

# Stem Cell Transplantation for Stroke: Recent Findings

*Highlights of the North American Stroke Meeting,  
December 4-6, 2003, Orlando, FL*

[Rev Neurol Dis. 2004;1(3):141-143]

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**Key words:** Stroke • Stem cells • Umbilical cord • LBS neurons

**T**he North American Stroke Meeting was held in Orlando, Florida on December 4-6, 2003. The meeting brought together stroke experts from around the world to discuss important topics related to stroke prevention, treatment, and rehabilitation. At this meeting, Lawrence R. Wechsler, MD, Professor of Neurology and Neurosurgery and Director of the Stroke Institute at the University of Pittsburgh, presented a conference entitled "Stem Cell Transplantation for Stroke."

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### Stem Cells

Stem cells capable of differentiating into nerve cells are found in fetal brain, in bone marrow, in the umbilical cord, and in the adult human brain. They have also been isolated from primitive tumors. Laboratory experiments have shown that some types of stem cells injected intravenously in rats with experimental stroke find their way to the lesion site and improve neurologic function. Presumably, signals emitted by the injured brain attract stem cells, a small proportion of which differentiate into neuronal cells. Functional improvement occurs relatively rapidly, which suggests a humoral mechanism. Based on promising animal results,

experiments involving stem cell transplantation have been carried out in humans with stroke.

Umbilical cord blood has been targeted as a source of stem cells. Harvesting stem cells from this organ obviates ethical considerations. The umbilical cord in humans is a source of stem cells with the potential to differentiate into neurons and with a lesser tendency to be rejected when transplanted to humans than cells harvested from a nonhuman source. Nonetheless, concerns regarding the safety of patients after intravenous injection of stem cells, reaching any system within the body, have become a strong consideration.

Immortalized cell lines derived

from primitive tumors or transformed by oncogenes can be preserved in cell cultures and maintained indefinitely. One such cell line, NT2 cells, derived from a testicular tumor and maintained in cell culture, can be induced to differentiate into neuronal cells with retinoic acid. These neuronal cells, called LBS neurons, exhibit neurotransmitter functions, including cholinergic,  $\gamma$ -aminobutyric acid-ergic, dopaminergic, and glutamatergic transmission. These cells do not pose the ethical problems of cells harvested from a fetal source. They can be mass-produced in cell cultures, cryopreserved, and shipped easily without losing their human cell characteristics.

### Studies in Patients With Stroke

Preclinical studies in animals with experimental stroke lesions have shown that after the transplantation of LBS neurons, there is improvement of function and evidence of axonal growth and synaptic formation at the site of the lesion. Furthermore, the functional improvement is proportional to the number of surviving cells. Rats with stroke after transplantation learn passive-avoidance tasks faster. Transplantation of cells to patients with stroke offers several advantages. The stroke lesion is localized and exhibits a measurable deficit. Furthermore, a small number

of cells might have a large impact, and there is no effective treatment for stroke.

### Phase 1 Trial

A phase 1 trial in humans recruited 12 individuals with basal ganglia strokes and major motor deficits. Strokes had occurred between 7 and 55 months before recruitment to the

trial. The European Stroke Scale, used to measure objective changes in neurologic function, showed improvement in some patients. Patients receiving  $6 \times 10^6$  cells improved more than those receiving  $2 \times 10^6$  cells. Positron emission tomography (PET) scan studies in 7 patients showed increased metabolic function at the stroke site, and two thirds

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*LBS neurons can be mass-produced in cell cultures, cryopreserved, and shipped easily without losing their human cell characteristics.*

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trial. The method involved the stereotactic injection of cryopreserved cells at the site of the stroke. Individuals received either  $2 \times 10^6$  cells in 3 injections over 1 pass or  $6 \times 10^6$  cells in 9 injections over 3 passes. All patients were treated with cyclosporine A for 1 week before and 8 weeks after transplantation to suppress possible rejection. Adverse events included nausea, seizures, and new stroke in a different arterial territory. None of the adverse events were considered related to the transplanted cells. Two patients died of unrelated causes in 2 years of follow-up.

Subjective report of patients indicated improvement in walking, strength, memory, and speech. Because the trial was not controlled, a placebo effect could not be ruled

of those with increased metabolism by PET also exhibited functional improvement. An inflammatory response or host reaction at the stroke site rather than enhanced genuine neurologic function could not be ruled out as the source of the increased metabolic effect.

A 71-year-old patient died 27 months after receiving transplantation of  $2 \times 10^6$  cells, and an autopsy study was obtained. He had shown no change in functional scales, but the PET scan exhibited increased metabolic function. The histologic study of brain tissue showed glial scarring with viable neurons at the stroke site. Deoxyribonucleic acid probes demonstrated that some viable transplanted neurons survived 27 months after transplantation.

### Main Points

- Immortalized cell lines derived from primitive tumors or transformed by oncogenes can be preserved in cell cultures and maintained indefinitely; they do not pose the ethical problems of cells harvested from a fetal source.
- Based on promising animal results, experiments involving stem cell transplantation have been carried out in humans with stroke.
- In a phase 1 trial, 12 individuals with basal ganglia strokes and major motor deficit received injections of cryopreserved stem cells at the site of the stroke; subjective report of patients indicated improvement in walking, strength, memory, and speech. The trial was not controlled, thus a placebo effect could not be ruled out.
- In a phase 2 trial, which included 4 observational controls, 14 patients with basal ganglia stroke received stem cell transplantation; 4 patients receiving  $5 \times 10^6$  cells showed improvement in stroke scales, but only 2 patients receiving  $10 \times 10^6$  cells improved.

### Phase 2 Trial

A phase 2 trial recruited 14 patients with basal ganglia stroke occurring 3–6 years before and included 4 observational controls. They received either  $5 \times 10^6$  or  $10 \times 10^6$  LBS cells

conducted so far has raised several issues. Timing of the injection will have to be optimized to achieve best results. The size of the stroke and site of the injection will have to be defined, as well as the number of

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### *Deoxyribonucleic acid probes demonstrated that some viable transplanted neurons survived 27 months after transplantation.*

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in transplantation. Adverse events included syncope, seizures, and subdural hematoma. None of these events were considered directly related to the cell transplants. Four patients receiving  $5 \times 10^6$  cells showed improvement in stroke scales, but only 2 patients receiving  $10 \times 10^6$  cells improved; this discrepancy remains unexplained. Neuropsychological testing showed interesting trends toward improvement on specific subtests after 6 months, compared with baseline results. No changes were seen in controls.

### Future Considerations

The limited research in transplantation of cells to humans with stroke

cells to be injected. It remains unclear whether transplant recipients require immunosuppression and for how long. Furthermore, the long-term effects of the procedure remain unknown. The future calls for more animal studies and more human research focusing on cognitive issues. ■

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