

USC researchers unlock stem cell communication secrets

'The results are totally surprising. There is complex coordination not apparent to the naked eye.'

—Cheng-Ming Chuong, professor of pathology at the Keck School

By Pauline Vu

In one of the first studies to look at the population behavior of a large pool of stem cells in thousands of hair follicles, Keck School of Medicine scientists deciphered how hair stem cells in mice and rabbits can communicate with each other and encourage mutually coordinated regeneration.

The team, whose work appears in the April 29 edition of the journal *Science*, collaborated with mathematical biologists from the University of Oxford on the article, "Self-Organizing and Stochastic Behaviors During the Regeneration of Hair Stem Cells," which was just named an Editor's Choice in *Science Signaling*, a sister publication of *Science*.

The researchers analyzed over many months the changes in the hair growth patterns on shaved mice and rabbits, which indicate cyclic progression between active and quiescent states by stem cells in hair follicles.

"The results are totally surprising. There is complex coordination not apparent to the naked eye," said Cheng-Ming Chuong, professor of pathology at the Keck School and the principal investigator of the study funded by the National Institutes of Health. The "complex coordination" Chuong refers to is the ability of the large hair stem cell population to communicate with each other to reach robust hair growth, manifesting in a constantly shifting hair wave pattern that



© Phil Channing

Cheng-Ming Chuong

often looked like a piece of abstract artwork "painted" on the rabbit's skin.

The scientists found that hair stem cells coordinate their regeneration with the aid of a pair of molecular activator

Wnt and inhibitor BMP. When Wnt and BMP signals are used repetitively among a population of thousands of hair follicles across the entire skin surface, complex regenerative hair growth behavior emerges via the process of self-organization.

The research holds potential for finding a cure for alopecia, or hair loss, by improving their environment for communication. Alopecia occurs in humans partially because stem cells in human hair follicles, unlike those in mice and rabbits, have lost the ability to communicate with each other.

"When each human hair follicle wants to regenerate, it can only count on itself; it's not getting help from other

See **STEM CELL**, page 4

\$3 million NIH grant paves way for expanded radiology services

By Leslie Ridgeway

Diagnostic imaging at the Keck School of Medicine Department of Radiology just took a giant step forward with the award of a \$3.1 million National Institutes of Health (NIH) grant to purchase a new cyclotron for USC's Molecular Imaging Center.

While the grant means a boost in capacity for diagnostics in oncology, cardiology, neurology and other clinical disciplines, it also has an impact on basic and translational research throughout USC, said Peter Conti, professor of radiology, biomedical engineering and pharmacy.

"This has broad based implications for the university," he said. "The School of Pharmacy, the Chemistry and Biology departments at the USC Dornsife College, and the USC Viterbi School of Engineering are just some of the units that will see this as a core resource. Novel uses of this technology are being defined every day by teams of researchers in a spectrum of fields from stem cell biology to material sciences."

A cyclotron is used to create short-lived isotopes used for basic research and development of new diagnostic imaging tests in humans and animals, Conti said. They are produced on an as-needed basis for same day experimentation. Recently,

purchasing these isotopes from local outside companies was necessary to maintain clinical and research activities due to the poor reliability of the aged instrumentation at USC, adding costs and delays and affecting the university's ability to obtain research grants, he said.

"This reinvigorates our research program," he said. "It also gives us the ability to do more clinical trials and attract

more patients. Many patients on clinical trials require access to novel diagnostic agents not available from commercial manufacturers, but now we will be able to create materials on site so that they can be used in such studies."

The new cyclotron's technological advances will yield reductions in energy consumption and overall operating costs, which could result in eventual cost savings for

patients, according to Conti. He also said the new technology is self-contained, minimizing radioactive exposure to workers and the community.

As plans are made for facility upgrades to house the new cyclotron, including incorporation of a GMP (Good Manufacturing Procedures) production facility, Conti's institutional knowledge will come in handy. When he was hired at USC 20 years ago, the

university had just installed its first cyclotron.

"When we installed that first unit here, I remember sitting in on many planning sessions," he said. "We'll work closely with university facilities, vendors and contractors in the next six months, and address quality control issues and staff training. I hope to have the cyclotron up and running by the end of the year."



Tania Chatila

USC CELEBRATES NATIONAL HOSPITAL WEEK

Nurses Marie Asuncion-Maitz (left) and Valencia Webb-Streeter grab boxed In-N-Out Burger lunches on May 9 as part of National Hospital Week festivities at USC University Hospital and USC Norris Cancer Hospital. Hospital administrators hosted events to recognize employees and physicians all week long, including an ice cream social, raffles for Los Angeles Dodgers tickets, a guest speaker and a special gift giveaway. National Hospital Week is the nation's largest health care event and is celebrated all across America.

Donors honor Zelman with endowed lectureship

By Pauline Vu

The night before the inaugural Vladimir Zelman Distinguished and Endowed Lectureship on April 28, friends and colleagues gathered at the Jonathan Club in downtown Los Angeles to honor Zelman, a clinical professor of anesthesiology at the Keck School of Medicine of USC. Having grown up in Russia, Zelman was lauded for his work “building bridges.”

“Since he came to the United States, Vladimir has been the consummate ambassador between two initially disparate cultures and civilizations,” said Philip Lumb, chair of the Department of Anesthesiology. “And Vladimir continues to create that bridge, to make that alliance, to make that partnership, to make that sensation of oneness more and more effective.”

Real estate developer and philanthropist Guilford Glazer, who along with his wife Diane donated \$100,000 to establish the annual lectureship, likewise praised Zelman for his ability to bring people together.

“Good doctors, like Vladimir, have a dual role if they want to accept it. In foreign relations, we’re at war with a big part of the world, and the only people who have the right currency to talk to the other side are the doctors,” said Glazer, who has known Zelman for more than 30 years.

He went on to say that Zelman has brought many Russians to USC for health care, drawing people who otherwise would not come to the United States.

Doctors “can be our best emissaries to our neighbors,” Glazer said. “And Vladimir is



Keck School professor Vladimir Zelman (left) shares a laugh with philanthropist Guilford Glazer, who donated \$100,000 to establish an annual endowed lectureship in Zelman’s honor.

one of those fellows. He’s a diplomat.”

Zelman earned his first doctorate in medicine in 1958 at the Novosibirsk Medical Institute in the then-USSR. He earned numerous honors in the USSR and moved to the United States in the mid-1980s.

Zelman often returns to Russia. Just a few days before the dinner, he was in Moscow meeting with Russian President Dmitry Medvedev and Medvedev’s wife Svetlana, a good friend. Thanks to that relationship, there will soon be a USC-affiliated women’s health program in Russia.

“Bridges, understanding and cooperation is probably one of the important things of today’s international relationships,” Zelman said. “This will make the world safer.”

The people who came to the dinner reflected Zelman’s international prominence. In attendance was Los Angeles County Sheriff Lee Baca, who has worked with Zelman to reach out to the Russian community in Los Angeles, and Roald Sagdeev, the former director of the USSR’s Space

Research Institute, who was crucial in promoting perestroika, the 1980s political movement that helped lead to the end of the Cold War.

Zelman said the Glazers told him they wanted to donate money to USC in his honor and asked him how he wanted to use the gift. He decided a lectureship featuring a world-renowned expert in the neuroscience field would provide the best benefit to students, residents and doctors on the Health Sciences Campus.

The inaugural speaker, James Cottrell, spoke in Aresty Auditorium about fragile and aging brains. Cottrell, the Distinguished Professor and Chairman of the department of anesthesiology at SUNY Downstate Medical Center, is a former president of the American Society of Anesthesiology. In 2008, he was awarded the society’s prestigious Distinguished Service Award.

“Dr. Zelman ... is so well thought of and he’s contributed so much to the development of our specialty that I was just delighted and honored to be asked to speak,” Cottrell said.

‘Since he came to the United States, Vladimir has been the consummate ambassador between two initially disparate cultures and civilizations.’

—Philip Lumb, chair, Department of Anesthesiology

The Weekly Etcetera

The 30th annual USC Academic Honors Convocation was held on April 6 at Town & Gown, with two members of the Health Sciences Campus receiving honors.

Qi-Long Ying received a 2011 Phi Kappa Phi Faculty Recognition Award. The award honors faculty “for recent scholarly, scientific or creative works that can make a contribution of the highest order to their respective disciplines.”

Yujiao Jennifer Sun, a Keck School of Medicine doctoral student, received a Phi Kappa Phi Student Recognition Award, honoring graduate and undergraduate students for creative and scholarly achievements. Sun received recognition for her paper, “Fine-tuning of Pre-balanced Excitation and Inhibition During Auditory Cortical Development.”

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A Carpinteria high school student recently won the Los Angeles Brain Bee—a competition sponsored, in part, by the Zilkha Neurogenetic Institute at USC—and then went on to win first place in the National Brain Bee contest.

In March, Thanh-Liem Huynh-Tran of Cate High school in Carpinteria won the Los Angeles Brain Bee, a neuroscience competition for high school students designed to test their knowledge, wit and comprehension of brain facts and principles.

The annual event is hosted by the Los Angeles City College and co-sponsored by the Brain Research Institute at UCLA and Zilkha Neurogenetic Institute.

Pat Levitt, director of

the Zilkha Neurogenetic Institute, said the event is one of several research collaborations with the Brain Research Institute, adding, “The joint sponsorship of the Los Angeles Brain Bee also reflects our common goals of promoting the burgeoning scientific interests of our best and brightest young students. Teaming up to support our Los Angeles teens, and for Than-Liem to win the national title, is a wonderful validation of this joint venture.”

Huynh-Tran will represent the United States and compete at the International Brain Bee in Florence, Italy this summer.

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The Albert Schweitzer Fellowship has selected two Keck School students—**Crystal Ives** and **Kavita Renduchintala**—as 2011-2012 fellows. As fellows, they will create and carry out service projects that address the unmet health needs of underserved individuals and communities.

Ives plans to address the lack of opportunity for controlled detoxification from opiates for low-income individuals in downtown Los Angeles by starting a short-term outpatient buprenorphine detoxification program at an established needle exchange site.

Renduchintala will tackle the need for access to health and wellness education among local underserved minority middle-school and high-school students by creating interactive small-group health workshops that focus on various teen health issues.

The Weekly

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Keck School touts benefits of stem cell research at Beverly Hills event

By Imelda Valenzuela

Forty people attended a reception honoring Keck School of Medicine Dean Carmen A. Puliafito for his reappointment to the California Institute for Regenerative Medicine (CIRM) board.

Held on April 27 at the Peninsula Beverly Hills Hotel, the event, “Transforming Medicine with Stem Cell Research,” was hosted by Keck School alumnus Jeffrey Ross Gunter, a dermatologist and chair of the advisory board for the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC.

“I truly believe that stem cell research will be one of the most influential modalities of treatment in the next 50 years of medicine,” said Gunter, explaining why he supports regenerative medicine at USC.

“Many causes are attractive because you can see immediate results. I’m more concerned about generations to come and I believe that stem cells will play a huge role in health care and it will take people with vision and



Keck School of Medicine Dean Carmen A. Puliafito presents an award to Jeffrey Ross Gunter, chair of the advisory board for the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC..

Brian Morris

stamina to bring that to a reality,” he added, referring to Puliafito and Martin Pera, director of the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC.

“I came to USC three and a half years ago and one of the reasons I came was that California is the stem cell capital of the world,” said Puliafito, a practicing ophthalmologist whose patient was featured in a video shown at the event. “I am aware of the tremendous challenges that patients face every day. As a physician, there is nothing more compelling than dealing with the patient and the patient asking, ‘What can

you do to solve my problem?’”

USC is one of a few institutions in the world that have been funded by CIRM to develop a stem cell cure for macular degeneration, according to Puliafito, who explained that clinical trials would be underway soon.

He also emphasized that implications from the studies would impact other areas including heart disease, Parkinson’s disease, Alzheimer’s diseases, diabetes and spinal cord injuries—categories in which he said “there is tremendous hope” with regard to stem cell research.

Pera also addressed the audience. “With stem cells, we have a source of healthy human tissue that may be able to treat any kind of disease,” he said. “We can even take cells from animal tissues, we can endow them with the properties of embryonic stem cells, which means we can take adult cells and turn them into cells that can make all the tissues of the body. It’s a very, very exciting time to be working in this field.”

‘I believe that stem cells will play a huge role in health care and it will take people with vision and stamina to bring that to a reality.’

— Jeffrey Ross Gunter, chair of the advisory board for the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC

USC Norris researchers to test new drug that may alleviate multiple diseases

By Leslie Ridgeway

A clinical trial has begun for a promising new drug that is the first in its class and, in preclinical studies, has shown the potential to benefit patients suffering from several diseases and conditions, including cancers, degenerative diseases and fibrotic disorders. The Phase I clinical trial is being conducted at the USC Norris Comprehensive Cancer

Center and Hospital, under an investigational new drug application sponsored by PRISM BioLab Corp.

The drug, PRI-724, is the first to specifically target the Wnt pathway, a network of proteins fundamental in the development of all major human organs, as well as an important pathway that is over-stimulated in both liquid and solid tumors.

“I am ecstatic that 10 years of basic bench research is now moving into the clinic through our partnership with my clinical colleagues Heinz-Josef Lenz and Anthony El-Khoueiry,” said Michael Kahn, who, with Lenz, was instrumental in developing PRI-724. All three are faculty at the Keck School of Medicine.

“We believe that this class

of molecules safely targets an extremely fundamental cell biological switch and are very excited about the broad potential to treat a wide array of diseases even beyond cancer, based upon our preclinical results to date,” Kahn said.

The clinical trial, led by principal investigator El-Khoueiry, is enrolling patients with advanced cancer that has failed standard therapy. The two main goals of the trial are to identify the safe dose of the drug as well as identify the dose that achieves the best modulation of the Wnt pathway. Once the safe dose is identified, the trial will focus on treating patients with metastatic pancreatic and colon cancers to determine the drug’s effect on their tumors.

Given the mechanism of action of PRI-724 and based on preclinical studies, the drug may have potential applica-

tions in patients with neurologic diseases (Parkinson’s disease, Alzheimer’s disease, multiple sclerosis), cardiac disorders, idiopathic pulmonary fibrosis and osteoporosis. Subsequent clinical trials for such diseases are planned for the future.

The trial is expected to last 12 to 18 months, and is not a randomized trial.

PRI-724 is the first drug to be produced by the USC Norris Comprehensive Cancer Center and the new USC Center for Molecular Pathways and Drug Discovery. The new Center was launched in May 2010 with the goal of accelerating the development of new drugs and bringing them more quickly to patients.

The USC Center for Molecular Pathways and Drug Discovery is co-directed by oncologist Lenz and molecular biologist Kahn.

NIH awards \$1 million to Occupational Therapy, Physical Therapy

The USC Division of Occupational Science and Occupational Therapy will join with the Division of Biokinesiology and Physical Therapy for a five-year program to train nine postdoctoral scientists in clinical trials research.

Funded by a \$1 million award from the National Institutes of Health, the interdisciplinary program will also involve colleagues from the Keck School of Medicine, the Viterbi School of Engineering and the School of Pharmacy to offer a coordinated fellowship experience with individualized mentorship plans, core coursework, training seminars, immersion in externally funded projects and writing of grant proposals and research publications.

The goal of the program is to improve participants’ ability to independently conduct randomized clinical trials, including comparative effectiveness studies, and an increase in both the quantity and rigor of rehabilitation science publications. In the long term, the program aims to promote the development and testing of interventions that improve the effectiveness of rehabilitation services.

The Weekly NEWSMAKERS

On Apr. 28 *Bloomberg Businessweek* ran a HealthDay News story which reported a study led by **Jessica Rayhanabad**, a fellow in the breast surgery division at the Keck School of Medicine, which found that breast implants affect breast cancer diagnosis but not prognosis. The story also ran in *U.S. News & World report*, EmaxHealth, Doctors Lounge and The Stir.

A May 2 article in *The New York Times* highlighted a study by **Pat Levitt**, director of the Zilkha Neurogenetic Institute, and colleagues, finding that the placenta plays a key role in fetal brain development in the early stages of pregnancy. The placenta synthesizes serotonin and ships it right to the forebrain, the story stated. “It makes sense that those circuits involved with mood, emotions and confronting

challenges in the environment were themselves shaped by the environment early on,” Levitt said.

A May 2 story on KTAL News quoted **Pisit Piyukcheewanont**, pediatric endocrinologist at Children’s Hospital Los Angeles, about premature puberty in girls all over the world.

On May 3 Fox News Los Angeles affiliate KTTV-TV reported that students

at the Keck School of Medicine are using a massive photo database app called Visual DX that works on an iPad that aids doctors in the diagnosis of illnesses.

On May 5 HLN network’s “Dr. Drew” show welcomed **Douglas Prisco**, assistant professor of clinical medicine at the Keck School of Medicine, as he discussed sleep disorders and treatment.

Ph.D. student wins international dental research award

By Beth Dunham

Herman Ostrow School of Dentistry Ph.D. candidate Marcelo Freire has been awarded the International Association of Dental Research's 2011 Bernard G. Sarnat Award in Craniofacial Biology, an honor given to the predoctoral or postdoctoral student who conducts original and outstanding research in craniofacial growth and development.

Among hundreds of applications submitted from around the world, only 10 abstracts were chosen as poster session finalists. From the finalists, Freire's abstract was selected as the winner.

"When I heard my name, it was a big surprise," said Freire, who trained as a periodontist before enrolling in the school's Ph.D. in Craniofacial Biology program. "I was really proud to represent



Marcelo Freire

our school. I hope it inspires students to participate in research and go beyond what is thought of dentistry."

His winning project, "Bioengineering Bone by Monoclonal Antibodies," examined the possibility of developing new bone growth by modulating the extracellular environment using therapeutic antibodies. To test the possibility, monoclonal antibodies—antibodies cloned from the same parent cell—were designed and immobilized on collagen scaffolds to tether growth factors, including BMP-2, or bone morphogenetic protein 2.

These membranes surgically were placed in critical-size rat calvarial models designed to mimic bone defects found in humans. After several weeks, CT scans and tissue analysis revealed increased bone formation in sites with antibodies when compared to controls.

"Such novel methodology is an advance in science and technology, and we hope one day this will translate to treat patients with skeletal defects or injuries, including congenital defects involving the jaw, palate and face," Freire said.



Jon Nalick

REBUILDING THE HEART—In the last Dean's Translational Medicine series lecture for the 2010-2011 school year, the Keck School of Medicine invited the University of Hong Kong's Hung-Fat Tse to present his groundbreaking research in the field of cardiovascular regenerative medicine. Tse discussed the application of stem cells for treatment of severe coronary artery disease, a major cause of mortality and morbidity worldwide.

Calendar of Events

This Calendar of events is also online at www.usc.edu/hscalendar for the Health Sciences Campus community

Wednesday, May 18

Noon. Medicine Grand Rounds. "Hematological Manifestations of Alcoholic Hepatitis," Shreya Kapoor, USC. IPT Conference Rm. B. Info: (323) 226-7558

Friday, May 20

8 a.m. Pathology and Laboratory Medicine Grand Rounds. "Medico-Legal Death Investigation in LA County – Unusual Case Scenarios," Lakshmanan Sathyavagiswaran, USC & UCLA. NOR 7409. Info: (323) 442-1180

11:45 a.m. USC PSOC Seminar. "Histone Variants, Nucleosome Dynamics, and Epigenetics," Steven Henikoff, Fred Hutchinson Cancer Research Center. NRT Aresty Aud. Info: (323) 442-3849

Noon. Pharmacology and Pharmaceutical Sciences Seminar. "PTEN and Tumorigenesis," Hong Wu, UCLA. PSC 104. Info: (323) 442-2184

Noon. Medicine Grand Rounds. "Antiphospholipid Syndrome," Due Phan, USC. IPT Conference Rm. B. Info: (323) 2226-7556

Monday, May 23

4 p.m. Neurology Grand Rounds. "fMRI in Disease: Applications, Challenges, and Solutions," Scott Small, Columbia Univ. UPC: Tutor Campus Center, 352. Info: (323) 442-7686

Tuesday, May 24

9 a.m. Neurology Grand Rounds. "Zooming in on Hippocampal Dysfunction: MRI Maps to Molecular Mechanisms," Scott Small, Columbia Univ. ZNI 112. Info: (323) 442-7686

Noon. Psychiatry Grand Rounds. "Mental Illness in the Homeless Population," Suzanne Wenzel, USC. ZNI 112. Info: (323) 442-4065

Noon. Women In Management Seminar. "Heart Disease in Women," Helga Van Herle, USC. NRT LG 503/504. Cost: \$15 members, \$18 non-members. Info: (323) 442-1865

Saturday, June 4

8 a.m. – 4 p.m. Continuing Medical Education Seminar. "Pulmonary Updates 2011," Various speakers. Los Angeles Marriott Hotel, Downtown Los Angeles. Info: (323) 442-2547

Notice: Deadline for calendar submission is 4 p.m. Monday to be considered for that week's issue—although three weeks' advance notice of events is recommended. Please note that timely submission does not guarantee an item will be printed. Send calendar items to *The Weekly*, KAM 400 or fax to (323) 442-2832, or e-mail to ebalauw@usc.edu. Entries must include day, date, time, title of talk, first and last name of speaker, affiliation of speaker, location, and a phone number for information.

STEM CELLS: Study elucidates hair growth activation

Continued from page 1
follicles," Chuong said. "But when a rabbit hair follicle regenerates, it can count on two inputs: its own activation, and the activation signal from its neighbors. Rabbits have very active hair growth, and that is essential for their survival in the wild."

If the mechanism of stem cell "communication" can be awakened in human stem cells, it will be possible to significantly increase the proportion of human hairs in a growing phase, said Maksim Plikus, the paper's lead author, now a postdoctoral research associate at the University of Pennsylvania. While conducting the study Plikus was with the Keck School and was supported by the postdoctoral training grant from California Institute for Regenerative Medicine.

The study's results are promising enough that the USC Stevens Institute for Innovation has already applied for a patent on the composition and method to modulate hair growth.

The findings also provide insight into potential stem cell behavior in other organs, which holds ramifications for regenerative medicine research.

The fact that a large population of a rabbit's hair stem cells can encourage each other to regenerate and to take turns resting implies it may be possible for other organs' stem cells—including

in humans—to similarly communicate and spur growth with high efficiency.

"This work should stimulate the search for similar population-level behaviors among stem cells in other key regenerative systems, such as the gastro-intestinal tract and bone marrow," Plikus said.

The study builds upon an earlier paper that a team led by Plikus and Chuong published three years ago in the journal *Nature*. That study looked at the hair growth patterns on mice and found that the macro-environment, which includes subcutaneous adipose tissue and body

hormone changes, could influence the regenerative behavior of individual hair follicles.

It also found new functionally distinct, but morphologically indistinguishable phases in a hair follicle's growing and resting stages.

"Combined together, our 2008 *Nature* and 2011 *Science* papers push our understanding of the regenerative processes in an adult organ to a new level," Plikus said.

Chih-Chiang Chen, Damon de la Cruz and Randall Wideltz of the Keck School's Department of Pathology were also authors on the study.

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