Hydrogel Implant Coatings for Peripheral Nerve Regeneration

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Statement of Purpose: Our previous work has shown that braided nerve conduits made of a new polymer (Fig. 1) are flexible, kink resistant and biocompatible [1]. In this study, we have developed hydrogel coatings that can prevent scar tissue infiltration by modulating the porosity of the nerve conduits. Here, we show the effect of two hydrogel coatings: (i) Hyaluronic Acid to which cells don't attach easily and (ii) Fibrin Glue to which cells can easily attach. The conduits coated with these hydrogel coatings were evaluated in a 1 cm rat sciatic nerve injury model for 16 weeks and assessed for nerve regeneration.

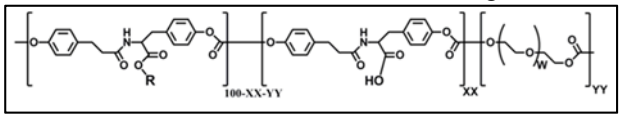

Fig. 1 General structure of tyrosine-derived polycarbonates. For E1001(1k): xx is 10% DT (desaminotyrosyl tyrosine) and yy is 1% PEG (poly(ethylene glycol)) of molecular weight 1kDa).

Methods: E1001(1K) was extruded from a single screw extruder to get thin polymer fibers. These fibers were then spooled onto braiding spindles. A tubular braiding machine equipped with 24 carriers was used to braid conduits over a 1.5 mm thick Teflon mandrel. A cell friendly fibrin glue (FG) hydrogel and a cell-repelling Hyaluronic Acid hydrogel were used to form a secondary coating onto the braided nerve conduits. In-vitro degradation and stability of these coatings was evaluated by SEM. For functional recovery in-vivo, 1 cm rat sciatic nerve injury model was used to assess the efficacy of these coatings by measuring the compound muscle action potentials (CMAP) at the dorsal and plantar foot muscles. Histomorphometric analysis was done by staining the midsections of the explants at 16-week endpoint by Toluidine Blue. Tibialis Anterior and Gastrocnemius muscles harvested at 16-week endpoint were evaluated for muscle weight recovery.

Results: The braided conduits fabricated had pore size varying between 15-100 µm. SEM micrographs of the HA and FG hydrogel coatings on the conduit surface show the uniform and smooth coverage of the macro-pores (Fig. 2A-C). The hydrogel coatings remain structurally intact till 6 weeks and degrade over the period of 16 weeks (Fig. 2D). FG coating degrades faster than HA coating. In terms of nerve regeneration, histological analysis of the 1µm midsections of the uncoated braided conduits at 16-weeks (Fig. 3A) showed a nerve cable with numerous axon bundles, but with large amount of scar tissue infiltration inside the lumen. Conduits coated with the FG coating (Fig. 3B) had extensive fibrous tissue infiltration inside the lumen without the presence of a nerve cable. In comparison, conduits coated with HA (Fig. 3C) outperformed by preventing scar tissue infiltration and with presence of an increased density of myelinated axons and a well-defined nerve cable inside the conduits. Animals implanted with conduits with HA coating showed significant recovery in the wet muscle mass, CMAP amplitude, nerve conduction velocity and axonal density when compared with uncoated and FG coated conduits. The hydrogel coatings did not affect the mechanical properties of the braided conduits.

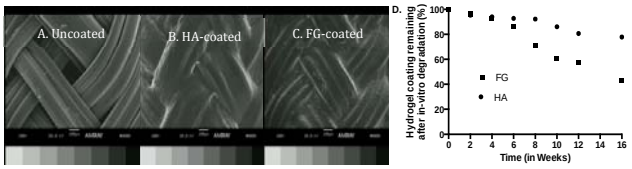

Fig. 2 SEM image of a (A) uncoated braided E1001(1K) conduit (B) HA coated conduit (C) FG-coated conduit (D) In-vitro percent mass loss of the hydrogel coatings till 16 weeks.

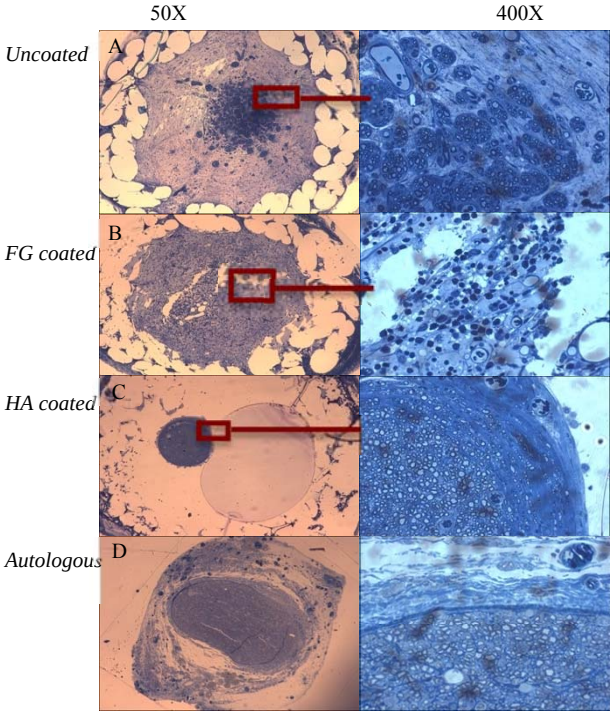

Fig. 3 Toluidine blue stained 1 µm thick cross sections of conduits explanted after 16 weeks in vivo. 50x images show the whole conduit and nerve cable (dark stain), 400x images show the interface between axonal tissue and surrounding inter-luminal area **(A)** Uncoated braid, **(B)** FG coated braid, **(C)** HA coated braid **(D)** Autologous

Conclusions: Hydrogel coated braided conduits were porous, flexible, and kink resistant. Both hydrogel coatings covered the conduit surface but HA coating outperformed the FG coating in terms of functional recovery and better nerve regeneration. HA hydrogel coating remained structurally intact till 6 weeks on the conduit surface and prevented scar tissue infiltration compared to uncoated and FG coated conduits. These results will guide us further to use the HA hydrogel coating to deliver growth factors for a prolonged time and improve functional recovery in longer nerve gaps.

References:

[1] "Braided tyrosine-derived polycarbonate nerve conduits for peripheral nerve regeneration", Basak Clements et al.; TERMIS 2011.