USC Stem Cell NEWS

NIH award sets postdoc Joanna Smeeton on the pathway to independence

After her breakthrough discovery that zebrafish can be used to study arthritis, postdoctoral fellow Joanna Smeeton has received a prestigious National Institutes of Health (NIH) Pathway to Independence Award. Known as the K99/R00, the award will help her transition from the postdoctoral to the faculty stage of her career.

Q: Tell me about your NIH fellowship project.

A: My project uses the highly regenerative zebrafish to investigate the role of stem cells in rebuilding cartilage and ligaments of joints after injury. Human joints have a poor intrinsic healing capacity, but I recently found that zebrafish are able to robustly regenerate ligaments and cartilage following surgery-induced damage. I aim to uncover the mechanisms by which zebrafish can regenerate their joints after injury and characterize the joint-resident stem cells contributing to the effective repair. The ultimate goal is to harness the insights from my work with zebrafish joint stem cells to awaken similar cells in human joints to improve repair for injuries and degenerative joint diseases like osteoarthritis.

Joanna Smeeton with her husband Jeremy Morris and their twins Edie and Isaac (Photo/Sandra Kielback)

Q: How did your previous postdoctoral fellowships—supported by the California Institute for Regenerative Medicine (CIRM) and The Broad Foundation—contribute to your success?

A: The generous support from these two previous fellowships gave me the scientific freedom to explore joint biology and regeneration in zebrafish. I had never worked with fish or joints before my postdoc, but with the financial support from fellowships and the incredible guidance of my mentor, Gage Crump, I jumped headfirst into studying arthritis and fish joints. In the past three years, we established the first genetic model of arthritis in fish, which we published in the journal *eLife* in 2016, and created the new joint repair model that I am currently investigating.

Q: How do you spend your free time?

A: Most of my free time is spent chasing after my 10-month old twins, Edie and Isaac. When we do get out of the house, my husband and I love to hike and explore the mountains, deserts and all that the US National Park system has to offer … now with the addition of 20-pound kids strapped to our chests in baby carriers!

About USC Stem Cell

USC Stem Cell is a collaborative and multidisciplinary effort working to translate the potential of stem cell research to the clinical imperative of regenerative medicine.

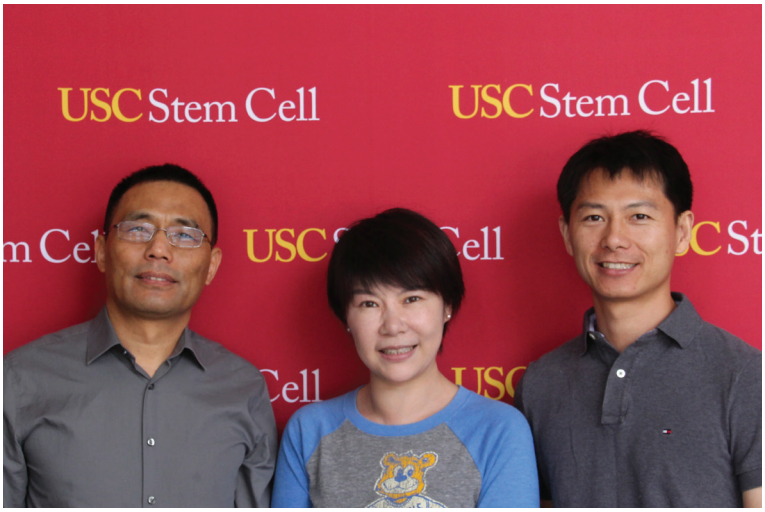
The initiative brings together nearly 100 research and clinical faculty members from the Keck School of Medicine of USC, Children's Hospital Los Angeles, the USC Viterbi School of Engineering, the USC Davis School of Gerontology, the Ostrow School of Dentistry of USC, the USC School of Pharmacy, and the USC Dornsife College of Letters, Arts and Sciences.

Min Zhou supports scientific serendipity in Qi-Long Ying's lab

To foster the spirit of unexpected discovery, Chinese biotechnology entrepreneur Min Zhou has given an unrestricted gift of $500,000 to Qi-Long Ying's lab, which studies how stem cells self-renew or differentiate into many specialized cell types.

Zhou has chosen to provide unrestricted support for this pioneering research, because of her first-hand understanding of the serendipitous nature of early scientific discovery. She is both a medical doctor who has performed postdoctoral research at UCLA, and the founder of Kedgene Biology, a biotech company developing therapies for cancer and other diseases.

"I hope that our gift can help a distinguished scientist like Professor Qi-Long Ying accelerate breakthrough findings in stem cell research," said Zhou. "I hope that human beings can benefit from such scientific endeavors as soon as possible."



From left, Qi-Long Ying, Min Zhou and Ying Lab postdoc Shi (Steve) Yue (Photo/Cristy Lytal)

High school student Richard Lopez gets an early start

Richard Lopez is still in high school, but he can already tell you a thing or two about the ureteric bud, metanephric mesenchyme and developing kidney. More impressively, he was familiar with these terms before starting his summer internship in the lab of Andy McMahon, kidney researcher and director of the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC.

"I knew I was going to come here," he said. "So from December on, I was just reading papers that were written by Dr. McMahon's lab."

Lopez undertook this intense preparation as part of the Science Research Program at his boarding school, Choate Rosemary Hall in Connecticut. But Lopez didn't start his high school career at Choate. Growing up in Lennox, a small city near the Los Angeles International Airport, he attended the local public schools until his sophomore year in high school. At that point, his exceptional scores on the California Standardized Test (CST) attracted the attention of the Young Eisner Scholar program, which empowers underserved students to fulfill their potential. As a Young Eisner Scholar, he earned both admission and a full scholarship to attend Choate.

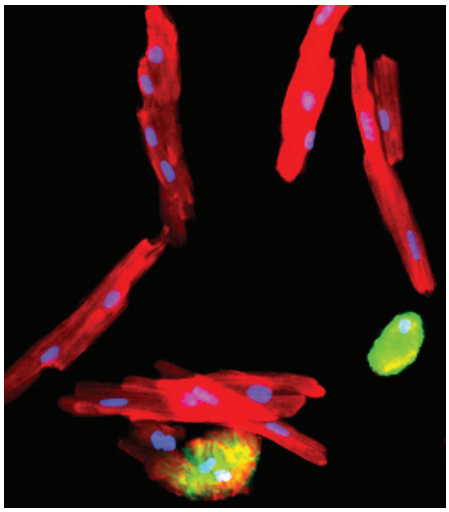
In the McMahon Lab, Lopez has learned about the molecular signals that drive the branching development of the kidney, and practiced laboratory techniques.

To get to the lab every day, Lopez bike commutes a total of 32 miles from his home in Lennox to USC's Health Sciences Campus. He's run the Los Angeles Marathon once and the San Francisco Marathon twice. In November, he's planning to celebrate his eighteenth birthday with his first Ironman Triathlon. Through these events, he's raising sponsorship money for the Partnership Scholars Program, which provides underserved junior high and high school students with educational and cultural experiences, such as restaurant outings and college tours. His goal is to raise $54,000 to fund three new scholars.

"I was very lucky," he said. "So I want to raise money for the scholarships that have helped me out along the way."

USC Stem Cell discovery refreshes the heart

Some people are better than others at recovering from a wounded heart, according to a new USC Stem Cell study published in *Nature Genetics*.



Heart muscle cells (red) with nuclei (blue). On the far right is a regenerative cell, which only has one nucleus, called a mononuclear diploid cardiomyocyte. (Image/Michaela Patterson)

In the study, first author Michaela Patterson, a postdoctoral fellow in the laboratory of Henry Sucov, and her colleagues focused on a regenerative type of heart muscle cell called a mononuclear diploid cardiomyocyte (MNDCM). Zebrafish and newborn mammals, including mice and humans, have large numbers of MNDCMs and a relatively robust ability to regenerate heart muscle. However, adult mammals have few MNDCMs and a correspondingly limited capacity for regeneration after an injury such as a heart attack.

Even so, the situation for adult mammals is not uniformly dire: Patterson and her co-authors observed a surprising amount variation in the number of MNDCMs among different strains of adult mice. In some strains, MNDCMs accounted for only 1.9 percent of heart muscle cells. In others, a full 10 percent were MNDCMs. As expected, the higher the percentage of MNDCMs, the better the mice fared in regenerating their heart muscle after injury.

"This was an exciting finding," said Patterson. "It suggests that not all individuals are destined to permanent heart muscle loss after a heart attack, but rather some can naturally recover both heart muscle mass and function. If we can identify the genes that make some individuals better at it than others, then perhaps we can stimulate regeneration across the board."

Using an approach called a genome-wide association study, the researchers indeed identified one of the key genes underlying this variation: Tnni3k. By blocking this gene in mice, the researchers produced higher percentages of MNDCMs and enhanced heart regeneration. In contrast, activating this gene in zebrafish decreased MNDCMs and impaired heart regeneration.

Sucov—senior author and professor of stem cell biology and regenerative medicine, integrative anatomical sciences, and biochemistry and molecular biology—described how this early discovery could be a first step towards a preventive strategy to mitigate heart disease, the leading cause of death in the Western world.

"The activity of this gene, Tnni3k, can be modulated by small molecules, which could be developed into prescription drugs in the future," he said. "These small molecules could change the composition of the heart over time to contain more of these regenerative cells. This could improve the potential for regeneration in adult hearts, as a preventative strategy for those who may be at risk for heart failure."

Additional co-authors include Lindsey Barske, Ben Van Handel, Peiheng Gan, Avneesh Sharma, Yukiko Yamaguchi, Hua Shen, Gage Crump, Hooman Allayee and S. Ram Kumar from USC; Ying Huang, Ching-Ling (Ellen) Lien and Takako Makita from Children's Hospital Los Angeles; Christoph D. Rau, Aldons J. Lusis and Matt Denholtz from UCLA; and Shan Parikh and Thomas I. Force from Vanderbilt University.

Ninety percent of this work was supported by $1.08 million of private and non-federal funding from three sources: a Doerr Stem Cell Challenge Grant; an award from USC's Provost Office; and a California Institute for Regenerative Medicine Training Grant (TG2-01161). Ten percent of the project was funded by $120,000 from National Institutes of Health grants (NHLBI NRSA 1F32HL124932, K08HL121191, HL123295, HL114137, and NS083265).

Research Highlights

Andy McMahon's lab described gene activity in the progenitor cells that drive the branching development of the kidney in mice and humans. They also detailed which gene activity is specific to the kidney, and which is shared with other branching organs, such as the lungs. *(Development)*

Andy McMahon's lab, in collaboration with Jay R. Lieberman's group, also identified skeletal progenitor cells that contribute to fracture repair of the adult mammalian long bone. *(Bone)*

Yang Chai's team elucidated the role of a key group of molecules, called the BMP signaling pathway, in promoting the differentiation of stem cells into tooth roots in mice. *(Development)*

Gage Crump, Michael Bonaguidi and colleagues used a genomics and computational biology approach to understand how the different parts of the facial skeletal form in zebrafish, shedding new light on craniofacial disorders. *(Development)*

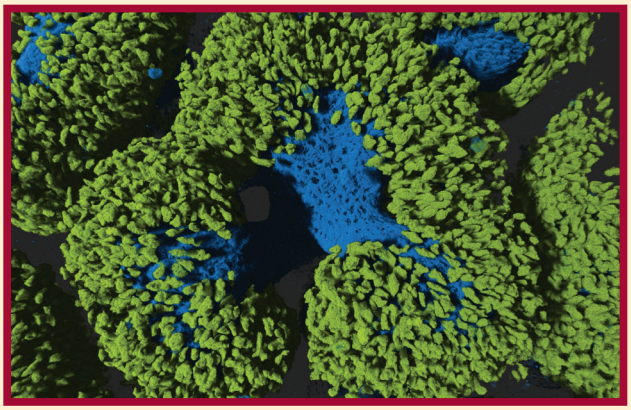
Scott Fraser's lab used stem cell-derived retinal organoids and non-invasive enhanced imaging technologies to provide real-time structural and functional information about normal retinal development and the onset of disease. *(Investigative Opthalmology and Visual Science Journal)*

Megan McCain's lab established how the metabolism of engineered cardiac tissues is regulated by features such as cell alignment and the mechanical properties of their environment—two features that jointly remodel in developing hearts and hearts affected with disease. *(American Journal of Physiology: Heart and Circulatory Physiology)*

Megan McCain's lab also engineered a new "MicroMyocardium" platform to efficiently measure the contraction of miniature cardiac tissues, which can be used in the future to study human genetic diseases and screen drugs for cardiotoxic side effects. *(Integrative Biology)*

Qi-Long Ying's lab discovered that a protein called TAZ can send very different signals—either self-renewal or differentiation—depending upon not only which variety of stem cell (primed versus naïve), but also which part of the stem cell (cytoplasm versus nucleus) receives the signal. TAZ could provide a new tool for generating cells for cell replacement therapy. *(Stem Cell Reports)*

Featured Image



Filtration System: This image depicts nephron progenitors (green) in the developing human kidney. The nephron progenitors give rise to approximately one million blood-filtering nephrons in each kidney. (Image by Nils Lindstrom/McMahon Lab)

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