Local Hydrogel Delivery to the Spinal Cord

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Statement of Purpose:

Local delivery to the spinal cord is hampered by the blood-spinal cord barrier, necessitating local delivery strategies. Both bolus injection and external pump/catheter technologies are limited by the lack of tissue penetration and infection. We have developed a novel, minimally-invasive hydrogel delivery strategy that provides sustained local release of the therapeutic molecules at the site of injury. The hydrogel, a physical blend of hyaluronan and methyl cellulose, met a series of design criteria and had some therapeutic effect in animal models of spinal cord injury. Herein, our focus is on the use of this hydrogel for the delivery of therapeutically-relevant models and its design for longer release.

Methods:

Hyaluronan and methyl cellulose were sterile-filtered and then lyophilized prior to dissolution in an artificial cerebrospinal fluid, buffered solution (aCSF). The hydrogel consists of 2 wt% HA and 7 wt% MC and is called HAMC. The blend was studied in terms of its rheological properties *in vitro* and its degradation *in vivo* using fluorescent markers.

To examine neuroprotective strategies, erythropoietin (EPO) was dissolved in HAMC and studied in terms of EPO release *in vitro* and its therapeutic benefit *in vivo*. EPO delivered in HAMC to the intrathecal cavity (IT) that surrounds the spinal cord was compared to intrathecal HAMC alone, intrathecal EPO alone and EPO delivered in the intraperitoneal cavity (IP).

To examine neuroregenerative strategies, nanoparticles have been incorporated into the HAMC design, thereby providing a mechanism for longer release, and HAMC itself has been modified to enhance its stability *in vivo*. PLGA nanoparticles are used to encapsulate neuroregenerative factors and their release has been followed *in vitro*.

Results:

HAMC is a viscoelastic solid that forms a gel at room temperature due to the salting out of MC by HA. The gel maintains its injectable properties due to the shear thinning nature of HA.

HAMC, injected *via* 30-gauge syringe into the intrathecal space, degrades within 7 days in rat animal models of compressive spinal cord injury. By comparing the injection of HAMC to that of aCSF, those animals injected with HAMC had less tissue lost, a reduced inflammatory response, and a greater functional outcome in terms of locomotor function (1).

The delivery of EPO in HAMC in the intrathecal space showed less tissue lost than injection of HAMC alone and greater neural sparing than injection of EPO alone in either the intrathecal space or the intraperitoneal space (2).

Polymeric nanoparticles of PLGA encapsulated therapeutically-relevant biomolecules and demonstrated their controlled release over a 30 day period. A similar release profile was observed when these nanoparticles were incorporated in HAMC and a modified HAMC with a longer degradation time. Figure 1 shows how the release of several biomolecules is affected by their encapsulation in PLGA nanoparticles or their dispersion in HAMC alone.

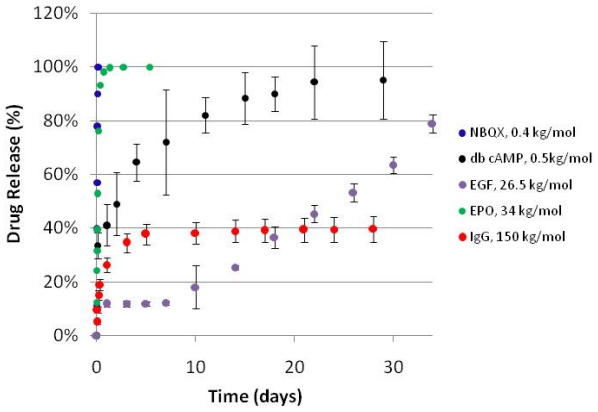

Figure 1: NBQX, dbcAMP and EPO are released from HAMC alone whereas EGF and IgG are released from PLGA nanoparticles, which results in a longer, controlled release period.

Conclusions: A novel, minimally-invasive, local delivery strategy has been pioneered to allow the delivery of therapeutically-relevant biomolecules to the injured spinal cord. The delivery method and the materials chosen have been shown to be safe and efficacious. The release can be controlled by the inclusion of nanoparticles in the injectable hydrogel.

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References:

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