CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

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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—December 2012

New Way to Reprogram Cells Is Faster, More efficient

A CIRM-funded team led by Juan Carlos Izpisua-Belmonte at the Salk Institute, with collaborators at Scripps and UC San Diego, have developed a new method to reprogram adult cells. Instead of taking the cells all the way back to the embryonic-like state of iPS cells, or directly reprogramming them to a different adult tissue, they take them part way back to intermediate progenitor cells, and then push them to mature to the desired adult cell from there. The work was published online in *Nature Methods* December 4.

Creating a desired adult cell by first creating iPS cells is a slow and inefficient process. Inducing the pluripotent stem cells and then directing them to the desired adult tissue can take two months. Even at the end, you still have to worry about any lingering pluripotent cells that could cause tumors. Directly reprogramming one adult cell to another is also relatively inefficient and results in cells that generally don't proliferate, so you may not have enough cells for clinical use. The Salk team's method exposed human skin tissue to the traditional factors used in iPS conversion, but only for a few days. This took the cells part way back to the pluripotent state but not all the way. At this point they had multi-potent progenitor cells that could become endothelial cells like those in blood vessels, or smooth muscle cells. They could then multiply those cells or mature them into adult tissue with the entire process taking just 15 days.

The numerous examples of direct reprogramming of one adult tissue to another in the past year or so have added an exciting option to developing cell-based therapies. But it has been difficult to propose ways to scale up those techniques to produce enough cells for clinical therapies. This new technique, which the team calls Indirect Lineage Conversion, seems to offer a way around that obstacle.

Data Suggest New Heart Cells Come From Old Cells, Not Stem Cells

Researchers at Harvard and Brigham and Women's Hospital have provided compelling evidence that the few new heart cells mammals generate each year come from existing heart muscle cells, not stem cells. The team led by Richard Lee published its work in *Nature* online December 5.

Working with mice, the team first set out to investigate the lingering uncertainty about just how much of a mammal's heart regenerates each year. It is generally believed to be a small proportion but estimates vary widely. So they injected the mice with a marker that would only attach to cells that are actively dividing. This provided data suggesting that cardiac muscle tissue renews at a

rate of 5.5 percent per year in young adults and a rate of 2.6 percent per year in older animals. Next they bred mice to express florescent markers in their heart muscle tissue. To detect new cells they used a newly developed imaging technique called Multi-isotope Imaging Mass Spectrometry. This allowed them to see that new heart muscle expressed the same florescent marker as old heart muscle. Cells generated from resident stem cells or progenitor cells would not have the marker. They also induced heart attack-like damage in some mice and saw a slight increase in new cell growth, again from older heart muscle, but not enough to yield significant repair of the damage.

These findings provide important insight into the normal regeneration of heart muscle and all teams looking to use stem cells to augment this process should keep these data in mind. A second paper in the same issue of *Nature* offers an intriguing option for turning up the regenerative capacity using small snippets of RNA called microRNA. The team led by Mauro Giacca at the International Centre for Genetic Engineering in Trieste, Italy, screened hundreds of microRNAs and found two that were able to trigger significant regrowth of damaged heart tissue in mice.

Study Shows Power of Embryonic Stem Cells to Shed Light on Disease

A team led by Dalit Ben-Yosef at Tel-Aviv Sourasky Medical Center has for the first time created an embryonic stem cell line containing the mutation for Fragile X syndrome and showed that they mature into neurons with the same defects as those in patients with this most common form of intellectual disability. The work was published online December 14 in *Developmental Biology*.

As with many genetic diseases, scientists have not been able to develop a good animal model for Fragile X syndrome. The mutation in Fragile X results in the nerves failure to produce a certain protein, but only in the later stages of development. From studying fetal tissue at various stages of development, we know that this protein is produced up to about 14 weeks of gestation and then slowly disappears during later stages of neural development in people with Fragile X. Work with this syndrome produced some of the earliest clues that reprogrammed, or iPS cells retain some memory of having been the adult tissue they were created from. Reprogrammed stem cells from Fragile X patients never produce the protein missing in Fragile X, not even in the earliest stages of development.

The Israeli team started with a blastocyst from an IVF clinic that had been screened through Pre-implant Genetic Diagnosis (PGD). The stem cells they created did produce the missing Fragile X protein and so did the cells in the early stages of maturing into neurons. Only during the later stages of neuron development did the protein disappear, perfectly mimicking natural development in this condition. This research highlights key differences between iPSCs and embryonic stem cells. It also provides future researchers with a tool to look for potential interventions for Fragile X syndrome.

Developing new stem cells lines from blastocysts sorted through PGD screening is becoming increasingly common. Nine of 12 new embryonic cell lines added to the NIH registry this December came from PGD blastocysts. Since no stem cell line creation can be done with federal funding, this increased use of new PGD-derived cell lines underscores the importance of private and state funding such as the grants CIRM provides.

Genetic Variation Only Tells Part of the Story on Cancer Spread

A Toronto team led by John Dick has found that functional behavior of cancer cells may tell more about their sensitivity to chemotherapy than their genetics. The research from the team based at Princess Margaret Cancer Center with collaborators at St. Jude Research Hospital and the University of Southern California was published online in *ScienceXpress* December 13.

Dick was first to discover cancer stem cells, in leukemia in 1994 and went on to discover cancer stem cells in colon cancer, the topic of the current paper, in 2007. The current research is a great reminder that as we begin to target cancer stem cells in therapies, we also need to remember the behavior and sensitivity of all cancer cells. Much contemporary work has focused on developing genetic fingerprints of each tumor and selecting therapy agents based on that fingerprint. But the Toronto team found that rapidly proliferating cancer cells and slower growing or dormant cells had the same genetic mutations. But only the rapidly proliferating cells were susceptible to chemotherapy. It was the behavior, not the genetics that determined the sensitivity.

The team used viral markers to track cells from ten human colon cancers in immune-compromised mice. They were able to detect both rapid and slowly proliferating cells and determine their genetic make-up and their sensitivity to chemotherapy.

The researchers suggested that figuring out a way to turn dormant cells into proliferating cells might make them susceptible to chemotherapy and eliminate one cause of recurrent cancer.