Materials for peripheral nerve repair constructs: natural proteins or synthetic polymers?

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Abstract

The efficacious repair of severe peripheral nerve injuries is currently an unmet clinical need, and biomaterial constructs offer a promising approach to help promote nerve regeneration. Current research focuses on the development of more sophisticated constructs with complex architecture and the addition of regenerative agents to encourage timely reinnervation and promote functional recovery. This review surveyed the present landscape of nerve repair construct literature with a focus on six selected materials that are frequently encountered in this application: the natural proteins collagen, chitosan, and silk, and the synthetic polymers poly-ε-caprolactone (PCL), poly-lactic-co-glycolic acid (PLGA) and poly-glycolic acid (PGA). This review also investigated the use of cell therapy in nerve repair constructs, and in all instances concentrated on publications reporting constructs developed and tested *in vivo* in the last five years (2015-2020). Across the selected literature, the popularity of natural proteins and synthetic polymers appears to be broadly equivalent, with similar number of studies reporting successful outcomes *in vivo*. Both material types are also utilised as vehicles for cell therapy, which has much potential to improve the results of nerve bridging for treating longer gaps.

1. Introduction

Peripheral nerves house axons that transmit action potentials, allowing skeletal muscle movement and the perception of sensation in addition to the execution of autonomous processes controlled by smooth muscle. Although peripheral axons have some capacity to regenerate, severe traumatic injury with a loss of nerve tissue may permanently affect motor and sensory function as axonal guiding architecture is removed and the likelihood of successful target reinnervation is reduced. An autologous nerve graft (autograft) is the most efficacious microsurgical approach for nerve gap repair at present, however this technique causes donor site morbidity and donor tissue is limited. Moreover, the autograft has been found to produce dissatisfactory recovery in more than half of patients (Ruijs et al., 2005).

1.1. Nerve repair constructs

Nerve repair constructs made from biocompatible materials may act as an effective substitute for the autograft by providing axonal guidance and containment, without the significant drawbacks of transplanting native nerve tissue. However, constructs currently approved by the FDA are not indicated for the repair of defects greater than 30 mm (Kornfeld et al., 2019). In order to aid regeneration in more severe injuries, the construct biomaterials and the processes used to fabricate them should be selected for a number of attributes, including cellular attachment and compatibility, sufficient porosity, suitable mechanical properties, and biodegradation over an appropriate timeframe. Materials or processes that can generate aligned topography may further enhance regeneration, as neurite outgrowth is more rapid and directional in the presence of these cues (Omidinia-Anarkoli et al., 2020; Thomson et al., 2017). Current nerve repair research focuses on generating complex materials that more closely mimic the native nerve environment, an approach which often uses novel fabrication techniques to generate a scaffold and the incorporation of regenerative agents such as small molecules, neurotrophic factors, extra-cellular matrix (ECM) molecules and/or cells.

1.2. Biomaterials

The materials used for artificial nerve repair constructs are usually polymeric and can be broadly split into naturally occurring and synthetic options. In preclinical research natural proteins like collagen, chitosan and silk are often employed for their cellular compatibility. Other natural proteins widely used in repair constructs are gelatin, alginate and hyaluronic acid (Fornasari et al., 2020). In contrast, synthetic materials such as polyesters may be used for their superior mechanical properties and ease of processing. Polyesters are a group of biodegradable synthetic polymers, and are considered the most commercially competitive polymers for biomedical applications due to their biocompatibility, cost-effectiveness and diverse characteristics (Manavitehrani et al., 2016). The majority of synthetic materials investigated for nerve scaffolds are polyester-based, however other polymers such as poly-ethylene glycol (PEG) are being explored as pro-regenerative agents (Paskal et al., 2019).

1.3 Fabrication by electrospinning

A fabrication approach that is used extensively in the field at present and features heavily in this review is electrospinning, a technique that produces fibres from micro- to nanoscale by application of a high voltage. Electrospinning has been widely used to create artificial tissues,

owing to the structural similarities of these fibrous scaffolds and natural ECM (Jun et al., 2018). As natural proteins are less amenable to forming fibres in this process, electrospinning is still mainly carried out using synthetic polymers. However, their use is increasing and many natural polymers including chitosan, cellulose, alginate, collagen and silk have now successfully been electrospun into fibres for the delivery of biological products (Stojanov and Berlec, 2020).

1.3. Review scope

This review focuses on selected relevant studies that describe new constructs fabricated using either collagen, silk, chitosan, poly-ε-caprolactone (PCL), poly-lactic-co-glycolic acid (PLGA) or poly-glycolic acid (PGA) components, and those using cell therapy, which have been developed and assessed *in vivo* in the last five years (Table 1). This timeframe was selected to provide a concise overview of recent advances in the field, and readers are directed to earlier reviews (Belanger et al., 2016; Dalamagkas et al., 2016) for a comprehensive study of prior work. These six materials were chosen as they are widely used in pre-clinical construct development, and those publications in which they were the main component comprise the majority of recent nerve repair research literature.

This review will first introduce natural and synthetic materials commonly used in preclinical nerve repair research and evaluate recent advances made using these biomaterials to bridge nerve defects *in vivo*, then will focus on developments in the use of biomaterials with cell therapy for this application.

2. Natural materials

2.1. Collagen

Collagen is certainly the most frequently applied natural protein in preclinical nerve constructs, which is unsurprising given its abundance in peripheral nerve ECM and its role in providing mechanical support to regenerating axons after injury (Koopmans et al., 2009). As such collagen is an excellent substrate to aid the cellular processes that mediate regeneration, and it is the main component of four out of nine FDA-approved artificial tubes for the reconstruction of peripheral nerves (Kornfeld et al., 2019). Towards the development of more complex constructs, a recent clinical trial assessed the suitability of collagen tubes filled with aligned collagen filaments fabricated by extrusion to repair defects ≤ 30 mm (Saeki et al., 2018). After 12 months, recovery of sensory function was not inferior to the patient group that received autografts, although the mean defect length was 6 mm longer in the autograft group (Saeki et al., 2018).

Collagen continues to be used extensively in preclinical research, although it may be said that its popularity is decreasing in favour of synthetic options. To explore this assertion a search of nerve construct development publications from the last year (October 2019-October 2020) that used one of the six selected materials as a main component was conducted (Figure 1). It found that collagen was the main component in 11% of the 65 publications, lower than that of silk and chitosan and considerably lower than that of the synthetic polymer PCL (Figure 1). The popularity of the latter could be due to the greater tensile strength and stiffness that can be achieved, properties that are useful in conduits to withstand tension and prevent collapse, as the chemical or physical modification required to

attain this mechanical performance in collagen may be detrimental to its useful biological properties (Dong and Lv, 2016).

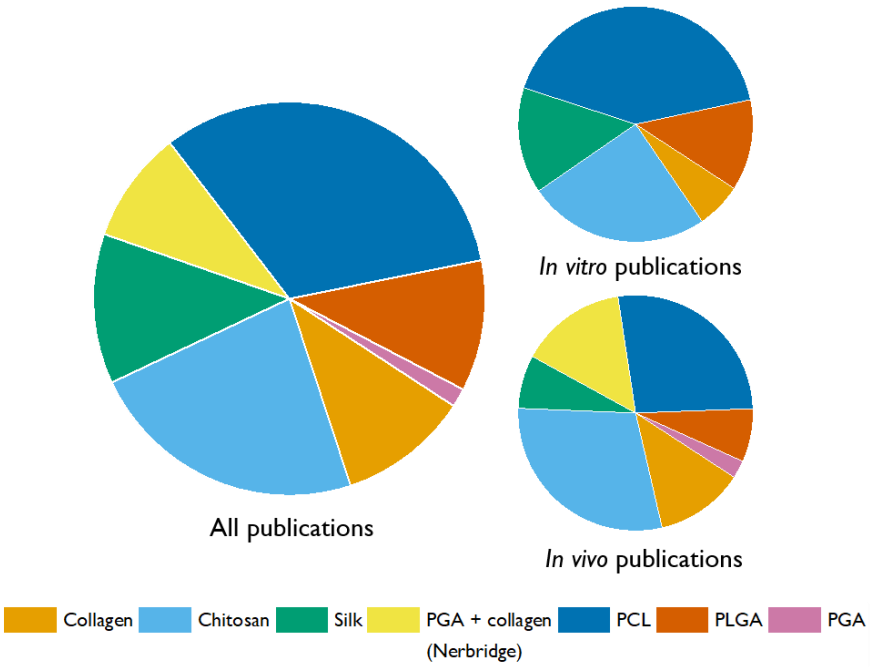

Figure 1

Collagen was recently combined with chitosan, a polysaccharide derived from marine organisms, to form a conduit with longitudinally aligned microchannels by unidirectional freezing (Peng et al., 2018). The conduit was used to repair a 30 mm sciatic nerve defect in a beagle model, and was found to facilitate nerve regeneration and functional recovery equal to an autologous graft group over 24 weeks (Peng et al., 2018). These results serve to demonstrate the efficacy of collagen-based conduits with an aligned architecture, even in the absence of additional regenerative agents. However, the presence of these agents may further improve outcomes: regeneration across a 15 mm rat sciatic nerve defect bridged by a conduit fabricated from the robotic deposition of orientated collagen 'strings' was improved when the conduit contained adsorbed basic fibroblast growth factor (Fujimaki et al., 2017). Similarly, regeneration across a 35 mm facial nerve defect in a miniature-swine model using a collagen/nano-sized β-tricalcium phosphate conduit filled with collagen filaments was more successful when the filaments were first incubated with nerve growth factor (NGF) (Zhang et al., 2019).

2.2. Silk

Silk is a material usually sourced from *Bombyx mori,* a species of silkworm, but can also be sourced from spiders. The main proteins in silk are fibroin and sericin, and for biomedical applications silk is usually processed to remove the sericin and form what is referred to as silk fibroin or regenerated silk fibroin (Su et al., 2019). Silk fibroin is biodegradable and biocompatible, and is able to support the outgrowth of neurons from rat DRGs and facilitate the survival of Schwann cells (Yang et al., 2007), and as such has become a desirable

biomaterial for peripheral nerve repair. In fact, its use as the main component in construct development in relevant publications from the last year was found to be higher than both synthetic polymers PLGA and PGA, and collagen, which historically has been commonly used in this application (Figure 1). A tri-layered silk conduit, fabricated from silk fibroin using electrospinning and a textile braiding process, has recently been developed and used to repair a 10 mm rat median nerve defect (Fregnan et al., 2020). The conduit possessed high compression strength and produced functional recovery of the median nerve in 24 weeks that was not significantly different from an autograft control group – the authors add that these promising results have led to a first-in-human study in which four patients with digital nerve injuries have undergone repair using the construct (Fregnan et al., 2020).

An emerging approach in preclinical development involves combining a biomaterial with an electroconductive polymer in an attempt to improve regeneration through electrical stimulation. Polypyrrole (PPy) is a popular choice for conductivity due to its compatibility with the cells and tissues of peripheral nerve (Wang et al., 2004), and has been combined with silk in a number of recent studies for nerve repair. For example, a composite nerve construct based on silk has been generated by bioprinting of aligned fibres of silk fibroin coated in PPy, followed by the electrospinning of aligned and random silk fibroin fibres to form a tube with aligned architecture in the lumen (Zhao et al., 2020). These conduits were implanted into rats to bridge a 10 mm sciatic nerve defect, and conduits that were electrically stimulated every two days throughout the study period aided functional recovery in 24 weeks that was similar to an autologous graft group (Zhao et al., 2020). The authors suggest that the electrical stimulation upregulated neurotrophic factors and activated pro-regenerative protein kinase signalling pathways (Zhao et al., 2020). Similarly, researchers that developed a spider silk and poly-lactic acid conduit using electrospinning with PPy/lysine doping that was used in the repair of a 20 mm rat sciatic nerve defect found that electrical stimulation of the conduit each day for three days post-implantation improved electrophysiological outcomes in ten months, compared to the same conduit without stimulation (Zhang et al., 2015).

2.3. Chitosan

Chitosan is a polysaccharide formed by the deacetylation of chitin, a material derived from the exoskeletons of arthropods that is second only to cellulose in terms of mass production by natural biosynthesis (Periayah et al., 2016). Chitosan is an appealing material for biomedical applications as it biodegrades into non-toxic metabolites (Boecker et al., 2019) and has excellent cellular compatibility, an attribute which is now known to be influenced by the degree of deacetylation (Carvalho et al., 2017). In a film formulation, chitosan has been shown to promote the adhesion and proliferation of immortalised, neonatal and adult rat Schwann cells in addition to axonal outgrowth from sensory neurons (Wrobel et al., 2014). Given these useful qualities, a chitosan tube was FDA-approved in 2015 for peripheral nerve repairs of ≤ 1 cm and intensive preclinical research into more complex constructs continues, in order to extend the gap over which it can successfully facilitate regeneration. Chitosan continues to be a popular choice of material: in a search of select literature over the past year, it was the second most commonly used material as the main construct component out of the six biomaterials in the search (Figure 1).

A chitosan-based conduit consisting of a corrugated outer tube (for increased flexibility) with two inner chambers separated by a perforated film was recently tested in a 10 mm rat median nerve defect, a model which the researchers selected over the more common sciatic nerve in order to better replicate high-mobility repair of human digital nerves (Dietzmeyer et al., 2019). Although the rate and extent of functional recovery over 16 weeks was greatest in the autograft group, the experimental conduit showed an improved recovery rate over non-corrugated conduits both with and without a two-chambered structure (Dietzmeyer et al., 2019). Another chitosan tube used in the repair of a 10 mm rat sciatic nerve gap, here filled with a statin-loaded Pluronic® F-127 hydrogel, was found to improve regeneration over an empty tube - potentially by increasing the expression of growth factors related to regeneration (Guo et al., 2018). Chitosan also has gel-forming capabilities, and has been used within a poly-DL-lactic acid conduit in a hydrogel formulation as carboxymethyl chitosan with sodium alginate and PPy for electrical conductivity (Bu et al., 2018). Although outcomes were best in an autologous transplant group, the experimental conduit encouraged regeneration and had improved outcomes over a conduit without PPy doping (Bu et al., 2018). A chitosan film has also been developed into a 'self-rolling' conduit in combination with either a spider silk film, aligned silk fibres or an anisotropic collagen cyrogel in the construct lumen (Aigner et al., 2020). Neurite outgrowth from PC12 cells was greatest when cells were seeded on the latter combination (Aigner et al., 2020), evidencing the value of aligned microstructure and collagen as a cell growth substrate.

3. Synthetic materials

Polyesters

The synthetic materials discussed here are all polyesters, as these are the most commonly investigated polymers for nerve repair applications. Polyesters are biodegradable and are broken down in the body by hydrolysis of their ester linkages into products which are eliminated in urine (Lasprilla et al., 2012), and can be selected for biodegradation across a timeframe appropriate for the application, i.e. axonal regeneration. Four tubes made of poly(DL-lactide-ε-caprolactone), a copolymer of the polyesters poly-DL-lactic acid and PCL, are currently FDA-approved for repair of nerve gaps up to 30 mm. The popularity of synthetic polymers continues to increase rapidly in nerve repair research, as these materials can offer sufficient strength to support the regenerating nerve and ensure appropriate surgical handling properties, and sufficient stiffness to maintain a patent lumen in a tubular conduit.

3.1. PCL

PCL has become widely used in nerve repair constructs. A search of relevant literature from the past year suggests it was the most widely used material as the main element of nerve constructs, out of the six materials assessed in the search (Figure 1). In order to aid regeneration over longer gaps in nerve tissue, synthetic polymers are often employed alongside regenerative agents like growth factors and small molecules. For example, a PCL conduit containing microspheres with encapsulated glial cell line-derived neurotrophic factor (GDNF) used to bridge a 50 mm median nerve defect in a rhesus macaque model produced higher nerve conduction velocity and similar functional recovery to an autograft group after one year (Fadia et al., 2020). Electrospun conduits have also been frequently investigated in

combination with neurotrophic growth factors. An electrospun scaffold made from a solution of 70% PCL, 20% collagen, and 10% nanobioglass with an NGF loaded gel in the lumen had similar motor and sensory recovery to an autograft group across a 10 mm rat sciatic nerve gap over 12 weeks (Mohamadi et al., 2018). However, a conduit group without NGF also produced functional recovery similar to the autograft group (Mohamadi et al., 2018). A construct fabricated from aligned electrospun PCL fibres with a gradient of bound NGF used to bridge a 15 mm rat sciatic nerve defect encouraged axonal regeneration and functional recovery to a similar extent as an autologous graft group over 12 weeks, and was superior to a conduit with uniform NGF distribution (Zhu et al., 2020).

The use of natural proteins within PCL-based conduits has also been demonstrated to improve regeneration. An aligned fibre conduit, here formed from PCL sheets and polyethylene-glycol diamine fibres, used the addition of the ECM protein laminin and was tested in a 15 mm rat sciatic nerve model over 12 weeks (Chang et al., 2020). Although inferior to an autograft group, the laminin-enriched conduit encouraged more extensive regeneration than a polymer-only conduit (Chang et al., 2020). Another group of researchers created an electrospun conduit using a solution of PCL and gelatine, where the protein was employed as its structure contains the Arg-Gly-Asp (RGD) sequence which is beneficial for cell attachment and proliferation (Samadian et al., 2020). The conduits were used to repair a 10 mm rat sciatic nerve defect, and conduits that were filled with a platelet-rich plasma gel containing the small molecule citicoline aided greater motor and sensory recovery after 12 weeks than conduits without citicoline (Samadian et al., 2020). Recently, another PCL-gelatine conduit was generated by electrospinning and the inclusion of gelatine was found to increase the elasticity, Young's modulus and tensile strength of the constructs, although failure strain was reduced compared to PCL-only constructs (Mohammadi et al., 2020). An electrospun conduit fabricated from a mixture of PCL and collagen was also found to enhance motor recovery compared to a PCL-only conduit over eight weeks in a 10 mm rat sciatic nerve defect (Yen et al., 2019).

3.2. PLGA

Polyesters other than PCL are also used to fabricate constructs for nerve repair. PLGA is an attractive choice for biomedical devices as its degradation is tuneable based on the ratio of lactic acid to glycolic acid monomers, where a larger proportion of lactic acid yields a slower degradation (Hirenkumar and Steven, 2012). An assessment of select publications over the last year indicates that its use was equal to collagen as the main component of nerve repair constructs (Figure 1). A research group have recently used capillary force lithography and salt leaching to generate a porous PLGA conduit with grooved inner walls, with a luminal filler of aligned electrospun PLGA fibre sheets (Jeon et al., 2020). The conduit demonstrated significantly improved regenerative performance compared to grooved conduits filled with random fibres and non-grooved conduits filled with either random or aligned fibres over eight weeks in a 10 mm rat sciatic nerve defect (Jeon et al., 2020). Aligned electrospun PLGA fibres have also been used in combination with mussel adhesive peptides and IKVAV, a peptide derived from laminin, to form a construct that was used to repair a 15 mm rat sciatic nerve defect (Cheong et al., 2019). Over a period of eight weeks the construct enabled functional recovery superior to constructs without IKVAV and to

PLGA-only constructs, and was comparable to an autologous nerve graft group (Cheong et al., 2019).

3.3. PGA

Other polyesters may be less useful for nerve repair. Researchers that studied regeneration across a 10 mm rat sciatic nerve defect using an empty collagen conduit and a PGA conduit filled with collagen fibres found that both an autograft and the empty collagen construct produced superior motor regeneration compared to the PGA construct, possibly due to rapid degradation and insufficient porosity of PGA (Saltzman et al., 2019). A literature search of relevant publications in the last year that used PGA as the main construct component found just a single study (Figure 1), a lack of popularity which is consistent with the suggestion that properties of PGA may not be ideal for nerve repair. Despite this, the publication search did reveal a number of studies investigating Nerbridge (Figure 1), a conduit made from PGA and collagen recently clinically approved in Japan. This combination of natural and synthetic components may be more useful in the creation of a pro-regenerative environment than PGA alone.

4. Biomaterials and cell therapy

Alongside delivery of growth factors and small molecules directly from materials, cells can be used as a source of therapeutic agents and as therapeutic agents themselves. Given that nerve regeneration is Schwann cell-mediated, it is unsurprising that cell therapy using Schwann cells (Rodrigues et al., 2012) and stem cells differentiated to adopt a Schwann cell phenotype (Kubiak et al., 2020) have been thoroughly investigated for nerve regeneration. These implanted cells secrete growth factors, cytokines, extracellular vesicles (Andersson et al., 2020) and ECM molecules at biologically relevant concentrations to accelerate axonal growth and promote myelin formation, so enhancing regeneration (Yi et al., 2020). Current preclinical research utilising a cell therapy strategy employs both natural proteins and synthetic polymers as the biomaterial scaffold for cell delivery and implantation.

4.1. Natural proteins

A stabilised collagen hydrogel encapsulating self-aligned cells differentiated from a clinical grade conditionally immortalised human neural stem cell line was used within a commercially available conduit to bridge a 12 mm rat sciatic nerve defect (O'Rourke et al., 2018). The construct was found to support regeneration over eight weeks, serving as an example of how an off-the-shelf allogeneic cellular biomaterial could be used in nerve repair (O'Rourke et al., 2018). Another collagen hydrogel formulation, here containing aligned Schwann cells and formed rapidly using a gel aspiration-ejection technique, has been used within a silicone tube to repair a 10 mm rat sciatic nerve defect (Muangsanit et al., 2020). The cellular biomaterial demonstrated similar tensile strength and Young's modulus to native rat nerve endoneurium and encouraged greater regeneration over four weeks compared to an empty silicone tube, however neurite growth failed to match that of an autograft group (Muangsanit et al., 2020).

4.2. Synthetic polymers

Another research group used a PCL sheet with PCL/PEG-diamine fibres containing NGF to form a conduit, which was cultured with bone marrow stem cells (BMSCs) using a novel

rotating culture system to obtain better cell coverage across the construct (Zhou et al., 2020). This construct had a number of improved outcomes over conduits with just BMSCs or NGF when tested in a 15 mm rat sciatic nerve gap over 12 weeks, but there were no statistically significant differences between the performance of the experimental conduit and a conduit with BMSCs and NGF (no cell culture system) or a conduit with just BMSCs cultured with the novel system (no NGF) (Zhou et al., 2020).

Multi-channel constructs fabricated from electrospun PCL and poly-L-lactic acid (PLLA) have also been developed recently, and a suspension of autologous adipose-derived stromal and stem cells was injected into the lumen of the nerve guides during implantation to bridge a 10 mm rat sciatic nerve gap (Frost et al., 2018). Over a recovery period of four weeks, the PCL conduit was very poorly tolerated and although the PLLA conduit supported regeneration it was outperformed by a hollow silicone tube – the implanted cells also appeared to incite an inflammatory response and the authors hypothesise that they may have negatively affected endogenous Schwann cell proliferation so impacting axonal regeneration (Frost et al., 2018). Adipose derived stem cells from the stromal vascular fraction (SVF), and the SVF itself, have also been used inside a PGA-collagen conduit to bridge a 7 mm rat facial nerve defect over 13 weeks (Shimizu et al., 2018). Although both cellular conduits were beneficial for regeneration compared to an empty tube, the SVF conduit produced higher CMAPs and axon diameters and authors felt the use of these cells was more practical as less processing was required (Shimizu et al., 2018).

A silicone tube seeded with Schwann cells modified to overexpress GDNF was assessed in a 5 mm rat cavernous nerve defect model (May et al., 2016). At 12 weeks, erectile function was restored in significantly more rats that received the experimental conduit than received an autograft (May et al., 2016). However, function was also restored in twice as many rats that underwent repair using an empty tube compared to autograft repair (May et al., 2016).

4.3. Combination of natural and synthetic materials

A PLGA-chitosan tube coated with laminin was used to bridge a 5 mm laryngeal nerve defect, and a Matrigel matrix containing rat Schwann cells and neural stem cells was injected into the lumen of the conduit during implantation (Li et al., 2018). After 12 weeks electrophysiology indicated latency and peak amplitudes were superior to an autologous nerve group, although TEM images of the injured nerves indicated the positive control group had a thicker myelin sheath (Li et al., 2018). Regeneration was notably poor in the neural stem cell-only group, and the authors attribute this to poor viability *in vivo* without a supporting co-culture of Schwann cells (Li et al., 2018).

5. Summary and future perspectives

5.1. Material selection

This review has identified studies published in the last five years that report the development of novel constructs for the repair of severe peripheral injuries (Table 1). Nine of these constructs demonstrated comparable or equivalent functional outcomes to an autograft, including four conduits fabricated from natural proteins (Fregnan et al., 2020; Peng et al., 2018; Saeki et al., 2018; Zhao et al., 2020) and five from synthetic polymers (Cheong et al., 2019; Fadia et al., 2020; May et al., 2016; Mohamadi et al., 2018; Zhu et al., 2020). It is

also interesting to note that all five synthetic conduits and only one natural polymer conduit employed some kind of regenerative agent. This may suggest that natural proteins are innately more pro-regenerative, however across these selected studies, the use of natural and synthetic materials appear to be equally efficacious approaches. In fact, these strategies are currently implemented with virtually identical frequency by researchers - in the literature search for 2019-2020, 29 publications used a synthetic material as the main construct component and 30 used a natural protein (Figure 1).

Future research focussing on the development of cellular biomaterials for nerve repair may help to realise the potential of cell therapy in promoting regeneration. This approach is certainly becoming more common, but despite the pro-regenerative aspects outcomes generally do not yet match that of autografts and methods to improve the long term viability of implanted cells *in vivo* are needed.

5.2. Model selection

It is notable that three of the autograft-comparable studies used higher animal models or human subjects, which illustrates the usefulness of rodent models of regeneration and how these technologies can be transferred to larger species with retained efficacy. However, it is important to interpret these findings carefully, since in rodent models there is a narrow window of opportunity for reliable comparison between experimental groups (Brenner et al., 2008). Longer time points and shorter gaps can result in robust regeneration even in negative control groups, so if comparisons with autografts are to be made reliably then it is essential that 'critical-length' gaps are used and appropriate time points selected (Kaplan et al., 2015; Windebank et al., 2012), where there is a significant difference between a nerve graft and a negative control.

5.3. Fabrication route

The prevalence of constructs formed in major part by electrospinning is also apparent in the literature, and this technique was utilised in five of the autograft-comparable repair conduits (Cheong et al., 2019; Fregnan et al., 2020; Mohamadi et al., 2018; Zhao et al., 2020; Zhu et al., 2020). There is little evidence to suggest this means of fabrication is losing popularity, which is to be expected given the accessibility of its apparatus and the tissue-like structures that can be created.

Ref	**Construct description**	***In vivo* model (species, nerve, gap length, timepoint)**	**Control groups**	**Outcomes**
(Saeki et al., 2018)	Collagen fibre tube containing longitudinally aligned collagen fibres	Clinical trial Sensory Mean defect of 12.6 ± 7.03 mm 12 months	Autograft with mean defect of 18.7 ± 6.46 mm	Recovery of sensory function not inferior to autograft patient group
(Peng et al., 2018)	Collagen and chitosan scaffold with longitudinally	Beagle 30 mm sciatic 24 weeks	Autograft No repair	Nerve regeneration and functional recovery

	orientated microchannels*			equivalent to that of autograft
(Fujimaki et al., 2017)	Aligned collagen strings with adsorbed bFGF	SD rat 15 mm sciatic 8 weeks	Construct without bFGF No repair	Superior nerve regeneration and functional recovery
(Zhang et al., 2019)	Collagen/nβ-TCP tube filled with collagen/NGF filaments	Miniature swine 35 mm facial 6 months	Autograft Construct without NGF Collagen conduit with collagen filaments with and without NGF	Autograft was best, experimental construct promoted regeneration more than other constructs
(Fregnan et al., 2020)	Trilayered silk conduit with an inner textile braided layer and outer fibre layers	Wistar rat 10 mm median 24 weeks	Autograft	Functional and morphological recovery similar to autograft, no negative control
(Zhao et al., 2020)	Aligned silk fibroin fibres with PPy coating and outer silk fibroin fibres	SD rats 10 mm sciatic 24 weeks ES	Autograft Construct without ES Silicone tube with and without ES	Functional recovery similar to autograft and improved over silicone conduit
(Zhang et al., 2015)	Spider silk and PLLA fibres with lysine/PPy and NGF	Wistar rats 20 mm sciatic 10 months ES	Construct without ES No repair	Best electrophysiology performance
(Dietzmeyer et al., 2019)	Corrugated outer chitosan tube with a perforated film forming two chambers	Lewis rats 10 mm median 16 weeks	Autograft Non-corrugated chitosan tube Non-corrugated chitosan tube with film	Autograft was best, experimental conduit accelerated rate and degree of functional recovery compared to other conduits
(Guo et al., 2018)	Chitosan tube filled with simvastatin-loaded Pluronic® F-127 hydrogel	SD rats 10 mm sciatic 10 weeks	Conduit without hydrogel	Improved regeneration over empty tube
(Bu et al., 2018)	PDLLA tube filled with a carboxymethyl chitosan and sodium alginate hydrogel doped with PPy	SD rats 10 mm sciatic 2 months	Autograft Construct without PPy doping	Autograft was best, PPy-doped conduit aided regeneration more than no doping
(Fadia et al., 2020)	PCL tube with encapsulated microspheres containing GDNF	Rhesus macaque 50 mm median 12 months	Autograft Construct without GDNF	Similar functional recovery and higher conduction velocity than autograft
(Mohamadi et al., 2018)	PCL, collagen and nanobioglass fibre tube filled with NGF loaded gel	Wistar rats 10 mm sciatic 12 weeks	Autograft No repair Conduit without gel filler	Motor and sensory recovery in two conduit groups not significantly different from autograft
(Zhu et al., 2020)	Aligned PCL fibre conduits with a concentration gradient of NGF	SD rats 15 mm sciatic 12 weeks	Autograft Conduit without NGF Conduit with uniform NGF	Similar extent of functional recovery to autograft, better than uniform NGF conduit
(Chang et al., 2020)	PCL sheet and aligned PEG diamine fibres with crosslinked laminin	SD rats 15 mm sciatic 12 weeks	Autograft Construct without laminin	Autograft was best, regeneration was better than in construct without laminin

(Samadian et al., 2020)	PCL and gelatine fibre tube filled with platelet-rich plasma gel containing citicoline	Wistar rats 10 mm sciatic 12 weeks	Autograft No repair Construct without gel filler Construct without citicoline	Autograft was best, experimental conduit was better than construct without citicoline
(Yen et al., 2019)	PCL and collagen fibre conduit	SD rats 10 mm sciatic 8 weeks	Silicone conduit PCL only conduit	Enhanced motor recovery compared to PCL only conduit
(Jeon et al., 2020)	Porous PLGA conduit with grooved inner walls and luminal filler of aligned PLGA fibres	SD rats 10 mm sciatic 8 weeks	Construct with random fibres Non-grooved conduit with random fibres Non-grooved conduit with aligned fibres	Functional recovery best for both grooved conduits, experimental conduit had best regenerative outcomes
(Cheong et al., 2019)	Aligned PLGA fibres with mussel adhesive protein and IKVAV peptides	SD rats 15 mm sciatic 8 weeks	Autograft PLGA only conduit Construct without IKVAV No repair	Number of outcome measures including functional recovery comparable or better than autograft, functional recovery in PLGA conduit not significantly different to autograft
(Saltzman et al., 2019)	PGA conduit filled with collagen fibres	SD rats 10 mm sciatic 16 weeks	Autograft Collagen tube	Autograft and empty collagen construct produced superior motor recovery to experimental construct
(O'Rourke et al., 2018)	Stabilised collagen hydrogel with aligned cells differentiated from human neural stem cell line**	Athymic nude rats 12 mm sciatic 8 weeks	Autograft Collagen tube	Electrophysiology showed improved functional performance over autograft but other outcomes were poorer
(Muangsanit et al., 2020)	Collagen hydrogel with aligned SCs*	SD rats 10 mm sciatic 4 weeks	Autograft Silicone tube	Autograft was best, followed by experimental conduit
(Zhou et al., 2020)	PCL sheet with PCL/PEG-diamine fibres containing NGF, cultured with BMSCs using novel culture system	SD rats 15 mm sciatic 12 weeks	NGF only conduit BMSC seeded only conduit BMSC and NGF conduit Conduit without NGF	Functional recovery similar in all groups, experimental conduit improved other outcomes but non-significantly
(Frost et al., 2018)	Multi-channel PCL and PLLA fibre constructs with autologous ASCs*	Wistar rats 10 mm sciatic 4 weeks	Autograft Silicone tube	Autograft was best, PCL conduit poorly tolerated and PLLA conduit outperformed by silicone tube
(Shimizu et al., 2018)	PGA/collagen conduit filled with collagen gel containing ASCs or SVF	Lewis rats 7 mm facial 13 weeks	PGA/collagen tube	Both experimental conduits promoted regeneration but SVF conduit had highest CMAP and axon diameter, SVF was also more facile to prepare
(Li et al., 2018)	PLGA-chitosan tube coated with laminin, filled with Matrigel containing SCs and NSCs	SD rats 5 mm laryngeal 12 weeks	Autograft Conduit with just Matrigel Conduit with SCs only Conduit with NSCs only	Electrophysiology indicated superior recovery in experimental conduit compared to autograft

(May et al., 2016)	Silicone tube seeded with SCs modified to overexpress GDNF	Fischer rats 5 mm cavernous 12 weeks	Autograft Silicone tube SCs in silicone tube	Functional recovery was better than in autograft, function also restored in more rats that received empty tube than autograft

Table 1

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