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—March 2012

Antibody Drug Targeted to Leukemia Stem Cells, Hits Solid Tumors, too

CIRM-funded research in Irving Weissman's lab at Stanford has shown that an anticancer antibody first developed for leukemia shrinks many human solid tumors when they are transplanted into mice. The work was published online March 26 in the *Proceedings of the National Academy of Sciences.*

Several years ago the Weissman team showed that a cell surface protein, called CD47, found on leukemia cells—and in particular on leukemia stem cells—acts as a "don't eat me" signal. It prevents the cancer cells from being engulfed and destroyed by our immune cells tasked with surveillance and control of tumors, the macrophages. The team subsequently was awarded a CIRM Disease Team grant to develop antibodies able to attach to this surface protein in order to block its action and allow the macrophages to do their job and destroy the tumor.

In the current work they have shown that the same CD47 cell surface protein exists on many human solid tumors, including ovarian, breast, colon, bladder, brain, liver and prostate cancers. They also showed that the same anti-CD47 antibody they developed for our Disease Team also results in shrinking each of these solid tumors when transplanted into mice, as well as preventing their spread through metastasis. When the tumors were small, the researchers found some evidence that the cancer may have been completely eliminated. This could result in a very widely applicable clinical application that has risen from very basic science trying to understand the interplay between cancer and our immune system.

Signal Network Crosstalk Is What Keeps a Stem Cell a Stem Cell

In the March 2 issue of *Cell Stem Cell* Vol. 10(312) a team led by Stephen Dalton at the University of Georgia reported the most complete understanding to date of what happens in an embryonic stem cell to maintain its stem cell state.

Understanding stem cell fate, whether the cells renew to form new stem cells or mature into adult cells, is the crux of stem cells' use in regenerative medicine. While many cell signaling pathways have been shown to impact cell fate, researchers have not reached a fundamental understanding of how some stem cells retain their pluripotency and renew as stem cells. Scientists had generally assumed individual cell signaling molecules acted in step-by-step linear process. The work by Dalton's team suggests that complex interplay of several molecules controls a "switch" that determines if a stem cell remains a stem cell or goes on to become a specific adult tissue. This crosstalk involves both suppressing signals that would trigger maturation into adult cells and stimulating signals to remain a stem cell.

The team spent five years testing various hypotheses about which signaling combinations were key. The painstaking result should aid our fundamental understanding of embryo development and facilitate the use of pluripotent stem cells in regenerative medicine.

New Method Labels and Tracks Cells after Transplant

A team at the National Institute of Health's Clinical Center led by Joseph Frank has developed a method to label cells so that they can be tracked after they are transplanted intravenously. The paper was published in the March *Nature Medicine* Vol. 18 (3).

For many therapeutic uses of cells, it is likely the Food and Drug Administration will demand evidence that the cells are getting to where they are intended to have an impact. The Frank team used three already FDA-approved drugs to accomplish this with magnetic resonance imaging (MRI). One way to see cells with MRI is to load them with molecules that have magnetic properties. The NIH researchers used a drug with iron oxide as well as two other compounds: one that has a strong negative charge, heparin, and one that has as strong positive charge, protamine. Together they form a complex in the cells that can be detected by the magnetic field set up in an MRI scanner. These chemical complexes did not seem to damage the cells.

Pending regulatory approvals, the method will be tested in humans first by a CIRM funded team led by Karen Aboody at City of Hope. This testing will be in the on-going clinical trial using neural stem cells to carry a pro-drug to gliomas, a type of brain cancer. This trial is a preview of a second trail with a different drug that CIRM is funding through our Disease Team program.

Neurons Grown from hESCs Repair Huntington-like Damage in Mice

An international team from University of Wisconsin and multiple institutions in Shanghai reported that they were able to grow the specific type of neuron damaged in Huntington's Disease from human Embryonic Stem Cells (hESC), transplant them into a mouse model of the disease, and correct the motor deficit in the animals. The paper has been published online and is scheduled for the April 6 print issue of *Cell Stem Cell* Vol. 10 (1).

In Huntington's disease motor function deteriorates because of the degradation of a type of nerve cell called a medium spiny GABA neuron. This team was able to direct hESCs to become robust populations of GABA neurons and transplanted those into the brains of mice that had man-made lesions in the area of the brain responsible for motor function. But the real issue, and the one that has made other transplant strategies less successful, is the need for neurons in this region to grow over a relatively long distance compared to other parts of the brain and to both transmit and receive signals to and from neighboring cells. They showed that their transplanted cells were able to grow into the correct part of the brain and to correctly process the right cell-to-cell signals. In turn, these effects corresponded with corrections in the mice's ability to move.

Though any clinical trial could only come after much more pre-clinical work, this study does suggest that a cell-replacement strategy could work for Huntington's patients who already have damaged neurons.