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—January 2013

Tissue Created from iPS Cells Did Not Trigger Immune Rejection

A Boston University team led by Ashleigh Boyd turned reprogrammed stem cells (iPSCs) into more mature cells from three types of tissue and none of them triggered immune rejection when transplanted into genetically identical mice. The work was published online in *Cell Stem Cell* January 24, prior to print publication April 4, Vol 12 (1-6).

The research represents a rebuttal of work done by a UC San Diego team published in 2011 that showed iPSCs triggered an immune response, but embryonic stem cells did not. One key difference with the studies is the San Diego team transplanted undifferentiated stem cells directly into the genetically identical animals. That is something that clinicians would be highly unlikely to consider doing. The Boston team transplanted cells that had been matured into endothelial tissue, hepatocytes or neural cells, all tissues more likely to be used clinically. They saw no signs of rejection in the days after transplant and up to three months afterward. Both teams did parallel experiments with embryonic stem cells (ESC), but only the San Diego saw a difference, with no sign of rejection for the ESCs. Both cell types behaved the same in the Boston studies.

This question of whether or not tissue created from iPSCs made from a patient's own cells will be rejected upon transplantation is the crux to determining the relative value of starting with iPSCs or ESCs. In humans it is not feasible make genetically identical tissues from ESCs. The Boston team did a meticulous series of experiments that go a long way to increasing the chances that personalized therapy with iPSCs can become a reality. But it certainly is not the final word.

Data Suggest Brain Cells Not as Hard-Wired as We Thought

Harvard researchers Caroline Rouaux and Paola Arlotta have shown that a brain cell already committed to being one type of neuron can be turned into another type of neuron with just one reprogramming factor. The work was published online in *Nature Cell Biology* January 21.

Of all the cells in a mammal, neurons have always been considered among those cells most likely to have the same function for the entire life of the organism. The Harvard team succeeded in getting neurons to change type and function in living mice. They did it with just one reprogramming factor, Fezf2, which biologist have for some time linked with the development of a type of neuron called corticospinal neurons in the embryo.

One caveat, they found this flexibility in very young brains. They measured the change in the brains of newborn mice after they had injected the reprogramming factor directly into the cortex of their brains. They also introduced a florescent marker so that they could track the growth of various cells in both the experimental mice and in controls. Through elaborate measures on brain tissue taken from pups several days after birth, they could confirm the nerve cells had changed form to become corticospinal neurons and migrated to areas of the brain where the original neuron type is not found.

The corticospinal neurons are one type of nerve cell that deteriorates in Amyotrophic lateral Sclerosis (ALS), or Lou Gehrig's disease. The current experiment, though it is only one very early first step, suggests that one day it may be possible to reprogram those types of nerve cells that survive in ALS patients into the nerve cells they are loosing.

Single Factor Creates Neurons from Other Tissues

A team led by Xiang-Dong Fu at UC San Diego has converted several different tissue types directly into neurons using a type of RNA. The work, done with collaborators at Wuhan University in China, was published on line January 17 in *Cell*.

While other teams have succeeded in converting skin and other tissues into neurons, they have all used a fairly complex mix of reprograming factors to accomplish the task. For most clinical uses of this technology, the optimal method would involve converting one cell type to another in vivo—directly in the patient. This would be much simple and easier for regulatory approval if you were introducing one factor into the patient instead of several.

The current team used technology based on RNA, a class of molecules that acts as the middleman for reading genes in DNA and creating the coded protein. A subclass of these molecules called microRNAs, has emerged in recent years as major regulatory factors at an early stages of gene expression, determining which genes get the opportunity to be read, or switched on. In every cell of our bodies except neurons, one of these microRNAs keeps a certain protein repressed. That protein called PTB is known to be a prime driver in creating neurons in the developing fetus. The team used another type of RNA called small-interfering RNA to block the action of its cousin microRNA. When the microRNA was blocked it releases the PTB to do the job it does during embryo development and converted the tissues into neurons. The researchers also tested some of the cells and found they functioned like neurons. All the work was in the laboratory, not in live animals.

With one in four Americans expected to experience a neurodegenerative disease at some point in their life, any advance that could lead to the reprograming of surviving brain tissue to replace damaged cells is welcome.

iPS Technology Used to Increase Immune Cells Aimed at Cancer, HIV

Two Japanese teams have created iPS cells from mature T cells then directed them to become T cells again and found these newly rejuvenated cells were able to multiply better than the older T

cells they were derived from. Both teams published papers, one using cells from a cancer patient and one using cells from an HIV patient, in the Jan 3 *Cell Stem Cell* Vol 12, (31-36).

Our immune systems are generally very effective at searching out and destroying nascent tumors and foreign pathogens, but sometimes there are just not enough immune cells to fight back a fast-growing tumor and persistent invader like HIV. So both teams tried to create a more robust batch of the immune systems T cells. The reprogramming process that creates iPS cells resets the tips of of chromosomes called telomeres. These tips get worn down after older cells have divided many times and cells with shortened telomeres don't replicate readily. But once the cells were given youthful telomeres they were able to produce large quantities of T cells. More importantly the new T cells were able to remember what they were programmed to attack. The cells from the HIV patient could identify the virus and the cells from the cancer patient could detect the same tumor.

The cancer field has seen countless attempts at augmenting our immune response to tumors, often called adoptive immunotherapy. Generally, the approaches to date have had minimal effect. This technique could advance the efforts in a way that impact many types of cancer as well as some intractable infections.

The cancer work was led by Hiroshi Kawamoto of the Riken Center at Kyoto University and the HIV work was led by Hiromitsu Nakauchi at the University of Tokyo. One team member worked with both groups.

Leprosy Bacteria Can Reprogram Adult Cells into Stem Cells

A University of Edinburgh team led by Anura Rambukkana has discovered that the leprosy bacteria is able to reprogram the cells it targets for infection into a stem cell-like state. They published the surprise finding in *Cell* Vol 152 (51-67) January 17.

The team was originally trying to figure out how the bacteria spreads around the body. Its initial site of infection is in Schwann cells, the cells that act as insulation around nerves that are outside the central nervous system. They found the bacteria reprogrammed their host cell to progenitor stem cells of mesenchymal tissues and could develop into skeletal and smooth muscle cells. These cells then migrated around the body with the bacteria tagging along for the ride infecting tissues all around the body.

The team speculated that this induced cellular plasticity might represent an underlying mechanism for some other infectious diseases as well and could become a target for therapy. The process could also become another way of turning adult cells into stem cells in the laboratory.