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 2013

Glial Cells in Brains of Mice Directly Reprogrammed to Nerves

A team led by Gong Chen at Pennsylvania State University has succeeded in using one growth factor to reprogram protective glial cells into functional neurons in mouse brains and in human cells in the lab. The team reported on their work in *Cell Stem Cell* online December 19.

Astrocytes and other glial cells perform various protective and supportive roles for the neurons that carry out the work of the brain. They generally do a good job, but sometimes, after nerves are damaged by injury or disease, the glial cells get a little too zealous. They get summonsed to the damage in mass, sort of clogging the area, releasing factors that inhibit nerve growth and eventually form scar tissue. Chen reasoned that those glial cells could be an abundant starting source for repair of the damage if they could be reprogrammed into neurons.

They began by working with a growth factor, NeruoD1 that is known to be active in new nerve growth in at least one part of the brain. They engineered a virus to carry the gene for the growth factor directly into glial cells in mice with brain injury and in mice that had a form of Alzheimer's disease. In both models they saw conversion to neurons. More important, two different types of glial cells converted into two different types of neurons, excitatory neurons and inhibitory neurons. Getting a balance of those nerves is critical to normal brain function. They also verified that the new neurons were able to send and receive brain signals in a manner integrated with the animal's existing neurons.

The team then sought to verify this was not a mouse-only phenomenon. They used the virus to insert the growth factor gene into human glial cells growing in the lab and found that again they were able to generate both excitatory and inhibitory nerves. The work seems to set up a framework for a potential therapeutic approach to many causes of nerve loss.

Stem Cells Pushed to Create Multiple Types of Functional Lung Cells

A Columbia University team led by Hans-Willem Snoeck has found a more efficient way to generate the precursor cells for lung from pluripotent stem cells and to get them to mature into at least six types of cells found in functional lung. The work using both embryonic and reprogrammed iPS type stem cells was published online December 1 in *Nature Biotechnology.*

The team had previously published a protocol that drove pluripotent stem cells to become those lung precursor or progenitor cells, but the efficiency was less than 40 percent and those cells could be coaxed to become only the cells that line the airways, not the rest of the lung tissues.

Since that time they tested a wide variety of combinations of factors that enhanced or inhibited the function of various genes. They eventually came up with a combination that almost uniformly produced lung progenitors. Those cells, both in lab cultures and when transplanted in mice, were able to mature into six types of lung tissue including the critical surface cells that make and react to surfactant, the material that lets us absorb oxygen.

The progenitor cells, however, were not completely pure and that resulted in a surprise finding. Lung tissue comes from cells known as endothelial, but a few of the cells that were transplanted were from the mesoderm lineage, which is associated with muscle formation rather than the soft interior tissues of the lung. But the lung does need some mesoderm for support, and it turns out the lung progenitors seemed to have the ability to instruct the few mesoderm cells to become the type of tissues that would be found in lung.

While the authors suggest this work is an early step toward creating replacement lungs, they note that result would be many years down the road, and they state that the more immediate use of the research would be to create models of lung disease in the lab. Those in turn could be used to test potential drug therapies.

Immune Cells Assist Stem Cells in Healing Muscle

A Harvard Medical School team working in the lab of Diane Mathis and Christophe Benoist has shown that a type of immune cell known at Regulatory T cells is required for muscle stem cells to do their job. The work was published in *Cell* December 5, Vol. 155 (1282-1295).

Those immune cells, often just called Tregs, have the primary role of tempering the immune response so that it does not get out of control. The Harvard team found a distinct subset of Tregs that gets summonsed to the site of muscle injury shortly after the initial inflammatory response has begun. Those cells secrete a growth factor that activates muscle stem cells known as satellite cells to begin the repair process.

They tested the hypothesis that the Tregs were necessary for the stem cells to do their job in two models. When they genetically removed the Tregs from mice, when the animals were given a muscle injury, the inflammatory response was prolonged and the muscle repair was impaired. In a mouse model of muscular dystrophy, when they increased Treg activity they saw diminished muscle wasting and when they decreased Treg activity, they saw increased muscle wasting.

The most immediate therapeutic candidate from this work may be from a second experiment the researchers conducted. Once they verified that this subpopulation of Tregs produced the growth factor Amphiregulin they tested the growth factor's ability to activate muscle satellite cells directly. Both in the lab dish and in animals, it did increase the activity of the stem cells. So it could be come a candidate for drug intervention in muscle injury and wasting.

Team Developed Road Map for the Right Cartilage Needed for Joints

A CIRM-funded team at the University of California, Los Angeles, identified the cells that are the progenitors for articular cartilage, and created a molecular road map of the steps needed to drive

those progenitor cells to become the type of cartilage needed for joint repair. The team led by Denis Evseenko published their work in *Stem Cell Reports* online December 12.

Numerous attempts to use adult stem cells to produce durable articular cartilage that can stand up to the pressure and wear in our joints have failed. Although the mesenchymal stem cells found in bone marrow are clearly capable of making cartilage, they may be too far down the development continuum to be efficient at making this type of cartilage. Using that as a premise, the UCLA team worked with pluripotent stem cells, both embryonic and reprogrammed iPS type cells.

We know that this type of cartilage begins to develop at around week five of human fetal growth. So, working with donated tissues of that stage of development and later, the UCLA team first identified five cell surface markers that allowed them to sort for those cells responsible for the earliest stage of developing chondrocytes, the cells that produce articular cartilage. Once they had those cells isolated, they did elaborate genetic tests to see which genes were selectively turned on in those cells. They eventually identified three cell-signaling pathways that are key to the development of chondrocytes capable of make strong articular cartilage. They then turned to their pluripotent stem cell lines and verified that these pathways were key to generating articular cartilage.

The team has given the field two valuable tools: the cellular dog tags of the desired progenitor cells and the molecular pathways active in developing chondrocytes. With these tools researchers now should be able to make substantial progress in cartilage tissue engineering using pluripotent stem cells.