

President's stem cell research picks - May 2011

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 - May 2011.

Master Lung Stem Cells Isolated, Can Create Two Lines of Tissue

P. Anversa and colleagues at Harvard's Brigham and Women's Hospital reported in the May 12 *New England Journal of Medicine* that they had isolated a lung stem cell type expressing c-kit that is capable of giving rise to both the epithelial and mesodermal tissues required to form complex lung tissues.

The prior paradigm held that lungs contained regional groups of stem cells capable of producing only a limited very specific set of cells. Now, the Anversa team has isolated stem cells from human lung tissue that, when expanded 100,000 fold in vitro and transplanted into immune-suppressed mice, were able to regenerate many of the elements of an injured lung and to organize into complete respiratory units. These newly isolated cells expressed the protein c-kit, the same marker previously found on a range of multi-potent adult stem cells.

In an accompanying editorial, H. Chapman of UCSF suggested the finding should energize the field of regenerative medicine for finding ways of regenerating healthy lung tissue. He noted that although the current study did not provide evidence that the new respiratory units integrated into the host tissue sufficiently to help with lung function there was reason to believe integration of the new tissue could be achieved over time.

First Time Directly Reprogrammed Cells Replace Organ Function—the Liver

Nature published online May 11 a report from Lijian Hui at Shanghai Institutes for Biological Sciences that details a method to directly reprogram mouse skin cells into liver cells that were at least partially functional when put back into the mouse.

The team started out working with 14 transcription factors known to be important for liver development and function. They were able to narrow the group down to three activating factors and one suppressor, the latter for p19, a tumor suppressor gene that you would not normally want to have turned off for too long, limiting the clinical utility of this particular method. But the cells were able to rescue some mice lacking a gene needed to detoxify certain metabolites. All the mice that did not receive the transplanted cells died but five of 12 who did get the new cells survived.

On the same day, *Science Translational Medicine* published a paper from Yoon-Young Jang's team at Johns Hopkins in which they used an established differentiation protocol to turn human iPS cells into hepatic cells and then succeeded in showing that they engrafted in an immune-deficient mouse with induced cirrhosis and that the cells secreted liver proteins.

Another Hurdle for iPS Cells: Immune Rejection Even with Genetic Match

CIRM grantee Yang Xu at UC San Diego had a paper published online by *Nature* May 13 in which he showed that iPS cells were rejected by the immune systems of mice of the same inbred strain from which the reprogrammed skin cells had come.

Xu's team created both embryonic stem cells and iPS cells from the same strain of mice. When transplanted into other syngeneic mice of the same strain the embryonic cells were not rejected, but the iPS cells often were. The degree of rejection seemed to be partly determined by the way the cells were made. Cells made by retroviral integration of the transcription factors were more likely to be rejected than cells reprogrammed by a method that does not result in the integration of the reprogramming factors into the host genome. We could expect iPS cells to be targeted by Natural Killer cells because they express low levels of histocompatibility genes, but the cells are also targeted by T cells because of over expression of particular genes presented as a consequence of the iPS process.

While this is yet another issue that needs to be addressed by researchers in the iPS field before the cells can be used clinically, its significance is to be determined. Rejected cells in this experiment were differentiated teratoma cells. More specifically differentiated cell types may not be so immunogenic. We need to continue to explore tolerance for both ES cells and iPS cells.

iPS Cells Continue to Shine as Disease Models—This Time for Schizophrenia

CIRM grantee Fred Gage and his team at the Salk Institute published a report in the April 13 *Nature* showing that neurons generated from iPS cells derived from schizophrenic patients made fewer connections with each other than normal neurons and that an antipsychotic drug commonly used to treat the disease restored neuronal connectivity in the iPS cell neurons.

The team reprogrammed skin cells from four schizophrenic patients with a hereditary history of the disease. As the cells differentiated into neurons in a dish they used a modified rabies virus as a tracer to see the neuronal connections and were able to see not only fewer connections but also fewer projections growing out of the neuronal cell bodies. They used gene expression profiles to identify genes whose activity was different from neurons of normal patients—they showed abnormalities in a number of critical signaling pathways indicative of a complex multi-genetic pathology.

They tested a number of anti-schizophrenic drugs on the growing neurons, and only Loxapine, was able to correct the connectivity defect. The cause of the disease is believed to be a mix of genetic predilection and environmental factors, so having a disease-in-dish model will provide a great tool for teasing out the interplay of the various factors.

Pluripotent Stem Cells Finally Yield Blood Stem Cells in Useful Quantities

CIRM grantee Inder Verma, also of the Salk Institute, and his team published a protocol in the May 4 issue of *Stem Cells* for producing hematopoietic progenitor cells from pluripotent stem cells in much larger quantities than has been previously achieved.

Many more cancer and blood disorder patients could benefit from stem cell transplants if large numbers of blood forming stem cells could be grown in the laboratory. Because mature hematopoietic stem cells (HSCs) don't expand well in culture, researchers have been trying to grow these cells from pluripotent stem cells, both embryonic stem cells and reprogrammed iPS cells. Most of these attempts have generated very low numbers of bone marrow colonizing blood precursors, and none have shown robust generation of transplantable HSCs. Now, Verma's team has shown that with five iPS cells lines and two embryonic lines that they can efficiently generate precursors and progenitors of HSCs.

The group achieved their goal by breaking down the differentiation process into multiple steps that attempt to mimic early fetal development. They developed the protocol by meticulously adjusting concentrations and timing of the addition of various cytokines, extra cellular matrix components and small molecules.

Some Hope for Men with Hair Loss—With Implications for More Serious Issues

CIRM funded research in the lab of University of Southern California's Cheng-Ming Chuong was published in the April 29 *Science* showing how hair follicle stem cells in mice and rabbits communicate with each other during periods of robust hair growth.

The work lead by CIRM Scholar Maksim Plikus found that the molecular activator WNT and the inhibitor BMP act as coordinating signals when sections of hair follicle move in unison from a quiescent phase to and active phase. It appears that in alopecia, male pattern baldness in humans, the hair follicle stem cells have lost this ability to communicate with each other and individual follicles have to act on their own.

While this may in fact lead to treatments for baldness, and USC has applied for a patent related to the finding, the research could have more meaningful results if it stimulates the search for other population-wide behaviors of stem cells in areas like the gastro-intestinal tract.

Method Can Create Clinically Useful Quantities of Neural Precursor Cells

CIRM funded work published in the April 25 issue of the *Proceeding of the National Academy of Sciences* outlines a protocol for creating large quantities of neural precursors from embryonic stem cells (ESCs) for the first time. The co-senior authors were Sheng Ding, who recently moved to the Gladstone Institutes, affiliated with UCSF, and UC San Diego's' Zhang Kang.

The team's protocol uniformly captures and maintains primitive neural stem cells from ESCs that retain the ability to expand rapidly and to differentiate into the various neuronal cell types when confronted with the proper signals. They used a cocktail of chemicals to hold the primitive stem cells in that intermediate state. These cells can be expanded in large numbers and could be used to generate the desired end product cell line for any number of neurological disorders.