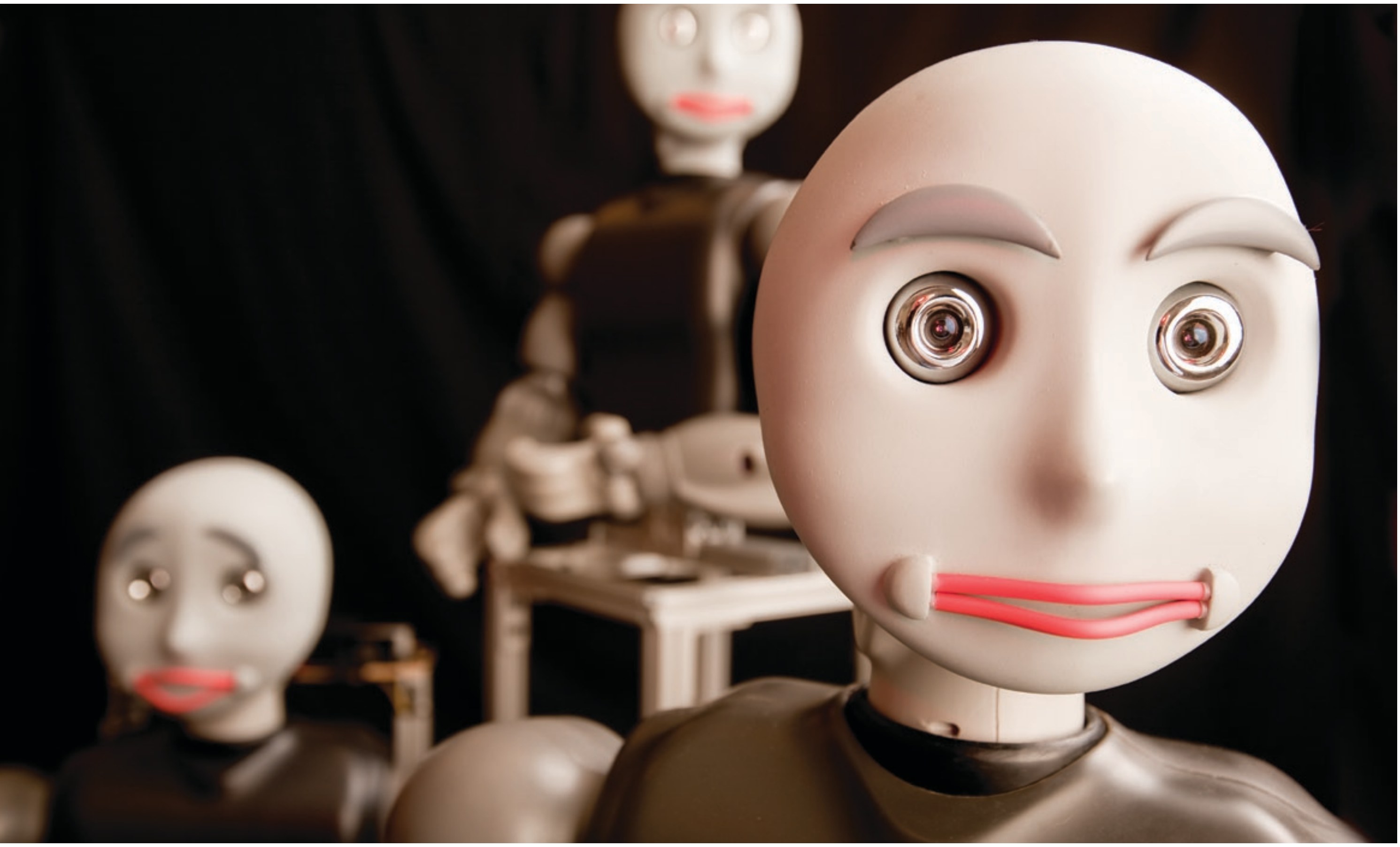
THE SABAN RESEARCH INSTITUTE OF CHILDRENS HOSPITAL LOS ANGELES

BENCH *to* BEDSIDE

SUMMER
2009



A NEW VOCABULARY

More than ever, scientists and engineers are reaching across their respective disciplines to decode the mysteries of human biology, unravel complex genetic relationships, capture and scrutinize millions of bits of data and formulate new strategies against diseases that affect children. This is molecular biology meets advanced mathematics, made possible by accelerating developments in computers and sophisticated methodologies of biomedical data collection and analysis.

The Saban Research Institute

ChildrensHospitalLosAngeles
International Leader in Pediatrics

A MESSAGE FROM THE DIRECTOR

GREAT SCIENCE DOESN'T OCCUR IN SILOS

Major scientific discoveries still often are the result of one individual's brilliant mind. However, with the complexity of science and its dependence on technology, scientific breakthroughs increasingly will come from the fertile exchange of ideas between investigators, often from different disciplines.

At The Saban Research Institute of Childrens Hospital Los Angeles, we actively cross the "knowledge divide" to seek collaborations that can advance the cause of pediatric health. Boundaries between biology and other sciences are disappearing, as we come to rely on sophisticated mathematical modeling, information technologies and powerful equipment. One of our most exciting collaborations is with our colleagues in the USC Viterbi School of Engineering.

Working with these innovative engineers, we are finding ways to share critically needed research data with scientists around the globe, develop more powerful monitoring devices,

BIOLOGY CROSSES DISCIPLINES TO MEET ENGINEERING IN A SPIRITED DIALOGUE

Developmental biologists, oncologists, cardiologists, pulmonologists, engineers and bioinformatics experts are learning to speak each other's languages and — in the course of working together on mighty problems that affect children and adults — creating a new, shared vocabulary.

Nowhere is this conversation more spirited than between the investigators of The Saban Research Institute of Childrens Hospital Los Angeles and their engineering colleagues at the USC Viterbi School of Engineering.

Together, these interdisciplinary thinkers are trying to find answers for such diseases as cancer, inherited blood diseases, respiratory and intestinal disorders, cardiovascular disease, autism and other cognitive issues — as they set the stage for a future of personalized medicine.

The days of a single investigator working in a laboratory, assisted by a graduate student, are over. "It's a collaborative world," says Timothy J. Triche, MD, PhD*, chair of the Department of Pathology and Laboratory Medicine and pathologist-in-chief at Childrens Hospital and a member of the Cancer Program in The Saban Research Institute. "Major research assumes that you will have multiple investigators from different points of view," he adds. "This reality has made things possible that once were impossible."

John C. Wood, MD, PhD, of The Saban Research Institute

Dr. Triche's own research is a perfect example. He and his team — along with colleagues at the Viterbi School and elsewhere — are attempting to unleash the potential of nanotechnology to defeat stubborn cancers. He wants to tap into this miniature world to employ nanoparticles as a cancer-fighting delivery system targeted at specific tumor cells. The complexity of this task "is like building a space shuttle," says Dr. Triche. Fortunately, his collaborations are aided by his own multifaceted background — in particular his undergraduate degree in physics.

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

explore the miniature world of nanotechnology and conduct experiments we otherwise wouldn't be able to perform in patients. In this *Bench to Bedside*, you'll read about some of these productive exchanges.

Just as we partner with our colleagues to make advances in research, we value the partnership with our donors. On behalf of our young patients, we offer special thanks to you, our generous supporters, led by Cheryl Saban, PhD, and Haim Saban. Their vision and transformative gift of $41 million, made in 2003, have inspired and enabled us to make progress toward finding new treatments for diseases that impact children at home and around the world. We invite you to join us in this important cause.

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

Cheryl Saban, PhD, and Haim Saban, the largest individual donors to Childrens Hospital Los Angeles

Other physician-scientists at Childrens Hospital also boast engineering or physics backgrounds, enabling them to feed both sides of this conversation, including:

» Thomas G. Keens, MD*, head of the Postdoctoral Fellowship Training Program in the Division of Pulmonology at Childrens Hospital, whose research focuses on respiratory and sleep disorders. He wrote his undergraduate thesis on famed physicist Albert Einstein. "Neither of us — physicians and engineers — could do this research without the other half," he says. "We've made progress we wouldn't make without each other."

» Shahab Asgharzadeh, MD*, an oncologist in the Division of Hematology/Oncology in the Childrens Center for Cancer and Blood Diseases at Childrens Hospital and a member of the Cancer Program in The Saban Research Institute. Armed with an undergraduate degree in biomedical engineering, he is focused on gene expression profiling and genomic aberrations analysis in an effort to identify "molecular signatures" of tumors and devise highly targeted strategies against cancer.

» John C. Wood, MD, PhD*, cardiologist and director of Cardiovascular Magnetic Resonance Imaging (MRI) for the Heart Institute at Childrens Hospital and an investigator in The Saban Research Institute's Imaging Program. A pioneer in medical imaging, he earned his undergraduate degree in electrical engineering and his doctoral degree in bioengineering. He believes physicians and engineers "share a common love of trying to figure out how things work."

» Thomas D. Coates, MD*, section head of Hematology in the Childrens Center for Cancer and Blood Diseases and director of one of only 12 federally funded Basic and Translational Research Programs studying sickle cell disease in the United States — and the only such research program on the West Coast. Dr. Coates has used his undergraduate degree in physics to study neutrophils (a type of white blood cell) and vascular response in sickle cell disease.

The Saban Research Institute

The Saban Research Institute of Childrens Hospital Los Angeles is among the largest, most productive pediatric research facilities in the United States. It ranks eighth nationwide among 25 standalone institutions and 11th among 101 academic pediatric centers in funding from the National Institutes of Health. Childrens Hospital Los Angeles has been treating the most seriously ill and injured children in Los Angeles for more than a century, and it is acknowledged around the world for its leadership in pediatric and adolescent health. Childrens Hospital is one of America's premier teaching hospitals, affiliated with the Keck School of Medicine of the University of Southern California since 1932.

On the cover: *Robots like these are being employed in autism research by investigators from The Saban Research Institute and the USC Viterbi School of Engineering.*

Thomas D. Coates, MD, of Childrens Hospital Los Angeles

Sickle Cell Anemia

Dr. Coates' undergraduate degree is in physics. In high school, he held an advanced Federal Communications Commission radio license and built transmitters out of the parts from television sets. In college, he earned extra money by wiring together various electrical devices for his fellow physics graduate students. Even now, in his laboratory at Childrens Hospital, soldering irons and power drills share cabinet space with computerized microscopes.

He is using his knowledge of medicine and physics — and his inventive streak — in the fight against sickle cell anemia and other chronic blood diseases.

Currently he is principal investigator in a $2.4 million, multi-year study funded by the National Institutes of Health (NIH) to investigate the impact of blood viscosity (resistance to flow) on oxygen delivery in people with sickle cell anemia.

The team Dr. Coates is leading represents a brain trust from Childrens Hospital, the Keck School of Medicine of USC and the Viterbi School. Its members include Dr. Wood; Herbert Meiselman, ScD, professor and vice chair of physiology and biophysics at the Keck School of Medicine; and Michael C.K. Khoo, PhD, chair of the Department of Biomedical Engineering in the Viterbi School.

The researchers suspect that the autonomic nervous system (ANS) plays a role in triggering or influencing episodes of "sickling," when normally flexible red blood cells become rigid and sickle-shaped. That transformation can prevent the cells' passage through small blood vessels.

The ANS — essentially the body's life support system — is responsible for maintaining homeostasis (the constant state of the internal environment) and coordinating such involuntary functions as breathing, digestion and heart rate.

Previous studies have shown that ANS reactivity in patients with sickle cell is different than in people without the disorder, which may help in predicting future sickling events. One stumbling block is that doctors don't have any means yet for distinguishing the cause or predicting such an event.

"This is pure translational research," says Dr. Coates, "basic science rooted in mathematics and engineering, which ultimately will be turned into medical devices for better measurement of blood flow and viscosity."

Suvimol Sangkatumvong, a biomedical engineering graduate student at USC, is conducting data analysis gleaned from a non-invasive physiological monitoring system called a Lifeshirt™. It can measure human heart rate variability, blood pressure, body temperature and other functions. That activity is then analyzed using a computer model of cardiovascular autonomic control. "We're using all these toys we're wiring together with the help of Dr. Khoo and his students at USC," says Dr. Coates.

"This is pure translational research — basic science rooted in mathematics and engineering."

— THOMAS D. COATES, MD

Imaging

Dr. John Wood is contributing his expertise in signal processing — the extraction of clinically significant information from physiological signals — to the sickle cell anemia project. He and Dr. Coates met more than a decade ago, then joined forces to combine their interests in signaling, cardiology and inherited blood diseases that affect hemoglobin and cause anemia. (Hemoglobin is a protein in red blood cells that carries oxygen and nutrients to cells.) This year, Dr. Wood and Dr. Coates became co-recipients of the H. Russell Smith Award for Innovation in Pediatric Biomedical Research from The Saban Research Institute.

Their collaboration has produced a series of breakthroughs in MRI techniques for measuring iron overload. In patients with the blood disease thalassemia, excess iron accumulates in the body because of enhanced iron absorption produced by the disease and the need for repeated blood transfusions.

"By studying the interactions of water protons with iron, we have developed accurate methods to quantify iron deposition in the heart and liver tissues," says Dr. Wood. He has earned multi-year grants from the NIH's National Heart, Lung and Blood Institute for his internationally recognized research in MRI quantification.

One key to systematically breaking down biological events, he says, has been "Monte Carlo modeling," a class of computational algorithms that rely on repeated random sampling.

The results allow researchers to study, test and predict changes caused by the body's different disease states, as well as to determine which imaging method will be the best tool for quantifying the iron in a particular part of the body. That's particularly crucial when trying to detect and quantify iron overload in organs, such as the brain, where invasive techniques like biopsies can be dangerous.

One of Dr. Woods' recent collaborators has been Nilesh R. Ghugre, MS, a graduate student in the Viterbi School's Department of Biomedical Engineering. Dr. Wood and Mr. Ghugre have been invited to collaborate with scientists in Bogotá, Colombia, on a project to quantify different types of iron in the heart and other organs.

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

An estimated 1,000 people in the United States live with thalassemia; there are an unknown number of carriers. However, the disease's numbers rise into the millions in other countries, particularly in South Asia and the Middle East. Estimates are that seven percent of the world's population — or about 420 million people — are carriers.

Dr. Wood, whose MRI collaborations are now in São Paulo, Brazil, and Bangkok, Thailand, says, "We have to find ways to better share what we've learned with other parts of the world." He's hoping to do just that by tapping into a Grid computing system pioneered by researchers at Childrens Hospital and the Viterbi School — Globus MEDICUS (Medical Imaging and Computing for Unified Information Sharing).

Information Sharing

When it debuted in 2006, Globus MEDICUS essentially broke the medical image communications barrier. This networking technology relies on Globus open-source Grid collaboration software developed at the Viterbi School's Information Sciences Institute (ISI) and Argonne National Laboratories. (Grid computing applies the resources of many computers in a network to a single problem at the same time.)

Today, Globus MEDICUS is connecting 40-plus member hospitals of the nationwide Children's Oncology Group, enabling them to quickly share medical images and data. It also is being used by the 15-institution New Approaches in Neuroblastoma Therapy research group, led by Robert C. Seeger, MD*, head of the Cancer Program in The Saban Research Institute and the Childrens Center for Cancer and Blood Diseases.

In the past, doctors and hospitals have had to rely solely on the electronic medical imaging system created by the Digital Imaging and Communication In Media (DICOM) standards committee. DICOM allows a range of commercial imaging devices (X-ray, MRI and CT scans) to display and manage images from each other.

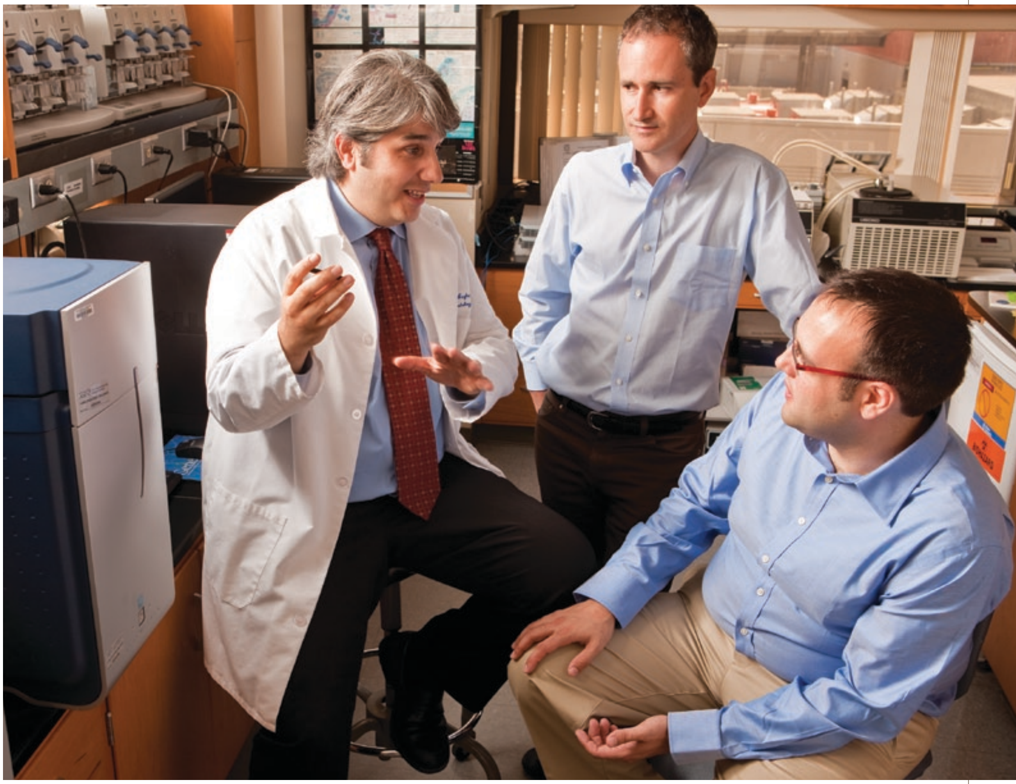
However, access to the data has been limited to the hospital where the images are acquired. Patients either have to leave their digitized images at the originating hospital or carry them on a CD-ROM. "This is not the 21st century health care we need in a networked society," says Stephan G. Erberich, PhD*. A few years ago, Dr. Erberich, director of Functional Imaging and Biomedical Informatics at Childrens Hospital, approached Carl Kesselman, PhD, director of ISI's Center for Grid Technologies. Dr. Erberich's idea: to create MEDICUS by translating DICOM into Grid. Dr. Erberich developed the DICOM-to-Grid interface and led the collaboration between the engineering and clinical teams, working with Marvin D. Nelson, MD*, chief of the Department of Radiology at Childrens Hospital.

DICOM records located anywhere now are easily accessible and exchangeable over Grid-secured Internet connections, using the DICOM Grid Interface Service. Today, Dr. Erberich and Dr. Kesselman co-lead ISI's new Medical Information Systems division.
In 2007, Globus MEDICUS was honored with the prestigious Internet2 IDEA award.

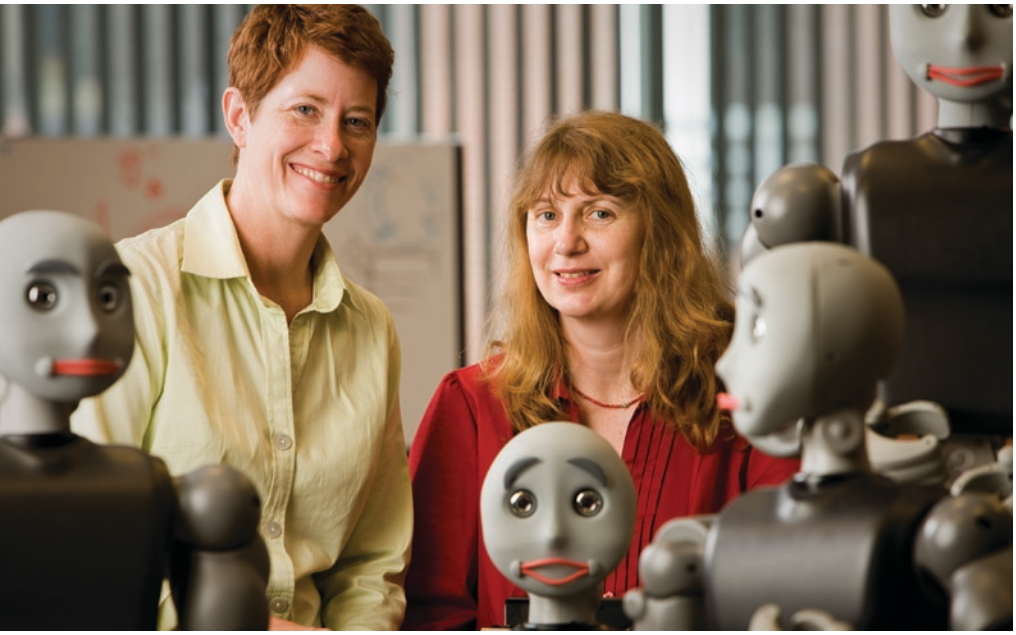
Cancer Genomics

The next generation of cancer therapies depends on being able to pinpoint tumors based on their genetic makeup. Dr. Asgharzadeh and Dr. Seeger are pursuing this strategy under a National Cancer Institute (NCI) grant, part of the NCI's nationwide initiative called Childhood Cancer Therapeutically Applicable Research to Generate Effective Treatments (TARGET).

The process involves imprinting gene chips with millions of spots representing genes; these molecular microarrays are analyzed to determine the activity of each gene. (A microarray is a device, similar to a semiconductor, used to detect the RNA or DNA makeup of a human cell.) The TARGET project aims to catalogue the molecular profiles of more than 300 neuroblastoma tumors using microarray technologies and to ensure rapid access of the data to researchers worldwide. This information could be used to identify prognostic signatures and lead to



Left to right: Shahab Asgharzadeh, MD, of Childrens Hospital, with two of his Viterbi School collaborators, Antonio Ortega, PhD, and Roger Pique-Regi, PhD



Michele D. Kipke, PhD, of The Saban Research Institute, left, with Maja Mataric, PhD, of the USC Center for Robotics and Embedded Systems

identification of therapeutic targets in children with aggressive forms of neuroblastoma, a malignant tumor of the nervous system.

The work results in extremely large data sets, making powerful statistical tools and data processing capabilities essential. "Biomedicine is changing rapidly," notes Dr. Asgharzadeh. "Today we are able to generate a volume of data over a week's time that was impossible to do even a few years ago."

In 2008 and 2009, Dr. Asgharzadeh was lead author on two papers published in the prestigious journal, *Bioinformatics*, on DNA arrays and copy number variations. (Like other types of genetic variation, some copy number variations have been associated with susceptibility or resistance to disease.) Other study participants included two colleagues from the Viterbi School: Antonio Ortega, PhD, a professor of electrical engineering noted for his work in signal compression theory and applications, and Roger Pique-Regi, PhD, then a doctoral student at USC.

Sleep Disorders

Engineering tools also are leading to greater understanding of respiratory and sleep disorders that impact children and adults — a prime interest to Dr. Keens and his fellow pediatric pulmonologist Sally L. Davidson Ward, MD*, medical director of the Childrens Hospital Sleep Laboratory.

Dr. Keens and Dr. Ward have joined forces for the past several years with Dr. Khoo in the Viterbi School to investigate the autonomic nervous system's role in these disorders. Dr. Khoo's own studies focus on improving the modeling of biological control systems, including the heart and lungs.

The collaboration has "elevated our mutual research to a whole new level," says Dr. Keens. Their latest project — conducted under the umbrella of the Viterbi School's Biomedical Simulations Resource (BMSR) — is exploring autonomic and metabolic dysfunction in obese children with sleep-disordered breathing. The program is funded by the NIH's National Institute of Biomedical Imaging and Bioengineering.

Obstructed sleep apnea syndrome isn't just an adult problem. Newborns with craniofacial abnormalities have smaller-than-normal upper airways, while young children with enlarged tonsils and adenoids also may have sleep problems.

The current study subjects — overweight Hispanic adolescents — may develop sleep apnea due to fat deposits in the upper airways. In this life-threatening condition, patients are vulnerable to high blood pressure, pulmonary pressure and cardiac arrhythmias. Researchers expect to enroll about 50 subjects in the study, now in its second year, with the aim of shedding light on issues of sleep apnea, autonomic nervous system function and insulin response.

BMSR's computer modeling enables the team to transform physiological signals into a mathematical model and track such telling clues as heart rate and changes in breathing and blood pressure. "We can begin to see patterns," says Dr. Keens. "This gets to the mechanism of what's happening inside the body, then goes beyond what's happening to help us understand why."

Study findings most likely will benefit others as well. One of Dr. Keens' longstanding research priorities is Sudden Infant Death Syndrome (SIDS) and its relationship to sleep disorders.

"The kinds of abnormalities we're studying in older kids are the same types that may happen in SIDS babies," he says. "To the extent we have a better understanding of how the autonomic nervous system works, this knowledge also may help us prevent or treat SIDS."

Autism Spectrum Disorders

Robots once were solely the purview of science fiction. Today, robotics has become increasingly important — in manufacturing, sea and space exploration, transportation and health care.

Now, researchers at Childrens Hospital and the Viterbi School are exploring the use of robots in encouraging and testing social interaction skills of children with Autism Spectrum Disorders (ASD). ASD affects one in 150 children in the United States, causing impairment in thinking, language and the ability to relate to others.

The new CHLA-USC Institute for the Developing Mind (IDM) at Childrens Hospital is linking research into brain development and autism with comprehensive clinical services for diagnosis and treatment. In 2008, the IDM launched the Boone Fetter Clinic

*Faculty member, the Keck School of Medicine of the University of Southern California to provide comprehensive assessment and treatment services, funded by a gift from the Boone Family Foundation. Additional support has come from the Hearst Foundation.

The IDM plans to recruit additional faculty, aided by funding from the Las Madrinas Endowment for Autism Research, Interventions and Outcomes. "Studies have shown that children treated in the context of a research environment have better outcomes," notes Michele D. Kipke, PhD*, director of the Community, Health Outcomes and Intervention Research Program in The Saban Research Institute.

Autistic children often don't respond to body language and facial cues in the same way as children unaffected by ASD.

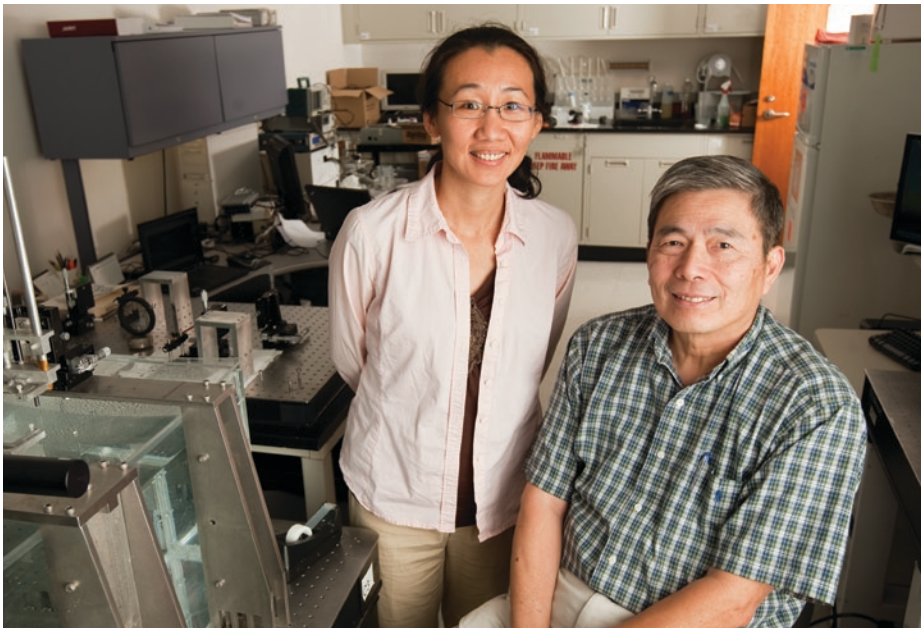
Through a variety of strategies — contingent play (in which the adult responds to a child's action with a similar action), parent participation and the use of both mechanical and humanoid robots — researchers hope to find ways to improve social interaction of these children.

To further this cause, Dr. Kipke and other Childrens Hospital investigators have partnered with members of the Viterbi School who are exploring the role that technology can play in assisting humans.

Maja J. Mataric, PhD, is director of the USC Center for Robotics and Embedded Systems and co-director of the Robotics Research Lab. She has used robots to assist people who have Alzheimer's disease or sufffer from strokes. Shrikanth Narayanan, PhD, director of the Speech Analysis and Interpretation Laboratory and member of the Viterbi School's Signal and Image Processing Institute, is creating computer programs and characters that encourage a child's speech and language development and social engagement.

In early experiments, the scientists replaced toys with rolling robots that have horns and bubble blowers and humanoid robots capable of smiles. An unseen video camera recorded the children's reactions. These preliminary studies confirmed anecdotal reports that children with ASD in many cases react more easily with mechanical devices than humans. The investigations are continuing.

Dr. Kipke is enthusiastic about these studies for what they represent: "a chance to explore how research can ensure that we deliver cutting-edge care to children with autism and their families."



Ching-Ling (Ellen) Lien, PhD, of The Saban Research Institute, left, with Kirk Shung, PhD, of the Viterbi School

Regenerative Medicine

While other research groups at Childrens Hospital are working to apply biomedical engineering tools immediately to patient care, Ching-Ling (Ellen) Lien, PhD*, is using them to study a smaller member of the animal kingdom — the zebrafish.

A freshwater fish, the zebrafish can regrow healthy heart tissue after severe cardiac injury. This regenerative ability intrigues Dr. Lien in the Cardiovascular Research Program of The Saban Research Institute. Her investigations already have identified specific genes and growth factors that are required for the progenitor cells to become heart muscle cells and blood vessels.

However, conducting detailed physiological studies on a fish that measures one inch in length — with a heart just one millimeter in diameter — presents "tremendous technological challenges," says Dr. Lien.

Monitoring the entire regenerative process requires imaging tools capable of extremely high resolution. On most current instruments, probes are too large and resolution too low. So Dr. Lien is collaborating with two groups at the Viterbi School.

One team led by Tzung "John" Hsiai, MD, PhD, in the Department of Biomedical Engineering, is developing a "micro-electrocardiogram," which measures a heart's electrical activity. A second team is led by K. Kirk Shung, PhD, a pioneer in biomedical ultrasonics and director of USC's Ultrasonic Transducer Resource Center, where engineers are creating high-frequency ultrasonics.

Dr. Lien's background is in molecular and developmental biology. "Sometimes, they may not fully understand the process we are studying," she says of her engineering colleagues. "Sometimes we can't understand the limits of their technologies. By coming together, we find there is so much more we can learn from each other and can come up with something that can lead us to the information we need and push the limit of the technology to another level." The collaborators have published two scientific research papers on their progress, most recently in the *Annals of Biomedical Engineering*, 2009.

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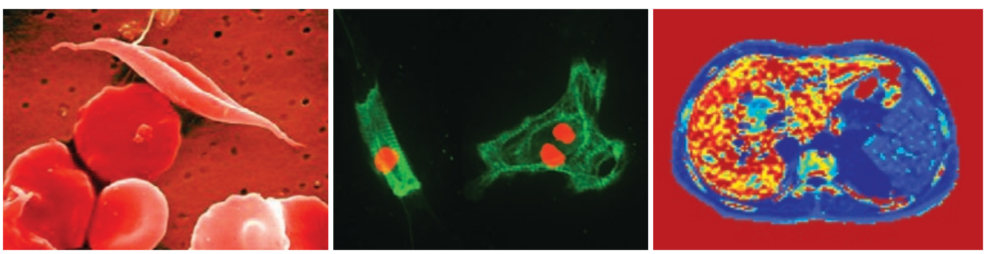
EDITOR: CANDACE PEARSON **CREATIVE SERVICES MANAGER:** ROBIN MOORE-DECAPUA **DESIGN:** WARREN GROUP | STUDIO DELUXE **PHOTOGRAPHY:** WALTER URIE



From left to right: Red blood cells beginning to "sickle" or deform into crescent shapes; zebrafish stem cells; an iron content color map of the liver — blue indicates low iron content, while red equals high.

CONTINUED FROM PAGE 7

Nanotechnology

When most people think nanoscale, they think small — and rightly so. After all, it takes 24.5 million nanometers to equal one inch. A typical germ is about 1,000 nanometers, while a water molecule is under one nanometer in diameter.

Yet, nanotechnology holds big potential for targeted cancer therapies. That potential is still a long way away, says Dr. Triche, a member of the USC Provost's Biomedical Nanoscience Initiative. Other members include faculty from the Viterbi School of Engineering, as well as the Keck School of Medicine of USC.

Dr. Triche wants to send nanoparticles in to fight cancer as customized delivery systems, packed with toxic agents. His particular interest is in Ewing's sarcoma, a rare and often deadly bone cancer that generally strikes children and young adults.

The plan sounds ingenious, but the hurdles are many. "We need a delivery system that is 100 percent reliable, reproducible and works every time before we can consider launching it into a patient to knock out the cancer-causing genes," says Dr. Triche.

His lab in The Saban Research Institute has been successful in targeting Ewing's sarcoma in mice using nanoparticles filled with silencing RNA (siRNA) that turn off the genes necessary for tumor growth.

The process is "fiendishly difficult," he says. Every aspect of nanoparticles — size, composition, flexibility, concentration and shape — influences how they behave. Viterbi engineers are working on such issues as nanoparticle composition, as well as size, deformability and solubility. Other projects are exploring advanced tools to monitor, image and measure the process at work. At only 70 nanometers in diameter, these nanoparticles are too small to see with conventional instruments.

Most recently, Dr. Triche's team has focused its efforts on refining and perfecting surface characteristics of nanoparticles "so they'll stick to what you want and don't stick to what you don't want, and aren't rejected by the immune system."

The scientists also are experimenting with different targeting agents, which tell the nanoparticles where to travel. Of current interest is CD99, a cell surface molecule expressed in virtually all Ewing's sarcoma.

Through it all, Dr. Triche is motivated by a question that has fascinated him for decades: why do patients with similar tumors react differently to the same therapy? "We believe in the potential for targeted, personalized medicine," he says. "We're finding out new information at every step."

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

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