The State of the Art

Stem cell science, while not new, has captured the attention and imagination of scientists and the public over the past decade. While it holds great potential, much remains to be learned, particularly about human embryonic stem cells and the secrets of human development. Sue O'Shea, Ph.D., the Crosby-Kahn Collegiate Professor of Cell and Developmental Biology and co-director, with Gary Smith, Ph.D., of the U-M A. Alfred Taubman Medical Research Institute's Consortium for Stem Cell Therapies, enlightens us on the status of stem cell science, which this year garnered researchers from the United Kingdom and Japan the Nobel Prize in Medicine. →

Interview by Rick Krupinski

SCOTT SODERBERG, MICHIGAN PHOTOGRAPHY

Q: Where does stem cell science stand today?

A: As for human embryonic stem (ES) cell science, I'd say it's emerging. It's a complicated field and we don't entirely understand the biology of the ES cell. On the other hand, we've been doing hematopoietic stem cell transplants since the 1950s. We use artificial skin, blood transfusions, and we're putting neurons from human cell lines into the brain and seeing improvements, so when we consider stem cells in the broader definition, we've done pretty well.

I think many people are waiting for "the big breakthrough." It's coming, but I'm not sure it will be transplantation of embryonic stem cells, but perhaps something that we learn about a disease from the stem cell itself. In either case, the embryonic stem cell will always be the gold standard for understanding pluripotency and stem cell behavior.

Q: As of this interview, there are 178 embryonic stem cell lines on the National Institutes of Health registry, eligible for federally funded research. How do they differ?

A: Each line corresponds to one individual, so each is inherently different from another. But also, when the first human embryonic stem cell lines were derived, we knew very little about their biology. We knew a lot from studying the mouse ES cell, and we applied those culture conditions to human cells. But growing the cells on mouse embryonic fibroblasts led to concern about mouse products contaminating the cells. Since then we've learned more about the biology of the human ES cell. Now as we derive new lines, we can grow cells on human embryonic fibroblasts in medium without animal products. As our understanding improves, new lines are being derived without fibroblasts and in different oxygen concentrations, and with improved culture medium so they could eventually be used for implantation. Another big difference is that now there are lines on the registry that carry identified disease.

Q: Eight of the lines were derived at the U-M. What distinguishes them?

A: We're particularly interested in creating lines that carry genetic disease. Using them to study a disease that the donor family carries is, I think, a really important contribution and that's where much of our effort is focused.

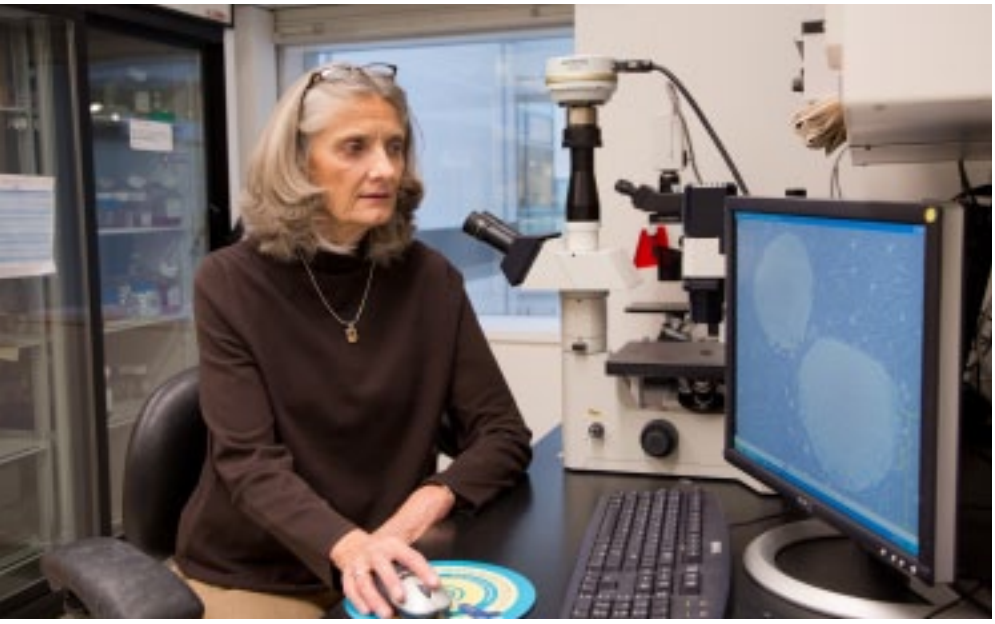
Q: How do cell lines derived from human embryonic stem cells differ from those created with induced pluripotent stem (iPS) cells?

A: First, we can derive iPS cells from patients when ES cells are not available. Second, if I biopsy my skin and add pluripotency factors, my cells can transform from adult skin cells into cells that behave like embryonic stem cells, but the starting material is very different from ES cells. Because the cells have been on my hand for a while, they have seen the medicines, radiation, and other damage that I've been exposed to throughout my life, so even though we drive the skin cells back to a more primitive stage, the new iPS cells may be somewhat different from the primitive cells from an early embryo. We're learning a lot about those differences and that tells us about both the embryo and adult somatic cells. It also tells us about cell differentiation and may eventually inform us about cancer.

Q: What insights will be gained by understanding how embryonic stem cells differentiate?

A: We can't alter genes in human embryos like we can in mouse embryos, and with a mouse model we're only inferring that its development might be similar to humans. Understanding embryonic stem cell differentiation gives us a hint about gene expression and early human development — which we know effectively nothing about. For the first time ever we can explore the role of a particular gene in lineage differentiation (into endoderm, mesoderm and ectoderm), from its start as a pluripotent cell into, for instance, a mature neuron. Understanding how to promote

> IF WE COULD UNDERSTAND HOW TO PERSUADE THE BODY'S OWN STEM CELLS TO REGENERATE LOST TISSUE, THERE WOULD BE NO CONCERN WITH IMMUNE REJECTION OR TUMOR FORMATION.



SCOTT SODERBERG, MICHIGAN PHOTOGRAPHY

differentiation of a particular cell type will also make it possible to derive and transplant pure populations of cells for replacement therapies.

Q: How important has private support been to stem cell science?

A: NIH funds can't be used to derive new ES cell lines, and it's that critical gap where private support has been absolutely essential. The Geron Corporation funded several labs around the world to derive the first human embryonic stem cell lines, and absent that private support, those original lines would not exist.

At the U-M, support from the Endowment for the Basic Sciences and from former Executive Vice President for Medical Affairs Bob Kelch's office allowed us to set up the culture and derivation labs, and the Taubman Institute has made it possible to derive the new human embryonic stem cell lines. We also have support from the Heinz C. Prechter Research Fund and the Steven M. Schwartzberg Memorial Fund to develop iPS cell lines for bipolar research. This work simply wouldn't have happened without philanthropic support. For the very first time we have a cell model to study bipolar disorder.

Q: What stem cell treatments are being used or studied in the U.S. today?

A: Leukemia is an obvious one; there's a lot of interest on the cancer stem cell front; skin; neurological disease; and stem cell treatments for spinal cord injury. There's considerable research interest in developing beta cells for diabetes, and in identifying alternative sources of stem cells, like shed baby teeth which are a source of bone-forming cells. If we could determine how to persuade the body's own stem cells to regenerate lost tissue, there would be no concern with immune rejection or tumor formation. That's where much basic research is going. It's not an effective therapy yet, but advances in stem cell biology will pave the way for future therapies.

Q: There are treatments touted that have little or no proven effectiveness. How do we separate reality from hype?

A: It's known as stem cell tourism. For $50,000 you can go to Portugal and get olfactory epithelial cells from your nasal cavity grown in culture and then put into your spinal cord. In Russia, human embryonic stem cells have been infused systemically to treat disease. The problem is that in many other countries there's very little control and often no FDA-equivalent to say this is safe or not safe. On top of that, many studies aren't published, so we typically don't know the outcome. You don't want to dampen the hope stem cells offer, but you don't want to over-promise, which happened early on in this field.

Q: How do we educate the public?

A: Many people still believe that human embryonic stem cells are derived from fetuses, rather than from pre-implantation embryos that would not otherwise be used. That's our failure, and it's a particular frustration given that we're a university.

We recently wrote an NIH grant that, if funded, will allow us to bring high school science teachers from all over Michigan to U-M to educate them about the many types of stem cells and provide units to teach stem cell biology. That's our real job. People have the right to their own beliefs, and once they understand the source of the cells and the science, they should make their own decisions. [M]