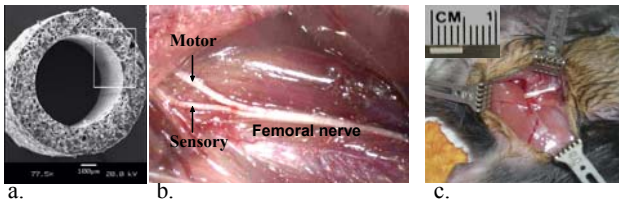
Tyrosine-derived Polycarbonate Conduit to Improve Functionality of Peripheral Nerve Regeneration

Mindy Ezra [1,3], Jian Chen[2,3], Shirley Masand[3], Melitta Schachner[2,3], David Shreiber[3], and Joachim Kohn[1,3]
[1]New Jersey Center for Biomaterials and [2]W. M. Keck Center for Collaborative Neuroscience and [3]Rutgers University, Piscataway, NJ, 08854, USA

Statement of Purpose: Following peripheral nerve injury functional recovery is poor due to the limited ability of extending neurons to navigate long gaps and reconnect with their targets in the distal nerve. One method commonly used to guide regeneration and increase functional recovery is known as tubulization [1]. This method allows factors and cells to remain in contact with the nerve, provides direction, and protects the wound space [2]. A hollow tube or conduit is used to bridge together nerve gaps <10mm, however this method cannot be used for larger gaps [3]. In these critical cases, neurons are more likely to extend randomly across the nerve gap, making improper reconnections. A more complicated internal structure is necessary inside the tube in order to guide regeneration over large gaps.

Methods: The approach used in this study to foster nerve regeneration in critically large gaps is to fabricate a biodegradable, polymeric scaffold using tyrosine-derived polycarbonates (PC) that provides physical and biologic guidance. This scaffold consists of an outer porous tube (Fig.1a) filled with an internal biological component.



a. b. c.

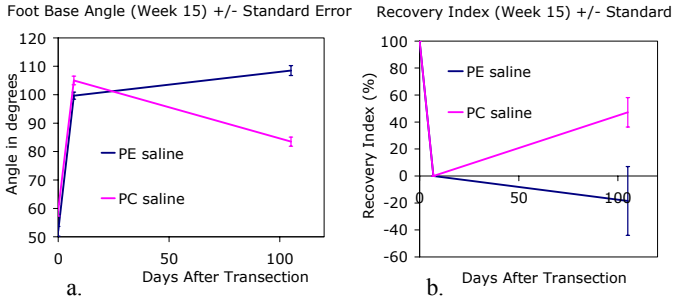
Figure 1. a. SEM image of cross-section of porous tube
b. Mouse femoral nerve showing motor and sensory branch.
c. Placement of conduit. Inlay shows actual conduit dimensions.

HNK1, an epitope from the human natural killer cell, helps guide nerves during normal development. When used *in vivo* in soluble form, the HNK1 peptide mimic helps guide regenerating axons to their proper branch, and increases neuronal survival and rate of growth [4, 5]. In the current study, HNK1 peptide mimic is provided to the injured nerve in a local manner; it is covalently attached to type I collagen. This peptide-grafted collagen is injected into the inner lumen of the porous tube.

The PC tubes were evaluated using a mouse femoral nerve injury model (Fig.1b). Polyethylene (PE) tubes (Becton Dickinson, Sparks, MD) were used as a control. Compared to the commonly used sciatic nerve model, the femoral model bifurcates into a motor branch and a sensory branch (Fig.1b) and evaluates not only nerve growth through a conduit, but also correct targeting of the neurons into the proper branch of the nerve. All tubes were used to bridge a 5-mm transection (Fig.1c). The lumen of the tubes was filled with saline, native collagen, or peptide-grafted collagen.

Animals were videotaped pre-injury and weekly for 15 weeks post-implantation. Functional recovery was assessed using a single-frame motion analysis approach to quantitatively evaluate gait via two parameters, the foot base angle (FBA) and the recovery index (RI). Recovery is indicated by the FBA returning to its original value of ~55º and RI returning to 100%. Retrograde labeling was performed to quantify correct reconnections and femoral nerves were dissected for morphological analyses.

Results: The FBA shows that animals treated with PC conduits showed significant improvement at week 15 as compared to animals treated with PE conduits (Fig.2a). In addition, animals treated with a PE conduit continued to regress over time, maintaining a strongly negative RI (Fig.2b). In contrast, animals treated with PC conduits showed significant recovery over the same 15 week period (Fig.2b). No significant differences were observed among groups with varying filler materials however all groups with native collagen or peptide-grafted collagen resulted in positive functional recovery and motor axons reconnected properly. Continuing analysis of the targeting efficiency and nerve histology is being completed in order to confirm the use of this biomaterial for peripheral nerve regeneration.



a. b.

Figure 2 a. FBA of mice treated with PC conduits improves, while mice treated with PE conduits show no improvement.
b. The RI shows improvement of animals treated with PC conduits as compared to PE conduits. ** Injury was performed at day 7 as indicated by a sharp increase in the FBA angle and a sharp decrease in the RI from day 0 (intact nerve) to day 7 (injury).

Conclusions: The potential use of tyrosine-derived polycarbonate as the base material for nerve regeneration conduits is supported by this study. Using the mouse femoral nerve model a significant increase in the functional recovery of the nerve was found when treated with a PC conduit as compared to a PE conduit. From these findings, the polymer composition used for this application can be better optimized and the design of the scaffold improved to enhance regeneration further.

References:

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