Researchers advance genome editing of blood stem cells

By Cristy Yfutal

Genome editing techniques for blood stem cells just got better, thanks to a team of researchers at USC and Sangamo BioSciences.

In an upcoming study in Nature Biotechnology, co-first authors Colin M. Eudline, PhD, from USC and Juanbin Wang, PhD, from Sangamo BioSciences describe a new, more efficient way to edit genes in blood-forming or “hematopoietic” stem and progenitor cells (HSPGs).

“Gene therapy using HSPGs has enormous potential for treating HIV and other diseases of the blood and immune systems,” said co-corresponding author Paula Cannon, PhD, professor of molecular microbiology and immunology, pediatrics, biochemistry and molecular biology, and stem cell biology and regenerative medicine at the Keck School of Medicine of USC.

“And using genome editing techniques now allows us to make very precise changes that could repair genetic mutations — the gene types — that can cause disease.”

Despite the enormous potential of such targeted gene medicine to cure patients, getting genome editing to work has proven challenging in human HSPGs — especially in the most primitive, least differentiated cells with the greatest ability to become any blood cell type.

Cannon’s group, working with a team at Sangamo, has been using “genetic scissors” called zinc finger nucleases (ZFNs) to cut a cell’s DNA at a precise location or segment. The cell normally uses a copy of the cut DNA sequence as a template to repair the DNA break. During this process, there is the introduction to introduce See DNA, page 3.

For minority students who dream of being doctors, ‘Keck is where you want to be’

By Amanda Busick

A trending medical school can seem like a pipe dream for many students, particularly minorities, but the Bridging the Gaps Summer Research Program at the Keck School of Medicine of USC can turn that dream into a reality.

“They were created to address the under-representation of minority students within medicine and the biological sciences and with hopes of attracting them to Keck,” said program director Joyce Richey, PhD, chief diversity officer and assistant dean of educational affairs.

In the four years since the program began, 71 minority undergraduate students have participated overall. About two-thirds of those students have applied to the Keck School and 17 applicants have been accepted. Alumni of the summer program are now part of the Trojan family and enrolled in the MD, PhD and Global Medicine programs.

In addition to the Keck School students, 95 percent of Bridging the Gaps participants overall have been successful in gaining acceptance and matriculating in their desired medical or graduate programs at other prestigious institutions such as Columbia and Yale.

Bridging the Gaps runs for eight weeks during the summer in the laboratories of Keck School faculty members who also serve as mentors for the students. During this time, the students work on research projects alongside their mentors. In addition to lab research, students have the opportunity to witness the impact of the diseases they are studying while shadowing faculty physicians. The program embraces a true bench-to-bedside model.

One program participant, Vanessa Arientyl, studied how oxytocin affected social behavior in mice.

“It was nice learning how to really build a project from the beginning. I got to learn how research really works, collect the data and present it,” recalled Arientyl, who is now a second-year medical student See DREAM, page 3.

Keck Medicine launches new center focusing on innovation

By Douglas Morino

A new center dedicated to developing and translating innovation in the delivery of health care has been established at Keck Medical Center of USC.

The USC Center for Health Systems Innovation (CHSI) will focus on turning research and education into measurable and sustainable improvements in outcomes and experience for patients and staff.

It will be led by Executive Director Carol Peden, MD, MPH, a professor in the Department of Anesthesiology at the Keck School of Medicine of USC.

“This is about bridging the gap between innovation and implementation, to deliver health care safely, effectively and efficiently, while ensuring the best possible patient and staff experience,” Peden said.

“The center will focus on a very practical approach. We will... See CHSI, page 2.

National AYA program honors Stuart Siegel with Trailblazer Award

Professor Stuart Siegel, MD, of the Keck School of Medicine of USC was recently awarded the Archie Bleyer AYA Trailblazer Award by Critical Mass, a leading organization supporting the cause of adolescents and young adults (AYAs) with cancer.

Siegel’s involvement in the AYA movement has been long and productive. In the 1990s, he championed the development of a program at Children’s Hospital Los Angeles called “Teen Impact,” which was one of the nation’s first support group-based programs focusing on the needs of AYAs and their families.

A professor of pediatrics and medicine at the Keck School of Medicine and the director of the Center for Global Health at CHLA, Siegel is also the founding director of the Children’s Center for Cancer and Blood Diseases and the Center for International Health at CHLA. In addition, he serves as co-medical director of the Adolescent and Young Adult Cancer Program at USC (AYA@USC).

“Dr. Siegel has been a... See SIEGEL, page 6.
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The gene Prkci promotes the generation of differentiated cells (red). However, low activity is reduced or absent, neural stem cells (green) are promoted.

use the wealth of resources across the university, harnessing the knowledge and skills of many of USC’s schools to better design and deliver care.”

The center will facilitate faculty-driven research projects and create new interdisciplinary programs in health care quality and safety. By January 2017, the CHSI will establish fellowships in health systems innovation for medical and non-medical graduate students.

Peden, an anesthesiologist and intensive care physician, joined Keck Medicine of USC in September from the United Kingdom, where she gained extensive experience in leading local and national improvement projects. She is a believer in data for improved and developed a national surveillance system for emergency surgery outcomes. Peden chaired the executive board of Global Surgery Trials, a group of 44 of the world’s leading institutions that share data for improvement.

Peden said her commitment to improving care across health systems stemmed from her clinical work as a physician.

“Through my work as an intensive care doctor, I sometimes saw critically ill patients in whom a simple step earlier in their pathway could have prevented disease progression,” she recalled. “The enormous challenge of recovering from critical illness for the patient and their family could have been avoided. I started to think about the whole system of health care more.”

CHSI developed from a partnership among several USC schools, including the Viterbi School of Engineering, the Pacific Center for Innovation and Technology in Health, and the School of Policy, Planning and Development.

Peden was previously associate medical director for NHS England, responsible for clinical quality for 13.5 million people. Her expertise in improvement was developed as a fellow at the Institute for Healthcare Improvement (IHI) in Boston. She has also developed and led leadership courses for institutions such as the University of Oxford and University College London.

The CHSI’s strength will be the academic input from USC, but the center will be of real relevance to the health system,” Peden said. “It will be integrated into patient care and deliver real improvements for the experience for everyone in the health system, both our patients and our staff.”

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Aroseth, the leading cause of disability in the U.S., involves the loss of a specific type of cartilage cell lining the joints. In a study appearing on the cover of the latest issue of Developmental Cell, first author Amjad Askary—a PhD student in the USC Stem Cell lab of Gage Crump, PhD—and his colleagues identify roles for a family of genes, called Iroquois (Irx) genes, in protecting these joint cartilage cells.

Some types of cartilage serve as temporary scaffolds that are later replaced by bone, but joint cartilage remains perpetually cushiony, flexible and immune. In order to better understand how this works, the researchers took advantage of the fact that a joint in the zebrafish jaw, called the hyoid joint, contains high levels of one member of the Irx family, Irx5. When the researchers used gene editing to create mutant zebrafish lacking this gene, the wrong type of cartilage formed at this joint. They then showed that Irx genes promote joint flexibility by turning off genes that stiffen more mature cartilage.

Next, the researchers explored whether Irx genes play a role in species outside the fish tank. To do so, Crump’s team collaborated with the neighboring labs of Justin Ichida, PhD, Francesca Mariani, PhD, and Andy Mcmahon, PhD—all located in the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC—to show that a related Irx gene could repress the maturation of cartilage in mice.

“The Irx genes may be a core machinery that prevents cartilage maturation in species across the animal kingdom,” said Crump, the study’s corresponding author and associate professor of stem cell biology and regenerative medicine at USC. “This raises intriguing questions: Can we harness the effects of these genes to encourage stem cell differentiation in new cartilage, and do mutations in these genes play a role in inherited osteoarthritis?”

Additional co-authors on the study from USC include Lindsey Monk, PhD, Sandeep Paul, PhD, Xinjun He, PhD; Audrey Izuhara; and Suhasni Gopalakrishnan, PhD; plus Sunja Dabuljekic and Rodney Dale from Loyola University Chicago.

Funding came from the National Institutes of Health, March of Dimes, an A.P. Giannini Foundation fellowship for PhD; Audrey Izuhara; and Suhasni Gopalakrishnan, PhD; and Sangamo BioSciences. Richard Surosky, PhD, and Li, PhD, David Shivak, PhD, and Suhasni Gopalakrishnan, PhD, said co-corresponding author Michael C. Holmes, PhD, vice president of research at Sangamo Biosciences. “This significantly advances our progress towards applying genome editing to the treatment of human diseases of the blood and immune systems.”

Additional co-authors include Nick Llewellyn, PhD, from USC, and Joshua D’Clercq, Samuel Hayward, Patrick Wu-Lian Lu, PhD, David Shak, Richard Sumsky, PhD, and Philip Gregory, DPhil, from Sangamo Biosciences.
Stanczyk chosen as Distinguished Researcher

Frank Z. Stanczyk, PhD, professor of research at the Keck School of Medicine of USC, is the recipient of the 2015 Distinguished Researcher Award from the American Association of Reproductive Medicine (ASRM).

This award recognizes an ASRM member who has made outstanding contributions to clinical or basic research in reproduction published during the previous ten years. Recipients must demonstrate sustained long-term commitment to advancing the frontiers of research in reproductive sciences and educating future scholars in the field.

In a letter of congratulations, ASRM President Rebecca Z. Sokol, MD, MPhil, recognized Stanczyk’s role in establishing other members of the organization, and she noted his “many fundamental contributions that have advanced our knowledge of the human reproductive system and the development of contraceptive technologies.”

Stanczyk received the award Oct. 19 during the 2015 ASRM annual meeting in Baltimore, MD.

As the association’s Distinguished Researcher, Stanczyk will present an exchange lecture about his research in July 2016 when the Society for the Study of Reproduction (SSR) meets in Washington, DC.

SIEGEL: Organization honors pioneer in AYA medicine

Continued from page 1

Travis Freyer was struck by the passion and determination of AYA trailblazer. He said he was “truly impressed” with the impact he has had nation wide and in his own practice, and noted that Siegel has “worked tirelessly and with a big smile on his face.”

Siegel has long pushed to develop new talent to support and benefit the field, and he has helped develop innovative AYA oncology training programs for fellows and medical students. He was instrumental in the 2006 formation of the LIVSTRONG Young Adult Alliance (which later was renamed Critical Mass), and the organization’s announcement of the award noted that he has “worked tirelessly to develop standards for AYA oncology care and expand formal education in AYA oncology, as evidenced by his leadership on seminal position papers in these areas.”

The award is named for Archie Bleyer, MD, another AYA advocate whose work made possible the annual AYA Conference in Chicago. David R. Frey, DO, MS, professor of clinical obstetrics and gynecology at the Keck School, first shared the good news about the award in an email to colleagues in September.

Freyer wrote, in part, that the “choice of Stu for this award truly reflects the broad impact he has had nationally on so many individuals and the field itself through influencing development of studies, publishing of key data, disseminating important findings, creation of care standards, and advancing public policy — all in addition to the transformational AYA-focused work we know he has carried out over the course of many years leading to AYAHUSC.”

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Stanczyk is the director of the Reproductive Endocrine Research Laboratory and the technical director of the USC Reproductive Endocrine Clinical Laboratory, which are part of the Department of Obstetrics and Gynecology. He is an internationally recognized expert in steroid biochemistry, he has been a listed contributor to more than 400 academic papers. In addition, Stanczyk has provided laboratory training and didactics to more than 80 fellows who received board certification in Reproductive Endocrinology and Infertility.

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