Stem Cell Research and Kidney Disease

By Gordon Lore

Stem cell research is one of the hottest, controversial, and ethical topics on the medical and political fronts. While research on adult stem cells (ASCs) is proceeding apace, studies on embryonic stem cells (ESCs), which many scientists believe will yield more positive and lasting results, has been stymied by ethical, political and religious concerns. Nonetheless, the eventual application of stem cell research to ongoing clinical application seems destined to be a major revolution in the history of medicine.

What are stem cells? Let's start with the basics...

Basic Building Blocks

Cells comprise the body's basic building blocks. They are found in the skin, muscles, bones, and the internal organs and are important indicators as to how our bodies function. There are perhaps thousands of specialized cell types in the adult human body. Their purpose is to perform specific functions for the organs or tissues which they comprise.

Those cells that have shown the greatest promise of replacing diseased organs with healthy new ones are stem cells.

What Are Stem Cells?

Stem cells are unspecialized entities that distinguish themselves from other body cells in two important ways:
(1) Their numbers can be replenished for long periods of time by means of their division; and
(2) Once they receive certain chemical signals, they can transform

themselves into specialized units with specific functions such as a heart or nerve cell.

Cell Types

Stem cells can develop into different types, including:

- ✓ *Totipotent stem cells* can become any of the body's cell types, including the placenta, which nourishes the embryo.
- ✓ *Pluripotent stem cells* descend from the embryo's totipotent stem cells. They can differentiate into any type of cell except for totipotent and placenta.
- ✓ *Multipotent stem cells*. These descendants of pluripotent stem cells are primarily found in the bone marrow and "give rise to all of the cells found in the blood."
- ✓ *Progenitor cells* (unipotent stem cells) produce only red blood cells.

Adult vs. Embryonic Stem Cells

For some time, research scientists have been conducting studies to see if the stem cells found in the adult body have the same ability and promise for development as those in embryos. They discovered that ASCs appear to be less versatile while ESCs have far greater potential for treating and/or curing a wide variety of serious ailments.

Why? Because they may develop into virtually every type of cell found in the body. ASCs, however, may be able to develop into only a limited number of cell types. ESCs can divide indefinitely when placed in a culture dish while this may not apply to ASCs, thereby reducing their capacity to form new types of cells. Scientists believe that studies of both ESCs and ASCs should continue since both "are critical to our understanding of the etilogy, progression, and treatment of disease."

Embryonic Stem Cells

ESCs are produced from four-to-five day-old embryos. At this stage, they are known as "blastocytes." Scientists create ESC cultures by transferring a blastocyte's cell mass into a culture dish. The cells are then removed and placed into fresh culture dishes. After being repeated many times, millions of ESCs are eventually produced.

Blastotytes that are utilized for treating ESC lines are gotten from eggs that were fertilized in in vitro fertilization clinics but were never placed in a woman's uterus. The embryos that result were frozen and donated for research purposes. There are believed to be more than 400,000 unused frozen embryos in fertility clinics throughout the US.

Adult Stem Cells

ASCs are found in smaller numbers in most adult tissues. Their primary function is to maintain and repair their host tissues.

One advantage of using a patient's own ASCs is that they can be expanded in culture dishes, then differentiated into the desired cells and reintroduced into the patient. Using the patient's cells would guarantee that they would not be rejected by the immune system. Compared to ESCs, however, there is a disadvantage in that it is harder to expand the numbers of ASCs in cell culture. [2]

In his research, a writer for the *Los Angeles Times* found that ASCs "do not bear the same ethical baggage as their embryonic counterparts because they can be harvested without creating or destroying new life. But scientists also believe they probably lack the wide-ranging curative potential that embryonic cells have." [6]

New Organs

Most scientists seem convinced that the work done in stem cell research is so promising that it is only a matter of time before widespread therapy derived from this research is routinely used. This includes treating kidney disease and/or growing new organs for transplant.

One major challenge revolves around tissue rejection. As in organ transplants, the immune cells in the body will attack transplanted cells as "foreign." This would trigger an immune rejection that could cause failure of the transplant and even endanger the life and welfare of the patient.1 But pluripotent stem cells could well be a source of replacement cells and tissues to treat many diseases, including Parkinson's and Alzheimer's, spinal cord injuries, stroke, burns, diabetes, osteoarthritis, and rheumatoid arthritis. Widespread use of this therapy could also help ease the great shortage of organs available for transplantation.2

The National Kidney Foundation believes that "scientists studying stem cells may hold the key for the thousands of people currently on the list for donor organs and the 17 candidates who die daily waiting for hearts, lungs, kidneys, or livers that never come." Since stem cells have the ability to adapt and regenerate into different types of cells, they "have the potential to replace tissues damaged by disease. It is hoped that such tissue engineering might someday help doctors eliminate the need for many transplants and the anti-rejection drugs used in transplantation."

Cloning new organs may be one way stem cells can benefit those waiting for donor organs. This involves "reprogramming a cell by replacing its nucleus with that of another cell so it becomes the generic equivalent of the original." Known as a nuclear transfer, the process "raises both hope as well as ethical concerns regarding the possibility of cloning humans for organs."3

Early-Stage Research

As scientific investigation goes, stem cell therapy research is still in its infancy. Scientists have been able to do experiments with ESCs only since 1998. This is when James Thompson, MD, at the University of Wisconsin, used a technique he developed to both isolate and grow the cells. Real research was slow to continue, however, since federal funds to support limited ESC research have only been available from the time when President George W. Bush announced the decision to fund it in August 2001.2 The funding applies to research using only the 21 ESC lines existing at that time. [9]

Currently, because of the mandated limited research on ESCs, ASCs are the only kind of stem cells commonly used to treat human diseases. Actually, doctors have been transferring hematopoietic stem cells (HSCs) in bone marrow transplants for more than 40 years. In recent years, scientists have developed more advanced techniques of "harvesting" HSCs to treat leukemia, lymphoma, and several inherited blood disorders.

Information on National Institutes of Health (NIH) clinical trials using stem cells can be found at: www.ClinicalTrials.gov. [2]

While waiting for the political and ethical firestorms to subside regarding the use of ESCs, research on ASCs continues.

Treating Kidney Damage

In 2001, scientists from the Imperial Cancer Research Fund and the Imperial College School of Medicine, London, England, "discovered that cells in bone marrow can be turned into tissue, which could help treat kidney damage caused by cancer or other diseases." They studied female kidneys transplanted into male patients with bone marrow transplants. They discovered that "the bone marrow cells had transformed into kidney tissue."

"Doctors could use stem cells from the patient's own bone marrow to replenish cells lost by injury," stated Professor Nick Wright of Imperial Cancer's Histopathology Unit. "This would be of huge benefit as the kidney is very poor at repairing itself. There would be much less complication with the kidney rejecting the new cells because they would come from the patient's own body." [5]

Organ Size and Regenerative Capacity

Harvard Stem Cell Institute Co-Director Doug Melton, MD, and his colleagues published a study in the journal Nature that "helps to explain the variation in organ regenerative capacity and in organ size determination as well. The findings also underscore the value of [ESCs] as tools to study normal development."

This particular study involved the pancreas, but the thinking is that it could also eventually apply to the kidney. Melton and his colleagues discovered that "the ultimate size and regenerative capacity of... the pancreas is determined by the specific number of progenitor cells that are set aside during a very early time in development." That determines the size of the pancreas in the animal for the rest of its life and most likely holds true for humans as well.

Melton believes his work is important because "it shows there are different kinds of mechanisms to control size, or tissue mass, for different organ systems."

"This is another in a long list of examples where [ESCs] are extremely useful [in helping us] understand the basic facts about how tissues are made and maintained," Melton continued. [4]

Sidestepping "the Knotty Ethical Dilemmas"

Scientists at the Whitehead Institute for Biomedical Research Cambridge, MA, "have created [ESCs] without using eggs or destroying embryos, an advance that may sidestep the knotty ethical dilemmas that have slowed stem cell research." The experiments on mice "returned mature cells... to a primordial, embryonic state... Those reprogrammed cells had the same properties as true [ESCs] such as the ability to turn into muscle, heart, nerve, and other tissue types."

The researchers cautioned that their current research is "very far" from being turned into routine clinical medical treatments. Their findings were published in the journal Nature. [7]

Curing Renal Failure in Rats

Researchers at the University of Tokyo claimed they succeeded in curing kidney failure in rats by transplanting somatic stem cells of the kidneys from healthy rats.

"Somatic stem cells [SSCs]... can multiply and develop into a variety of other cells of that specific organ," the researchers stated in the June 20, 2007, issue of the Journal of Cell Biology. "Such cells cannot, however, transform into cells of other organs."

Some scientists have said that human kidneys have similar SSCs. Therefore, the method can eventually be applied to cure renal failure in humans. In the experiment, the researchers transplanted 10,000 kidney somatic cells into the diseased kidney of the rats.

"Blood tests conducted on the rats seven days later found that their kidney functions had returned to normal," the researchers explained.

The Japanese scientists said they were ready "to study how to multiply

[SSCs] extracted from human kidneys [in order to] develop a method for returning artificially multiplied cells back to the patients' kidneys."8

NIH Chief Calls For Lifting Restrictions

Meanwhile, scientists, legislators, and others continue their effort to lift the restrictions on further ESC research. In a surprise move expected to mobilize opinion on Capitol Hill in March 2007, Elias A. Zerhouni, Director of the NIH, broke with the stance of the Bush administration by telling members of the US Senate Health Appropriations Subcommittee that he favored an end to restrictions on federal funding for ESC research.

"It is clear today that American science... and the nation will be better served if we let our scientists have access to more stem cell lines," Zerhouni remarked. "We cannot... be second best in this area... It is important for us not to fight with one hand tied behind our back..., and NIH is the key to that."9

His comments are the strongest yet supporting the lifting of the President's 2001 ban restricting government funding to research using ESC lines. [10]

Stem Cell Protection Act Introduced

In introducing the Human Cloning Ban and Stem Cell Protection Act of 2007, Senator Orrin Hatch (R-UT), also had something to say about stem cell research.

"Many scientists believe that we are on the verge of a new revolution in medicine created by human stem cells," Hatch remarked. "The reason stem cells are important... is that many organs cannot make a sufficient number of new cells to replace damaged or lost ones... [An] example of how stem cells may treat common diseases is renal failure, which occurs in an estimated 40% of critical care patients. Dr. Christof Westenfelder, Professor of Medicine and Physiology at the University of Utah, has found that injecting stem cells into failing kidneys improves kidney function, prevents tissue injury, and accelerates regeneration." [11]

Congress Urges Lifting of ESC Research Ban

On June 7, 2007, the US House of Representatives voted to send legislation that would remove the limits placed on ESC research to the White House for signing into law by President Bush. The House vote was 247 to 176. This vote, however, was 35 short of the two-thirds majority needed to override a Presidential veto. [12]

As he promised, on June 20, 2007, Bush used his powerful veto pen to knock the proposed legislation out of the political arena. This is the second consecutive year Bush has nixed such a bill. In announcing his veto, the President said he was encouraged from recent studies indicating it could be possible to grow stem cells from sources other than those derived from human embryos.

"Researchers are now developing promising new techniques that offer the potential to produce pluripotent stem cells without having to destroy human life," Bush remarked.

The President also issued an executive order to the NIH requesting that scientists conduct their research on stem cells that are "derived without creating a human embryo for research purposes or destroying, discarding, or subjecting to harm a human embryo or fetus." Critics, however, were quick to accuse Bush of using his Presidential powers to openly give the impression that he was supporting stem cell research when he was actually holding it back. [14]

Conclusion

Christopher Thomas Scott, Director of the Stanford Program in Stem Cells and Society, said in his book that, by the year 2010, more than two million Americans are predicted to have end-stage renal disease at an aggregate cost of a whopping $1 trillion. Scott added that, despite the current future promise, developing new treatment therapies from stem cell research may take so long that "many diseases will have to wait for cures from other quarters of medicine."

One reason cures from stem cell research may take so long has to do with the slow and very expensive method of discovering, testing, and manufacturing a new drug. It can take 10-15 years and cost nearly a billion dollars to have a new drug approved by the US Food and Drug Administration and brought to market. [13]

Despite the drawbacks, the many challenges, and the long time needed to bring their work to the patient's bedside, most scientists still believe that stem cell therapy will eventually revolutionize medical treatment. It's not a matter of if, but when. [1]

Author's Note:

An important scientific breakthrough that has been hailed as "a landmark achievement" as well as "the biological equivalent of the Wright Brothers' first airplane"15 and the "Holy Grail"16 of stem cell research was widely reported just before Thanksgiving 2007. Even President Bush, who vetoed two bills that would provide federal funding for embryonic stem cell research, said he was "very pleased" by the breakthrough. Teams led by Shinya Yamanaka, MD, of Kyoto University in Japan and Junying Yu at the University of Wisconsin-Madison have reportedly created "the equivalent of embryonic stem cells from ordinary skin cells, a breakthrough that could someday produce new *treatments for disease without the explosive moral questions of embryo cloning."* [15]

Using stem cells could eventually "allow doctors to create stem cells with a specific patient's genetic code, eliminating the risk that the body would reject transplanted tissues or organs." A great advantage of the new technique involves its simplicity: "it takes just four genes to turn the skin cell back into a stem cell." This can be done in a standard biological laboratory. Also, skin cells can be much more easily harvested than embryonic cells. There are still problems with finding a safe way to transform the skin cells, but scientists are optimistic about solving this dilmma. [16]

The researchers indicated that "the rejuvenated cells were able to grow into all the main tissue types in the body," and "the discovery provides a clear road map for creating genetically matched replacement cells that could be used to treat patients for a variety of diseases."17 Also, the breakthrough will enable the Bush administration to "approve funding for a promising new line of research." Proponents of embryonic stem cell research, however, said that their approach was "too far along to abandon "and that "the two kinds of scientific research will probably move in tandem for some time." [18]

References

1. Stem Cell Research Foundation. Frequently Asked Questions. Website: www.stemcellresearchfoundation.org/AboutFAQ.htm. Accessed June 8, 2007.
2. Stem Cells and Diseases. In *Stem Cell Information.* National Institutes of Health, US Department of Health and Human Services. Website: stemcells.nih.gov/info/health.asp. Accessed April 24, 2007.
3. National Kidney Foundation. Do Stem Cells Hold the Key for the Future of Transplantation? Website: www.kidney.org/news/newsroom/printfact.cfm?id=4Accessed April 12,

2007.
4. Colen, BD. Stem cell research sheds light on organ regeneration. *Harvard University Gazet*te, February 22, 2007. Website: www.news.harvard.edu/gazette/2007/02.22/05-pancreas.html. Accessed March 13, 2007.
5. Goodenough, P. Adult Stem Cells May Help Treat Kidney Disease. CNSNews.com, July 25, 2001. Website: www.cnsnews.com. Accessed April 12, 2007.
6. Healy, M. Stem Cell Hope, Hype, Health. *Los Angeles Times*, March 5, 2007.
7. Naik, G. Stem-Cell Advance May Skirt Ethical Debate. *Wall Street Journal*, June 7, 2007.
8. Stem Cell News.com. Stem Cell Transplant Succeeds in Curing Kidney Failure in Rats. *Mainichi Daily News*, June 21, 2005. Website: www.stemcellnews.com/articles/stem-cells-kidney-failure.htm. Accessed June 7, 2007.
9. Alonso-Zaldivar, R, and Kaplan, K. Loosening of Stem Cell Limits Backed. *Los Angeles Times*, March 20, 1997.
10. Bridges, A. Bush's Own NIH Chief Opposes Stem Cell Ban. The Associated Press/abc News. Website: abcnews.go.com/Technology/print. Accessed April 12, 2007.
11. Carr, P. Hatch, Feinstein Promote Stem Cell Research, Human Cloning Ban. News Release from Orrin Hatch, United States Senator for Utah, March 8, 2007. Website: hatch.senate.gov. Accessed April 12, 2007.
12. Haveman, J. Stem cell bill passes House, but faces certain veto. *Los Angeles Times*, June 8, 2007.
13. Scott, CT. Stem Cell News: From the Experiment That Shook the World to the New Politics of Life. Pi Press. Website: www.npr.org/templates.story/story.php?storyId=5204335. Accessed April 12, 2007.
14. Reynolds, M. Bush vetoes embryonic stem cell funding. *Los Angeles Times*, June 21, 2007.

15. Ritter, M. Stem Cell Breakthrough Uses No Embryos. November 20, 2007. Website: news.aol.com/story/_a/stem-cell-breakthrough-uses-no-embryos/20071120161309990001.
16. AFP. Breakthrough opens door to organ transplants grown in lab. November 20, 2007. Website: afp.google.com/article/ALeqM5iLLQiJ8nHM4MYWfKhSC_g0_CkKeQ.
17. Kaplan, K. *Stem cell milestone achieved. Los Angeles Times*, November 21, 2007.
18. Alonso-Zaldivar, R. Science can't escape debate. *Los Angeles Times*, November 21, 2007.

About the Author

Gordon Lore was the Editorial Coordinator of KidneyTimes.com until 2007 and formerly was the Editor of several nephrology journals.