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—August 2013

Cancer Fighting T Cells Created by Genetically Modifying Stem Cells

A team at New York's Memorial Sloan-Kettering Cancer Center produced cancer fighting T Cells through gene modification of reprogrammed iPS type stem cells. The team led by Michel Sadelain was able to expand the number of cells in sufficient quantities that it could lead to an off the shelf immune therapy for blood cancers. They published the results online in *Nature Biotechnology* August 11.

Over the past couple years Sadelain and others have shown that you can isolate adult immune system T cells and genetically modify them so that they recognize and kill B cells that have become cancerous in leukemia and lymphoma. They use a type of gene modification known as chimeric antigen receptor (CAR) technology. Earlier this summer, they reported significant clinical benefit in leukemia patients infused with cells modified with the CAR technology.

These early tests have relied on isolating appropriate T cells from the patient or an immune-matched donor. This limits the potential for the new therapy. Because of the nature of their underlying disease, many patients cannot use their own cells, and matching donors are hard to find, and even when available, their cells carry risk of serious side effects. Also, earlier efforts to create T cells from pluripotent stem cells have resulted in mixed cell types. They have not been able to produce large quantities of one type of cell primed to fight a specific cancer. So being able use pluripotent stem cells to create a limitless supply of T cells primed to fight certain blood cancers is a potential major advance.

There is some evidence that iPS cells remember the type of cell they were as adult cells prior to reprogramming to the embryonic-like state. So the Sloan-Kettering team started with adult T cells from healthy volunteers and turned them into iPS cells. They modified the stem cells with the CAR technology so that they would recognize a specific receptor on cancerous B cells, the CD19 antigen. They then directed the stem cells to become T cells, and were successful in developing a protocol that expanded them 50 fold after three weeks of growth in the lab.

The reprogramming to iPS cells was done with viruses so the reprogramming step will either need to be modified or go through considerable safety tests before this is ready for patients. However, it certainly holds great promise for many people with treatment-resistant cancer.

Functional Thymus Tissue Created from Human Embryonic Stem Cells

Two teams have succeeded in using human embryonic stem cells to produce functional thymus tissue. Both teams, one from Peking University and one CIRM-funded group from the University of California San Francisco, published their work in the August 1, *Cell Stem Cell* Vol. 13, 219-236.

Most important, the rudimentary thymic tissue created in the lab, when transplanted into mice, was able to mature and promote the development of the immune system's T cells. This is one of the critical roles of the thymus, one of our tiniest organs. Early in life, the thymus helps sort and mature T cells directed against many invaders. Those T cells generally stay with us throughout our lives. But as we age, the thymus gets exhausted and does not do as good a job, and some of its earlier T cells progeny start to dissipate as well. This makes us more vulnerable to infections, which can be exacerbated by chemotherapy or radiation therapy. So, being able to revitalize this function has many potential therapeutic benefits.

There is also a huge long-term potential benefit to the stem cell field more broadly. Since the thymus also teachers T cells not to attack our own tissues, if thymic tissue can be generated from the same stem cells used to create repair tissue—say a cell patch for a damaged heart—the thymic cells might induce tolerance for the needed repair and avoid immune rejection without suppressant drugs.

While research teams had created functional thymus tissue from mouse embryonic stem cells, all prior attempts with human cells had failed to get beyond non-functional intermediate stage cells. The UCSF team, led by Matthias Hebrok, and the Chinese team, led by Hongkul Deng, both succeeded in getting the more mature tissue by going back and looking at the normal cellular switches that are active when early thymic cells are being created in the embryo. By using three gene promoters and two gene inhibitors they were able to mimic those early stages of development.

The same issue of the journal carries a commentary on the two papers by former colleague and CIRM collaborative funding partner, Richard Boyd and associates at Monash University in Australia. In it, they caution that the thymic tissue in the current work is not fully functional and cannot do all the things we need from a thymus. But they did call the proven ability to promote T cell development a "quantum advance" in one of the great challenges of modern immunology.

Human iPS cells Repopulate Scaffold of Mouse Heart and Begin to Beat

A team led by Lei Yang at the University of Pittsburgh has derived from human iPS cells an intermediate cell type that can form all three types of tissue needed to repopulate the scaffold of a heart. The work was published online in *Nature Communications* August 13.

The current work re-enforces a trend found by many others in stem cell science: the best cell to produce a desired end is often an intermediate or progenitor cell and in order to get them to mature into the desired cell types you have to place them in the right environment. Yang's team started by reprogramming human skin cells into iPS cells. They then directed them to become the intermediate cells they called Multipotential Cardiovascular Progenitors (MCPs). They seeded those cells on the scaffold left behind after they used chemicals to remove all the live cells from a mouse heart. The MCPs were able to produce the three cell types in the heart: cardiomyocytes, smooth muscle cells and endothelial cells. The researchers postulated that the heart scaffold matrix sent signals to the MCPs telling them what cells to become and where.

After 20 days the heart tissue spontaneously started to contract, but only at a pace of about 40 beats a minute. The rate and strength of contractions were not nearly strong enough for an artificial organ, but the team is hoping they can use the technology to create smaller patches that might work for cardiac repair after a heart attack.

Blood-forming Stem Cell Found that Is Primed to Make Platelets

A British team at the Medical Research Council's Weatherall Institute for Molecular Medicine has isolated a subtype of blood forming stem cell in mice that is primed to produce large quantities of blood platelets. The team, lead by Claus Nerlov and Sten Eirik Jacobsen, published their findings in *Nature* online August 12.

For some time, researcher have been able to isolate subsets of blood-forming stem cells that are predisposed to form our immune system cells, but not for the platelets that are essential for proper blood clotting. Chemotherapy often wipes out the platelets of cancer patients leaving them vulnerable to life-threatening bleeds, and donor platelets for transfusion are often in short supply. So having these new cells as a target for either donor cells or drugs that could get the patient's own cells to do a better job would be a great advantage.

The team went to great lengths to verify that the stem cells they found were a unique subset and that they could consistently self-renew and produce platelets in significant quantities. Just one of these cells transplanted into a mouse that lacked functional bone marrow was able to generate ten percent of the normal level of platelets. Now, they need to verify similar cells exist in humans.

Reducing the Chances Embryonic Stem Cells Produce Tumors

Two teams have developed new methods for reducing the chances that cells derived from embryonic stem cells will produce tumors after they are transplanted into patients. A Korean team led by Hyuk-Jin Cha at Sogang University published its work with small molecules in the *Proceedings of the National Academy of Sciences* online August 5. A German team led by Alexander Pfeifer at the University of Bonn published its work with gene manipulation July 30 in *PLOS One* Vol. 8, (7).

The Koreans found that pluripotent cells use certain genetic factor to prevent routine cell death known as apoptosis. So, they searched for small molecules that can inhibit those factors. They found two compounds that were able to induce the pluripotent cells to die, but not impact the viability of the more mature cells that had been produced by the stem cells—the cells needed for therapy.

The Germans used a lentivirus, which has been used safely in human gene therapy trails, to insert a gene into pluripotent stem cells. They placed the new gene in a position so that it would only be expressed when genes known to be responsible for pluripotency are active. The added gene makes the cells vulnerable to the drug gancilovir. When the drug was added to a mixed culture of pluripotent stem cells and more mature cells in the lab, only the pluripotent cells died. Also, when those cells were injected into mice, if the animals were given the drug, no tumors formed.

These are just two of many strategies researchers are developing to maximize the beneficial impact of pluripotent stem cells while minimizing the risk of tumors. These two approaches are quite different, but are emblematic of the importance of this line of work to stem cell science.