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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 2014

Stress Turns Adult Cells into Pluripotent Stem Cells

An international team led by Charles Vacanti at Harvard and Brigham and Women's Hospital has used stress in the form of exposure to an acidic environment to turn adult cells into stem cells that appear pluripotent. Joined in the effort by Japanese researchers in Kobe and Tokyo the team reported on their work in a pair of papers in *Nature* January 30, Vol. 505 (641-649 and 676-681).

These papers garnered a great deal of media attention, much of it calling the work a breakthrough. It may eventually turn out to earn that moniker, but the cells have some significant differences from embryonic stem (ES) cells. Those differences may be easy to work around; the team seems to have already found a way around one of the differences. Of course, all good science must be replicated, and since the new technique has a speed and efficiency that greatly surpasses that of traditional iPS type cell reprogramming many teams are sure to join in that effort

They dubbed the new cells Stimulus-Triggered Acquisition of Pluripotency (STAP) cells. With as little as half an hour of exposure to acid slightly milder than average vinegar, cells began to show markers of pluripotent stem cells in just three days and a significant proportion of cells showed the markers after seven days. Common iPS adult cell conversion takes several weeks. The STAP process showed greater efficiency, too, with eight to nine percent of the original cells converting to stem cells compared to the one percent or so common with most iPS procedures.

However, there are many caveats. The greater efficiency could be attributed to the fact the team used cells from newborn mice, which are known to be more plastic or versatile that cells from older animals. When they tried the procedure on cells from mature mice, a much lower percent of cells converted to the stem cell state. Also, the STAP cells themselves have a limited ability to self renew and could not be kept growing in the lab for long periods of time, unlike ES cells. The team did succeed in further altering the STAP cells with a hormone and a growth factor to get them to convert to self-renewing stem cell lines more like traditional lines.

It has been known that in plants stress situations can cause adult cells to convert into stem cells. So, the possibility that this function is genetically preserved across the two kingdoms is reasonable and was a starting point for the team. Let's see how it plays out in the hands of others.

Genetic Trick Protects Offspring of Stem Cells from Immune Rejection

Another international team has found a way to use genetic manipulation to protect tissue grown from stem cells from immune rejection. The team, with one group led by Yang Xu using CIRM funding at the University of California at San Diego and another group led by Xumei Fu at Shezhen Children's Hospital in China, published their findings in *Cell Stem Cell* January 2, Vol. 14 (121-130).

The researchers were investigating pathways our bodies normally use to prevent immune system cells from attacking our other tissues. Historically it has been hard to show the relevance of these pathways to inducing tolerance to human Embryonic Stem Cells (ESCs) because mouse models have not replicated the human immune system at that level. So, the first task for this team was to create an appropriate mouse model. They created humanized mice by reconstituting their immune systems with transplants of human fetal thymus tissue.

They then set about creating human ESCs that were genetically altered to over produce two molecules known to inhibit immune response to foreign cells. When they matured those stem cells into skin cells and into heart muscle cells neither was rejected when transplanted into the humanized mouse model.

However, that mouse model also did not recognize and destroy teratomas that grew when the ESC were transplanted directly. It was suggested that a suicide gene might be inserted to enable elimination of the transplanted cells if they became cancerous, but this would also eliminate those donor cells contributing to needed tissue and organ function. Hence inability of our immune system to recognize tumors that might arise from these cells makes this specific process by itself probably unusable clinically. But it does point to a pathway forward that might be developed to overcome donor graft rejection and lead to ways to preemptively protect against dangerous changes to donor cell phenotype.

Tiny Packets Inside Cells Guide their Fate after Transplantation

A team led by Jeffrey Karp at Harvard affiliated Brigham and Women's Hospital has developed a procedure to load progenitor cells with tiny packets loaded with molecules that can direct the fate of how they mature. Working with colleagues at the State University of New York at Buffalo and the Nanyang Technological University in Singapore they published their work in *Nature Protocol* January 10, Vol. 9 No. 2.

This work has the narrative of the children's story in which Goldilocks was testing beds to find one that wasn't too hard or too soft. Researchers have long been able to treat stem cells in the lab with various chemicals of genetic factors and get them to become the type of progenitor tissue or adult tissue they want. They have also begun to perfect loading nanoparticles with those same factors and inserting them into cells hoping they could help drive progenitor cell fate after transplantation. But neither process quite gets to the ultimate goal of a well-defined cell population that persists in the same role days after transplantation. When you do the manipulation in the lab you loose control of their fate after transplantation. With the nanoparticles, the tiny delivery packets are so small the cells natural transport machinery has no problem grabbing the foreign particles and shipping them out of the cell within a day or two, or sometimes only hours. So, the Brigham team created slightly larger micro-particles that seem to persist in cells for weeks after transplant continuing to direct their fate.

The researchers have in essence turned cells into pre-programmable units. The micro-particles can be loaded with molecules that tell the cells how to mature, but they can also direct how the cells function. Since mesenchymal stem cells are often used to try to reduce inflammation or alternately.

to stimulate growth of new blood vessels, they could be loaded with particles that would instruct them to promote one specific function. The authors suggest cells could be pre-loaded and cryo-preserved for when patients need them.

Data Suggest Two Types of Caner Stem Cells Needed for Metastasis

A team lead by Max Wicha at the University of Michigan has parsed out the different roles of two types of cancer stem cells (CSCs), and shown CSC can morph between the two states, and that both states are needed to cause metastasis. The team, with collaborators at the University of Science and Technology in China, Methodist Hospital in Houston and INSERM in France, published their work in *Stem Cell Reports* January 14, Vol. 2 (78-91).

While many studies seem to be confirming the existence of CSCs and are starting to find cellular markers for identifying them, there remains much uncertainty about the pathways they use to cause cancer metastasis. The current team tried to parse this out using breast cancer stem cells (BCSCs). They show that BCSCs exist in two distinct states, one they call mesenchymal-like BCSCs and one they call epithelial-like BCSCs.

While in the mesenchymal-like state the cancer stem cells are quiescent and don't proliferate but reside near the surface of tumors and can seed into the blood stream. While in the endothelial-like state the cancer stem cells reside more centrally in the tumor and proliferate readily. The team also showed that BCSCs are quite plastic and can morph between the two states, so one type of stem cell can seed into distant sites and once there transition to the type of BCSC capable of rapid proliferation.

The findings have significant implications for targeting cancer therapy. Clinicians currently subdivide breast cancer into molecular subtypes and target therapy specifically to each subtype. But Wicha's team showed that the two types of stem cells have the same gene expression profile across the various molecular subtypes of breast cancer. This suggests that therapies that target BCSC may have very broad utility in controlling the cancers. The literature also shows similar genetic profiles in cancer stem cells including those in pancreas, colon, lung, ovary and prostate tumors.

The CSC story is evolving rapidly and the knowledge gained should start to benefit patients soon.