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Innovations

Will Human Embryonic Stem Cell Therapies Finally Grow Up?

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The spotlight has again focused on the human embryonic stem cell (hESC) discussion in the United States. But this time, the discussion goes beyond talk about funding issues. In the 8 years since a federal ban was placed on federal support of hESC research, new stem cell technologies have been developed that some believe may hold near equal promise as hESC. Others disagree, but shifting policies under the new US administration place hESC research—and planned commercial applications—once again front and center.

In August 2001, US President George W. Bush issued an order barring the use of federal money to support stem cell research using donated embryos from in vitro fertilization (IVF) clinics that resulted in the destruction of the embryos. The current US President, Barack Obama, seemingly reversed this policy in March 2009 with his own executive order to again make the National Institute of Health (NIH) funds available for hESC research.

In the 8 years from the start of the federal funding ban, however, basic stem cell researchers have gone quietly about their business devising new technologies to advance the field.

2001 through 2009: Time Not Wasted

The classical hESC is isolated from a donated blastocyst from an IVF clinic. The inner cell mass region of a blastocyst contains a small group of 50–100 pluripotent cells. These cells, human embryonic stem cells, can eventually give rise to all the cells, somatic tissues, and organs in the body.

Going beyond this template, researchers throughout the world, including those in the US, continued on the quest for stem cell advances. As a result, several new types of stem cell technologies were developed, the most notable of which is the inducible pluripotent stem cell, or iPS cell, first described in 2006 by Shinya Yamanaka of Kyoto University, using adult mouse skin cells (Takahashi and Yamanaka, 2006) Embryonic tissue is not involved in their generation. Instead, the classical way of making them involves reprogramming of an adult cell through introduction of four genes, Oct4, Sox2, c-Myc and Klf4, found in pluripotent stem cells.

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There are a variety of ways to do this, some using viruses, DNA constructs, or protein transduction. Regardless of how it is achieved thus far, the reprogrammed cell shows what appear to be the same properties of an ESC.

"Yamanaka's 2006 cells met the definition of pluripotency," explains M. William Lensch, Ph.D., Affiliate Faculty, the Harvard Stem Cell Institute. "But if you tried to make mice out of them, they would only develop so far. He never got live-born pups." These cells did not advance far enough to make germline (oocyte or sperm cell) contributions.

But 1 year later, in the summer of 2007, Yamanaka and others used the exact same reprogramming process to isolate a different population from that reprogrammed pool (Okita et al., 2007). Those cells were able to make live-born pups and they also went germline. "That tells us that in this reprogramming process there are probably different functional subpopulations and you have to try and find the best ones," says Lensch.

But the world of iPS research is not without its own concerns. Some researchers are concerned that the tools needed to reprogram the adult cells, such as viruses and introduced novel genes, may trigger oncogene expression or cause other as yet unknown harm. Using natural hESCs by definition avoids these concerns, one of the many reasons some companies remain dedicated to using them for clinical applications.

Geron Leading the Field

Perhaps no other company involved in hESC work has remained as dedicated to its mission as Geron Corporation in Menlo Park, CA. Over the past decade, Geron has spent $175 million on its hESC platform, all of it from private funds. The company is pursuing hESC cell replacement therapy, focused initially on patients with spinal cord injury. In January 2009, the U.S. Food and Drug Administration (FDA) granted Geron the first-ever US approval to initiate a human clinical trial with hESCs. "All of our intended treatments are single injections," says Thomas Okarma, Geron CEO. "That is the power of this therapy. We show in animal models that these cells live indefinitely and the repair is permanent." The trial, which Geron hopes to initiate beginning in the summer of 2009, involves eight centers and is aimed at establishing safety. "It is a relatively low dose of cells and that is done for safety purposes," says Okarma. "We are injecting them into patients with complete thoracic injuries. These cells are alive, they migrate through the lesion, and they divide. They multiply after they are injected, so there is a finite possibility that even at this low dose these patients might have a durable partial response and that is how we compute the risk benefit ratio for these patients." Okarma stresses he does not expect to see improvement in the patients in this study, but it may be a possibility.

"The other forms of pluripotent stem cells, which are really only iPS in terms

of other alternatives to embryonic, are really nowhere near where embryonics are,'' offers Okarma. ''We've been working with these cells for 10 years and they are the gold standard for naturally occurring, normal human pluripotent stem cells. Everything else is a proxy.'' His belief is that iPS cells will have utility when derived from patients with genetic diseases from which certain differentiated cells could be made and then used for screening, for drugs, or for unraveling abnormal pathways. ''These iPS cells are definitely mutant cells,'' says Okarma. ''They are abnormal. Regardless of how they are made, even if eventually chemicals can be used to reprogram them, they are by definition absolutely different from one another and ESCs in their gene expression pattern. And I can say that having gone through the labors of getting hESCs through the FDA, that the gene-modified stem cell as the beginning of a process to manufacture a differentiated cell therapy would never fly with the FDA.''

A Party to Both Camps

Other companies are taking a more diverse approach to stem cell commercialization. Novocell, Inc., of San Diego, CA, for example, is developing hESCs from embryonic tissue and has also partnered with iPS developer Shiya Yamanaka to explore the promise of iPS technology for making pancreatic islet cells. ''At this point, hESCs are the gold standard for making a cell-replacement therapy for most cell replacement applications, in our opinion,'' says E. Edward Baetge, Ph.D., Chief Scientific Officer at Novocell. ''But we are very interested in looking at cells such as iPS cells that have the same properties as hESCs. I don't think they are exactly identical to hESC at this point, but they are the closest that anyone has ever been able to make. The future of ESC biology may reside with iPS cells, so we are very interested to understand how well these types of cells perform in comparison to hESC.'' The company is targeting pancreatic islet cells for cell replacement therapy in diabetes.

''When you make an iPS cell, what you are doing is reprogramming something that is an adult cell that doesn't have any embryonic properties whatsoever, and you're counting on those four genes to actually reprogram that skin cell all the way back to the ESC state you can get from a blastocyst,'' says Baetge. ''Is the iPS cell a perfect replica of a hESC? If you ask most people who work in this field, the answer would be no.''

An Academic's View

''We have everything on the table,'' says Lensch, who is also a senior scientist in the laboratory of well-known stem cell researcher George Daley at Boston's Children's Hospital. ''We have derived our own ESC lines. And we are also one of the labs which has done a lot of work on inducible pluripotent cells, cord blood work, lots of different complementary approaches. The fact that we do all these things side by side in the lab gives us a unique perspective.''

Stem cell researchers use the mouse ESC system to dig deeper into stem cell machinery, performing assays and techniques not ethically possible with human embryonic stem cells. ''What the field is trying to do as a whole, especially by being able to take advantage of things in mouse systems, is to take the cells we know function the best, like mouse ESCs, and ask why some of these reprogrammed cells are better mechanistically than others,'' says Lensch. ''Hopefully, we then would come to understand the intracellular machinery of what makes truly terrific pluripotent cells and see if we can use that as a surrogate signature for any reprogrammed cell that comes forward.'' But even in the mouse system where researchers have done a variety of amazing things, ''we still have not been able to reprogram a cell to be the functional equivalent of your average ESC,'' he says. ''How are we going to be able to find that cell? Because we have a cell that is functional in every way—the embryonic stem cell—and we can use it in comparisons to all these other types. It is definitely the gold standard.''

Researchers engaged in basic ESC work in the US understandably welcome President Obama's executive order. Currently, approximately 22 hESC lines are eligible for NIH funding. ''But after 6 dedicated hours searching online, I counted nearly 800 cell lines developed by researchers throughout the world,'' says Lensch. ''That is a huge resource that as of today we can't get NIH funding to study.'' And he admits that an influx of NIH funding would alleviate some of the separate tracking required in his laboratory between ''NP'' (for non-Presidential) research and federally funded projects.

But at the end of the day, Lensch believes that most people working in the field are not focused on the mechanism of reprogramming. ''What they want are large quantities of pluripotent cells because they want to study the development of a specific type of tissue.''

The scientific discussion rolls on just as the details of the Obama executive order are negotiated. To date, no federal funds have been released for the study of human embryonic stem cell research under the Obama plan. Final recommendations and guidelines from the NIH are pending once the public commentary period closes in late May 2009.

REFERENCES

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