CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

ALAN O. TROUNSON
MSc, PhD, Dr. Hon Cau, FRCOG, FRCAOG
Emeritus Professor, Monash University
President, CIRM

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—August 2012

Molecule Found that Greatly Increases Heart Cell Production

CIRM-funded research at the Sanford-Burnham Research Institute discovered a compound that can efficiently direct embryonic cells to become heart muscle and not other tissues. The team, lead by Mark Mercola included collaborators at Harvard, the Salk Institute and the company ChemRegen, published their research in Cell Stem Cell Vol 11 (242) August 3.

The team used a chemical biology approach to screen large libraries of molecules to look for ones that could drive embryonic or progenitor cells to become heart muscle, working with both mouse and human cells. They named the highly effective compound they discovered ITD-1, an acronym for a complex name that describes its function. Rather than stimulating heart cells directly, it stimulates the degradation of a cell surface receptor that is key to the formation of other types of tissue. It in essence, opens the door to forming heart tissue by closing other doors.

Defining this fundamental pathway makes IDT-1 immediately valuable to researchers trying to further understand some poorly understood parts of embryo development. But it also has the potential for use in growing large quantities of heart cells in the lab for potential transplantation, or for the possibility that this compound or a related one could be used directly in patients to give their own repair mechanisms a boost. The Sanford-Burnham team is working with ChemRegen on these possibilities.

Nanofibers Used to Enhance Blood Vessel Growth, Heart Healing

A team lead by Yi-Dong Lin at Taiwan's Institute for Biomedical Science, reported in the August 8 *Science Translational Medicine* Vol 4 (146) that they had used a nanofiber scaffold to deliver a growth factor to damaged hearts and had seen arteries grow along with new heart muscle. Team members worked at several institutions in Taiwan as well as at UC San Francisco.

The researchers assembled the nanofibers into lattice-like structures still small enough they could be injected. They then loaded them with the growth factor VEGF and injected this material into the hearts of rats and pigs in which they had recently induced a heart attack. They were able to show that the VEGF summonsed the naturally circulating bone marrow stem cells to the site of injury where they induced growth of tiny blood capillaries. But over time they also detected other heart related stem cells thought to be needed for the growth of larger arteries and new heart muscle.

Other groups have tried injecting VEGF but it doesn't stick around in the heart tissue long enough to get significant growth of new vessels. But Lin's team saw 70 percent of the scaffold fiber still there after 28 days. They credited this prolonged delivery of the growth factor with the growth of the more complex arteries and heart muscle. This was one of the first experiments performed that injected biomaterials into larger animals, something that will be key to clinical trial approval.

Once You Make New Heart Muscle Does It Beat Right with the Host?

A team led by the University of Washington's Michael Laflamme reported that they were able to mature human Embryonic Stem Cells (ESCs) into progenitors of heart muscle and show that when they were transplanted into guinea pigs they beat in sync with the host heart. The paper was published online August 5 in *Nature* and included collaborators at Shinshu University in Japan, The George Washington University in the District of Columbia and Geron Corporation.

A number of teams have shown that you can turn human ESCs into heart muscle cells, transplant them into mice and rats with damaged hearts and see some improvement in heart function. But because those small rodents have hearts that beat three times as fast as a human heart, and because it is impossible to make significant increases in the speed of cells grown from human ESCs, no one has been able to verify if those transplants really couple with the host tissue. However, Guinea pig hearts beat only slightly faster than humans allowing the current team to verify that the new cells did beat in sync with the host. What's more, the new cells not only did not cause abnormal rhythms as many had feared, but actually reduced the risk at arrhythmias. The scar tissue that forms where a heart attack occurs often leads to abnormal rhythms, but the healing effect of the transplanted cells seems to have mitigated this impact.

The team used a clever trick to verify the heart beat of the new cells compared to the host. They inserted a gene for a protein that is activated when the heart pumps. But it wasn't just the normal gene, it was a version that had a florescent component that flashed light when it was activated. They could look into the chest cavity of the animals and see the new cells flash and could match that with the readout of a traditional ECG monitoring the host heart.

Newly Discovered Brain Stem Cell Builds Neurons Used to Think

A CIRM funded team lead by Ulrich Muller at Scripps has discovered a brain stem cell that is responsible for generating neurons that make up the outer layers of the brain, the cortex, which is responsible for higher brain functions such as integrating information and forming memories. Their results were published in the August 10 Science Vol 337 (746).

They tracked down this stem cell by following the activity of a cell-signaling molecule that is normally only active in neurons in the cortex. This signal is called Cux2. Working in a mouse model, the team tracked whether Cux2 was turned on or off at various points in embryo development. They, too, made clever use of gene modification to insert florescent markers, this time two, one red and one green. Neurons were green if Cux2 was turned on and red if it was turned off. The cortex forms in the later stages of development, generally after the lower layers of the brain have already been formed. And indeed they did see that almost all the neurons that formed the cortex at his late stage glowed green. But there were a few green cells at the very earliest stages of development, which turned out to be this new class of brain stem cell.

This finding turns around two decades of assumptions that a neuron's fate is determined by the date it is created during brain development. This research suggests that it is not date alone, but also the identity of the subset of stem cells from which the neuron arose. This revelation opens the door to important follow-on research to further refine our understanding of brain development. It also points to opportunities to produce large quantities of these upper layer neurons for potential therapies. It has been difficult to generate these in the past.

Stem Cell Science Could Yield a Male Contraceptive

A team lead by James Bradner at Harvard has found a compound that shuts off the sperm-making capacity of testicular stem cells. They published their findings in Cell Vol 150 (673) on August 17 along with colleagues at Texas A&M, Baylor College of Medicine in Houston, and George Washington University in Washington D.C.

Bradner's immediate team, based at Harvard-affiliated Dana-Farber Cancer Institute, normally searches for potential drugs to interfere with cell signal pathways that lead to cancer. They were looking at a set of pathways called bromodomains and a particular inhibitor named JQ1. It turned out that JQ1 was not particularly good at blocking the cancer-related signal they were working with, but it did work on a related cell signal that they did not recognize. When they looked at the scientific literature it turned out this cell signal is only turned on in the stem cells in testes, and only during the generation of sperm. So, that is when they assembled the multi-institutional team to include experts in fertility.

When they gave JQ1 to male mice and allowed them to mate, they were infertile. But, when they stopped the medication, the mice were once again able to produce offspring. Because the target signal is only used by the body for one function, sperm production, it becomes a great target for a male contraceptive. JQ1 is not quite specific enough in only shutting down this one signal to be a good candidate drug. The team is already begun the process of looking for related, but more specific drugs that could be a candidates for clinical trials.

New Technique Could Increase Red Blood Cell Supply for Transfusion

A team at Albert Einstein College of Medicine in New York has developed a technique for creating red blood cells from stem cells with 10-fold to 100-fold greater efficiency than prior methods. The group, lead by Eric Bouhassira, published their findings online August 2 in Stem Cells Translational Medicine, the new journal supported by CIRM. Part of the funding for this work came from New York's state stem cell funding agency.

Bouhassira's team got the efficiency in generating red cells no matter what type of stem cell was their starting point. They used several different types of stem cells, including embryonic stem cells and those from cord blood, circulating blood and fetal tissue. They used a cocktail of approaches to get the large number of cells, including steps at three different stages of the maturation process that turns a stem cell into a red cell. They also used a steroid to foster conversion to the red cells at a more efficient pace.

The researchers state in their paper that they consider the technique able produce the cells needed for wide-scale manufacture of red cells. That could potentially end the perennial shortages of donor cells for transfusions that the health care system struggles to overcome.