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UC San Diego
University Archives. RSS 6020

Human Stem Cell Treatment Restores Motor Function in Paralyzed Rats

May 30, 2007

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Rats paralyzed due to loss of blood flow to the spine returned to near normal ambulatory function six weeks after receiving grafts of human spinal stem cells (hSSCs), researchers from the University of California, San Diego (UCSD) School of Medicine report. The study, led by Martin Marsala, M.D., UC San Diego professor of anesthesiology, is published in the June 29, 2007 issue of the journal *Neuroscience*, which is now online.

"We demonstrated that when damage has occurred due to a loss of blood flow to the spine's neural cells, by grafting human neural stem cells directly into the spinal cord we can achieve a progressive recovery of motor function," said Marsala. "This could some day prove to be an effective treatment for patients suffering from the same kind of ischemia-induced paralysis." Marsala is currently testing the human stem cell therapy for safety and efficacy in other animal models, and hopes to move to clinical trials in humans by next year.

Paraplegia from spinal cord ischemia is a serious complication that occurs in 20 to 40 percent of patients undergoing a surgical process called aortic cross-clamping. When the surgeon works on the aorta, a major blood vessel, to correct a potentially lethal aneurysm, blood flow from the heart must be temporarily blocked with a clamp. After 30 minutes, this lack of blood flow can result in the death of specialized spinal cord neurons called spinal inhibitory neurons, leading to irreversible spasticity and rigidity, or loss of muscle control, in the lower limbs, even though the spinal cord is intact.

"The important difference between spinal cord ischemia and spinal cord trauma, such as might occur in a diving or car accident, is that in the ischemia model, no mechanical damage has occurred to the spinal cord," said Marsala. "The spinal cord and brain motor centers are still partially connected, but there has been a selective loss of inhibitory neurons in the spinal cord. Since these cells are necessary for coordinated motor activity, our research aims to replace these lost neurons by grafting new spinal stem cells, which repopulates the pool of degenerated neurons."

For this study, nine of 16 rats with induced spinal cord ischemia were injected with human spinal stem cells 21 days after paralysis. The other seven were injected with medium that contained no stem cells. The recovery of motor function was evaluated in seven-day intervals, showing a progressive recovery of ambulatory functions in the rats that received stem cells.

Three of the nine rats injected with hSSCs returned to walking at six weeks, and three others had improved mobility in all lower extremity joints. All nine animals grafted with hSSCs achieved significantly better motor scores than those in the control group, and showed a consistent presence of transplanted cells in the spinal area. In all the rats grafted with the stem cells, the majority of transplanted human spinal stem cells survived and became mature neurons, according to Marsala. A second study was conducted over a three-month period, with similar results.

"Other human stem cell transplants in the spinal cord have focused on repairing the myelin-forming cells," said co-author Karl Johe, a researcher at Neuralstem, the company that manufactures the hSSCs used in the study. "In this study, we succeeded at reconstructing the neural circuitry, which had not been done before."

The researchers believe that the therapy may eventually be proven even more effective in human patients, who would be able to receive physical therapy once treated.

"Physical therapy may accelerate integration of the grafted stem cells and enhance their therapeutic benefit," Johe said, adding that the goal is to provide a significant gain in functional mobility of the patient's legs.

This study builds on Marsala's previous work in rat models using human neuronal stem cells, published in October 2004 in the *European Journal of Neurosciences.* In that study, significantly improved motor function, measured by a suppression of spastic movements and improved muscle tone, was shown in 40 to 50 percent of the animals tested. A post-mortem study of those animals showed a robust maturation of neurons and an increase in the expression of inhibitory neurotransmitters in the spinal cords of rats that received transplanted neuronal cells.

Current treatment for debilitating muscle spasticity is continuous systemic or spinal drug treatments using implanted pumps. These approaches, while effective to a degree, are often accompanied by side effects and eventual drug tolerance that lessens their efficacy.

"These research findings could offer great hope to people with spinal ischemic injury who suffer from resulting spasticity and rigidity," said Marsala.

Additional contributors to the paper include Dasa Cizkova, Osamu Kakinohana, Karolina Kucharova, Silvia Marsala, Karl Johe, Thomas Hazel and Michael P. Hefferan. The study was supported in part by grants from the NIH. This research was supported by grant NS 40386 (M.M.), Neuralstem Inc., MD and Centrum of Excellence APVV 51-002105 grant (D.C.).

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