

Controlled Release of Glial Cell Line-derived Neurotrophic Factor from Biodegradable Nerve Conduits

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INTRODUCTION: Growth factors are promising candidates to improve functional outcome upon peripheral nerve regeneration. However, little is known about the impact of different release kinetics on nerve regeneration.

We therefore developed a biodegradable, multi-ply delivery system with adjustable release kinetics for glial cell line-derived neurotrophic factor (GDNF). A porous supporting hollow cylinder made of collagen was coated with concentric layers of release-modifying polymer (PLGA), in-between which GDNF was embedded. Changes in the stacking sequence and type of polymer (lactide to glycolide ratio, molecular weight and free versus esterified end groups) allowed us to tailor different release kinetics.

METHODS: Nerve conduits (NC) were produced by spinning mandrel technology. A suspension of insoluble collagen (2.5 % w/w, Avitene from Davol, Cranston, RI, USA) was deposited onto a spinning steel mandrel from a syringe. The solvent was evaporated under a laminar airflow, and the resulting tube was cut into 6 mm long NC. Various types of PLGA layers were sprayed onto the NC with an ultrasonic spray nozzle (Resomer RG 503, RG 503 H, RG 752, RG 755, from Boehringer-Ingelheim, Ingelheim, Germany; the first two digits refer to the amount of lactide (75 vs 50 %), and the third one to the intrinsic viscosity). All polymers are end-group capped, except for 503 H. GDNF in buffer (1.2 µg per NC) was deposited on top of the first PLGA layer in the central part of the NC. *In vitro* release was measured by incubating the NC in citrate buffer (pH 5, 150 mM NaCl, 0.05% Tween 20) at 37°C. Buffer exchange was daily, and GDNF was assayed by ELISA.

RESULTS: GDNF release kinetics could be efficiently controlled by selecting appropriate PLGA types (Fig. 1). NC coated with PLGA 75:25 types (NC-C and NC-D) released GDNF, after the initial burst, at lower rates than the NC coated with the more hydrophilic PLGA 50:50 types (NC-A and NC-B). Interestingly, the end-group uncapped PLGA 503 H (NC-A) mediated a slower GDNF release than the less hydrophilic end-group capped PLGA 503 (NC-B).

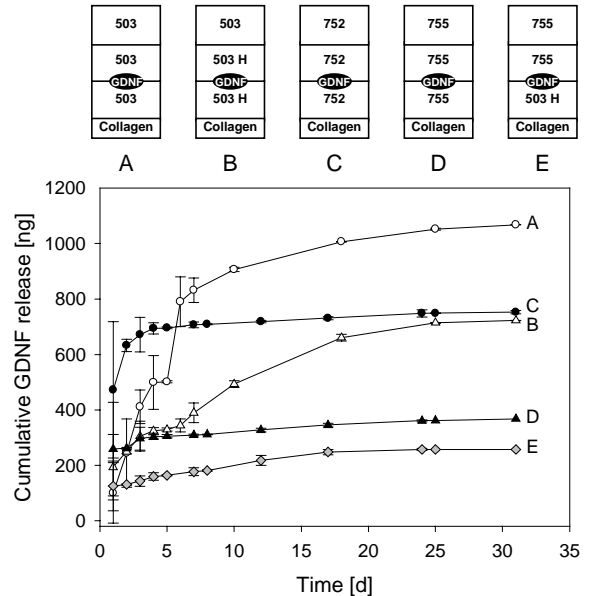


Fig. 1: Effect of polymer type on release kinetics of GDNF. The top panel illustrates the various NC construct (PLGA types are denoted by the code of the corresponding Resomers). The dimensions shown do not reflect the real proportions of the layers. The wall of the collagen tube was about 10 times thicker than the total thickness of all PLGA layers together. The bottom panel shows the *in vitro* GDNF release curves obtained with the different NC constructs. Means with standard deviation ($n=4$).

DISCUSSION & CONCLUSIONS: We developed biodegradable, multi-ply nerve conduits with adjustable release kinetics that permit control of GDNF delivery kinetics in the low ng/day range for several weeks. Changes in polymer type and coating thickness resulted in distinctly different release kinetics, although incomplete release of some formulations also revealed stability issues of GDNF. Employing NC with different release kinetics in models of peripheral nerve regeneration *in vivo*, we expect to gain insights into the optimal delivery regimen for GDNF and finally improve functional outcome after traumatic nerve injury.

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