Sponge-mediated Lentivirus Delivery to the Chronically Injured Spinal Cord

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Introduction: Transgene delivery to the spinal cord has traditionally required either injection of a gene therapy vector[1] or implantation of a gene-delivering biomaterial[2] directly into the spinal cord. However, both methods have the potential to (re-)injure the spinal cord beyond the delivery site. Here, we characterize the ability of porous sponges to deliver lentivirus when placed on top of spinal cord tissue, which can reduce the trauma required for gene therapies.

Methods: Lentivirus (1-4 x 10^7 particles) encoding for firefly luciferase was adsorbed onto the surface of a gelatin (Gelfoam®; Pfizer, New York, NY) or poly-(ethylene glycol) sponge and evaluated for its ability to transduce cells and promote transgene expression *in vivo* in the mouse spinal cord. In brief, a laminectomy was performed to expose the spinal cord to allow for placement of the lentivirus-delivering sponge. To assess performance after an acute injury or chronic injury, a Hemisection lesion was performed at or rostral to the delivery site and a porous, poly(lactide-co-glycolide) multiple channel bridge was placed inside the gap to create a defined injury site as in previous studies[2]. All animals were treated according to the animal care and use committee at Northwestern University.

Results: Placement of the lentivirus-delivering sponge on the uninjured spinal cord achieved over 12 weeks of transgene expression (Figure 1a), over one-third of which resided in spinal cord tissue directly underneath the delivery site (Figure 1b). Histological analysis revealed transduced cells were found throughout—from the central canal to the dorsal root (Figure 1c-f). Morphological analysis revealed multiple cell types present in the uninjured spinal cord were transduced, which was confirmed with antigen-specific staining. Studies revealed robust gene expression could be generated when the lentivirus-delivering sponge was placed immediately (acute) or 4 weeks (chronic) after induction of the injury, whether the sponge was placed above or caudal to the injury site.

Conclusions: Using this strategy, we were able to deliver transgenes to uninjured, acutely injured, and chronically injured spinal cords with minimal potential damage to the parenchyma. Furthermore, these sponges can be placed anywhere along the spinal cord to create trophic factor gradients that peak at or beyond the injury site to tailor gene expression profiles. In this way, this platform can develop translatable therapies for spinal cord injury.

References:

1. Taylor L et al. J Neurosci 2006;26(38):9713-21.
2. Thomas AM and Shea LD. J Controlled Release. 2013;170(3):421-9.

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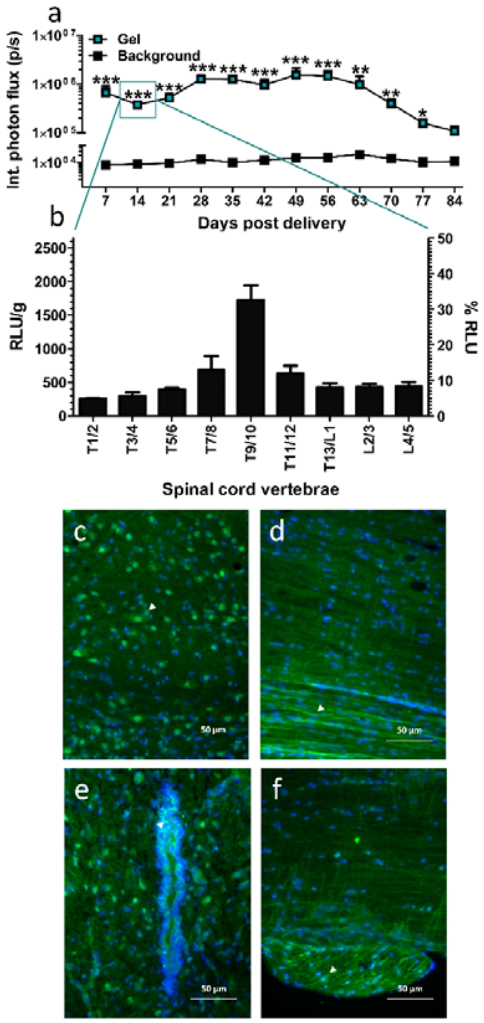

Figure 1. Transgene expression of firefly luciferase in the uninjured spinal cord using the gel-mediated lentivirus delivery platform. (a) Gene expression levels assessed using the *In Vivo* Imaging System for over 12 weeks after delivery. (b) Location of expression along the spinal cord 2 weeks after delivery using a luciferase assay. (c-f) Transduction of cells present in the spinal cord reside in the (c) grey matter, (d) white matter, (e) central canal, and (f) dorsal root.