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PRESIDENT'S UPDATE ON ADVANCES IN STEM CELL SCIENCE

Highlights of recently published papers from CIRM grantees and other leading research teams around the world—June 2012

International Stem Cell Gathering Showed a Maturing Field

This year's annual meeting of the International Society for Stem Cell Research (ISSCR) in Yokohama June 13-16 showcased a broad range of research revealing the growing power of stem cell science as a tool for understanding the fundamentals of human development. It also pointed to ways to turn some basic discoveries of past years into paths toward therapies.

Several researchers presented work that built on knowledge the field has assembled about normal organ development to use stem cells to grow complex tissues rather than just one end stage cell type. Hans Clevers from The Netherlands showed he could grow gastric units he called organoids in culture, transplant them and have them integrate with the native gut tissue. He also showed that a particular gene controls gut stem cells and used a molecule that turns on that gene to repair colon damage in mice when the molecule was injected into the bloodstream. Yoshiki Sasai from Japan, last year coaxed mouse embryonic stem cells to develop into the multiple layers that make up the optic cup, and this year he showed data repeating the work with human cells. That move to human from mouse is often difficult, so it was good to see it quickly bridged. Also from Japan, Takanori Takebe created what he called the first functional organ with networks of blood vessels—a piece of liver tissue that could metabolize some drugs. The feat required first turning pluripotent stem cells into liver hepatocytes and then at the right moment adding two other progenitor cell types that could grow the vessels.

Another Japanese team headed by Teruo Okano presented work using multi-layer sheets of muscle cells to create patches to place at the site of heart attack injury. Like with injecting single cells, they did not see the cells turn into beating heart tissue, but rather an increase in new blood vessels at the site of injury. But because the patches stayed at the site longer than injected cells, they saw markedly improved vessel growth.

Direct reprogramming, turning one functional adult cell into a different type of functional adult cell, was a breakthrough from past meetings but saw many advances this year. Teams are learning how to reprogram more types of tissue, do it with better efficiency and do it in ways more compatible with clinical therapies.

Another theme of the meeting was an increasing understanding of the critical role of one class of genetic product, the various RNAs, play in stem cell fate.

Vein Grown from Girl's Own Stem Cells Works after Implantation

A team at the University of Gothenburg in Sweden lead by Michael Olausson reported in the *Lancet* online June 14 that they had successfully tissue engineered a new vein for a 10-year old girl with an obstructed portal vein and restored normal blood flow.

The portal vein drains blood from the intestine and spleen to the liver and a blockage in it can stunt the growth of a child and lead to the need for a liver transplant. Surgeons generally replace a blocked portal vein with a vein taken from another location in the patient, but this child's potential donor veins were considered unfit for grafting, making her a candidate for this experimental procedure.

In a process that took about two weeks they took stem cells from her bone marrow and prodded them into becoming endothelial cells and smooth muscle cells. They then took those cells and seeded them onto a matrix that was a vein from a cadaver that had been decellularized—all the soft tissue cells had been removed. After the stem-cell generated cells grew onto the matrix in the laboratory the new vein was implanted and immediately restored normal blood flow. After nine months it started to develop an obstruction at one end and at one year that section had to be replaced with a second tissue engineered graft, which once again restored normal blood flow.

The authors of the paper note that this procedure is probably too time consuming to become a standard procedure but suggested ways that it could be done more efficiently, noting that companies are developing off-the shelf scaffolding matrices.

Direct Reprogramming Creates Neural Stem Cells Using a Single Factor

A team led by Yadong Huang at the Gladstone Institutes reported using a single reprogramming factor to turn skin cells—not into another type of adult cell—but rather into neural stem cells that can self renew as well as form many types of brain cells. The paper was published online June 6 in *Cell Stem Cell* Vol. 11 (1-10)

The Gladstone team, which is affiliated with UCSF, accomplished this significant improvement in direct reprogramming in both mouse and human cells. The resulting neural stem cells could create multiple types of neurons as well as other types of brain cells, which after a month in culture created neural networks. When the mouse cells were implanted into mice, the team detected integration of the cells with the host brain tissue.

Direct reprogramming to an adult stem cell gets around two problems. If you took cells all the way back to a pluripotent state, creating iPS cells, you can use them to grow large quantities of desired brain cells but have the risk of lingering iPS cells causing tumors. And if you reprogram directly to the desired adult brain cell you cannot effectively expand them in culture to get enough cells to be clinically useful. This work provides both readily expandable starter cells and a reduced risk of tumor formation.

Also, on the basic science front, it proves that the one factor they used, Sox2, is the master regulator for driving the development of brain cells.

New Method Gives Major Boost to Efficiency in Producing Heart Cells

A University of Wisconsin team led by Sean Palecek has developed a procedure for efficiently turning pluripotent stem cells, either embryonic or iPS cells, into cardiomyocytes, the cells that form beating heart muscle. Their results were published online in the *Proceedings of the National Academy of Sciences* May 29.

Over the past few years a number of groups have developed protocols to create cardiomyocytes from pluripotent stem cells but they have been inefficient, generally producing only about 30 percent of the desired cell type and have often required expensive cell sorting procedures to isolate those cells. The Wisconsin team achieved direct production of heart cells with up to 98 percent purity with a protocol that is inexpensive because it relies on chemical modulation of a single cell-signaling pathway.

The researchers relied on emerging knowledge of the key role of the cell-signaling pathway known as Wnt in controlling the generation of heart muscle. In particular, they looked at its downstream impact on the protein Beta-catenin. They were able to up-regulate or down-regulate this signaling pathway using a single chemical, however the timing of the manipulation was critical. After extensive experiments they were able to find the exact right moments to modulate the signaling pathway to drive the stem cells to become heart tissue.

This technique should become immediately useful to pharmaceutical companies wanting to test potential new drugs on human heart cells. Down the road, it increases the likelihood that iPS cells could be used to create personalized therapy.

Vascular Stem Cells Join Cancer Stem Cells as Bad Actors

CIRM-funded research in Song Li's lab at UC Berkeley has produced dramatic results that challenge conventional theories on the origins of vascular disease suggesting it could be caused by errant stem cells. The work, published in *Nature Communications* online June 6, could provide completely new targets for therapies for vascular disease.

The smooth muscle cells that line blood vessels don't multiply, but generally accepted theory has cast them as central players in the build up of plaque that causes vascular disease. When cholesterol damages the artery wall it causes an immune response and the field has thought that during this inflammatory response the smooth muscle cells de-differentiate to a more immature cell that can divide. But when Li's team looked at the vessels in a rat that had been genetically modified so that its smooth muscle cells grow green, none of the new cells at the site of a vessel injury glowed green. When they looked more carefully at those new cells they had markers like those on stem cells. They also could find cells with markers for progenitors of multiple types of cells including nerve, muscle, cartilage and bone. They named the new cell Multi-potent Vascular Stem Cells (MVSCs).

The team also found cells with the same stem cell markers in human cadaver vessels, which could provide a whole new front for potential therapies to control vascular disease. The multi-potent nature of MVSCs also could explain a mystery of vascular disease and why it is sometimes called hardening of the arteries. It has never made sense that smooth muscle could get brittle, but since the MVSCs have the capacity to become progenitors of cartilage and bone, there is now a logical path to what anatomists and surgeons have always seen.