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Review Article

The Role of Tissue Engineering and Three-Dimensional–Filled Conduits in Bridging Nerve Gaps: A Review of Recent Advancements

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Tissue-engineered nerve guidance conduits (NGCs) are an area of research interest and investment. Currently, two separate three-dimensional, filled NGCs have Food and Drug Administration approval in the management of nerve gaps up to 3 cm in length, with more on the horizon. Future NGC options will leverage increasingly intricate designs to mimic the natural biology and architecture of native nerve tissue. To enhance the development of next-generation NGCs, experimental protocols and models should be standardized. For the NGCs currently on the market, more clinical data and randomized comparative studies are needed.

Peripheral nerve injuries (PNIs) are commonly encountered and challenging to manage. Peripheral nerve injuries have been estimated to impact 2.3% of patients presenting to the emergency department after trauma.[1] Typically associated with crush injuries, joint dislocations, and motor vehicle accidents, PNIs carry with them significant comorbidity and subsequent societal cost.[2]

When possible, tension-free primary repair of nerve lacerations remains the ideal treatment of PNIs. In situations where direct repair is precluded by the presence of a nerve gap, nerve autograft is the gold standard treatment. Autograft carries with it significant limitations, including added surgical time, additional risk, and donor site morbidity. Because of this, other approaches have been advocated, including venous and arterial autograft conduits, nerve allografts, and interpositional nerve guidance conduits (NGCs).

Early NGCs comprised various hollow tubes made of silicone or polyglycolic acid (PGA), placed between lacerated nerve ends.[3] In the years since, multiple hollow NGCs have received Food and Drug Administration (FDA) approval for the repair of nerve gaps.[4] One drawback to hollow NGCs is a limited efficacy in gaps greater than 1–1.5 cm.[5] As knowledge of the pathophysiology of nerve degeneration and repair has improved, advancements in tissue engineering have enabled more sophisticated NGCs to be imagined along with the promise of bridging longer gaps. These developments leverage three-dimensional (3D) architectural and biochemical signals in an attempt to replicate native nerve regeneration and optimize the regenerative potential of contemporary NGCs. Given the promise of modern tissue engineering techniques along with the considerable research effort being poured into nerve gap repair, the purpose of this review was to report on recent advancements in the management of PNIs with a specific focus on newer, 3D-filled nerve conduits.

Nerve Injury and Healing Response

Nerve injuries comprise a spectrum of trauma increasing in severity from neurapraxia to axonotmesis and neurotmesis described by Seddon and Sunderland.[6,7] Following neurotmesis, severed axons degenerate in a staged process known as Wallerian degeneration within 24–48 hours.[8] The initial phase of this process involves Schwann cell- and macrophage-mediated phagocytosis of myelin debris to leave an empty endoneurial tube. This is followed by Schwann cell proliferation and formation of bands of Bunger, which provide a scaffold for subsequent regeneration via the axonal growth cone originating from the proximal stump. This process is mediated by phenotypic changes in the Schwann cells at the area of injury, which leads to upregulation of specific adhesion molecules, secretion of extracellular matrix proteins, and release of numerous neurotropic growth factors and cytokines.[9] Improved understanding of the interplay between these cues and factors has provided more targets for modern tissue-engineered NGCs to replicate the

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Table 1
FDA-Approved Synthetic Nerve Guidance Conduits as of January 1, 2023

Product	Company	Material	Structure	Degradation (Wk)	Approval Date
Reaxon Plus	Medovent GmbH	Chitosan	Hollow	74–77	4/2018
RFCNC	Collagen Matrix, Inc	Type I Collagen	Hollow	26	6/2017 and 4/2020
NeuraGen 3D	Integra	Type I Collagen	Collagen and GAGs	91–122	1/2017
Axoguard Nerve Connector	Cook Biotech Inc	ECM	Hollow	N/A	10/2016
Nerbridge	Toyobo Co	PGA	Porous Collagen	N/A	6/2016
Neurolac Nerve Guide	Polyganics, Inc	PLDL	Hollow	41	10/2011
SaluBridge/SaluTunnel	Salumedica	PVA	Hollow	∞	8/2010
Neuroflex/Neuromatrix	Collagen Matrix, Inc	Type I Collagen	Hollow	10–20	9/2001
NeuraGen	Integra	Type I Collagen	Hollow	91–122	6/2001
Neruotube	Synovis	PGA	Hollow	8	3/1999

RFCNC, Reinforced flexible collagen nerve cuff.

optimal mechanical and biologic cues available in nerve autograft or primary repair.

Properties of an Ideal Conduit

Although hollow NGCs avoid donor site morbidity and provide structural support and guidance capabilities, they fail to capture the complexity of a nerve autograft. The ideal NGC leverages tissue engineering techniques to replicate biochemical and architectural signals known to support regenerating axonal bodies and guide them to their intended target.[10] Physical properties of optimal NGCs include biocompatibility, degradation, suturability, and adequate strength and elasticity to withstand physiologic motion. Biocompatibility protects against inflammatory response and subsequent scarring of regenerating nerves.[11] Degradation of NGCs in the months to years after grafting avoids the risk of later external compression from the conduit itself and involves a delicate balance where the rate of degradation does not outstrip regenerative capacity. Practically, NGCs must be able to tolerate suture coaptation to nerve ends and subsequent physiologic levels of motion without sustaining damage or kinking.

To nurture axonal regeneration, NGCs must also provide biological support. This includes being permeable to allow diffusion of nutrients and oxygen while not allowing fibroblast infiltration, which may lead to glial scar formation.[12] The 3D microarchitecture of NGCs must account for the fascicular organization of the proximal and distal nerve stumps and serve as a guidance conduit to the distal endoneurial target. Furthermore, interior conduit design must provide structural support to regenerating axons, which includes containing appropriate adhesion molecules and extracellular matrix protein components.[13] Finally, NGCs ideally would be designed to provide sustained neurotropic growth factor and Schwann cell support, potentially in gradients that provide directional cues.[10]

Current Conduit Options

Kehoe et al[4] identified seven FDA-approved NGCs as of 2010. Since then, six new conduits have received FDA approval (Table 1). Four of these are hollow conduit designs of varying materials. NeuraGen 3D and Nerbridge are the first approved implants to offer 3D structure beyond the hollow tubular structure of standard NGCs (Fig. 1). These novel 3D conduits may ultimately allow for bridging longer gaps beyond 1.5 cm, but clinical data are currently lacking.

NeuraGen 3D is a type 1 collagen tube filled with a longitudinally aligned inner matrix of collagen and chondroitin-6-sulfate, which is an extracellular matrix protein upregulated in nerve injury and demonstrated to mediate Schwann cell migration.[14] Preclinical studies compared a prototype of the NeuraGen 3D NGC with reversed autograft, hollow conduit (NeuraGen), and conduit with collagen matrix alone in a 1 cm rat sciatic nerve gap model.[15] They found that NeuraGen 3D performed comparably with reversed autograft and better than hollow or collagen-filled NGCs in terms of nerve fiber density and myelinated axon count at 12 weeks.[15] In vivo studies have demonstrated robust Schwann cell ingrowth along the collagen-glycosaminoglycan matrix.[16] Follow-up clinical studies are needed.

Nerbridge is a woven PGA tube filled with a porous collagen matrix and external collagen coating. Kusuhara et al[17] reported on the use of Nerbridge to bridge 20 digital nerve gaps at multiple centers with a mean length of 17 mm in which 90% of patients had meaningful recovery of sensibility. Although these results are promising, a comparative study using a rat sciatic nerve model found that Nerbridge performed worse than autograft and hollow collagen conduit on the maintenance of compound muscle action potential, maximal tetanic force generated, and maintenance of weight of the tibialis anterior muscle at 3–4 months postinjury.[18]

Query of ClinicalTrials.gov identified three registered clinical trials involving other engineered NGCs not currently approved by the FDA. One (NCT02970864) is ongoing and seeks to evaluate the safety and efficacy of Polynerve (University of Manchester), a Poly DL-lactide-co-ε-caprolactone (PLCL) tube with a microgroove inner luminal structure, on human digital nerve injuries.[19] Second (NCT03673449) involves the use of a silk fibroin NGC (SilkBridge) with two electrospun layers to reconstruct digital nerve defects with results not yet published. The other trial (NCT01884376) involved Neuromaix (Matricel GmbH), a collagen conduit with inner collagen microchannels, which was shown to be safe when used in humans to bridge sural nerve gaps of 20–40 mm after sural nerve biopsy.[20]

Advances in Conduit Materials

A wide array of conduit materials has been described and tested to varying degrees. Many provide adequate macrostructure and physical properties required of nerve grafts such as flexibility, strength, and suturability.[10] Collagen, PGA, polyvinyl alcohol (PVA), PLCL, and chitosan conduits are well described and have all been approved for human use by the FDA (Table 1). Conduit material can be further characterized by biodegradability. Collagen, PGA, chitosan, and PLCL conduits are eventually resorbed in vivo, whereas silicon and PVA implants are not. Other biomaterials, such as silk, are investigational. Brief summaries of selected commonly studied conduit materials are to follow.

Collagen

Collagen is an abundant structural protein found in nerves and other human tissues. Collagen conduits are semipermeable, are biocompatible, and exhibit good neuronal and Schwann cell

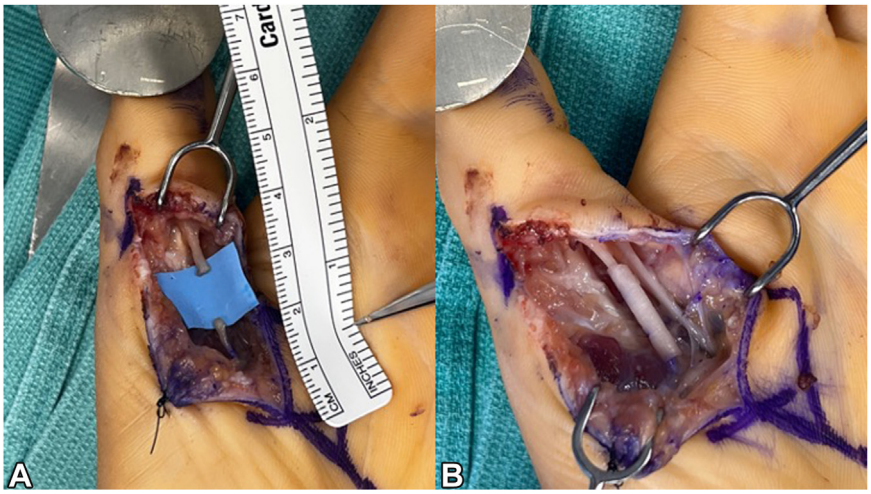

Figure 1. **A** One-centimeter digital nerve gap **B** bridged with the NeuraGen 3D conduit.

attachment.[9] This explains how they have been the cornerstone of NGC engineering approaches for the last 30 years with multiple FDA-approved NGCs including NeuraGen, NeuraGen 3D, Axoguard, and NeuroFlex. Degradation time varies by implant but has been reported to range from 3 months to multiple years.[4] Collagen guides have been the first to include 3D architectural supplementation in the form of an inner matrix of collagen and glycosaminoglycan in NeuraGen 3D and in the form of microchannels in Neuromaix.

Poly DL-lactide-co-ε-caprolactone

Poly DL-lactide-co-ε-caprolactone is a common polymer used in a wide variety of tissue engineering applications.[9] Poly DL-lactide-co-ε-caprolactone is amenable to 3D printing techniques and demonstrates highly tunable features including mechanical properties, porosity, and supplementation with other materials, which make it a promising material in the development of next-generation composite NGCs. Neurolac is an FDA-approved NGC made of PLCL, and Polynerve is a 3D-grooved NGC in clinical trials for use in digital nerve injury. Incomplete resorption of Neurolac conduits has been reported at 16 and 24 months.[21] In one of the few comparative studies available on motor recovery in a rat sciatic nerve defect model, PLCL performed comparably with autograft and better than collagen in some but not all analyses.[22]

Polyglycolic acid

Polyglycolic acid is used in Neurotube, one of the early FDA-approved hollow NGCs. Hallmarks of PGA guides include its more rapid degradation, permeability, and flexibility compared with other NGCs.[3] Polyglycolic acid guides are limited by the cost of production as well as poor structural integrity, leading to early collapse of the conduits in vivo by 12 weeks and complete degradation by 3 months.[4,22] Shin et al[22] reported that PGA grafts performed the worst of the clinically available NGCs including PGA, collagen, and PLCL grafts on 10 mm rat sciatic nerve gaps.

Polyvinyl alcohol

Polyvinyl alcohol is a synthetic polymer used in FDA-approved NGC Salubridge. Polyvinyl alcohol is not resorbable, which is considered a disadvantage versus other available biodegradable grafts, owing to the concern for extrinsic constriction of the regenerating nerve. Stocco et al[23] engineered a biodegradable-oxidized PVA conduit that demonstrated efficacy in a rat sciatic nerve model and merits further study.

Chitosan

Chitosan is a natural biopolymer that has become increasingly popular in NGC design. The FDA-approved Reaxxon hollow NGC is made of chitosan. Chitosan can be manufactured to exhibit a variety of forms including tubes and hydrogels.[24] Chitosan fibers have been demonstrated to enhance the aligned orientation of axons and Schwann cells[25] and, further, can be easily handled and sutured.

Silk

Silk is a remarkable natural biomaterial with numerous characteristics that make it promising in the field of tissue engineering, including its strength, flexibility, modifiability, and relatively low expense.[26] Silk is widely used as a suture material due to its biodegradability and muted local tissue response.[27] Active research into how to optimally tune silk NGCs to provide optimal degradation time, topographical cues, and Schwann cell binding sites is ongoing. Dinis et al[28] reported production of multiple-channel silk NGCs using an electrospinning technique, and a silk NGC is being evaluated in an active FDA trial on digital nerve repair using SilkBridge.

Advances in Conduit Architecture and Filler

Conduit fillers enhance nerve repair by creating a more natural and biologically friendly environment.[11,29] Common fillers include natural polymers like fibrin, laminin, collagen, and agarose and synthetic polymers like polyamide and PGA among others.[29] Topography is another active area of research promise in NGC development. Aligned channels or grooves may enhance directional guidance of regenerating neurons via surface interactions and physical support in a manner that mimics endoneurial tubes[15,26] (Fig. 2). Architectural modifications take place on the marco- and micro-scale, ranging from multiple-channel NGC lumens similar to endoneurial architecture to nanoscale microchannels and grooves.

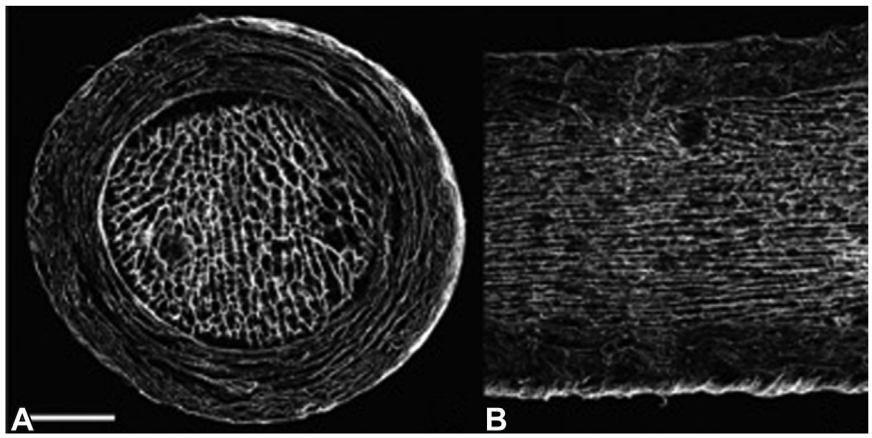

Figure 2. NeuraGen3D conduit cross-section and long section demonstrating longitudinal orientation of matrix as visualized by electron microscopy. Image adapted from Integra promotional materials.

Future NGCs will almost certainly incorporate 3D structure and topographical modifications to better support and directionally guide regenerating axons and Schwann cells. This is reflected in the recent FDA approval of NeuraGen 3D and Nerbridge, and the three actively registered clinical trials on nerve gap repair, which all involve unique 3D NGC approaches.

Biologic Enhancement

Because of the drawbacks associated with nerve allografts and autografts, tissue-engineered nerve grafts are being developed to incorporate biologic factors including stem cells, neurotrophic factors, and platelet-rich plasma (PRP) that may help promote regrowth of the nerves.[13] Nerve guidance conduits with biologic augmentation reduce the risk of rejection or immunosuppression associated with using allografts. Future work on biologic augmentation may be able to address gap length limitations of current NGC designs, with promising approaches described below.

Cell level supplementation

Given their central role in nerve regeneration, NGC augmentation with Schwann cells has unsurprisingly demonstrated promise. In animal models, nerve grafts seeded with Schwann cells had similar functional recovery to those with autografts.[30] Schwann cells can be further modified to express factors specific to nerve regrowth and potentially increase axonal regeneration, myelination, and electrophysical recovery.[31] Stem cells with the ability to differentiate into Schwann cells are also under investigation, including bone marrow stem cells,[32] adipose-derived cells,[33] and skin-derived precursors.[34]

Neurotrophic factors

Along with Schwann cells, supplementation of NGCs with particular neurotrophic factors may also improve nerve gap repair outcomes. Brain-derived neurotrophic factor, ciliary neurotrophic factor, and neurotrophin-3 have all shown promise in effecting axonal regeneration, myelination, and functional recovery.[35]

Platelet-rich plasma

Similarly, PRP supplementation may affect nerve regeneration via multiple mechanisms, including fibrin clot scaffolding, cell proliferation, and neurotrophic factor delivery.[36] Platelet-rich plasma has been reported to be an effective adjunct to nerve repair in two cases, one in a large ulnar nerve gap[37] and the other with a radial nerve gap.[38] Further study of PRP is needed to determine its efficacy in nerve repair.

Drug delivery in conduits

Tacrolimus and erythropoietin have both been shown to enhance nerve regeneration and are amenable to encapsulation and delivery with microsphere technology.[39,40] Nerves exposed to tacrolimus were shown to have significant improvements in muscle mass, myelination of axons, and action potentials.[39] Erythropoietin use in nerve conduits may also repair performance of grafts and accelerate healing of nerves.[40]

Electrostimulation

Finally, electrical stimulation may accelerate the healing of peripheral nerves.[11] Conduits or hydrogel fillers that conduct electricity have been shown to be highly effective at restoring muscle action potentials, motor unit potentials, and nerve conduction velocity in peripheral nerves when combined with Schwann cells.[41,42]

Engineering Approaches

Improvements in 3D printing have allowed novel NGC designs to mimic the architecture, biocompatibility, and mechanical properties of actual nerves.[43] Three common ways in which NGCs are being printed include stereolithography, which builds complex conduits by using ultraviolet light to mold a resin of choice; extrusion-based printing, which deposits a stream of the material of choice in a layer-by-layer fashion ultimately creating the 3D object; and, finally, inkjet printing, which uses tiny droplets of a polymer and places them in a highly controlled manner allowing for the creation of specific, complex 3D structures.[10,44] These technologies are capable of adding finely tuned pores and embedding conduits with growth factors and adhesion molecules to direct Schwann cell migration and neurite outgrowth.[10] What's more, leveraging 3D scans of peripheral nerves to generate patient-specific, personalized conduits is now being discussed as a future direction.[10,45]

Limitations to Adoption

Considerable work still needs to be done before the ideal conduit can be used in the clinical setting. Currently, most studies of NGCs are limited to the laboratory or nonhuman mammals, many of which have superior nerve regenerative capacity compared with humans. Furthermore, the manner of nerve injury along with the size of the defect being studied with experimental NGCs are not standardized. Comparison groups are not standardized between studies (allograft, autograft, and coaptation), and assessment of conduits should focus on gap distances that are not amenable to end-to-end repair. In summary, although initial results are exciting, more work is needed to confirm the capabilities of 3D-filled NGCs.

Conflicts of Interest

No benefits in any form have been received or will be received related directly to this article.

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