



**Vickie and Jack Farber
Institute for Neuroscience**
Jefferson Health®

OUTCOMES & RESEARCH: VOLUME 1

CELL-BASED THERAPIES AND SPINAL CORD INJURY



A MESSAGE FROM THE CHAIR

Dear Colleagues,

It is an especially exciting time at Thomas Jefferson University Hospital's Department of Neurosurgery and the Vickie and Jack Farber Institute for Neuroscience – Jefferson Health. I am pleased to share this report, the first in a series that outlines some of the innovative work that our departments are engaged in many research projects. Our physicians and scientists are looking for new ways to treat spinal cord injuries (SCIs) and the use of cell-based therapies for these disabling injuries has emerged as on strategy.

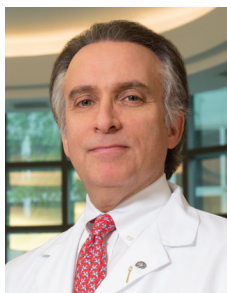
Dr. James Harrop, Chief, Division of Spine and Peripheral Nerve Surgery, and his team are driving these advances that set us apart from other academic programs. Whether it's finding ways to refine surgical techniques for SCIs or furthering our understanding of complex neurological conditions, the work of our team is leading to ever better care for patients. We see outstanding results every day as patients return to their lives with improved and restored function and performance.

We are fortunate to have clinicians who value research. Current research into SCI at Jefferson Health includes but is not limited to looking at outcomes and treatment in thoracic spinal cord injury; engaging in safety studies of intramedullary transplantation of human neural stem cells; developing treatments for thoracolumbar spine fractures; and creating viable treatments for complex patients with degenerative cervical myelopathy.

Research into SCI is a main focus and remains a crucial part of our mission. One technique that has shown particular promise in the central nervous system is the use of gene therapy or genetic transfer agents. Ground-breaking studies more than three decades ago demonstrated the intrinsic capacity of injured neurons to regenerate. At the same time, a rapid evolution and comprehension of stem cell biology and application has evolved. As a result, there has recently been considerable interest in the use of cellular therapies, including stem cells, for traumatic SCI to improve neurological recovery and outcomes – with Jefferson Health leading the way.

I invite you to explore in the pages ahead some of the ways we're working to enhance the quality of life of our SCI patients.

Sincerely,



A handwritten signature in black ink that reads "Robert H. Rosenwasser". The signature is fluid and cursive, with a long horizontal flourish at the end.

Robert H. Rosenwasser MD, MBA, FACS, FAHA
Jewell L. Osterholm, MD, Professor and Chair, Department of Neurological Surgery
Professor of Radiology, Neurovascular Surgery, Interventional Neuroradiology
President/CEO: Vickie and Jack Farber Institute for Neuroscience
Medical Director, Jefferson Neuroscience Network
Senior Vice President, Jefferson Enterprise Neuroscience

CELL-BASED THERAPIES AND SPINAL CORD INJURY RESEARCH

The search for innovative therapies is the mission of Jefferson Health's spine program at the Vickie and Jack Farber Institute for Neuroscience. With the beginning of a new year, Jefferson continues to look for new treatments and discoveries for spinal cord injuries (SCIs), which affect more than 10,000 people annually in North America alone, with a prevalence of over a million people.

Spinal trauma is an area in which Jefferson Health has significant expertise. Our neurosurgeons are part of a spine care program that has been recognized as a high-volume Center of Excellence for more than 30 years. We are a Level 1 Trauma Center and Regional Spinal Cord Injury Center, and as such, treat more than 2,000 patients annually—far exceeding any other program in the region.

Our neurosurgeons are active in clinical research initiatives to investigate new technologies and techniques to treat SCIs, and we continually coordinate and participate in clinical trials for the benefit of our patients. While pathophysiology of SCIs has evolved over the last 50 years, patients continue to have major neurological impairment and quality of life issues. We are exploring innovative treatments, from electrical therapy to pharmacology, with research into cell-based therapies emerging as a promising treatment.

Some research projects in stem-cell treatment and other therapies for SCI at Jefferson Health include:

- Promising advances in targeted cellular based therapies: treatment update in spinal cord injury
- Emerging safety of intramedullary transplantation of human neural stem cells in chronic cervical and thoracic spinal cord injury
- A phase I/IIa clinical trial of a recombinant rho protein antagonist in acute spinal cord injury
- Evaluation of clinical experience using cell-based therapies in patients with spinal cord injury
- Natural history, predictors of outcome, and effects of treatment in thoracic spinal cord injury: a multi-center cohort study from the North American Clinical Trials Network
- Managing the chronic SCI such as degenerative cervical myelopathy: completion of randomized surgical protocol and pharmacologic trial
- Hypothermia treatment to cool and restore neurologic function to the injured spinal cord
- And more trials are emerging each week

Exciting and Dynamic Research Is the Cornerstone of Jefferson Health's Neurosurgeons

One of Jefferson Health's pioneering researchers, James S. Harrop, MD, Chief, Division of Spine and Peripheral Nerve Surgery; Neurosurgery Director of Delaware Valley SCI Center; and Neurosurgery Director for Adult Reconstructive Spine, and the SCI team, are engaged in leading-edge research and treatment of SCI.

Our neuroscientists participate in breakthrough multidisciplinary research, some of which is looking into the use of cell therapies. Recent experimental data suggests that cell delivery can replace and repair lost and degenerating cells, especially when multi-agent approaches are taken.

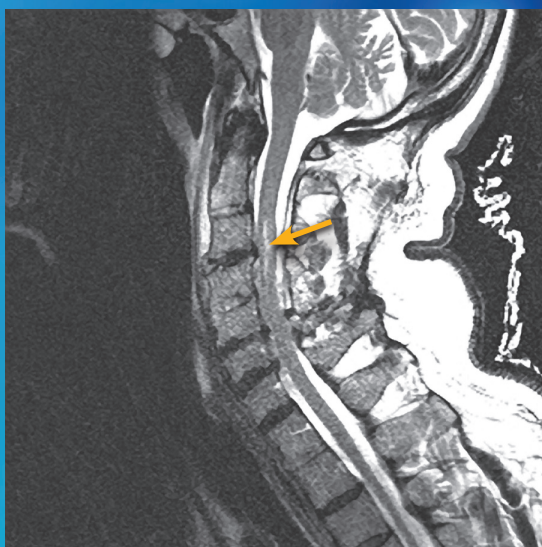


Figure 1: Sagittal T2-weighted MRI demonstrating post spinal cord injury with increased signal and edema within the cervical cord (arrow) along with superimposed cervical stenosis



Figure 2: Intraoperative lateral radiograph demonstrating post-surgical instrumented posterior cervical fusion hardware

Source: James S. Harrop, MD

TYPE OF CELL-BASED THERAPIES	BENEFITS	DISADVANTAGES	DISCUSSION
Marrow stromal cells	<ul style="list-style-type: none"> • Has neuroprotective properties • Demonstrates ease of harvesting and implantation • Improved invasive techniques 	<ul style="list-style-type: none"> • Not resulted in exceptional clinical improvements • Effectiveness in differentiating into NSCs and reconstituting normal spinal cord architecture has not been clearly demonstrated 	<ul style="list-style-type: none"> • Bone marrow derived stem cells are well-studied in phase I trials • Show limited morbidity • Results confounded by small sample size, lack of a control, relatively short term follow-up, and general phase I design
Olfactory ensheathing cells (OECs)	<ul style="list-style-type: none"> • Derived from nasal mucosa • Promotes recovery & relaying information across injury sites • No AEs in phase I results 	<ul style="list-style-type: none"> • Patients require immunosuppression, raising possibility of morbidity 	<ul style="list-style-type: none"> • OECs alternative option for transplant consideration • Suffer from limitations of graft morbidity and limitations in the small neural cell stock derived from nasal mucosa.
Schwann Cells	<ul style="list-style-type: none"> • Harvested from peripheral nerve (sural nerve or single intercostal nerve) with limited patient morbidity (ie, loss of sensation) • Safe intradural placement of autologous Schwann cells in the post-SCI environment, without outcome data 		<ul style="list-style-type: none"> • Further reports on Schwann cell use will be expected upon the conclusion of Phase I studies initiated at major US institutions
Neural Stem cells	<ul style="list-style-type: none"> • Directly harvest from human fetal tissues or from pluripotent sources such as human embryonic stem cells (ESCs) harvested from a blastocyst or from an induced pluripotent stem cell (iPSC) • Promising source for cell replacement • Capacity to replace lost neural cells 		<ul style="list-style-type: none"> • First multicenter trial in the US involving transplantation of cellular therapy for SCI

Figure 3: Cell-based Therapies¹

Numerous important questions critical to cell therapy remain to be solved through preclinical translational and clinical studies. However, cell implantation will ultimately be part of a multi-agent approach to SCI that will include the use of neuroprotection, modulation of the inflammatory response, biomaterials, and optimized activity to shape post-injury plasticity. Spinal cord repair is an exciting discipline whose discoveries may have broader application for several neurological diseases.

Here is a look at several studies published recently.

STUDY #1: Evaluation of clinical experience using cell-based therapies in patients with spinal cord injury: a systematic review²

Currently, there is continued interest in the use of cellular therapies, including stem cells, for traumatic SCIs to improve neurological recovery and outcomes. Jefferson Health was involved in a systematic search and critical review of the literature published through mid-January 2012 looking at cellular therapies for traumatic SCI. Those where cellular therapies employed in humans with SCI were reviewed:

- Bone marrow mesenchymal and hematopoietic stem cells (8 studies)
- Olfactory ensheathing cells (2 studies)
- Schwann cells (1 study)
- Fetal neurogenic tissue (1 study).

Several different cellular-mediated strategies for adult SCI have been reported to be relatively safe with varying degrees of neurological recovery. This is an innovative strategy and there continues to be a need for improved preclinical studies and prospective, controlled clinical trials.

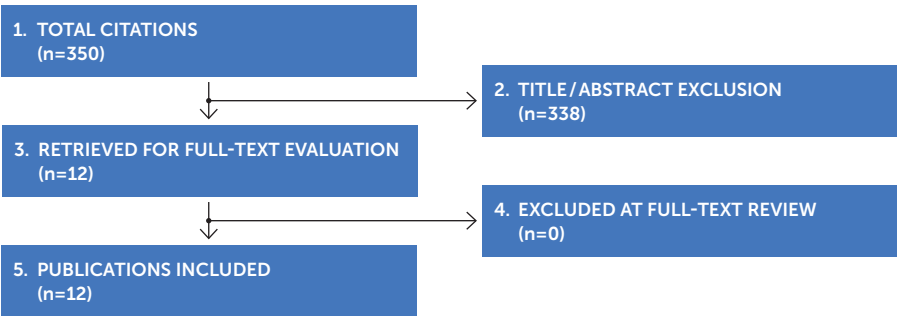


Figure 4: Flowchart showing the results of the literature search used in this study²

"Cell-based therapies hold promise for a host of neurological diseases. In my lab, we are developing technology that derive stem cells non-invasively through skin samples—a type of stem cell called induced pluripotent stem cell. These cells can be expanded in tissue culture, then differentiated into any cell type (ie, nerve cells). They are transplanted back into the spinal cord injury donor who provided the skin sample, which removes the need for chronic administration of toxic immune suppression drugs to the transplant recipient. This is just one of the techniques that Jefferson is using to help these patients."

—Angelo C. Lepore, PhD
Director, Neuroscience Graduate Program
Associate Professor, Department of Neuroscience

STUDY #2: Emerging safety of intramedullary transplantation of human neural stem cells in chronic cervical and thoracic spinal cord injury³

Spinal cord injuries do not self-repair, so cellular replacement or regenerative strategies are critical in these types of injuries. There are a number of cellular therapies based on pluripotent and multipotent cell sources that show therapeutic promise. There is ongoing concern of tumorigenesis with cells derived from ES cells (i.e., pluripotent stem cells). Human neural stem cells, or neural progenitor cells (NPCs), in contrast, are multipotent and have the potential to self-renew and differentiate into central nervous system (CNS) cell types.

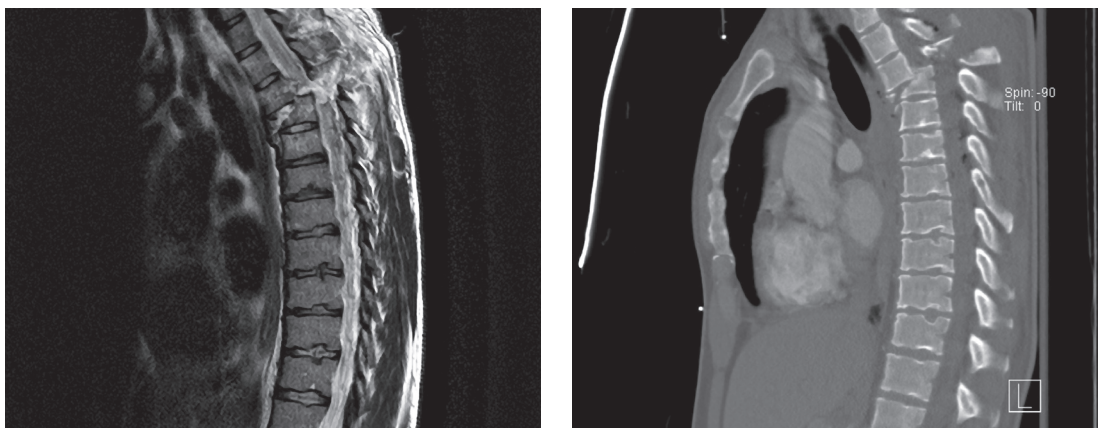


Figure 5: (Left) Sagittal T2-weighted MRI and (Right) CT scan demonstrating a thoracic flexion-distraction injury (fracture dislocation) causing severe spinal cord compression

Source: James S. Harrop, MD

As part of a multi-site phase I/II thoracic study and phase II cervical study, neurosurgeons at Jefferson Health's Thomas Jefferson University Hospital performed an intramedullary free-hand (manual) transplantation of HuCNS-SC cells in subjects with thoracic (n=12) and cervical (n=17) traumatic SCI. No safety concerns were considered related to the cells or the manual intramedullary injection.

The study showed that a total cell dose of 20 M cells via 4 and up to 40 M cells via 8 perilesional intramedullary injections after thoracic and cervical SCI, respectively, proved safe and feasible using a manual injection technique. This study demonstrated a surgical approach and free-hand technique for HuCNS-SC administration after chronic SCI. Injection of HuCNS-SC into perilesional tissues above and below the thoracic and cervical SCI demonstrates an excellent safety profile. While various methods for cell delivery are under study, our surgical experience with a free-hand technique appears to be well-tolerated, feasible, and scalable for larger clinical trials. Further studies to investigate and confirm biological activity and clinical efficacy are being prepared.

REFERENCES

1. Ghobrial GM, Haas CJ, Maulucci CM, Lepore A, Fischer I, Harrop JS. Promising advances in targeted cellular based therapies: treatment update in spinal cord injury. *J Stem Cell Res Ther.* 2014; 4(2)
2. Harrop JS, Hashimoto, Norvell D, Raich A, et al. Evaluation of clinical experience using cell-based therapies in patients with spinal cord injury: a systematic review. *J Neurosurg Spine.* 2012; 17:230-246
3. Levi A, Okonkwo DO, Park P, Jenkins AL, Kurpad SH, Parr AM, Ganju A, Aarbi B, Kim D, Casha S, Fehlings, MG, Harrop JS, et al. Emerging safety of intramedullary transplantation of human neural stem cells in chronic cervical and thoracic spinal cord injury. *Neurosurgery*; 2018; 82:562-575.



Vickie and Jack Farber Institute for Neuroscience Jefferson Health®

Patient Appointments: 1-800-JEFF-NOW

Patient Transfers: 1-800-JEFF-121

Physician Referrals: 215-503-5700

JeffersonHealth.org/Farber

PHILADELPHIA • MONTGOMERY COUNTY • BUCKS COUNTY • SOUTH JERSEY