FROM BIRTH TO DEATH AND BENCH TO CLINIC

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CHAPTER 34

Stem Cells

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stem cells

by Insoo Hyun

Framing the Issue

Stem cells are undifferentiated cells that have the capacity to renew themselves and to specialize into various cell types, such as blood, muscle, and nerve cells. Embryonic stem cells, found in five-day-old embryos, eventually give rise to all the different cells and organ systems of the embryo. Embryonic stem cells are pluripotent because they are capable of differentiating along each of the three germ layers of cells in the embryo, as well as producing the germ line (sperm and eggs). The three germ layers are the ectoderm (skin, nerves, brain), the mesoderm (bone, muscle), and the endoderm (lungs, digestive system).

During later stages of human development, minute quantities of more mature stem cells can be found in most tissue and organ systems, such as bone marrow, the skin, and the gut. These stem cells are responsible for renewing and repairing the body's specialized cells. Although the lay public often refers to them as "adult" stem cells, researchers prefer to call them multipotent because they are less versatile than pluripotent stem cells. Most stem cell scientists believe multipotent stem cells can only differentiate into cells related to the tissue or organ systems from which they originated. For example, blood stem cells can develop into different types of blood cells, but not into nerve cells or brain cells.

While multipotent stem cell research has been around for more than 40 years and has led to clinical therapies for leukemia and other blood disorders, the field of human embryonic stem cell research is still relatively new, and basic discoveries have yet to be directly transitioned into clinical applications. Human embryonic stem cells were first isolated and maintained in culture in 1998 by James Thomson and colleagues at the University of Wisconsin. Since then, more than a thousand different isolates—"lines" of self-renewing embryonic stem cells—have been created and shared by researchers worldwide.

The main ethical and policy issues with stem cells concern the derivation and use of embryonic stem cells for research. A substantial minority of Americans objects to the destruction of embryos that occurs when stem cells are harvested. Embryonic stem cell research is especially controversial for those who believe that five-day-old preimplantation human embryos should not be destroyed no matter how valuable the research may be for society.

To bypass this ethical controversy, the President's Council on Bioethics recommended in 2005 that "alternative sources" of

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HIGHLIGHTS

- Stem cell research is proceeding rapidly around the world.
- Stem cells hold great promise for treating degenerative conditions such as Parkinson disease and diabetes, for understanding genetic illnesses, and for answering fundamental questions about human development.
- The main ethical objections are to embryonic stem cell research, in which early-stage embryos must be destroyed. There is also concern over the fair treatment of embryo donors.
- Induced pluripotent stem (iPS) cells, created by reprogramming human skin cells, avoid these ethical problems.
- Despite this advance, iPS cells are unlikely to eliminate the need for human embryonic stem cells in research for many reasons.
- Standards for preclinical testing and regulation of clinical trials involving stem-cell-based therapies are urgently needed.

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Stem Cell Glossary

Pluripotent – Capable of differentiating into all cell types.

Multipotent – Capable of differentiating into a limited variety of cells related to a particular tissue system.

Somatic cell nuclear transfer (SCNT) – Research cloning; replacing the DNA of an unfertilized egg with the DNA of a cell from a patient.

Retrovirus – A type of virus that is useful for transferring genes into cells.

Induced pluripotent stem (iPS) cells – Normal body cells that are reprogrammed with retroviruses to behave like embryonic stem cells.

pluripotent stem cells be pursued. Some alternatives have been developed—most notably, the induced pluripotent stem (iPS) cells, which are human skin cells reprogrammed to behave like embryonic cells. But embryonic stem cell research will remain necessary because there are some questions only embryonic stem cells have the potential to answer.

Disease-in-a-Dish: The Promise of Embryonic Stem Cells

Embryonic stem cells are necessary for several aims of scientific and biomedical research. They include addressing fundamental questions in developmental biology, such as how primitive cells differentiate into more specialized cells and how different organ systems first come into being. By increasing our knowledge of human development, embryonic stem cells may also help us better understand the causes of fetal deformations.

Other important applications lie in the areas of disease research and targeted drug development. By deriving and studying embryonic stem cells that are genetically matched to diseases such as Parkinson disease and juvenile diabetes, researchers hope to map out the developmental course of complex medical conditions to understand how, when, and why diseased specialized cells fail to function properly in patients. Such "disease-in-a-dish" model systems would provide researchers with a powerful new way to study genetic diseases. Furthermore, researchers can aggressively test the safety and efficacy of new, targeted drug interventions on tissue cultures of living human cells derived from disease-specific embryonic stem cells. This method of testing would reduce the risks associated with human subjects research.

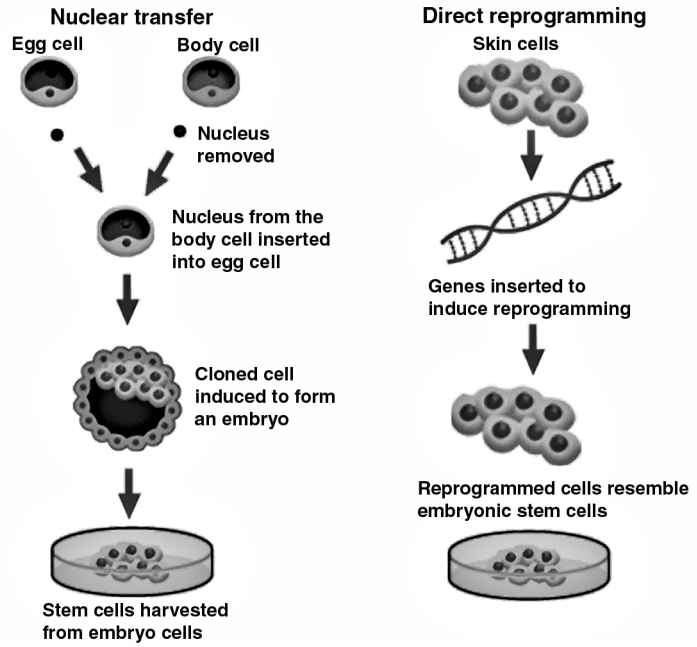
To date, stem cell scientists have succeeded in producing a few disease-specific stem cell lines using unwanted fertility clinic embryos that had tested positive for serious genetic diseases, such as cystic fibrosis and spinal muscular atrophy. However, no methods exist to screen embryos for more complex diseases like Lou Gehrig and Alzheimer disease; thus scientists must develop their own disease-specific stem cell lines for these and many other diseases they wish to study.

One possible way of deriving disease-specific stem cells is through a technique called somatic cell nuclear transfer (SCNT), otherwise known as "research cloning." By replacing the DNA of an unfertilized egg with the DNA of a cell from a patient's body, researchers may be able to produce embryonic stem cells that are genetically matched to the patient and his or her particular disease. SCNT has worked recently in nonhuman primates to produce cell-donor-matched primate stem cells, suggesting that it is possible for human research (see Chapter 6: Cloning).

Another technique for creating disease-specific stem cells was pioneered in 2006 by Shinya Yamanaka and colleagues in Kyoto, Japan. They took mouse skin cells and used retroviruses to insert four genes into them to create iPS cells. In 2007, teams led by Yamanaka, James Thomson, and George Daley each used similar techniques to create human iPS cells. The iPS cell approach is promising because disease-specific stem cells can be created using skin samples from patients and because, unlike SCNT, it does not require the procurement of scarce human eggs for research.

However, despite these advances, scientists do not believe iPS cells can replace human embryonic stem cells in research. For one, embryonic stem cells must be used as controls to assess the behavior and full scientific potential of iPS cells. Furthermore, iPS cells may not be able to answer some important questions about early human development. And safety is a major issue for iPS cell research aimed at clinical applications, since retroviruses can cause harmful mutations in the stem cells, increasing the risk of cancer. In light of these and other concerns, iPS cells may perhaps prove to be most useful in their potential to expand our overall understanding of stem cell biology, the net effect of which will provide the best hope of discovering new therapies for patients.

Creating Patient-Specific Stem Cells



Source: adapted from an illustration from the Science Media Centre

Ethical and Policy Issues: Present and Future

Many who oppose embryonic stem cell research believe for religious or other personal reasons that all preimplantation embryos have a moral standing equal to living persons. On the other hand, those who support embryonic stem cell research point out that not all religious traditions grant full moral standing to early-stage human embryos. According to Jewish, Islamic, Hindu, and Buddhist traditions, as well as many Western Christian views, moral standing arrives much later during the gestation process, with some views maintaining that the fetus must first reach a stage of viability where it would be capable of living outside the womb. Living in a pluralistic society such as ours, supporters argue, means having to tolerate differences in religious and personal convictions over such theoretical matters as when during development moral standing first appears.

Other critics of embryonic stem cell research believe that all preimplantation embryos have the potential to become full-fledged human beings and that they should never have this potential destroyed. In response, stem cell supporters argue that it is simply false that all early-stage embryos have the potential for complete human life—many fertility clinic embryos are of poor quality and therefore not capable of producing a pregnancy (although they may yield stem cells). Similarly, as many as 75–80% of all embryos created through intercourse alone fail to implant. Furthermore, no embryos have the potential for full human life until they are implanted in a woman's uterus, and prior to this essential step an embryo's potential exists only in the most abstract and hypothetical sense.

Despite the controversies, embryonic stem cell research continues to proceed rapidly around the world, with strong public funding in many areas. In this country, money for embryonic stem cell research has come mainly from states and private sources ever since the federal government limited its funding to research with embryonic stem cell lines derived before August 9, 2001. Scientists point out, however, that these "presidential stem cell lines" lack genetic diversity, have accrued genetic mutations, and are prone to infection from animal viruses introduced by the "mouse feeder layers" on which they were grown. The result is that these stem cell lines are not as scientifically useful as newer stem cell lines, many of which have been grown on feeder systems free of animal products. And as these newer stem cell lines age and begin to accrue their own mutations, more new stem cell lines will have to be created for research.

In light of the ethical concerns, the National Academy of Sciences (NAS) established guidelines in 2005 for the conduct of human embryonic stem cell research. According to these guidelines, all privately and publicly funded scientists working with pluripotent stem cells should have their research proposals approved by local embryonic stem cell research oversight (ESCRO) committees. ESCRO committees are to include basic scientists, physicians, ethicists, legal experts, and community members to look at stem-cell-specific issues relating to the proposed research. These committees are also to work with local ethics review boards to ensure that the donors of embryos and other human materials are treated fairly and have given their voluntary informed consent to stem cell research teams. Although these guidelines are voluntary, universities and other research centers have widely accepted them.

At the global level, in 2007 the International

Society for Stem Cell Research (ISSCR) released guidelines for pluripotent human stem cell research. Like the NAS, it also endorses the formation of local committees to oversee and maintain high ethical standards. However, the ISSCR guidelines add the further recommendation that stem cell lines be banked and freely distributed to researchers around the world to facilitate the field's progress on just and reasonable terms.

The potential for overcommercialization and restrictive patenting practices is a major problem facing the stem cell field today that may delay or reduce the broad public benefit of stem cell research. The promise of broad public benefit is one of the justifying conditions for conducting stem cell research; without the real and substantial possibility for public benefit, stem cell research loses one of its most important moral foundations.

However, providing useful stem-cell-based therapies in the future is not a simple proposition, either. Currently there are no international guidelines for researchers who wish to translate basic pluripotent stem cell research into effective clinical applications for patients. The ISSCR is drafting guidelines to fill this void. Developing a roadmap to bring stem cell research into the clinic will involve many complex steps. They include:

- Uniform standards for cell processing and manufacturing
- Preclinical testing requirements developed using animal models before first-in-human clinical trials can begin with pluripotent stem-cell-based biological products
- Fair and appropriate procedures for enrolling human subjects in early clinical trials
- Standards for assessing risk-benefit ratios and the use of placebo controls.

These and other difficult issues have to be sorted out soon if stem cell research in all its forms is to fulfill its promise.

RESOURCES

Web sites

- www.isscr.org – the International Society for Stem Cell Research. Includes a stem cell resources page with literature highlights, a news roundup, a page devoted to ethics and public policy, and a FAQ.
- www.nasonline.org – the National Academies of Science. Includes multimedia presentations on human embryonic stem cells, therapeutic cloning, and related topics.

Recent news

- Rob Stein, "Scientists Reprogram Adult Cells' Function; Advance Stirs up Debate on Embryos," Washington Post, August 28, 2008.
- Rick Weiss, "Monkey Embryos Cloned for Stem Cells" and "States Assess Breakthrough on Stem Cells," Washington Post, November 15 and 22, 2007
- Ricardo Alonso-Zaldivar, "Science Can't Escape Debate," Los Angeles Times, November 21, 2007.
- Nicholas Wade, "Biologists Make Skin Cells Work Like Stem Cells, New York Times, June 7, 2007.

Further reading

- Insoo Hyun, Konrad Hochedlinger, Rudolf Jaenisch, and Shinya Yamanaka, "New Advances in iPS Cell Research Do Not Obviate the Need for Human Embryonic Stem Cells," *Cell Stem Cell*, October 11, 2006.
- George Q. Daley et al., "The ISSCR Guidelines for Human Embryonic Stem Cell Research," *Science*, February 2, 2007.
- Russel Korobkin, *Stem Cell Century: Law and Policy for a Breakthrough Technology*, Yale University Press, 2007.
- Dina Gould Halme and David A. Kessler, "FDA Regulation of Stem-Cell-Based Therapies," *New England Journal of Medicine*, October 19, 2006.
- National Academies, *Guidelines for Human Embryonic Stem Cell Research*, National Academies Press, 2005.

See online-only campaign appendix at www.thehastingscenter.org/briefingbook