childrens hospital
LOS ANGELES

Bench to Bedside

The Saban Research Institute
of Childrens Hospital Los Angeles

Our investigations build bridges between basic research and patient care through translational medicine, which connects the laboratory bench to the patient's bedside. In this way, we are finding new solutions to diseases and birth defects for the children who need them.

BASIC SCIENCE

Uncovering Mysteries of Lung Development

Chronic lung disease and emphysema in adults – the fourth most frequent cause of death in the United States – has long been thought of primarily as a disease of aging smokers. However, fewer than 25 percent of adult smokers actually get emphysema, leading scientists and public health experts to realize there must be other susceptibility factors causing the high rates of this disease.

Wei Shi, MD, PhD*, has found a significant clue in innovative investigations at The Saban Research Institute of Childrens Hospital Los Angeles. His work at the laboratory bench is an example of the breakthroughs in our fundamental understanding of human biology that may eventually lead to new treatments at the patient's bedside.

Dr. Shi is discovering developmental gene networks and cellular processes that determine how well the lung develops and how well it will stand up to life after birth and to such clinically relevant injuries as second-hand smoke. For the first time, he has shown that incomplete development of the lung predisposes it to more rapid "aging" or degeneration and that specific genetic mutations drive the lung's susceptibility to cigarette smoke and possibly to traffic pollution and industrial exposures as well.

Specifically, Dr. Shi is focusing on a cellular network relay system called the Transforming Growth Factor (TGF-beta) signaling cascade. (Signaling cascades or pathways are essentially a sequence of enzymatic reactions by which external signals are transmitted into the nucleus of a cell.) Dr. Shi has found that mutations in the TGF-beta signaling pathway may be particularly dangerous for healthy lung development.

His interest lies in a critical signaling protein in this pathway known as Smad3. One function of the Smad

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protein family is to prevent tumors. "In the developing lung, Smad3 not only has a positive effect on neonatal lung development, but its absence may predispose the lung to emphysema later in life," he says.

Another question he's attempting to unravel is the role of a proteinase (an enzyme that breaks down proteins into amino acids). Matrix metalloproteinase-9 (MMP-9) is a member of a big family of enzymes thought to play a major role in cell behaviors and tissue structure remodeling. In the lab, MMP-9 appears in higher-than-normal activity levels during the destruction of lung tissue at a particular stage in development. "We're trying to find out why," says Dr. Shi.

David Warburton, DSc, MD, FRCP, FRCS*, director of the Developmental Biology Program, says that Dr. Shi's work carries "a major take-home message" for public health. "This is very important information for the many ex-preemies who survived respiratory distress syndrome (RDS) and chronic lung disease as newborns in the 1970s and later, and who are now entering their twenties and thirties," he notes. "Further, it shows that if you fall into this category and have a mutation in the TGF-beta pathway, you would be very unwise to smoke. And if you are a preemie, and your parents smoke around the house, that may be even worse for you."

Babies affected by abnormal lung development often suffer from RDS, an acute lung disease, and have trouble breathing due to diminished lung volume and surface area for gas diffusion.

Dr. Shi is looking at other crucial processes in the body – including the role of bone morphogenetic proteins (BMP) in lung development and diseases. BMPs are members of a growth factor family of proteins involved in organ formation and development. Inadequate BMP signaling causes a variety of birth defects and can disrupt the healthy development of the embryonic lung. The result can be severe respiratory distress, collapse of the developing lung's airways and death. "We're trying to pinpoint the chain of events taking place at the molecular level so we can potentially devise interventions," he says.

His BMP investigations are supported by a grant from the National Heart, Lung, and Blood Institute of the National Institutes of Health, which was renewed in 2006 for a second five-year period.

In addition, Dr. Shi and Dr. Warburton are collaborating with scientists at Harvard University's genome sequence database in an attempt to pinpoint the frequency of changes in key genes in the population of children with asthma. Ultimately, Dr. Shi and Dr. Warburton would like to know whether newborns with abnormal neonatal lung development develop lung diseases such as asthma and chronic obstructive pulmonary disease as adults.

Dr. Shi understands that he's doing the work of a long-distance runner. "This isn't like developing a new drug that may be used in three to five years," he says. "Instead, our investigations may have some impact in five years in changing the thinking about how lung disease happens and even in how we address the disease."

Almost every major advance in health care has taken decades of research. As with any exploratory process, it can be difficult to predict the ultimate benefits. "We are working to identify each piece of the puzzle of development," says Dr. Warburton. "The implications are tremendous, but it takes patience."

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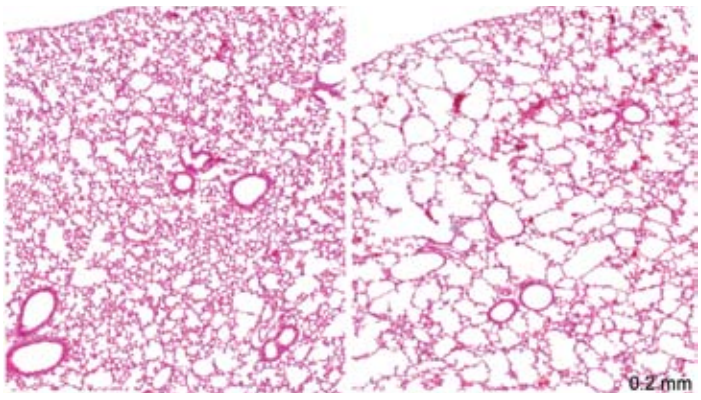

Lung tissue after exposure to cigarette smoke. Left: Mice that have the Smad3 signaling protein. Right: Mice that are Smad3-defective.

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FROM BENCH TO BEDSIDE:
Translational Research in Action

For more than 15 years, we've called our research publication *Bench to Bedside* because that phrase best expresses the kind of research we do. Translational research – the "translation" of basic research into real therapies – enables the most promising ideas to make that all-important journey from the laboratory bench to patients' bedsides.

At Childrens Hospital Los Angeles, our physician-scientists and PhD scientists work in an environment that continually reminds us of the ultimate purpose of our research: to improve the health of children. Physician-scientists leave the lab to care for patients, then return with questions that only basic science can answer. Not only do PhD researchers encounter children and their families in the hospital, some even participate in medical rounds and patient conferences – opportunities they wouldn't have in a lab located away from our pediatric campus.

This genuine interface between laboratory, hospital and community is the driving force of Childrens Hospital's successful research enterprise. In this issue of *Bench to Bedside*, you will read about a range of translational research: basic studies in lung development that may change our thinking about lung disease, advanced imaging techniques that serve as disease predictors, laboratory investigations in neuroblastoma that have led to novel clinical trials, community research into obesity that may prompt questions in the lab and clinical research into chronic abdominal pain.

With your support, this energetic exchange can continue and, together, we can bring the best ideas forward to help children. Thank you.

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

To support the innovative investigations at The Saban Research Institute, please contact Melany Duval, associate vice president of Major and Planned Gifts, at 323-361-1705 or mduval@chla.usc.edu.

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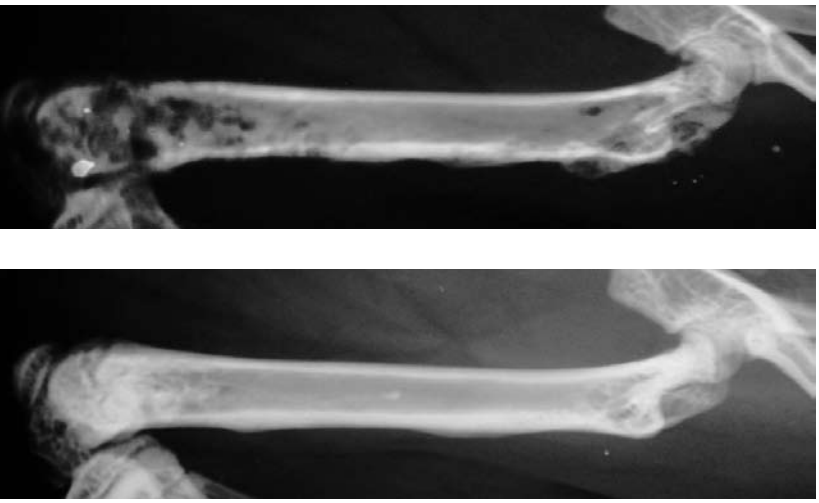

Top: X-ray of a mouse leg with neuroblastoma bone metastasis. Black areas indicate bone destruction by cancer cells. Bottom: X-ray of a mouse leg after bone destruction has been blocked by treatment with Zometa®, a medication that prevents bone resorption. These laboratory studies have led to a new clinical trial.

TRANSLATIONAL SCIENCE

Improving the Odds Against a Deadly Cancer

Among the most aggressive of all childhood cancers, neuroblastoma is a solid tumor of the nervous system that grows outside the brain. One child in 6,000 is diagnosed by age five and roughly half of those battle a high-risk form of the disease, facing only a 40 percent chance of long-term cure.

Improving these odds is the mission of the New Approaches to Neuroblastoma Therapy (NANT) consortium, a nationwide clinical trials research consortium of 13 academic institutions headquartered within the Childrens Center for Cancer and Blood Diseases at Childrens Hospital Los Angeles. NANT investigators design new treatments for children who have failed to respond to standard therapy using laboratory and clinical information. If the treatments are successful for these children, they may be even more successful as a "first-line" treatment.

NANT is a central project of a National Cancer Institute-funded Program Project Grant (PPG) entitled "Biology and Therapy of High-Risk Neuroblastoma." It is led by Principal Investigator Robert C. Seeger, MD*, deputy division head for Research in the Division of Hematology/Oncology and head of the Cancer Program in The Saban Research Institute of Childrens Hospital Los Angeles. Three PPG laboratory projects that provide the foundation for NANT studies are run by Dr. Seeger; Yves DeClerck, MD*, director of The Saban Research Institute; and C. Patrick Reynolds, MD, PhD*, director of the Developmental Therapeutics Program in the USC-CHLA Institute for Pediatric Clinical Research.

Judith G. Villablanca, MD*, is medical director of the NANT Operations Center and co-leader of the clinical trials project. "Our approach is straightforward," she explains. "The basic research is meant to generate new drugs and ideas for using established drugs, which we then implement in patients."

Dr. Villablanca understands this bench-to-bedside philosphy. She was part of the research team at The Saban Research Institute that redefined standard therapy for neuroblastoma by demonstrating that the three-year survival rate more than tripled when chemotherapy was augmented with bone marrow transplantation and follow-up high doses of accutane (a derivative of Vitamin A).

With 60 percent of neuroblastoma patients still failing, NANT keeps looking for better therapeutic strategies. Some explore what Dr. Villablanca calls "cell-killer drugs" to shrink bulky tumors. Other agents being developed for trials may act by blocking the blood supply feeding a tumor, prompting the immune system to destroy cancer cells from within or blocking pathways cancer cells use to survive.

NANT tests combinations of well-established and experimental drugs. Dr. Villablanca chairs a Phase I clinical trial that is adding buthionine sulfoximine (BSO), a synthetic amino acid, to melphalan, a standard chemotherapy agent for neuroblastoma. "Some kids may initially respond to chemotherapy, but their tumor grows back months later, resistant to the drug," explains Dr. Villablanca. "So we need to find new solutions for them." BSO has been shown to re-sensitize tumor cells, offering doctors another chance to utilize melphalan.

Dr. Villablanca, together with Heidi Russell, MD, at Texas Children's Hospital, also is heading up the first-ever clinical trial of Zometa®, a medication that prevents bone resorption, in children with neuroblastoma bone metastasis. The clinical trial was prompted by observations made in Dr. DeClerck's laboratory at The Saban Research Institute into how neuroblastoma cancer cells metastasize into bone. Dr. DeClerck's findings were published in the journal, *Cancer Research* (October 2007).

NANT will begin other clinical trials soon. The more, the better, says Dr. Villablanca. "It can take years for a promising drug to be fully tested and, ultimately, they don't all prove effective. Different therapies may work better for a particular child's neuroblastoma." By running several projects concurrently, the investigators can multiply their chances for success.

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COMMUNITY RESEARCH

Zeroing In on Childhood Obesity – a Growing U.S. Health Problem

Available food choices can impact community health.

The rapid rise in obesity in the United States over the past two decades has become a full-blown public health crisis. The federal Centers for Disease Control and Prevention (CDC) reports that 65 percent of adults are overweight or obese. In addition, from 1980 to 2004, the percentage of overweight children has nearly tripled for ages two to five, more than doubled for ages six to 11, and more than tripled for ages 12 to 19.

Such statistics raise the specter of diabetes – the sixth leading cause of death nationwide – along with other serious health concerns.

"Our findings suggest the community is an important environment that could potentially contribute to childhood obesity," says Dr. Michele Kipke, "and that much can be done to reduce neighborhood-level risks."

In 2007, investigators from the Community, Health Outcomes and Intervention Research Program (CHOIR) in The Saban Research Institute of Childrens Hospital Los Angeles took to the streets of East and South Los Angeles to assess the ground-level impact of this growing health problem. Using their expertise in participatory-based research, they partnered with residents, educators and service providers within these communities and zeroed in on questions related to the available healthy food options as well as the quality and utilization of local parks.

"Research focused on the neighborhood food environment – availability, proximity and the balance of healthy vs. unhealthy options – represents a new form of public health research related to childhood obesity," says Michele Kipke, PhD*, director of the CHOIR program.

Some of the team's findings recently were presented at the North American Association for Obesity Prevention and also were published in the *Journal of Adolescent Health, 2007.* The researchers tallied 190 food outlets in East Los Angeles, nearly half of which were fast-food outlets, with 63 percent of those within walking distance of a school. By comparison, they found 62 grocery stores, only 18 percent of which sold fresh fruit and/or vegetables.

Investigators also found that the five community parks within East Los Angeles accounted for only 37.28 acres of open space, which translated to just 0.543 acres per 1,000 residents. In addition, although these parks provided such amenities as walking paths, recreational equipment and well-groomed fields, many community members chose not to spend time there because of concerns about gang-related violence.

"Our findings suggest the community is an important environment that could potentially contribute to childhood obesity," says Dr. Kipke, "and that much can be done to reduce neighborhood-level risks. Given these and other findings, we have already established a farmer's market within East Los Angeles."

In addition, community groups are working with elected officials to address local violence, while researchers at Childrens Hospital are working with schools and youth-serving agencies to offer new after-school fitness programs.

The CHOIR team has been conducting its research as part of the Keck Diabetes Prevention Initiative (KDPI), a collaboration of Childrens Hospital and the Keck School of Medicine of the University of Southern California (USC). The initiative got its start in 2004 with a $2 million planning grant from the W.M. Keck Foundation and a mandate to identify and address the interrelated factors that lead to obesity and diabetes in East Los Angeles and South Los Angeles.

Co-principal investigators for the KDPI are Francine R. Kaufman, MD*, head of the Division of Endocrinology, Diabetes and Metabolism at Childrens Hospital, and Anne Peters Harmel, MD, director of the USC Clinical Diabetes Program.

"Our goal," says Dr. Kaufman, "is to effect fundamental changes in individual and family behavior, social norms, health-care delivery, the physical environment and public policy to make an impact on this epidemic."

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Dr. Vicente Gilsanz, director of the Childrens Imaging Research Program

TRANSLATIONAL RESEARCH

Innovative Imaging Looks Inside the Body to Predict & Possibly Prevent Future Disease

Vicente Gilsanz, MD, PhD*, is convinced that one key to effective prevention of all-too-common adult diseases – such as cardiovascular disease, diabetes, stroke and osteoporosis – lies in identifying useful biomarkers for their early detection in childhood through the use of advanced imaging techniques.

When he first championed this idea in the late 1980s, "people were doubtful," says Dr. Gilsanz, director of the Childrens Imaging Research Program at The Saban Research Institute of Childrens Hospital Los Angeles. Now, the scientific community accepts this concept – thanks in large part to the research he and his team are pursuing.

Radiology has long played a role in clinical diagnoses. Today's digital imaging not only can provide valuable clinical information but quantitative data, offering new ways to study physiology and the biology of disease. "We have powerful imaging tools that can be used to predict health outcomes," says Dr. Gilsanz.

For example, ultrasound can reveal a thickening carotid artery wall, which may warn of future vascular disease and stroke. Computed tomography can track bone acquisition in growth, low bone density and the risk for fractures. Magnetic Resonance Imaging can measure fat in the abdomen, liver, pancreas and muscle, which may signal a risk for diabetes.

Dr. Gilsanz' studies in children and adolescents were the first of their kind to indicate that bone acquisition is at its greatest during puberty and that peak bone density – a major factor in the susceptibility for fractures in the elderly – is achieved soon after puberty.

Childrens Hospital Los Angeles is a key participant in a multi-center, multi-year study funded by the National Institute of Child Health and Human Development of the National Institutes of Health (NIH), with the main aim of providing data that will aid in the identification of children predisposed to low peak bone mass and osteoporosis in adulthood. "This work, like other studies, could not have been successfully completed without the close interaction of pediatricians, endocrinologists, engineers, orthopaedists, computer scientists and radiologists, who were essential in applying new imaging techniques in innovative ways," says Dr. Gilsanz.

Among the collaborators at The Saban Research Institute he cites are Francine R. Kaufman, MD*, head of the Center for Endocrinology, Diabetes and Metabolism (CEDM); Steven Mittelman, MD, PhD*, a CEDM physician-scientist; Pisit Pitukcheewanont, MD*, clinical director of the pediatric bone program in the CEDM; and investigators Tishya Wren, PhD*; John Wood, MD, PhD*; and Stefan Blüml, PhD*.

Dr. Gilsanz also is collaborating with Michael I. Goran, PhD, associate director of and professor in the Department of Preventive Medicine (Research) in the Keck School of Medicine of the University of Southern California. The NIH-funded study is focusing on ethnic differences in the risk for obesity and type 2 diabetes in teenagers.

Dr. Gilsanz envisions a day when pediatric medicine will expand to include the use of imaging in routine identification of children at risk for common adult diseases decades before the clinical manifestations appear. The goal is to intervene as early as possible during the silent phase of these conditions, devise more effective preventive strategies and change the course of some children's lives for the better.

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CLINICAL RESEARCH

Asking Questions About Chronic Abdominal Pain in Children

Chronic abdominal pain accounts for up to five percent of all pediatric office visits.

The inspiration for a new research project can come from a chemical interaction in a laboratory beaker, years of connecting mysterious cellular processes or a single moment in a lecture hall.

Brynie Collins, MD, is in the third year of a three-year clinical fellowship in pediatric gastroenterology at Childrens Hospital Los Angeles. One day in 2006, she heard Henry Lin, MD, then at the University of Southern California, talk about the role of bacterial overgrowth in adults with irritable bowel syndrome (IBS), and "an idea just clicked," she says. "I thought, 'We should do a study like this in our pediatric patients.'"

Chronic abdominal pain in children and teens can be an insidious condition, often isolating its young sufferers and perplexing doctors with its wide range of associated symptoms. Estimates are that it accounts for two to five percent of all pediatric office visits and affects between 13 and 20 percent of middle and high school children.

In adults, recent data suggest that intestinal bacteria plays a major role in conditions such as IBS, in which adults have chronic abdominal pain often associated with diarrhea, constipation, nausea and/or bloating. In certain circumstances, bacteria travels from the large intestine to the small intestine, causing small intestinal bacterial overgrowth. Studies with adults have shown that 75 to 80 percent of subjects with IBS have bacterial overgrowth compared to only 20 percent of healthy controls. More impressively, when that overgrowth is treated with antibiotics, their symptoms improve.

Whether chronic abdominal pain in children is a precursor to IBS in adults remains to be proven, but a growing body of evidence suggests a link between the two conditions, says Dr. Collins.
In 2007, she received a Career Development Fellowship Award from The Saban Research Institute for her study, "Defining the Prevalence and Role of Small Intestinal Bacterial Overgrowth in Children with Chronic Abdominal Pain." Her mentors: Dr. Henry Lin and Edward D. Gomperts, MD*, associate director of The Saban Research Institute.

The double-blind, placebo-controlled study seeks to evaluate the prevalence of small intestine bacterial overgrowth in children with chronic abdominal pain and to determine if their symptoms improve with treatment using the antibiotic rifaximin.

To study this drug, which has been approved for use in adults, Dr. Collins had to submit an Investigational New Drug Application to the federal Food and Drug Administration, which approved her request in August 2007. She also had to pass a rigorous review by the hospital's Committee on Clinical Investigations. Enrollment started in February, and is expected to go through early 2008. Dr. Collins expects to test 80 kids with chronic abdominal pain and 40 healthy controls, drawn from siblings and family members. Her subjects are between eight and 18 years old, which means their parents get involved, too.

Often difficult to diagnose, children with these complaints are sometimes not taken seriously enough by the medical system and by schools that think they're exaggerating the symptoms or even

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

Translational research takes the most promising findings from the laboratory into clinical trials to test their safety and efficacy. The end result: new treatments for the kids who need them.

"neurotic." But parents and kids know better. "I've had so many parents tell me, 'We're so glad you're doing this study. Nothing we have done so far is working,'" says Dr. Collins.

To test her young subjects, Dr. Collins uses a noninvasive lactulose breath hydrogen test, which measures bacterial fermentation of the nonabsorbable sugar lactulose. Breath is collected every 15 minutes during a three-hour visit and analyzed for byproducts of fermentation. Two-thirds of subjects with chronic abdominal pain are given the antibiotic and one-third receive a placebo. The breath test is repeated after the 10-day treatment course.

At the study's conclusion, Dr. Collins expects to see similar results as in the adult population with IBS – that 75 to 80 percent of children with chronic abdominal pain have bacterial overgrowth. Whether the antibiotics help with symptoms remains to be seen.

The more research she does, the more she enjoys it. She already has other studies in mind, including the role of intestinal bacteria in such pediatric gastroenterology diseases as cystic fibrosis, where malabsorption of nutrients is a major problem. "I've learned during this project that I was meant to do clinical research," says Dr. Collins. "I love the interaction with the patients. All research starts in some way in the laboratory, but I enjoy seeing the clinical response."

Bench to Bedside

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