

The State of Stem Cell Research

Where we are and where we're headed in 2009.

BY TOM VALEO

Will the brain benefit if President Obama reverses the Bush administration's restrictions on embryonic stem cell research? That depends. In the meantime, the Bush ban has had one positive side effect: researchers have begun investigating the therapeutic potential of other types of human cells.

Scientists have ideas on how to use stem cells to alleviate a variety of neurological conditions—Parkinson's disease, amyotrophic lateral sclerosis (ALS), Huntington's disease, multiple sclerosis, spinal cord injury, and brain damage caused by stroke or trauma—as well as vision and hearing loss. They've been constrained from fully exploring those ideas, however, because President Bush cut off federal funding for embryonic stem cell research except for a few pre-existing cell lines.

Removing the restrictions will encourage the development of new treatments for these disorders, but only if funding increases at the same time.

"What's holding us back is money," says Lorraine Iacovitti, Ph.D., interim director of the Farber Institute for Neurosciences and professor of neurology at Thomas Jefferson University Medical College in Philadelphia, PA. "Reversing the Bush ban on stem cell lines will mean greater availability, but without more money that won't mean much. Funding at the National Institutes of Health is lower than it's been in my 25-year career."

PARKINSON'S DISEASE

Dr. Iacovitti has been exploring ways to use stem cells to produce dopamine, a



neurotransmitter that people with Parkinson's disease lack. When President Bush limited federal funding on stem cells, Dr. Iacovitti turned to a technique that involves transforming a patient's own cells into a type of stem cell.

"We hoped we could avoid controversy about embryonic cells," she says. "In my lab we were very excited about taking standard adult stem cells from bone marrow and trying to make those cells into dopamine-producing neurons."

This approach is difficult because stimulating a cell taken from an adult to produce dopamine requires complex manipulation of the cell's genetic machinery. On the other hand, a patient's own cells pose no danger of rejection, which can be a life-long threat for people who receive stem cells derived from an embryo.

"I believe the embryonic stem cell lines are the gold standard because they're the only stem cells that reliably become dopamine neurons after they're transplanted into the brain," says Dr.

Iacovitti. "But the ultimate goal is to make adult-derived tissue behave like embryonic stem cells. That will be the wave of the future because it will allow patients to provide their own replacement tissue. We can't go back and get your embryonic stem cells, but we can take a skin cell from a Parkinson's patient and reprogram the nucleus to produce dopamine. And those cells will be seen as self—they won't be rejected."

ALS

Researchers at Harvard and Columbia universities have used a

similar technique to coax skin cells from an 82-year-old woman with ALS into a "pluripotent" state, which enables them to turn into any one of a variety of cells. The cells produced motor neurons in the lab. The scientists hope that someday they will be able to use such cells to regenerate motor neurons in people with ALS.

Researchers at the University of Wisconsin-Madison are taking a different approach. From bone marrow, they are developing stem cells that will protect existing motor neurons in patients with ALS. The bone marrow cells are genetically engineered to produce glial cell-line-derived neurotrophic factor (GDNF), according to Masatoshi Suzuki, D.V.M., Ph.D., an associate scientist at the University's Waisman Center. While this technique would not cure ALS, it would slow its progression, Dr. Suzuki believes. How GDNF does this remains unknown, but "many studies have shown that GDNF protects motor neurons from degeneration," Dr. Suzuki says. "In our approach,

GDNF may contribute to the protection of neuromuscular connections.”

VISION PROBLEMS

Stem cells also could be used to restore vision, according to Beatrix Kovacs, Ph.D., a researcher in the Laboratory for Retinal and Neural Developmental Biology and Genetics at Rush University in Chicago.

In experiments with mice she has implanted retinal progenitor cells taken from newborn mouse eyes. While not as versatile as embryonic stem cells, which can turn into any type of cell in the body, progenitor cells have advantages. These progenitor cells, which are more differentiated than stem cells, are still capable of turning into a variety of retinal cell types.

“Stem cells can become any type of cell, that’s true,” Dr. Kovacs says, “but you have to tell them what to become. Retinal progenitor cells, on the other hand, are already committed to their retinal fate. They can migrate and integrate into the host tissue, and take up residence in the region where photoreceptors are found and become photoreceptor cells identical to those seen in the normal eye.”

Being able to replace photoreceptors

would help people suffering from retinitis pigmentosa, a genetic disorder that causes blindness, as well as from age-related macular degeneration and other types of vision loss.

“In retinitis pigmentosa,” Dr. Kovacs says, “the basic neural circuitry except for photoreceptors remains relatively intact. So if you could make photoreceptor cells, you could restore vision.”

Dr. Shunbin Xu, Ph.D., the director of the Rush University lab where Dr. Kovacs works, believes the new technology of induced pluripotent stem cells, so-called iPS cells, “may be the way to go” in treating diseases that cause retinal degeneration. Even if the federal restrictions on stem cell research are reversed, he would continue research into induced pluripotent stem cells because they are showing great promise. “But that does not diminish the importance of embryonic stem cells at all,” he says.

SPINAL CORD INJURY

Ping Wu, M.D., Ph.D., of the University of Texas Medical Branch in Galveston, is working on a way to use neural stem cells

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taken from human fetuses to replace damaged spinal cord motor neurons, thereby enabling paralyzed people to walk again.

The fetal cells are already committed to becoming

nerve tissue, which means they need less time to become motor neurons. That could be crucial when treating someone with a rapidly degenerating illness such as ALS.

“Sometimes you want cells right away because you want to treat the patient as soon as possible,” Dr. Wu explains.

Embryonic stem cells may take several weeks to become motor neurons, but the fetal cells may be ready for transplant in a week.

Transplants of fetal cells into animal spinal cords have been successful, according to Dr. Wu. When grafted around the area of injury, they become motor neurons, “but the survival rate of the cells is very low,” she notes.

Recently they have started injecting the cells into the ventricles of the brain, which are filled with spinal fluid. From there the cells migrate through spinal fluid to the injury site. “The damaged area attracts the grafted cells,” Dr. Wu says.

How soon will humans start to benefit from stem cell therapies? That depends on how soon researchers find ways to control the damage caused by neurological diseases. Transplanting new motor neurons in people with ALS would be a great advance, but would not produce much benefit if the disease process immediately destroyed them.

“We have made progress, but we’re still far away (from human trials),” Dr. Wu says. “Especially for diseases like ALS, we need to control the disease environment. Even a spinal cord injury produces a toxic environment, so controlling that is very important.” NN

WHAT ARE STEM CELLS?

Embryonic stem cells come from human eggs that have been fertilized in the laboratory and allowed to divide into a hollow ball of 50 to 150 cells known as a blastocyst. The cells lining the inside of the blastocyst are pluripotent, which means they have the potential to develop into any cell in the human body.

Adult stem cells, also known as somatic stem cells, cannot become any type of cell in the body, but they retain the potential to develop into the types of cell found in the organ where they originated. For example, stem cells produced in the hippocampus of the adult brain have the potential to become one of the three common cells found in the brain: astrocytes, oligodendrocytes, or neurons.

Induced pluripotent stem (iPS) cells are ordinary adult cells, such as skin cells, that have been returned to the pluripotent state of an embryonic stem cell by allowing a virus to enter the DNA and insert certain genes.