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Axonal Guidance Channels in Peripheral Nerve Regeneration

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In recent times, tissue engineering researchers have been attempting to provide the scientific and medical communities with improvements in the repair of peripheral nerve injuries using synthetic grafts. Although the nerve autograft still remains the clinical gold standard in bridging nerve injury gaps, many advances on several fronts have been made in developing a more effective nerve tubular construct to guide regenerating axons across the lesion. This review discusses several strategies that have been employed to enhance the regenerative effectiveness of artificial nerve guidance channels. These strategies include the use of scaffolds, the integration of contact-mediated cues within the tubular construct, and incorporation or delivery of exogenous growth factors into the conduit lumen uniformly or in a gradient form. Animal and clinical studies are reviewed to explain some of the ideas involved in developing a guidance channel of the future.
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Peripheral nerve injuries are common and serious disorders affecting 2.8% of trauma patients, many of whom acquire life-long disability.[1] In the United States alone, 360,000 people suffer from upper extremity paralytic syndromes on an annual basis, resulting in over 8.5 million restricted activity days and almost 5 million bed/disability days.[2] Peripheral nerve injuries are common in Europe as well, with over 300,000 cases occurring annually.[3]

Peripheral Nerve Injury and Repair

Peripheral nerve transection results in Wallerian degeneration in all of the axons distal to the injury site, as evidenced by the disintegration of axoplasmic microtubules and neurofilaments.[4] Most of the axons along the distal stumps of transected nerves are reduced to granular and amorphous debris within 24 hours; by 48 hours, the myelin sheath has begun to be transformed into short segments that then form into ovoids.[5] Activated macrophages migrate into the degenerating nerve stumps and phagocytose the disintegrating nerve fibers and myelin. Schwann cells proliferate in response to myelin debris and macrophage-derived cytokines[5] and form longitudinal Schwann cell bands (bands of Bungner) as they divide and remain within the basal-lamina-lined endoneurial tubes.[6]

Myelinated and unmyelinated fibers, at a distance proximal to the injury site where the axons are still intact, spontaneously sprout new daughter axons,[7] forming a "regenerating unit" that is surrounded by a common basal lamina.[6] The sprouts progress in a distal fashion. The regenerative sprouting of the proximal axon requires elongation of the axon, which is mediated by the growth cone.[4] The growth cone explores its surrounding environment as it advances. It accomplishes this search and sampling with the use of its filopodia that extend from a flattened sheet of lamellipodia.[4] Growth cones are guided to their targets by a combination of contact-mediated (haptotactic) and diffusible (chemotactic) cues that are either attractive or repulsive.[8] With time, only those axons that reach their targets mature, whereas the others are withdrawn,[9] resulting in reduced nerve function.[10]

Peripheral nerve injury repair strategies have been attempted for several hundred years, with the first reports in the 17th century.[11] Although many strategies have been attempted, management of large peripheral nerve gaps has been classified into the following 2 general categories: (1) bridge operations, which include all grafting, transposition, and tubulization techniques; and (2) manipulative nerve operations, which includes end-to-end apposition of the nerve

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stumps.[12] We now know that nerve regeneration is more effective with nerve grafting procedures than with manipulative measures that cause tension across a repair site of any substantial peripheral nerve gap.[13,14]

Nerve repair strategies aim to direct regenerating nerve fibers into the proper distal endoneurial tubes thereby guiding them to their appropriate end organs. This often requires resection of a neuroma and repair of the resulting nerve gap. Nerve autografts (nerve segments of autogeneic or self origin) remain the gold standard for peripheral nerve repair, bridging the proximal and distal stumps of gaps longer than 5 mm.[13,15,16] The clinical treatment of peripheral nerve injuries has changed relatively little, despite advances in our understanding of nerve pathophysiology. To date, no tubular or other type of conduit has proved superior to the autologous nerve graft, at least not for reconstruction of substantial human nerves such as the median or ulnar nerve trunks. The nerve graft contains Schwann cells and basal lamina endoneurial tubes,[17] which provide neurotrophic factors[18] as well as favorable cell and endoneurial tube surface adhesion molecules[19] to regenerating axons.[20]

Nerve autografting has inherent flaws; procuring the donor nerve incurs a new neurological deficit, in addition to donor site morbidity, such as scar and occasionally neuroma pain.[21] Additionally, there may be insufficient length and diameter of autogenous nerve to optimize reconstruction.[22] Another major shortcoming of the nerve graft technique is the biological constraint, which cannot be overcome by further progress in microsurgical techniques. Even with the most meticulous repair, the endoneurial tubes can never be reapproximated exactly, and this results in mismatching of regenerating axons at the site of suture, or within the graft, leading to inappropriate (nonspecific) and incomplete reinnervation and subsequent poor recovery in function.[23] This may be compounded by the grafted nerve, which contains thousands of linearly oriented basal lamina endoneurial tubes, each of which can impose nontopographic directionality to a regenerating nerve fiber, resulting in random and nonspecific reinnervation of the distal nerve stump.[23] Alternatively, an artificial (nonnerve) conduit interposed between the proximal and distal nerve stumps may provide a more suitable environment for regenerating fibers to sample and respond to appropriate directional cues.[16] Moreover, a bioengineered graft allows the incorporation of strategies that build on our rapidly expanding knowledge of axonal guidance and thereby offers the hope of providing an improved alternative to the nerve autograft.[24,25]

The use of nerve guidance channels, sutured in between the proximal and distal nerve stumps, has been actively pursued to obviate the need for the second surgery and perhaps to obtain better regenerative results than the autograft. Because fewer epineurial sutures are required for entubulation repair (because the nerve stumps are placed into the ends of the tube as opposed to simply abutting against the autograft), there should be less surgical trauma.[4] Moreover, guidance channels (or tubes) assist in directing axons from the proximal to the distal stump without any interference from imperfectly aligned degenerating fascicles of the nerve graft or the closely apposed distal stump.[4] Finally, guidance channels minimize the infiltration of fibrous scar tissue, which can hinder axonal regeneration, while at the same time maximizing the accumulation of soluble factors produced by the nerve stumps.[6]

Biological Nerve Grafts

Nonnerve tissues were used by Weiss as alternatives to suture repair of nerve to successfully bridge very short nerve gaps.[26,27] Since then, conduits from many different biological tissues have been used. These include the use of arteries,[27] veins,[28,29] muscle,[30-32] and other materials extensively reviewed by Doolabh et al.[15] Modified biological tissues such as laminin[15] and collagen[33,34] have also been used and have proved successful in specific situations.[15] There are a number of disadvantages with the use of blood vessel, muscle, and other biologic tissues in bridging peripheral nerve defects, including tissue reaction, early fibrosis, scar infiltration, and lack of precise control of the conduits' mechanical properties.[15] These limitations have led to the emergence of conduits made from novel synthetic materials; however, biocompatibility has now become an important consideration.

Regenerative Events Occurring within a Synthetic Chamber

When the 2 nerve stumps are positioned within the proximal and distal parts of a hollow tube, the conduit fills within a day with serous fluid, which has neurotrophic activity.[4] This fluid, which contains neurotrophic factors and affects sensory, sympathetic, and motor neurons, peaks in activity after 3 hours, 1 day, and 3 days, respectively.[4] Matrix precursors accumulate and over several days a coaxial, acellular-fibronectin-positive, laminin-negative matrix forms that acts as a scaffold for migrating cells from the nerve stump and the formation of a tissue cable that tapers from both proximal and distal stumps toward the center.[4,6] Regeneration of axons is constrained by the preformed tapered tissue cable. This tapering decreases with smaller diameter tubes and increases with longer tubes.[4]

Synthetic Guidance Channels

Because bioengineered nerve grafts are of synthetic origin, many of the graft properties (eg, length, diameter, wall thickness, permeability, degradability, interior surface morphology, conductivity) can be manipulated to meet the clinical requirements. A review by Belkas et al[24] describes each of these key biomaterial properties that one should consider when designing and developing potential guidance channel candidates.

Various strategies have been implemented that attempt to enhance the regenerative effectiveness of artificial conduits. These include the use of scaffolds, integration of contact-mediated cues within the channel, and incorporation or delivery of exogenous growth factors into the tube lumen uniformly or as gradients.

Scaffolds

Conduit gap limitations can be partially overcome by an oriented inner scaffold providing an environment that is both con-

ducive and inducive for axonal regeneration,[4] with some of the best results[35] obtained by inserting an internal gel matrix[4,36-39] such as one made from collagen.[40-44]

In an attempt to mimic the guidance structure of the peripheral nerve autograft, which consists of several tubes (bands of Bungner) surrounded by an outer tube,[14] the use of internal fibers and guidance channels has been proposed.[25] Peripheral nerve regeneration can also be further enhanced by prefilling nerve tubes with dialyzed plasma, which forms a fibrin gel.[45] This gel resembles the fibrin matrix formed during the early stages of regeneration. Therefore, longitudinally aligned fibers have been incorporated into the lumen of nerve tubes to test their effectiveness. A magnetically aligned type I collagen gel was found to have a directional effect on neurites and Schwann cells from dorsal root ganglia cultured in the gel surface, resulting in increased neurite ingrowth into the gel compared with the control collagen gel.[46] Ceballos et al demonstrated that collagen tubes filled with magnetically aligned type I collagen gel significantly improved in vivo regeneration over tubes filled with a control collagen gel.[47] It was hypothesized that the aligned collagen gels guided the growth cones and Schwann cells by contact-mediated cues.[46] Silicone tubes prefilled with aligned collagen or laminin-containing gels improved the quality of regeneration in the mouse sciatic nerve.[48] A recent in vitro study showed that magnetically aligned fibrin gels also guided axons.[49] Arai et al reported that silicone tubes inserted with longitudinally aligned polyamide, catgut, polydioxanone, normal polyglactin, or quickly absorbed polyglactin filaments each exhibited a regenerating bridge and some degree of functional recovery across a 15-mm-long rat sciatic nerve gap that was not seen with empty silicone tubes after 3 months postimplantation.[50]

Haptotactic Cues

Axons are guided to their targets by growth cones that respond to the coordinated action of contact-mediated and diffusible cues, which are either attractive or repulsive.[8,51,52] Contact-mediated cues such as extracellular matrix proteins or cell adhesive peptides can be incorporated within a scaffolding structure.

Extracellular matrix proteins, mainly collagen, laminin, and fibronectin, are haptotactic cues that guide growth cones during regeneration. Axonal elongation can be further stimulated with the inclusion of these proteins into tubes. The incorporation of collagen gels within guidance channels has been shown to improve regeneration relative to saline-filled tubes in several studies.[38,40,53] Laminin-filled tubes also promoted regeneration compared with control tubes.[36,54] Incorporating a laminin-soaked collagen sponge into a guidance channel is also promising because it has shown comparable results to tubes enhanced with collagen fibers.[55]

Cell adhesion molecules, such as neural cell adhesion molecule, L1, myelin-associated glycoprotein, and neuron–glia cell adhesion molecule, affect cell interactions during the development, maintenance, and regeneration of the nervous system.[4] Specific cell-surface receptors such as integrins[56] bind to extracellular matrix proteins such as laminin and fibronectin,[57] in which the amino acid sequences arginine–glycine–aspartic acid (RGD) have been found to be important for binding.[58,59] The sequence tyrosine–isoleucine–glycine–serine–arginine (YIGSR) on the β1 chain of laminin has been shown to enhance cell adhesion of neural cells,[60] whereas the sequence isoleucine–lysine–valine–alanine–valine (IKVAV) on the α chain of laminin has been found to promote neurite outgrowth of pheochromocytoma (PC12) cells.[61] Several investigators have found that peptide-modified surfaces enhance cell adhesion.[62-67] Within in vitro systems, YIGSR, IKVAV, and RGD can enhance the interaction of primary neuronal cells with fluoropolymers,[68,69] YIGSR and IKVAV act synergistically,[60] and neuron adhesion and outgrowth can be directed .[63,70] Recently, the adhesive fibronectin peptide fragment glycine–arginine–glycine–aspartic acid-serine (GRGDS) was also found to guide axonal outgrowth in vitro.[71]

Chemotactic Cues

Neurotrophic factors (NTFs) support survival, differentiation, and growth of neurons in the developing nervous system and promote nerve regeneration.[18,72,73] Members of the neurotrophin family that have been used in nerve guidance channel studies include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NT-3).[16] When these factors bind to their specific receptors, they activate important intracellular signaling and activation. Neurotrophin family members are small homologous proteins (sharing 50-60% amino acid identities) that promote survival and differentiation of specific groups of neurons by transducing signals through distinct but related tyrosine receptor kinase (Trk) molecules.[74,75] Each neurotrophin demonstrates greatest affinity for specific members of the Trk receptor family: NGF for TrkA, BDNF and NT-4/5 for TrkB, and NT-3 for TrkC.[74] Each neurotrophin also binds the low-affinity p75 neurotrophin receptor (p75).[72,76] The p75 receptor is one of the receptors that regulates the direction of axonal elongation[77] and is important for motoneuronal survival during development,[78] but p75 expression after injury has also been demonstrated to inhibit axonal regeneration.[78]

NGF has trophic and tropic actions on the following 3 main classes of cells: peripheral sympathetic and sensory neurons and central cholinergic neurons.[79] Approximately 50% of the sensory neurons in dorsal root ganglions, the small-sized population that subserve pain and temperature reception, express high levels of trkA and are responsive to NGF.[80] Atrophy and decreased Trk-A expression after axotomy can be reversed by the addition of exogenous NGF,[81] which also upregulates neurofilament expression[82] and promotes growth of dorsal root ganglion axons in the peripheral nerve[83] and the dorsal columns of the spinal cord.[84] The overall effect on functional nerve regeneration in vivo is mixed,[18,85] perhaps because collateral sprouting may predominate over regeneration.[86] The Schwann cells in the nerve stump distal to axotomy not only provide an increased amount of NGF,[87] but also upregulate expression of the p75 NGF receptor,[88,89] thereby providing both a trophic substrate and a chemotactic gradient to axons sprouting from the proximal stump.

BDNF supports survival of embryonic sensory neurons[90] and is produced by peripheral glia,[91] target-derived from skeletal muscle[92,93] and retrogradely transported to motoneuron cell bodies promoting their survival during devel-

opment.[94] In the adult, exogenous BDNF can replace the lack of availability of endogenous factor after peripheral axotomy,[95] thereby preventing the death of motor neurons[92,96,97] and promoting their regeneration[96-98] and remyelination.[93,99-101] Several guidance tubes have been used with BDNF incorporated into their lumen.[43,98,102-104]

NT-3 is potently neurotrophic for sympathetic neurons[105,106] and for large sensory neurons that express high levels of TrkC,[107] particularly those that subserve muscle spindle and limb proprioceptive function.[74,107-110] Exogenous administration of NT-3 may be especially beneficial because its levels are decreased in the neuron after peripheral axotomy at the same time as the proximal nerve stump expresses increased levels of TrkC.[111] Indeed, NT-3 augments peripheral nerve regeneration,[112] likely due to its trophic effects on large sensory[107,112] and motor neurons.[113,114] NT-3 has been used in numerous nerve conduit studies in recent years.[43,103,104]

The fibroblast growth factor (FGF) family of polypeptides are strong heparin-binding proteins that were originally purified from bovine pituitary and brain.[115,116] The prototype family members, FGF-1 and FGF-2 (acidic and basic FGF, respectively), are important regulators in the growth and development of mesodermal and neuroectodermal tissue, including angiogenesis and Schwann cell proliferation.[116] FGF-1 is enriched in neurons,[116] produced within the cell body and anterogradely transported along the axon.[117] After axotomy there is a dramatic reduction in FGF-1 levels in the distal stump undergoing degeneration.[117] In vitro, FGF-1 mediates survival and differentiation of several types of central and peripheral neurons,[118-120] whereas in vivo application of FGF-1 induces both peripheral[37,119,121] and spinal cord axonal[122,123] regeneration.

Some other neurotrophic and neurotropic factors that have shown success in nerve regeneration studies include basic FGF-2, insulin-like growth factor, platelet-derived growth factor, ciliary neurotrophic factor, interleukin-1, and transforming growth factor beta.[25,124]

There have been many other studies that incorporated various components into the lumen of tubes to promote nerve regeneration, including testosterone, gangliosides, catalase,[125] adrenocorticotropin,[126] glial-derived protease inhibitor,[127] forskolin,[128] pyronin,[129] matrigel,[130] and hyaluronic acid.[131]

It has long been recognized, since Cajal's pioneering work,[132] that axons from a severed peripheral nerve exhibit tropism, or the tendency to extend across a gap toward and into the denervated distal stump. Only recently has it been verified that the distal nerve indeed provides neurotropic support,[133,134] rather than just a source of migrating cells.[32] These in vivo observations support a wealth of in vitro data. Multi-compartment experiments demonstrate that NGF exerts a tropic effect on the regenerating neurite,[135] which is best explained by gradients of soluble NGF[136] and other peripheral-nerve-derived factors[137] directing axonal regeneration. The sampling, comparing, and decision-making procedure accomplished by the growth cone at the nerve fiber terminus is believed to be a concentration-gradient-dependent action,[138,139] which evokes a set of intracellular events involving cytoplasmatic second messenger.[139,140] A gradient of the cytoplasmatic second messenger may signal the preferential incorporation of new plasma membrane material and asymmetric cytoskeleton reorganization at the growth cone that is required for the appropriate orientation of neurites.[140] Various studies have used concentration gradients of growth factors in vitro to direct and enhance the extension of growing neurites.[141-143] Hence, the inclusion of gradients of growth factors may be another potential strategy to improve peripheral nerve regeneration in vivo.

Delivery of Growth Factors

Tissue engineering offers the promise of healing damaged parts of the human body through the implantation of artificial materials and biological agents or cells to stimulate the body's own tissues to regenerate themselves. This often involves seeding precursor cells onto materials and then implanting the composite construct into a defect site in which the cells will then naturally differentiate into the desired tissue. Complex tissues that have an intricate network architecture, such as neural tissue, may probably require the delivery of molecular signals at different spatial locations and times during the process of regeneration to engineer the proper tissue structure for functional recovery. For instance, it is well known that gradients of NGFs direct and guide axonal growth during development and that the varying concentrations of growth factors can influence the differentiated state of the cells in neural tissue. Similarly to the natural process of development, regeneration is regulated in a stepwise fashion by temporal and spatial molecular cues and cellular responses. The spatial and temporal delivery of various regulatory molecules may prove to be important for successful neural tissue engineering in the adult nervous system, as has been suggested.[144]

Growth factors have been most commonly delivered with the use of implantable osmotic pumps[145] or implanted into the nerve injury site with a variety of carriers such as gelfoam,[146,147] fibrin glue,[122,123] and genetically engineered cells including Schwann cells[99,148-151] and fibroblasts.[152] The growth factor can also be incorporated into the matrix substance within the guidance channel.[4] Utley et al demonstrated that direct delivery into the local environment where axons are regenerating promoted better axonal regeneration compared with osmotic pump release.[98] Two significant limitations of delivering factors within a matrix are inadequate bioavailability or bioactivity and the uniform concentration delivered across the device. Neurotrophic factors were encapsulated by Cao and Shoichet in biodegradable microspheres that slowly released their contents as they degraded, which improved bioavailability and bioactivity.[153]

In our recent work, poly(2-hydroxyethyl methacrylate-comethyl methacrylate) hydrogel tubes have been used to bridge 10-mm-long rat sciatic nerve injury gaps. When filled with 10 μg/mL of FGF-1 dispersed in a 1.28 mg/mL collagen-1 gel matrix, these tubes demonstrated comparable regeneration to nerve autografts at 8 weeks postimplantation and superior regeneration compared with channels filled with other types of growth factors (Table 1, Fig. 1).[40] Future studies in this area of tissue engineering will attempt to enhance in vivo nerve regeneration over the long term.

Table 1 Total Fibre Count in the Distal Nerve (Mean ± SEM) of Rats 8 Weeks After Nerve Repair With a PHEMA-MMA Guidance Channel

Group	Total Fiber Count
FGF-1 (1 μg/mL)	740.70 ± 224.21
NT-3	507.61 ± 139.58
BDNF	867.77 ± 426.62
FGF-1 (10 μg/mL)	2534.26 ± 933.76
Autograft	2271.01 ± 137.87
Collagen only	535.69 ± 209.37
Empty tubes	219.66 ± 108.59

This is a partial table. Adapted with permission from the *Journal of Neurosurgery*.[40]

Nerve Conduits Used in Clinical Trials

Some of the experimental studies described above have led to clinical trials with nerve conduits to improve peripheral nerve regeneration. Successful reconstructions of the ulnar[154] and the median nerves[155] were accomplished with silicone conduits in 3 young adult male patients with gap lengths that ranged from 3 to 5 mm. However, these impermeable nonbiodegradable tubes elicited an inflammatory and fibrotic reaction and produced chronic nerve compression,[156] which ultimately required their removal after regeneration had occurred through them.

Expanded polytetrafluoroethylene has been used in the clinical setting with some success in repairing median and ulnar nerve gaps up to 4 cm in length.[157] Excellent sensory recovery was seen in 13 of the 16 patients for the repair of digital nerve gap lengths averaging 1.7 cm and in 3 of 4 patients with a 2.4-cm average gap length in median nerves[158,159] with the use of biodegradable polyglycolic acid conduits. In a randomized prospective study, polyglycolic acid tubes have also been proven to be successful in the clinical repair of digital nerves with defects up to 3 cm.[160] Polyglycolic acid tubes (Neurotube, Neuroregen, Bel Air, MD) were approved by American regulatory agencies for the repair of peripheral nerve injuries partly based on these results. Also, collagen nerve tubes (NeuraGen, Integra Neurosciences, Plainsboro, NJ) have also obtained similar approval based on their success in nonhuman primates[34,161] as well as in Phase I-II clinical safety studies. In 2001, SaluMedica (Atlanta, GA) and Collagen Matrix (Franklin Lakes, NJ) each received approval for their tubular constructs used in repairing peripheral nerves. By using a repeated freeze-thawing technique, SaluMedica produces a hydrogel tube made from polyvinyl alcohol, whereas Collagen Matrix has developed a collagen nerve cuff made from collagen fibers. Most recently, Polyganics (Groningen, The Netherlands) employed a dip coating procedure to manufacture a resorbable poly(DL-lactide-caprolactone) tube (Neurolac). However, many of the clinical studies used by these companies are limited primarily to short defects of the small-caliber digital nerve. A recent comprehensive review of the literature pertaining to the clinical use of nerve conduits is provided by Meek and Coert[162] and Freier et al.[163]

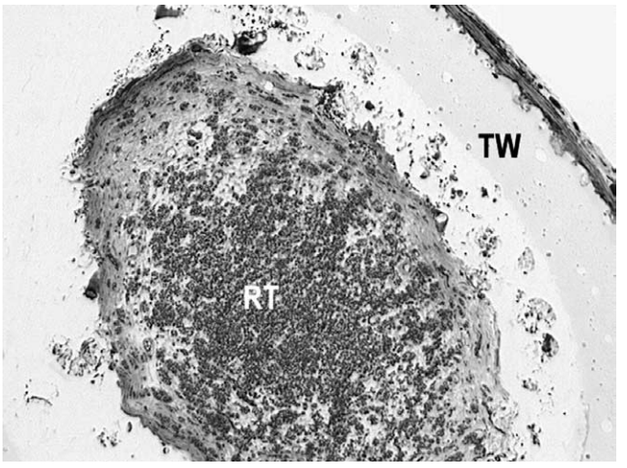

Figure 1 Representative low-power photomicrograph of 1-μm toluidine-blue-stained cross-sections of 8-week poly(2-hydroxyethyl methacrylate-comethyl methacrylate) tubes at mid-graft level. Note the contained nerve regenerating tissue (RT) within the tube walls (TW). Magnification 50×.

Conclusions

As tissue engineering progresses forward, the development of additional novel biomaterials and new ideas will likely allow the scientific and medical communities to improve functional

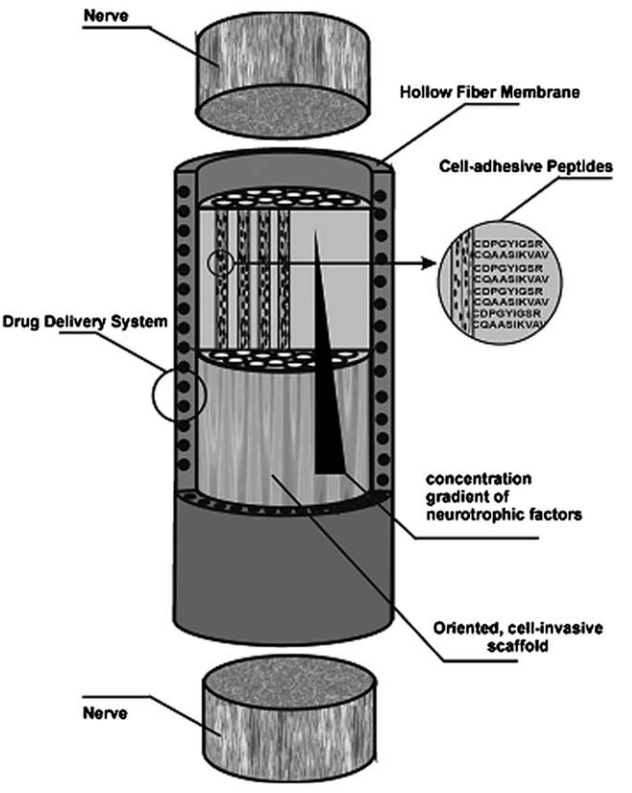

Figure 2 Design of a multicomponent peripheral nerve guide that incorporates many different strategies to optimally promote peripheral nerve regeneration. These approaches include the incorporation of haptotactic (cell-adhesive molecules) and chemotactic (neurotrophic factors) cues, an oriented scaffold, and a drug delivery system for controlled release of neuroactive agents. Reprinted with permission from Cao and Shoichet.[164]

recovery after nerve injuries. Furthermore, biotechnology is a rapidly expanding field that has great potential to improve peripheral nerve regeneration, such as the development of genetically modified cells seeded into the lumen of a conduit that release neurotrophic/neurotropic factors. The future of axonal guidance channels will likely include the design of a multicomponent nerve guidance device (such as that suggested in Fig. 2) that incorporates multiple strategies to improve peripheral nerve regeneration, including cells.

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