only hospital in California to receive this distinction.

Children’s Hospital Los Angeles is the only children’s hospital in the western United States, and one of only seven in the nation, to receive the Top Hospital designation from The Leapfrog Group.

A lifetime achievement award was presented to Robertson Parkman, MD, from the Pediatric Blood and Marrow Transplant Consortium, for his 40 years of contributions to clinical practice, research and teaching in pediatric bone marrow transplantation and immunology.

The following researchers were elected into the Society of Pediatric Research:

- Shahab Asgharzadeh, MD
- Elizabeth R. Lawlor, MD, PhD
- Guy A. Young, MD
- Steven Mittelman, MD, PhD
- Leo Mascarenhas, MD, MS
- Sebastien G. Bouret, PhD

Fatih Uckun, MD, PhD, was awarded $2.5 million by the NIH-National Cancer Institute to support development of a new class of anti-cancer drugs against acute lymphoblastic leukemia.

A grant of $1.68 million from the NIH-National Institute of Diabetes and Digestive and Kidney Diseases was awarded to Sebastien G. Bouret, PhD, to support investigation into the role of leptin in the development of neurological structures that regulate metabolism and body weight throughout life.

Yves A. DeClerck, MD, was inducted as inaugural holder of the Richard Call Family Endowed Chair in Pediatric Research Innovation during the 2010 Saban Research Institute Symposium.
Children’s Hospital Los Angeles, an academic partner of the Los Angeles Basin Clinical and Translational Science Institute, received funding for two pilot grants and three research training awards. Pilot grants were awarded to Yaniv Bar-Cohen, MD, for development of a fetal pacemaker, and Michael Valente, MD, to study cerebral perfusion during pediatric and neonatal transport. Career development awards went to Robert J. Brown, MD, in Pediatric Neuro-Oncology; Melissa Warden, MS, in Oncology; and Ian Holloway, MSW, MPH, in Community, Health Outcomes and Intervention Research.

Trauma surgeon Jeffrey S. Upperman, MD, co-authored a call to action for filling a significant gap in pediatric public health care and seeking federal oversight to establish the framework for a pediatric applied trauma research network.

The U.S. Department of the Army awarded Timothy J. Triche, MD, PhD, $1.05 million to implement next-generation gene sequencing to assist in the diagnosis and treatment of high-risk childhood cancer. He also received $2.9 million from the NIH-National Cancer Institute to study the translation of predictive cancer biomarkers into clinical practice.

Robert C. Seeger, MD, received renewal of a program project grant for $8.2 million on the biology and therapy of neuroblastoma. He was also awarded $1.4 million by the NIH-National Cancer Institute to investigate the clinical use of a highly-sensitive molecular assay for neuroblastoma cells in bone marrow and blood.

Markus Müschen, MD, was awarded two research grants from the NIH-National Cancer Institute. He received $1.8 million to study pre-B cell receptor signaling in acute lymphoblastic leukemia and $1.8 million for his work on AID-induced genetic instability in leukemia.

The NIH-National Cancer Institute granted Steven Mittelman, MD, PhD, $2 million to investigate the role of adipocytes in leukemia relapse.

Thomas Coates, MD, received $1.09 million from the California Institute of Regenerative Medicine for his research into sickle cell disease.

Ching-Ling (Ellen) Lien, PhD, received an NIH grant of $1.9 million to investigate the molecular mechanism of zebrafish heart regeneration.

The NIH-National Heart, Lung and Blood Institute awarded Barbara Driscoll, PhD, $1.6 million for her research into the development and repair of alveolar epithelial cells.

Kasper Wang, MD, received $1.4 million from the NIH to establish the Childhood Liver Disease Research and Education Network.

The California Institute of Regenerative Medicine awarded a training grant to David Warburton, DSc, MD, in the amount of $2.5 million.

Barbara Wheeler, PhD, of the USC University Center for Excellence in Developmental Disabilities at Children’s Hospital, received a $917,000 grant from the Department of Health and Human Services to fund a minority training program with California State University, Los Angeles.

Children’s Hospital Los Angeles was awarded $7 million as partner in the Los Angeles Basin Clinical and Translational Science Institute (CTSI) for accelerating medical discoveries from the lab to the clinic. Michele Kipke, PhD, director of the Community, Health Outcomes and Intervention Research Program, was named CTSI associate director of Community Engagement.
NEW FACES
D. Brent Polk, MD, was named director of The Saban Research Institute, chair of the Department of Pediatrics and vice president of Academic Affairs at Children’s Hospital Los Angeles. He also serves as chair of Pediatrics and vice dean for Clinical Affairs at the Keck School of Medicine of the University of Southern California (USC). Polk served most recently as chief of the D. Brent Polk Division of Pediatric Gastroenterology, Hepatology and Nutrition, director of the Vanderbilt Digestive Disease Research Center and a tenured professor of Pediatrics and Cell and Developmental Biology at Vanderbilt University.

Alexander R. Judkins, MD, became pathologist-in-chief of the Department of Pathology and Laboratory Medicine at Children’s Hospital. He also serves as vice chair of the Department of Pathology and Laboratory Medicine at the Keck School of Medicine of USC. Judkins is recognized for his diagnostic expertise and research in pediatric brain tumors. He previously served as the chief of the Division of Neuropathology, Department of Pathology and Laboratory Medicine at Children’s Hospital of Philadelphia (CHOP) and assistant professor of Pathology and Laboratory Medicine at the University of Pennsylvania School of Medicine.

Stephan G. Erberich, PhD, was named director of Biomedical Informatics at The Saban Research Institute. Erberich returns to Children’s Hospital from the USC Viterbi School of Engineering, where he was appointed division director at the Information Sciences Institute in Health Informatics.

Fatih Uckun, MD, PhD, became head of Translational Research in Leukemia and Lymphoma at the Children’s Center for Cancer and Blood Diseases at Children’s Hospital and Professor of Research Pediatrics at the Keck School of Medicine of USC.

Heather Volk, PhD, MPH, was recruited with joint appointments in the Community, Health Outcomes and Intervention Research Program at The Saban Research Institute and in Preventive Medicine and the Zilkha Neurogenetic Institute at USC. Volk’s research focuses on gene-environment interactions and autism.

Yang Lu, PhD, a health economist from RAND, accepted a joint appointment in the Community, Health Outcomes and Intervention Research Program at The Saban Research Institute and in the Schaeffer Center for Health Policy and Economics. Lu’s research interests include the economics of obesity and policy-relevant health issues, such as the use of emergency departments for non-emergent pediatric care.

Takako Makita, PhD, of Johns Hopkins School of Medicine, joined the Neuroscience Program at The Saban Research Institute. Her research focuses on neuro-vascular interactions during embryonic development. Makita’s work on the role of endothelins as axonal guidance cues for sympathetic axons was published in Nature.
NOVEL THERAPY AT A LOW COST

In pursuit of an effective, inexpensive treatment for meningitis
Bacterial meningitis strikes an average of 1,500 Americans each year. Thirty percent of those infected will die.

In the United States, meningitis resulting from *E. coli* infection primarily occurs in newborn infants, and especially vulnerable premature and low birth weight babies are at four times greater risk for developing the disease. *E. coli* is the leading cause of meningitis in developing countries, where the mortality rates are higher than in the U.S.
“I wanted to make a significant impact on this worldwide health problem,” says Prasadarao V. Nemani, PhD, a researcher in the Microbial Pathogens and Immunology program at The Saban Research Institute. “We set the bar high—not only did we need a new way to treat meningitis, but it had to be inexpensive. Novel therapy and low cost don’t usually go together.”

Without treatment, the mortality rate approaches 100 percent. Even with effective therapy, 15 to 30 percent of affected babies will die. The majority of those who survive face lifelong consequences, including loss of vision, loss of hearing and brain damage.

The disease occurs when bacteria replicate and eventually break through a physical structure called the blood-brain barrier. Comprised of a single layer of specialized cells, the blood-brain barrier is normally very effective in protecting the brain against invading bacteria.
SO WHAT GOES WRONG?

“There is a type of white blood cell, a macrophage, that typically removes bacteria from the bloodstream,” Nemani explains. “But something happens—the cell becomes a traitor. Instead of killing the bacteria, the macrophage helps it survive in the blood and enter the brain. We need to find out what causes that change. Once we know that, we have the basis for preventing meningitis.”

Nemani and his group not only are working to prevent the disease, but they’re also exploring truly innovative strategies for treatment.

“Meningitis is generally diagnosed when bacteria are present in cerebrospinal fluid,” he explains. “By then, brain damage is already occurring. And with large numbers of circulating bacteria, introducing antibiotics causes dead bacteria to release toxins, resulting in septic shock and organ failure. Clearly, we need a better way.”

They may have found it. One of a class of proteins known as cytokines, IL-10 is a molecule normally present in the body that is involved in immune function. Not only does IL-10 eliminate bacteria, but it also appears to repair the first signs of damage to the brain. Results of this study were reported in The Journal of Experimental Medicine.

“We found that during an episode of bacteremia, when a large number of bacteria are circulating in normally sterile blood, IL-10 acts to clear antibiotic-sensitive and antibiotic-resistant E. coli from the circulation of infected mice,” says Rahul Mittal, PhD, a post-doctoral fellow in Nemani’s lab.

Nemani and Mittal have determined that E. coli infection causes damage to the mouse brain comparable to that seen in humans. Three-dimensional imaging studies of infected animal and human infant brains showed similar gross morphological changes.

“When we gave IL-10 to mice 48 hours after infection, those changes to the brain were reversed,” says Mittal. “Since diagnosing meningitis is difficult until bacteria reach the central nervous system, finding an agent that can clear the bacteria while also preventing or restoring the damaged brain is very exciting.”

Nemani returns to the other part of the problem: price. “We could produce IL-10 using recombinant technology and inject it,” he explains. “But that would be expensive. So we began looking for an alternative.”

Together with his team, Nemani, an associate professor of Research at the Keck School of Medicine of the University of Southern California, has identified a receptor on white cells that controls the production of IL-10 during E. coli infection. Using an inexpensive small molecule medication, the team believes that they can stimulate the patient’s immune system to increase production of IL-10 by manipulating expression of this receptor and allowing the patient to heal on his or her own.

An effective, low-cost treatment to battle the ravages of meningitis? Sounds like just what the doctor ordered.

“We set the bar high—not only did we need a new way to treat meningitis, but it had to be inexpensive. Novel therapy and low cost don’t usually go together.”

Prasadarao Nemani, PhD
Acute lymphoblastic leukemia (ALL) is a cancer of malignant white blood cells that multiply with damaging and deadly abandon. It’s the most common form of pediatric cancer, and just 40 years ago, only one in five children survived.

The development of powerful chemotherapies has changed that: almost 80 percent of patients these days can expect to be cured.
Unfortunately, in the case of early relapse, even these drastic measures usually fail. Less than 20 percent of ALL-relapse patients remain disease-free over the long term. Most die within one year of relapse because, as it turns out, these leukemia cells are intrinsically resistant to radiation.

“Unlike bacteria and antibiotics, where the germs become resistant after repeated exposure, with radiation resistance, some leukemia cells are resistant even if the patient had never been treated with radiation before,” says Fatih M. Uckun, MD, PhD, an ALL expert at The Saban Research Institute of Children’s Hospital Los Angeles and former Stohlman Memorial Scholar of the Leukemia Society of America.

To reduce and perhaps prevent ALL relapses, scientists needed to discover why leukemia cells seemingly defy radiation. “We knew that we could kill radiation-resistant leukemia cells if we only knew what made them so resistant, so we set out to determine the mechanism,” says Uckun, professor of Research Pediatrics at the Keck School of Medicine of the University of Southern California (USC) and a member of the Developmental Therapeutics Program in the Norris Comprehensive Cancer Center at USC. “Once we determined the mechanism, the next step was obvious: to rationally design a drug that would take out that specific target.”

In late 2010, a research team led by Uckun did just that, developing a novel approach that renders leukemia cells more vulnerable to radiation therapy. The scientists showed in a proof-of-principle study that their approach works in mice challenged with an otherwise invariably fatal dose of radiation-resistant human leukemia cells.

“The goal was to not only kill more leukemia cells, but more importantly to do so with low doses and so avoid short-term and long-term side effects associated with higher doses of radiation,” he says.

The team’s breakthrough came in two parts.

First, researchers discovered a link between an enzyme called SYK tyrosine kinase and radiation resistance in leukemia cells. In normal immune system cells, SYK kinase is one of several gatekeeper proteins conducting similar functions. Leukemia cells, however, have genetic defects in the regulatory apparatus that normally keep the survival-promoting function of SYK in check.

As a result, says Uckun, the SYK enzyme “is hijacked to a unique and non-redundant survival-promoting role. That’s how leukemia cells survive high doses of radiation.” The work was published in back-to-back papers in the Proceedings of the National Academy of Sciences.

But in the other 20 to 25 percent of patients with ALL, the cancer returns, requiring additional rounds of intense chemotherapy and radiation. Doctors must sometimes resort to the extreme measure of total body irradiation and very high-dose “supralethal” chemotherapy to kill as many leukemia cells as possible—relying on bone marrow transplantation to restore healthy cells also killed in the process.
The scientists concluded that if the SYK kinase pathway in leukemia cells could be blocked, cancer cells would be less resistant to radiation and more likely to be completely eradicated by total body irradiation (in the context of bone marrow transplantation). Thus, the chances of relapse would be significantly reduced.

The second part of the breakthrough was the discovery of a drug specifically designed to target the SYK kinase pathway. Dubbed C-61, the drug binds to and blocks SYK kinase activity, leaving leukemia cells fatally sensitive to radiation.

In experiments using mice carrying human leukemia cells, injections of C-61 prior to radiation and afterward were much more effective in killing cancer cells than current approaches. This work was published in *Radiation Research*, the journal of the Radiation Research Society.

Uckun and his colleagues have since developed a stronger, second-generation SYK inhibitor and hope that it might provide the foundation for personalized radiation therapy regimens that are less toxic and more effective.

While creating better treatments for ALL has been the scientists’ primary focus, Uckun says recent studies suggest SYK kinase is a key player in other cancers, such as non-Hodgkin’s lymphoma, chronic lymphocytic leukemia, acute myeloid leukemia and head and neck cancer.

“Further development of SYK inhibitors like C-61 may lead to therapeutic innovation in other forms of leukemia and non-Hodgkin’s lymphoma,” he says. “Targeting SYK to overcome radiation resistance by combining a SYK inhibitor with radiation therapy would be a potentially paradigm-shifting treatment strategy.”

Uckun will continue to pursue the use of SYK inhibitors as a new class of radiation sensitizers with a new $1.7 million grant award from the National Cancer Institute.

In addition, he and his colleagues have joined the National Cancer Institute Alliance on Nanotechnology Against Cancer and have created nanoparticles of C-61 that are much more potent than the original drug. This work will be presented later this year at the Gordon Conference on Nanotechnology.

With another $2.5 million grant award he received from the National Institutes of Health, Uckun says he hopes to develop clinically usable, state-of-the-art nanomedicine within five years.

“The goal was to not only kill more leukemia cells, but more importantly to do so with low doses and so avoid short-term and long-term side effects associated with higher doses of radiation.”

Fatih M. Uckun, MD, PhD
The numbers are stark. Between 2002 and 2006, the Centers for Disease Control and Prevention reported a 57 percent increase in the number of children affected by autism.

Air pollution, specifically the variety related to vehicular pollutants, could be one factor related to the developmental disorder. Just ask Heather Volk, PhD, MPH, a scientist at The Saban Research Institute of Children’s Hospital Los Angeles.
Volk penned a recent study that found children born to mothers living within 309 meters, or just over 1,000 feet, of a freeway at birth appeared to be twice as likely to develop autism. Her findings have ricocheted throughout the pediatric developmental sciences world—not to mention those of many parents—and suggest that pollution from vehicles like cars and trucks increases the risk for autism.

The study is the first of its kind to link the two.

“There was good biologic reasoning that this might be possible since other research points to lasting adverse health effects among children living near highways,” Volk says. She holds a joint appointment in the Department of Preventive Medicine and the Zilkha Neurogenetic Institute in the Keck School of Medicine of the University of Southern California (USC).

The study, which appeared online in the journal *Environmental Health Perspectives*, supports a theory that environmental factors, in conjunction with a strong genetic risk, may be one possible explanation for the drastic increase in autism. Volk worked with a team of researchers from the Keck School of Medicine of USC and the UC Davis MIND Institute.

While little is known about the role of environmental pollutants in autism, air pollution exposure during pregnancy has been seen in other studies to have physical and developmental effects on the fetus. Exposure to air pollution during the first months of life also has been linked to cognitive developmental delay.

Autism has long been attributed to genetics. So why is it on the rise? Changes in diagnostic criteria and increased awareness are thought to be contributing factors. But many, including Volk and her fellow researchers, felt that those factors don’t tell the whole story.

“There was some rationale that air pollution could be associated with autism,” she says.

Researchers analyzed data from the Childhood Autism Risks from Genetics and the Environment (CHARGE) study, a population-based case-control study of preschool children. Volk focused on children with autism and typically developing children, who served as controls. The children in the study were between the ages of 2 and 5 years old at the start of the study and lived in communities around Los Angeles, San Francisco and Sacramento. Population-based control groups were recruited from the state of California.

The study examined the locations of the children’s homes during the first, second and third trimesters of their mothers’ pregnancies and at the time of their birth, and looked at the proximity of these homes to a major road or freeway.
Volk next hopes to uncover exactly when and how developmental effects occur. She’s working to pinpoint the amount of air pollution children are exposed to during all levels of pregnancy, including specific trimesters, through the first two years of life. This might help scientists understand the timing of autism and identify thresholds of pollutants associated with the disorder.

As her studies evolve, she and other researchers expect to find other environmental factors that contribute to autism, as it is highly likely that most of them operate in conjunction with other exposures and/or with genes.

“Autism is a debilitating disorder that is increasingly prevalent among children,” Volk says. “By working to understand environmental risks that work with genetics, we can understand more of what causes autism and can begin to identify treatments and preventive factors.”

Volk’s co-authors on the study include Rob McConnell, MD, from the Department of Preventive Medicine at USC; Irva Hertz-Picciotto, PhD, and Lora Delwiche, MS, from UC Davis; and Fred Lurmann of Sonoma Technology, Inc.

This study was supported by grants from the National Institute of Environmental Health Sciences, the Environmental Protection Agency, the MIND Institute, the Southern California Environmental Health Sciences Center, Autism Speaks and the Las Madrinas Endowment for Autism Research, Intervention and Outcomes.
Women often look at pregnancy as a time for guilt-free eating. It doesn’t matter how much you eat, because you’re eating for two, right? Researchers at Children’s Hospital Los Angeles are finding that this is far from true. What and how much women eat while pregnant can affect their child’s health for the rest of his or her life.
Childhood obesity is an alarming trend. Recent statistics estimate that 22 million children under the age of 5 are overweight worldwide. And epidemiological evidence confirms that obesity and other diseases can have their underpinnings in a mother’s diet during pregnancy.

Data go all the way back to a famine in the Netherlands during World War II—studies have shown that children born during the famine had higher rates of obesity, diabetes and other health problems. Researchers at The Saban Research Institute of Children’s Hospital Los Angeles are exploring the reasons for this connection.

“We’ve known for decades that the brain is very important to regulating appetite,” says Sebastien G. Bouret, PhD, who is studying the role of perinatal hormones and nutrition in lifelong appetite regulation. “In addition, the human body evolved to promote weight gain to protect us from environmental challenges like famine.

“We have found that obesity risk is greatly influenced by two factors: the nutritional and hormonal conditions of the mother during pregnancy, and the nutritional and hormonal conditions of the infant—with both malnutrition and over-nutrition increasing a child’s risk.”

The hormone leptin, derived from fat cells, is key to this process. Findings from Bouret’s lab indicate that the majority of neurons in the hypothalamus, a part of the brain that plays a role in eating and body weight regulation, develop during mid-gestation under the influence of leptin. Alterations in the intrauterine environment like maternal obesity may have long-term and potentially irreversible consequences on the number of cells comprising the hypothalamus during a period in development when this part of the brain is especially vulnerable.

Bouret, an assistant professor of Pediatrics at the Keck School of Medicine of the University of Southern California, was awarded a four-year, $1.68 million grant from the National Institutes of Health and the National Institute of Diabetes and Digestive and Kidney Diseases to support his lab’s research. His most recent discovery indicates that ghrelin, a hormone produced by the stomach, also plays a major role in brain growth.

“Timing is everything,” Bouret says. “Ghrelin initiates hunger, and leptin controls satiation. We’ve discovered that ghrelin, like leptin, also acts very early in life to affect other processes, such as brain development. While leptin promotes growth of the hypothalamus, ghrelin seems to tell it when to stop.”

His research may provide new insight into how prenatal nutrition leads to obesity and diabetes in children, as well as point to new treatments for these disorders. Bouret stresses that based on these discoveries, early intervention is the key. “Many key physiological processes, including appetite regulation, are established during the perinatal period—that time just prior to and soon after birth—affecting a child’s entire life. By managing an optimal metabolic environment in pregnant mothers and children, we may promote a lifetime of metabolic health.”

“These studies are providing new ways for us to impact the obesity epidemic,” says Richard B. Simerly, PhD, deputy director of The Saban Research Institute and director of the Institute’s Neuroscience Program. “By understanding the effects of too little or too much nutrition during pregnancy and early infancy, we have an opportunity to intercede and prevent a lifetime of serious health problems resulting from childhood obesity.”
Long associated with poor health, obesity has been implicated once again—this time as a cause of the most common form of childhood cancer, leukemia.

In the first study of its kind, research led by Steven Mittelman, MD, PhD, determined that obesity directly accelerates the progression of acute lymphoblastic leukemia (ALL). Through his research, Mittelman has found that fat cells act as a beacon to cancer cells, providing a place to “hide out” while fueling the malignant cells and rendering treatments ineffective.
It has previously been shown that obese people have a higher risk of getting leukemia. However, until this study, published last year in Cancer Prevention Research, it was not known whether obesity caused the increased incidence of leukemia—or if the increase was associated with genetic, lifestyle, health or socio-economic factors.

“It wasn’t clear if obese children might be more exposed to certain things in their diets that could predispose them to developing leukemia,” Mittelman explains. “Or perhaps there are genes that increase the risk of both obesity and leukemia in children.”

He and his colleagues fed a high-fat diet of mouse pellets to induce obesity in two mouse models with cancer. Mice were randomized to a high-fat diet—60 percent of calories from fat—or a control diet consisting of 10 percent of calories from fat. Investigators found that obesity increased the risk of cancer in both models, particularly in older mice.

This observation was consistent with the type of cumulative effect seen with other exposure-related cancers, such as lung cancer related to smoking and breast cancer resulting from increased estrogen exposure. The noted difference in older animals also was in sync with other obesity-related illnesses, such as heart disease, diabetes and arthritis.

“These data imply that some hormone or factor in overweight individuals, perhaps produced by fat tissue itself, may signal leukemia cells to grow and divide,” says Mittelman, an assistant professor of Pediatrics and Physiology and Biophysics at the Keck School of Medicine of the University of Southern California. “Since leukemia is the most common type of childhood cancer, understanding how obesity may increase its incidence could have important public health implications.”
The quest for determining what causes the increase in cancer among overweight children began with another study, conducted by cancer researchers at Children’s Hospital, which found that kids who were obese when diagnosed with leukemia had a 50 percent higher chance of relapsing than leaner children with the disease. Mittelman’s research went on to demonstrate that fat cells can cause chemotherapy resistance in leukemia cells.

With the publication of his most recent study, he continues to focus his work with hopes of designing therapies that will better treat the disease.

Among other studies, he is working to determine if leukemia cells migrate into fat tissue based on signals sent out by fat cells. During the most recent study, leukemia cells were found in the fat tissue of mice—believed to be caused by SDF1, or stromal cell-derived factor 1. There, the fat cells are thought to protect and fuel cancer.

Mittelman also was recently awarded a three-year grant from Gabrielle’s Angel Foundation to investigate whether fat cells provide fuel to leukemia cells. It is believed that fat cells produce amino acids such as glutamine, which fuels cancer cells like leukemia and can make them resistant to certain chemotherapies.

“These are the first steps in understanding the challenges of treating overweight children with cancer,” Mittelman says. “Once we determine exactly how obesity impacts leukemia and its treatment, we can design therapies that can directly attack these mechanisms. I hope these findings will increase awareness of patients and their families and physicians about the possible impacts of obesity on their disease.”

Co-authors of the study included Jason P. Yun, James W. Behan, Nora Heisterkamp, PhD, Anna Butturini, MD, Lars Klemm, John Groffen, PhD, Lingyun Ji and Markus Müsschen, MD, PhD, all of Children’s Hospital Los Angeles.

The study was funded by grants from the National Institute of Child Health and Human Development, the National Cancer Institute and the Children’s Cancer Research Fund.

Mittelman’s findings confirm that obesity’s reputation for compounding issues of poor health is well deserved. It’s a reputation that will no doubt be exploited further in the interest of discovering better treatments for children.

“Once we determine exactly how obesity impacts leukemia and its treatment, we can design therapies that can directly attack these mechanisms.”

Steven Mittelman, MD, PhD
Increasingly, common adult diseases are found to have fetal or early childhood origins. Diabetes, cardiovascular disease and obesity have all been associated with biological “memories” of experiences occurring early in life that weaken physiological systems, resulting in disease years later.

“Improving this trajectory begins in early childhood, allowing us the capability to prevent disease rather than treat it,” says Vicente Gilsanz, MD, PhD, director of Clinical Imaging at The Saban Research Institute of Children’s Hospital Los Angeles. Gilsanz recently co-authored a paper in the *Journal of Pediatrics* linking osteoporosis in adults to late-onset puberty in teens.
Gilsanz reports that the onset of puberty was the primary influence on adult bone mineral density, or bone strength. “We found that, within the normal ranges, those who started puberty earlier had greater bone mass, while those who started later had less.”

Reduced bone mineral density leads to osteoporosis, resulting in bones becoming increasingly brittle and at risk for fracture. With the cost of treatment in 2010 estimated at $10 billion, osteoporosis is a significant public health issue that affects 55 percent of Americans age 50 and older.

“Puberty is a time of significant bone development,” explains Gilsanz. “During this time, bones grow and increase in density. At the end of puberty, the epiphyseal plates close, terminating the ability of the bones to lengthen. When that occurs, the teenager has reached his or her maximum height and, soon after, peak bone mass.”

The 2000 National Institutes of Health Consensus Development Conference on Osteoporosis Prevention, Diagnosis, and Therapy identified bone mineral deposition during adolescence as a critical determinant of osteoporosis risk later in life. The care of patients with osteoporosis is difficult, and most therapies increase bone density by small amounts, yet require long periods of treatment. In contrast, during puberty large increases in bone density occur over a short period of time.
Given that the rate of decline of bone mass in adulthood is approximately 1 to 2 percent each year, a 10 to 20 percent increase in bone density resulting from a naturally-occurring early puberty corresponds to an additional 10 to 20 years of protection against the normal, age-related decline in bone strength.

“People think that regardless of whether puberty begins early or late, your bone health is unaffected,” Gilsanz says. “We now know that is not always true.”

For example, in the past, adolescents with short stature sometimes underwent medical intervention to delay puberty in an effort to achieve greater height. The study suggests that adolescents considering this step, along with their parents, need to be aware of the effect that delaying puberty can have on their later life. They may end up taller, but their bones will have less density, resulting in increased risk for osteoporosis years earlier.

By employing sensitive instruments for measuring bone mass at the beginning of puberty, Gilsanz and his colleagues can extrapolate what a teenager’s peak bone mass will be at the end of puberty.

Using this information, they can potentially identify adolescents at risk for decreased bone density at the beginning of puberty, when there is still time to intervene and take advantage of the tremendous deposition of bone that occurs before puberty ends.

Gilsanz, a professor of Pediatrics at the Keck School of Medicine of the University of Southern California, also is looking at how variations in body composition affect bone gains, hypothesizing that all types of fat are not created equal when it comes to building bone. The accumulation of fat, especially inside the abdomen, is bad for bone, whereas increases in fat in other areas, similar to lean muscle, are beneficial. Gilsanz’s research is supported by the Associate groups, who raise money and good will for Children’s Hospital Los Angeles.

“If visceral fat in adolescents results in reduced bone density, early lifestyle changes not only improve the strength of the child’s skeleton, but also allow that child to develop into a healthy adult,” says Gilsanz.

His study of the relation between the onset of puberty and bone accretion illustrates how early-life experiences can influence later-occurring events. And with time to intervene, the path toward preventing disease—rather than simply treating it—may have just become easier to navigate.

“People think that regardless of whether puberty begins early or late, your bone health is unaffected. We now know that is not always true.”

Vicente Gilsanz, MD, PhD
Less than two inches long and a member of the multitudinous minnow family, the zebrafish (*Danio rerio*) generally doesn’t attract much attention, even in aquariums where it’s most commonly found.

But the tiny tropical freshwater species boasts at least one astounding, if not immediately obvious, ability—it can completely regenerate its heart after injury or amputation.
In research published last year, Ching-Ling (Ellen) Lien, PhD, and her colleagues identified a key biological factor that helps zebrafish rebuild themselves. Lien is an assistant professor at The Saban Research Institute of Children’s Hospital Los Angeles.

The discovery, published in the Proceedings of the National Academy of Sciences late last year, could help scientists eventually develop new therapeutic treatments for cardiovascular disease in people, including perhaps the possibility of self-repair in human hearts.

The key factor discovered by Lien and her colleagues in the Heart Institute and Developmental Biology and Regenerative Medicine Program is the role of platelet-derived growth factors, or PDGFs, in promoting the proliferation and transformation of epicardial cells—a type of cell that surrounds heart muscle and contributes to construction and structure of blood vessels.

PDGFs are found in many species—including humans—and they appear to carry out a number of functions. In mice, for example, they are involved in blood vessel formation, both in development and disease (tumor angiogenesis).

Less is known about PDGFs in zebrafish—Lien’s group is the first to clone the PDGF-B and PDGFRβ genes in the species—but the little fish clearly provides an insightful model for studying the workings of the human heart.

In this case, Lien and colleagues demonstrated that PDGF signaling in zebrafish was required to prompt epicardial cells to multiply and transform, and trigger the formation of coronary blood vessels after injury to heart tissue. Newly formed coronary vessels supplied blood to the damaged heart, allowing it to completely regenerate.

The process is similar to what happens when a heart develops in mouse embryos, Lien says. Researchers found biochemical markers consistent with embryonic development in regenerated zebrafish hearts.

When scientists blocked PDGF signaling, it impaired epicardial cell proliferation, the expression of mural cell (a type of vessel-supporting cell) markers and particularly, coronary vessel development. Regeneration didn’t stop completely because other growth factors are involved and continued to function.

Of course, the human heart cannot regenerate, but Lien says her research might provide clues for medicine to move in that direction.

“Zebrafish are conserved with humans,” Lien says. “That is, nature tends to use the same or similar biological mechanisms and tools in very different species. There are PDGF homologs in humans. Our results suggest that PDGFRβ signaling is important for neo-vascularization during heart repair. In addition, epicardial cells play an important role during heart repair. If we can direct the epicardial cells to contribute to new coronary vessel formation, like the way it happens in fish, increased vascularization of the myocardium might be achieved after injury.”

Naturally, much work remains to be done. Lien, an assistant professor of Surgery at the Keck School of Medicine of the University of Southern California, says potential therapeutic applications of PDGF signaling would need to be carefully controlled, and that different forms of PDGF may produce very different effects and results.

But someday, it might be possible to not just fix a broken heart, but to regrow it good as new. If that happens, a large debt of gratitude will be due to a very small fish.
Infants born prematurely are at increased risk for many problems, including a gastrointestinal disease called necrotizing enterocolitis, known as NEC. Since NEC is often associated with a rapid clinical deterioration that can result in death, early treatment is essential.

Sometimes, in spite of every medical intervention, treatment fails, and a difficult decision must be made to stop bacteria from leaking into the abdomen from the severely damaged intestine, causing a life-threatening infection. As the surgeon removes the diseased small intestine, the child’s life has been forever changed.
Without an adequate length of small intestine, the child cannot digest food or absorb nutrients. The baby’s survival will depend upon total parenteral nutrition (TPN), a form of intravenous feeding. Further complicating this already cloudy picture is the risk associated with long-term use of TPN—liver damage is common, especially in pre-term infants.

Another option for this baby is a small intestine transplant. However, there is only a 50 percent chance that the grafted organ will last as long as five years, and the child will require many medications for immunosuppression to “tolerate” the transplanted organ.

Is that really the best that modern medicine can do for these very small patients? Tracy Grikscheit, MD, doesn’t think so. Grikscheit is an investigator at The Saban Research Institute of Children’s Hospital Los Angeles and an assistant professor of Surgery at the Keck School of Medicine of the University of Southern California.

“I believe the solution for these problems will come from within,” she says. “The small intestine is an exquisitely regenerative organ. The cells are constantly being lost and replaced over the course of our entire lives. Why not harness that regenerative capacity to benefit these children?”

After an initial “proof of concept” study in rats, Grikscheit performed an experiment in 6-week-old pigs since they are similar in size to premature newborns. Results of this study appeared in the Journal of Surgical Research. First, Grikscheit used a biodegradable scaffolding and “seeded” it with stem cells harvested from the intestinal walls of adult pigs. She then placed the structure into the baby pig’s abdomen, in a place with a sufficient blood supply, and closed the incision.

The small intestine is composed of a number of different cell types: epithelium, muscle, nerve and blood vessels. Grikscheit wondered two things: would the implanted stem cells be able to differentiate into the various cell types, and would the cells grow in the appropriate places so that the engineered structure could actually function as a small intestine?

Seven weeks later, she removed the engineered intestine and examined it under a microscope. It looked like a small intestine. The cells had aligned themselves into perfect formation. They “knew” what to do. Not only had the cells formed the microscopic structures present in the small intestine, but they also had developed an adequate blood and nerve supply.

Anatomically, the engineered small intestine has everything it needs to work. In preliminary experiments, Grikscheit has implanted the tissue-engineered small intestine into pigs, and it appears to contain all of the relevant components of functioning intestine. If careful follow-up studies confirm these early results, clinical testing is not far off.

Just a short length of engineered intestine could change the future for those very small patients who now face an uncertain outlook. Grikscheit sums it up: “Many patients won’t need tissue-engineered intestine. But for those patients who do, it could change their lives.”
Cheryl Saban, PhD, and Haim Saban are among the largest individual donors in the history of Children’s Hospital Los Angeles. Their transformative gift of $40 million established The Saban Research Institute and named The Saban Research Building. The Sabans’ cumulative giving to Children’s Hospital now totals nearly $50 million, and they’ve supported a number of innovative programs and projects. Cheryl serves on the Board of Trustees for the hospital, as well as on The Saban Research Institute Committee.

In addition to numerous research initiatives, their generous support funds an international exchange between Children’s Hospital Los Angeles and The Saban Children’s Hospital at the Soroka University Medical Center, Ben-Gurion University of the Negev, in Be’er Sheva, Israel. The program, which offers residents from both hospitals the opportunity to work at the other for two- to four-week visits, aims to bridge cultural divides and promote clinical, educational and scientific collaborations.

Most recently, the Sabans have generously committed to fund a bridge across Sunset Boulevard, in cooperation with Board of Trustees Co-chair Marion Anderson and her husband, John E. Anderson. The hospital is working toward city approvals for the structure, which will connect the 4601 Sunset Blvd. parking structure to the main hospital on the south side of Sunset Boulevard, and symbolically bridge The Saban Research Institute with the hospital’s clinical services.

Cheryl Saban, PhD, and Haim Saban

CHERYL SABAN, PhD, AND HAIM SABAN
We are proud to recognize the following donors who made gifts of $1,000 and above during the last fiscal year to advance research at Children's Hospital Los Angeles. The dedicated investigators at The Saban Research Institute of Children's Hospital Los Angeles would like to extend their deep appreciation for the support of all of our donors. We offer our sincerest thanks to Cheryl Saban, PhD, and Haim Saban, without whom our dream of a world without pediatric disease would not be possible. We also offer our special thanks to the hospital's many Associate and Affiliate groups for their exceptional and longstanding philanthropic support of research.

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Children’s Hospital Los Angeles has once again been named to the elite Honor Roll of children’s hospitals in the U.S. News & World Report rankings. Only 11 children’s hospitals in the United States achieved Honor Roll status for 2011-12, and Children’s Hospital Los Angeles is the only hospital in California to make the list.

You can view the rankings online at usnews.com/childrenshospitals.