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—September 2011

Another Look at Embryonic & iPS Stem Cells Says They Seem Similar

In a study published online September 13 in *Nature Methods*, Vol. 8(821) a University of Wisconsin team led by Joshua Coon found that the proteins produced by induced Pluripotent Stem cells (iPSCs) are 99 percent similar to proteins produced by embryonic stem cells (ESCs).

While every cell in the body could technically make every possible protein, what determines a cells function is what genes are turned on and producing protein at any one time. So, finding 99 percent overlap in the proteins produced suggests a high level of sameness in the two cell types' function. The team looked at over 6,000 individual proteins using newly available highly accurate mass spectrometry, a method of identifying proteins based on their mass.

For much of the last year, there has been considerable hand wringing about differences seen in the two types of pluripotent stem cells. This study suggests a much closer functional similarity than many of those earlier studies might suggest. But it does still show a potential one percent variance in functional proteins. Those could be relatively meaningless, or highly significant. One concern that may exist is that the study utilizes a population of cells, so proteins profiles will be averaged out across the whole population. It would be very informative if single cell studies could be performed to determine the actual nature of cells from ESCs and iPSCs. However, this is probably beyond present technology. So another case of "stay tuned."

Well Proven BMT Still Open to Major Improvements

Two papers this month show that even an old standard therapy that has been used more than 30 years can be significantly improved. A group at the Stowers Institute in Kansas City led by Linheng Li found a way to get bone marrow stem cells to expand significantly in culture, which they published in the September 15, *Genes and Development*, Vol. 25(18). Another group at Thomas Jefferson University in Philadelphia led by Dolores Grosso published September 19 online in *Blood* a way to make blood stem cell transplants work even when only half the immune markers are matched.

Half-match transplants would triple the pool of suitable donors giving new hope to patients with terminal leukemia, lymphoma and sickle cell anemia. Currently fewer than half of white people and only about 10 percent of minority groups can find a closely matched donor. Previous trials with half-matched donors have had relatively poor track records. The Jefferson team tried splitting the transplant into two boluses. The first is just T-cells followed by a dose of cyclophosamide to induce immune tolerance and then the second bolus is transfused, this one the stem cells. The 27 patients were all severely ill at the time of transplant and three-year survival was just under 50 percent, so more work still needs to be done.

The Stowers groups' work was in mice and needs to be replicated with human cells, but if it resulted in the ability to expand the few stem cell available in cord blood it could greatly increase

the number of patients who could be treated with the cells from one cord rather than two, which would decrease the chances of immune complications. They found that cell expansion happened when two intracellular pathways were activated at the same time, the Wnt/beta-catenin and the PI3K/Akt pathways. But it had to be an activation that could be turned off to restart the cells' ability to replace the various mature cell types of the blood system.

Uterine Stem Cells Successfully Treated Diabetes in Mice

In a work published in *Molecular Therapy* August 30 a team led by Hugh Taylor at Yale converted stem cells from the uterine lining into insulin-producing cells. They were working with human stem cells from the endometrium transplanted into a mouse model of diabetes. While there remains some doubts about how these cells would functionally substitute for beta cells, it is important to take note of all data arising in the filed.

The Yale team bathed endometrial stem cells in cultures containing specific nutrients and factors and the cells adopted the characteristics of beta cells, those cells in the pancreas that normally sense glucose and produce insulin. The incubation took about three weeks and the cells took on the shape of beta cells and began producing proteins made by beta cells, including insulin when exposed to glucose. After transplantation the cells continued producing insulin for six weeks when the study was ended.

The authors suggest that endometrial cells could be stored in a tissue bank and that it would be relatively easy to find a compatible tissue for a woman who no longer had her uterus, or for men. Clearly further study is needed to determine the usefulness of this approach for human medicine.

Dogma on Tissue Regeneration Overturned

CIRM funded work in the lab of Stanford's Irving Weissman, published in the August 24 *Nature*, Vol. 476(7361) seems to overturn a long-held belief on what type of cell is responsible for the ability of mammals, albeit limited, to regrow the tips of fingers or toes.

This is the type of paper that can prevent wasting huge investments in a scientific pathway that is a deadend. This issue of digit tip regeneration has intrigues our field because it is a potential window onto the much more robust ability to rergow whole limbs seen in animals like salamanders. There seem to be three plausible ways a digit tip could regrow: The local cells just start to multiply and create more cells just like themselves, tissue specific stem cells are called in to generate all the various cell types within their cell line, or one of the local cells can be turned back into an embryonic-like state that has been called a blastema and generate all the needed tissues. The latter has been the dogma for how salamanders do their neat trick and the favorite among some scientists as the likely way we accomplish our more modest repair.

The Weissman lab team showed that what is happening in their mouse model is definitely not coming from a blastema. They labeled the adult cells of each tissue type with a different color of florescent marker and after regrowth they saw a very clear demarcation of color between various tissue types. The skin formed skin and the bone cells formed bone. They could not tell whether the new cells were from old mature cells dividing or from tissue-specific stem cells. Interestingly there has been at least one recent paper that has suggested the salamanders are not using a master cell blastema either.

Incremental but Critical to Eventual Success

This month's scan of the literature yielded much of the primary building blocks of science — investigators taking a significant advance and refining it, making it more efficient, or understanding what is really going on at the the cellular level, or in the whole body. An article in *PLoS One* Vol. 6 (8) by a team led by J. Yamashita with Shinya Yamanaka at Kyoto University is a classic example. It shows a way to improve our ability to grow and purify cardiomyocytes.

At this point many labs have turned human embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) into cardiac myocytes, something that could be a great starting point for heart repair after heart attack. The current paper addresses one of the early roadblocks to this clinical use. It increases the efficiency of turning ESCs and iPSCs into those progenitor heart cells and if found a cell surface marker, VCAM1, that let them develop an efficient and scalable purification method for the cells. But it was not easy. They screened 242 antibodies to find this one marker that was highly specific for the desired cells.

Other teams this month reported similar incremental steps to get beyond later stage road-blocks to an effective heart repair. One, for example, found ways to increase the level of 3-demensional organization of in-vitro grown heart. All these incremental advances contribute to the end goal of effective cardiovascular therapies.