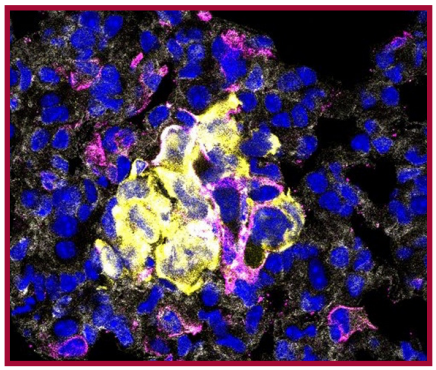
USC Stem Cell NEWS

Particle shows promise for treating the most deadly type of breast cancer

Researchers from the laboratory of Min Yu have positive news for patients with triple-negative breast cancer (TNBC), the most deadly type of breast cancer. By inhibiting a protein called TAK1, postdoc Oihana Iriondo and her colleagues reduced lung metastases in mice with TNBC, as described in a new study in *Nature Communications*.

In the 20 percent of breast cancer patients with TNBC, it appears that TAK1 enables malignant cells from the breast to survive in the unique environment of the lungs, and form new metastatic tumors. Metastases are the most common cause of cancer-related death.



Metastatic breast cancer cells (yellow) interacting with macrophages (magenta) (Image by Oihana Iriondo)

There's already a potential drug, called 5Z-7-Oxozeaenol or OXO, that can inhibit TAK1—and presumably make it much more difficult for breast cancer cells to form lung metastases. However, OXO is not stable in the blood, and therefore wouldn't work in patients.

To overcome this obstacle, Yu and her lab teamed up with the laboratory of Pin Wang at the USC Viterbi School of Engineering. Wang's team developed a nanoparticle—consisting of a tiny fatty sac—that can effectively carry drugs through the bloodstream and deliver them to tumors.

The scientists loaded this nanoparticle with OXO, and used it to treat mice that had been injected with human breast cancer cells. While OXO did not shrink primary tumors in the breast, the potential drug greatly reduced metastatic tumors in the lungs—with minimal toxic side effects.

"For patients with triple-negative breast cancer, systemic chemotherapies are largely ineffective and highly toxic," said Yu, an assistant professor of stem cell biology and regenerative medicine, and principal investigator at the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research, and the USC Norris Comprehensive Cancer Center. "So nanoparticles are a promising approach for delivering more targeted treatments, such as OXO, to stop the deadly process of metastasis."

Additional co-authors include Grace Lee, Mostafa Elhodaky, Christian Jimenez, Lin Li, and Julie Lang from the Keck School, and Yarong Liu from USC Viterbi.

Funding came from the National Cancer Institute (K22 CA175228-01A, DP2CA206653, and P30CA014089) and the USC Ming Hsieh Institute for Engineering Medicine for Cancer.

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.

Centered at the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research, the initiative brings together researchers and clinicians from USC and Children's Hospital Los Angeles.

When it comes to balancing the immune system, some blood stem cells are better than others

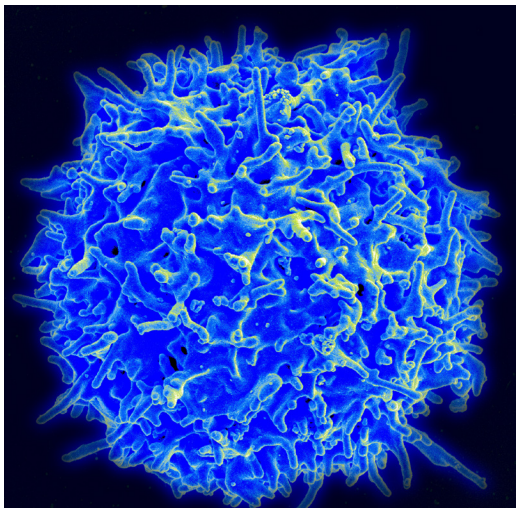
In your body, blood stem cells produce approximately 10 billion new white blood cells, which are also known as immune cells, each and every day. Even more remarkably, if some of these blood stem cells fail to do their part, then other blood stem cells pick up their slack and overproduce whichever specific type of immune cell is lacking, according to a new USC Stem Cell study published in the journal *EMBO Reports*.

USC PhD student Lisa Nguyen and colleagues in the laboratory of Rong Lu observed this phenomenon by tracking the individual blood stem cells that reside in the bone marrow of mice. To create the tracking labels, the scientists attached a unique piece of genetic code to each blood stem cell. During blood production, each blood stem cell passes its unique genetic label onto its progeny—which include two types of immune cells, known as B cells and T cells.

To test the contributions of these uniquely labelled blood stem cells, the scientists performed a series of bone marrow transplantations in mice. Mice received a combination of normal blood stem cells and deficient blood stem cells with a genetic mutation that prevented them from producing either B cells only, or both B and T cells.

The scientists found that the normal blood stem cells compensated for the B and T cell deficiencies. When co-transplanted with B-deficient stem cells, the normal stem cells overproduced B cells to keep the immune system in balance. And when co-transplanted with B- and T-deficient stem cells, the normal stem cells compensated by overproducing both B and T cells to maintain a balanced immune system.

Furthermore, the scientists found that a few specific blood stem cells were doing most of the work. These key blood stem cells proliferated dramatically to compensate for the immune cell deficiencies in the recipient mice, and these cells continued to proliferate when they were transplanted into different recipient mice. Furthermore, these highly productive blood stem cells showed changes in gene activity that enhanced their ability to oversupply deficient types of immune cells.



A healthy T cell (Image/National Institute of Allergy and Infectious Diseases)

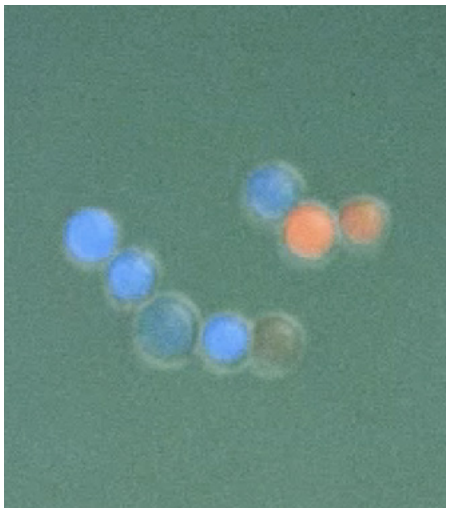
"These stem cells' ability to compensate provides some degree of resilience to disruptions of the blood and immune system—such as the aging process, the early stages of many blood cancers and disorders, and bone transplantation," said Lu, an assistant professor of stem cell biology and regenerative medicine at USC. "By understanding and ultimately harnessing this innate capacity of stem cells, we can potentially optimize treatments for a wide range of diseases."

Additional co-authors include Zheng Wang, Adnan Y. Chowdhury, Elizabeth Chu, Jiya Eerdeng and Du Jiang from the Lu Laboratory.

Funding came from the National Institutes of Health (R00HL113104, R01HL135292, R01HL138225, P30CA014089, T32HD060549, and F31HL134359), the Rose Hills Foundation Science and Engineering Fellowship, the USC Provost's Undergraduate Research Fellowship, the California Institute for Regenerative Medicine Training Grant, the Hearst Fellowship Award, the USC Office of Research, and the Norris Medical Library.

Synthetic "tissues" build themselves

In a study in the journal *Science*, researchers have demonstrated the ability to program groups of individual cells to self-organize into multi-layered structures reminiscent of simple organisms or the first stages of embryonic development.



Engineered mouse cells (Image/Leonardo Morsut)

Leonardo Morsut, an assistant professor of stem cell biology and regenerative medicine at USC, contributed to the research as a co-corresponding author when he was a postdoctoral researcher in the lab of Wendell Lim at the University of California, San Francisco (UCSF).

A critical part of development is that, as biological structures form, cells communicate with one another and make coordinated, collective decisions about how to organize themselves. To mimic this process, the new research relied on a powerfully customizable synthetic signaling molecule called synNotch (for "synthetic Notch receptor"), which allowed the researchers to program cells to respond to specific cell-cell communication signals with bespoke genetic programs.

SynNotch was originally developed in the Lim lab by Morsut and co-author Kole Roybal, now an assistant professor of microbiology and immunology at UCSF.

In the current study, using synNotch, the researchers engineered cells to respond to specific signals from neighboring cells by producing Velcro-like adhesion molecules called cadherins as well as fluorescent marker proteins. Remarkably, just a few simple forms of collective cell communication were sufficient to cause ensembles of cells to change color and self-organize into multi-layered structures akin to simple organisms or developing tissues.

In their simplest experiment of this sort, the researchers programmed two groups of cells to self-organize into a two-layered sphere. The researchers went on to program groups of cells to self-assemble in increasingly complex ways, such as building a three-layered sphere. They even engineered cells that formed the beginnings of "polarity"—the distinct front-back, left-right, head-toe axes that define the "body plans" of many multicellular organisms—by expressing different types of cadherin adhesion molecules that instructed the cellular assemblages to divide into "head" and "tail" sections or produce radial "arms."

These experiments demonstrated that cells could be programmed to develop over time to form more complex structures, much like a single fertilized egg divides and differentiates to form different parts of the body and distinct tissues like skin, muscle, nerve and bone. Lim, Morsut and the team showed that these complex spheroids were also self-repairing: when the researchers cut the multi-layered spheroids in half with a micro-guillotine developed by co-authors Lucas R. Blauch and Sindy Tang of Stanford University, the remaining cells quickly re-formed and reorganized according to their intrinsic program.

In the future, the researchers imagine programming ever more complex tissue-like cellular structures through multiple layers of synNotch signaling. In this way, the scientists envision programming the self-organization of elaborate structures needed for growing tissues for wound repair or transplant.

UCSF postdoctoral researcher Satoshi Toda was lead author of the new study. The research was supported by the National Institutes of Health (K99 1K99EB021030, 5P50GM081879, T32GM008412), the National Science Foundation–funded Center for Cellular Construction at UCSF (DBI-1548297), the US Defense Advanced Research Projects Administration (DARPA) Engineered Living Materials program, the Howard Hughes Medical Institute, the Japan Society for the Promotion of Science (JSPS), the Human Frontiers of Science Program (HFSP), and the European Molecular Biology Organization (EMBO).

Research Highlights

Researchers at the USC Roski Eye Institute collaborated with other California institutions on a phase 1/2a clinical trial showing that a stem cell-based retinal implant is feasible for use in people with advanced dry age-related macular degeneration. *(Science Translational Medicine)*

Andy McMahon's lab demonstrated that the progenitor cells that form the kidney's filtering units, called nephrons, mature into entirely different types of cells based on when they arrive to the scene of nephron formation. *(Developmental Cell)*

Andy McMahon's lab also published three studies that detailed how the development of mouse kidneys differs from that of human kidneys. *(Journal of the American Society of Nephrology)*

Gage Crump's lab revealed the role of Fox genes in the development of the zebrafish face, including certain cartilage, teeth and jaw. *(Development)*

Gage Crump's lab also revealed how key genes guide the development of the zebrafish jaw. *(Developmental Cell)*

Pat Levitt and collaborators uncovered genetic connections between common psychiatric illnesses, including ADHD, bipolar disorder, depression and schizophrenia. *(Science)*

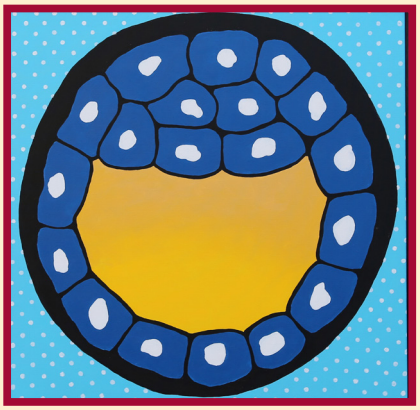
Marcelo P. Coba and colleagues identified 150 proteins affecting cell activity and brain development that contribute to mental disorders, including schizophrenia, bipolar disorder and depression. *(Biological Psychiatry)*

Denis Evseenko and collaborators described the promise of a new molecule named "Regulator of Cartilage Growth and Differentiation," or RCGD 423, for treating osteoarthritis. *(Annals of Rheumatic Diseases)*

Justin Ichida's lab described how a mutation in a gene, called C9ORF72, leads to toxicity in nerve cells—causing 10 percent of all cases of ALS, and an additional 10 percent of frontotemporal dementia. *(Nature Medicine)*

Preet M. Chaudhary and colleagues used the same enzymes that cause deep sea creatures to glow in order to create a test to see whether a therapy is killing cancer cells. *(Scientific Reports)*

Featured Image



The Blastocoel: Human stem cells are pluripotent, meaning they can differentiate into many cell types with uses in regenerative medicine. (Painting by Kella Vangsness, graduate of the USC master's program in stem cell biology and regenerative medicine)

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