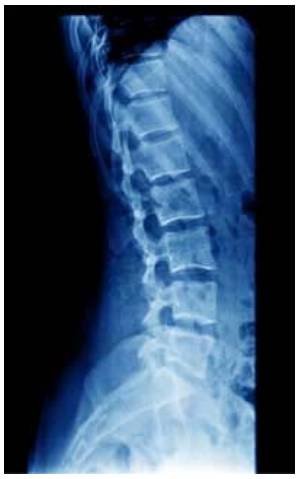
Cellular Therapy for Spinal Cord Injury

Cellular therapy for spinal cord injury, or SCI, is a hot topic in regenerative medicine. It invokes images of paralysis victims walking away from their wheelchairs and is a highly visible research area in which successes and failures could buoy or depress perception and support for stem cell therapy and regenerative medicine. Recently, two announcements of cellular therapy projects to treat SCI have been widely reported in the news. Stem Cells, Inc., based in Newark, Calif., announced interim results of its phase I/II trial of a preparation of human fetal neural stem cells, while the Miami Project to Cure Paralysis was approved to conduct a phase I clinical trial to test an autologous Schwann cellular therapy. To understand why there are so many approaches to treat this type of injury, and to appreciate the progress made so far, it is important to understand the nature of the injury.



The Complexities of Spinal Cord Injury

The bundles of nerve fibers responsible for conducting electrical signals up and down the spinal cord are part of a complex organization of support cells, blood vessels, protective membranes, and cerebrospinal fluid. These tissues nourish, protect, and assist in the function of nerve cells. For example, oligodendrocytes create the myelin that ensheaths and insulates the axon of each neuron. Without myelin, the axon fails to conduct electrical signals appropriately and can atrophy. Another support cell, the astrocyte, supplies neurons with nutrients and oxygen and insulates adjacent neurons from each other. These cells also perform functions of the immune system by destroying pathogens and removing dead and dying neurons.

Traumatic injury substantial enough to sever the nerve fibers destroys the surrounding tissues and support cells. Loss of support cells can cause ongoing death of neurons that occurs after the initial trauma. To make matters worse, traumatic spinal cord injury is followed by aggressive processes the body employs to limit tissue damage: inflammation brings cells that prevent infection and clear away damaged tissue; and scar tissue is formed to seal the wound site. This process creates a cystic cavity that interrupts the fiber of nerves and support cells. The scar tissue prevents the extension of new axons and neural support cells into and across the gap. Downstream neurons that are cut off from transmitting excitatory signals regress and atrophy, disconnecting from muscles at their termini. As time goes by, regeneration of new functional nerve fibers becomes more challenging.

To treat spinal cord injury, many different strategies can be deployed. A first plan of action is to reconstruct the injury site and protect surviving neurons and support cells from damage due to the processes that occur in the aftermath of injury. A second strategy is to replace the neural support cells to create an environment that enables natural recovery of the nerve fibers. A third strategy is to replace the lost neurons and guide the extension of their axons to form functional synapses. Each of these therapies also can incorporate strategies to remodel the injury site such that the gap may be bridged by functional nerve fibers. For example, enzymes can be deployed to reduce and remodel the scar tissue. Clinical trials of cellular therapy for spinal cord injury fall into one or more of these categories.

Cellular Therapy Clinical Trials: Protection of Surviving Tissues

Mesenchymal stem cells isolated from bone marrow, umbilical cord blood, and adipose tissue are known to moderate the body's immune response. In that way, mesenchymal stem cells can protect living tissue during an immune reaction. These cell types have been tested in clinical trials for immune related disease such as rheumatoid arthritis, chronic foot ulcers, and type 1 diabetes. In addition to protecting surviving tissues, mesenchymal stem cells are known to secrete factors that can stimulate regeneration of damaged tissues by native cells.

Injection of mesenchymal stem cells has enhanced recovery in animal models of spinal cord injury. Seventeen clinical trials employing an injection of mesenchymal stem cells as part of the therapy for spinal cord injury have been initiated around the world. According to two recent reviews on the topic, these studies have shown that the procedure has a good safety profile, but has not caused large improvements in functional recovery.[1,2] Furthermore, the collective results are difficult to interpret because of a lack of consistency among the studies.[1] "Mesenchymal stem cells are neuroprotective and secrete neurotrophic factors, but the data is not convincing that they can cause regeneration of damaged neurons in the patient or enact a cure," said Michael Fehlings, MD, FRCSC, PhD, of the Toronto Western Research Institute. "Their biggest effect may be immunomodulation at the injury site." Such results suggest that mesenchymal stem cells could be useful as adjunctive therapy for other regenerative approaches, to protect both remaining host tissue and grafted cells.

Cellular Therapy Clinical Trials: Replacing the Support Cells

A well-known clinical trial for spinal cord injury garnered headlines for being the first clinical trial of a cellular therapy derived from embryonic stem cells. This trial, launched by Geron in 2009, employed progenitor cells that form oligodendrocytes after implant at the site of injury. As support cells, these oligodendrocytes were intended to protect existing neurons and replace their lost myelin. After the first few patients were treated, Geron in June 2011 publicized that the cellular therapy had a good safety profile, but then halted the trial five months later ostensibly for commercial reasons. The trial was designed for patients with 'complete' thoracic spinal cord injury, to be treated within a week of injury whereas the published preclinical studies preceding the clinical trial used animals with incomplete spinal cord injury.

Stem Cells, Inc., in 2011, launched a clinical trial of human fetal neural stem cells in Switzerland with a different trial design than that used by Geron. Human fetal neural stem cells are shown to mature into oligodendrocytes, astrocytes, and neurons in the lab but they tend to form oligodendrocytes after spinal implantation.[3] This company generated headlines in September of this year with the announcement that two of the first three patients to receive the therapy regained sensation of touch, temperature and electrical stimulation on the abdomen below the injury site. The primary purpose of treating the first cohort of patients, which had severe spinal cord injury, was to evaluate the safety of the procedure. "Neural stem cells are pretty good at replacing oligodendrocytes and myelinating denuded axons in the host spinal cord and brain," explains Fehlings. "In animal models, if there is some preservation of neural cells, myelination by oligodendrocytes does support some recovery. Phase I clinical trials, however, enroll patients with thoracic injury that is more severe and more chronic than what is seen in the animal models. After demonstration of safety to the more severely injured patients, clinicians could move to patients with incomplete injury." The Stem Cells, Inc., trial has since been expanded to include patients with incomplete spinal cord injury and at different levels of the spinal cord. It is possible that these patients could exhibit greater recovery.

In another recent headline, the Miami Project to Cure Paralysis received U.S. FDA approval to begin a phase I clinical trial employing a similar support cell, the Schwann cell. Schwann cells are the equivalent in the peripheral nervous system to the oligodendrocytes in the central nervous system. Like oligodendrocytes, these cells nourish neurons and create the myelin sheath that insulates the axons, accelerating their transmission speed. In this trial, Schwann cells are harvested from a leg of the patient, expanded in culture for a period of weeks, and transplanted to the injury site. Dr. Lawrence Moon of King's College London described the advantages of Schwann cells, noting that these cells are relatively easily obtained, have a long research history in animal models including non-human primates and mini-pigs, and have been demonstrated to be safe and beneficial, especially when combined with other therapies. After harvest however, these cells must be expanded in culture for weeks before implant to the injury site and the optimal time for transplantation in humans will need to be identified empirically. Like other phase I trials of patients with severe thoracic spinal cord injury, the primary goal of this autologous approach is to determine the safety of the procedure in humans.

Neurons that are responsible for transmitting the sense of smell reside in the nasal epithelium and extend axons to a structure in the brain termed the olfactory bulb. These neurons regenerate and extend new axons throughout life. Olfactory neurons are nourished by a special type of support cell called the olfactory ensheathing cell, or OEC. A clinical trial of OECs as cellular therapy for SCI began in Australia in 2005.[4] In this trial, OECs were harvested from the nasal epithelium, grown in the lab for a period of weeks, and injected into the spines of patients with complete thoracic spinal cord injury. Like the trials employing oligodendrocytes, this trial demonstrated the procedure to have a good safety profile, but in this case did not show significant gains in neural function except that one of the treated patients had an increase in light touch and pin prick sensation below the injury. A second phase I clinical trial employing OECs is underway at the Wroclaw Medical University in Poland, according to www.clinicaltrials.gov.

Moon explained that the use of OECs present their own challenge. "OECs are more difficult to harvest through surgery," he said. "In addition, the preparations of OECs following surgery vary among labs and therefore are difficult to compare. However, because many independent researchers have shown benefits of OEC transplantation in various animal models of SCI, it will be exciting to see how the clinical trials proceed."

Cellular Therapy Clinical Trials: Replacing and Guiding New Neurons

With the exception of the fetal neural stem cells that have the potential to form functional neurons, a cellular therapy clinical trial employing a replacement neuron, as opposed to a neural support cell or mesenchymal cell, has not been reported. Such a clinical trial may be on the horizon, however, as this September an international research team published data that neural stem cells derived from fetal spinal cord matured into functional neurons, extended axons over long distances, and mediated partial recovery in a rat model of complete spinal cord injury.[5] That study used cells generated by Neuralstem, Inc. Neuralstem has applied to the FDA for the go-ahead to perform a human clinical trial of this therapy.

Conclusion

Currently, several clinical trials are underway to evaluate cellular therapy interventions for spinal cord injury. It is unclear, however, how close this effort is to developing a therapy that will allow a patient of chronic spinal cord injury to recover fully. "Cellular therapies show promise, but it is important to differentiate hype from hope," said Fehlings. "Cellular therapy may mediate partial recovery but it is unlikely that it will cause complete cure. However, benefits such as improved control over limbs, less neuropathic pain, and better control over autonomic functions can have a significant impact on patient quality of life."

Considering the heterogeneity of cells that can be used as a cellular therapy for spinal cord injury, and the heterogeneity in their mechanisms of action, a combinatorial therapy that includes one or more cell types and/or drug therapies might be most effective. Such a combinatorial therapy could include creating an optimal milieu for tissue recovery that includes mesenchymal stem cells, and the use of support cells and replacement neurons to form relays across the lesion. "Combination therapy is likely to be more effective than monotherapy strategies," said Moon. "However, overcoming regulatory hurdles is more difficult. Although monotherapy will likely have a smaller clinical benefit, the shorter term goal is to demonstrate safety and efficacy so that they can be used in combinatorial therapies in future clinical trials."

Optimal combinatorial strategies could be devised if the safety profiles and the optimal use of each cellular therapy in the context of patient recovery were better understood. That goal probably is within reach because the information gathered in these novel clinical trials will inform scientists working to optimize regenerative therapies for spinal cord injury.

1. Ruff CA, Wilcox JT, Fehlings MG. Cell-based transplantation strategies to promote plasticity following spinal cord injury. Exp Neurol 2012;235:78-90.
2. Thomas KE, Moon LD. Will stem cell therapies be safe and effective for treating spinal cord injuries? Br Med Bull 2011;8:127-42.
3. Fehlings MG, Vawda R. Cellular treatments for spinal cord injury: The time is right for clinical trials. Neurotherapeutics 2011;8:704-20.
4. Mackay-Sim A, St John JA. Olfactory ensheathing cells from the nose: clinical application in human spinal cord injuries. Exp Neurol 2011;229:174-80.
5. Lu P, Wang Y, Graham L, et al. Long-distance growth and connectivity of neural stem cells after severe spinal cord injury. Cell 2012;150:1264-73.

Return to AABB CellSource Fall 2012