A Comprehensive Combinatorial Approach: Modulation of the Spinal Cord Microenvironment to Induce Regeneration Using Epidural Stimulation with Scaffolds Containing Genetically Modified Schwann Cells

Anthony Windebank, MD; Igor Lavrov, MD, PhD; Nicolas Madigan, MB, BCh, BAO, PhD

Purpose
Current therapies for SCI are associated with limited functional recovery, due to events that occur in the secondary injury phase after the primary insult. These events include cell death, axonal loss, demyelination, glial scarring, inflammation, cyst formation, extracellular matrix (ECM) remodeling, and an increase in inhibitory molecules. Many therapies are currently being investigated to target one or more of these events. One approach has been to use epidural electrical stimulation (EES) to electrically stimulate the lumbosacral spinal cord to drive rhythmic motor circuitry.

EES can induce robust stepping behavior in transected rats. In clinical human trials, including one in progress by our group, EES has promoted voluntary movement, standing, and stepping-like behavior after motor training. However, it is unclear whether electrically bypassing the injury, or rebuilding functional tissue across the lesion to strengthen bidirectional axonal growth and signaling, leads to the best functional recovery.

Hypothesis
Combining epidural electrical stimulation with exercise and cell-loaded tissue engineered scaffolds will promote axonal regeneration and functional recovery after spinal cord injury.

Method of Research
We are using bioengineered, schwann cell-loaded hydrogel scaffolds to fill the gap formed after injury. The scaffolds also release the antifibrotic drug rapamycin. Our lab has shown that glial cell derived neurotrophic factor (GDNF) secreting Schwann cells, seeded in a positively charged oligo(poly(ethylene glycol)fumarate) (OPF+) scaffold, enhanced functional and anatomical recovery after SCI compared to transplantation of OPF+ scaffold alone and OPF+ scaffold with wild type Schwann cells. The use of OPF scaffolds can also be enhanced through the incorporation of the anti-fibrotic drug rapamycin into the OPF in microspheres in addition to the seeded Schwann cells. In the proposed study groups of rats will be treated with scaffolds (loaded with cells and rapamycin) and compared with rats treated with the same cell-loaded scaffolds combined with post-operative exercise and EES. Post-operative function will be studied for 6 weeks after injury using computer assisted evaluation of motor function, electrophysiology and histomorphometry.

Expected Results
This combinatorial approach will promote functional recovery.