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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—July 2011

Neural Stem Cells Can Repair Damage from Radiation Therapy

CIRM funded research in the lab of Charles Limoli at U.C. Irvine published in the July 15 issue of *Cancer Research* Vol. 71(14) shows that human neural stem cells can repair brain damage like that caused by radiation therapy for brain tumors in a rat model.

The damage radiation therapy does to surrounding tissue is often the factor limiting the dose of therapy and its effectiveness in eradicating the tumor. The impact on cognitive function can continue to progress over the years following therapy making the effects of radiation particularly devastating for pediatric patients. The commonly held theory is that the radiation destroys the endogenous neural stem cells that should be in the patient's brain ready to make repairs. Thus this is a natural target for replacement cell therapy.

Limoli's team placed as few as 100,000 cells in the hippocampus of rats two days after radiation. One month and four months later the transplanted mice had enhanced learning and memory skills compared to irradiated rats that did not get the cells and their behavior was comparable to non-radiated control animals. When the team tracked the implanted cells they saw them become the three types of neural tissue: neurons, astrocytes and oligodendrocytes.

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Tissue Engineered Small Intestine Functions

In the July issue of *Tissue Engineering* Vol. 17(13 and 14) a report by the CIRM funded team at Children's Hospital Los Angeles lead by Tracy Grikscheit showed that you could use a complex set of cells to grow functional intestine on a biodegradable scaffolding.

Intestinal epithelium regenerates itself every three to seven days through the proliferation of various stem and progenitor cells. Grikscheit, who is also on faculty at USC, and her team took intestinal tissue from mice, broke it down into multi-cell components they called organoid units and then loaded them onto the artificial intestine-shaped polymer scaffold before implanting the entire structure into an immune-compromised mouse.

The engineered small intestine developed the various components of functional epithelium and innervated muscle tissue. Lineage tracers showed they were all from the donor tissue and they formed the types of crypts that house the replenishing stem cells in normal intestine.

ANOTHER Lung Stem Cell Isolated, This One for Mucus Glands

CIRM grantee Brigitte Gomperts at UCLA had a paper published in *Stem Cells* June 27 in which her team identified a new stem cell in mice that participates in the repair of the large airways of the lungs.

It has been known that basal stem cells can repair the airway's surface epithelium, but it is generally believed that these cells cannot repair the more complex tissues under the surface. Gompert's team used florescent activated cell sorting methods to isolate mucosal duct cells that were able to regenerate the sub-surface mucosal gland tubules as well as the surface epithelium. Markers verified that it was not the previously known basal cells making these repairs.

The finding could provide a model mucosal gland that could be used to study diseases where too much mucus is produced such as cystic fibrosis and some forms of asthma, and potentially identify targets for traditional drug therapy.

Two Groups Build on Groundbreaking Conversion of Skin to Neuron

Two *Nature* papers a week apart reported creating neurons directly from skin that were more functional than ones reported in May and with greater efficiency. In a paper published online July 3, V. Broccoli of San Raffaele in Milan showed direct reprogramming of skin into dopaminergic neurons. Online July 13, a report from Stanford's Gerald Crabtree increased the efficiency of converting skin to neuron from two or three percent to 20 percent.

The May paper also was from Stanford, from Marius Wernig's lab. That research used four transcription factors and had the modest two-to–three percent efficiency and produced cells with limited electrical signaling ability. Crabtree's team started out with two factors; both were the short chains of genetic material known as microRNAs. These two factors were known to be involved in the maturation of neural stem cells, but alone they only yielded two to three percent neurons again. However, adding just two of Wernig's factors upped the efficiency to 20 percent and maintained the improved electrical functionality they had seen with just the microRNAs.

The Milan team reprogrammed skin cells using three transcription factors known to be active during the time an embryo is producing dopaminergic neurons. The resulting cells release dopamine and show electrical activity consistent with the pacemaker activity seen in the brain's dopaminergic neurons. The group speculated that its work could be used for disease modeling as well as early steps toward cell replacement therapy.

A Simpler Way to Turn Embryonic Cells into Heart Muscle

CIRM grantees at Sanford-Burnham and the Human Biomolecular Research Institute published a paper in the July 7 *Circulation Research* Vol. 109 outlining an efficient process for driving embryonic stem cells(ESCs) to become cardiomyocytes.

The initial step of turning ESCs into heart is well characterized. Many groups have succeeded in the initial step of turning ESCs into the mesoderm progenitor cell type that heart tissue originates from. It is the following steps that have been a bit of a mystery and a trial and error procedure. Now, the team led by Sanforf-Burnhams' Mark Mercola tested 550 known pathway modulators in a high throughput screening system. They found that a small molecule that inhibits the well-known cell signaling gene Wnt was very efficient in driving ESCs to become cardiomyocytes.

The Wnt inhibitor was very specific and did not drive any of the mesoderm cells to other mesoderm-derived cell types, such as other muscle types. This specificity led the authors to suggest this inhibitor might lead to a process for creating personalized heart repair tissue from ESCs but also might be used to activate the endogenous adult heart stem cells we all have.

HOPE FOR Prodding Adult Heart Stem Cells into Doing a Better Job

Researchers at University College London led by Paul Riley and at Harvard led by William Pu published a paper in *Nature* Vol 474 (7353) that went online June 8 that suggests adult heart progenitor cells, which are generally not active enough to repair much damage, may be able to be prodded into action with a chemical.

The compound they used is thymosin β4 (Tβ4), which is already in human clinical trials because it appears to spur the growth of new blood vessels after a heart attack. In the recently published study the team induced heart attack-like damage in mice and then injected them with Tβ4. The compound appeared to activate the endogenous heart stem cells causing them to divide and make new heart muscle tissue. When they examined the animals' hearts they found clusters of new cells around the site of injury.

This is an example of an animal study having the potential to have an immediate impact on a clinical trial. CIRM grantee Deepak Srivastava of the Gladstone Institutes is involved with a company conducting Tβ4 trial for its heart vessel boosting properties. He has been quoted in the media suggesting this could change plans for duration of dosing in the next phase of the trial, hoping to get a double benefit of vessel growth and heart stem cell activation.

Another Option for Genetically Modifying Stem Cells

Rudy Jaenisch's team at the White Institute in Cambridge, MA, reported in the Nature Biotechnology that went online July 7 that a process dubbed TALEN is at least as effective as the now popular zinc finger technology for altering genes in stem cells.

Jainisch has long been a proponent of the belief that genetic engineering of stem cells will be necessary to exploit their full potential. TALEN stands for transcription activator-like effector nucleases. A mouthful, but the important thing is the field has another option to efficiently and precisely modifying the genes of stem cells. This is something three of our disease teams want to do, two to cause a mutation that will make T-cells resistant to HIV, and one to correct a mutation that causes sickle cell disease.