Promoting Axon Regeneration and Neurological Recovery Following Traumatic Peripheral Nerve Injuries

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Abstract

Following a peripheral nerve crush, or when a peripheral the nerve is transected and the nerve stumps anastomosed, neurological recovery is generally excellent. This is because the axons merely have to regenerate through the distal portion of the nerve through the existing extracellular matrix of the denervated Schwann cells that direct and promote them to their distant denervated motor and sensory targets. However, when a length of a peripheral nerve is destroyed, and anastomosis is not possible, the standard surgical repair technique is to graft a length/s of autologous sensory nerve into the gap. Neurological recovery is generally good if the nerve gap is <2 cm in length, the repair is performed <4 months post trauma, and the patients are <25 years of age. Because the nerve trauma parameters of large numbers of patients lie outside these limitations for the ability of nerve grafts to restore neurological function, many individuals suffer permanent neurological deficits. Although many alternative techniques have been tested for their ability to promote axon regeneration and neurological recovery, none is more effective than sensory nerve grafts and therefore, such grafts remain the clinical "gold standard" for nerve repairs. New techniques are required that induce more extensive axon regeneration and improved neurological recovery. This paper reviews the literature on many of the techniques tested for inducing axon regeneration across nerve gaps and inducing neurological recovery following traumatic peripheral nerve injuries, and discusses several novel techniques that clinically induce axon regeneration and neurological recovery under conditions where no other technique, including sensory nerve grafts, is effective.

Keywords: Nerve gaps; Nerve lesion; Neurological recovery; Axon regeneration

Repairing Peripheral Nerves following Traumas

Nerve crush

Within several days of crushing a peripheral nerve, the injured axons begin to regenerate through their distal pathway until they reach their original targets with which they restore neurological function. The larger the number of axons that regenerate through the distal nerve, the greater the extent of neurological recovery [1-3]. The number of axons that regenerate, and thus neurological recovery, is influenced by the physiological state of the distal denervated nerve pathway [4-7].

Following a peripheral nerve crush, the injured axons begin to regenerate within 2 days of injury [8]. They may regenerate to their targets through their original pathway in association with and promoted by its Schwann cells, the neurotrophic factors they release, and the Schwann cell extracellular matrix [1,4,9-14]. Thus, the distal nerve provides a simple means for promoting and directing the regenerating axons to their original targets [15-18]. However, when a nerve has a gap, the gap must be bridged with a material that is permissive to and promotes axon regeneration across the entire gap to reach the distal nerve stump, through which the axons must then be able to regenerate.

The Schwann cells in the denervated distal nerve release neurotrophic factors that promote axon regeneration, but also release extracellular matrix components that promote and inhibit axon regeneration [19-26]. Thus, regeneration through the distal nerve is a balance of the influences of factors that both promote and inhibit regeneration. If the Schwann cells are present, such as after a simple nerve crush, virtually 100% of the axons regenerate and they innervate all the denervated synaptic sites. If the Schwann cells within the distal nerve pathway are killed, leaving only the extracellular matrix intact, the number of axons that regenerates to their targets decreases by 94%. This is because the factors required to trigger the regenerating axons to branch at extracellular matrix branch points are missing, axons do not branch, and therefore each axon reinnervates only a single denervated muscle fiber. Thus, Schwann cells along the distal nerve pathway and a

diffusible the cocktail of Schwann cell-released factors are critical for promoting axon regeneration and branching and good reinnervation of distant denervated nerve targets [1-27].

The Schwann cell basal lamina of the extracellular matrix (ECM) promotes nerve regeneration following nerve transection by promoting Schwann cell colonization and promoting axonal guidance due to the presence of laminin within the ECM [28,29]. Thus, axon regeneration can be promoted by mimicking the native basal lamina by using basal lamina proteins from Matrigel (growth factor-reduced) extracted and electrospun to deposit nonwoven nanofiber mats. Such fabricated nanofiber mats support the attachment of cultured embryonic chick dorsal root ganglion explants, the elongation of neurites, and the migration of Schwann cells in a similar fashion compared to electrospun collagen type-I fibers repair. The extension of neurites and Schwann cell replication is significantly increased by the presence of nanorough surface features repair [29].

Nerve transection – nerve gaps

When a nerve is transected, the nerve stumps normally withdraw from one another by about 3 mm. If the nerve stumps are immediately sutured together (anastomosed), neurological recovery is generally excellent [30]. The better the alignment of the nerve stumps to their original orientations [31,32] and the shorter the distance between the ends of the nerve stumps [33-36] the better the accuracy of neurological recovery. However, even without aligning the nerve stumps, when a

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short gap <3 mm in length is present between the nerve stumps, the axons find the distal nerve stump and innervate their original targets. This indicates that specific molecular cues indicate to sensory and motor axons their respective distal sensory and motor pathway [20,37]. Newer evidence indicates that in spite of long nerve gaps, up to 3-12 cm in length, regenerating axons can still precisely reinnervate their appropriate sensory and motor distal pathways [38,39]. Although the specificity of denervated sensory and motor nerves decreases over time, electrical stimulation of the denervated nerve restores the specificity of attraction of their appropriate sensory and motor axon types [40-42].

When a nerve pathway is damaged destroying a length of a nerve pathway (i.e. causing a nerve gap that is <3 mm long), neurological recovery may occur without surgical intervention. This is due to a cascade of events by which fibrinogen seeps out of leaky blood vessels in the injury site where it combines with thrombin, causing fibrinogen polymerization and formation of a 3-dimensional fibrin matrix (scaffold) within the nerve gap [39,43-45]. Although a fibrin clot promotes axon regeneration, the influence of pure fibrin within a nerve gap is not extensive, but its influence is increased by the migration of Schwann cells into the fibrin from the cut central and distal nerve stumps. Once in the nerve gap, the Schwann cells release a physiological cocktail of neurotrophic and wound healing factors that bind to the pure fibrin converting it from a 3-dimensional matrix that passively supports axon regeneration to one that actively promotes axon regeneration, while increasing the number of axons and the distance they regenerate into the fibrin and across the nerve gap [46-48].

The fibrin clot that forms within a nerve gap normally contains platelets that promote axon regeneration by several different mechanisms: (1) Fibrin within the PRP clot polymerizes creating a 3-dimensional fibrin matrix that supports but does on its own not promote axon regeneration. For the fibrin to promote axon regeneration, requires it must bind and interact with various neurotrophic factors released by the platelets and mesenchymal stem cells within the PRP clot. (2) Platelets and mesenchymal stem cells release neurotrophic and other factors that act directly on the axons [49-51]. (3) Platelets and mesenchymal stem cells release factors that cause the denervated Schwann cells of the distal nerve to proliferate and release of neurotrophic factors that promote regeneration of injured axons. (4) The mesenchymal stem cells within the PRP clot differentiate into Schwann cells within the nerve gap, where they release neurotrophic and other factors that promote regeneration of injured axons [52]. (5) Mesenchymal stem cells release angiogenic factors causing vascularization that is essential for axon regeneration [53,54].

When nerve gaps are longer than 3 mm, no fibrin clot forms because the fibrin flows away from the gap before it can polymerize within the gap. Without a fibrin scaffold to support and promote axon regeneration, no axons regenerate and there is no neurological recovery [4,55-63].

In the presence of a 3-dimensional matrix across a nerve gap, axon regeneration into the fibrin and across the nerve gap is directed across the nerve gap due to neurotrophic factors released from the Schwann cells in the distal nerve. The distal nerve stump acts as a point source of a physiological cocktail of neurotrophic factors [16,64]. As the neurotrophic factors diffuse sway from the end of the stump, and across the nerve gap, they form a concentration gradient of factors with its highest concentration at the end of the distal nerve stump, and its lowest concentration at the central nerve stump.

Growth cones extend fine processes that probe and sample the

environment around them in search of factors to which they can adhere and that promote their elongation. In the absence of a regeneration-promoting environment there is little neurite outgrowth [16,65]. However, in the presence of a concentration gradient of neurotrophic factors, the axons regenerating out of the central nerve stump are directed up the concentration gradient of Schwann cell-released factors, across the gap, and to the distal nerve stump [1,66-69]. The regeneration of axons that reach the distal nerve stump continues to be directed into the distal nerve by the concentration gradient of Schwann cell-released factors ahead of them within the denervated distal nerve.

Various diffusible and substrate-bound molecules promote growth cone adhesion and elongation both in vivo and in vitro. Among these are laminin, Chondroitin Sulfate Proteoglycan (CSPG) [70], brain-derived neurotrophic factor (BDNF) and netrin [67,69,71-74]. When these substances have a uniform distribution around a growth cone, they promote longer neurite outgrowth, but the neurites extend in a random manner. However, when these factors are presented as a substrate bound concentration gradient, the neurite and axons turn and regenerate up the concentration gradient [67,69,71,75].

In vivo and in vitro, diffusible concentration gradients of neurotrophic and other factors may develop that both promote and direct axon regeneration. Some of these factors include acetylcholine, denervated muscle fiber-released factors, and Schwann cell-released neurotrophic factors [15,69,76-78]. Like substrate-bound factors, when these are distributed in a uniform concentration around a neuron in vitro, its neurites extend randomly in all directions [76]. However, when a concentration gradient of these factors is presented to a neurite growth cone by releasing them from the tip of a micropipette, the growth cone turns and moves up the concentration gradient [15,76,79,80]. Similarly, in vivo, as neurotrophic factors diffuse away from a length of denervated nerve or denervated muscle fibers, a diffusible concentration gradient of these factors is formed [9,76]. Regenerating axons respond by turning and growing up these diffusible concentration gradients of denervated target-derived factors that are effective in directing axon regeneration over distances of several centimeters [9,76,81-84].

Bridging long nerve gaps – sensory nerve grafts

When nerve gaps are longer than about 3 mm, a fibrin scaffold does not form because the fibrin does not polymerize within the gap but becomes dispersed. Therefore, the Schwann cells within the central and distal nerve stump cannot migrant into the nerve gap, the axons have no scaffold on which to regenerate, and there is no neurological recovery [4,55-58,60-63]. To induce axons to regeneration across nerve gaps longer than 3-mm requires the gaps be bridged with a conduit or material that both supports and promotes axon regeneration.

Axons are induced to regenerate across nerve gaps bridged with autologous nerve grafts of cutaneous saphenous or sural nerves [61,85-87]. Autologous (allogeneic / homogenetic) nerve grafts have also been extensively studied in animal models [88-90]. However, sensory nerve grafts suffer from many limitations in their ability to promote axon regeneration and neurological recovery.

1. Sensory nerve grafts do not promote good motor axon regeneration because sensory and motor nerves express distinct sensory and motor phenotypes that support the regeneration or their specific axon phenotype [35,91-94]. Although motor nerve grafts are more effective in promoting axon regeneration across a nerve gap than sensory nerve grafts, they are not used because it is considered unethical to sacrifice a motor nerve function.

2. The number of axons that regenerate and the extent of neurological recovery decrease with increasing gap length [95]. Although regeneration is good to excellent for bridged nerve gaps <2 cm in length [95-101], it becomes increasingly limited as bridged gaps reach 4 cm in length [97,100], and decreases significantly with increasing graft length, with few axons regenerating across grafts of 8 cm in length [95,98,99,102], and no regeneration is seen for gaps more than 10 cm in length [30,102-106].

3. The number and distance axons regenerate in association with sensory nerve grafts decreases with increasing time between nerve trauma and nerve repair [97,107,108]. Neurological recovery is good in 49% of patients who undergo a nerve repair ≤14 days post trauma, with repairs performed 0.5-6 months post- lesion leading to reasonable motor recovery in 28% of patients, and the incidence of recovery decreases with greater delays [107]. There are only a few examples of neurological recovery for repairs performed >12 months post trauma [30,97,107,109-111].

4. The extent of neurological recovery decreases with increasing patient age, with best recovery being for patients up to 20-25 years of age [97,105,112-117]. Similar decreases in the efficacy of axon regeneration are seen for rats with increasing age [118].

5. The small graft diameters can lead to the grafts becoming ischemic and necrotic or fibrosed, which creates a toxic environment that inhibits axon regeneration [119,120].

6. The small diameter of the sensory nerve compared to that of the mixed sensory /motor nerve being repaired, typically requires the use of multiple nerve grafts. Securing multiple grafts requires the use of large numbers of sutures to connect the grafts to the central and distal nerve stumps, and sutures often cause inflammation and scarring, both of which inhibit axon regeneration [119,121].

7. Harvesting lengths of sensory nerve to use for the graft requires sacrificing a sensory nerve function creating a neurological deficit [122-125].

8. Histological examinations of sural nerve bridges show that the regenerating axons do not grow through the sural nerve graft in intimate association with the Schwann cells as they do when they regenerate through a motor nerve bridge [2,20,23,126-127]. Rather, the axons grow in association with the extracellular matrix sheaths of the Schwann cells [1,4]. Thus, sensory nerve grafts serve predominantly as a passive scaffold across which the axons regenerate, not as a pathway that actively promotes axon regeneration.

Alternative tested techniques for bridging nerve gaps

Biodegradable collagen tubes have been used to bridge peripheral nerves gaps for cat peripheral nerves. The collagen shows biocompatibility, and does not cause any adverse events, such as reactive or toxic alterations of the epineurium in contact with the implant [128]. Within one year of the nerve repair the nerve tube is replaced with a well vascularized connective tissue. In other experiments, transected peripheral nerves repaired with sutures (anastomosis of the nerve stumps), or with a collagen tube, show no difference in axon regeneration and neurological recovery [129]. These data show that the use of a collagen tube to bridge nerve gaps has no adverse influences on axon regeneration and neurological recovery [130].

Due to the limitations of sensory nerve grafts in inducing axon regeneration and neurological recovery many different materials have been tested for their ability to promote axon regeneration. Among these are: acellular nerve grafts [131-134], empty collagen tubes [135-138], collagen tubes filled with pure fibrin [139], nerve grafts plus fibrin [140], grafts of CNS tissue [141,142], dissociated Schwann cells [143-145], acellular autografts filled with Schwann cells [94], biocompatible non-collagen tubes [146], hydrogel tubes containing neurotrophic factors [134,106,147-155], empty Gore-Tex conduits [156,157], empty Gore-Tex tubes [156], Gore-Tex tubes filled with mesenchymal stem cells [158], synthetic hydrogel tubes [98,145,159], empty conduits made of arteries, veins [160-162], muscle tubes [163], silicon conduits [161], conduits filled with pure fibrin, with and without added neurotrophic factors [164,165], collagen gel tubes [166], bio-artificial nerve graft seeded with Schwann cells [167], Schwann cells modified to over-express specific growth factors [168-170], conduits of synthetic materials [147,153,171,172], the infusion of antibodies [173], gradients of factors within tubes [174], allographs [175], factors that induce inflammation [149,176], pseudo nerves [177], alginate gel [178], biodegradable polymer tubes [179], tubes filled with platelet-rich plasma [180-182], and arteries, veins and muscle tubes [160,183,184]. None of these techniques induces more effective axon regeneration than autologous sensory nerve grafts [20,31,185-188]. Therefore, despite their significant limitation in inducing axon regeneration, sensory nerve grafts remain the "gold standard" for clinical peripheral nerve repair [3,99,110,106,148,189-193].

Non-biological conduits to bridge nerve gaps

Conduits (tubularization) that can be used to bridge nerve gaps have the advantage over nerve grafts in that they do not induce or permit the migration of fibroblasts into the injury site where they inhibit axon in-growth. In addition, tubularization serves to significantly reduce excessive collagen and scar formation, and prevent axons from escaping into surrounding tissues [56,194-196]. Finally, conduits allow Schwann cells to migrate into the nerve gap from the distal stump and together with the in-growing axons [57,58,197,198].

Although conduits bridging nerve gaps have not yet proved very successful for promoting axon regeneration across gaps much longer than 2-cm in length, they have been highly useful for investigating the sequence of cellular and molecular events during peripheral nerve regeneration [57,177,199,200]. The conduit captures the natural exudate of the nerve stumps (fibrin), which polymerizes into longitudinally oriented fibrin fibers that serves as a conductive scaffold along which Schwann cells migrate from both the central and distal nerve stumps [57,58,177,197,201]. Thus, conduits promote more extensive axon growth through a nerve gap than takes place in the absence of a tube and are used clinically for nerve defects up to 2-cm long [86,194].

Empty Nerve Tubes

Within hours of implanting an empty tube it becomes filled with a fluid enriched with neurotrophic factors, extracellular matrix and other molecules which exert neurotrophic [86,202,203], and neurotropic influences [204]. During days 3-7 the fluid is replaced by an acellular fibronectin positive, laminin negative fibrous matrix, which is critical for Schwann cell proliferation and for Schwann cells to migrate into the tube [57,58,196,205,206]. Fibroblasts and Schwann cells migrate from both nerve stumps within 2 weeks of implantation [144,207-209]. These tubes promote the regeneration of axons across gaps only up to 1-cm long.

3-Dimensional Matrix Filled Tubes

Pre-filling tubes grafted into nerve gaps with various materials improves axon growth across nerve gaps. Gelfoam, (Pharmacia &

Upjohn), a collagen matrix [60] and artificial fibrin sponge (Gelaspon) [199-201,210] are suitable matrices that enhance the migration of Schwann cells [199] and subsequent axon in-growth. The success and the quality of regeneration across long nerve gaps are increased if the nerve gap-bridging conduit is filled with aligned collagen within laminin gels [211,212]. However, in spite of these approaches, axons do not regenerate through tubes longer than 2-cm.

Addition of Cells to the Conduits Bridging Nerve Gaps

Another approach has been the placement of a series of short lengths of nerve placed, several millimeters from one another across a nerve gap, referred to as "stepping stones" [213-215]. This technique induces axon regeneration across a nerve gap, but the lengths of nerve are not stable within the long tube due to the cells becoming ischemic, which creates a toxic environment within the tube, which inhibits axon regeneration [215].

An alternative approach is the addition of dissociated Schwann cells to the matrix within a tube bridging a nerve gap [144,208] or spinal cord gaps [216]. These Schwann cells secrete their neurotrophic factors which enhance axon regeneration through the tube [20,194,203,217]. One limitation with this approach is that Schwann cells have a limited distance they will migrate and a limited number of times they proliferate [199,218,219]. Thus, there is an insufficient concentration of Schwann cells within the conduit to promote axon regeneration. However, Schwann cell proliferation and migration can be increased by the application of insulin and insulin-like growth factor in the matrix within the nerve gap. The presence of these factors induces axons to regenerate across nerve gaps up to 2-cm in length [177,199,200].

Addition of Neurotrophic Factors, Cytokines, and Other Factors to Conduits Bridging Nerve Gaps

As indicated, insulin stimulates the regeneration of peripheral nerves [220] and when infused into a tube bridging a nerve gap enhances axon in-growth [221]. Insulin [199,200], and insulin-like growth factor-1 [220-224] within a bridging tube significantly increase the number of Schwann cells that migrate into the tube. Additional factors that induce Schwann cell proliferation are platelet-derived growth factor-B (PDGF-B), acidic and basic fibroblast growth factors (b-FGF and a-FGF) [225], transforming growth factor (TGF-β) [226,227] and neuregulins [224,228,229]. Axolemmal membrane also stimulates proliferation of cultured Schwann cells [230-234], while NGF added to a tube enhances axon ingrowth [235-237]. Multiple injections of a mixture of laminin, testosterone, ganglioside GM1 into the chamber also significantly increases the diameter and vascularization of nerve outgrowth [238]. Fibronectin-laminin and fibronectin [237] added to tubes enhances axon regeneration through a 1.8-cm tube, predominantly by enhancing Schwann cell migration.

Axon regeneration could potentially be increased by the addition of other factors that promote nerve regeneration, such as the putative neurotrophic cytokines or neurokines [239,240]. These factors derived from versatile fibroblast growth factor family, are made up of 7 members: FGF-1-7, the transforming growth factors beta (TGF-β), or the cholinergic differentiation factor (CDC)/ ciliary growth factor (CNTF)/ leukemia inhibitory factor (LIF) [241]. While some (FGF-1, FGF-2 (acidic FGF), CNTF, and LIF) seem to act as postnatal survival factors involved in the maintenance of distinct central and peripheral neurons, others seem to act as neuropoietic and/or neural differentiation factors (CDF/LIF, TGF-β) with defined spatiotemporal expression during early postnatal development [242] and could also play significant roles in promoting axon regeneration [240].

Influence of Time Between Nerve Lesion and Repair on the Extent of Neurological Recovery

The length of time between a nerve lesion and its repair significantly influences the extent of neurological recovery. Immediate anastomosis of a lesioned radial nerve leads to almost perfect neurological recovery [243]. However, anastomosis up to 14 days post injury leads to good recovery in only 49% of the patients, anastomosis from 14 days to 6 months following the lesion leads to reasonable neurological recovery in only 28% of the patients, while anastomosis after 10 months [30] leads to no neurological recovery.

Pre-degenerated nerve grafts provide more rapid initial axon in-growth than fresh nerve grafts [18,218,244,245], but do not influence the rate of regeneration [218,244]. The influence of pre-denervation is predominantly due to the proliferation of Schwann cells within the graft [246] and the increased concentration of neurotrophic factors released by the significantly increased number of Schwann cells [60,194,207,236,246-249]. Another approach for improving axon outgrowth is to use pre-denervate nerve that is cut and left in situ for 5 days to allow the Schwann cells to proliferate [250-253]. A length of the denervated nerve is then harvested, dissociated, and the dissociated Schwann cells injected into the tube bridging a nerve gap [254,255]. Although the presence of the Schwann cells improves the number of axons and distance they regenerate, there is no protocol for using this technique clinically. However, axons do not tend to regenerate through long-term denervated allographs [88], and as stated above, no neurological recovery take place if the distal nerve has been denervated for more than 10 months [30].

Decrease in Neurological Recovery Decreases with Increasing Patient Age

The success of axon regeneration across nerve gaps decreases with patient age, such that recovery is only relatively good for patients up to 20-25 years of age [97,112-115,117]. For rats insulin-like growth factor 1 (IGF-1) is a potent neurotrophic factor that decreases in the distal portion of a transected nerve with increasing age [116]. Thus, while sciatic nerve axon regeneration is good in young rats it is poor in older rats. However, the application of locally delivered IGF-1 significantly improves axon number, diameter, and density. IGF-1 also significantly increases myelination and Schwann cell activity and preserves the morphology of the postsynaptic neuromuscular junction for both young and old rats [116].

Inhibition of Axon Regeneration into the Distal Denervated Nerve Segment

As stated earlier, following denervation, the Schwann cells in the distal nerve up-regulate the synthesis and release of a collection of neurotrophic and extracellular matrix factors. Among the extracellular matrix factors are laminin and chondroitin sulphate proteoglycans (CSPGs) [22,256,257]. While laminin and neurotrophic factors promote axon regeneration, CSPGs inhibits axon regeneration [70,258]. Although the overall balance of axon regeneration-promoting and -inhibiting favors axon regeneration, if the CSPG in a denervated nerve is eliminated, axon regeneration is faster and more extensive [26,258-261]. Therefore, to enhance neurological recovery, lesioned axons must first be induced axons to regenerate across a nerve gap, and then down the distal nerve, which requires eliminating the factors that inhibit axon regeneration [258]. CSPGs can be eliminated by the application of the enzyme C-ABC that digests CSPG or by blocking its synthesis via intramuscular injections of β-D-xyloside [259,260]. β-D-xyloside acts

by preventing the glycosylation of the proteoglycan side chains, which are required for inhibition of axon regeneration [257].

Virtually none of the techniques developed in animal models has been applied clinically because almost all require the use of materials, such as antibodies, enzymes, recombinant neurotrophic factors, materials for the tubes, and materials placed in the nerve tubes, which are not FDA approved. Obtaining FDA approval requires years of effort and is extremely expensive for each material or factor to be used. Finally, each factor must be tested separately and subsequently in various combinations prior to being tested clinically. Therefore, economical reasons prevent some of these techniques with great potential from being tested clinically.

Pure Fibrin and Platelet-Rich Fibrin Glue for Peripheral Nerve Repair

Fibrin glue is extensively used to repair lesioned peripheral nerves repair and sectioned central nervous system tissue [262-267]. It is also extensively used to anastomose lesioned peripheral nerves [190,262-273]. In fact, fibrin glue is a better for anastomosing peripheral nerves than sutures [268,273-277]. Fibrin glue is both faster and easier to use than sutures, leads to more successful neurological recovery than sutures, and causes fewer complications, such as infections and inflammation [268,273-276].

Conduits composed of pure fibrin glue can be used to bridge 2 cm adult rat sciatic nerve gaps and promote axon regeneration, although in general the axons do not regenerate entirely across 2 cm fibrin-filled nerve gaps [123]. Although fibrin is part of the physiological mechanism by which the body attempts to promote axons to regenerate across a peripheral nerve gap, physiological fibrin within a nerve gap is not pure fibrin but fibrin plus platelets containing neurotrophic factor and wound healing factors [3,265,276,278]. These platelet-contained factors are released over about 4-7 days following platelet activation by injury. Thus, the autologous platelet-rich plasma enriches the fibrin with axon regeneration-promoting factors and promotes excellent axon regeneration [3,262,269,277,279]. This fibrin within conduits does not induce reliable promotion of axon regeneration across long nerve gaps, which requires fibrin to bind and interact with various neurotrophic and other factors to become effective in promoting axon regeneration.

Schwann Cells and Bone Marrow-derived Mesenchymal Stem Cells

Cellular prostheses composed of a resorbable guide seeded with autologous Schwann cells are an alternative for repairing long gaps in injured nerves, approaching the success of autografts [280,281]. However, conduits containing syngeneic Schwann cells did not improve the extent of axon regeneration with respect to acellular guides [280]. Transplanted Schwann cells survive within the nerve guide for 1-3 months after implantation, and an even larger number survive when they are autologous rather than syngeneic cells [280].

Filling conduits with primary Schwann cell-like differentiated bone marrow-derived mesenchymal stem cells (dMSC), and Schwann cell-like differentiated adipose-derived stem cells (dASC) promote axon regeneration across 1 cm rat sciatic nerve gaps [122]. For mice, ASCs added to Matrigel (Sigma-Aldrich, St. Louis), a 3-dimensional matrix or extracellular matrix (ECM) components, within nerve gaps induce axon regeneration [282]. This may result from the cells expressing numerous genes of neurotrophins, particularly brain-derived neurotrophic factor (BDNF), and ECM proteins required for the nerve growth and myelination [282,283].

Spider silk conduits promote excellent axonal regeneration and functional recovery across adult rat peripheral recovery gaps [284]. In vitro, synthetic basal lamina fibers induce neurite spreading and Schwann cell migration, suggesting that it may be beneficial in vivo in promoting axon regeneration and peripheral nerve repair [29]. Spider silk fibers, alone or supplemented with Schwann cells, facilitate Schwann cell proliferation and migration and promote extensive axon regeneration across 2 cm rat sciatic nerve gaps compared to gaps bridged with Matrigel within a conduit [285]. These data indicate that spider silk is a viable guiding material for Schwann cell migration and proliferation as well as for axonal re-growth in a long-distance model for peripheral nerve regeneration [285].

Matrices composed of Matrigel, microfilaments, and heregulin, which induce Schwann cell proliferation, synergistically induce significant improvements in the number and longitudinal organization of Schwann cells and axons across nerve gaps [286]. High molecular weight basic fibroblast growth factor support the regeneration of the injured axons across 15 mm long adult sciatic nerve across gaps bridged with silicone tubes filled with Matrigel or a mixture of Schwann Cells (SC) and Matrigel [287].

In an animal model and clinically, autogenous venous nerve conduits (AVNC) induce axons to regenerate across gaps of a maximum of 3 cm [288]. It has been claimed that the addition of autologous Schwann cells to these conduits increases the upper limit of nerve gaps across which AVNC conduits induce axon regeneration to 6 cm [288].

Acellular Nerve Allografts

Although nerve allografts promote axon regeneration across nerve gaps up to about 2 cm in length, nerve conduits of virtually no other composition induce axons to regenerate such a distance. The following section describes a number of different compositions of cells, factors and materials that have been shown to induce axons to regenerate across longer nerve gaps.

Acellular nerve allografts (ANAs) have been proposed as a good alternative to autografting and allotransplantation. ANAs have been shown to have similar capabilities as autografts in supporting axonal regeneration across short nerve gaps [125]. Although they promote axon regeneration, their efficacy depends on their ability to induce host tissue Schwann cell proliferation of [125]. Further, axonal regeneration and functional recovery induced by ANAs decreases as the graft length increases, while the performance of isografts is superior to ANAs at all lengths [125]. This is because of the development of senescent by long-time denervated host Schwann cells, which is indicated by the appearance of senescence associated beta-galactosidase, p16INK4A, and IL6 [125]. Since Schwann cells proliferation and migration decreases with increasing time of denervation, Schwann cell senescence plays a role in the limited axonal regeneration across nerve grafts of increasing gap lengths [289]. Finally, seeding ANAs with Schwann cells promotes a similar extent of axon regeneration across sciatic nerve gaps to that induced by allografts [290].

Tissue-engineered Nerve Grafts

Tissue-Engineered Nerve Grafts (TENGs) are an alternative to nerve autografts that are recognized as the "gold standard" for surgical repair of peripheral nerve gaps. TENGs typically consist of a neural scaffold included with support cells and/or growth factors, and represent a promising alternative to autologous nerve grafts for surgical repair of large peripheral nerve gaps [291]. TENGs have been constructed by incorporating autologous bone marrow Mesenchymal

Stem Cells (MSCs) into a neural scaffold composed of a chitosan conduit inserted with poly(lactic-co-glycolic acid) (PLGA) fibers. Axon regeneration can be induced across 25-mm-long canine tibial nerve gaps by treating PLGA nerve conduits with pulsed plasma and Ciliary Neurotrophic Factor (CNTF) plus chitosan [292]. However, in general their influence is not more extensive than that induced by autologous nerve grafts [292]. At 12 months post-surgery in which a 6 cm long dog sciatic nerve gaps were bridged by TENGs, of chitosan/PLGA scaffolds, or nerve autografts, the TENGs induced similar axon regeneration results to that of autografts, but better than those induced by scaffolds alone [291,293].

The transplantation of adult neural stem cells (ANSCs) inside an autologous venous graft across a pig 30 mm long nerve gap in adult pigs induces axon regeneration and neurological function [294,295]. This is due to ANSCs increasing CNPase expression, indicating the activation of intrinsic Schwann cells [295].

Poly epsilon-caprolactone (PCL) conduits for rat sciatic nerve gaps induce axons to regenerate across gaps up to 1 cm in length [125,289].

Repair of large nerve defects with ANAs is an appealing alternative to autografting and allotransplantation. Although ANAs have similar influences to autografts in supporting axonal regeneration across short gaps, they are not effective for larger nerve defects [289,296,297]. ANAs depend on the addition of Schwann cells and their extensive proliferation to support axonal regeneration. However, the longer the ANA the greater Schwann cell proliferative that is required, which can create stress in those Schwann cells and their subsequent senescence [289]. Thus, ANAs plus Schwann cells are less effective in inducing axon regeneration across bridged nerve gap as the gap increase in length from 2 to 4 to 6 cm [289]. However, the extent of axon regeneration can be enhanced if the Schwann cells are transfected with the ciliary neurotrophic factor (CNTF) gene to increase their neurotrophic influence on the axons [298].

Gene therapy with vascular endothelial growth factor (VEGF) significantly improves axon regeneration, neuronal survival, and muscle activity [124]. Granulocyte colony-stimulating factor (G-CSF) synergizes with VEGF to improve the functional outcome after sciatic nerve transection [124]. However, treating animals with both G-CSF plus VEGF significantly increases the number of regenerated myelinated fibers, blood vessels, the number of neurons in the DRG and motor neurons in the spinal cord, and recovery of motor function than either alone. This suggests that these factors act synergistically and optimized the nerve repair potential, improving axon regeneration after a transection lesion [124].

Electrical Stimulation

Electrical stimulation of the transected axons induces a 2.3-fold increase in axon sprouting vs. unstimulated control neurons [299]. It also increases by 34% the number of neurons that extend axons [300,301] and speed of axon regeneration [302]. This influence is in part due to electrical stimulation promoting both Schwann cell migration and proliferation, and by acting directly on neurons to induce them to increase the distance axons are extended [303]. Electrical stimulation also gives rise to significantly increase in Calcitonin Gene-Related Peptide (CGRP)-immunolabeled Schwann cells, and the recruitment of a significkantly higher number of macrophages to the distal portion of the transected sciatic nerve [304]. Electrical stimulation also induces the Schwann cells of the distal portion of the transected nerve to up-regulate their synthesis and release of neurotrophic factors that act on the injured axons to promote regeneration that would otherwise not

take place [305,306]. While electrical stimulation is usually applied pre-cutaneously for facilitating peripheral nerve regeneration, when applied directly to rat sciatic nerves with 8-mm gaps, it induces a 50% increase in the number of axons that regenerate vs. control animals [307,308].

Part of the influence of electrical stimulation is attributed to inducing the stimulated neurons to up-regulate their levels of cyclic-AMP and a number of growth-associated genes [306]. In turn, this increased cAMP concentration induces motor neurons to up regulate their expression and synthesis of the endogenous neurotrophic factor BDNF and its trkB receptor mRNA [309-313]. This induced increase in endogenous BDNF increases the extent of axon regeneration.

Both clinically and in animal models, electrical stimulation also shortens the onset time of axon outgrowth, increase the speed of axon regeneration [301,309,314-316], increase the distance axons regenerate across nerve gaps [317], and increase the accuracy of sensory vs. motor axon innervation of their appropriate distal nerves [41,315,318]. Even one hour of 20 Hz electrical stimulation of the proximal nerve stump prior to a nerve repair enhances the rate of axon regeneration [315].

In addition to electrical stimulation of the central nerve stump of a transected peripheral nerve, the use of electrically conductive biodegradable hydrogel consisting of oligo (polyethylene glycol) fumarate (OPF) and polypyrrole (PPy) increases neurite outgrowth [319], and when containing single-walled carbon nanotubes (SWCNT) support the viability of Schwann cells within the nerve gap [303]. Thus, an electrically-conductive SWCNT collagen I-Matrigel biomaterial may be suitable for neural tissue engineering and by sustaining populations of Schwann cells [303]. Similarly, electrical stimulation via an electrically conductive biodegradable polymer composite, enhances the rate of neurite outgrowth from cultured PC12 cells [315]. However, it is not known whether combining electrical stimulation with other nerve repair techniques may further enhance the rate and extent of axon regeneration and neurological recovery.

Combining adipose-derived stem cells (ADSC) with ANA increases axon regeneration across 10 mm long nerve gaps, compared to axon regeneration induced by ANA alone [320]. This is potentially due to the release by ADSCs of neurotrophic factors [321].

By 3 months post-repair, Bone-Marrow-Derived Mesenchymal Stem Cells (BMSCs) and Adipose-Derived Mesenchymal Stem Cells (ADSCs) incorporated into acellular nerve grafts promote more extensive sciatic nerve regeneration and functional recovery than is induced by autografting and Schwann cells alone, and more than that induced by acellular nerve allografting alone [322]. Similarly, Schwann cells derived from induced Bone Marrow Stromal Cells (BMSCs) may be useful for promoting axon regeneration across peripheral nerve gaps [323]. Combining BMSCs with laminin-modified chitosan multi-walled nerve conduits bridging 10 mm long rat sciatic nerve gaps, the number of axons that regenerate increases, as does the muscle mass. These data suggest that BMSCs suppress neuronal cell death and promote axon regeneration by suppressing the inflammatory and fibrotic response induced by chitosan after long-term implantation [324].

Polyvinyl chloride (PVC) tubes implanted within a 19-mm long sciatic nerve gaps become surrounded by collagen, which remains after the PVC tube is removed. These collagen tubes induce similar axon regeneration to that induced by of autologous nerve [130].

Macrophages

Following nerve injury there is a slow increase in the concentration of macrophages in the region of the nerve injury [325-327]. This

increase persists up to 28 days and is accompanied by an up-regulation of inflammatory mediators, including oncomodulin. Intraganglionic cAMP injection also resulted in an increase in macrophages [327].

In vitro arecoline significantly promotes the survival and outgrowth of cultured Schwann cells compared to cells in control cultures. In vivo the arecoline significantly increases the number and the density of myelinated axons compared to controls. In addition, the number of macrophages recruited in the distal sciatic nerve increases as the concentration of arecoline is increased. Thus, arecoline stimulates local inflammatory conditions, thereby improving axon regeneration and the recovery from severe peripheral nerve injury [328].

The rate of axon regeneration across 15 mm rat sciatic nerve gaps is faster if macrophages with a pro-healing (M2a and M2c phenotype) vs. pro-inflammatory phenotype are combined with polymeric nerve tubes [329]. This can be accomplished by the local delivery of either Interferon-gamma (IFN-gamma) or Interleukin-4 (IL-4), within the tubes [329]. The neuron-macrophage interactions involved in eliciting a pro-regenerative phenotype in macrophages may be a novel target to induce long-lasting regenerative processes after axonal injuries in the CNS [327].

Commercial Nerve Gap Conduits

Commercial conduits that are effective in inducing axon regeneration across nerve gaps are composed of type I collagen, Integra NeuraGen (NG) nerve guides, and processed rat allografts, which have similar efficacy to AxoGen's Avance human decellularized allograft [134,330]. For 14-mm sciatic nerve gaps, the efficacy of isografts is superior to processed allograft, which is more effective than the NeuraGen grafts. However, for a 28-mm graft model, isografts are more effective than processed allografts [134,330].

3-Dimensional Scaffolds

Filling a nerve gap with a 3-dimensional Matrigel promotes axon regeneration entirely across gaps [281,331]. This influence is increased if Schwann cells overexpressing high molecular weight FGF-2 is combined with the Matrigel [287]. An alternate approach is to use conduits to bridge nerve gaps that contain intraluminal guidance structures, vs. unstructured conduits. Such conduits increase both Schwann cell migration and axon regeneration across nerve gaps [193].

The Schwann cell basal lamina of the ECM promotes nerve regeneration following nerve transection by promoting Schwann cell colonization and promoting axonal guidance due to the presence of laminin within the ECM. Thus, axon regeneration can be promoted by mimicking the native basal lamina by using basal lamina proteins from BD Matrigel (growth factor-reduced) extracted and electrospun to deposit nonwoven nanofiber mats. Such fabricated nanofiber mats support the attachment of cultured embryonic chick DRG explants, the elongation of neurites, and the migration of Schwann cells in a similar fashion compared to electrospun collagen type-I fibers repair. The extension of neurites and Schwann cell replication is significantly increased by the presence of nanorough surface features repair [29].

The Schwann cells in the denervated distal nerve release neurotrophic factors that promote axon regeneration, but also release ECM components that promote and inhibit axon regeneration, [20,22-26,332,333]. Thus, regeneration through the distal nerve is a balance of the influences of factors that both promote and inhibit regeneration. If the Schwann cells are present, such as after a simple nerve crush, virtually 100% of the axons regenerate and they innervate all the denervated synaptic sites. If the Schwann cells within the distal nerve

pathway are killed, leaving only the ECM intact, the number of axons that regenerates to their targets decreases by 94%. This is because the factors required to trigger the regenerating axons to branch at ECM branch points are missing, axons do not branch, and therefore each axon reinnervates only a single denervated muscle fiber. Thus, Schwann cells along the distal nerve pathway and a diffusible the cocktail of Schwann cell-released factors are critical for promoting axon regeneration and branching and good reinnervation of distant denervated nerve targets [1].

One mechanism used to bridge nerve gaps is laminin and Laminin-Polycaprolactone (PCL) blend of nanofibers fabricated to mimic peripheral nerve basement membrane. When the nanofibers are oriented parallel to the orientation of the nerve, there is extensive axon regeneration, vs. little axon regeneration when the nanofibers have a random orientation. However, under both circumstances axon regeneration is better than through an empty conduit [334].

Concentration Gradients of Factors

The uniform distribution of Schwann cell released neurotrophic factors (peripheral nerve conditioned medium, CM) around neurons in culture medium induces both adult sensory and motor neurons to extend axons 10-fold longer than in the absence of these factors [65,335]. However, presentation of a concentration gradient of CM across nerve gaps, or applying it directly to the central stump of a nerve, increased significantly the number of axons that regenerated, and the gradients of CM factors was effective across distances of 4-cm in length [16,249,336,337].

Mini osmotic pumps (Alzet Pump, Durect Corp) have been loaded with CM and a catheter attached to the pump. When the open end of the catheter is positioned at the distal end of the nerve gap, the pumps (Alzet 2004, Durect Corp.) infuses CM into the matrix within the gap at a constant rate of 0.5 µl per hour for 4 weeks. Diffusion of the factors in the CM away from the end of the catheter and into the nerve gap creates a concentration gradient of the factors, with its highest concentration at the tip of the catheter, and it's lowest at the central nerve stump. Such diffusible concentration gradients of neurotrophic factors induce axons to regenerate up the gradient and towards the distal nerve stump. This technique increases by 50% the number of axons that regenerate across the 4 cm long gaps compared to control preparations without CM infusion (N = 6) [337].

CM is obtained by placing a 2-cm length of sciatic nerve in 3 ml of culture medium for 5 days. During this time, the Schwann cells synthesized and released various neurotrophic as they do physiologically in situ. The CM is then harvested, filtered to remove cellular debris and maintains it biologically activity when kept at 37°C for more than 3 months, or for several years when kept at -85°C (Kuffler, unpublished observations).

Axon regeneration is also directed by bound concentration gradients of nerve growth factor (NGF) within a conduit bridging a nerve gap [84,338-341]. Herein, combining differential adsorption of NGF/silk fibrin (SF) coating, the gradient of NGF-immobilized membranes (G-Ms) and nanofibrous nerve conduits (G-nNCs) can be fabricated. Furthermore, 12 weeks after implantation in rats with a 14 mm gap of sciatic nerve injury, the sciatic nerve function index (SFI), compound muscle action potentials (CMAPs), total number of myelinated nerve fibers, thickness of myelin sheath are similar to G-nNCs and autografts, with the G-nNCs having a higher density of axons than the autografts. These results demonstrate the significant role of the introducing NGF gradients into scaffolds in promoting nerve regeneration [84]. Similarly,

diffusible concentration acetylcholine direct the outgrowth of DRG neurons in vitro [78].

Dissociated Schwann Cells within the Fibrin Matrix

As stated earlier, dissociated Schwann cells from pre-denervated peripheral nerve release neurotrophic factors that induce axons to regenerate across nerve gaps [255]. Similarly, Schwann cells dissociated from a freshly removed nerve enhance axon regeneration across nerve gaps [252,342].

Mesenchymal Stem Cells

The transplantation of human embryonic stem cell-derived mesenchymal stem cells (hESC-MSCs) into a 2 mm long sciatic nerve gap induced axon regeneration across the gap and recovery in nerve function [343,344]. It has been proposed that hepatocyte growth factor and insulin-like growth factor-binding protein-1 released from the hESC-MSCs are responsible for promoting the axon regeneration [344].

Additional Methods that Increase the Rate and Extent of Axon Regeneration

Several techniques have been shown clinically and in animal models to enhance the number of axons that regenerate and the distance they regenerate. Among these are electrical stimulation of the central nerve stump, and the administration of the immunosuppressant FK506 (tacrolimus), and the administration of β-D-xyloside.

Immunosuppressants

Animal model studies have shown that motor nerve grafts induce axons to regenerate significantly longer distances than sensory nerve grafts [33,99]. Typically such studies involved the use of motor grafts harvested another animal of the same or different species, i.e. xenographs or allographs respectively. To use such grafts requires the use of an immunosuppressive agent to prevent the foreign nerve graft from being rejected by the immune system of the host animal, and one immunosuppressants used was FK506 [345]. During these studies it was observed that the administration of FK506, at concentrations far below that required for its immunosuppressant function (5 mg/kg/day down to 0.05 mg/kg/day for 4 weeks), influenced axon regeneration. FK506 (1) induces a 2-fold increase in the number of axons that regenerate, (2) increases the speed of axon regeneration across 4 cm gaps, (3) increases the number of myelinated axons by 40% , (4) significantly increases myelin thickness, (5) increases the specificity of sensory and motor target reinnervation, and (6) increases the extent of neurological recovery [346-356].

In a nerve repair study on an animal model, FK506 was administered directly to the severed ends of axons within an inside-out vein graft used to bridge nerve gaps. An advantage of administering FK506 locally like this is that it avoids systemic exposure to FK506 that may be toxic. Delivered in this form, FK506 increases both the rate and extent of axon regeneration [357]. FK506 also reduces by half the time to achieve neurological recovery, although it does not induce a significant improvement of long-term neurological recovery compared to control animals [358,359].

Clinically, FK506 has also been tested for its influence on axon regeneration when administered at 5 and 8 ng/ml//kg/day for a total of 60 days. Clinically FK506 induces more rapid axon regeneration than is seen in control patients [360]. Similar to the results from animal model studies, the final extent of recovery of neurological function is not better than that of patients who do not receive FK506 [360].

The influences of FK506 in increasing the rate and extent of axon regeneration can be enhanced if FK506 is administered in conjunction with other factors. Thus, the simultaneous administration of FK506, NGF and bFGF within a nerve conduit bridging a nerve gap leads to axons regenerating longer distances than when these factors are administered alone [358,361-364].

The extent of restoration of neurological function decreases with increasing time between nerve trauma and repair . Nerves that are denervated for 4 or more months are referred to as chronically denervated nerves and they support little or no axon regeneration. This is because the Schwann cells of such nerves no longer synthesize and release the neurotrophic factors that are required to promote axon regeneration . However, the administration of FK506 increases the number of axons that regenerate into and though chronically denervated nerves [358]. This is best explained by explained by results showing that the FK506 derivative, jnj460, acts on Schwann cells altering their gene expression causing them to release factors that promote neurite outgrowth from DRG neurons in vitro . These observations argue that FK506 or its analogues should be administrated in clinical cases where a nerve repair must be performed long after nerve trauma.

β-D-xyloside and Suppression of the Synthesis of Chondroitin Sulfate Proteoglycan (CSPG)
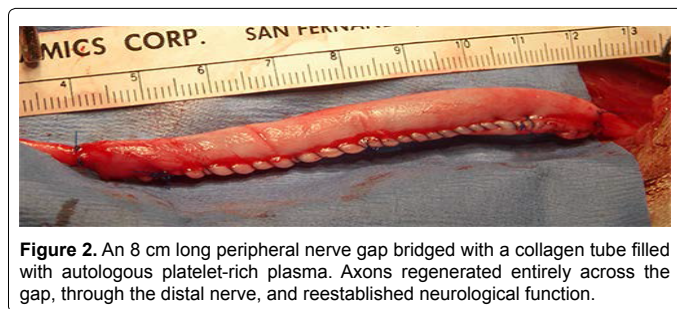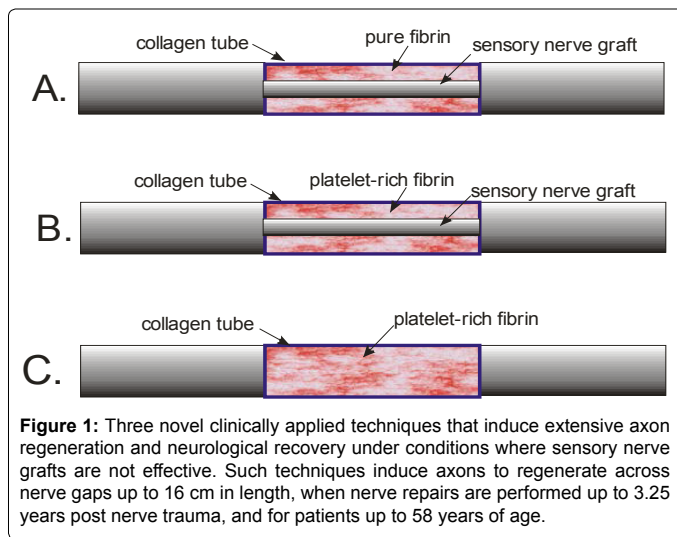
Following a nerve crush or transection, Schwann cells exhibit a 7-fold increase in their synthesis of chondroitin sulfate proteoglycan (CSPG) . CSPG binds to and inhibits the neurite-promoting activity of laminin, thus retarding axon regeneration. β-D-xyloside is an inhibitor of the synthesis of CSPG, and its administration reduces CSPG by 90% within 4 days and subsequent completely disappearance of CAPG . As the concentration of CSPG within a denervated distal portion of a nerve decreases, so does its regeneration-inhibiting influence, which results in a 60% increase in the rate and distance an axon regenerates [26].

The mechanisms by which PRP, electrical stimulation, β-D-xyloside, FK506 and other methods enhance axon regeneration differ. This suggests that the simultaneous administration of β-D-xyloside and PRP would have additive effects and promote more extensive axon regeneration than when they are administered singly, but this has not yet been tested. Therefore, studies are needed in which these different methods are applied simultaneously to determine whether when combined, more axons regenerate longer distances and give rise to more extensive recovery of neurological function than when the axons are exposed to any one singly.

Novel Clinically Effective Nerve Repair Techniques

Recently three novel nerve repair techniques have been tested that induce axon regeneration under conditions where no other technique is effective. Each technique is based on the physiological method by which axons are promoted to regenerate across short (<3 mm long nerve gaps. The three techniques have been tested clinically. The techniques involve bridging nerve gaps with a collagen tube containing: (1) a sensory nerve graft plus pure fibrin, (2) a collagen tube containing a sensory nerve graft plus platelet-rich plasma, and (3) a collagen tube containing only platelet-rich plasma [39]. Figure 1 shows a schematic of these techniques. Figure 2 shows a nerve that had an 8-cm long nerve gap repaired with a collagen tube plus a single sensory nerve graft filled with platelet-rich plasma. The repaired nerve induced the recovery of both sensory and motor function [39]. All three techniques induced more extensive axon regeneration and neurological recovery than the standard clinical nerve gap repair method, which uses only a sensory nerve graft.

Figure 1: Three novel clinically applied techniques that induce extensive axon regeneration and neurological recovery under conditions where sensory nerve grafts are not effective. Such techniques induce axons to regenerate across nerve gaps up to 16 cm in length, when nerve repairs are performed up to 3.25 years post nerve trauma, and for patients up to 58 years of age.

Figure 2. An 8 cm long peripheral nerve gap bridged with a collagen tube filled with autologous platelet-rich plasma. Axons regenerated entirely across the gap, through the distal nerve, and reestablished neurological function.

Platelet-rich plasma can be obtained by separating it from a patient's or animal's own whole blood in the operating room using differential centrifugation of the whole blood. This separation is a routinely used in many operating rooms, for the repair of damaged dura, soft tissue, or in orthopedic surgery where as a glue to hold bone chips in place. It has also been found that PRP enhances the extent of axon regeneration across adult rat nerve gaps of 1.5 cm.

Bridging nerve gaps with all three of these novel techniques leads to axon regeneration and neurological recovery under conditions where sensory nerve grafts are not effective: across nerve gaps up to 16 cm in length, for nerve repairs performed up to 3 years post nerve trauma, and for patients up to 50 years of age [39]. Further studies are required with these techniques to determine whether the techniques can be improved to induce more axons to regenerate longer distances more reliably can to restore more extensive d neurological recovery.

Conclusions

A variety of techniques increase the number of axons and the distance axons regenerate across a nerve gap and into the distal nerve. Sensory nerve grafts are the standard clinical technique, but have many limitations in inducing axons to regenerate across gaps >2 cm in length. Other techniques include seeding nerve gaps with Schwann cells, creation of concentration gradients of Schwann cell-released factors (CM) the nerve gap, enhancing the rate of axon regeneration with FK506 and eliminating regeneration inhibiting factors (CSPG). However, additional techniques are effective, such as elevating c-AMP in neurons, providing neurotrophic factors, and gene manipulations that enhance axon regeneration. Recently three novel clinically applicable nerve repair techniques have been shown

to induce axon regeneration and neurological across longer nerve gaps, for nerve repairs performed many years post nerve trauma and in older patients, conditions under which no other technique is effective. However, since various other techniques induce axon regeneration via a different mechanism, it is reasonable to assume that several techniques could be used together with these novel techniques to induce more reliable and extensive axon regeneration and neurological recovery.

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