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Designing ideal conduits for peripheral nerve repair

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Abstract

Nerve tubes, guides, or conduits are a promising alternative for autologous nerve graft repair. The first biodegradable empty single lumen or hollow nerve tubes are currently available for clinical use and are being used mostly in the repair of small-diameter nerves with nerve defects of < 3 cm. These nerve tubes are made of different biomaterials using various fabrication techniques. As a result these tubes also differ in physical properties. In addition, several modifications to the common hollow nerve tube (for example, the addition of Schwann cells, growth factors, and internal frameworks) are being investigated that may increase the gap that can be bridged. This combination of chemical, physical, and biological factors has made the design of a nerve conduit into a complex process that demands close collaboration of bioengineers, neuroscientists, and peripheral nerve surgeons. In this article the authors discuss the different steps that are involved in the process of the design of an ideal nerve conduit for peripheral nerve repair.

Keywords

biomaterial; growth factor; nerve conduit; nerve guide; nerve tube; polymer; Schwann cell

In the last 25 years, the concept of the nerve tube has evolved from a tool to investigate regeneration to a device that is now being used clinically in patients as an alternative for autologous nerve graft repair. Although their clinical use has been limited, mainly to the repair of relatively small defects (< 3 cm) in small-caliber digital nerves,[7,49,56] the potential for extending clinical application to the repair of larger defects and larger mixed or motor nerves[48] has made the development of an ideal nerve tube appealing for both scientists and the medical device industry. At the moment several nerve tubes are being marketed (including Neurotube [Synovis], Neurolac [Ascension], SaluBridge [SaluMedica], and Neura-Gen [Integra]). The basic design of these tubes (hollow tubes in which the nerve ends are inserted [Fig. 1]) is similar, but they are made of different biomaterials (synthetic: PGA, PLC, hydrogel; and natural: collagen) using various fabrication techniques (rolling of a mesh,[13] precipitation on a rotating mandrel,[33] or dip-coating of a rotating mandrel[14]). As a result these nerve tubes also differ in physical properties. Currently, there is little information as to which tube functions

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better in the repair of small nerve gaps. In the original articles,[4,5,13,15] all nerve tubes were reported to lead to results comparable to autograft repair. It is difficult, however, to compare the results of these studies, because different animal models, nerve gaps, and evaluation techniques were used.[12] Also, functional results in most studies were not included, and physical properties were not determined for all conduits in detail. In our opinion therefore, there is still potential for improvement of even the common hollow nerve tube for the repair of small nerve gaps, especially because the goal of an ideal nerve tube is to perform better than the autograft.

In more recent years, research has been focused mainly on improving the single lumen nerve tube to bridge larger nerve gaps (Fig. 1 and Table 1). Different techniques have been applied to make nerve tubes permeable. Nerve tubes have been filled with collagen and laminin-containing gels, Schwann cells, and growth factors. Also, the internal microarchitecture of the nerve tube has been modified (for example, filaments, sponges, and multichannel nerve tube structures). Experimentally, these modifications have been demonstrated to increase the gap that can be bridged (Table 1). Clinically, however, the use is still limited, possibly because of practical disadvantages (for example, the harvest and culture of Schwann cells before reconstructive surgery) and because, in the repair of larger gaps, physical characteristics of the nerve tube become more important. This combination of chemical, physical, and biological factors has made the development of a nerve tube into a complex process that requires close collaboration of bioengineers, neuroscientists, and peripheral nerve surgeons. In this article we discuss the different steps that are involved in the design of an ideal nerve conduit for peripheral nerve repair, including the choice of biomaterial and fabrication technique and the various potential modifications to the common hollow nerve tube. Although most modifications are aimed at increasing the nerve gap that can be bridged, it must be noted that these can also be used to improve entubulation or nerve tube repair of smaller gaps.

Choice of Biomaterial and Fabrication Technique

The choice of biomaterial and fabrication technique is an important first step in the development of a nerve tube. In general, biodegradable materials are preferred because nonbiodegradable ones eventually may lead to compression.[8,41] Biodegradable nerve tubes ideally should not be toxic or elicit an immunological response (no local tissue reaction or allergic response). Synthetic biodegradable materials in an ideal situation are therefore preferred over natural ones (although most synthetic materials also cause foreign body reactions). Different synthetic biodegradable materials have been used for nerve tube fabrication (mostly polymers of lactic and glycolic acid, and caprolactone) with various fabrication techniques. Both these factors influence the physical properties of the nerve tube that are important for entubulation repair including permeability, flexibility, swelling, and degradation.

Permeability of a conduit is an important nerve tube property because nutrients and oxygen need to diffuse into the site of regeneration before the tube becomes vascularized. In addition, permeability might be needed for the viability of supportive cells (in case these are added). Also, permeability may affect the formation of the fibrin matrix in the initial stage of regeneration.[64] Nerve tubes can be made permeable with different techniques (for example, by cutting holes into the wall,[27] rolling of meshes, [13,44] fiber spinning,[1] adding salt[58] or sugar crystals[46] that are leached after fabrication, and injection-molding solvent evaporation[10]). Permeability, however, also depends on hydrophilic properties of the material, which can be measured from the contact angle of a water drop on the material.[9]

Flexibility is an important nerve tube property, especially in the repair of larger nerve gaps, because the ends might not be in the same plane/line and the gap that needs to be bridged might cross a joint. More flexible materials, however, are also often weaker, which might lead to kinking, breaking, and/or tearing of the suture from the conduit. To find the right balance

between these different mechanical properties, various polymers, polymer molecular weights, and/or copolymer ratios can first best be tested in vitro. Eventually, however, bending studies will have to be performed for the nerve tube, because dimensions (wall thickness, lumen diameter, and presence of internal frameworks, in case these are added) and porosity may also affect the mechanical properties. Ideally, the influence of degradation on the mechanical properties of the nerve tube should also be determined.[6,39]

Swelling and degradation are important nerve tube properties, because swelling might occlude the lumen for regeneration or cause compression of regenerated axons. The rate of degradation might contribute to this swelling by the formation of small degradation products that increase the osmotic pressure of the conduit.[10,14] Too rapid degradation may lead to swelling, but too slow degradation may later lead to compression and/or a chronic foreign body reaction. The ideal nerve tube should remain intact for the time axons need to regenerate across the nerve gap and then degrade gradually with minimal swelling and foreign body reaction. As for the mechanical properties, by changing the nerve tube dimension[14] or copolymer ratio,[10] the swelling and degradation properties may be optimized.

In conclusion, one should consider the desired physical properties of the nerve tube in choosing the biomaterial and fabrication technique. These properties can best first be tested in vitro. We have recently introduced a series of methods to characterize nerve tubes, especially for nerve tubes with more complex internal structures.[10] Permeability of single-lumen and multichannel nerve tubes was tested from the rate of diffusion of different size fluorescent dextran molecules from the outside of the tube to the inside of the lumen/channels by comparing the color intensity on the inside to the color intensity of the known outside concentration. Mechanical properties were analyzed by 3-point bending on a dynamic mechanical analyzer. The ends of the nerve tube rested on a holder of 2 points, and a third point was lowered from above in between those 2 points with increasing force. Stiffness was subsequently calculated from the force needed to displace the tube. Swelling of tubes made of different ratios of PLGA (50:50, 75:25, and 85:15) was analyzed for the mass swelling ratio and the change in nerve tube dimensions. In the same experiment degradation was determined for the mean molecular weight of the residual tubes with gel permeation chromatography. The results of this study demonstrated that swelling of the tubes increased for lower PLGA ratios, probably as a result of more rapid degradation. Currently, however, the choice of biomaterials is still limited. Novel polymers with controlled physical properties are therefore being developed.[26]

In addition to these nerve tube properties, the ideal nerve tube should also be easy to handle and suture (transparent is preferable), and must be capable of being sterilized without compromising the physical properties. Finally, any modifications will also need to be considered in the choice of biomaterial and fabrication technique.

Modifications to the Single-Lumen Nerve Tube

Different types of modifications to the common hollow nerve tube have been investigated (Fig. 1 and Table 1). These modifications can grossly be divided into separate categories of collagen- and laminin-containing gels, internal frameworks, supportive cells, growth factors, and conductive polymers, but combinations have also already been used. Table 1 summarizes the details of some of the studies that have investigated these different modifications. Most modifications have been shown to increase the gap that can be bridged from 10 to 15–20 mm in a sciatic nerve model in rats. More recently, some modifications have also been applied in clinical nerve repair (for example, an interposed nerve segment in PGA tube repair of a 4-cm gap in the median nerve,[25] collagen sponges in PGA nerve tube repair of facial nerve branches,[25a] and PGA filaments in chitosan nerve tube repair of a 35-mm gap in the median nerve[18]). In the paragraphs that follow, we only discuss the mechanisms by which these modifications

might enhance regeneration, the factors that must be considered in design and analysis of the nerve tube, and the practical application of these modifications in patients.

Collagen- and Laminin-Containing Gels/Solutions

Collagen- and laminin-containing gels can enhance regeneration by the formation of a fibrin matrix for the guidance of regeneration. This matrix is also formed in the repair of defects up to 1 cm in empty hollow nerve tubes,[59] but it does not form in the repair of larger defects. The addition of collagen and laminin gels or solutions can enhance regeneration by the presence of a larger amount of matrix components and potentially by a more homogeneous distribution. This prefilling with extra matrix components may provide a substrate for the early ingrowth of neural and nonneural cells and the binding of neurotrophic factors. Longitudinal alignment of these components (for example, by magnetic induction) may further enhance regeneration.[55] Different factors must be considered in the use of collagen- and laminin-containing gels including the concentration of the gel/solution and the presence of pores/permeability of the nerve tube, which may interfere with the organization of the matrix.[54] Practically, collagen- and laminin-containing gels can be easily added to the nerve tube (the ends should be sealed to prevent leakage). However, a disadvantage often is the source of the collagen and laminin (tumor cells or bovine source [Table 1]), although recently laminin-derived oligopeptides have also been synthesized.[63] These laminin-derived peptides can also be used to coat the inside of nerve tubes and internal filaments[38] to provide guiding cues for regenerating axons.

Intrinsic Frameworks

Intrinsic frameworks such as filaments, collagen sponges, denatured muscles, and multichannel nerve tubes may enhance regeneration by stabilization of the fibrin matrix that is formed inside the nerve tube and/or contact guidance (Table 1). In addition, the internal structure provides more surface area for cell attachment and local release of incorporated growth factors. Interposed nerve segments (the so-called stepping-stone procedure) may increase the gap that can be bridged by providing a source of Schwann cells, trophic factors, and extracellular matrix molecules in the middle of the tube or between two tubes.

In the design of conduits with modified microarchitecture it is important to realize that internal structure may affect the physical properties of the nerve tube (for example, permeability and flexibility) and reduces the total cross-sectional area that is available for regeneration. Also, in the in vivo analysis it is important to realize that the internal structure may interfere with the accuracy of regeneration across the nerve tube. In our opinion, results should therefore not only be analyzed with standard methods, such as nerve morphometry and electrophysiology, but also with, for example, simultaneous and sequential retrograde tracing. In the most commonly used model of experimental nerve repair, the rat sciatic nerve model, 2 different tracers can be applied simultaneously to the tibial and peroneal nerve branches to determine the dispersion of regenerating axons originating from the same neuron, or the 2 tracers can be applied to the same nerve branch before and after repair to determine the correct direction of regenerating axons.[11]

As for the practical application, the number of filaments and channels that can be introduced to the nerve tubes is currently limited by the size in which these can be produced. Furthermore, it is important to realize that longitudinally oriented structures might not mimic the fascicular structure of the nerve, which frequently consists of an intraneural plexus. In the future, this problem might be overcome by reconstructing the internal fascicular structure of the nerve with 3D printing or stereolithography. [31,32]

Supportive Cells

The addition of supportive cells, especially Schwann cells, to the nerve tube probably is the most extensively investigated modification to the single-lumen nerve tube. Schwann cells might enhance regeneration by different mechanisms. In the repair of small defects with empty hollow nerve tubes, Schwann cells are also involved in the process of regeneration. After weeks of implantation they migrate along the fibrin matrix that has formed inside the nerve tube from both the proximal and distal nerve ends. Again, this matrix does not form if the gap is too long. Schwann cells might increase the gap that can be bridged by forming a cable along which axons can regenerate. Other mechanisms by which Schwann cells might enhance regeneration are the production of extracellular matrix molecules (for example, laminin) and growth factors (for example, nerve growth factor).

In the design of the conduit, not only permeability is an important property to allow the diffusion of nutrients and oxygen, but also the surface texture and hydrophilic properties of the material for the attachment of cells. The latter is especially important in case microfilaments are added or the multichannel structure is used to increase the surface area for cell attachment. In the in vivo analysis, different factors must be considered including the purity of cell culture (potential contamination with fibroblasts), the source of cells (for example, neonatal or adult, and heterologous or autologous, see Table 1), the medium in which Schwann cells are suspended, and the density of Schwann cell suspension. Furthermore, in the analysis of results it is important to realize that endogenous Schwann cells might contribute to the success of regeneration and that the addition of Schwann cells might induce branching of regenerating axons. These problems can be overcome by labeling Schwann cells[28] and using retrograde tracing techniques to determine the number of regenerated motor and sensory neurons. As for the clinical use of Schwann cells it is important to realize that these cells will have to be harvested (and still require the use of an autograft, because autologous cells are preferred) and will have to be cultured before reconstructive surgery. Although the difficulty of harvesting might be overcome by the differentiation of bone marrow stem cells from the patient into Schwann cells,[43] the culturing of these cells will be demanding (require special facilities) and cannot be readily performed in an acute setting at this time. Advantages of culturing, however, are that the Schwann cell phenotype can be modulated, for example into motor or sensory Schwann cells,[23] and that the cells can be genetically modified to overexpress certain factors.

Growth Factors

Different growth factors including NGF, GDNF, neurotrophin-3, and FGF have been added to single-lumen nerve tubes (Table 1). Growth factors may enhance regeneration by several mechanisms, for example, by promoting axonal outgrowth and neuronal survival. These effects may be particularly interesting for the delayed repair of nerve lesions (which is often the case in the repair of larger nerve gaps). Another interesting application of growth factors might be that they can be used to selectively stimulate different subgroups of motor and sensory neurons.

As for the design of the nerve tube, growth factors can be added directly (in solution) or through a delivery system. Delivery systems are generally preferred, because the effect of growth factors is often dose dependent and requires the release over extended periods of time. Besides, solutions may leak from the nerve tube. Different carriers and delivery systems have been used including absorption to fibronectin mats, collagen matrices, BSA, and microspheres (Table 1). An advantage of matrices is that they also provide an internal structure for regeneration. An advantage of microspheres is that they can be added to the structure of the nerve tube (wall or internal structure) during the fabrication process. Different gradients of growth factors can thereby be incorporated over the length of the nerve tube to attract regenerating axons and to sustain regeneration throughout the tube to prevent trapping of axons (the so-called candy store phenomenon). [53] Currently, however, there is still little information on the release kinetics of

incorporated growth factors and their biological activity. Ideally, these characteristics should be tested in vitro and in vivo. Furthermore, in the in vivo analysis, it is important to include both positive and negative controls, and to correct again (as discussed for the addition of Schwann cells) for the potential effect on branching of regenerating axons by using retrograde tracing.

For clinical use, nerve tubes with incorporated growth factors are, in our opinion, more practical than the addition of Schwann cells because of the special facilities required for the culturing of the cells (see *Supportive Cells*). Limitations of growth factors, however, might be the loss of biological activity over time or after sterilization of the nerve tubes.

Conductive Polymers

Finally, conductive polymers (for example, polypyrrole) might enhance regeneration by accelerated axonal elongation on the charged surface.[2,50] In addition, electrical stimulation might be used to guide axonal regeneration. Currently conductive polymers are not frequently used, probably because most are nonbiodegradable, but with the development of novel polymers, these materials may provide interesting opportunities for nerve repair.

Conclusions

We have discussed the various steps that are involved in the design of an ideal conduit for peripheral nerve repair. In the first step (the choice of biomaterial and fabrication technique), it is important to consider the desired physical properties of the tube. Especially in the repair of larger nerve gaps, permeable and flexible tubes are preferred with controlled degradation rates and limited swelling. Second, the design of the common hollow nerve tube can be modified to enhance regeneration: various factors can be added including laminin, collagen, Schwann cells, growth factors, and internal filaments, and the nerve tube microarchitecture can be modified. We believe that a combination of various modifications (for example micro-filaments with Schwann cells or multichannel nerve tubes with incorporated growth factors) with controlled physical properties of the conduit will ultimately lead to the best results of regeneration. More research is still needed to solve some of the limitations discussed in this article. In our opinion, the future of nerve tube repair is bright provided that newly developed conduits are analyzed in detail in vitro and in vivo before clinical use.

Abbreviations in this paper

BSA	bovine serum albumin
FGF	fibroblast growth factor
GDNF	glial derived neurotrophic factor
NGF	nerve growth factor
PGA	polyglycolic acid
PLC	poly(DL-lactide-ε-caprolactone)
PLGA	poly(lactic-coglycolic acid)

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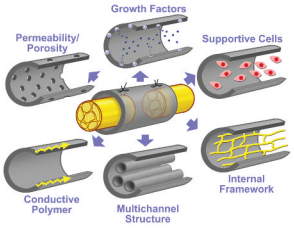

Fig. 1.

Modifications to the single lumen nerve tube. Modified from Hudson TW, Evans, GR, Schmidt, CE: Engineering strategies for peripheral nerve repair. *Clin Plast Surg 26:*617–628, 1999. With permission from Elsevier.

TABLE 1

Modifications to the single-lumen nerve tube*

Collagen- & Laminin-Containing Gels/Solutions

Authors & Year	Collagen/ Laminin	Gel/ Solution†	Nerve Tube	Animal	Nerve	Gap Size (mm)	Methods	Controls	Follow-Up	Outcome
Madison et al., 1985	laminin	Matrigel	poly-D,L-lactates	mouse	sciatic	4–5	retrograde HRP labeling	empty tubes	2 wks	labeled neurons in all animals w/ laminin-containing gels, 0 in empty
Valentini et al., 1987	collagen & laminin	Vitrogen, Matrigel	semipermeable PVC‡	mouse	sciatic	4	NM	semipermeable tubes w/ saline	12 wks	fewer axons in gel-filled semipermeable tubes
Madison et al., 1988	collagen & laminin	Vitrogen, Matrigel	silicone	rat	sciatic	15, 20	HRP labeling, distance regeneration	empty tubes	16 wks	2x increase in max distance of axonal elongation
Labrador et al., 1998	collagen & laminin	Vitrogen, Matrigel	silicone	mouse	sciatic	4, 6	NM, sweating test, pinprick, CMAP, CNAP	diff conc, PBS, hyaluronate gel, plasma	up to 4 mos	higher levels of target reinnervation w/ diluted gels
Verdu et al., 2002	aligned collagen, laminin	Vitrogen, Matrigel	silicone	mouse	sciatic	6	NM, sweating test, pinprick, CMAP, CNAP	horizontal/vertical polymerization, magnetic§	up to 4 mos	higher no. of MF for magnetically aligned gels

Intrinsic Frameworks

Authors & Year(s)	Framework	Material, No.	Nerve Tube	Animal	Nerve	Gap Size (mm)	Methods	Controls	Follow-Up	Outcome
Lundborg et al., 1996 & 1997	filaments	polyamide, 8	silicone	rat	sciatic	10, 15	NM, NF staining, pinch reflex	empty tubes, no repair	4 wks	response to pinch & positive staining for NF distal to tube in all cases w/ filaments, 0 in empty tube
Yoshii et al., 2001 & 2003	filaments	no tube, NA	collagen, 2000, 4000 filaments	rat	sciatic	20, 30	NM, presence of ankle flexion	autograft, collagen tube	8 & 12 wks	regeneration across 20- & 30-mm gaps, more MF for 4000 filaments
Nakamura et al., 2004	sponge	collagen, NA	PGA tube	dog	peroneal	15	NM, MEP, CNAP	autograft	up to 6 mos	shorter latency, larger peak voltage & larger MF for PGA-collagen tubes
Meek et al., 2001	denatured muscle	muscle, NA	PLC	rat	sciatic	15	NM	nonop side	up to 12 wks	regeneration across 15-mm gap in all cases

Collagen- & Laminin-Containing Gels/Solutions

Authors & Year	Collagen/ Laminin	Gel/ Solution†	Nerve Tube	Animal	Nerve	Gap Size (mm)	Methods	Controls	Follow-Up	Outcome
Francel et al., 1997	nerve segments	autologous, 12-mm segment	silicone	rat	sciatic	15	NM, electrophysiol, SFI	empty tubes, autograft	16 wks	no regeneration across empty tubes
de Ruiter et al., 2008	multichannel	7 channels	75:25 PLGA	rat	sciatic	10	NM, CMAP, muscle fiber size & type, sim & seq tracing	single-lumen tubes, autograft, normal	8 & 12 wks	no. of MN & MF not sig diff for single-lumen & multichannel nerve tubes despite 2× smaller cross-sectional lumen/ channel area

Schwann Cells

Authors & Year	Source of SC‖	Suspension	Nerve Tube	Animal	Nerve	Gap Size (mm)	Methods	Controls	Follow-Up	Outcome
Guenard et al., 1992	syngen, heterol, adult	Matrigel, diff dens	PAN/PVC, permeable	rat	sciatic	8	NM	empty, Matrigel, autografts	3 wks	more MF for high dens SC, more MF for syngen than for heterol SC
Ansselin et al., 1997	syngen, adult	RPMI 1640, diff dens**	collagen	rat	sciatic	18	NM, SFI, CMAP	PBS	6 mos	more MF for high dens SC
Kim et al., 1994	syngen, FG-labeled	collagen gel	collagen	rat	sciatic	10	NAP	empty, collagen gel autografts (sural)	60 & 120 days	NAP & no. of MF equal for SC & auografts, but lower for collagen alone
Rodriguez et al., 2000	syngen, isogen, autol, adult	Matrigel	PLC, permeable	mouse	sciatic	6	NM, CMAP, CNAP, sweating, pinprick	autograft	4 mos	best results for autologous SC
Evans et al., 2002	allogen, neonatal	Vitrogen	PLLA, permeable	rat	sciatic	10	NM, SFI, gastroc muscle weight	diff dens, collagen, silicone, isograft,	4 mos	MF density in distal nerve in all groups lower than for isografts
Sinis et al., 2005	syngen, isogen neonatal	Matrigel	TMC/CL, permeable	rat	median	20	grasping test, FDS muscle weight, CMAP	empty, autograft, normal	9 mos	regeneration only after repair w/ autograft or nerve tube w/ SC

Growth Factors

Authors & Year	Growth Factor(s)	Carrier/Delivery System	Nerve Tube	Animal	Nerve	Gap Size (mm)	Methods	Controls	Follow-Up	Outcome
Hollowell et al., 1990	NGF	saline solution	silicone	rat	sciatic	8	NM, HRP labeling	solution cyt C	10 wks	no. of MN & DRG not sig dif

Collagen- & Laminin-Containing Gels/Solutions

Authors & Year	Collagen/ Laminin	Gel/ Solution†	Nerve Tube	Animal	Nerve	Gap Size (mm)	Methods	Controls	Follow-Up	Outcome
Derby et al., 1993	NGF	solution	silicone & permeable PS	rat	sciatic	7 & 12	NM (MF & UMF), behavoral tests	solution cyt C	4, 8 wks, & 6 mos	at 3 wks 3x more MF, at 4 wks no diff
Whitworth et al., 1996	NGF	fibronectin mats	rolling of mat	rat	sciatic	10	immunostaining, NM	plain mats	up to 60 days	increased penetration distance, slightly greater no. of MF in distal nerve at 60 days
Lee et al., 2003	NGF	fibrin-based, diff conc	silicone	rat	sciatic	13	NM	empty, fibrin, isograft	6 wks	no. of MF mid- & distal to tube not sig diff from isograft for diff conc
Xu et al., 2003	NGF	microspheres	PPE	rat	sciatic	10	NM, reflex response	silicone, saline, BSA	3 mos	more MF in the distal nerve compared w/ all other repair groups
Fine et al., 2002	GDNF & NGF	BSA	EVA	rat	sciatic	15	NM, FG labeling	BSA alone	47 days, 42 days	no. of MF: GDNF 4942, NGF 1199, BSA 5; no. of MN: GDNF 98.1, NGF 20.0, BSA 0; no. of DRG: GDNF 22.7, NGF 3.3, BSA 0
Sterne et al., 1997	NT-3	fibronectin mats	rolling of mat	rat	sciatic	10	immunostaining, NM	plain mats	up to 8 mos	max effect at 15 days w/ increased penetration distance, greater no. of MF in distal nerve at 8 mos
Midha et al., 2003	FGF	collagen gel	PHEMA-MMA	rat	sciatic	10	NM	empty, collagen gel, autograft	8 wks	no. of MF in distal nerve comparable to autograft & higher than other groups

*CMAP = compound muscle action potentials; CNAP = compound nerve action potentials; conc = concentrations; cyt = cytochrome; dens = densities; diff = different; DRG = dorsal root ganglion cells; electrophysiol = electrophysiology; EVA = ethylene-vinyl acetate copolymer; FDS = flexor digitorum superficialis; FG = Fluoro-Gold; gastroc = gastrocnemius; HRP = horseradish peroxidase; MEP = muscle evoked potentials; MF = myelinated fibers, MN = motor neurons; NA = not applicable; NAP = nerve action potential; NF = neurofilament; NM = nerve morphometry; NT-3= neurotrophin-3; PAN/PVC = acrylonitrile vinylchloride; PBS = phosphate-buffered saline; PHEMA-MMA = poly(2-hydroxyethyl methacrylate-co-methyl methacrylate); PLLA = poly(L-lactic acid); PPE = poly(phosphoester); PS = polysulfone; PVC = polyvinylchloride acrylic copolymer; SC = Schwann cell; seq = sequential; SFI = sciatic function index; sig = significantly; sim = simultaneous; subcut = subcutaneous; TMC/CL = trimethylenecarbonate-co-ε-caprolactone; UMF = unmyelinated fibers.

†Matrigel is a solubilized basement membrane preparation containing laminin, type IV collagen, heparane sulfate proteoglycans, entactin, nidogen, and trace amounts of growth factors (12 mg/ ml), obtained from Engelbreath-Holm-Swarm sarcoma. Vitrogen is a solution of purified bovine dermal collagen, containing 95– 98% type I collagen.

‡Molecular weight cutoff 50,000 D.

§Magnetic induction by placement of filled tubes with the longitudinal axis perpendicular to a 9-T magnetic field for 2 hours at 37° C.

[||] Syngeneic (syngen) indicates that the Schwann cells were obtained from the same strain; isogeneic (isogen), from the same litter; allogeneic (allogen), from same species, but genetically different; heterologous (heterol), from different species; and autologous (autol), from the same animal.

[**] The RPMI 1640 medium contains 1.25 U Dispase/ml, 0.05% (wt/vol) collagenase, and 0.1% hyaluronidase.