Chapter 9

Scaffolds for Peripheral Nerve Regeneration, the Importance of *In Vitro* and *In Vivo* Studies for the Development of Cell-Based Therapies and Biomaterials: State of the Art

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Abstract

Human adult peripheral nerve injuries are a high incidence clinical problem that greatly affects patients' quality of life. Although peripheral nervous system has intrinsic regenerative capacity, this occurs in an incomplete or poorly functional manner. When a nerve fiber loses its continuity with consequent damage of the basal lamina tubes, axon spontaneous regeneration is disorganized and mismatched. These phenomena translate in an inadequate nerve functional recovery and consequent musculoskeletal incapacity. Nerve grafts still remain the gold standard in peripheral injuries treatment. However, this approach contains its disadvantages such as the necessity of primary surgery to harvest the autografts, loss of a functional nerve, donor site morbidity and longer surgery procedures. Therefore, biomaterials and tissue engineering can provide efficient resources and alternatives to nerve injury repair not only by the development of biocompatible structures but also, introducing neurotrophic factors and cellular systems to stimulate optimum clinical outcome. In this chapter, a comprehensive state-of-the art picture of tissue-engineered nerve grafts scaffolds, their application in nerve regeneration along with latest advances in peripheral nerve repair and future perspectives will be discussed, including our own large experience in this field of knowledge.

Keywords: nerve regeneration, peripheral nerve, biomaterials, hydrogels, tube-guides, neurotrophic factors, cell-based therapies, functional assessment, mesenchymal stem cells, Schwann cells, tissue engineering, scaffolds

1. Introduction

Tissue engineering was originally defined by Skalak and Fox, in 1988 [1] as 'the application of the principles and methods of engineering and life sciences towards the fundamental understanding of structure-function relationships in normal and pathological mammalian tissues and the development of biological substitutes to restore, maintain, or improve functions'. Later, Langer and Vacanti [2], in a widespread review paper, defined three main pillars of tissue-engineering principles, the (a) isolated cells and substitutes—cellular systems; (b) tissue-inducing substances—bioactive molecules; and (c) scaffolds, biomaterials and/or matrices.

The first strategy concerns cell-based therapies in which cells in a small volume or in cell sheets are transplanted into the body. Cellular system includes a wide range of cells and most significantly stem cells [3–7]. Stem cells are responsive undifferentiated cells with varying degrees of self-proliferation and differentiation plasticity [8]. Although the number of stem cells is higher before birth, in adults there are still several 'niches' with significant number of stem cells [9]. The second pillar focuses on the [5, 7, 10] bioactive molecules that can be signalling molecules, proteins and oligonucleotides that can enhance cell migration, cell growth and/or differentiation. These bioactive molecules are roughly divided into mitogens, growth factors and morphogens. Finally, the third pillar is the three-dimensional structure that provides shelter and structure for the cellular system [5–7, 11]. Usually, the biomaterials or scaffold mimics the environment and natural extracellular matrix (ECM) of the place of implantation and should be biocompatible such as their metabolites. Also, scaffolds can be used as drug-delivery system in the controlled release of bioactive molecules [9, 12, 13].

Biomaterials according to the American National Institute of Health describes 'any substance or combination of substances, other than drugs, synthetic or natural in origin, which can be used for any period of time, which augments or replaces partially or totally any tissue, organ or function of the body, in order to maintain or improve the quality of life of the individual'. Earlier, the Williams Dictionary of Biomaterials [14] defined biomaterial as 'any substance intended to interact with the biological system in order to replace living matter which has lost its function. It can serve as a vehicle or not, matrix, support, or for stimulating new tissue growth'. The selection of the most adequate material for a given application should fulfil several requirements of physical, mechanical, chemical and biological properties. The most important features of biomaterials must be [7] (i) biocompatibility, that is, the biomaterial itself must not cause any harm in the living system; (ii) biofunctionality, since the biomaterial must feature mechanical and physico-chemical properties adequate to the function and intended application; and (iii) sterilizability, while materials must be able to undergo sterilization procedures, especially the polymeric materials. Biocompatibility is considered the main feature of a biomaterial and represents the response of the living system to the introduction of a foreigner material. It can be defined as the 'ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in

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the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response to that specific situation, and optimizing the clinically, relevant performance of that therapy' [14]. However, biocompatible biomaterials are not useful if they are not biofunctional. Similarly, bioactive devices cannot be used if they are not biocompatible. The term biofunctionality can be simply explained as the suitability to the function [7]. Scaffold porosity is an important desirable feature in the majority of scaffolds, as it promotes cell seeding and cell-matrix interaction and leads to increased neovascularization. However, the exact pore size depends on application, the average pore diameter of 20–125 μm is adequate of skin tissue and >300 μm, in bone tissue [11, 15]. The macro- and micro-topography and other physico-chemical properties of the scaffolds influence cell attachment, migration, proliferation and differentiation and promote protein and other factors adsorption and therefore the success of the system [11, 16]. The mechanical properties and specially the degradation kinetics also is a key feature, especially for musculoskeletal and neuromuscular repair due to the slower repair rates.

In this chapter, a comprehensive state of the art of tissue engineering focused on peripheral nerve repair and the advances on materials and nerve grafts will be discussed, as well as our own large experience in this field of knowledge and the future perspectives.

2. Peripheral nerve regeneration

Peripheral nerve injury remains a major public health problem with an estimated incidence of 13–23 cases per 100,000 persons [17, 18]. These injuries may have a traumatic or an iatrogenic cause and usually are associated with pain, decrease of function and sensory sensibility with devastating effects on patients and family lives [3, 17, 19, 20].

Aegineta et al. [21] for the first time performed nerve repair and wound closure in wounded soldiers, as a military surgeon. Then, in 1873, Hunter [22] first described the epineural nerve repair procedure, still in use today. Sunderland portrayed the principles of nerve repair resourcing to microsurgical techniques, and Kurze and Smith were able to apply those principles in 1964, thanks to the advance in microscopy [23–25].

Peripheral nerve injuries treatment understands the most challenging surgical procedures, and despite the major breakthroughs in this area, complete nerve recovery and nerve function in all clinical cases have not yet been achieved [17, 20, 26]. Despite the exquisite surgical techniques, poor recovery outcome results from nervous system intrinsic and extrinsic factors, such as the integrity of the surrounding tissues post lesion, type and level of the injury itself, the effect on the spinal cord and neurons, the compromising of end organs and with key importance the timing of the surgery [17, 27–29]. Also, although peripheral nervous system has spontaneous regeneration ability, there is a very limited prospective of spontaneous recovery, mostly concerning the complete functional neuromuscular recovery [20].

2.1. Peripheral nerve anatomy

The peripheral nerve system is composed by neurons, Schwann cells (SCs), fibroblasts, macrophages and interconnected blood system [20, 30]. Motor and sensory neurons are polarized cells whose bodies reside in the spinal cord and with long cytoplasm called axon. Their terminations, called dendrites, target a site of innervation. The signal conduction originates in the axon hillock, in the cell body and projects itself in synapses with target end organs. Axons plasma membrane is partially enclosed by the SCs that produce myelin that encapsulates the axon and helps with signal transmission. Myelin is therefore an insulator that enhances the signal transmission efficiency down the axon. Then, there is a connective tissue net that surrounds the individual axons called the endoneurium. An arrangement of axons, designed fascicles, is surrounded by the perineurium, and groups of fascicles are separated by the epineurium. External to this layer is the blood supply derived from major arteries and the latter involved by the mesoneurium (**Figure 1**). The conservation of fascicles patterns and connective tissue is vital for optimal nerve repair and regeneration. Therefore, more commonly, the epineurium is sutured in end-to-end suture (called epineural end-to-end suture), and all nerve surgical interventions are strictly directed at these connective tissue layers. The most important feature is the fact that these sutures must be tension free; otherwise, they will compromise the nerve blood supply and the process of regeneration itself [20, 30–32].

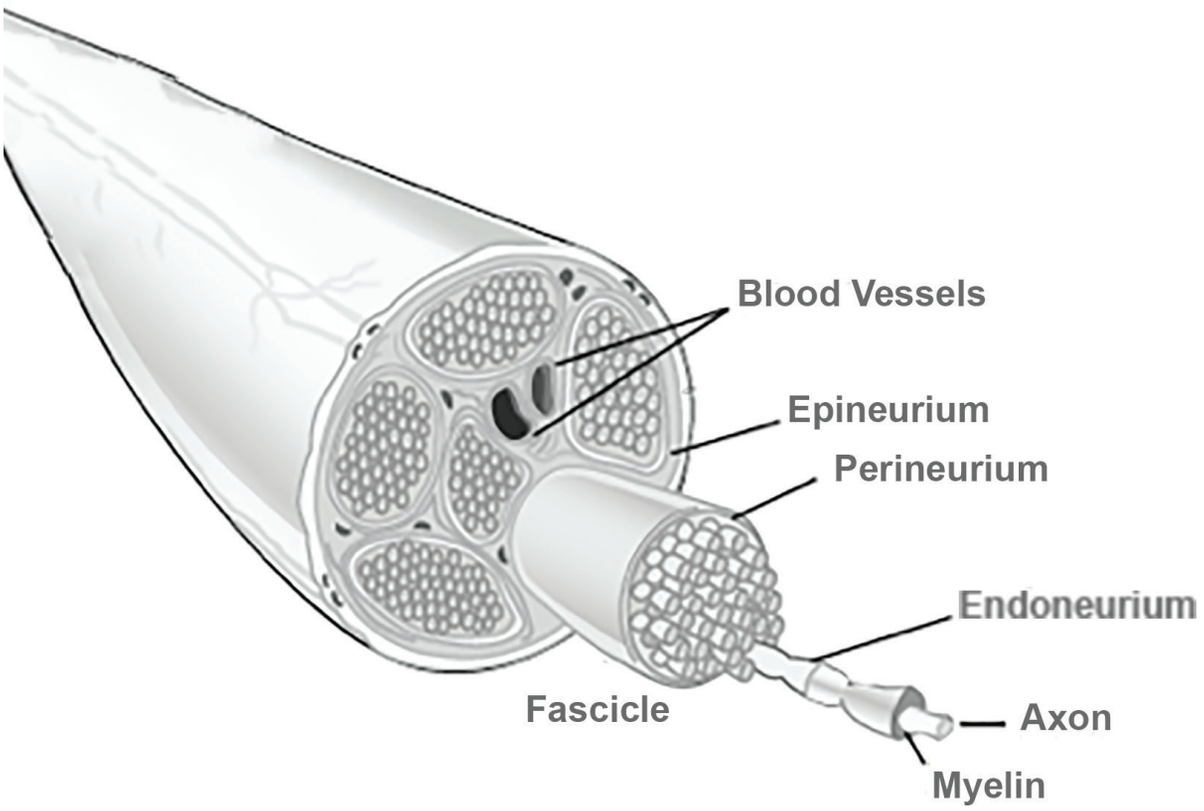

Figure 1. Peripheral nerve anatomy. The figure was adapted from Ref. [30].

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2.2. Nerve response to injury

Nerve injuries can be from a chronic or acute nature, and SCs are the major cause of chronic injuries [20, 30]. Acute injuries are mediated by axonal degeneration and occur in a sequence of events proximally and distally from the zone of trauma. The initial stages of degeneration occur proximally to the lesion as programmed cell death, called chromatolysis [33, 34], and distally to the lesion, through Wallerian degeneration of the distal axonal segment [35, 36]. Within 24–48 h of the injury, SCs degrade the myelin and phagocytes debris from distal axons [37, 38]. The proximal portion of the axon also degenerates up to the node of Ranvier, where the axonal regrowth occurs. Then macrophages recruitment occurs, originating growth factor release and fibroblast and SCs proliferation. The SCs form organized longitudinal structures inside the endoneurium—called bands of Büngner [30, 34]—that are critical to the axonal regeneration. At the distal site of lesion, the node of Ranvier, around 50–100 finger-like sprouts, starts to form a growth cone directed to the distal nerve stump [39]. Proteases are also released from the growth cone by the influence of several factors, clearing the way towards the target tissue. Nerve growth factor (NGF), brain-derived growth factor (BDNF) and other neurotrophic factors are upregulated by SCs, and their expression is increased which promotes the migration and proliferation of the SCs [20]. Axon existing actin allows axon elongation and which occurs in a 1–3 mm/day rate [36] until a receptor is reached. If no receptor or endoneurial tube is reached, axon continues to grow but in a disorganized manner, causing neuroma and clinically painful lesions [40]. In severe nerve injury, axon regeneration is further disorganized with additional scaring and pourer regeneration.

2.3. Nerve injury grading

Nerve injuries were firstly classified into neuropraxia, axonotmesis and neurotmesis by Seddon [41], after his World War II experience in treating nerve-injured soldiers. Neuropraxia is characterized by the segmentation of the myelin without disturbance of the axon, usually a consequence of a compression. Typically, it resolves itself, once the myelin is restored, within 12 weeks. Axonotmesis concerns axonal injury and occurs from a crush mechanism. In this case, connective tissue and nerve continuity are not affected but are followed by Wallerian degeneration. Axonal regeneration occurs at 1–3 mm/day rate [36], and depending on the distance of the lesion, an incomplete recovery may happen. Neurotmesis comprehends the anatomical and physiological section of the axons and connective tissues. Therefore, no spontaneous regeneration may occur and needs surgical reconstruction [30, 42]. Sunderland later expanded this classification by including five types of injury, based on histological knowledge that allowed further distinction between axonotmesis injuries [25, 43]. Sunderland grade Type I classification is equivalent to neurapraxia. The Type II, III and IV classifications differentiate axonotmesis injuries based on the commitment of the connective tissues. In Type II class injury, there is axonal damage without commitment of the endoneurium, and therefore, it is possible to achieve a full recovery. In Type III lesions, we find axon impairment affecting the endoneurium, and in Type IV besides endoneurium, there is perineurium damage. Sunderland grades III and IV may heal spontaneously, but there is attendant scaring and increasing axon and connective tissue damage that causes incomplete recovery. Type IV

lesion usually implies surgical intervention and results in extensive scaring. Scars are associated with pain and nerve conduction impairment and may require reconstructive surgery. Type V Sunderland classification corresponds to neurotmesis [30, 42]. Finally, Mackinnon and Dellon [44] described a mixed type of lesion degree, a Type VI addition to the Sunderland classification. This classification represents probably the most common type of lesions, with several layers of injury and not necessarily traditional model as described by Sunderland. The recovery potential and also the treatment approach vary, according to the type of lesion, considering the three classifications mentioned earlier.

In **Table 1**, the major findings in nerve injury grading according to Seddon [41], Sunderland [25, 43] and Mackinnon and Dellon [44] addition are described.

2.4. Diagnosis

Nerve injury may involve variable lengths of nerve impairment, and the degree of the lesion is affected by the type of lesion [45]. Also, the prognosis is dependent on the age of the patient, location of the lesion—distal fare better than proximal lesions—and also demographics [42]. In terms of nerve electrical signal and electrophysiology, the absence of electrical conduction may not indicate severe nerve damage, since conduction may be recovered after just 1 week. Clinical examination (including the functional evaluation) and surgical inspection still are the most accurate means to obtain diagnosis. However, non-invasive procedures such as nerve conduction studies (NCSs) and electromyograms (EMGs) have a diagnostic role in the delayed setting, when muscle fibrillation occurs [30, 42]. NCS assesses both motor and sensory functions through a voltage stimulator applied to the skin at different points of

Sunderland	Seddon	Characteristics	Spontaneous recovery potential
Type I	Neuropraxia	Injury to myelin sheath only	Full
Type II	Axonotmesis	Injuries involve the axon only	Full
Type III	Axonotmesis	Injuries involve the axon and disrupt the endoneurium	Usually slow or incomplete
Type IV	Axonotmesis	Injuries involve the axon and disrupt the endoneurium and perineurium	Poor to none
Type V	Neurotmesis	Complete disruption of the nerve; with the epineurium	None
Type VI*	Mixed	Combination of Types II, III and IV	Variable, can be poor to none

*Mackinnon and Dellon [44] addition to the Sunderland [25, 43] classification.

Table 1. Nerve injury classification according to Sunderland and Seddon.

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the nerve. A sensor detects response at the muscle (motor function) or nerve (sensory function). This is the initial screening test for the presence or absence of conduction signal. The EMG assesses only the motor function, and in this test, a needle is inserted in the muscle to assess the resting electrical activity and voluntary motor unit analysis [30]. In **Figure 2**, the representation of an algorithm of best treating approach selection according to the type of lesion, length and also complementary diagnostic results is shown. Sciatic Function Index (SFI) is one of the most widely used forms of functional assessment. It compares parameters from footprints and mathematically infers about sensory-motor gait function mediated by the sciatic nerve, without requiring terminal assessment [46, 47]. Sciatic Static Index (SSI) was first introduced by Bervar [48, 49] and is another way of assessing recovery of function after sciatic injury in animal models. It also uses the footprints in a static position and minimizes bias related to gait's velocity. Also, the SSI improves the acquisition of footprints and is more repeatable and accurate than the SFI. Other motor performance index is measuring

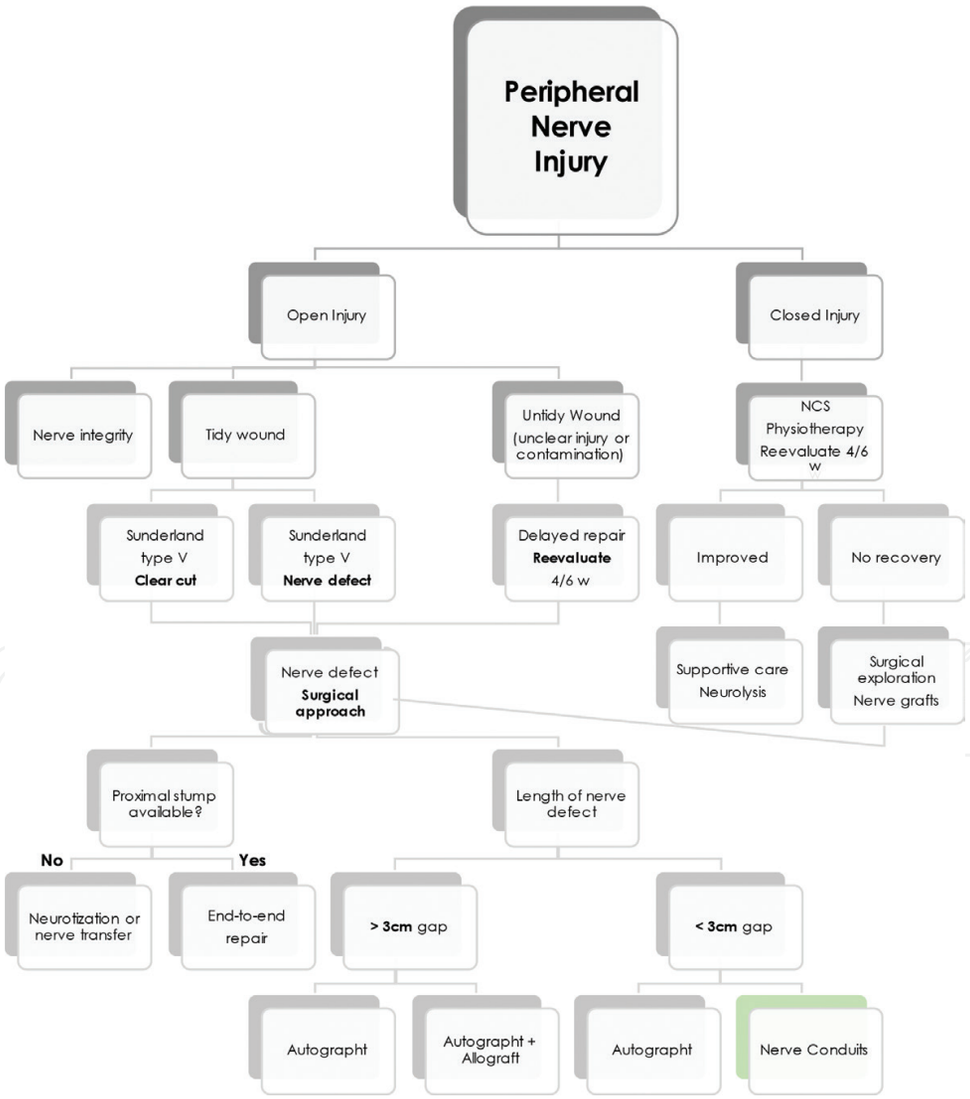

Figure 2. Peripheral nerve repair treatment diagram.

the extensor postural thrust (EPT) and nociceptive function using the withdrawal reflex latency (WRL). EPT is induced by lowering the affected hindlimb towards the platform of a digital balance supporting the animal by the thorax. During the test, the rat extends the hindlimb and the distal metatarsus and digits connect with digital platform balance [50–54]. Nociceptive function using the withdrawal reflex latency was described by Masters and colleagues [55] and is based on the fact that rats without sciatic nerve injury withdraw their paws from the hotplate within 4.3 s or less, when this period of time is increased, it is a symptom of impaired nerve conduction [51–53, 56–61]. Nuclear magnetic resonance (RMN) imaging could become a valuable tool in nerve injury diagnosis since it allows fine, detailed evaluation nerve anatomy and pathology due to excellent image resolution [42]. Also, functional diffusion tensor imaging (DTI), a new diagnosis tool, has been showing peripheral nerve sheath tumours; however, its application on differentiating various grades of injuries remains to be tested [42].

2.5. Timing of medical intervention

After peripheral nerve injury, repair events begin to take place. Primary repair events occur within the first couple of days. However, the rate of axon regeneration is very slow, as previously referred—it is 1–3 mm/day [36]—and no therapeutic methods have yet improved this regeneration rate [30]. However, it is consensual that early nerve repair results in improved functional outcomes, as described by Mackinnon and Dellon [44]. Furthermore, there is a set period of 12–18 months in which muscle re-enervation can occur before irreversible motor end-plate degeneration occurs, and the neurogenic atrophy takes place [30]. Slow axonal regeneration associated with muscle structural changes and increasingly degraded stromal environment contribute for an incomplete functional recovery. Muscle fibrosis and atrophy phenomena begin immediately after denervation and are called neurogenic atrophy. After 4 months, a plateau is reached, when 60–80% of muscle mass is lost, and although motor end plates increase, beyond a 12-month period, a functional muscle re-enervation is highly unlikely [30, 39, 62]. The time frame for sensory re-enervation is longer but not endless, and early repair also grants better results [30, 39]. In **Figure 2**, we present the peripheral nerve injuries repair algorithm which helps to understand the variables taken into account in the selection of best nerve repair strategy.

2.6. Nerve repair strategies

2.6.1. Direct nerve repair

Direct nerve repair with epineural end-to-end sutures using microsurgery techniques is still the gold-standard surgical treatment for severe neurotmesis injuries, but only in cases where well-vascularized tension-free coaptation can be achieved [30, 37, 63–65]. The procedure involves rough fascicular matching between proximal and distal nerve ends and the alignment of nerve fascicles and epineural blood vessels [30, 66]. Other types of direct repair consist in fascicular repair or grouped fascicular repair. This requires intranerval dissection and direct matching and suturing of fascicular groups. Despite better fascicle alignment, this procedure is no better than epineural repair in functional outcomes and in fact is associated with more traumas and scaring [30, 63, 66]. Complementary assistance techniques of histologic staining

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using acetylcholine esterase and carbonic anhydrase, electrical stimulation during the procedure in awaken patients and visual observation of surface vessels, are visual orientations to the surgeon that grant the success of the procedure [63, 67]. Another possible approach is the use of tissue adhesives such as fibrin glue to supplement or replace sutures, creating a gel-like clot at the nerve ends. The advantages of this procedure are the efficiency and practicality, the reduced trauma and scaring due to a barrier effect. The major disadvantage of this technique is the inferior holding strength more subject to stress [63, 68].

2.6.2. Nerve grafts

When peripheral nerve injury originates a significant gap (>3 cm) between the nerve ends with excessive tension for direct epineural repair and reversed interposition, nerve grafts are required [30, 63]. Such gaps may occur in severe neurotmesis lesions or in axonotmesis stretch injuries in which long regions of the nerve may be damaged in the setting of a lesion-in-continuity [63, 69]. Nerve grafts are single, cable, trunk, interfascicular or vascularized portions of the nerve with similar diameter to the affected [30, 70, 71]. Nerve grafting may be from autologous or allograph origin. Xenografts have been described as viable alternatives but require extensive immunosuppression and prionic diseases transmission if they are from ruminants [72, 73]. Nerve autografts are considered the gold standard since they provide appropriate neurotrophic factors and viable SCs, both essential for axonal regeneration without immune compromise [63, 74]. For the choice of the autologous grafts, many factors must be taken into account, such as the size of the nerve gap, the location of proposed nerve repair and associated donor-site morbidity [63, 74]. Grafts are either sutured to the epineurium of single nerves or more commonly to the perineurium of individual fascicles, depending on nerve calibre, type and location [30, 63, 74]. The interfascicular nerve graft was described by Millesi et al. [75]. Vascularized nerve graft was designed by Taylor and Ham, whereby the donor nerve is transposed with its arterial and venous supply into the graft site [76]. Terzis and Kostopoulos [71] clinically demonstrated that medium-sized trunk grafts, which would normally undergo central necrosis, could be transferred as vascularized nerve grafts and survive. However, autografts sacrifice a functioning nerve, usually a sensory nerve, to substitute a more important injured motor nerve. Therefore, sensory loss and scarring at the donor site, where neuroma and pain phenomena, are expected [30, 63, 77]. Autologous nerve graft undergoes Wallerian degeneration and therefore just provides support and guidance for the ingrowing axon. Also, fascicle mismatch, scarring and fibrosis of the repair site is unavoidable and is caused by the injury, tissue handling and suture itself. [30, 63, 77]. An alternative to autologous nerve grafting is the use of nerve allografts. The advantages of allografts are no donor supply limitations or donor-site morbidity, accessibility and unlimited supply of neuronal tissue. However, there are significant costs and complexity with their use, such as immunosuppression [30, 63, 72, 73, 77]. Several techniques have been used to reduce allograft antigenicity, such as cold preservation, irradiation and lyophilization and certainly patients' immunosuppressive therapy. However, it is proven that immune response is caused by SCs, and once their migration has occurred, approximately 24 months after nerve repair, systemic immunosuppression can be withdrawn [74, 78]. To avoid immunosuppression, nerve allografts are decellularized by a process of chemical detergent, enzyme degradation or irradiation, resulting in an acellular nerve scaffold [30, 63, 79]. Similarly, in tendon transfer, a distal function is treated at the expenses of a secondary function [30, 63, 79].

2.6.3. Nerve transfers and free-functioning muscle transfer

The definition of nerve transfer is the surgical coaptation of a healthy nerve donor to a denervated nerve [30, 63, 80]. The procedure was first described by Harris in 1921 [81], in the treatment of low median nerve injury suffered during World War I. The major disadvantage is finding an expendable donor nerve near the target muscle with a large enough motor fibre population [30, 63]. Free-functioning muscle transfer (FFMT) is another treatment approach, in severe injuries and especially in secondary reconstructions. The procedure entails the transfer of a healthy muscle and its neurovascular pedicle to a new location to assume a new function [71, 82]. Since it is a complex procedure, it is only considered as a secondary reconstructive surgery.

2.6.4. Nerve conduits

Nerve gap repair and nerve grafts have its complications. In the procedures described earlier, the nerve repair requires a second incision site for autograft harvest, donor-site morbidity, loss of a functional, usually sensory nerve, and long-surgery procedure [63, 65]. The described disadvantages triggered the development of nerve conduit or nerve guides to bring a new approach for nerve gap repair [40, 83]. Also, developments in tissue engineering and regenerative medicine, and research in artificial and natural biomaterials have enabled the development of the first nerve conduits [73]. Nerve tubulation approach to the repair of peripheral nerve gaps can be traced back to the nineteenth century. Gluck (Gluck, 1881) performed the first experiment of nerve tabulation, with a tube of decalcified bone to aid the approximation of transected nerve ends, in animals [78, 84, 85]. Later, Dahlin and Lundborg [86] developed the first synthetic tube, made of silicone. Their work was also pioneer in the characterization of the mechanism of regeneration within the lumen of the engineered tube [78, 86]. A nerve conduit is a tubular structure made of biological or synthetic materials designed to bridge the gap of a sectioned nerve. It is used when primary end-to-end direct repair is not possible, to protect the nerve from scar formation, to prevent fluid from leaking from the nerve stump and to guide the axon nerve cone into the distal nerve stump [63, 65, 78]. The fluid formed from the transected nerve ends is essentially made of fibrin, which forms a matrix or a hydrogel matrix between the nerve ends that is able to support cell migration. Cell migration within the fibrin matrix creates some linear bands—bands of Büngner—that steer the growth of the nerve cone [78, 86]. The mechanism through which neurite growth cone forms within the lumen of the conduit depends on the volumetric ratio [87, 88]. If the gap is too long or the diameter of the inner lumen is too large, the growth cables are too thin, and due to the fibrin matrix, the growth cone takes on an hourglass figure that affects axonal regeneration. Nectow et al. [89] also studied the effect of the defect size in the regenerative process through nerve conduits. Nerve conduits provide control environment to outgrowing axons, migration of SCs and neurotrophic stimulation by the distal stump crucial for optimal regeneration of nerve function [40, 90]. This approach is usually reserved for gap defects between 1.5 and 3 cm [91, 92]. As early as 1994, Brunelli et al. [91] defined four factors for an ideal nerve conduit material: (i) biocompatibility, (ii) easy preparation and tailoring, (iii) incorporation of neurotrophins and stimulating substances, and (iv) protection against scaring. Recently, Arslantunali et al. [93] defined the desirable features for a nerve conduit, as

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flexibility, biocompatibility, biodegradability, high porosity, neuroinductivity, neuroconductivity, easy handling and sufficient endurance. Nowadays, the second- and third-generation nerve conduits are becoming Food and Drug Administration (FDA) approved and reaching the marked, so, many more pre-clinical and clinical trials are demonstrating major breakthrough in this area. In **Figure 3**, we represent the major features of nerve conduits, and the modification researchers have made to introduce neurotrophic elements that enhance nerve regeneration and peripheral nerve repair.

2.6.5. Biological conduits

The use of non-neuronal tissue as conduits was first reported by Büngner (Büngner, 1891), when he successfully used a segment of human brachial artery to regenerate a gap in sciatic nerve [84]. The use of arterial grafts has been demonstrated [94, 95] but is associated with high morbidity. Also, lack of donor vessels makes this a less popular approach in nerve repair. However, it has been described that neurovascular injuries in the hand have benefited from the use of homolateral arteries in the repair [40, 84]. Frerichs et al. and Kim at al. [96, 97] have used acellular allogenic nerve grafts effectively in the regeneration nerve gaps in a rat sciatic model. A similar approach was approved by such Food and Drug Administration and is commercially available as Avance®, by AxoGen, Inc. (Alachua, FL, USA) (**Table 2**). Veins have also been a viable option for nerve repair. The risk of vein collapse led to their filling with

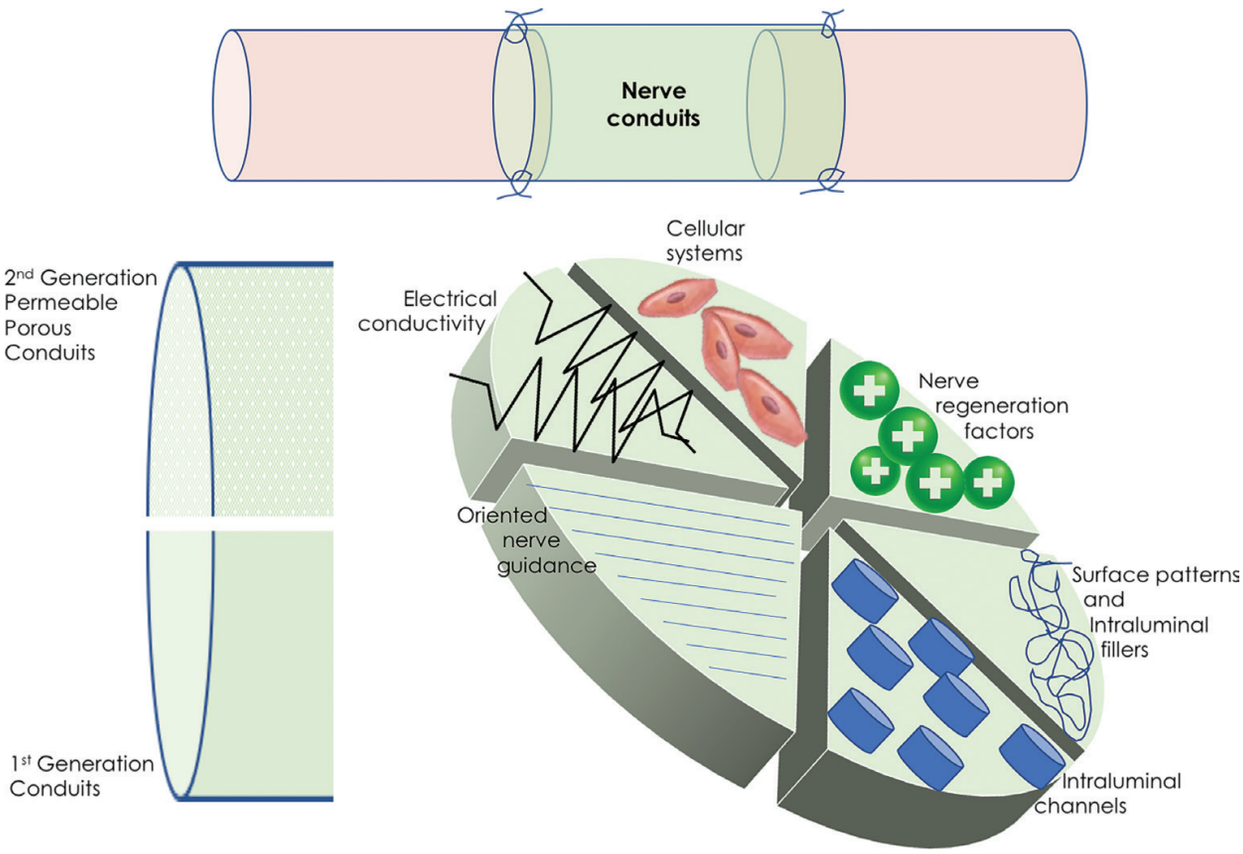

Figure 3. Different types of nerve conduits and their main features. Nerve conduits modification that functions as nerve regeneration enhancers.

nerve or muscle tissue. This supplementation has the added advantage of supplying neurotrophic factors and ECM (muscle fibres) and has been described to facilitate nerve regeneration across longer gaps by promoting SCs migration, cell proliferation and guidance of the axonal growth cone [84]. Another type of biological conduit is tendon autograft. Although with only theoretically and historic interest, ECM macrostructure and the presence of hyaluronic acid have been described to enhance regenerating in the nerve cone [84]. AxoGuard™ is the only FDA-approved device composed by small intestine submucosa (SIS) extracellular matrix (**Table 2**). Preliminary studies in rat sciatic model showed distally directed growth of the proximal nerve [98]. Later further in vivo studies revealed better EMG response for distal motor latency and amplitude [99].

2.6.6. Manufactured conduits

Manufactured nerve conduits can be divided as first-, second- and third-generation conduits. The first-generation conduits are non-resorbable, synthetic tubes made of silicone or polytetrafluoroethylene (ePTFE, Gore-Tex®) [65]. These conduits require a second surgery in order to remove the non-resorbable material. The original idea was to provide support, structure to guide axonal regrowth and form a stable barrier against connective tissue infiltration [73, 100, 101]. Synthetic nerve conduits made of ePTFE were successfully applied in a 4-cm nerve gap, in human [102]. Second-generation nerve conduits are resorbable, biocompatible tubes and are FDA approved and commercially available through different materials. The main advantage of these conduits is their permeability and resorbability that spares patients of a second surgery procedure. Third-generation nerve conduits contrary to second-generation may incorporate controlled release/delivery of neurotrophic factors, electroconductive material, stem cells or SCs, extracellular matrix proteins, surface micropatterning or luminal fillers [73, 103]. Already, two third-generation products have been approved by the FDA, namely NeuraGen® 3D from Integra LifeSciences Corporation and Nerbridge from Toyobo Co., Ltd. NeuraGen® 3D (K130557, approved in 2014) is a bovine Type I collagen conduit with a porous inner hydrogel matrix of collagen and glycosaminoglycan (chondroitin-6-sulfate). Nerbridge™ (K152967, approved in 2016) is a flexible, resorbable and semipermeable tubular membrane matrix filled with porous collagen that provides a non-constricting encasement for injured peripheral nerves for protection of the neural environment.

2.7. Materials

2.7.1. Collagen

Denaturated collagen conduits are available from a wide number of manufacturers and are in fact the most exploited material in nerve conduits [73, 78]. Collagen is a structural protein ubiquitous in the human body, particularly in the peripheral nerve system. Also, collagen supports cell proliferation and tissue regeneration [65, 73, 104]. As nerve conduits collagen allows the establishment of topographical cues that guide axons to regrow [105, 106] and has shown excellent cell adhesive properties that encourage cell attachment and proliferation [106, 107]. The degradation time of the collagen conduits is relatively prolonged and takes up to 48 months which can cause nerve compression and fibrosis [84]. The first commercially available collagen

Name	Composition	Structure	Length (cm)	Degradation Time (months)	Manufacturer	FDA approval
NeuroTube	Polyglycolic acid	Absorbable woven mesh tube	2–4	3	Synovis Micro companies	1999
Saluleridge nerve cuff	Polyvinyl alcohol	Flexible tubular membrane	6.35	No degradation	Salumedica LLC	2000
NeuraGen	Collagen Type I	Fibrillar, semipermeable	2–3	3–4	Integra LifeSciences Co.	2001
NeuroFlex	Collagen Type I	Flexible, Semipermeable and tubular	2.5	4–8	Collagen Matrix, Inc.	2001
NeuroMatrix	Collagen Type I	Flexible, Semipermeable and tubular	2.5	4–8	Collagen Matrix, Inc.	2001
Surgesis nerve cuff	Type I, III, IV and VI collagen	Extracellular collagen matrix	5	Reabsorbable	Cook Biotech	2003
Neurolac	Poly-DL-lactide-caprolactone	Tubular	3	16	Polyganics BV	2003/2005
NeuraWrap	Collagen Type I	Flexible, Semipermeable longitudinal slit	2–4	36–48	Integra LifeSciences Co.	2004
NeuroMend	Collagen Type I	Semipermeable wrap that curls and enrols	2.5–5	4–8	Collagen Matrix, Inc.	2006
SaluTunnel	Polyvinyl alcohol	Tubular	6.35	No degradation	Salumedica LLC	2010
Avance	Processed human nerve allograft	Tubular	Variable	No data	AxoGen, Inc.	2010
Cova ORTHO-NERVE	Type I collagen	Rollable membrane	2.5–6	3–4	Biom'Up S.A.	2012
AxoGuard	Extracellular matrix derived from porcine intestine	Semipermeable, and absorbable tube	Variable	No data	AxoGen, Inc.	2013
Flexible Collagen Nerve Cuff	Collagen Type I	Flexible, Semipermeable and tubular	2.5	No data	Collagen Matrix, Inc.	2014

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Name	Composition	Structure	Length (cm)	Degradation Time (months)	Manufacturer	FDA approval
Nerve cuff	Type I, III, IV and VI collagen	Extracellular collagen matrix	1–5	Reabsorbable	Cook Biotech	2014
Neuragen 3D	Type I collagen and glycosaminoglycan (chondroitin-6-sulphate)	Flexible, pliable tube with collagen-glycosaminoglycan inner matrix	6.35	9–12	Integra LifeSciences Corporation	2014
Reaxon Plus	Chitosan	Flexible, pliable tube	3	3	MEDOVENT GmbH	2015
Nerbridge	polyglycolic acid and Type I and III collagen	flexible, semipermeable tubular membrane filled with porous collagen	3–5	3–4	TOYOBO CO., LTD.	2016

Table 2. Commercially available and FDA-approved nerve conduits.

nerve conduit was NeuraGen®, from Integra Lifesciences, Princeton, NJ, FDA approved in 2001 (**Table 2**). Several studies regarding the efficacy of collagen conduits in peripheral nerve injuries have been stated. Bushnell and colleagues [108] performed in 2008 a retrospective study of the utilization of collagen conduits in digital sensory nerve gaps of up to 20 mm and demonstrated a significant recovery rate of 89%. In a retrospective review, Wangensteen and Kalliaine [109] reported on a large number of sensory nerve gaps of 2.5–20 mm repaired with collagen conduits in multiple body regions and concluded that clinically successful outcomes were only observed in 43% of the cases. A prospective cohort study was performed by Lohmeyer and colleagues in 2009 [110] in digital and palmar nerve gaps of 6–18 mm, and results showed meaningful recovery in 75% of patients. Later, in 2011, Taras et al. [111] reported a 73% meaningful recovery in 5- to 15-mm isolated digital nerve lacerations repaired with collagen conduits. In a niche approach, collagen conduits have been used in children suffering from plexus brachialis injury during birth [112]. Also, a significant number of in vivo studies on collagen conduits showed good functional outcomes in nerve reconstructions in rat, cat, dog and primate models [113–115]. Researchers and surgeons have, however, raised their concern about these conduits due to its high cost, conduit stiffness, lack of flexibility and poor enhancement of nerve regeneration [116, 117]. Also, collagen conduit application on major peripheral nerve injuries is limited to median and ulnar nerve repairs at the wrist and only observed as an alternative to the classic epineural suture repair [78]. In a recent study, Monaco and colleagues [118] investigated the effect of three different sterilization methods, dry heat, ethylene oxide and electron beam radiation, on the properties of cylindrical collagen scaffolds with longitudinally oriented pore channels, specifically designed for peripheral nerve regeneration. Ethylene oxide exposure demonstrated to be the most suitable method for the sterilization of the proposed scaffolds, since β-sterilization significantly augmented scaffold enzymatic degradation. Currently, there are 10 commercially available and/or FDA-approved collagen nerve conduits (**Table 2**).

2.7.2. Fibrin

Fibrin is a fibrous, non-globular protein involved in the clotting of blood. It is a commonly used biomaterial as fibrin glue in nerve repair. Nonetheless, it can also be engineered into a hydrogel with aligned matrix or shaped into tubular conduits [84]. As fibrin glue, it is widely used in sutures, thanks to its semisolid structure that enhances haemostasis and integrity of the repair and also due to its angiogenesis, chemotaxis, leucocytosis and macrophage proliferation stimulation [119, 120]. When used in a conduit, fibrin has shown to promote axon regeneration and functional recovery in small gaps [116, 121, 122]. Rafijah and colleagues [123] have reported the use of collagen conduits filled with fibrin glue in 10-mm rat sciatic nerve defect. After 12 weeks, no inhibitory effect was observed on function, axonal regeneration and compound motor action potential compared to hollow collagen conduit.

2.7.3. N-fibroin

N-fibroin is a soluble protein, derived from silk with great potential due to their superior biocompatibility and low immunogenicity and mechanical stability upon degradation [73, 124]. Several studies have demonstrated the potential of N-fibroin in the regeneration of peripheral nerve injuries [124–128]. Silk fibroin-based nerve guidance conduit with oriented

filaments was produced by Yang and colleagues [129] and originated successful results in rat sciatic model. Researchers have also shown that silk-based conduits [130] and silk nanofibres [131] enhance cell-material interactions like cell adhesion, proliferation and differentiation. A new approach entails the development of conduits with multi-walled silk fibroin/silk sericin internal lumen, beneficial to nerve regeneration and outer sheath (the hollow poly(lactic-co-glycolic acid) conduits that provide strong mechanical protection. Engineered bionic conduit showed promising in vivo results [132]. Research has also reported the development of silk fibroin conduits loaded with nerve growth factors [133–138]. Despite the promising results, no silk conduit has yet been FDA approved.

2.7.4. Chitosan

Chitosan is a natural polymer currently under investigation as nerve conduits due to its favourable biocompatibility, biodegradability and bioactivity [139]. Our group research tested the nerve-regenerative potential of chitosan membrane with N1E-115 cellular system in rat sciatic nerve crush injury. Results showed that freeze-dried chitosan Type III without N1E-115 cell addition was the only type of membrane that significantly improved post-traumatic axonal regrowth and functional recovery [52]. Recent study showed meaningful motor and sensory recovery in 30-mm defect in the nerve of the distal right forearm [140].

2.7.5. Polyglycolic acid

Polyglycolic acid (PGA) was the first FDA approved and commercially available nerve conduit—NeuroTube®, from Synovis Micro Companies Alliance, Birmingham, Ala. PGA is a common suture material and is more flexible and porous than silicone. PGA is degraded into lactic acid in 6–12 months [73, 90]. Therefore, critics claim that PGA may degrade faster than the regeneration process and resulting lactic acid may a have toxic effects [84, 141–143]. Dellon and Mackinnon [144] were the first to report the use of PGA conduits as secondary reconstitution of digital nerve defects 3 cm or smaller in 15 clinical cases in monkeys. After 1 year, 86% meaningful recovery was reported. Later, in an attempt to compare PGA conduit results to conventional autograft repair, Weber et al. [145] conducted a randomized prospective multicentre trial in the reconstruction of long sensory nerve gaps up to 3 cm. After 1 year, 74% meaningful recovery was noted in the PGA group compared with 86% in the standard techniques group ($P > 0.05$). Further analysis showed that PGA conduits were equivalent or superior to traditional autografts in less than 4- and 9–30-mm gaps [145]. Other researchers also compared PGA conduits and vein grafts to repair digital nerve gaps up to 4 cm and equivalent or superior recovery was obtained [146, 147]. Further experiments have demonstrated the success of bioabsorbable PGA nerve conduits in the regeneration of nerve defects [148–151]. The most recent FDA-approved PGA conduit is Nerbridge®, from Toyobo Co., Ltd., which is a flexible, semipermeable tubular membrane filled with porous Type I and III collagens (**Table 2**).

2.7.6. Poly (D, L lactide-co-ε-caprolactone)

Poly-D, L lactide-co-epsilon-caprolactone (PCL) consists in lactic acid and caprolactone monomers. Their nerve conduits are resolvable polyester with the advantage of being transparent and with less acidic degradation product that therefore causes less toxic reaction [60, 84, 116, 152].

Also, PCL conduit is easy to produce, has a low-cost processing and has a long degradation time up to 16 months. However, resulting conduits have higher rigidity and more difficult to handle in clinical settings [84]. Also, Duda et al. [153] reported a strong foreign body response in PCL conduits. Currently, Neurolac® [154–156] is the only FDA-approved caprolactone conduit (**Table 2**). Several reports have been made in the application of PCL conduits in sciatic rat nerve repair [157–162]. Bertleff et al. [154] performed a randomized prospective multicentre study where PCL conduits were comparable to either primary end-to-end repair or nerve autograft. However, latter research showed no meaningful recovery in digital nerves repair [155, 156]. Secer and colleagues [163] studied the use of PCL in the recovery of 455 patients with ulnar nerve injuries. PCL conduits filled with muscle tissue showed superior results in comparison to single PCL conduits in 10- and 15-mm gap in sciatic nerve rat model [36, 156, 164–168].

2.7.7. Polyhydroxybutyrate

Polyhydroxybutyrate (PHB) is a polyester polymer, also used in sutures and wound dressings [116, 169]. PHB has a long degradation time, up to 24–30 months [116, 169]. It has been reported that PHB has a neuroprotective effect and can help axon regeneration [170, 171]. Recently, Axongen Pharmaceuticals has a pending approval order of a PHB conduit. A study in which PHB wrap implants were used in human patients showed promising results compared to epineural suture [172].

2.7.8. Polyvinyl alcohol

Polyvinyl alcohol (PVA) [36, 89, 93] is the only nondegradable synthetic nerve conduit approved by the FDA—SaluBridge and SaluTunnel, from SaluMedica LLC, Atlanta, GA, USA (**Table 2**).

2.7.9. Polyhedral oligomeric silsesquioxane

Polyhedral oligomeric silsesquioxane (POSS) can be described as the smallest particles of silica [116]. The combination of POSS and PCL has been employed in the fabrication of peripheral nerve conduits and in vivo clinical studies to show the potential translation into clinics [117].

2.8. Optimizing nerve regeneration

Although nerve conduits provide sufficient guidance for regeneration of nerve defects, the development of new generation of scaffolds is under way. Third-generation conduits include artificial conduits that may incorporate controlled release/delivery of neurotrophic factors, electroconductive material, stem cells, SCs, extracellular matrix proteins, surface micropatterning, luminal fillers and guidance structures [73, 103].

2.8.1. Conduits structure modulation

Surface micropatterning and the inclusion of extracellular matrix proteins are new approaches that can provide suitable nanostructure topography for adequate neural growth and simulate topographical dimensions that mimic native nerve extracellular matrix [103, 173]. Coating of

peripheral nerve conduits can enhance nerve regeneration process and solve longer nerve gaps repair. Resource to extracellular matrix materials, such as fibronectin, laminin and collagen, give naturally hydrophobic scaffolds a hydrophilic surface that promotes cell adhesion [73, 116, 174]. Collagen Type I conduits coated with laminin and fibronectin have shown improved neural regeneration [175, 176]. With that intend, new peptides have been engineered to mimic the active binding domains of various extracellular matrix molecules [177, 178]. Coating with arginylglycylaspartic acid (RGD) sequences (the tripeptide Arg-Gly-Asp) also obtained very good results [117, 179–182]. Structure pore design is a great strategy to promote nerve regeneration. Controlling the architecture of the conduit wall is possible to develop a microporous inner layer and macroporous outer layer and obtain a bidirectional permeability [86, 103]. The diameter of the pores plays a critical role in the efficiency of the scaffolds since it influences cell attachment, axon regeneration and diffusion of nutrients [183, 184]. Electrospinning is a frequently used technique in bioengineering to produce imprinted micropatterns and can be used as a luminal guidance strategy. The advantages associate with electrospun conduits are (i) highly flexible and porous materials; (ii) high surface area-to-volume ration, thereby great availability for protein absorption, stem cells migration and regeneration of axons; (iii) fibers can be preferentially aligned, resulting in increased SC alignment, proliferation and growth, and the promotion of guided axonal growth [116, 185, 186]. Uneven fibre distribution and nerve growth inhibition caused by fibre overlapping are some of the disadvantages associated with this type of conduits. However, association with wall guides helps to avoid this problem [105, 187, 188].

2.8.2. Luminal fillers

Biomaterials and other strategies as conduits luminal fillers aim to change its microenvironment in a favourable way. The goal of this strategy is to promote axon regeneration inside the conduit and the restoration of motor and sensory nerve function.

2.8.2.1. Cellular systems

Stem cell therapies have received increased attention in regenerative medicine [189–201]. The use of cellular systems inside nerve conduits is intended to promote axon regeneration [202–206]. Several cells have been used with this intention, SCs, bone marrow stem cells (BMSCs) including more specifically the mesenchymal stem cells (MSCs). SCs are the natural glia of the peripheral nervous system and have been used successfully with beneficial effects in nerve reconstruction [204, 207–210]. However, there is limited availability, and it requires previous surgery. Stem cells have the opportunity to show their potential since they are able to secrete neurotrophic factors and provide a favourable microenvironment for neurogenesis and the proliferation of SCs in peripheral nerve repair [211] and also are able to differentiate into Schwann cell-like phenotype [200, 212, 213]. MSCs therefore seem the most attractive approach as cellular system in peripheral nerve regeneration. MSCs all share mesenchymal markers that differentiate them from other cells that are positive staining for CD10, CD13, CD29, CD44, CD90 and CD105, and negative expression of haematopoietic markers [214]. Their main feature is their ability to proliferate and self-renew in a sustained manner, high plasticity and low immunogenicity, and differentiate into multiple

mesodermal cells, including neuron-like cells [215, 216]. Also, they are major histocompatibility complex (MHC) class II negative and also their MHC class I expression levels can be manipulated; therefore they do not require the use of immunosuppressive drugs [217, 218]. MSCs can be isolated from several origins, including skin, hair follicle, periosteum, amniotic fluid, umbilical cord blood adipose tissue and dental pulp [53, 56, 200, 215, 219–221]. Bone marrow represents the most commonly used tissue source of adult MSCs. BMSCs have limited availability especially in adult life and there is donor-site morbidity associated with its harvesting. Therefore, alternative sources have been reached. MSCs exist in the connective tissue (Wharton's jelly (WJ)) of human umbilical cord and can be harvested easily [214, 218, 222, 223]. Several researchers have demonstrated that umbilical cord–derived stem cells can be differentiated into neuronal phenotype [214, 218, 222, 223] and have demonstrated potential utility in neurodegenerative diseases [224, 225]. Our group research has vast experience in the application of mesenchymal stem cells in peripheral nerve regeneration [50, 52, 53, 56–61]. In our most recent work [56], we report the therapeutic value of MSCs isolated from the Wharton jelly in nerve repair associated to different tube guides made of biodegradable and biocompatible biomaterials. Biomaterials like PVA, PVA loaded with functionalized carbon nanotubes (PVA-CNTs), PVA loaded with polypyrrole (PVA-PPy) and PLC associated to MSCs were tested in terms of cytocompatibility and *in vivo* in the rat sciatic nerve neurotmesis injury model. The functional recovery was assessed serially for gait biomechanical analysis, by EPT, SFI and SSI, and by WRL. Results showed that MSCs enhanced the recovery of sensory and motor function in neurotmesis injuries showing a thicker myelin sheath. Other authors have reported the application of bone marrow stem cells and Schwann-like cells in the regeneration of facial nerves in rats [219].

Other sources of stem cells have been used in peripheral nerve injuries, such as adipose-derived stem cells [203, 206, 212, 226–231] and dental pulp stem cells (DPSCs) [232–236]. Dental pulp stem cells have also demonstrated differentiation capacity towards multiple other mesodermal and endodermal lineages, under appropriate conditions: adipogenic, osteo/dentinogenic, chondrogenic, neurogenic, endothelial, myofibroblastic [237] and hepatocytes [238]. DPSCs can be isolated from both the perivascular and the sub-odontoblastic compartments (the inner surface of the tooth and the outer part of the pulp tissue), by separate digestion of the tooth and extracted pulp tissue. Both populations presented identical cell size, doubling times and karyotype stability, differing only in morphology with rounder cells in the sub-odontoblastic compartment versus spindle-shaped cells with long processes in the perivascular one [239]. Pre-clinical experiments have demonstrated that stem cells show promising results in differentiation into neuronal-like cells [226, 228, 232, 233, 240] and their secretion of growth factors [229, 241, 242]. Shi and colleagues [243] stated the potential of glia-derived neurotrophic factor expressing neural stem cells in the regeneration of facial nerve gap in rats.

2.8.2.2. Neurotrophic factors

Growth factors and cytokines have a complex enhancing effect in tissue regeneration which can be exploited with great potential in nerve regeneration [73]. To date, several neurotrophic factors have been identified: transforming growth factor beta superfamily (TGF-β), nerve growth factor, neurotrophins 3, 4 and 5 (NT-3/4/5), ciliary neurotrophic factor (CNTF),

neuregulin-1 (NRG1), brain-derived neurotrophic factor, glial cell line–derived neurotrophic factor (GDNF) and vascular endothelial growth factor (VEGF). The controlled release of the neurotrophic factors in nerve conduits may take several approaches, namely topical application, subcutaneous injection, microosmotic pump and diffusion or affinity-based polymer microspheres [244–251]. In another approach, Cui and colleagues [252] loaded the neurotrophic factors into the wall of the nerve conduit with controlled diffusion into the lumen. NGF has been reported to promote neurite outgrowth in vitro in co-culture of neurons and astrocytes [253] and in vivo–enhanced axonal regeneration in sciatic nerve in rat model [248, 254]. Several researchers have demonstrated BDNF efficacy in the regeneration of rat motor nerves [253, 255, 256]. The dosage of BDNS has also been studied [257]. A high dosage, set as 12–20 mg/day, has been stated to interact with p75 receptors and therefore inhibits axonal regeneration. In fact, single exogenous dosage of BDNF has shown better results than continuous long-term applications [258]. It is reported that muscle regeneration causes the overexpression of GDNF which increases the number of motor axons in the neuromuscular junctions in vivo [259–266]. Also, GDNF is a potent protective factor against axotomy-induced motor and sensory neuron death [267–270]. CNTF has the ability to improve and regenerate muscle function after nerve injury in vivo [271, 272]. It has also demonstrated to enable peripheral nerve regeneration by promoting axon elongation and sprouting from axon distal stump [273]. Six main isoforms of NRG-1 are described. Due to their importance in nerve regeneration isoforms I, II and III are the most studied in the last few years [274]. Nerve-regenerative effect of NRG-1 is highly dependent on the isoform and its dosage [275, 276]. Several studies indicate that NRG-1 isoforms are capable of stimulating SCs proliferation a remyelinization [275–278]. Gambarrota and colleagues [279] recommended that initial high dosages of NRGA-1 stimulate SCs differentiation.

2.8.2.3. Pharmacological agents

Until now, there is no pharmacological method that can effectively enhance nerve regeneration. However, as mentioned earlier, neurotrophic and growth factors have demonstrated potential in enhancing nerve repair and regeneration by reducing neuronal death and promoting axonal outgrowth. Recent advances in molecular biology have indicated that targeting specific steps in molecular pathways may allow for purposeful pharmacologic intervention, potentially leading to a better functional recovery after nerve injury [63, 280]. Major molecular pathways implicated in neuron survival and neurite outgrowth include PI3K (phosphatidylinositol-3 kinase)/Akt (protein kinase B)-signalling cascade, Ras-ERK (rat sarcoma-extracellular signal-regulated kinase) pathway, the cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) and Rho-ROK signalling [280]. PI3K/Akt cascade seems to provide trophic support for neurons, block apoptosis, facilitate signal transmission and mediate cell growth and differentiation in neurons. Also, it is reported that NGF is mediated by PI3K/Akt/mTOR pathway [281–283]. Ras-ERK pathway is a key promoter of neurite outgrowth and also has been found to enhance axonal survival [284]. Rho–ROK pathway participates in neural growth and modulates neurite outgrowth [285]. Nectins and nectin-like molecules are cell-cell adhesion

molecules that participate in cell communication. Nectin-like molecule 1 (NECL1) is restricted to the nervous system and is responsible for the synapses formation, axon bundles, myelinated axons and cerebellar morphogenesis [286, 287]. In a recent study, Xu and colleagues [288] developed a PLGA scaffold coated with NECL1 to enhance adhesion of rat SCs and applied in the treatment of transected sciatic nerve in rat. Results also revealed that the final outcome of both motor and sensory regeneration and reinnervation. Other molecules with different clinical applications have, however, demonstrated beneficial effect in nerve regeneration process: erythropoietin (EPO) [289], tacrolimus (FK506) [290], acetyl-L-carnitine (ALCAR) [291], N-acetylcysteine (NAC) [292], ibuprofen [293], melatonin [294] and transthyretin [295].

2.8.2.4. Channels

The use of longitudinal channels inside nerve conduits is the usual strategy to promote axon guidance towards distal stump. The artificial micro-tubular structure mimics the endoneural tubes and fascicles of a peripheral nerve anatomy and therefore enhances neuroregeneration [296–298].

2.8.2.5. Hydrogels

As described earlier, conduits lumen can be filled with ECM components such as collagen and laminin which are involved in the process of regeneration by forming a substrate for neuron cell migration. Laminin-filled silicone conduits have demonstrated enhanced nerve regeneration [299, 300]. Collagen has also demonstrated to increase nerve regeneration [301]. BD Matrigel® and other *lamini* and collagen gels have been widely used as conduit fillings to incorporate or support cells and neurotrophic factors [302–304].

2.8.2.6. Conductive conduits

Electrical stimulation as a therapeutic in nerve injuries has been widely discussed in the academic community [305–313]. External electrical stimulation as peripheral nerve regeneration strategy has been demonstrated. Several conductive polymers such as polyaniline (PANI) and polypyrrole have been described with great potential for nerve regeneration due to their biocompatibility, tuneable conductivity, environmental stability and facility to produce. The great advantage of this material is the ability to continue to transmit the electrical signal in impaired nerves and physically stimulate cell growth and regeneration [314–316].

2.9. Future perspectives

Gene therapy involves the introduction of a foreign gene into living cells with the intention to overcome a disease [317]. The most efficient way to deliver transgenes into cells is through a vector, such as herpes simplex, adenovirus, lentivirus and adeno-associated viral vectors [318, 319]. Gene can reprogramme cells to produce neurotrophic factors, cell adhesion

or extracellular matrix molecules, and transcription factors. Therefore, in peripheral nerve injury, Schwann cells, fibroblasts and denervated muscle are potential targets for this breakthrough approach [63].

Bioactive glasses have been widely used as bone-filling materials and dental implants and have demonstrated its potential in soft-tissue regeneration. A comprehensive study on the application of bioactive glass in peripheral nerve regeneration has been conducted by Novajra and colleagues [320, 321]. Polymer-glass composite devices are made with bioactive glass powder and successfully applied in peripheral nerve repair. In other approach, this material can be used as fibres to produce nerve wraps, topographic patterns at conduit lumen or guidance channel to guide axonal growth. Their major advantage is the ions release from bioactive glasses, which have demonstrated angiogenic effects and the possibility of manipulation of glass composition; I order to include antibacterial ions, such as silver, gallium, zinc and copper, that can be useful in the prevention and treatment of infections resulting from the clinical intervention.

In conclusion, the vast field for improvement in peripheral nerve regeneration strategies has been well recognized. The ideal therapeutic alternative should be readily available, able to confine and direct axonal growth and be biofunctional, by the supplementation with bioactive molecules and/or cellular systems. Therefore, there is scope for improvement in the development of new and better alternatives of bioactive peripheral nerve repair complexes.

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Conflicts of interest

The authors confirm that they have no conflicts of interest to declare for this publication.

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Abbreviations

Akt	Protein kinase B
BDNF	Brain-derived neurotrophic factor
BMSCs	Bone marrow mesenchymal stem cells
cAMP	Cyclic adenosine monophosphate
CNTF	Ciliary neurotrophic factor
DTI	Diffusion tensor imaging
DPSCs	Dental pulp stem cells
ECM	Extracellular matrix
EMG	Electromyograms
ePTFE	Polytetrafluoroethylene
FDA	Food and Drug Administration
FFMT	Free-functioning muscle transfer
GDNF	Glial cell line-derived neurotrophic factor
MHC	Major histocompatibility complex
MSCs	Mesenchymal stem cells
NAC	N-acetylcysteine
NCS	Nerve conduction studies
NGF	Nerve growth factor
NRG1	Neuregulin-1
NT-3/4/5	Neurotrophins 3, 4 and 5
PANI	Polyaniline
PCL	Poly D, L lactide-co-epsilon-caprolactone
PGA	Polyglycolic acid
PHB	Polyhydroxybutyrate
PI3K	Phosphatidylinositol-3 kinase
PKA	Protein kinase A
POSS	Polyhedral oligomeric silsesquioxane

PPy	Polypyrrole
PVA	Polyvinyl alcohol
PVA-CNTs	PVA-functionalized carbon nanotubes
Ras-ERK	Rat sarcoma-extracellular signal-regulated kinase
RGD	Arginylglycylaspartic acid
SC	Schwann cells
SFI	Sciatic Functional Index
SIS	Small intestine submucosa
SSI	Static Sciatic Index
TGF-β	Transforming growth factor beta superfamily
VEGF	Vascular endothelial growth factor
WJ	Wharton jelly
WRL	Withdrawal reflex latency

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