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—May 2012

Muscle Stem Cells Successfully Summoned to Repair Muscle

CIRM-funded research in Julie Saba's lab at the Children's Hospital Oakland Research Center has shown how a specific protein can trigger putative stem cells called satellite cells to repair muscle damage, and they found that an existing drug can boost levels of that protein in mice. The work was published online May 14 in the *Public Library of Science ONE* Vol. 7 (5).

Saba's team has been working with the protein S1P (sphingosine-1-phosphate) for several years, first in fruit flies and most recently in mice that have a disease similar to Duchene Muscular Dystrophy. This mouse strain has a deficiency in S1P and other researchers have shown that S1P has the ability to activate satellite cells. The team used the mouse model to define the pathway through which S1P can activate satellite stem cells differentiation. They then used a drug that blocks the breakdown of S1P, in essence increasing the supply of the key protein, and they saw increased muscle regeneration.

An exciting aspect of this work is the fact that there are drugs that block S1P metabolism and boost its levels being tested in humans for other diseases. So the path to clinical trials may be accelerated, but they must first prove that the same pathway is at work in the human form of the disease.

Human Stem Cells Treat Muscular Dystrophy in Mice

A research team at the University of Minnesota lead by Rita Perlingeiro developed skeletal muscle progenitor cells from stem cells in sufficient quantities to treat Muscular Dystrophy in the same mouse model as the study above. The report in the May 4 issue of *Cell Stem Cell* Vol. 10 (610-619) included collaborators from iPierian in South San Francisco.

In the past, it has been impossible to generate muscle precursor cells from pluripotent stem cells in a way that was efficient and produced the cells in sufficient quantities to be effective in treating disease. The Minnesota team succeeded using both human embryonic stem cells (ESCs) and reprogrammed human adult cells, so called induced Pluripotent Stem Cells (iPSCs). They induced the cells to change by genetically modifying them so that they could regulate the levels of a protein, Pax7, which is essential for the repair of skeletal muscle. With this genetic modification they could prompt both ESCs and iPSCs to mature into muscle progenitor cells in large quantities. When they transplanted those cells into mice with muscular dystrophy they saw long-term muscle regeneration and improved muscle function.

The team used a virus to induce the genetic change, which may not be completely desirable for clinical trials, so they will now look for other ways to modify the satellite cells..

Two Teams Use Different Stem Cell Types to Grow Bone

A team led by Gordana Vunjak-Novakovic at Columbia University matured human embryonic stem cells (ESCs) into a type of mesenchymal progenitor cell and then developed a method of directing those cells to create bone in the lab that further matured when implanted in mice. The paper published online May 14 in the *Proceedings of the National Academy of Science* included work by a researcher funded by the New York Stem Cell Foundation (NYSCF).

A second team, funded by CIRM at UCLA, developed a method for sorting bone-forming perivascular stem cells from fat quickly, and combine those cells with a growth factor to get efficient bone formation in lab cultures that survived when transplanted into mice. The report, scheduled to be published online in the CIRM-supported *Stem Cells Translational Medicine* in June, had three senior authors: Chia Soo, Bruno Peault and Kang Ting.

The New York team cultivated the ESC-derived bone progenitor cells on a 3D scaffold in a bioreactor until they could see the formation of early bone structures. They then implanted those engineered bone tissues into mice and over the course of eight weeks saw the bone further mature, including blood vessel growth into the new tissue. The NYSCF-supported post doctoral fellow who was the lead author on the study is now working in the NYSCF in-house lab and is trying to replicate the work with cells derived from human iPSCs so that a personalized bone graft could be possible without the current trauma of harvesting bone from another part of the patient.

The UCLA team was trying to avoid two pitfalls of current methods for using the stem cells found in fat for bone growth. Obtaining pure adipose stem cells generally takes many weeks of growing cells in the laboratory. That drives many clinical scientists to try to use the mixture of cells that results when all you do is remove the actual fat cells from the fat harvested. The lack of purity and homogeneity of the cells that are left is more likely to cause unpredictable consequences that will affect federal approval of proposed therapies. Peault's team used an isolation method called FACS (florescence activated cell sorting) and were able to purify a line of cells they called human perivascular stem cells (hPSCs). In comparing the hPSCs ability to grow bone in mice to the ability of the mixed cell source, the purer implant performed considerably better. However, when they mixed it with a growth factor called NELL-1, they saw an even more significant increase in bone produced.

Together these two teams could provide new options for the therapeutically difficult problem of repairing large bone defects.

Two Teams Develop Ways to Reverse Impact of Aging on Stem Cells

A team led by Leanne Jones at the Salk Institute has mapped the pathway that results in a decrease in the number of adult stem cells with aging and found that intervening in that pathway can reverse the decline in stem cells. The team published their results in *Nature* online May 23.

A second team led by Hartmut Geiger found a protein that is responsible for the loss of function of blood-forming hematopoietic stem cells (HSCs) with age, and tested a compound that seems to reverse this loss of function. Geiger is on faculty at both the Cincinnati Children's Hospital Medical Center and the Ulm University Medicine in Germany and his team published their findings in the May 4 *Cell Stem Cell* Vol. 10, (520-530).

Jones' team at Salk worked with stem cells found in the testes of fruit flies because it let them closely monitor the relationship between the stem cells and the supporting cells that surround them called the stem cell niche. It turns out that a cascade of signals from those niche cells results in a decline in the number of stem cells that can be summoned to repair tissue. The first step in the pathway is a gene-regulating molecule called microRNA, in this case one called let-7. The team reversed the loss of the age-related decline in stem cells by intervening at the second step in the pathway, but they suggested that each step they identified could be a target for further research into possible drugs to block the decline.

Geiger's team built on earlier finding that showed a particular protein, Cdc42 was elevated in some tissues in older mice and in some immune cells in older humans. In their current work they showed increased levels of the protein in blood-forming hematopoietic stem cells (HSCs) from older mice and then worked to show that it was responsible for the decline in function. First they showed the protein could cause premature aging in HSCs in young mice and then showed that a drug that inhibited the protein was able to reverse the decline in function in mouse cells in lab culture. They then took these rejuvenated cells and injected them into mice and found function equal to young HSCs

Both of these studies remind us of an issue that has been discussed much among regenerative medicine researchers. If we transplant new stem cells into an aging environment will they have a reduced likelihood of succeeding in doing what we want them to do? Both studies suggest the answer in some cases may be yes, but they both also point to ways to bypass this obstacle.