

## Stem Cells

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**B**reakthroughs in stem-cell research have come across the newswires nearly every day for the past few months. Despite—and occasionally because of—continuing controversy over the use of embryonic stem cells, researchers continually learn more about how stem cells work and what medical uses they might eventually have.

Researchers at the Regenerative BioScience Center at the University of Georgia have **successfully induced embryonic stem cells to differentiate into motor neurons**. The research, reported in the June issue of *Stem Cells and Development* ([www.liebertpub.com/scd](http://www.liebertpub.com/scd)), involved NIH-approved human embryonic stem cells grown in culture. Soojung Shin, Stephen Dalton, and Steven L. Stice induced the cells to differentiate into motor neuron cells by adding basic fibroblast growth factor, sonic hedgehog protein, and retinoic acid to the culture medium. The initial experiments yielded motor neurons from 20–30% of the cells, a percentage the authors expect to increase as they refine their process.

A renewable supply of neuroepithelial cells that can be reliably induced to become motor neurons brings one step closer the possibility of using stem cells to treat damaged neurons.

Meanwhile, **a California company says it is routinely using stem cells to treat horses**.

According to a story in *Wired* magazine (Philipkoski K. Stem Cells Give Horses a Hoof Up. *Wired* April 13, 2005; [www.wired.com/news/medtech/0,1286,67197,00.html](http://www.wired.com/news/medtech/0,1286,67197,00.html)), Vet-Stem uses stem cells derived from patients' own fat cells to treat both prize race horses and well-loved average horses for bowed tendons, injured ligaments, and fractures. At the GTCbio stem-cell conference in San Diego in April, executives from Vet-Stem said horse injuries heal faster and with less scarring when treated with stem cells than when treated with traditional therapies. The company shares data with six human stem-cell companies owned by one of its investors. "All of our data that we collect on the vet side is shared with our human-therapy partners, which will help them decide what to do in the clinics," said Robert Harman, a veterinarian and CEO of Vet-Stem.

To treat the horses, a veterinarian removes a small fat sample from the horse's rump and sends it to the company. Using a process licensed from one of its human-therapy partners, company scientists distill the cells and returns them to the vet, who injects them into the horse at the injury site. Because the treatment uses the horse's own, unadulterated tissue, regulatory oversight is minimal.

Conference attendees questioned whether the results were from stem cells or other factors associated with fat. Harman said his researchers had identified cell markers indicating that stem cells were present in the therapies, but that definitive results were unavailable.

Veterinary work using stem cells from adult animals is one way to study stem cells without becoming embroiled in controversy. Attempts to bypass the ethical questions that surround embryonic stem-cell research have led to other interesting results in recent months.

At the International Conference on Stem Cells Research and Therapeutics in San Diego in April, Celgene Corporation announced its **isolation of pluripotent human placenta-derived stem cells**. Deriving the cells from placentas, which are typically discarded, removes the process from the ethics controversy.

"This study contributes to a growing body of evidence that the placenta is an important and novel source of stem cells that can potentially be used for the repair of damaged or diseased tissue," said Robert Hariri, president of LifebankUSA and Celgene Cellular Therapeutics. The study used human placentas donated following the birth of normal, full-term babies. Using a proprietary technique that anatomically perfuses the placenta, mononucleated cells were obtained, purified, and cultured. Fluorescence activated cell sorter (FACS) analysis was used for cell surface marker characterization, and reverse transcription polymerase chain reaction (RT-PCR) determined gene expression analysis.

Within two to four weeks, adherent cells with fibroblast-like morphology could be grown from the placenta perfusate culture. Morphologic examination and quantitative gene analysis showed that the cells expressed morphologic features and a gene transcript that are the hallmark of primitive stem cells. Under certain culture conditions, the cells were transformed into cartilage-like and fat-like tissue.

Other attempts to bypass the ethical controversy surrounding stem-cell research focus on adult stem cells. Although such cells have been largely dismissed by many scientists, a report in the *Los Angeles Times* (Kaplan K. Studies Revive Debate Over What Adult Stem Cells Can Do. *LA Times* April 24, 2005; [www.latimes.com](http://www.latimes.com)) discusses several studies that suggest such cells can produce a range of tissues.

Unlike embryonic stem cells, which can turn into every tissue type, adult stem cells can regenerate only a single type of cell. Some scientists have theorized that it might be possible to make them behave more like embryonic stem cells. At a teaching hospital affiliated with the Tufts University School of Medicine, scientists used human bone-marrow stem cells to build heart muscle and blood vessels in rats. Stem cells from mouse hair follicles became neurons in experiments conducted by AntiCancer, Inc. And scientists at the University of Indiana transformed mouse bone-marrow stem cells into neurons that facilitate hearing.

The studies have their critics. But even though supporters admit that "a lot of the initial studies may have been touted to be more positive than they were," they insist that the **evidence is accumulating to support the idea that adult stem cells are more flexible than once believed**.

Stem-cell research—embryonic, veterinary, placental, and adult—is exciting and holds great promise. All of the research is still years away from human treatments, and it is still too early to predict which field will offer the first—or most lasting—therapeutic potential. —CPS

## Neurology

PAUL MILLER (WWW.ISTOCKPHOTO.COM)

**A**lzheimer's disease is a phrase that strikes fear into most people. It seems to rob people of their essential selves without actually killing them. It's poorly understood, and has no good treatment. But researchers are working hard to better understand it in the hope of finding treatments.

Scientists at Rhode Island Hospital and Brown Medical School reported in the March issue of the *Journal of Alzheimer's Disease* ([www.j-alz.com](http://www.j-alz.com)) that they'd discovered insulin and its related proteins are produced in the brain. Reduced levels of both are linked to Alzheimer's. "What we found is that **insulin is not just produced in the pancreas, but also in the brain,**" says senior author Suzanne M. de la Monte. "And we discovered that insulin and its growth factors, which are necessary for the survival of brain cells, contribute to the progression of Alzheimer's."

Researchers were studying a gene abnormality in rats that blocks insulin signaling in the brain when they discovered that insulin and IGF I and II are all expressed in neurons in several regions of the brain. They also determined that a drop in insulin production in the brain contributes to the degeneration of brain cells typical of early Alzheimer's. "These abnormalities do not correspond to type 1 or type 2 diabetes, but reflect a different

and more complex disease process that originates in the central nervous system," the paper explains. De la Monte elaborates, "This raises the possibility of a type 3 diabetes."

Meanwhile, researchers at New York-Presbyterian Hospital/Weill Cornell Medical Center reported at the American Academy of Neurology meeting in April that a phase 1 clinical trial provided encouraging evidence that antibodies derived from human plasma can capture the beta-amyloid protein in blood and exert positive effects on patients' thinking abilities. Beta-amyloid's toxicity to brain cells is believed to be a prime cause of Alzheimer's disease.

Intravenous immunoglobulin (IVIg) has been found to contain antibodies that can draw beta-amyloid proteins out of the nervous system and reduce the burden on the brain. In this trial, eight Alzheimer's patients were treated with IVIg. Seven have so far undergone cognitive testing after six months of therapy. **Cognitive function stopped declining in all seven patients, and it improved in six of them.** The therapy, which is FDA-approved to treat other conditions, was well-tolerated.

"These initial results are really encouraging," says Norman R. Relkin, lead researcher on the study. "IVIg has the advantages of a well-established safety record and the benefits of containing antibodies that healthy individuals produce naturally as they age."

It's still a dread disease, and will remain one for the foreseeable future, but it may become a treatable disease soon. —CPS

## Gene Therapy

[HTTP://VISUALSONLINE.CANCER.GOV](http://visualsonline.cancer.gov)

**A**fter years of negative publicity—deaths in clinical trials, leukemia caused by experimental therapy—encouraging news from the world of gene therapy is a pleasant change.

Researchers at the University of Texas Southwestern Medical Center have **used a natural DNA repair process called homologous recombination to accurately and permanently correct mutations in disease-causing genes.** Matthew Porteus, working with researchers from Sangamo Biosciences ([www.sangamo.com](http://www.sangamo.com)), artificially initiated homologous recombination to replace a mutated version of the gene that encodes a portion of the interleukin-2 receptor in human cells, restoring both gene function and the production of the IL-2R protein.

Mutations in the IL-2R gene are associated with severe combined immunodeficiency disease (SCID). Previous gene therapy attempts for SCID have been only moderately successful because of difficulties with delivery methods. Porteus' strategy differs from earlier therapies because it essentially replicates a natural process, which is accurate enough that, in practice, it affects only the mutant gene.

Homologous recombination is a relatively rare event that happens when a chromosome is damaged during division. The wounded chromosome uses its healthy twin as a template to

repair itself. In the new technique, researchers introduced an enzyme into immune cells harboring the mutant IL-2R gene. Once bound to the mutant gene, the enzyme creates a break in the DNA sequence, initiating the recombination process. The change to the cells seems permanent, and the correct gene is easily maintained after many cell divisions, says Porteus.

Researchers at Washington University School of Medicine used gene therapy to restore newborn mice and dogs with hemophilia A to health. The technique introduced clotting factor VIII, missing because of a genetic defect, into the animals. "We are really pleased with the results, because **the animals produced about 20 times more factor than has been achieved in prior attempts using gene therapy for hemophilia A in dogs,**" says senior author Katherine Parker Ponder. The technique using newborn animals did not prompt an immune response, which in many other cases eventually blocks the clotting activity of introduced factor VIII. Since treatment more than a year ago, the blood of the mice and dogs in this study has maintained a normal level of clotting factor activity, and the animals have had no incidents of bleeding.

Gene therapy for hemophilia A has been challenging because the gene for factor VIII is large, making it difficult to fit into the viral vectors used for gene delivery. In this study, the researchers eliminated parts of the factor VIII gene and other components to reduce the material needed and used a large vector called gamma retroviral vector. They also included a short DNA promoter sequence in the vector to make the gene active only in liver cells, one of the sites of factor VIII production in nonhemophiliacs. —CPS