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 2012

First Published Data on Embryonic Stem Cell-Derived Cells in Humans

A team lead by Advanced Cell Technology's Robert Lanza and UCLA's Steven Schwartz published the first paper ever with data from a clinical trial using cells derived from human embryonic stem cells (hESC) in *Lancet* online January 23. The very early results with just two patients showed that the cells appeared to be safe, at least for the first four months, and suggested they might provide some benefit to the patients.

The patients were the first enrolled in two separate clinical trials, one for dry age-related macular degeneration (AMD) and the other for Stargardt's macular dystrophy. Both received retinal pigment epithelial (RPE) cells that ACT had derived from hESCs because in both diseases the degradation of the RPE layer in the retina leads to loss of photoreceptors and subsequent loss of vision. The UCLA members of the team injected 50,000 RPE cells in the sub-retinal space of one eye in each patient.

After four months the injected cells appear to be safe so far. They team could not detect any signs of tumors, other abnormal growths, retinal detachment or immune rejection. Both patients reported some improvement in vision and scored better than before the treatment on certain visual acuity tests. However, the AMD patient had improvement in both eyes, the treated and the untreated eye, which led Schwartz to suggest that this patient might be experiencing a placebo effect. In an accompanying commentary in the journal, Wake Forest's Anthony Atala suggested this might also be attributed to the immune suppression regimen both patients were taking.

This is clearly a milestone paper for the field but it is far from definitive on safety and provides only suggestive hints on efficacy. Both trials are scheduled to enroll 12 patients, and Schultz treated a second Stargardt's patient the day after the paper was published. The entire field will be anxiously awaiting the larger data set that the team expects to finalize in 2013.

RPE Might Be Able to Regenerate Its Own Repair Cells for the Blind

A paper published in the January 6 *Cell Stem Cell* Vol. 10 (88-95) by a team lead by Sally Temple at Albany Medical College showed that the eye's retinal pigment epithelium (RPE) actually has cells within it that can become multi-potent stem cells. In the lab, they were able to make layers of RPE cells from those stem cells, which could potentially be used to cure the blindness that results from degradation of the RPE layer that supports the retina.

Several teams, including the ACT group above and a CIRM Disease Team, are trying to recreate the RPE layer in eyes with pluripotent stem cells. Temple's group used tissue from donor eyes from cadavers, but she said that these cells can be isolated through needle biopsy from living patients. Normally RPE cells do not divide after embryonic development.

The Albany team found that when taken out of their normal environment, about 10 percent of adult RPE cells, if cultured on the right medium with the right growth factors, become multi-potent stem cells that can self renew and can be directed to become RPE cells and certain nerve progenitor cells, as well as certain cells from the mesenchymal lineage including progenitors of fat and bone. That latter could explain certain rare eye diseases in which mesenchymal cells are inappropriately made in the eye.

The most obvious role for these newly isolated cells is to generate layers of RPE cells from a patient's own adult cells turned into stem cells and use these to repair the damage done in macular degeneration or Stargardt's disease. However, since the cells seem to be multi-potent, you might also be able to direct some of the cells to become the neural tissue lost in the retina itself in response to the degradation of the RPE in these diseases. They may also be useful in generating replacement nerve cells for other diseases marked by damage to nerve tissue.

Young Muscle Stem Cells Return Vigor to Aged Stem Cells

A University of Pittsburgh team lead by Johnny Huard found that muscle stem cells from young mice, when injected into older mice, were able to restore the ability of the recipients to grow youthful muscle. They published their findings in *Nature Communications* Vol 3 (608) published online January 3.

As we age, most of our adult stem cells have significantly reduced ability to replicate and repair our various tissues. So, Huard's team decided to see if muscle stem cells from young mice could replace this function in naturally aging mice and in a mouse model of progeria, a disease that causes premature aging. They did find new muscle growth and were able to measure muscle fibre sizes that were larger and more like those found in young mice. But those newly robust tissues did not have the markers that the team had placed on the donor cells. They were cells from the recipient mice suggesting that the donor stem cells did their good work by secreting proteins and various factors that redirected the older muscle stem cells to a younger state.

If future work determines exactly what these secreted factors are, it could lead to the development of traditional drugs to simulate their effect on aging muscle.

Alzheimer's in a Dish Yields Clues to Early Diagnosis and Therapy

A CIRM-funded study published online in *Nature* January 25 by UC San Diego's Larry Goldstein and his team now at the Sanford Consortium showed that nerves grown from reprogrammed iPS cells from Alzheimer's patients do function differently than cells grown from individuals who did not have dementia.

The Sanford team made six sets of iPS cells from skin biopsies: two from patients with familial Alzheimer's, two from patients with what appeared to be sporadic Alzheimer's and two from individuals with no signs of dementia. They were able to mature those cells to create cultures that were 90 percent pure neurons. The neurons from both patients with familial disease had significantly higher levels of the amyloid beta and tau proteins that form tangles and plaques in the brains of advance Alzheimer's patients. They saw the same thing in cells from one of the patients who was thought not to have a familial form of the disease.

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Goldstein's group is the second to show that neurons grown from iPS cells from Alzheimer's patients function differently than normal ones. Last year a Columbia University team used a different reprogramming technique to create iPS cells from patients with a different Alzheimer's mutation than the ones in San Diego. Yet they found the same molecular defects, raising the odds these cellular changes are caused by the Alzheimer's associated genes and not by the process of reprogramming to create iPS cells. In a news item in the same issue of Nature, Goldstein suggested that these changes might be seen early enough to allow for diagnosis of the disease prior to significant damage to the brain, and that the defects point to options for therapy.

Proteins Found to Be Key to ESC's Fate: Self-Renew or Differentiate

A pair of papers in the January 6 *Cell Stem Cell* Vol. 10 identified a key set of proteins that help an embryonic stem cell (ESC) decide whether to produce new copies of itself or to differentiate, to mature down a path to an adult cell type. One paper was published by Luciano Di Croce's team at the Centre for Genomic Regulation in Barcelona and one by Jesus Gil's team at Imperial College London. The journal also printed a Preview article discussing the importance of the papers by Harvard's Chad Cowan and Raymond Camahort.

ESCs maintain self-renewal by expressing pluripotency genes and repressing genes that would lead them to mature down a path to a particular adult cell. Conversely, they differentiate by repressing pluripotency genes and activating various genetic factors that can initiate the multi-step process that leads to adult cells. It has been known for some time that large aggregates of proteins, called Polycomb repressive complexes, mediate these alternative on-and-off switches. What the two teams discovered in the current papers is that a subset of the proteins in those complexes seems to hold the key levers in ESC fate. This subunit of the protein complexes is made up of the Cbx family of proteins and both teams fingered a particular member of this family as the key to embryonic cells' ability to self-renew. And as the Harvard authors noted, because they used quite different experimental methods to arrive at this conclusion, its reliability is heightened.

This represents very basic research, but the type of fundamental discovery likely to help many very divergent future investigators. The question of what drive self-renewal versus differentiation impacts countless research teams daily at all stages of the research pipeline.