Minimally Invasive Magnetic Resonance Imaging-Guided Delivery of Neural Stem Cells into the Porcine Spinal Cord

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Target Audience: Translational neuroscientists and clinicians interested in minimally invasive therapeutic delivery to the spinal cord parenchyma

Purpose: Stem cell-based therapies are under clinical evaluation for the treatment of a range of degenerative and traumatic diseases of the spinal cord, such as Amyotrophic Lateral Sclerosis (ALS), Spinal Cord Injury (SCI), and Multiple Sclerosis (MS). These indications are met with limited treatment options and a poor prognosis. Transplantation of cellular therapeutics to the spinal cord is conventionally done with either systemic administration or local injection following surgical exposure of the spinal cord[1]. Our group developed an MR-compatible spinal cord injection system capable of replacing invasive surgical procedures. **The purpose of this study was to demonstrate the proof-of-principle for minimally invasive, percutaneous transplantation of stem cells into the spinal cord of a live pig under MRI guidance.**

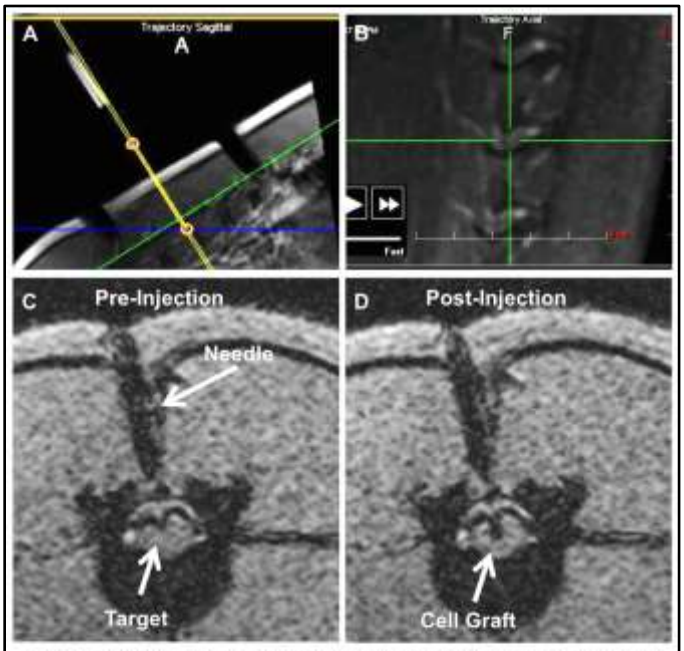

Figure 1: MR-Guided Intraspinal Stem Cell Transplantation in the Porcine Spinal Cord. Intraoperative T1-weighted images were acquired after device attachment and used to plan a trajectory to the spinal cord with the Clearpoint software (**A**). Target pathway reconstruction showed the trajectory through the inter-laminar space (**B**). Minimal intensity projections (MIP) of GRE T2*-weighted images showed the infusion needle in the spinal cord (**C**) before injection and after a magnetic nanoparticle-labeled human neural progenitor cell graft was injected (**D**). MIPs of three slices were made in Osirix.

Methods: An MRI-compatible injection platform was designed to attach to the ClearPoint SmartFrame device[2] (MRI Interventions, Inc.) and rigidly fixate to the spine with custom-made titanium percutaneous pedicle screws. The procedure was done on a 3T Siemens Trio Trim full-body MRI scanner. Briefly, a female Göttingen minipig (15 kg) was placed in the scanner in the prone position in a sling to reduce respiratory motion under general anesthesia. Appropriate sterile preparation and draping was done over the thoracolumbar spine. The platform was attached to the vertebra rostral and caudal to the target site. Two phased-array body coils were sterile draped and placed over the region. Pre-entry sagittal T2 TSE, sagittal T1 3D, and axial T2* GRE images (TE/TR=10/159 msec, Flip Angle=30°, Averages=4, Resolution = 0.9 x 0.9 x 1.5 mm) were acquired over the fiducial markers of the system and the spinal cord. The ventral horn of the spinal cord was chosen as the target and a trajectory was planned using software that calculated angular and planar adjustments to be made by on the device to align the actual trajectory to the planned trajectory and target (**Fig. 1A**). The trajectory traversed the interlaminar space (**Fig. 1B**), allowing access to the spinal cord through the bony elements of the spine. A ceramic cannula with a titanium stylet was advanced along the trajectory to the surface of the dura mater. The stylet was removed and GRE imaging confirmed the cannula was along the correct trajectory. A fused silica glass injection needle was passed through the cannula and in to the ventral horn of the spinal cord (**Fig. 1C**). The tip of the injection needle is not visible under MRI. 250,000 human neural progenitor cells (hNPC)[3] labeled with ferumoxytol magnetic nanoparticles were infused into the spinal cord. Post-injection GRE imaging was performed and the system was removed from the animal. After recovery from anesthesia, the animal was monitored until euthanasia 21 days after surgery. The spinal cord was removed by necropsy, serially sectioned and stained for the presence of ferumoxytol labeled cells with Perl's Prussian blue. Baseline and follow-up neurological exam including sensory stimulation and locomotor function of all four limbs was performed.

Figure 2: Histological Identification of Transplanted Cell Graft. Perl's Prussian blue staining (blue) with background Eosin stain showed a ferumoxytol-labeled hNPC graft located in the ventral horn. 4X mag.

Results: Immediately following injection, a hypointense focus representative of the negative contrast produced by ferumoxytol-labeled hNPCs was observed in the spinal cord (**Fig 1D)**. No neurological deficits were observed following injection and recovery from anesthesia. Histochemical staining for Iron with Perl's Prussian blue revealed the iron from the hNPC graft located on target in the grey mater of the ventral horn (**Fig. 2**), confirming the signal observed on MRI.

Conclusions: We report on the first MRI-guided, percutaneous stem cell transplant into the spinal cord. This supports the proof-of-principle for transplantation of stem cells into the spinal cord of a large animal under the guidance of MRI. Additional studies are underway to assess the safety and accuracy of the procedure in repeated experiments. This MRI-guided, minimally invasive approach could be used to directly deliver therapeutics to the spinal cords of patients with ALS, SCI lesions, or MS plaques without the need for an invasive surgical procedure.

References: 1. Riley J et al. *Neurosurgery,* 2013. 2. Starr PA et al. *J. of Neurosurgery,* 2010. 3. Klein SM et al. *Human gene therapy,* 2005.