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—Febuary 2013

Brain Progenitor Cells from iPS Replace Damaged Coating on Nerves

A Rochester University team led by Steven Goldman turned reprogrammed stem cells (iPSCs) into a type of early brain cell that can form the myelin layer that wraps and protects nerves. The work, published February 7 in *Cell Stem Cell* Vol 12 (252-264), showed the cells were able to replace the missing myelin in an animal disease similar to multiple sclerosis.

Many teams have been able to coax iPS cells to become nerve cells. This is due, in part, to the fact that nerves appear pretty early during development in the fetus and don't have that many intermediary steps. The myelin forms much later and has many more intermediary steps. In this case the intermediary cell required is called on oligodendrocyte precursor cell. It took the Rochester team four years to determine the precise set of chemical signals and the timing of using them to develop a process that resulted in efficiently generating large quantities of the precursor cells. When those cells were injected into an animal model, they were more effective at creating myelin than similar cells from adult stem cells.

Other teams have made these precursor cells from embryonic stem cells and from adult brain stem cells, but those have generally not been very efficient processes and yield cells that would be recognized as foreign by a patient's immune system. This work opens up the possibility of personalized therapy using cells that start with the patient.

Alzheimer's Patients' iPS Cells Suggest Opportunity to Target Therapy

Two Japanese teams, one led by Haruhisa Inoue at Kyoto University and one led by Nobuhisa Iwata at Nagasaki University, created reprogrammed stem cells (iPSCs) from four patients and found functional differences in the nerves that grew from two of those cell lines suggesting an opportunity to target therapy to certain patients. The work was published online February 21 in *Cell Stem Cell* in advance of publication scheduled for April 4, Vol 12 (1-10).

The teams made iPS cells from two patients with familial Alzheimer's and from two patients with sporadic Alzheimer's who did not have a known family inheritance of Alzheimer's related genes. They matured the stem cells into two kinds of brain cells, neurons and astrocytes. The latter are support cells for the neurons. In the cells from two patients, one with familial disease and one with sporadic, they saw specific signs of stress in some of the cellular machinery that is normally inside all cells and keeps them running and healthy. They did not see these same signs of stress in the cells from the other two patients.

What is most interesting about the current study is that a drug that has been tested and failed in clinical trails was able to alleviate the signs of stress in the cells from the two patients that showed that change in function. That drug, an Omega-3 fatty acid called DHA, had been tested in two large-scale trails, in part because it is a primary structural component of the brain. But the trials failed to show benefit across the whole population of patients enrolled. This study suggests it may be possible to divide clinical trail patients into subsets and find a benefit in certain groups.

Two Studies Point to Ways to Grow Blood Stem Cells in Large Amounts

Two teams have made significant advances in an area that has frustrated researchers for years: how to grow blood forming stem cells outside the body (ex-vivo) in large quantities. A CIRM-funded team led by Bruno Peault, who has appointments at UCLA and the Scottish Center for Regenerative Medicine, published its findings in *Blood* online February 15. A team at University of Texas Southwestern led by Sean Morrison published its findings in *Nature* online February 24.

Morrison's work continues his efforts to define the environments in the body where stem cells are nurtured and grow. The current paper suggests that stem cells may reside in different neighborhoods at different times in their path to an adult cell, and that the intermediate or progenitor cells for each type of blood cell may claim a different neighborhood. The earlier work showed that a certain type of cell lining the blood vessels in bone marrow, called perivascular cells, create an environment that nurtures the basic blood-forming stem cell. Now he has shown that the progenitor cells that give rise to infection-fighting T cells and B cells thrive in an environment known as the osteoblastic niche. That is an area of the bone that makes new bone.

Morrison's group first identified a growth factor needed by the infection-fighting progenitor cells. They then looked for the cells that were secreting that growth factor and it turned out to be the osteoblastic area. He suggests that the same approach can be systematically used to find the niche that is home to every type of blood cell and that with that map we can begin to recreate similar environments in the lab.

The Peault team worked on understanding and refining the lab conditions used to try to grow blood forming stem cells currently. They played off of Morrison's early work that showed that the perivascular cells nurture blood-forming stem cells. Researcher have typically tried to grow blood-forming stem cells on a support layer formed from mesenchymal stem cells, the second kind of stem cell found in bone marrow. But the Peault team sorted the mixed bag of many different types of mesenchymal cells usually used, and purified a specific type of perivascular cell identified as CD146+ cells. When they grew blood forming stem cells on those CD146+ cells they not only multiplied well but also maintained their ability to mature into all types of blood cells. When those cells were infused into a mouse that had its immune system wiped out, they were able to restore a fully functioning blood system.

The team went on to show that they could isolate the same DC146+ cells from the mesenchymal cells found in adipose, or fat, tissue. So we might have an all too ready supply of the needed support cells to grow blood-forming stem cells for life saving transplants for cancer patients and others with blood disorders.

Newt May Not Be a Model for Regeneration that Can Be Duplicated

A team led by Thomas Braun at Max Planck Institute in Germany has shown that many of the genes a Newt uses to regenerate tissue do not have comparable genes in humans. They published their work online in *Genome Biology* February 21.

The Newt has 10 times more genes than we do, so the shear size of its gene pool has made direct comparison with humans difficult. The German team got around this by looking at only those genes that were turned on during development of certain tissues, heart, limb and eyes, which are known to regenerate in newts. They did this by looking for the RNAs that were produced. The first step in making a protein coded for in a gene is to turn the DNA into RNA, so it is a ready sign of an active gene. They found RNA for 15,000 proteins and of those, 826 were unique to the newt.

Many in the field have long held hope that we have the same ability to regenerate tissues as newts and certain other animals, but it is dormant. The theory has been that if we can understand the genes the newt uses, we could find a way to turn those back on in humans. That now seems unlikely. But it does not mean we can't still garner knowledge from the way the newt gets the job done, to do something similar, albeit with different genes, in the human.