Multifunctional Hydrogel Nerve Guidance Scaffolds for Central and Peripheral Nerve Repair

Paralysis is a devastating condition with no viable therapy. In 2004, approximately 1.9% of the U.S. population reported living with some form of paralysis. Those afflicted are financially burdened by the excessive cost of treatment, and often report a lower quality of life. Thus, there is a clear and compelling need to develop a viable therapy for spinal cord and peripheral nerve injuries. The goal of this doctoral work is to design, fabricate, functionalize, and study in vivo nerve guidance scaffolds (NGS) capable of guiding and promoting neuronal regeneration after injury. To this end, this work represents progress towards the development of the ideal NGS exhibiting drug delivery potential.

NGS were designed and fabricated using a novel templating process exhibiting hexagonally close-packed, linear microchannels. The implant has clinically relevant dimensions, and consists of agarose; an ultraporous, biocompatible hydrogel. NGS were fabricated from the selective etching of multicomponent fiber optic bundles (MCFB). By modifications to the MCFB, the microchannel diameter and spacing were tailored to vary the open area available for nerve ingress between 40-80%. In addition, the microchannels were determined to be linear and discrete throughout the length of the implant. To scale the technology to human clinical size of 2cm, however, it was necessary to fabricate MCFBs
exhibiting relatively stiffer PMMA cores, which significantly improved the microchannel linearity.

To promote axonal regeneration in vivo, acellular release of growth factors, such as brain derived neurotrophic factor (BDNF), must be provided over periods of weeks at a 50 ng/mL daily concentration. Lysozyme, an analog of BDNF, was released from hydrogen-bonded layer-by-layer (LbL) deposited onto the surface of agarose hydrogel. LbL is a surface deposition technique that utilizes alternating stacks of pH-responsive polymers capable of delivering drugs. Because LbL is a surface deposition technique, its drug delivery potential could be improved by tailoring the hydrogel surface area. The addition of sucrose during agarose gelation was found to augment the pore structure of the hydrogel, creating smaller and more uniform pores. Consequently, the surface area of the hydrogel increased, as measured by nitrogen adsorption and scanning electron microscopy. As the surface area of the hydrogel increased, more agarose crosslinks were available for LbL deposition, resulting in a higher cumulative release of lysozyme. Although promising for drug delivery applications, the kinetics of LbL deposition and release were not fully understood. To investigate this, kinetic studies using lysozyme were conducted to characterize the effects of LbL assembly conditions and substrate diffusion distance on release dose. Incorporating these methods allowed LbL precursors to better permeate and deposit throughout hydrogel network, resulting in higher cumulative lysozyme release. The results of this work also demonstrated self-limiting deposition of LbL, as LbL uniformly deposited throughout the pore network.

Although lysozyme was believed to be an appropriate analog for BDNF due to its similar size and isoelectric point, release of BDNF from LbL has not been reported in literature. This dissertation is the first report of BDNF successfully delivered from LbL-coated hydrogel scaffolds, demonstrating dosages of over 5000 ng/mL-microchannel initially and 800-60 ng/mL-microchannel for two weeks. This LbL-released BDNF, when exposed to fibroblasts expressing tropomyosin receptor kinase B (TrkB), produced an over 8-fold increase in cell proliferation. Additionally, when implanted in vivo LbL-coated agarose NGS demonstrated biocompatibility, comparable to previous studies involving uncoated scaffolds.

By fabrication of multi-luminal agarose NGS capable of continuous BDNF release, a high density of regenerating axons can be guided and expediently grown across the injury site, providing a viable therapy for spinal cord and peripheral nerve injuries.
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