Journal of Controlled Release 163 (2012) 342–352

Contents lists available at SciVerse ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Review

Biochemical engineering nerve conduits using peptide amphiphiles

Aaron Tan [a], Jayakumar Rajadas [b], Alexander M. Seifalian [a,c,*]

[a] Centre for Nanotechnology & Regenerative Medicine, UCL Division of Surgery & Interventional Science, University College London, London, UK
[b] Biomaterials & Advanced Drug Delivery Laboratory, Department of Neurology & Neurological Sciences, School of Medicine, Stanford University, CA, USA
[c] Royal Free London NHS Foundation Trust Hospital, London, UK

ARTICLE INFO

Article history:
Received 12 June 2012
Accepted 7 August 2012
Available online 15 August 2012

Keywords:
Drug delivery
Peptide amphiphiles
Nerve conduit
Biochemical engineering
Nerve tissue engineering

ABSTRACT

Peripheral nerve injury is a debilitating condition. The gold standard for treatment is surgery, requiring an autologous nerve graft. Grafts are harvested from another part of the body (a secondary site) to treat the affected primary area. However, autologous nerve graft harvesting is not without risks, with associated problems including injury to the secondary site. Research into biomaterials has engendered the use of bioartificial nerve conduits as an alternative to autologous nerve grafts. These include synthetic and artificial materials, which can be manufactured into nerve conduits using techniques inspired by nanotechnology. Recent evidence indicates that peptide amphiphiles (PAs) are promising candidates for use as materials for bioengineering nerve conduits. PAs are biocompatible and biodegradable protein-based nanomaterials, capable of self-assembly in aqueous solutions. Their self-assembly system, coupled with their intrinsic capacity for carrying bioactive epitopes for tissue regeneration, form particularly novel attributes for biochemically-engineered materials. Furthermore, PAs can function as biomimetic materials and advanced drug delivery platforms for sustained and controlled release of a plethora of therapeutic agents. Here we review the realm of nerve conduit tissue engineering and the potential for PAs as viable materials in this exciting and rapidly advancing field.

Contents

1. Introduction

Peripheral nerve injury is a critical and disabling condition. Every year, around 100,000 patients in the USA and Europe undergo nerve surgery for the purpose of rectifying it [1]. With a small transection gap of less than 20 mm between nerves, it is possible to surgically repair it by reapproximating the ends of the injured nerve via direct apposition using sutures. However, when lesion gaps are greater than 20 mm, current clinical gold standard dictates the performance of autologous nerve grafting [2]. Nevertheless, there are significant complications associated with this technique. An autologous nerve graft is harvested from another part of the body (the donor site) for use in the lesion (recipient site) in question. This necessitates the generation of a secondary injury at the donor site. Unresolved issues

* Corresponding author at: Nanotechnology & Regenerative Medicine, University College London, London NW3 2QG, United Kingdom. Tel.: +44 207 830 2901.
E-mail address: a.seifalian@medsch.ucl.ac.uk (A.M. Seifalian).

0168-3659/$ – see front matter
http://dx.doi.org/10.1016/j.jconrel.2012.08.009

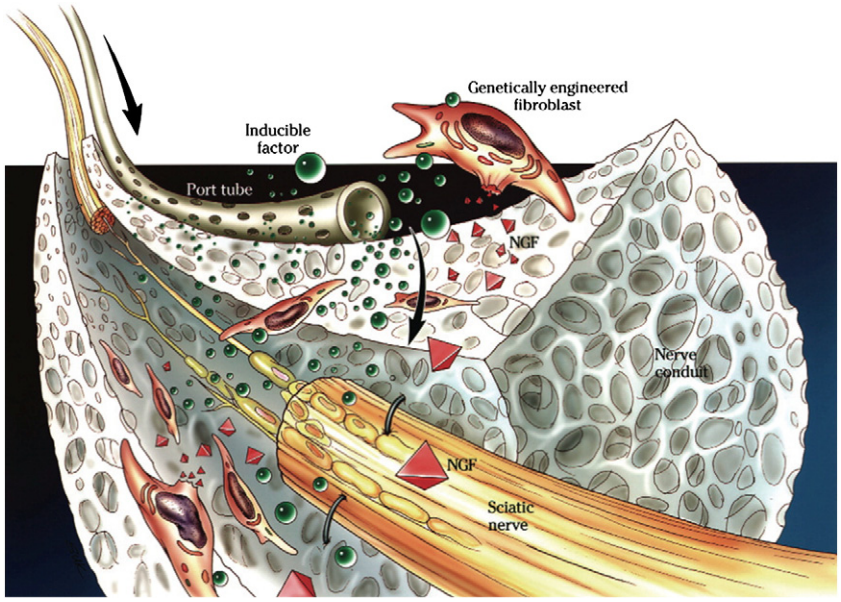

Fig. 1. An ideal nerve conduit. A nerve conduit should ideally possess attributes that would allow it to support the growth and regeneration of neural cells. Nutrients and growth factors are vital for neural cell regeneration. Copyright © 2006 Foundation for Cellular and Molecular Medicine/Blackwell Publishing Ltd. Reproduced with permission from [4].

include tissue scarring; insufficient length of nerve graft; formation of neuroma; and the possible loss of sensation and function at the donor site [3].

To address these disconcerting attributes of autologous nerve grafting, biochemical engineering of nerve conduits has emerged as an alternative technique. A nerve conduit should ideally possess features that permit the regeneration and reanimation of both endogenous and exogenous neural cells [4] (Fig. 1).

The most important characteristic that a bioartificial nerve conduit must possess is biocompatibility. This means that the material must not be toxic, and its presence in the body should not elicit an immunological response. If the material used is biodegradable, its degradation kinetics should match the rate of nerve tissue regeneration to ensure an optimal healing process. Design parameters should encompass aspects like adequate porosity to facilitate the delivery of nutrients to the regenerating neural cells, and appropriate nanotopography to promote cell adhesion and proliferation [5]. Furthermore, these nerve conduits should also be engineered in such a way that the constituent fibers possess adequate tensile strength without compromising flexibility [6].

Recent evidence suggests that peptide amphiphiles (PA) are able to fulfill these design criteria, and are emerging as a viable material for bioengineering nerve conduits [7]. PAs have a dual functionality of simultaneously being hydrophobic and hydrophilic, with the additional ability of delivering bioactive molecules to the site of injury [8]. Their supramolecular arrangement allows for the spontaneous self-assembly of nanofibers [9] (Fig. 2).

This balance of polarity between attractive and repulsive forces within the nano-molecular construct further alludes to their novel properties [10]. In this review, we seek to explore the realm of bioartifical nerve conduit engineering, and expound on the concept of using PAs for the biochemical engineering of nerve conduits.

2. Biochemical engineering nerve conduits

2.1. Overview

Nerve tissue engineering is a rapidly evolving and expanding field in the realm of biomedicine. A multitude of in vitro and in vivo studies have been conducted to assess the viability of different materials, and feasibility of different fabrication methods for building the ideal nerve conduit (Table 1).

Materials used for manufacturing nerve conduits can be categorized into 2 classes: synthetic [11] and natural [12]. Synthetic materials include aliphatic polyesters, polyurethanes, polyphosphoesters, piezoelectric polymers, and hydrogel-based materials. In contrast, natural materials are derived from animals, with some examples including decellularized scaffolds, polysaccharides (e.g. chitosan), and collagen.

Aliphatic polyesters are a class of polymers, and some examples are: polylactic acid (PLA), polyglycolic acid (PGA)[13,14], polycaprolactone (PCL)[15–17], poly(3-hydroxybutyrate) (PHB), and poly(lactic-*co*-glycolic acid) (PLGA)[18–20]. These polymers are biocompatible, and can be synthesized into fibers via a method called electrospinning [21]. Electrospinning is a fabrication technique whereby an electric charge is used to produce exceedingly fine (in the nanoscale) fibers [22]. There is evidence to suggest that neural cells can adhere to and proliferate on these nanofiber assemblies [23–26].

Natural materials like laminin [27], collagen and chitosan [28,29] have also been investigated as scaffolds for nerve conduits. In addition, semi-natural materials like poly(epsilon-caprolactone)/gelatin and nanofiber-collagen composites have also been explored as possible materials for constructing nerve conduits [30,31]. These hybrid materials harbor the intrinsic qualities from both natural and synthetic materials [32–34].

2.2. Design considerations

In addition to selecting the appropriate material, it is imperative to have optimal design parameters that would allow nerve conduits to espouse characteristics of actual nerves. For instance, it is imperative for neural cells in the nerve conduit to obtain nutrients and growth factors [35] (Fig. 3).

Porosity is one factor that determines the flow of essential growth molecules, and plays an important role for neural and axonal regeneration [36,37]. Self-assembling peptide nanofibers have been propounded as possible materials for constructing nerve conduits [38,39], with several studies indicating their ability to support neural progenitor cell growth and differentiation [40,41].

Different nerve conduit materials have been experimented for use in humans (Table 2), and some examples include expanded

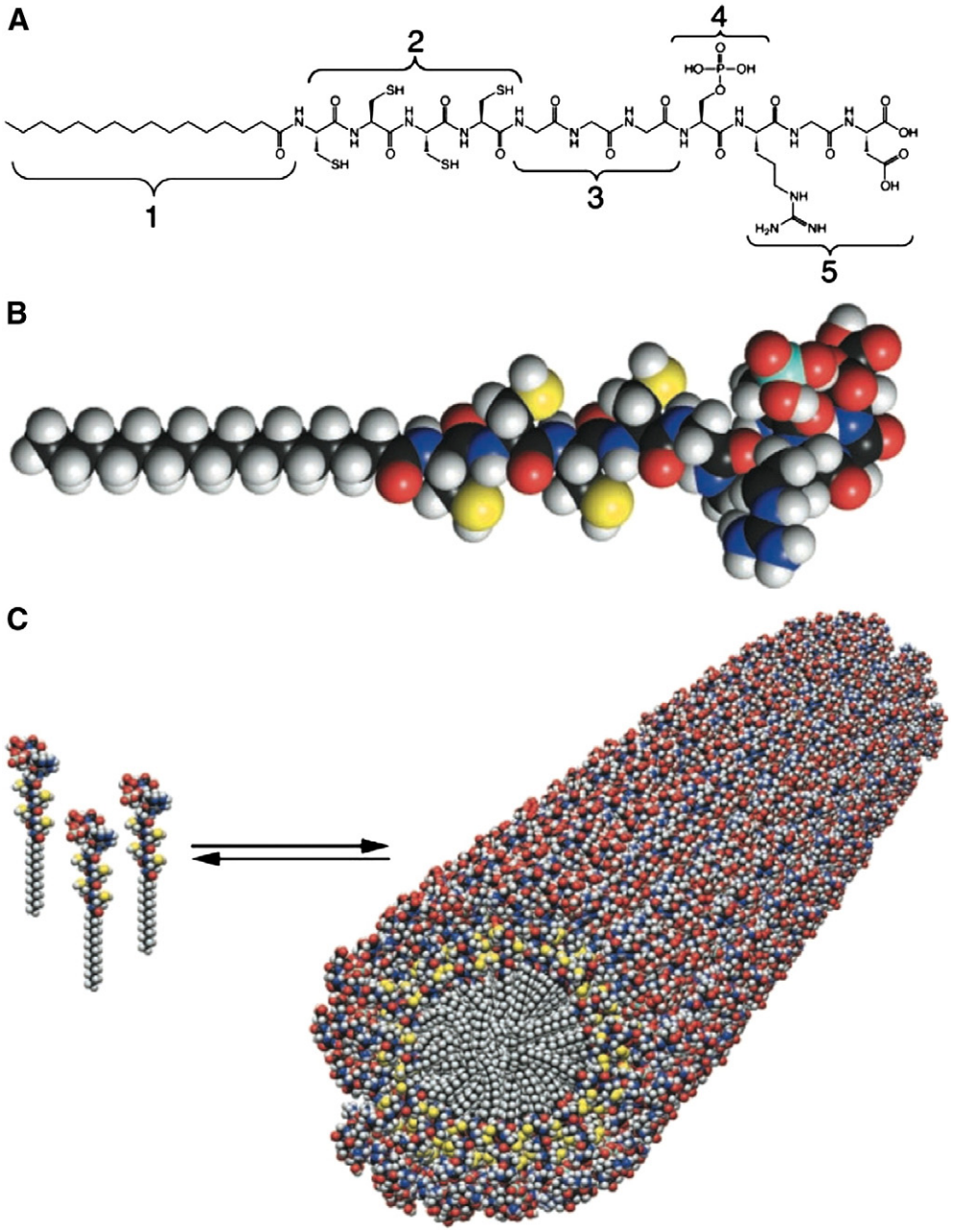

Fig. 2. Peptide amphiphiles. A Chemical structure of a peptide amphiphile, encompassing: (1) A hydrophobic alkyl tail, (2) Four cysteine residues for self-assembly, (3) Linker region of three glycine residues for hydrophilic head group, (4) A phosphorylated serine residue for mineralization, (5) A bioactive epitope. B Molecular model of a PA. C Self-assembly of PA molecules into a cylindrical micelle. Copyright © 2001 American Association for the Advancement of Science. Reproduced with permission from [9].

polytetrafluoroethylene (ePTFE)[42–45], polylactide-caprolactone (PLCL)[46,47], polyglycolic acid (PGA)[48–56], silicone [57–64] and collagen [65–69]. The US Food & Drug Administration (FDA) has approved several nerve conduits for clinical use (Table 3), and they are generally hollow tubes made from materials like collagen, PGA, PLCL or alcohol-based hydrogels [1,70,71] (Fig. 4).

3. Peptide amphiphiles

3.1. Structure

Peptide amphiphiles (PAs) are self-assembling peptides with the ability to form nanofibers. PAs typically have 4 regions: a hydrophobic alkyl chain, a beta-sheet forming segment, a peptide charged segment, and a customizable bioactive epitope [72] (Fig. 5). Its capacity for self-assembly can largely be attributed to the balance of attractive and repulsive forces within its nano-architectural arrangement [73]. Evidence indicates that PAs can be used to construct nerve conduits (Table 4). PAs are biodegradable [74] and does not elicit an appreciable immunological response, underscoring its potential to be a promising material for nerve conduits. Further, the products of degradation are sugars and amino acids, and therefore are not toxic to biological systems. In contrast to PAs, many polymers tend to degrade into products that might not always be biocompatible and can elicit an immune reaction. PAs can also be considered "polymers" of amino acids with charged groups. Hence, the configuration of its nano-architecture can be

Table 1
Bioengineering nerve conduits. Keys: ES, electrospinning; SD, Sprague–Dawley.

Scaffold material	In vitro/vivo	Fabrication technique	Overview	Ref
• Polyamide nanofibers • Functionalized with tenascin-C derived peptides	In vitro	ES	• Nanofibrillar • Synthetic • Neurites had a greater total length than on PLL control	[11]
Poly (2- Hydroxyethyl methacrylate-co-methyl methacrylate) (PHEMA-MMA) hollow porous tubes	Lewis rats	Molding via centrifugal forces	• Axonal regeneration within 8 weeks • Regeneration was comparable to autografts in 60% of rats	[36]
• Poly(3-hydroxybutyrate-co-3-hydroxyhexanoate)(PHBHHx) conduit • Uniform and non-uniform wall porosity	SD rats	Dipping-leeching method	Non-uniform wall porosity had results similar to autograft control	[37]
• Copolymer of ε-caprolactone and ethyl ethylene phosphate (PCLEEP) • Microfiborous scaffold functionalized nerve growth factor (NGF)	In vitro	ES	• Sustained release of NGF over 3 month period • Fibers partially aligned Stimulates neuronal differentiation	[16]
Poly(ε-caprolactone) (PCL) microfibers	In vitro	ES	• Cells align with fiber axis Schwann cells shown neuronal differentiation on both aligned and unaligned fibers	[15]
Polydioxanone (PDO) microfibers	In vitro	ES	• Aligned fibers directed neuronal growth • Directionality not observed on unaligned fibers	[21]
Poly-L-lactate (PLL) microfibers	In vitro	ES	Aligned fibers increase neurite length and direct growth	[13]
Self assembling peptide nanofiber	Syrian hamsters	Self-assembly	Functional return of vision after severing of the optic tract	[38]
• Self-assembling peptide nanofiber • RADA16 (Ac-RADARADARADARADA-COHN2) Functionalized with motifs from collagen, laminin, fibrin, fibronectin, osteopontin, and osteogenic peptides	In vitro	Self-assembly	• Scaffolds with bone marrow homing motifs significantly enhanced cell survival • On these scaffolds, the % of cells expressing neuronal markers was similar to that on Matrigel	[39]
Poly(3-caprolactone) and porcine gelatin blend	In vitro	ES	• Differentiation and proliferation enhanced with respect to PCL nanofibrous scaffolds • Randomly oriented fibers did show good results, but fiber alignment enhanced these effects	[30]
• Self-assembling peptide nanofiber scaffold • Pre-cultured with neural progenitor cells and Schwann cells prior to implant	SD rats	Self-assembly	• Progenitor cell survival, differentiation and migration observed both in vivo and in vitro • Vascularisation of scaffolds observed	[40]
• Micropatterned laminin • Patterned using aligned microfibers of poly(D, L-lactide-co-glycolic • acid) (PLGA) Functionalized with nerve growth factor	In vitro	ES	• Under the influence of fluid sheer stress, most cultured progenitors differentiated into neurons • Neurons aligned to fibers	[18]
• Poly(acrylonitrile-comethylacrylate (PAN-MA) sub-micron aligned fiber films • Films stacked within a hollow polysulfone nerve conduit	In vitro & rats	ES	• Aligned constructs promoted axonal regeneration across a 17 mm gap • Recovery of fine motor control was increased with respect to unaligned fibers	[23]
• Nanofibrous copolymer of methyl methacrylate and acrylic acid (PMMAAA) Functionalized by immobilization of collagen onto the nanofiber surface	In vitro	ES	Cell viability assay and metabolic activity assay indicate that this is a suitable material for cell growth.	[31]
• Nanofibrous blend of $(C28O4N4H47)n$ and $(C27O4.4N4H50)n$ Functionalized with tenascin-C derived peptides	SD rats	ES	• Functionalization increased axonal regrowth • Randomly orientated fibers impeded regrowth	[22]
Murine laminin-1 nanofibrous mesh	In vitro	ES	• Progenitors exhibited neurite growth without addition of growth factors • Rate and quality of attachment was greater than on laminin films	[27]
• Poly(L-lactide) (PLLA) nanofibers • Poly(lactide-co-glycolide) (PLGA) nanofibers • Surface treated with KOH to reduce surface tension	In vitro	ES	• Both substrates exhibited cellular growth and attachment • If the inter-fiber distance is greater than 15 μm, the neurons follow the fibers • Neurons travel perpendicular to the fibers at lower inter-fiber distances. • Neurites did not extend into regions with inter-fiber distances <1 μm	[19]
• Collagen tubes • Functionalized with luminal collagen filaments	Beagle dogs	Winding of fiber	• Does not elicit immune response • Minimal scar tissue formed • Functional recovery within 52 weeks	[12]
• Poly(lactic-*co*-glycolic acid) (PLGA)and polycaprolactone(PCL) blend • Nanofibrous tubes • Tubes filled with saline	SD rats	ES	• Regeneration of nerves through lesion • Functional nerve reconnection • No significant immune response	[20]
• Poly(L-lactide) (PLLA) nanofibers Covalently functionalized with bFGF and laminin	In vitro	ES	• Synergistic effect of fiber alignment and functionalization • Cell migration higher than in untreated group • Neurite extension was increased with respect to untreated animals	[14]
Nanofibrous PCL/chitosan blend	In vitro	ES	• Increased cell proliferation and attachment with respect to PCL alone • Schwann cells maintained phenotype after growth on scaffold	[32]
• 5 different microfibrous scaffold materials • Poly(3-hydroxybutyrate) (PHB) • Poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) (PHBV) • Poly(L-lactic acid) (PLLA) • Chitosan (CS) Polycaprolactone (PCL)	In vitro	ES/casting	• Cell attachment greatest on the PCL film • Cells were able to penetrate into all nanofibrous scaffolds except PCL	[33]

(continued on next page)

Table 1 (*continued*)

Scaffold material	In vitro/vivo	Fabrication technique	Overview	Ref
Poly-ε-caprolactone and collagen/poly-ε-caprolactone (c/PCL) blend nanofibers	In vitro	ES	• Both fiber types supported neurite outgrowth from dorsal root ganglia explants • Migration and neurite orientation of Schwann cells were improved on c/PCL blend compared to PCL alone	[34]
• Cross-linked poly(ε-caprolactone fumarate) of 3 molecular weights; 530, 1250, and 2000 g mol^{-1} Hollow tubular conduit	In vivo and in vitro, rats	Glass mold	• 2000 g mol^{-1} provided best cell attachment and proliferation • Myelinated nervous tissue was found within the conduit after both 6 and 17 weeks of implantation	[17]
• Poly(3-hydroxybutyrate) • Poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) • Microfibrous mats compared to films	In vitro	ES	• RT4-D6P2T cell attachment and proliferation were higher on films than fiber mats • L929 attach and proliferate better on fiber mats	[24]
• Self-assembling RADA16-I peptides • PFSSTKT functional epitope was interspersed within the RADA16-1 fibers • Glycerine spacers were used to separate the RADA16-1 and PFSSTKT within the fiber The no. of spacers was varied from 0 to 4	In vitro	Self-assembly	Spacers are important in ensuring that the PFSSTKT epitope is exposed to the environment, as opposed to being hidden within molecule	[41]
• Non-woven chitosan nano/microfiber mesh tubes Introduced glycine spacers into CYIGSR sequence	SD rats	ES and molding	Enhanced nerve regeneration	[29]
Chitosan non-woven micro/nanofiber mesh tubes	SD rats	ES and molding	Functions as a scaffold for neural cell migration, attachment and nerve regeneration	[28]
• Chitosan-poly-lactic acid mix • Hollow nerve conduit	SD rats	Rotating mandrel	• Material is not cytotoxic in vitro • Chitosan-PLA conduit more effective than silicone conduit at restoring sciatic nerve function	[25]
Aligned poly(ε-caprolactone) (PCL) nanofibers	In vitro	ES	• Promotes differentiation of cultured embryonic stem cells into neural lineages. • Aligned fibers direct neurite growth	[26]

modulated by changes in pH [75]. This therefore highlights the importance of designing the optimal self-assembly configuration of PAs in pH ranges which reflect biological systems [76,77].

3.2. Nerve regeneration

The nanofiber self-assembly framework of PAs promotes the migration and proliferation of neural cells [78]. Experimental data suggests that the bioactive epitope region of PAs promotes neural cell proliferation [79–81]. The bioactive epitopes of PAs are customizable to suit different purposes [82,83]. For instance, integrins would promote adherence of neural cells [84], while RGD motifs and IKVAV sequences facilitate neural cell growth and proliferation [85].

IKVAV is a pentapeptide, made up of a sequence of amino acids Ile-Lys-Val-Ala-Val, first identified in the A chain of laminin [86]. IKVAV is a neurite-promoting laminin epitope [87], and has been demonstrated to upregulate the proliferation of neural cells [88] (Fig. 6). In addition, the presence of IKVAV reduces astrocyte formation and hence minimizing the risk of glial scars [89]. Furthermore, it also inhibits apoptosis and mitigates astrogliosis [90] (Fig. 7). In terms of incorporation of a bioactive epitope on PAs, IKVAV and RGD appear to be the two most widely studied molecules for the application of developing nerve conduits.

Sonic hedgehog homolog (SHH) is a protein that is part of the hedgehog signaling pathway, and is thought to play a vital function in nerve regeneration during injury. Experimental data suggests

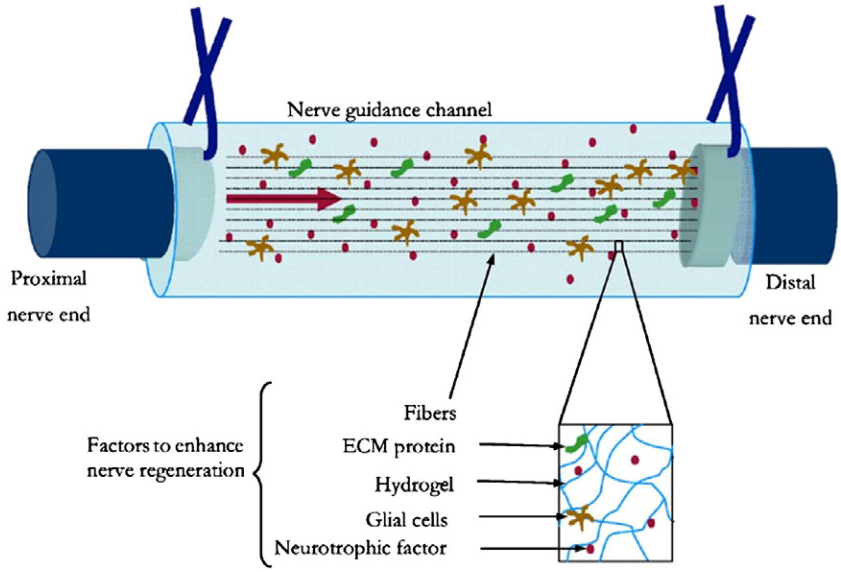

Fig. 3. Nerve conduit to support nerve regeneration. An artificial nerve conduit should function as a protective sheath, with the ability to deliver small molecules favorable for nerve regeneration. Copyright © 2006 Elsevier B.V. Reproduced with permission from [35].

Table 2
Nerve conduits used in humans. Keys: ePTFE, expanded polytetrafluoroethylene; Pat, patients; PGA, polyglycolic acid; PLCL, polylactide-caprolactone; NDL, nerve defect length.

Material	NDL (mm)	No. of pat	Outcome	Ref.
Silicone				
	3	3	• Highlights potential difficulties in using silicone as a sheath • Deterioration in nerve function required removal of silicone conduits.	[57]
	3	1	Recovery of motor and sensory functions in ulnar nerve in wrist	[58]
	3–5	2	Recovery of motor and sensory functions in median nerve in forearm	[59]
	3–5	11	Recovery of motor and sensory functions in median and ulnar nerves in forearm, using silicone as a sheath	[60]
	30–50	11	Motor and sensory recovery observed in median nerve, ulnar and radial nerve	[61]
	20–50	26	Recovery of motor and sensory function of median and ulnar nerve, with nerve injury gaps <3 mm.	[62]
	3–5	7	Recovery of motor and sensory functions in median and ulnar nerves in forearm	[63]
	3–5	17	5-year follow up of tubular repair of median and ulnar nerve in forearm indicates favorable results with little or no side effects.	[64]
ePTFE				
	29	1	Recovery of motor and sensory functions of a 2.9 cm ulnar nerve gap in wrist	[42]
	15–60	43	Recovery of motor and sensory functions of median and ulnar nerves, with gaps <40 mm	[43]
	2–15	7	Recovery of sensory function in 2 pats. Only effective with nerve gaps <3 mm	[44]
	3	6	• Poor results observed • ePTFE not recommended as nerve conduit	[45]
PGA				
	5–30	15	Recovery of sensory function digital nerves, with gap transections of up to 3 cm	[48]
	25	1	Recovery of motor and sensory function of inferior alveolar nerve	[49]
	2–12	98	Improved sensory function in digital nerves, with gaps of <4 mm	[50]
	20	1	Effective in mitigating neuroma pain by facilitating neural regeneration	[51]
	Not stated	1	Functional recovery of peripheral nerve in hip joint	[52]
	20–65	2	Attenuation of type II complex regional pain syndrome; motor and sensory recovery observed in digital nerves	[53]
	25–36	2	Functional recovery by 65 days after surgery in proper digital nerve and superficial peroneal nerve	[54]
	10–30	7	Motor and sensory recovery in facial nerve, with gap transections of <30 mm	[55]
	10–40	17	Good clinical results observed in digital nerve lesion	[56]
PLCL				
	5–12	2	Report of a technically successful operation	[46]
	2–20	17	Recovery of sensory nerve function in peripheral nerve defect of <20 mm	[47]
Collagen				
	2.5–20	96	Improvement in 45% of patients	[65]
	12.5	14	Functional recovery in 9 patients	[66]
	18–50	9	Functional recovery in all patients	[67]
	Not stated	9	Functional recovery in 8 out of 9 patients	[68]
	2.8–17.3	5	Functional recovery in all patients	[69]

that SHH-incorporated PAs reduce apoptosis and aid nerve regeneration in a cavernous nerve injury rodent model [8]. Furthermore, SHH-incorporated PAs ensure that the bioactive epitope is targeted locally rather than systemically, as activation of the SHH is linked to the progression of cancer.

RGD (Arg-Gly-Asp) is a tripeptide which features prominently in integrins, and is known to mediate peripheral neuron regeneration [91]. Integration of RGD into PAs demonstrated that these bioactive PAs promoted cell proliferation and differentiation. A plethora of peptide sequences can also be incorporated into PAs, making these nanofibers extremely versatile and customizable.

Unlike conventional materials used in nerve tissue engineering, PAs can be directly injected in vivo into models and spontaneously self-assemble into nanofibers in aqueous solutions. Furthermore, PAs can function as biomimetic materials exemplified by collagen-mimetic PAs [92]. Conventional materials often rely on electrospinning as a manufacturing method to achieve fiber-like structures suitable for use in nerve regeneration. The self-assembly nature of PAs allows them to circumvent costly manufacturing methods. However, in contrast to conventional manufacturing methods like electrospinning where quality and batch-to-batch variability can be tightly controlled, merely relying on self-assembly as a method of large-scale commercial production is still an experimental concept. Perhaps the next step would be to carefully compare and contrast the robustness of self-assemled PAs to electrospun nanofibers. Given that the constituent elements in PAs and external factors like pH can affect its structural assembly, parameters must be finely tuned and optimized in order for PA nanofibers to be used as a full-fledged commercialized medical product [93].

3.3. Controlled drug release & delivery

Apart from being purely constructs for nerve regeneration, PAs can also function as efficient drug and gene delivery platforms. Various therapeutic agents can be incorporated into PAs to augment the recovery process and minimize immune response. It has been shown that controlled release of the anti-inflammatory drug dexamethasone can be achieved when incorporated into PAs [94]. The sustained and controlled release of dexamethasone reduced the occurrence of inflammation, thereby speeding up recovery time, which is crucial in regenerative medicine. The application of PAs as gene delivery platforms has also been explored, using antisense oligonucleotide as a payload [95].

PAs can also function as biomimetic materials, as seen in a study where vascular endothelial growth factor (VEGF)-PAs and basic fibroblast growth factor (bFGF)-PAs were able to enhance bioactivity via direct cell signaling to promote angiogenesis [96,97], and was monitored over a month in a sustained release fashion. Along the same lines, heparin (which is prone to enzymatic degradation) was incorporated into PAs to promote angiogenesis and extend its period of bioactivity [98]. As heparin is derived from animals (which harbors a risk of immunogenicity), heparin-mimetic PAs were also developed

Table 3
FDA-approved nerve conduits, with date of approval. Keys: PGA, polyglycolic acid; PVA, polyvinyl alcohol.

Product Name	Date	Price	Material	Degradation time (months)	Company
Neurotube®	22 Mar 1999	€340	PGA	3	Synovis
NeuraGen®	22 Jun 2001	€1200	Type-I collagen	48	Integra NeuroSciences
NeuroMatrix NeuroFlex®	21 Sept 2001	€600	Type-I collagen	7	Collagen Matrix Inc.
AxoGuard™ Nerve Connector	15 May 2003	Not stated	Porcine small intestine mucosa	3	Cook Biotech Products
Neurolac®	10 Oct 2003	€700–€1800	Poly-DL-lactide-caprolactone	16	Polyganics BV
SaluBridge®	24 Nov 2003	Not stated	PVA hydrogel	Non-degradable	Salumedica LCC
SaluTunnel™ Nerve Protector™	5 Aug 2010	Not stated	PVA	Non-degradable	Salumedica LCC

to circumvent this [99]. This study highlights the potential of delivering molecules with a short half-life or inadequate retention in a sustained and controlled manner using PAs as biomimetic supramolecular structures, which preclude the need of repeated administration or injection.

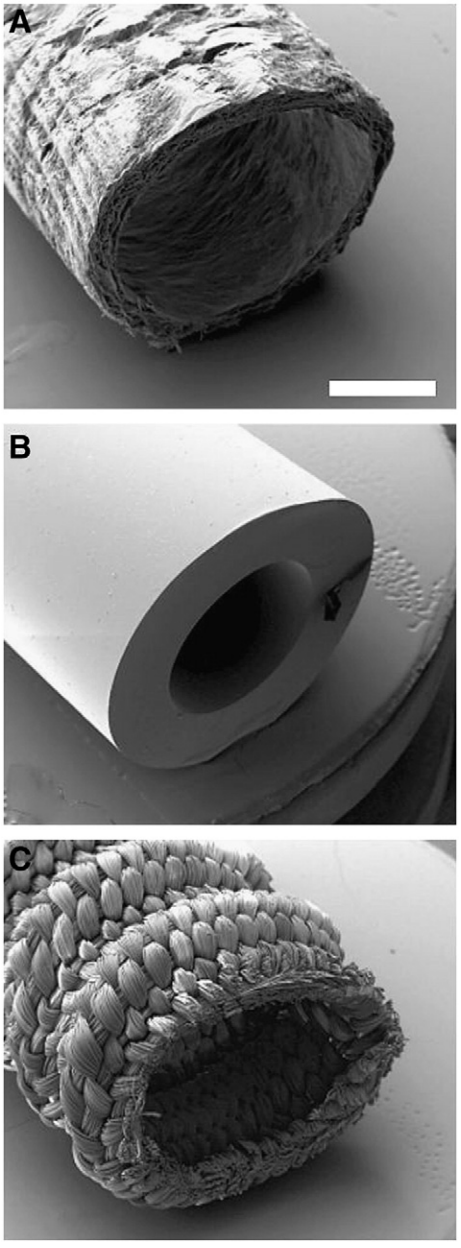

Fig. 4. FDA-approved nerve conduits. Scanning electron microscopy of A NeuraGen® (made from collagen), B Neurolac® (made from poly-DL-lactide-caprolactone), C Neurotube® (made from polyglycolic acid). Scale bar = 4 mm. Copyright © 2006 Congress of Neurological Surgeons. Reproduced with permission from [1].

Interestingly enough, PAs can also be incorporated into liposomes and would function as bioactive ligands for targeted drug delivery [100] (Fig. 8). This would open up the possibility of PAs having dual functionality of being used as nerve conduits and also drug delivery platforms to treat neoplastic neuromas. Conversely, it has been reported that inclusion of phospholipids into PAs can increase accessibility of the bioactive epitopes, enhancing its drug-releasing or cell-regenerative capacity [101].

4. Conclusion and perspectives

The field of bioengineering nerve conduits for regenerative medicine is advancing rapidly [102,103]. Despite the tremendous amount of research conducted in the search for appropriate materials for nerve conduits, the FDA currently approves only a few materials for that purpose, namely PGA, Type-I collagen, PLCL, and PVA. Furthermore, current materials used in FDA-approved nerve conduits suffer from various limitations. For example, PGA suffers from a high rate of degradation, which would compromise on mechanical properties. Collagen is a natural material, which still poses a risk of immunogenic response, and batch-to-batch variability in terms of the manufacturing process is still a teething problem. The relative rigidity and inflexibility of PLCL necessitate the use of a larger needle during suturing. Lumen blockage and incomplete degradation leading to neuroma formation are also limiting factors for PLCL. PVA is non-biodegradable which harbors a risk of nerve compression, which might have a detrimental effect on the recovery process.

Mounting evidence suggests that PAs can indeed function as viable materials for nerve conduits. The dynamic versatility of PAs being able to harbor bioactive molecules to sustain the growth and development of neurons is a fascinating insight to the realm of regenerative medicine. Indeed, much research has been conducted into elucidating the atomistic molecular dynamics and tunability of PAs and their ability to self-assemble into nano-structures [104–106]. At present, there are no in vivo studies comparing the use of FDA-approved nerve conduits with PAs. This would undoubtedly be a pertinent starting point to assess the comparative clinical potential for PAs to be used as nerve conduits.

Conflict of Interest

The authors declare that they do not have any conflict of interest.

Acknowledgments

The authors would like to acknowledge the funding from the Engineering and Physical Sciences Research Council (EPSRC) - Industrial CASE.

References

[1] B. Schlosshauer, L. Dreesmann, H.E. Schaller, N. Sinis, Synthetic nerve guide implants in humans: a comprehensive survey, Neurosurgery 59 (2006) 740–747 (discussion 747–748.).

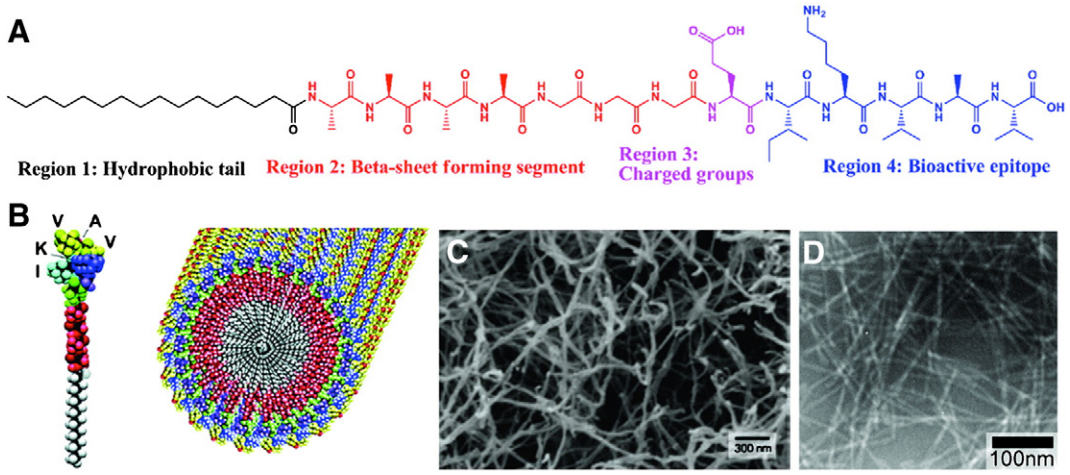

Fig. 5. IKVAV-incorporated peptide amphiphiles. A Chemical structure of a PA. B Molecular model of an IKVAV-incorporated PA. C Scanning electron micrograph of IKVAV-incorporated PAs. D Transmission electron micrograph of IKVAV-incorporated PAs. Copyright © 2010 Wiley Periodicals, Inc. Reproduced with permission from [72].

[2] I.V. Yannas, M. Zhang, M.H. Spilker, Standardized criterion to analyze and directly compare various materials and models for peripheral nerve regeneration, J. Biomater. Sci. Polym. Ed. 18 (2007) 943–966.
[3] J.S. Taras, V. Nanavati, P. Steelman, Nerve conduits, J. Hand Ther. 18 (2005) 191–197.
[4] C.T. Chalfoun, G.A. Wirth, G.R. Evans, Tissue engineered nerve constructs: where do we stand? J. Cell. Mol. Med. 10 (2006) 309–317.
[5] A. Subramanian, U.M. Krishnan, S. Sethuraman, Development of biomaterial scaffold for nerve tissue engineering: biomaterial mediated neural regeneration, J. Biomed. Sci. 16 (2009) 108.
[6] K.S. Straley, C.W. Foo, S.C. Heilshorn, Biomaterial design strategies for the treatment of spinal cord injuries, J. Neurotrauma 27 (2010) 1–19.
[7] V.M. Tysseling, V. Sahni, E.T. Pashuck, D. Birch, A. Hebert, C. Czeisler, S.I. Stupp, J.A. Kessler, Self-assembling peptide amphiphile promotes plasticity of serotonergic fibers following spinal cord injury, J. Neurosci. Res. 88 (2010) 3161–3170.
[8] C.W. Bond, N.L. Angeloni, D.A. Harrington, S.I. Stupp, K.E. McKenna, C.A. Podlasek, Peptide amphiphile nanofiber delivery of sonic hedgehog protein to reduce smooth muscle apoptosis in the penis after cavernous nerve resection, J. Sex. Med. 8 (2011) 78–89.
[9] J.D. Hartgerink, E. Beniash, S.I. Stupp, Self-assembly and mineralization of peptide-amphiphile nanofibers, Science 294 (2001) 1684–1688.
[10] F. Versluis, H.R. Marsden, A. Kros, Power struggles in peptide-amphiphile nanostructures, Chem. Soc. Rev. 39 (2010) 3434–3444.
[11] I. Ahmed, H.-Y. Liu, P.C. Mamiya, A.S. Ponery, A.N. Babu, T. Weik, M. Schindler, S. Meiners, Three-dimensional nanofibrillar surfaces covalently modified with tenascin-C-derived peptides enhance neuronal growth in vitro, J. Biomed. Mater. Res. A 76A (2006) 851–860.
[12] H. Okamoto, K.-I. Hata, H. Kagami, K. Okada, Y. Ito, Y. Narita, H. Hirata, I. Sekiya, T. Otsuka, M. Ueda, Recovery process of sciatic nerve defect with novel bioabsorbable collagen tubes packed with collagen filaments in dogs, J. Biomed. Mater. Res. A 92A (2010) 859–868.
[13] J.M. Corey, D.Y. Lin, K.B. Mycek, Q. Chen, S. Samuel, E.L. Feldman, D.C. Martin, Aligned electrospun nanofibers specify the direction of dorsal root ganglia neurite growth, J. Biomed. Mater. Res. A 83 (2007) 636–645.
[14] S. Patel, K. Kurpinski, R. Quigley, H. Gao, B.S. Hsiao, M.M. Poo, S. Li, Bioactive nanofibers: synergistic effects of nanotopography and chemical signaling on cell guidance, Nano Lett. 7 (2007) 2122–2128.
[15] S.Y. Chew, R. Mi, A. Hoke, K.W. Leong, The effect of the alignment of electrospun fibrous scaffolds on Schwann cell maturation, Biomaterials 29 (2008) 653–661.
[16] S.Y. Chew, J. Wen, E.K. Yim, K.W. Leong, Sustained release of proteins from electrospun biodegradable fibers, Biomacromolecules 6 (2005) 2017–2024.
[17] S. Wang, M.J. Yaszemski, A.M. Knight, J.A. Gruetzmacher, A.J. Windebank, L. Lu, Photo-crosslinked poly(epsilon-caprolactone fumarate) networks for guided peripheral nerve regeneration: material properties and preliminary biological evaluations, Acta Biomater. 5 (2009) 1531–1542.
[18] I.A. Kim, S.A. Park, Y.J. Kim, S.H. Kim, H.J. Shin, Y.J. Lee, S.G. Kang, J.W. Shin, Effects of mechanical stimuli and microfiber-based substrate on neurite outgrowth and guidance, J. Biosci. Bioeng. 101 (2006) 120–126.
[19] D.R. Nisbet, S. Pattanawong, N.E. Ritchie, W. Shen, D.I. Finkelstein, M.K. Horne, J.S. Forsythe, Interaction of embryonic cortical neurons on nanofibrous scaffolds for neural tissue engineering, J. Neural Eng. 4 (2007) 35–41.
[20] S. Panseri, C. Cunha, J. Lowery, U. Del Carro, F. Taraballi, S. Amadio, A. Vescovi, F. Gelain, Electrospun micro- and nanofiber tubes for functional nervous regeneration in sciatic nerve transections, BMC Biotechnol. 8 (2008) 39.
[21] W.N. Chow, D.G. Simpson, J.W. Bigbee, R.J. Colello, Evaluating neuronal and glial growth on electrospun polarized matrices: bridging the gap in percussive spinal cord injuries, Neuron Glia Biol. 3 (2007) 119–126.
[22] S. Meiners, I. Ahmed, A.S. Ponery, N. Amor, S.L. Harris, V. Ayres, Y. Fan, Q. Chen, R. Delgado-Rivera, A.N. Babu, Engineering electrospun nanofibrillar surfaces for spinal cord repair: a discussion, Polym. Int. 56 (2007) 1340–1348.
[23] Y.T. Kim, V.K. Haftel, S. Kumar, R.V. Bellamkonda, The role of aligned polymer fiber-based constructs in the bridging of long peripheral nerve gaps, Biomaterials 29 (2008) 3117–3127.
[24] O. Suwantong, S. Waleetorncheepsawat, N. Sanchavanakit, P. Pavasant, P. Cheepsunthorn, T. Bunaprasert, P. Supaphol, In vitro biocompatibility of electrospun poly(3-hydroxybutyrate) and poly(3-hydroxybutyrate-co-3-hydroxyvalerate) fiber mats, Int. J. Biol. Macromol. 40 (2007) 217–223.
[25] F. Xie, Q.F. Li, B. Gu, K. Liu, G.X. Shen, In vitro and in vivo evaluation of a biodegradable chitosan-PLA composite peripheral nerve guide conduit material, Microsurgery 28 (2008) 471–479.
[26] J. Xie, S.M. Willerth, X. Li, M.R. Macewan, A. Rader, S.E. Sakiyama-Elbert, Y. Xia, The differentiation of embryonic stem cells seeded on electrospun nanofibers into neural lineages, Biomaterials 30 (2009) 354–362.
[27] R.A. Neal, S.G. McClugage, M.C. Link, L.S. Sefcik, R.C. Ogle, E.A. Botchwey, Laminin nanofiber meshes that mimic morphological properties and bioactivity of basement membranes, Tissue Eng. Part C Methods 15 (2009) 11–21.
[28] W. Wang, S. Itoh, A. Matsuda, S. Ichinose, K. Shinomiya, Y. Hata, J. Tanaka, Influences of mechanical properties and permeability on chitosan nano/microfiber mesh tubes as a scaffold for nerve regeneration, J. Biomed. Mater. Res. A 84 (2008) 557–566.
[29] W. Wang, S. Itoh, A. Matsuda, T. Aizawa, M. Demura, S. Ichinose, K. Shinomiya, J. Tanaka, Enhanced nerve regeneration through a bilayered chitosan tube: the effect of introduction of glycine spacer into the CYIGSR sequence, J. Biomed. Mater. Res. A 85A (2008) 919–928.
[30] L. Ghasemi-Mobarakeh, M.P. Prabhakaran, M. Morshed, M.H. Nasr-Esfahani, S. Ramakrishna, Electrospun poly(epsilon-caprolactone)/gelatin nanofibrous scaffolds for nerve tissue engineering, Biomaterials 29 (2008) 4532–4539.
[31] W. Li, Y. Guo, H. Wang, D. Shi, C. Liang, Z. Ye, F. Qing, J. Gong, Electrospun nanofibers immobilized with collagen for neural stem cells culture, J. Mater. Sci. Mater. Med. 19 (2008) 847–854.
[32] M.P. Prabhakaran, J.R. Venugopal, T.T. Chyan, L.B. Hai, C.K. Chan, A.Y. Lim, S. Ramakrishna, Electrospun biocomposite nanofibrous scaffolds for neural tissue engineering, Tissue Eng. Part A 14 (2008) 1787–1797.
[33] P. Sangsanoh, S. Waleetorncheepsawat, O. Suwantong, P. Wutticharoenmongkol, O. Weeranantanapan, B. Chuenjitbuntaworn, P. Cheepsunthorn, P. Pavasant, P. Supaphol, In vitro biocompatibility of schwann cells on surfaces of biocompatible polymeric electrospun fibrous and solution-cast film scaffolds, Biomacromolecules 8 (2007) 1587–1594.
[34] E. Schnell, K. Klinkhammer, S. Balzer, G. Brook, D. Klee, P. Dalton, J. Mey, Guidance of glial cell migration and axonal growth on electrospun nanofibers of poly-epsilon-caprolactone and a collagen/poly-epsilon-caprolactone blend, Biomaterials 28 (2007) 3012–3025.
[35] R.V. Bellamkonda, Peripheral nerve regeneration: an opinion on channels, scaffolds and anisotropy, Biomaterials 27 (2006) 3515–3518.
[36] J.S. Belkas, C.A. Munro, M.S. Shoichet, R. Midha, Peripheral nerve regeneration through a synthetic hydrogel nerve tube, Restor. Neurol. Neurosci. 23 (2005) 19–29.
[37] Y.-Z. Bian, Y. Wang, G. Aibaidoula, G.-Q. Chen, Q. Wu, Evaluation of poly(3-hydroxybutyrate-co-3-hydroxyhexanoate) conduits for peripheral nerve regeneration, Biomaterials 30 (2009) 217–225.
[38] R.G. Ellis-Behnke, Y.X. Liang, S.W. You, D.K. Tay, S. Zhang, K.F. So, G.E. Schneider, Nano neuro knitting: peptide nanofiber scaffold for brain repair and axon regeneration with functional return of vision, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 5054–5059.
[39] F. Gelain, D. Bottai, A. Vescovi, S. Zhang, Designer self-assembling peptide nanofiber scaffolds for adult mouse neural stem cell 3-dimensional cultures, PLoS One 1 (2006) e119.

Table 4
Bioengineering nerve conduits using peptide amphiphiles. Keys: TE, tissue engineering; *, indicates in vivo study.

Bioactive epitope	Comments	Ref
Sonic hedgehog	• Biodegradable PAs provide a platform by which to deliver proteins to render directional guidance to axonal regeneration • PAs are scaffolds that can be delivered directly to nerve injury site	[74]*
RGD	• Self-assembly configuration of PAs entraps cells within nanofiber matrix • Cells remained viable within entrapment	[78]
RGD	• PA scaffold promoted the mouse fibroblast cell adhesion and proliferation • Cells only proliferated on bioactive ligand site	[79]
Amyloid β-peptide	• PA nanofiber configuration can be modulated via adjustment of pH • Demonstrated the effect of pH on nanoscale self-assembly	[75]
RGD	• Adherence and proliferation of human smooth muscle cells on the bioactive PA	[80]
12 different peptides	• Self-assembly into nanofiber networks was demonstrated using 12 variants of PA • Demonstrated a proof-of-concept that incorporation of bioactive epitopes still allows nanofiber self-assembly	[82]
RGD IKVAV	• Demonstrated nanofiber self-assembly over large areas via sonication-assisted solution embossing • This technique can be employed to cellular behaviors by directional tuning	[76]
MMP-2 & RGD	• Human glioma cells proliferated on PA nanofiber scaffold	[81]
GRGDSP & PHSRN	• Constructed a PA scaffold that mimics adhesion domains of the ECM	[84]
IKVAV	• PAs incorporated with IKVAV induced rapid proliferation of neuronal cells • Observation of a concomitant decrease in astrocyte formation	[89]
Lys, His & Asp	• Demonstrated that electrostatic control is important in PA constructs for TE purposes	[77]
EDOT monomer	• Constructed a conductive polymer when EDOT was incorporated into PAs • Demonstrated proof-of-concept that conductive polymer PA scaffolds can be used in nerve TE	[83]
IKVAV	• Inhibition of glial scar formation • Promoted neurite outgrowth from neurons • Reduction of astrogliosis while simultaneously increasing oligodendroglia	[90]*
None	• Elucidated the mechanism of self-assembly in PAs • Outlined the importance of hydrophobic interaction between alkyl tails and hydrogen bonds between peptide blocks	[73]
RGDS	• Demonstrated that stem cells were able to adhere to and proliferate on bioactive PAs	[85]*
RGD	• Demonstrated PA self-assembly via pH-controlled mechanism	[9]
Sonic hedgehog	• Sonic hedgehog protein delivered via PA nanofibers is effective in suppressing cavernous nerve injury-induced apoptosis	[8]*
IKVAV	• Promotion of neural progenitor cell survival and differentiation	[87]
IKVAV	• PA nanofiber-collagen hybrid promotes neural cell survival and maturation	[88]
IKVAV	• PA promotes plasticity of neural fibers after spinal cord injury	[7]*

[40] J. Guo, H. Su, Y. Zeng, Y.X. Liang, W.M. Wong, R.G. Ellis-Behnke, K.F. So, W. Wu, Reknitting the injured spinal cord by self-assembling peptide nanofiber scaffold, Nanomedicine 3 (2007) 311–321.
[41] F. Taraballi, A. Natalello, M. Campione, O. Villa, S.M. Doglia, A. Paleari, F. Gelain, Glycine-spacers influence functional motifs exposure and self-assembling propensity of functionalized substrates tailored for neural stem cell cultures, Front. Neuroeng. 3 (2010) 1.
[42] S. Stanec, Z. Stanec, Ulnar nerve reconstruction with an expanded polytetrafluoroethylene conduit, Br. J. Plast. Surg. 51 (1998) 637–639.
[43] S. Stanec, Z. Stanec, Reconstruction of upper-extremity peripheral-nerve injuries with ePTFE conduits, J. Reconstr. Microsurg. 14 (1998) 227–232.
[44] M.A. Pogrel, A.R. McDonald, L.B. Kaban, Gore-Tex tubing as a conduit for repair of lingual and inferior alveolar nerve continuity defects: a preliminary report, J. Oral Maxillofac. Surg. 56 (1998) 319–321 (discussion 321–312.).
[45] M.C. Pitta, L.M. Wolford, P. Mehra, J. Hopkin, Use of Gore-Tex tubing as a conduit for inferior alveolar and lingual nerve repair: experience with 6 cases, J. Oral Maxillofac. Surg. 59 (2001) 493–496 (discussion 497.).
[46] M.F. Meek, M.J. Bertleff, M.J. Ritt, P.H. Robinson, J.P. Nicolai, A degradable artificial nerve guide to bridge peripheral nerve defects, Ned. Tijdschr. Geneeskd. 147 (2003) 717–721.
[47] M.J. Bertleff, M.F. Meek, J.P. Nicolai, A prospective clinical evaluation of biodegradable neurolac nerve guides for sensory nerve repair in the hand, J. Hand Surg. Am. 30 (2005) 513–518.
[48] S.E. Mackinnon, A.L. Dellon, Clinical nerve reconstruction with a bioabsorbable polyglycolic acid tube, Plast. Reconstr. Surg. 85 (1990) 419–424.
[49] W.A. Crawley, A.L. Dellon, Inferior alveolar nerve reconstruction with a polyglycolic acid bioabsorbable nerve conduit, Plast. Reconstr. Surg. 90 (1992) 300–302.
[50] R.A. Weber, W.C. Breidenbach, R.E. Brown, M.E. Jabaley, D.P. Mass, A randomized prospective study of polyglycolic acid conduits for digital nerve reconstruction in humans, Plast. Reconstr. Surg. 106 (2000) 1036–1045 (discussion 1046–1038.).
[51] J. Kim, A.L. Dellon, Reconstruction of a painful post-traumatic medial plantar neuroma with a bioabsorbable nerve conduit: a case report, J. Foot Ankle Surg. 40 (2001) 318–323.
[52] A. Hagiwara, S. Nakashima, T. Itoh, C. Sakakura, E. Otsuji, H. Yamagishi, S. Okajima, K. Kusuzaki, H. Hase, S. Kubo, J. Soh, T. Miki, T. Toba, T. Nakamura, Y. Shimizu, Clinical application of PGA-tube for regeneration of intrapelvic nerves during extended surgery for intrapelvic recurrent rectal cancer, Gan To Kagaku Ryoho 29 (2002) 2202–2204.
[53] Y. Inada, S. Morimoto, Y. Takakura, T. Nakamura, Regeneration of peripheral nerve gaps with a polyglycolic acid-collagen tube, Neurosurgery 55 (2004) 640–648 (610.1227/1201.NEU.0000134388.0000186603.0000134311).
[54] Y. Inada, S. Morimoto, K. Moroi, K. Endo, T. Nakamura, Surgical relief of causalgia with an artificial nerve guide tube: Successful surgical treatment of causalgia (Complex Regional Pain Syndrome Type II) by in situ tissue engineering with a polyglycolic acid-collagen tube, Pain 117 (2005) 251–258.
[55] M. Navissano, F. Malan, R. Carnino, B. Battiston, Neurotube for facial nerve repair, Microsurgery 25 (2005) 268–271.
[56] B. Battiston, S. Geuna, M. Ferrero, P. Tos, Nerve repair by means of tubulization: literature review and personal clinical experience comparing biological and synthetic conduits for sensory nerve repair, Microsurgery 25 (2005) 258–267.
[57] M. Merle, A.L. Dellon, J.N. Campbell, P.S. Chang, Complications from silicon-polymer intubulation of nerves, Microsurgery 10 (1989) 130–133.
[58] G. Lundborg, L.B. Dahlin, N. Danielsen, Ulnar nerve repair by the silicone chamber technique. Case report, Scand. J. Plast. Reconstr. 25 (1991) 79–82.
[59] G. Lundborg, B. Rosen, S.O. Abrahamson, L. Dahlin, N. Danielsen, Tubular repair of the median nerve in the human forearm. Preliminary findings, J. Hand Surg. Br. 19 (1994) 273–276.
[60] G. Lundborg, B. Rosen, L. Dahlin, N. Danielsen, J. Holmberg, Tubular versus conventional repair of median and ulnar nerves in the human forearm: early results from a prospective, randomized, clinical study, J. Hand Surg. Am. 22 (1997) 99–106.
[61] Y. Luo, T. Wang, H. Fang, Clinical application of implantation of vascular bundle into silicone tube to bridge the peripheral nerve defect, Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi 11 (1997) 340–342.
[62] J. Braga-Silva, The use of silicone tubing in the late repair of the median and ulnar nerves in the forearm, J. Hand Surg. Eur. Vol. 24 (1999) 703–706 (British and European Volume).
[63] L.B. Dahlin, G. Lundborg, Use of tubes in peripheral nerve repair, Neurosurg. Clin. N. Am. 12 (2001) 341–352.
[64] G. Lundborg, B. Rosen, L. Dahlin, J. Holmberg, I. Rosen, Tubular repair of the median or ulnar nerve in the human forearm: a 5-year follow-up, J. Hand Surg. Br. 29 (2004) 100–107.
[65] K.J. Wangensteen, L.K. Kalliainen, Collagen tube conduits in peripheral nerve repair: a retrospective analysis, Hand (N.Y.) 5 (2010) 273–277.
[66] J.A. Lohmeyer, F. Siemers, H.G. Machens, P. Mailander, The clinical use of artificial nerve conduits for digital nerve repair: a prospective cohort study and literature review, J. Reconstr. Microsurg. 25 (2009) 55–61.
[67] B.D. Bushnell, A.D. McWilliams, G.B. Whitener, T.M. Messer, Early clinical experience with collagen nerve tubes in digital nerve repair, J. Hand Surg. 33 (2008) 1081–1087.
[68] A. Farole, B.T. Jamal, A bioabsorbable collagen nerve cuff (NeuraGen) for repair of lingual and inferior alveolar nerve injuries: a case series, J. Oral Maxillofac. Surg. 66 (2008) 2058–2062.
[69] W.W. Ashley Jr., T. Weatherly, T.S. Park, Collagen nerve guides for surgical repair of brachial plexus birth injury, J. Neurosurg. 105 (2006) 452–456.
[70] M.F. Meek, J.H. Coert, US Food and Drug Administration/Conformit Europe-approved absorbable nerve conduits for clinical repair of peripheral and cranial nerves, Ann. Plast. Surg. 60 (2008) 466–472.
[71] S. Kehoe, X.F. Zhang, D. Boyd, FDA approved guidance conduits and wraps for peripheral nerve injury: a review of materials and efficacy, Injury, 2011.
[72] H. Cui, M.J. Webber, S.I. Stupp, Self-assembly of peptide amphiphiles: from molecules to nanostructures to biomaterials, Biopolymers 94 (2010) 1–18.
[73] Y.S. Velichko, S.I. Stupp, M.O. de la Cruz, Molecular simulation study of peptide amphiphile self-assembly, J. Phys. Chem. B 112 (2008) 2326–2334.

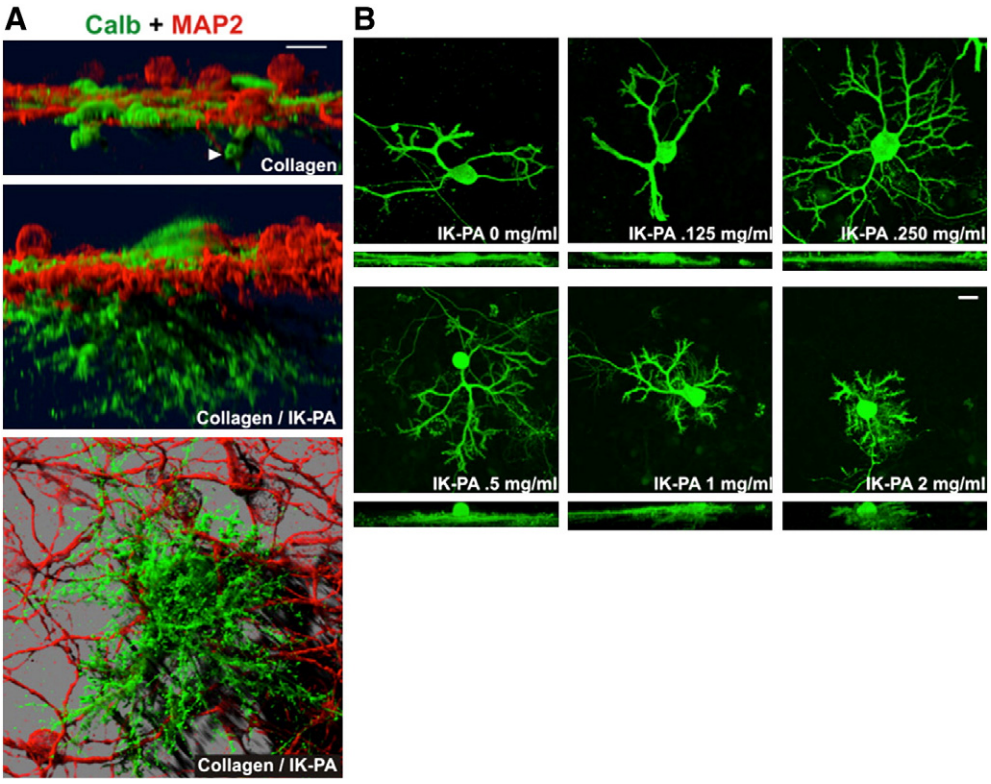

Fig. 6. Salutary effects of IKVAV-incorporated peptide amphiphiles-collagen hybrids on neural cells. A Simulated fluorescence process images of: neural cells cultured on collagen only (left upper image), on IKVAV-incorporated peptide amphiphiles-collagen hybrid (left middle and left bottom image). Green depicts calbindin; red depicts neurons. B Image pairs illustrate top view and side view of neural cells cultured on IKVAV-PA-collagen hybrids, in increasing concentrations. Copyright © 2012 Elsevier B.V. Reproduced with permission from [88].

[74] N.L. Angeloni, C.W. Bond, Y. Tang, D.A. Harrington, S. Zhang, S.I. Stupp, K.E. McKenna, C.A. Podlasek, Regeneration of the cavernous nerve by Sonic hedgehog using aligned peptide amphiphile nanofibers, Biomaterials 32 (2011) 1091–1101.

[75] M. Deng, D. Yu, Y. Hou, Y. Wang, Self-assembly of peptide−amphiphile C12−Aβ(11–17) into nanofibrils, J. Phys. Chem. B 113 (2009) 8539–8544.

[76] A.M. Hung, S.I. Stupp, Simultaneous self-assembly, orientation, and patterning of peptide−amphiphile nanofibers by soft lithography, Nano Lett. 7 (2007) 1165–1171.

[77] S. Toksoz, R. Mammadov, A.B. Tekinay, M.O. Guler, Electrostatic effects on nanofiber formation of self-assembling peptide amphiphiles, J. Colloid Interface Sci. 356 (2011) 131–137.

[78] E. Beniash, J.D. Hartgerink, H. Storrie, J.C. Stendahl, S.I. Stupp, Self-assembling peptide amphiphile nanofiber matrices for cell entrapment, Acta Biomater. 1 (2005) 387–397.

[79] M.A. Biesalski, A. Knaebel, R. Tu, M. Tirrell, Cell adhesion on a polymerized peptide–amphiphile monolayer, Biomaterials 27 (2006) 1259–1269.

[80] D.A. Harrington, E.Y. Cheng, M.O. Guler, L.K. Lee, J.L. Donovan, R.C. Claussen, S.I. Stupp, Branched peptide-amphiphiles as self-assembling coatings for tissue engineering scaffolds, J. Biomed. Mater. Res. A 78A (2006) 157–167.

[81] H.-W. Jun, S.E. Paramonov, H. Dong, N. Forraz, C. McGuckin, J.D. Hartgerink, Tuning the mechanical and bioresponsive properties of peptide-amphiphile nanofiber networks, J. Biomater. Sci. Polym. Ed. 19 (2008) 665–676.

[82] J.D. Hartgerink, E. Beniash, S.I. Stupp, Peptide-amphiphile nanofibers: a versatile scaffold for the preparation of self-assembling materials, Proc. Natl. Acad. Sci. 99 (2002) 5133–5138.

[83] J.D. Tovar, B.M. Rabatic, S.I. Stupp, Conducting polymers confined within bioactive peptide amphiphile nanostructures, Small 3 (2007) 2024–2028.

[84] A. Mardilovich, E. Kokkoli, Biomimetic peptide−amphiphiles for functional biomaterials: the role of GRGDSP and PHSRN, Biomacromolecules 5 (2004) 950–957.

[85] M.J. Webber, J. Tongers, M.-A. Renault, J.G. Roncalli, D.W. Losordo, S.I. Stupp, Development of bioactive peptide amphiphiles for therapeutic cell delivery, Acta Biomater. 6 (2010) 3–11.

[86] K. Tashiro, G.C. Sephel, B. Weeks, M. Sasaki, G.R. Martin, H.K. Kleinman, Y. Yamada, A synthetic peptide containing the IKVAV sequence from the A chain of laminin mediates cell attachment, migration, and neurite outgrowth, J. Biol. Chem. 264 (1989) 16174–16182.

[87] Y. Song, Y. Li, Q. Zheng, K. Wu, X. Guo, Y. Wu, M. Yin, Q. Wu, X. Fu, Neural progenitor cells survival and neuronal differentiation in peptide-based hydrogels, J. Biomater. Sci. Polym. Ed. 22 (2011) 475–487.

[88] S. Sur, E.T. Pashuck, M.O. Guler, M. Ito, S.I. Stupp, T. Launey, A hybrid nanofiber matrix to control the survival and maturation of brain neurons, Biomaterials 33 (2012) 545–555.

[89] G.A. Silva, C. Czeisler, K.L. Niece, E. Beniash, D.A. Harrington, J.A. Kessler, S.I. Stupp, Selective differentiation of neural progenitor cells by high-epitope density nanofibers, Science 303 (2004) 1352–1355.

[90] V.M. Tysseling-Mattiace, V. Sahni, K.L. Niece, D. Birch, C. Czeisler, M.G. Fehlings, S.I. Stupp, J.A. Kessler, Self-assembling nanofibers inhibit glial scar formation and promote axon elongation after spinal cord injury, J. Neurosci. 28 (2008) 3814–3823.

[91] W.Q. Liu, J.A. Martinez, J. Durand, W. Wildering, D.W. Zochodne, RGD-mediated adhesive interactions are important for peripheral axon outgrowth in vivo, Neurobiol. Dis. 34 (2009) 11–22.

[92] J. Luo, Y.W. Tong, Self-assembly of collagen-mimetic peptide amphiphiles into biofunctional nanofiber, ACS Nano 5 (2011) 7739–7747.

[93] X. Zhao, F. Pan, H. Xu, M. Yaseen, H. Shan, C.A. Hauser, S. Zhang, J.R. Lu, Molecular self-assembly and applications of designer peptide amphiphiles, Chem. Soc. Rev. 39 (2010) 3480–3498.

[94] M.J. Webber, J.B. Matson, V.K. Tamboli, S.I. Stupp, Controlled release of dexamethasone from peptide nanofiber gels to modulate inflammatory response, Biomaterials 33 (2012) 6823–6832.

[95] S. Bulut, T.S. Erkal, S. Toksoz, A.B. Tekinay, T. Tekinay, M.O. Guler, Slow release and delivery of antisense oligonucleotide drug by self-assembled peptide amphiphile nanofibers, Biomacromolecules 12 (2011) 3007–3014.

[96] M.J. Webber, J. Tongers, C.J. Newcomb, K.T. Marquardt, J. Bauersachs, D.W. Losordo, S.I. Stupp, Supramolecular nanostructures that mimic VEGF as a strategy for ischemic tissue repair, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 13438–13443.

[97] H. Hosseinkhani, M. Hosseinkhani, A. Khademhosseini, H. Kobayashi, Y. Tabata, Enhanced angiogenesis through controlled release of basic fibroblast growth factor from peptide amphiphile for tissue regeneration, Biomaterials 27 (2006) 5836–5844.

[98] K. Rajangam, H.A. Behanna, M.J. Hui, X. Han, J.F. Hulvat, J.W. Lomasney, S.I. Stupp, Heparin binding nanostructures to promote growth of blood vessels, Nano Lett. 6 (2006) 2086–2090.

[99] R. Mammadov, B. Mammadov, S. Toksoz, B. Aydin, R. Yagci, A.B. Tekinay, M.O. Guler, Heparin mimetic peptide nanofibers promote angiogenesis, Biomacromolecules 12 (2011) 3508–3519.

[100] E.M. Rezler, D.R. Khan, J. Lauer-Fields, M. Cudic, D. Baronas-Lowell, G.B. Fields, Targeted drug delivery utilizing protein-like molecular architecture, J. Am. Chem. Soc. 129 (2007) 4961–4972.

[101] S.E. Paramonov, H.W. Jun, J.D. Hartgerink, Modulation of peptide-amphiphile nanofibers via phospholipid inclusions, Biomacromolecules 7 (2006) 24–26.

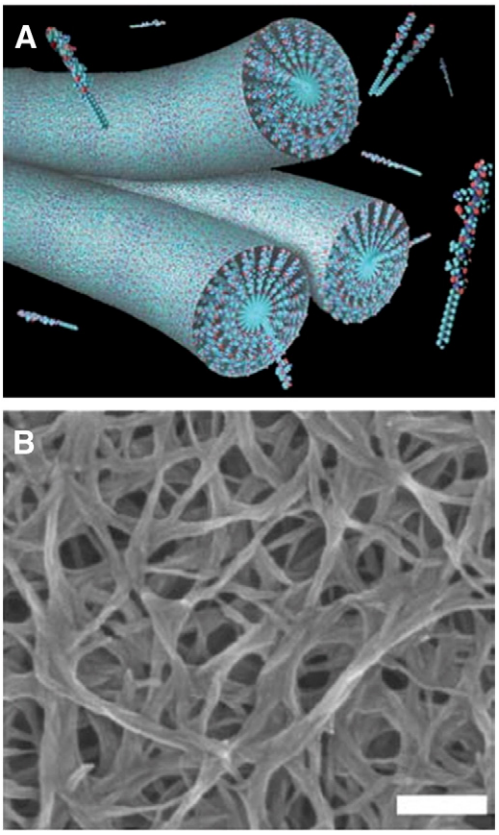

Fig. 7. IKVAV-peptide amphiphile self-assembled nanofibers. A Schematic illustration showing the self-assembly of individual IKVAV-PAs into nanofibers. B Scanning electron micrograph depicting a network of IKVAV-PA nanofibers. Copyright © 2008 Society of Neuroscience. Reproduced with permission from [90].

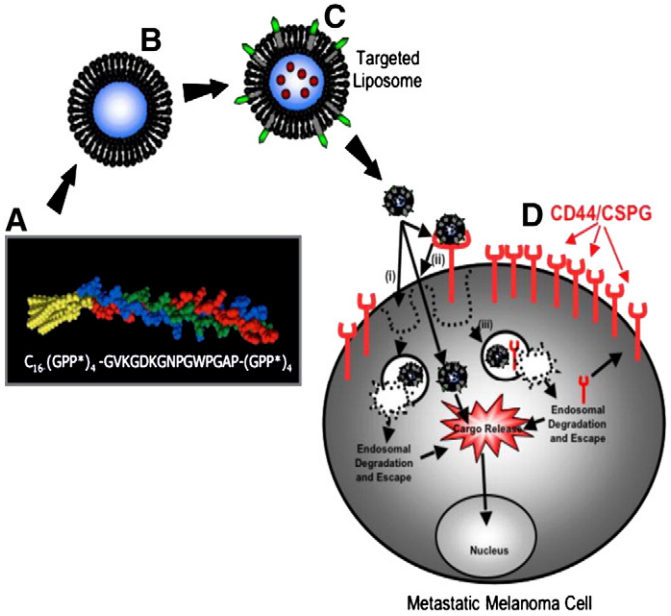

Fig. 8. Peptide amphiphiles (PAs) as drug delivery platforms. PAs can be incorporated into liposomes for enhanced targeted drug delivery. (a) PA sequence. (b) Liposome. (c) PA-incorporated liposome with drug payload. (d) Possible drug delivery vehicle for nerve-related cancers. Copyright © 2007 American Chemical Society. Reproduced with permission from [100].

[102] A. Pabari, S.Y. Yang, A. Mosahebi, A.M. Seifalian, Recent advances in artificial nerve conduit design: strategies for the delivery of luminal fillers, J. Control. Release 156 (2011) 2–10.
[103] T. Sedaghati, S.Y. Yang, A. Mosahebi, M.S. Alavijeh, A.M. Seifalian, Nerve regeneration with aid of nanotechnology and cellular engineering, Biotechnol. Appl. Biochem. 58 (2011) 288–300.
[104] O.S. Lee, S.I. Stupp, G.C. Schatz, Atomistic molecular dynamics simulations of peptide amphiphile self-assembly into cylindrical nanofibers, J. Am. Chem. Soc. 133 (2011) 3677–3683.
[105] Q. Meng, Y. Kou, X. Ma, Y. Liang, L. Guo, C. Ni, K. Liu, Tunable self-assembled peptide amphiphile nanostructures, Langmuir 28 (2012) 5017–5022.
[106] A. Ghosh, M. Haverick, K. Stump, X. Yang, M.F. Tweedle, J.E. Goldberger, Fine-tuning the pH trigger of self-assembly, J. Am. Chem. Soc. 134 (2012) 3647–3650.