THE SABAN RESEARCH INSTITUTE OF CHILDRENS HOSPITAL LOS ANGELES

BENCH *to* BEDSIDE

SPRING
2010

BRINGING RESEARCH TO LIFE

All treatment advances result from a process at once simple and complex, in which discoveries made at the laboratory bench are tested, then translated into practical applications for patients. It's a process commonly called "bench to bedside." Our clinical investigators put novel medications through the rigors of clinical trials and explore technology's potential to forge new therapies. Then we take the process another step — from "bedside to community" — to ensure that more children benefit from the best ideas.

The Saban Research Institute

ChildrensHospitalLosAngeles

International Leader in Pediatrics

TRANSLATING NOVEL IDEAS TO CLINIC & COMMUNITY

The spark that leads to a new treatment may start in the laboratory. It may begin in an observation at a patient's bedside or in the community, with recognition of a public health need. Great research flows in all directions.

In the past, the National Institutes of Health (NIH) and other federal agencies have invested heavily in basic research at the laboratory level. However, in recent years the NIH also has recognized the importance of supporting the translation of novel ideas to the clinic and community through clinical studies that can directly impact human health.

Clinical research is the subject of increased emphasis at Childrens Hospital Los Angeles, where basic scientists, physician-scientists and community-based researchers engage in a spirited dialogue. In this Bench to Bedside, you will read about just a few of our exciting projects, including artificial intelligence, virtual reality, cancer surivorship and new drug therapies.

EXPLORING QUALITY OF LIFE AFTER CANCER DIAGNOSIS

As recently as the 1970s and '80s, up to 80 percent of children diagnosed with cancer did not survive. Faced with such grim odds, pediatric oncology professionals focused on helping more children simply survive or helping families cope with the loss of a child.

Today, more than 80 percent of children diagnosed with cancer will survive — in fact, one in 550 young adults in the United States is now a cancer survivor. With these growing numbers come concerns about quality of life *after* cancer. Due to their disease and long-term effects of aggressive treatments, many survivors are predisposed to health problems that may not be apparent until years later.

It's a question that inspires the clinical research conducted by Kathleen Ruccione, RN, MPH, CPON, FAAN*, and the program she serves as co-director, the Hematology Oncology Psychosocial and Education (HOPE) Program in the Childrens Center for Cancer and Blood Diseases at Childrens Hospital Los Angeles.

The HOPE Program has helped to pioneer the scientific exploration of survivorship, psychosocial adjustment and improved health outcomes. "When people think about research, they often think in terms of laboratory science at a cellular or molecular level. The full spectrum of research at Childrens Hospital extends to the life-altering effects of illness and its treatment on well-being and quality of life," explains Ms. Ruccione, director of Center Communications, whose research interests also include health literacy, social networking and informed consent.

Left to right: Kathleen Ruccione, RN, MPH, CPON, FAAN, with Jacqueline Gilberto, MPH, and Susan Gantan, MPH, in the HOPE Program offices

HOPE Program findings are continually fed back to improve clinical supportive care. In addition, by evaluating the effects of treat-

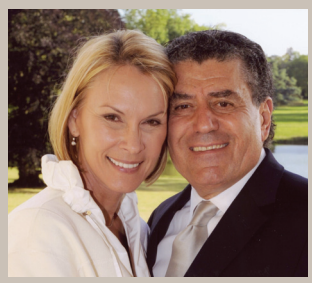
*Faculty member, the Keck School of Medicine of the University of Southern California

I want to take this opportunity to inform you that, as of April 1, 2010, D. Brent Polk, MD,* our new vice president for Academic Affairs and chair of the Department of Pediatrics at Childrens Hospital, will combine his position with that of director of The Saban Research Institute. This will allow for closer integration of the research enterprise with Childrens Hospital's Divisions and Centers of Excellence.

It has been my privilege to serve as director for 15 years and to work with hospital faculty, leadership and trustees in building The Saban Research Institute into a top-ranked pediatric research center.

Our success should be credited to the commitment of our institution, our leadership and our friends. I want to sincerely thank you for your generous support of our mission over the years.

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



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

ments on quality of life, researchers modify treatment designs to minimize acute toxicity and late or lingering effects.

The HOPE program is made possible with the generous support of Cheryl Saban, PhD, and Haim Saban, its largest annual donors. Other major donors include Jonathan Kellerman, PhD, and Faye Kellerman; Mindy Weiss; Paula Noah; Aura Kuperburg, PhD, and Fred Kuperburg; Derek Alpert; and the Audrey and Sydney Irmas Charitable Foundation.

Ms. Ruccione collaborates with her colleagues in HOPE, including co-director Ernest R. Katz, PhD, and Kathleen Meeske, RN, PhD, director, Health Outcomes and Cancer Control Research.

In addition, she extends her interdisciplinary reach as chair of the Nursing Committee for the Children's Oncology Group (COG), an international childhood cancer research network, where she has been instrumental in developing a visionary model for collaboration with nurse researchers.

"Nurses are on the front line of clinical cancer research, 24 hours a day," she notes. "While administering the rigorous treatment protocols, they constantly assess and address the physical and emotional well-being of patients and their families and help them manage the challenges cancer poses."

At Childrens Hospital, Ms. Ruccione steers several clinical research projects, including the Childhood Cancer Survivor Study, a 26-center project supported by the National Institutes of Health (NIH). Another NIH-funded project, the PROMIS Study — Patient-Reported Outcomes Measurement Information System — is developing ways to measure quality of life.

Ms. Ruccione also collaborates on health literacy with investigators at the USC University Center for Excellence in Developmental Disabilities, as well as with Margaret McLaughlin, PhD, professor of communication at the USC Annenberg School for Communication.

"My goal is to inform and empower patients and families to be active participants in their care," says Ms. Ruccione, "and to have the best possible quality of life during and after cancer."

www.celebratelifewithhope.org

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: *Zorash Montaño, wearing virtual reality goggles used in pain management studies.* *See page 6.*

Dr. Guy Young

Children are not adults in miniature, especially when it comes to taking medication. Metabolism, weight and hormones — each a key influence on how the body processes a drug — are in a state of constant change during childhood and teen years.

This reality makes pediatric drug dosing an intricate issue, further complicated by diet (some medications interfere with vitamin absorption) and the ability to take medication. Drugs only available in oral form are difficult to administer to infants and small children. Transdermal drugs may cause excess absorption in children, given their thinner skin.

Yet at least 70 percent of drugs in the standard *Physicians' Desk Reference* contain no dosing information for children — all of which presents a challenge for physician-scientists like Guy Young, MD*, director of the Hemophilia Treatment Center in the Childrens Center for Cancer and Blood Diseases at Childrens Hospital Los Angeles and an investigator in The Saban Research Institute.

In Dr. Young's case, he decided to confront the issue by initiating his own investigations into new therapies for a problem that concerns him: pediatric thrombosis.

Thrombosis — the formation of potentially harmful clots in blood vessels — may be more prevalent in adults, but it's a potentially life-threatening condition for children as well.

Risk factors include genetic defects, recent surgery, immobilization, congenital heart disease and — ironically — a technological advancement in the care of critically ill patients: the central venous catheter (CVC).

Also called a "central line," the CVC — a thin tube inserted into a vein in the neck, chest or groin — enables a medical team to administer medication or fluids and perform blood tests. Yet, its advent also has caused a sharp rise in pediatric thrombosis. "We're seeing more and more young patients with this condition," notes Dr. Young.

Inspired by the pressing need, Dr. Young began studying novel anticoagulant therapies in children with thrombosis more than a decade ago — and is now the first physician-scientist to test a new generation of anticoagulants in pediatric clinical trials. (An anticoagulant helps to decrease the blood's clotting ability and prevent clots from developing.)

When he began, clot-prevention medications for adults had some negative properties that were compounded when used in children. For example, Coumadin, the most widely prescribed anticoagulant drug in North America, is only available in pill form, and crushing it for easier delivery complicates its dosing in children.

By the late 1990s, Dr. Young noted the use of new anticoagulants for adults that he felt might benefit children. At his urging, The Medicines Company agreed to participate in a pediatric clinical trial of Bivalirudin, normally used in adults undergoing coronary angioplasty. Dr. Young's study involving newborns to infants six months of age was published in 2007. Its primary determination: that the drug was as safe and perhaps more effective in children than the standard drug, Heparin.

Thrombosis—the formation of blood clots—isn't just life-threatening for adults. "We're seeing more and more young patients with this condition."

— GUY YOUNG, MD

From 2003-2005, Dr. Young headed the first-ever pediatric clinical trial of GlaxoSmithKline's anticoagulant Argatroban. In 2006, he launched a pilot study of pediatric dosing levels, safety and efficacy of Fondaparinux, also manufactured by GlaxoSmithKline for prevention and treatment of deep vein thrombosis and embolism. That study was funded by the Food and Drug Administration (FDA) Office of Orphan Products Development, and involved three other sites in California, Ohio and Texas.

His work over the past several years led to a major award in 2008 from the National Institutes of Health (NIH) for a second study of Bivalirudin, this time involving children ages six months to 18 years. The seven-site NIH study is the only pediatric investigation into the drug's effectiveness against deep vein thrombosis.

In 2009, the German pharmaceutical giant Bayer AG asked Dr. Young to lead a pediatric trial of its new oral blood thinner, Rivaroxaban, which is undergoing review by the FDA. Childrens Hospital Los Angeles is the sole U.S. study site; others are in Canada, Austria, Germany, Italy, Israel and Australia.

Thrombosis can result in a complication called post-thrombotic syndrome, impairing blood flow through the veins. There is no treatment. "An 80-year-old who develops post-thrombotic syndrome will have to live with its consequences for perhaps 10 years," he notes. "A 12-year-old has to live with it for several decades."

SPOTLIGHT

Johnny Ponce: Clinical Trial Participant

For 16-year-old Johnny Ponce, deciding whether to participate in a clinical trial of a new anticoagulant medication at Childrens Hospital Los Angeles was a no-brainer.

He wanted in as soon as he learned he'd only have to take Fondaparinux Sodium (Arixtra) once-a-day, versus an alternative drug's twice-a-day regimen. "Any kid would rather take one shot than two," says Johnny, now 18.

Beyond that practical advantage, he also liked the idea of being part of a scientific experiment that could help generate valuable information about the drug and its impact.

Johnny took part in the study of Fondaparinux directed by Guy Young, MD, director of the Hemophilia Treatment Center in the Childrens Center for Cancer and Blood Diseases and a leader in pediatric thrombosis research.

Before Dr. Young's investigation, no one had looked at the safety and efficacy of Arixtra in pediatric patients. "I wasn't worried about trying it," says Johnny. "I knew that the drug had already been used by adults, and I was older, too, by Childrens Hospital standards."

His mother, Maria Aguilar, had no reservations about her eldest son being part of a clinical trial. "If we can help other families the way we've been helped, we want to do whatever we can," she says.

"Thanks to patients like Johnny and their families, we're able to expand our knowledge about promising new therapies and bring them to more children," says Dr. Young. "Their contributions are enormous."

Johnny developed a blood clot after being diagnosed with leukemia at Childrens Hospital in November 2007 — a diagnosis that turned the young athlete's world upside down. He remained on the anticoagulant 11 months, then asked to be taken off so he could resume playing football and baseball. However, within four months, another clot appeared, and he had to quit sports and resume taking Arixtra.

Johnny's treatments for leukemia ended this February. He's now attending Citrus College with an eye toward transferring to Azusa Pacific University to major in nursing. He plans to specialize in pediatric oncology. "I want to be the nurse that the kids with cancer can relate to, the one who's been through what they're going through."

Johnny Ponce

Dr. Randall Wetzel

HIGH-TECH **HEALING**

At The Saban Research Institute of Childrens Hospital Los Angeles, scientists work at the outer edges of new technologies — including artificial intelligence and virtual reality — in the search for ways to improve patient care.

For Randall C. Wetzel, MB, BS, FCCM, FAAP, MBA*, the quest focuses on artificial intelligence (AI), specifically, informatics — engineering novel database systems to support medical decision-making.

It's a passion that has inspired the energies of the chief of the Department of Anesthesiology Critical Care Medicine at Childrens Hospital for years. In 1998, Dr. Wetzel pioneered the hospital's Laura P. and Leland K. Whittier Virtual Pediatric Intensive Care Unit, which streams the world's largest database on pediatric critical care patients.

Dr. Wetzel's fascination with computer technology comes, he says, from years of practice in critical care medicine. "Every time I see a patient, what I most want to know is what other physicians have done for children very much like this one. Down to the tiniest granular detail, how were they treated? And what were the outcomes?"

His vision: to develop software that can hold and compile such a massive amount of medical data for meaningful review. Using this program, doctors could make treatment decisions based not only on their own professional experience, but on the experience from other practitioners in hundreds, even thousands, of relevant cases.

RESEARCH CONTINUUM

DISCOVERY ❯❯❯

An original observation based on a scientific hypothesis

DEVELOPMENT ❯❯❯

Verification of the hypothesis and the development of a treatment (drug) or tools (technology) to apply the observation to human health

In Vitro Testing
An observation or study made experimentally in a test tube environment (*in vitro* translates as "in glass")

***Pre-Clinical* Testing**
Testing the new drug or technology on non-human models

Generating new ideas

Generating new, less toxic drugs

Dr. Wetzel has had to wait years for technology to catch up with his vision. It finally has.

This year, with support from the National Institutes of Health (NIH), he will collaborate with scientists at the Jet Propulsion Laboratory in Pasadena. Their goal is to create an AI system that can archive and compare histories on pediatric critical care cases. In time, the research team will use the software to launch an initial database of 30,000 histories from Childrens Hospital, available online to hospitals nationwide that agree to gather and share comparable data.

"The ultimate goal," says Dr. Wetzel, "is one enormous information space that exists to improve patient outcomes, available to everybody through rapid data transfer."

Dr. Wetzel also hopes the project will be able to shrink lag time between research concepts and improved therapies. "It shouldn't take 15 years to go from a solid investigational idea to an accepted new medical practice," he says. Using AI systems like the one his team will design, he expects that hospitals eventually will conduct sophisticated research by treating similar patients differently, each as they think best. "A year later our analytics will tell them who's more correct and why."

Virtual reality

For his part, pediatric psychologist Jeffrey I. Gold, PhD*, explores how children perceive pain and how it can be relieved using virtual reality (VR). Imagine: children wearing head-mounted display units, playing in elaborate 3-D environments. As they ski down mountains with their partner, Penguin Racer, they hear wind blow and ice crackle. As they bounce off gigantic snow banks, they experience the exhilaration of flight — becoming so immersed in this arctic wonderland that tolerance to pain skyrockets.

The question isn't whether VR can reduce pain perception, says Dr. Gold, a member of Childrens Hospital's Comfort, Pain and Palliative Care Program, but how it accomplishes this feat. "I suspect it triggers a kind of analgesic effect, that VR actually engages the same neurochemistry as an opiate," he explains. "So even in the face of pain, the

CONTINUED ON PAGE 8

Dr. Jeffrey Gold with Angela Li, clinical research assistant

CLINICAL TESTING ››› *OUTCOME ANALYSIS*

Phase I: Safety
Researchers test a promising therapy in a small group of patients to evaluate its overall safety and side effects. Before the trial can begin, it must pass the scrutiny of an Internal Review Board called the Committee on Clinical Investigations.

Phase II: Efficacy
Once the initial safety is established, a Phase II trial is performed to assess how well a proposed drug works in a larger group of volunteers and patients — and to continue evaluating its safety.

Phase III: Comparison
These studies — typically randomized controlled multicenter trials on large patient groups — assess how effective the drug is compared with the current "gold standard" treatment.

Examining the long-term effects of a drug on quality of life

The Saban Research Institute
of Childrens Hospital Los Angeles
PO Box 27980
Los Angeles, CA 90027-0980

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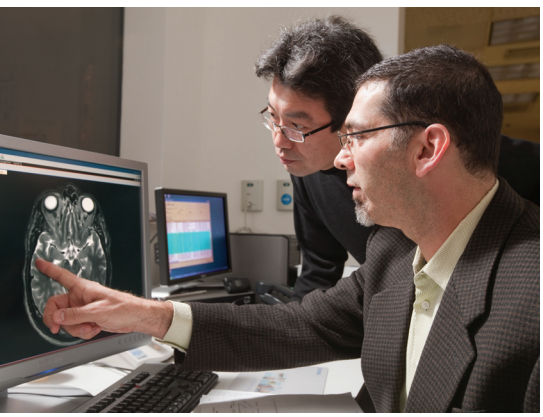
Left to right: Seven-year-old Samantha De la Torre with Kathleen Ruccione; Johnny Ponce, a clinical trial participant; and Angela Li demonstrating virtual reality tools.

HIGH-TECH HEALING

CONTINUED FROM PAGE 7



Dr. Vincent Chen, left, with Dr. Jeffrey Gold

brain generates this good feeling without the need for as much narcotic."

A recognized leader in pain research and director of the Pediatric Pain Management Outpatient Clinic at Childrens Hospital, Dr. Gold was the first scientist ever to receive The Saban Research Institute's Academic Career Development Award for clinical research, the year it was established in 2007. He used that key support to launch a functional magnetic resonance imaging (fMRI) study that explored how adult neural activity responds to a thermal pain stimulus, without VR immersion and while subjects engage in gaming.

Building on the success of that study in adults, Dr. Gold and his collaborator, Vincent Chen, PhD*, gained NIH funding in 2009 to conduct a similar study in adolescents ages 14 to 17. This March, they began enrollment in what will be the first fMRI study of its kind to focus on pediatric patients.

Dr. Gold expects a number of significant findings to emerge. First, he thinks his results may refute the theory that VR simply derails pain awareness. "While parts of the brain responsible for pain perception probably are deactivated when children get immersed in gaming, other neural centers maybe actually get stimulated," he says. In other words, VR may activate areas of the brain that can inhibit normal pain response.

The study also could lead to further investigations focused on children who live with chronic functional pain syndromes. "To establish that chronic pain does exist as a structural brain dysfunction," says Dr. Gold, "would validate everyday experience for many kids and invite further research on potential therapies. How cool would that be?"

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.