BEDFORD STEM CELL RESEARCH FOUNDATION

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"Off-the-shelf" Engineered Stem Cells: Are They Therapeutically Valuable?

FROM THE DIRECTOR

The astounding 2013 report by an Oregon research team of the successful creation of stem cells from a somatic cell nucleus transferred into an unfertilized human egg was met with surprising calm by the lay press and the bioethics community. This is in sharp contrast to the outcry a decade ago when similar experiments were denounced as "human cloning" and the U.S. congress rumbled with attempts to outlaw all such research with human eggs. Public concern was further fueled by an extraordinary scientific fraud in 2005 by a South Korean research team that falsely claimed to have created such stem cells.

The 2013 calm is a clear, positive sign that the newness -- and the shock -- of the promise of stem cell regenerative medicine has worn off. Thousands of young scientists have been trained since the 1999 cover of *Science* announced stem cells as the "breakthrough of the year."

So where are the stem cell therapies? Where are the cures for diabetes, spinal cord injuries/diseases, stroke, HIV/AIDS, Parkinson's disease, heart and kidney failure? Are they coming?

The answer is yes. But painfully slowly for the patients and families in need. Why?

Because new therapies involve both new scientific discoveries and additional tests for medical safety. Demonstrating that stem cells can turn into heart muscle or nerve cells in a petri dish is exciting, but very far from therapeutic use.

One big stumbling block is the source of the stem cells to be used for therapies. Must they be patient-specific? Or could a bank of fully characterized, "off-the-shelf" stem cells be created? Stem cells that could be administered immediately in the emergency room when the heart attack, stroke or spinal cord injury occurs? Perhaps while patient-specific stem cells were being created?

According to estimates, only a few hundred stem cell lines could tissue match more than 95% of the world's population.

This is an exciting prospect and an achievable goal. The stem cells could even be genetically engineered if needed to treat specific conditions, such as HIV/AIDS.

Bedford Research Foundation scientists are pursuing a promising example of engineering stem cells -- to have a resistance to HIV infection. The work follows a proof-of-principle report by a German medical team in 2009. Because HIV infects the immune system, it is theoretically treatable by bone marrow stem cell transplant. But past attempts have shown transplanted bone marrow becomes HIV infected, making it an unsuitable treatment approach for HIV disease. This changed when the bone marrow transplant in Germany resulted in an apparent cure of the patient's HIV disease -- because the transplanted bone marrow stem cells were naturally deficient in CCR5, an receptor on the surface of cells important for HIV infection.

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BSCRF Scientists Discover Developmental Differences Between Mouse Embryos and Parthenotes

The current goal of BSCRF research is to optimize the efficiency of deriving pluripotent stem cells from testis and unfertilized human eggs (parthenotes) for patient specific and perhaps stem cell bank use.

In 2009, Bedford Research scientists discovered that circadian rhythm genes are "on" in early human embryos, suggesting circadian signals may be important to stem cell derivation and stability. If true, new methods of culturing stem cells in laboratories that mimic circadian signals need to be developed.

In the body, the rhythm of circadian genes is supported by several types of signals, including light/dark cycles, hormone pulses, body temperature variations, and eating. The signals regulate the pattern of circadian genes turning "on" and "off" in 24 hour cycles. In contrast, to date, stem cells have been cultured in constant temperature in the dark, their only potential circadian signal being renewal of their culture medium.

To begin to understand the importance of circadian temperature oscillations to stem cell derivation and expansion, BSCRF scientists have taken advantage of their newly developed "circadian incubator time lapse videomicroscope" to chronicle the first five days of development of mouse embryos and parthenotes, which are being used as models because cell division is easy to see in a group of mouse embryos/parthenotes. The goal is to discover if temperature oscillations play an important role in stem cell derivation or differentiation into useful cell types, such as neurons or bone marrow stem cells. The work is ongoing.

As shown in Figure 2, results to date

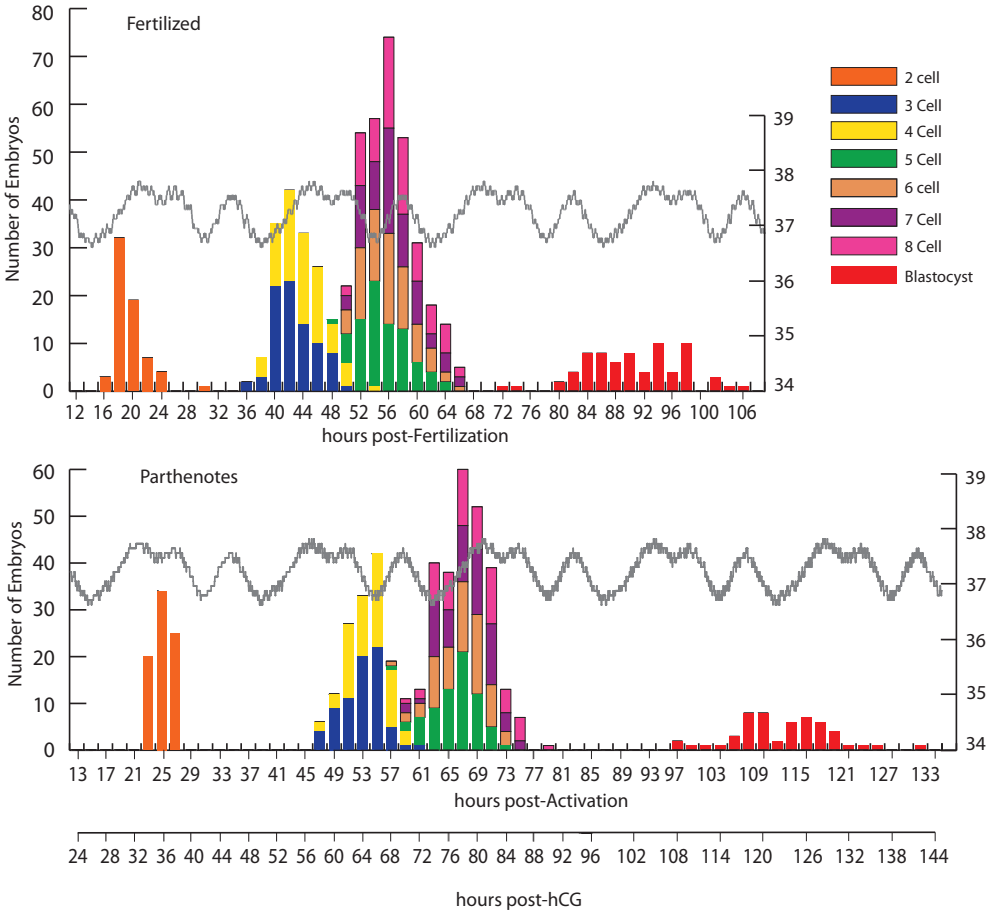

Figure 2: Histogram of timing of cell cleavages following fertilization (top) or parthenogenetic activation (bottom). Wavy background line is temperature (right axis).

indicate the first cleavage of a mouse egg to two-cells takes place at approximately the same time after fertilization or parthenogenic activation, the second cleavage to 3 cells and 4 cells is markedly delayed in the parthenotes, the intervals to the third cleavages (5 to 8 cells) are approximately the same, but development to blastocyst is again delayed in the parthenotes. This indicates the parthenotes need additional developmental support at the 2-cell stage and at the 8- to 16-cell stage. Discovering the needed support, and its relationship to circadian signals, may markedly improve testis and parthenote stem cell derivation, and speed up the project to derive genetically modified parthenote stem cells.

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Progress In Testis Stem Cells

Thanks to generous donations, BSCRF scientists are in Phase III of the human testis stem cell project

That the adult human testis contains pluripotent stem cells, in addition to sperm stem cells, was a surprising report by two research teams a few years ago. Thanks to private donations, Bedford Research scientists are determining the efficiency with which this naturally occurring source of pluripotent cells can be isolated and expanded into therapeutically useful, patient-specific stem cells. They have adopted Good Laboratory Practices for the testis stem cell derivation to shorten the time to FDA approval of derived lines.

Phase III is a collaboration with Dr. Martin Dym, Georgetown University, who has generously provided cryopreserved biopsies of the testis tissues their lab used. One of the challenges with testis stem cell derivation is distinguishing pluripotent stem cells (about 500 per gram of tissue) from the sperm stem cells (about 5 million per gram of tissue) that actively divide to produce many millions of sperm daily -- the proverbial needle in a haystack. If the cell dynamics are similar to bone marrow, the pluripotent stem cell is quiescent until activated, in contrast to the sperm stem cell that is actively renewing. Current experiments in the Bedford lab are taking advantage of this difference to help isolate the stem cells.

At The ISSCR

In June, 2013, BSCRF presented a poster and hosted a booth at the 11th Annual International Society for Stem Cell Research meeting. The poster titled, "Onset of Period 2 Oscillation Coincides with Differentiation of Mouse Embryonic Stem Cells" was selected from a record number of abstracts submitted. It reported the conclusion that the important circadian gene, Period 2, is turned on in stem cells, but begins to oscillate throughout the colony when the stem cells begin to differentiate. Although the importance of circadian rhythms to organ function is growing in recognition, the Foundation's report was one of only two on circadian rhythms at the ISSCR.

Dr. Kiessling (left) answers questions during a poster session at the meeting.

Prostate Disease Research Update

Dr. Robert Eyre

Patient recruitment into prostate cancer screening project is ongoing. The of the project is to develop semen screening tests that reflect overall male health as well as help diagnose and stage prostate cancer. Recent work suggests that the presence of viruses and bacteria in semen indicates a poorly functioning immune system. Even mild suppression of immune function could allow growth of cancers that would otherwise be naturally rejected. Fertility and Sterility, the journal of the American Society for Reproductive Medicine, has recently accepted a report by Bedford Research scientists that cytomegalovirus (CMV) in semen specimens is related to mildly decreased immune function in HIV infected men. CMV is common in humans, usually causes no symptoms, but can be life-threatening to patients receiving bone marrow and organ transplants.

New Staff

Alexis Agnew joins the team as our SPAR coordinator, bringing over ten years of medical experience in both private practice and the US Air Force. SPAR is instrumental in helping couples living with HIV disease safely parent.

Valia Dinopoulou, a one-year fellow, hails from the laboratory of Dr. Dimitrius Loutradis, Professor and Chairman of Obstetrics, Gynecology and Reproductive Biology, University of Athens, Greece. Valia will work on the project to genetically engineer parthenote stem cells.

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Postage and Fees Paid
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News Inside

(Continued from cover)

Without the receptor, cells are resistant to HIV infection.

Now the task at hand is to create stem cells missing CCR5 that are tissue matched to the HIV infected person. Deleting CCR5 in patient-specific (e.g. nuclear transplant, induced pluripotency, testis or parthenote) stem cells might work. "Off-the-shelf", engineered stem cells might also work if they tissue match the patient. Our 2013 Activated Egg Symposium brings together pioneers in genetic engineering (Mario Cappeccchi and Rudolf Jaenisch) with stem cell specialists (Treena Arinzeh, Gordon Carmichael, Kim Tremblay, Jose Cibelli, David DiGiusto) and a member of the Oregon SCNT team, David Battaglia, to present their work and perspectives in research areas important to move the work forward as fast as safely possible to patient therapies. Bedford Research scientists are positioned to move faster than some traditional academic laboratories because we are not dependent upon federal funds. The parthenote research, highly promising for modifying stem cell genes, cannot be funded by the NIH because of long-time federal funding restrictions. Much of our laboratory overhead is funded through fee for service laboratory testing, allowing research donations to go directly to research. We are accountable to individual donors to return the maximum value for every dollar given to the research. Private donations -- of all sizes -- are essential to achieving the research speed needed by patients.

Thank you for your support.

With gratitude,
Ann A Kiessling, PhD

Nov 8, 2013: Dr. Mario Capecchi, Nobel Laureate and Distinguished Professor of Human Genetics & Biology at the University of Utah School of Medicine, will keynote the tenth annual AES.

Dr. Rudolf Jaenisch, Professor of Biology, MIT, will present the dinner "Science Perspectives" talk.

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