

Augmenting peripheral nerve regeneration using stem cells: A review of current opinion

Neil G Fairbairn, Amanda M Meppelink, Joanna Ng-Glazier, Mark A Randolph, Jonathan M Winograd

Neil G Fairbairn, Amanda M Meppelink, Joanna Ng-Glazier, Mark A Randolph, Jonathan M Winograd, Department of Plastic Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, United States

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Correspondence to: Dr. Neil G Fairbairn, Department of Plastic Surgery, Massachusetts General Hospital, Harvard Medical School, 15 Parkman Street, Boston, MA 02114, United States. ngf174@hotmail.com

Telephone: +1-617-5152701

Fax: +1-617-7298998

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Abstract

Outcomes following peripheral nerve injury remain frustratingly poor. The reasons for this are multifactorial, although maintaining a growth permissive environment in the distal nerve stump following repair is arguably the most important. The optimal environment for axonal regeneration relies on the synthesis and release of many biochemical mediators that are temporally and spatially regulated with a high level of incompletely understood complexity. The Schwann cell (SC) has emerged as a key player in this process. Prolonged periods of distal

nerve stump denervation, characteristic of large gaps and proximal injuries, have been associated with a reduction in SC number and ability to support regenerating axons. Cell based therapy offers a potential therapy for the improvement of outcomes following peripheral nerve reconstruction. Stem cells have the potential to increase the number of SCs and prolong their ability to support regeneration. They may also have the ability to rescue and replenish populations of chromatolytic and apoptotic neurons following axotomy. Finally, they can be used in non-physiologic ways to preserve injured tissues such as denervated muscle while neuronal ingrowth has not yet occurred. Aside from stem cell type, careful consideration must be given to differentiation status, how stem cells are supported following transplantation and how they will be delivered to the site of injury. It is the aim of this article to review current opinions on the strategies of stem cell based therapy for the augmentation of peripheral nerve regeneration.

Key words: Peripheral nerve; Augmentation; Regeneration; Stem cells

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Core tip: Outcomes following peripheral nerve injury remain poor. Stem cells may increase Schwann cell numbers and longevity, prolonging their ability to support regeneration. At the level of the cell body, they may have the ability to rescue populations of neurons destined for apoptosis. They may also be used in non-physiologic ways in order to protect muscle targets from the detrimental effects of denervation. Aside from stem cell type, consideration must be given to differentiation status, scaffolding support and the mechanism of delivery. This article reviews current opinion on the strategies of stem cell-based therapy for the augmentation of peripheral nerve regeneration.

Fairbairn NG, Meppelink AM, Ng-Glazier J, Randolph MA,

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INTRODUCTION

Peripheral nerve injury, repair and challenges to recovery

Following nerve transection, the cell bodies of axons swell in anticipation of the increased metabolic demand of regeneration. Some nerve cells, particularly in response to proximal sectioning of axons, will then go on to apoptosis, lowering the number of regenerating neurons permanently. The Schwann cells (SCs), the principal glial cells of the peripheral nervous system and orchestrators of regeneration, switch from a myelinating to a phagocytic phenotype and, through chemotactic signaling, recruit circulating macrophages into the zone of injury. This heralds the beginning of Wallerian degeneration and serves to clear the distal stump of axonal and myelin debris in preparation for the reception of the regenerating growth cone. Through complex and incompletely understood cell signaling, arborized daughter axons extending from the proximal stump are attracted to columns of SCs known as the Bands of Büngner. These scaffolds nurture and guide regenerating axons towards their distal basal lamina tubes. Once SCs and the regenerating axon have been reunited, a growth promoting symbiosis is established. Any interruption in this process results in chronic SC senescence, down-regulation, a loss of axonal support and compromised recovery.

The gold standard method of nerve repair involves re-approximation using suture. Even with meticulous tissue handling and accurate, tensionless re-orientation of fascicular anatomy, outcomes are limited by suture inflammation, intra- and extra neural scar tissue, escape of axons and neurotrophic factors into the surrounding tissues, axonal mis-direction and the extremely slow rates of regeneration. These limitations are amplified following proximal limb injuries and in nerve gap reconstructions when axons must traverse two coaptation sites bridged by nerve grafts.

Autologous nerve grafts represent the gold standard bridging material for nerve gaps but these are limited by the morbidity of harvesting an “expendable” nerve. In addition, following severe trauma involving multi-limb amputation, demand for autologous material may exceed supply. In these situations, alternatives such as conduits or acellular nerve allograft (ANA) must be considered. The efficacy of hollow conduits is limited to short distances due to the lack of cellular components and extracellular matrix (ECM) to aid axonal guidance. Despite increasingly elaborate designs, these fail to replicate the efficacy of autogenous nerve. The use of ANA provides the most accurate representation of ECM, however, these grafts lack SCs and must be

repopulated with endogenous SCs migrating from adjacent nerve. As a result, outcomes following the use of these grafts for large gaps have typically been poor in comparison to autografts, though better than conduits. Improving the performance of conduits and allografts by adding stem cells, ECM components and growth factors is an area of intensive research, one that may have enormous clinical implications.

The overarching goal of any stem cell based approach to peripheral nerve injury is to establish a more favorable environment for regenerating axons and perhaps more importantly, maintain this support for an extended period of time. Repopulation of the depleted motor or sensory neuron pools with stem cells would potentially provide higher numbers of neurons for regeneration, which could aid regeneration in an additive fashion to the creation of a favorable environment. Preventing SC senescence and down-regulation during prolonged recovery periods, such as occurs in proximal injuries and long nerve gaps, and expediting the re-innervation of distal targets should translate to improvements in recovery. Finally, stem cell transplantation into denervated muscle may provide a means of preventing the expected sequelae of denervation, preventing atrophy and leaving the tissue more receptive to reinnervation over longer periods. It is the aim of this article to discuss how stem cell-based strategies have attempted to overcome these problems and how they may provide solutions in the future.

AUGMENTING NERVE REGENERATION USING STEM CELLS

The ideal stem cell for clinical application, including peripheral nerve repair, must be easily accessible, rapidly expandable in culture, capable of *in vivo* survival and integration into host tissue and must be amenable to stable transfection and expression of exogenous genes^[1]. If the process of nerve regeneration is deconstructed into a sequence of individual events, a strategy for optimizing outcome can be formulated. Emphasis has been placed on the importance of stem cell type, differentiation, cell scaffold and method of cell delivery^[2]. The influence on regeneration of each of these components has been thoroughly investigated. An overview of each of these, in addition to proposed mechanisms of action behind the therapeutic effect, will now be provided. Table 1 supplements the section on stem cell type, summarizing outcomes following the application of different stem cells in animal models.

Mechanism of action

Stem cells have the potential to replace lost neurons or increase the number of glial support cells. Replacing lost neurons has been widely demonstrated *in vitro* and has great potential in the CNS. Although not yet demonstrated in the dorsal root ganglia or ventral horn of the spinal cord, stem cells have the potential to rescue and replenish axotomized neurons as well as to manipulate the

Table 1 Summary of current evidence assessing the efficacy of different types of stem cell on peripheral nerve regeneration

Stem cell source	Author	Experimental model	Stem cell Diff.	Scaffold	Delivery system	Outcome
Embryonic	Cui <i>et al</i> ^[71]	Rat sciatic transection (10 mm gap)	D	Culture medium	Epineurium natural conduit	Cell survival and differentiation into SCs after 3-mo; superior regeneration of myelinated axons in comparison to culture media alone
	Lee <i>et al</i> ^[75]	Mouse sciatic transection (2 mm gap)	U	Matrigel	Direct injection of microspheres	ESC-derived MSC sphere-treated nerves recovered significantly greater CMAP, SFI and histological parameters than ESC-MSC single cell suspension
	Kubo <i>et al</i> ^[77]	Mouse tibial	D	PBS	Direct injection into gastrocnemius muscles following nerve transection and repair	Co-culture identified formation of new NMJs; muscle transplanted with stem cells experienced less atrophy 7 and 21-d post injury; cells transplanted after 2-wk were unable to provide any protective effect; motor recovery following repair superior in those muscles receiving stem cells
	Craff <i>et al</i> ^[76]	Rat sciatic + gastrocnemius muscle	D	PBS	Direct injection into gastrocnemius muscles following nerve transection	Muscles injected with stem cells retained muscle weight preservation and myocyte cross sectional area in comparison to control muscle after 7-d post injury. New NMJs observed. Benefits lost after 21 d
Neural	Fu <i>et al</i> ^[15]	Rat sciatic transection (15 mm gap; gene transfection)	U (gene therapy)	Culture medium (cells seeded directly onto conduit wall)	Poly(D,L-Lactide) conduit	Enhanced expression of BDNF and GDNF in transfected cells; conduits with transfected cells led to larger myelinated axons and improved functional and electrophysiological outcome
	Zhang <i>et al</i> ^[62]	Rabbit facial nerve transection (5 mm gap)	U	Collagen medium	HA-collagen composite conduit	Conduits with NSCs and NT-3 experienced superior outcomes in comparison to NSC alone; results equivalent to normal nerves after 12-wk
	Murakami <i>et al</i> ^[86]	Rat sciatic transection (15 mm gap)	U	Collagen gel	Silicone conduit	NSCs differentiated into astrocytes, oligodendrocytes and schwann cell-like cells; dNCSs implanted into 15 mm defects; Improved axon number, diameter and myelination compared with controls; labeled cells present after 10-wk; expressed markers of SC phenotype
	Guo <i>et al</i> ^[87]	Rabbit facial nerve transection (10 mm gap)	U	Collagen sponge	Chitosan conduit	Electrophysiological and histological outcomes and immunohistochemistry superior in chitosan conduits seeded with NSCs and NGF in comparison to conduit+NGF alone. Results comparable to standard autograft
	Liard <i>et al</i> ^[88]	Pig nervis cruralis transection (30 mm gap)	U	Neurosphere in culture medium	Autologous vein graft	Grafts containing NSCs recovered superior EMG recording and immunohistochemistry profiles in comparison to empty conduits; NSCs identifiable after 240 d follow-up.
	Johnson <i>et al</i> ^[89]	Rat sciatic crush, transection, (10 mm gap)	U (C17.2)	Culture medium	Direct injection	12/45 rodents developed neuroblastomas
	Zhao <i>et al</i> ^[160]	Rat sciatic transection (15 mm gap)	U	Fibrin glue	ANA	Survival of BMSCs within fibrin glue; growth factor secretion preserved (NGF, BDNF); equivalent results when cells injected directly into nerve compared with around nerve
Bone marrow	Hu <i>et al</i> ^[165]	Monkey median transection (50 mm gap)	U	Culture medium	Chitosan conduit with longitudinally aligned PGLA fibers	Functional and electrophysiological recovery and FG retrograde tracing after 1-year with BMSC-laden conduits equivalent to autograft and superior to empty conduits
	Dezawa <i>et al</i> ^[19]	Rat sciatic transection (15 mm gap)	U + D	Matrigel	Matrigel graft	Successful differentiation into SC phenotype; Axon number and elongation superior with dBMSCs
	Jia <i>et al</i> ^[32]	Rat sciatic transection (10 mm gap)	U	Gelatin	Acellular xenograft	Neurotrophic factor expression elevated in BMSC xenografts; regeneration and functional recovery significantly better than empty xenografts and equivalent to autograft
	Mohammadi <i>et al</i> ^[34]	Rat sciatic transection (10 mm gap)	U	Culture medium	Vein graft	Veins filled with uBMSCs had significantly improved functional, histological and immunohistochemical outcomes compared with veins filled with PBS
	Nijhuis <i>et al</i> ^[36]	Rat sciatic transection (15 mm gap)	U	Culture medium	Vein graft +/- muscle	BMSC identifiable after 6 and 12-wk follow-up; vein graft + muscle + BMSCs outperformed vein graft+muscle but inferior to autograft
	Salomone <i>et al</i> ^[39]	Rat facial nerve transection (3 mm gap)	U + D	Matrigel	Silicone conduit	Histological outcomes superior in conduits containing uBMSCs and dBMSCs compared to empty and matrigel containing conduits; functional outcomes superior using uBMSCs

	Wang <i>et al</i> ^[41]	Rat sciatic transection (15 mm gap)	U	Culture medium	Direct injection into ANA	BMSC produced NGF and BDNF; CSPGs reduced in grafts treated with ChABC Allograft containing BMSCs and ChABC resulted in superior functional, electrophysiological and histological outcome compared with BMSC alone
Adipose	di Summa <i>et al</i> ^[28]	Rat sciatic transection (10 mm gap)	D	Culture medium	Fibrin glue conduit	Reduced muscle atrophy in autograft, dADSC and dBMSC groups in comparison to empty conduits; dADSCs recovered greatest axon and fiber diameter, evoked potentials and regeneration of motoneurons; results comparable to autograft
	Tomita <i>et al</i> ^[21]	Rat common peroneal nerve transection (no gap)	D	Culture medium	Direct injection into distal nerve	dADSCs survived for at least 10 wk <i>in vivo</i> ; dADSCs associated with axons and participated in re-myelination; dADSCs resulted in regeneration superior to cultured SCs
	Zhang <i>et al</i> ^[31]	Rat sciatic transection (10 mm gap)	D	Collagen gel	Xenogenic acellular graft	dADSCs formed columns resembling bands of Büngner and expressed NGF, BDNF and GDNF; axon regeneration, retrograde labeling and electrophysiology were similar between dADSCs and SC supplemented grafts, superior to empty grafts but inferior to standard autograft
	Mohammadi <i>et al</i> ^[33]	Rat sciatic transection (10 mm gap)	U	Culture medium	Vein graft	No difference in functional, morphometric or immunohistochemistry between ADSCs and BMSCs
	Erba <i>et al</i> ^[45]	Rat sciatic transection (10 mm gap)	U	Fibrin	PHB conduit	Lack of sufficient quantities of viable cells 14-d after transplantation; conclusion that regenerative effect due to initial growth factor boost or paracrine effect on resident cells
	Sun <i>et al</i> ^[51]	Rat facial transection (8 mm gap)	D	Matrigel	Decellularized allogeneic artery	dADSCs persisted at repair site and integrated with regenerated tissue; conduits containing dADSCs achieved results comparable to those of SC-containing conduits and superior to matrigel-containing conduits alone; results inferior to autograft
Fetal	Pan <i>et al</i> ^[106]	Rat sciatic crush	U	Fibrin glue	Direct injection at site	High expression of BDNF, CNTF, NGF and NT-3 found in AFMSCs; motor function, CMAP and conduction velocity improved in those nerves augmented with AFMSCs; high levels of S-100 and GFAP and reduced fibrosis found at repair site
	Pan <i>et al</i> ^[111]	Rat sciatic crush	U	Fibrin glue	Direct injection at site	HBO therapy reduced production of inflammatory cytokines and macrophage chemokines following crush injury; when administered with AFMSCs, HBO reduced apoptosis of AFMSCs in comparison to AFMSCs alone; myelination and motor recovery superior in HBO + AFMSC group
	Pan <i>et al</i> ^[110]	Rat sciatic crush	U	Fibrin glue	Direct injection at site	Anti-apoptotic, anti-inflammatory agent G-CSF, when administered with AFMSCs, reduced crush-induced inflammation, and apoptosis in comparison to AFMSCs alone; myelination and motor function superior with AFMSCs + G-CSF in comparison to AFMSCs alone
	Matsuse <i>et al</i> ^[109]	Rat sciatic nerve transection (8 mm gap)	U + D	Matrigel	“Transpermeable” tube	Differentiated UC-MSCs regenerated greater number of myelinated axons and thicker nerve fibers compared with undifferentiated UC-MSCs; number of labeled cells greater in dUC-MSC nerves; results comparable to SC group
	Cheng <i>et al</i> ^[113]	Rat sciatic crush	U	Matrigel	Direct injection at site	AFMSCs successfully transfected; high expression of GDNF detected for 4 wk before subsiding; GDNF-modified AFMSCs recovered greatest SFI, conduction velocity, CMAP and muscle weight in comparison to AFMSCs alone
	Gärtner <i>et al</i> ^[108]	Rat sciatic crush	D	Culture medium	Cells seeded onto PLC wrap	Wraps seeded with UC-MSCs resulted in superior increased myelin thickness, motor and sensory function in comparison to unseeded wraps
Skin	McKenzie <i>et al</i> ^[120]	Mouse sciatic crush	D/ U	Culture medium	Direct injection at site	SKPs successfully induced into SKP-SCs; SKP and SKP-SCs associated with and myelinated axons
	Marchesi <i>et al</i> ^[123]	Rat sciatic transection (16 mm gap)	D	PBS	(1) Synthetic copolymer L-lactide and trimethylene carbonate; and (2) collagen conduit	SFI and CMAPs were significantly better in conduits filled with SDSCs; number of regenerated myelinated axons significantly greater in SDSC conduits; no significant difference in neurotrophic factor expression
	Walsh <i>et al</i> ^[124]	Rat sciatic transection (12 mm gap)	D	Culture medium	Direct injection into acellular freeze-thawed nerve graft	SKP-SCs maintained differentiation up to 8-wk; outcomes significantly improved in comparison to cell free grafts and comparable to cultured SCs; neurotrophic factor release greater in SKP-SCs
	Walsh <i>et al</i> ^[121]	Rat CP/tibial (Immediate <i>vs</i> chronic repair; no gap)	D	Culture medium	Direct injection into distal nerve	Muscle weight and CMAPs superior in SKP-SC group in comparison to media injected controls; significantly higher counts of axon regeneration in SKP-SC group equivalent to immediate suture group
	Walsh <i>et al</i> ^[22]	Rat sciatic transection [acute <i>vs</i> chronic <i>vs</i> ANA (12 mm gap)]	U/ D	Culture medium	Direct injection into nerve ends and ANA	SKP-SCs maintained <i>in vivo</i> viability and differentiation better than uSKP; viability poorest in normal nerve, best in acutely injured nerve; SKP-SCs remain differentiated over time and myelinate axons; neuregulin able to prevent apoptosis following transplantation
	Khuong <i>et al</i> ^[122]	Rat sciatic and tibial (12 mm gap)	D	Culture medium	Direct injection into ANA	SKP-SCs containing allografts resulted in superior functional and histological outcomes in both acute and delayed injury models compared with SCs and media controls

Hair follicle	Amoh <i>et al.</i> ^[135]	Mouse sciatic and tibial transection (no gap)	U	Culture medium	Direct injection at site	HFSC transplanted nerves recovered significantly greater function compared with untreated nerves; GFP-labeled cells differentiated into GFAP positive schwann cells and were involved with myelination
	Amoh <i>et al.</i> ^[135]	Mouse sciatic crush	U	Culture medium	Direct injection at site	HFSCs transplanted around crushed nerve differentiated into SC-like cells and participated in myelination; gastrocnemius muscle contraction significantly greater compared with untreated crushed nerves
	Amoh <i>et al.</i> ^[134]	Mouse sciatic transection (2 mm gap)	U	Culture medium	Direct injection at site	HFSCs differentiated into GFAP expressing SCs and were able to myelinate axons; gastrocnemius muscle contraction significantly greater compared with untreated nerves
	Lin <i>et al.</i> ^[136]	Rat sciatic transection (40 mm gap)	D	PBS	Direct injection into acellular xenograft	Differentiation into neurons and SCs maintained for 52-wk; number of regenerated axons, myelin thickness and ratio of myelinated axons to total nerve count significantly higher in dHFSCs compared with acellular grafts; conduction velocity slower in dHFSC nerves
Induced pluripotent stem cell	Ikeda <i>et al.</i> ^[146]	Mouse sciatic nerve (5 mm gap)	D	Microsphere seeded into conduit	Mixed PLA/PCL conduit +/- iPSC microspheres +/- bFGF	Regeneration was accelerated by combination of iPSCs + bFGF within conduits in comparison to iPSCs and bFGF alone; outcomes remained inferior to autograft controls; empty conduits performed least well
	Uemura <i>et al.</i> ^[148]	Mouse sciatic nerve (5 mm gap)	D	Microsphere seeded into conduit	Mixed PLA/PCL conduit +/- iPSC microspheres	Motor and sensory recovery was superior in iPSC group at 4, 8 and 12 wk in comparison to empty conduits. Axonal regeneration superior in iPSC group. Conduit structurally stable after 12 wk
	Wang <i>et al.</i> ^[149]	Rat sciatic nerve (12 mm gap)	D	Matrigel	PLCL/PPG/sodium acetate copolymer electrospun nanofiber conduit	Conduits filled with either (1) matrigel; (2) matrigel + NCSCs differentiated from ESCs; and (3) matrigel + NCSCs differentiated from iPSCs; NCSC differentiated into SCs and integrated into myelin sheaths; electrophysiology and histology showed equivalent regeneration in all NCSC containing conduits; no teratoma formation observed after 1-yr

ADSC: Adipose derived stem cell; ANA: Acellular nerve allograft; AFMSC: Amniotic fluid derived mesenchymal stem cell; BDNF: Brain derived neurotrophic factor; BDGF: Brain derived growth factor; bFGF: Basic fibroblast growth factor; BMSC: Bone marrow derived mesenchymal stem cell; CP: Common peroneal; CMAP: Compound muscle action potential; CSPG: Chondroitin sulphate proteoglycan; ChABC: Chondroitinase ABC; D: Differentiated; DMEM: Dulbecco's Modified Eagle's Medium; ECM: Extracellular matrix; EMG: Electromyography; ESC: Embryonic stem cell; FG: Fluorogold; GFAP: Glial fibrillary acidic protein; GDNF: Glial cell derived neurotrophic factor; G-CSF: Granulocyte colony stimulating factor; GFP: Green fluorescent protein; HA: Hyaluronic acid; HFSC: Human fetal derived stem cell; HBO: Hyperbaric oxygen; iPSC: Induced pluripotent stem cell; MSC: Mesenchymal stem cell; NCSC: Neural crest stem cell; NGF: Nerve growth factor; NMJ: Neuromuscular junction; NSC: Nerve stem cell; NT-3: Neurotrophin-3; PBS: Phosphate buffered saline; PCL: Poly-ε-caprolactone; PFTE: Polytetrafluoroethylene; PGLA: Polyglycolic lactic acid; PHB: Polyhydroxybutyrate; PLA: Poly-L-lactide; PLCL: Poly(L-lactide-co-caprolactone); PPG: Polypropylene glycol; SC: Schwann cell; SFI: Sciatic function index; SKP: Skin derived precursor; SKP-SC: Skin precursor derived Schwann cell; SDSC: Skin derived stem cell; U: Undifferentiated; USW: Ultra-short wave therapy.

microenvironment of the neurons during regeneration. In the peripheral nervous system, emphasis has been placed mostly on increasing SC number and activity. This approach is driven by the pragmatic difficulties associated with autologous SC culture. Achieving sufficient autologous SC numbers requires explantation of healthy nerve, extended periods of purification and expansion and consequently, delays to repair. Prolonged axotomy and denervation only exacerbate central cell body apoptosis and loss of SC-mediated axonal support in the distal nerve^[3,4]. As a result, the use of cultured SCs is considered impractical.

Exogenous stem cells differentiated into SC-like phenotype may integrate into Bands of Büngner and aid axonal guidance and re-myelination. Transplanted cells enhance growth factor secretion and ECM production. These factors may be released directly or, through cell-to-cell contact and paracrine signaling, can stimulate endogenous SCs to upregulate secretory activity^[5]. Increased recruitment of circulating macrophages into the area can potentiate this effect^[6].

ECM proteins such as collagen I, collagen IV, fibronectin

and laminin, and neurite guidance proteins such as netrin and ninjurin-2 have pro-regenerative effects^[7,8]. Other ECM components such as chondroitin sulphate proteoglycan are potent inhibitors of axonal regeneration and the degradation of this protein by liberated matrix metalloproteinase-2 has been shown to support regeneration^[9,10].

The production of nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), ciliary neurotrophic factor and neurotrophin-3 (NT-3) by endogenous SCs and transplanted stem cells has been described^[5,7,8,11-17]. Angiogenic factors such as vascular endothelial growth factor, basic fibroblast growth factor (bFGF), hepatocyte growth factor and angiopoietin-1 may also be released^[12]. Hypoxia has been found to potentiate the angiogenic and neurogenic influence of some stem cells, leading to improved blood vessel and nerve fiber formation^[7]. This has led some investigators to attempt pre-conditioning and differentiation in hypoxic environments^[7]. The expression of leukemia inhibitory factor and insulin-like growth factor has also been detected^[18]. These factors are thought to improve neuronal survival, promote corticospinal tract growth,

increase astrogliosis and potentiate the inflammatory response^[8,18]. The observed immunomodulatory effects of stem cells are believed to be due to the secretion of factors such as granulocyte and macrophage colony stimulating factor (G-CSF, M-CSF), interleukin-6, 7, 8, and 11 (IL-6, IL-7, IL-8, IL-11) and TNF- α ^[8]. Suppression of the host immune response may help reduce the detrimental impact of inflammation and fibrosis following nerve repair and is obviously desirable in the context of allotransplantation of cells. The relative contribution of each of these mechanisms and therefore the levels of ECM protein and growth factor production may vary not only with stem cell type but also with the differentiation status of transplanted cells.

Differentiation

Stem cells can be transplanted in their undifferentiated state or can undergo a period of *in vitro* differentiation into SC-like cells. This is commonly achieved with exposure to β -mercaptoethanol, all-trans retinoic acid, fetal bovine serum, forskolin, recombinant human bFGF, recombinant human platelet derived growth factor-AA, and recombinant human heregulin β -1^[19,20]. The purported benefits of differentiation include superior *in vivo* viability and an enhancement of neurotrophic factor secretion and myelinating ability^[14,21,22]. Many investigators have shown the beneficial effects on regeneration of these cells^[19-21,23-31]. Some claim that transplanting undifferentiated cells risks *in vivo* differentiation along unwanted, non-neuronal lines in response to other dominant cells in the area.

Interestingly, however, the positive effects of undifferentiated cells have also been widely reported^[5,7,13,32-51]. These investigators claim that *in vitro* differentiation incurs an unnecessary delay, limiting clinical applicability. In one study, the process of differentiation actually reduced the secretion of neurotrophic factors^[52]. Others have reported difficulties with maintaining *in vivo* neuronal differentiation, claiming that once *in vitro* differentiation cues are removed, cells tend to revert back to their original phenotype^[53]. Evidence suggests that undifferentiated cells may undergo *in vivo* differentiation in response to local stimuli^[20,40,54-56], although others have been unable to show this^[45,49,57]. A small number of direct comparisons have been performed and have shown either a small advantage for differentiated cells^[20,23], a small advantage for undifferentiated cells^[39] or no significant difference^[45,48].

Stem cell source

Embryonic stem cells: Thomson *et al.*^[58] described the isolation of pluripotent cell lines from human blastocysts in 1998. Since this discovery, stem cells have been harvested from a variety of different fetal and adult tissues (Figure 1). Embryonic stem cells (ESCs) can form derivatives of all three embryonic germ layers and can provide an unlimited source of cells with superior differentiation potential and long-term proliferation capacity in comparison to mesenchymal stem cells (MSCs)^[59]. Unlike adult sources, these cells are homogenous, are not susceptible to the

detrimental impact of age and disease and can be harvested without physical discomfort^[60]. However, differentiation down specialized neural cell lines is challenging and established protocols only exist for a limited number of lines^[61,62]. Additional disadvantages include immunogenicity, tumorigenicity and potential ethical controversy due to the fact that cells are harvested during the blastocyst stage of development and consequently result in the destruction of embryos.

ESCs have been shown to migrate and differentiate into neurons, and glial cells of the central and peripheral nervous system and have the capacity for *in vivo* myelination^[61,63-70]. Studies reporting the successful application of these cells to peripheral nerve repair are limited, perhaps reflecting the lack of facile clinical translatability^[71]. In recognition of the limitations, investigators have derived mesenchymal precursors from ESC^[59,72-74]. Augmentation of peripheral nerve regeneration following the transplantation of spheres of human MSCs derived from ESCs has been reported^[75]. Our group has shown in small animal models of sciatic and tibial nerve transection that ESCs transplanted directly into muscle can preserve short-term muscle mass and myocyte cross-sectional area following injury and repair^[76,77].

Nerve stem cells: Nerve stem cells (NSCs) naturally differentiate into neurons and glial cells. However, the process of neurogenesis almost exclusively occurs during embryogenesis and continues in the adult in response to injury only within very limited locations of the CNS^[78]. NSCs were first isolated from adult murine brain in the early 1990s^[79,80]. This was followed by similar discoveries in humans and non-human primates^[81,82]. The subventricular zone and the subgranular zone in the brain represent the primary sites of NSC differentiation in adult mammals (Figure 1). Most recently, populations of NSCs and neurogenesis have been discovered in adjacent areas of the adult human striatum^[83]. Neural crest stem cells have been isolated from fetal rat sciatic nerve but the existence of such cells in peripheral nerves of the adult human is unknown^[84,85].

Many have reported positive results following NSC implantation into peripheral nerve injury^[15,62,86-88]. Heine *et al.*^[9] showed that the beneficial effects of NSC transplantation are not confined to acute peripheral nerve injury. Transplantation of NSCs into chronically denervated nerve had a beneficial effect on morphological and electrophysiological recovery in comparison to controls. Immortalized murine C17.2 NSCs have become commercially available and are commonly used for *in vivo* animal studies. However, experience with C17.2 NSCs in the PNS has not been uniformly positive. Following the implantation of these cells into rat models of crush, transection and graft, high rates of neuroblastoma formation have been encountered^[89]. In addition to these concerns, pragmatic difficulties associated with cell harvest have limited their use.

MSCs: MSCs are multipotent stromal cells that originate from the bone marrow and a variety of non-marrow

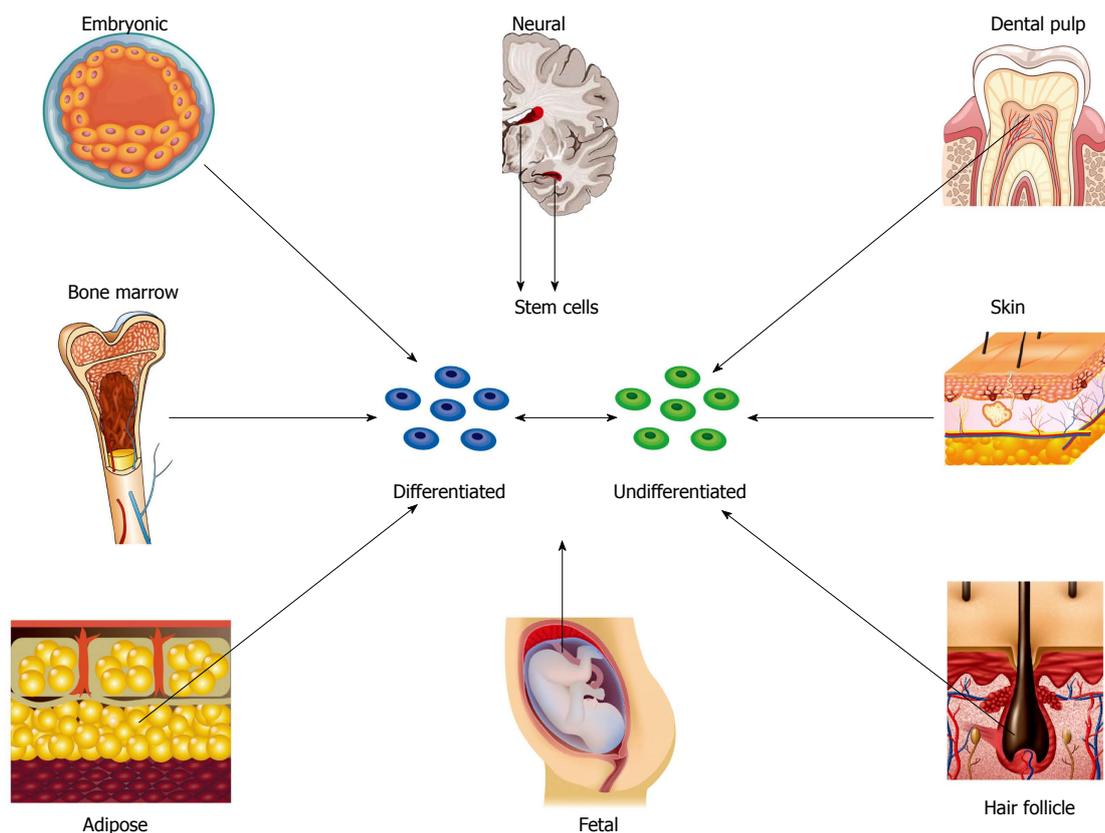


Figure 1 Different stem cell sources. Embryonic stem cells are obtained from the inner cell mass of the blastocyst and therefore require destruction of the embryo. Nerve stem cells are harvested from the subventricular layer of the lateral ventricle and the subgranular layer of the hippocampus. Bone marrow derived stem cells are harvested from the marrow cavity of long bones. Adipose derived stem cells are derived from subcutaneous fat and are abundantly available following commonly performed procedures such as liposuction. Skin derived precursors are harvested from the dermis and represent a related population of cells harvested from hair follicles. Fetal tissue provides populations of cells from amniotic membrane, amniotic fluid, umbilical cord blood, umbilical cord tissue and Wharton's jelly. Dental pulp stem cells can be harvested from deciduous teeth.

sources such as adipose tissue, fetal tissue, skin, hair follicle and dental pulp (Figure 1). Although the potency of these cells was originally considered to be limited to tissues of mesodermal origin, differentiation into non-mesodermal lineage is now generally accepted. It is precisely this characteristic that endows MSCs with the ability to support neuroregeneration. An overview of the main sub-types of MSC and the evidence behind their application to peripheral nerve regeneration will now be discussed.

Bone marrow derived stem cells: In contrast to embryonic and NSCs, bone marrow derived stem cells (BMSCs) are readily accessible and have no potential ethical concerns. Under appropriate conditions BMSCs can differentiate into non-mesodermal lineages such as neurons, astrocytes and SC-like cells^[90]. Many studies have shown that the addition of BMSCs to conduits and acellular grafts results in superior outcomes when compared with empty or cell deplete channels^[24,36-38,40,41]. Although some have failed to show that BMSCs can match outcomes achieved with cultured SCs^[20], the majority of reports show that performance is at least equivalent^[27,43,91]. There is a dearth of studies showing superiority over gold standard autograft although some report equivalent outcomes^[42,44]. Evidence suggests that these outcomes may be dose dependent^[92].

Although BMSCs are more clinically applicable than ESCs, NSCs and cultured SCs, stem cell fraction is low and in comparison with other sources, BMSCs generally have inferior proliferation capacity and differentiation potential. In addition, harvest is invasive and painful. This has driven the pursuit of less invasive MSC sources such as fetal tissue, skin, hair follicle and adipose tissue.

Adipose derived stem cells: Adipose tissue is abundant, easily harvested and is a frequent waste product of commonly performed procedures such as liposuction. It has a superior stem cell fraction in comparison to bone marrow and adipose derived stem cells (ADSCs) have superior proliferation and differentiation potential in comparison to BMSCs^[93,94]. Unlike BMSCs, donor age and site of harvest does not seem to significantly influence the therapeutic effect of ADSCs^[50].

Multiple neuronal and SC markers have been expressed from differentiated ADSCs^[7,30,95-97]. The expression of myelin protein zero, peripheral myelin protein-22 and myelin basic protein also suggest the retention of myelinating capability^[98]. Although some reports have found no difference in outcome between ADSC-filled conduits and cell deplete products^[49], the vast majority of studies show an augmented effect^[13,28,29,31,99]. Several studies have shown that

ADSCs are at least as effective as autologous SCs^[21,45,51]. As with BMSCs, a small number of investigators have reported equivalent outcomes in comparison to autograft^[13,28,29] with even fewer reporting superior outcomes^[48]. Studies directly comparing the performance of ADSCs to BMSCs have found no significant differences between the two^[33,45]. Low morbidity of harvest, wide availability and superior stem cell characteristics have helped establish ADSCs as the preferred option for pre-clinical studies.

Fetal derived stem cells: Fetal tissues represent the most primitive source of MSCs. These tissues are ordinarily discarded following birth and are therefore in abundant supply. Tissue age rarely exceeds 42-wk and therefore, in comparison to other adult sources, cells have accumulated less genetic damage due to age, environment and disease^[100]. Stem cells can be harvested from amniotic membrane, amniotic fluid, umbilical cord cells, umbilical cord blood and Wharton's jelly. These cells are readily expandable in culture and possess the ability to differentiate into neural phenotype^[101,102].

Wharton's jelly derived mesenchymal stem cells can differentiate into functional SC-like cells, produce neurotrophic factors such as NGF, BDNF and NT-3 and stimulate neurite growth *in vitro*^[103]. Amniotic fluid derived stem cells (AFDSCs) express characteristics of both mesenchymal and NSCs^[104], can differentiate into neural tissue^[105] and, following transplantation into rat sciatic nerve gap models, have been shown to promote peripheral nerve regeneration^[106,107]. Umbilical cord-derived mesenchymal stem cells have also been shown to improve outcomes following crush and transection injuries in rodent models^[108,109].

Survival of AFDSCs following transplantation can be limited and as a result, efforts have been made to improve *in vivo* survivability. Inhibition of inflammatory mediators can attenuate the apoptotic cascade^[110-112]. Cells can be genetically modified in order to over-express therapeutic genes. GDNF-modified human AFMSCs have been shown to improve viability, regeneration and motor outcomes in rodent models^[113]. Stromal cell-derived factor-1 α (SDF-1 α) is chemotactic towards MSCs and is expressed in several tissues in the rat, including injured nerve. By timing intravenous administration of AFDSCs with peak expression of SDF-1 α , this novel approach has been shown to improve AFDSC numbers at the repair site and nerve regeneration^[114].

Fetal tissue represents a promising alternative source of stem cells. However the use of autologous cells following injury is currently impractical. The use of allogeneic cells and their associated immunoreactivity are obstacles that are not encountered with other adult sources such as adipose tissue. Widespread banking of fetal products following birth offers a solution to this problem.

Skin derived precursors: Skin derived precursors (SKPs) reside in the dermis and are an accessible source of adult multipotent cells that are easily expandable in culture. SKPs

exhibit a remarkable similarity to embryonic neural crest cells, a migratory population of multipotent cells that gives rise to a diverse array of cell types such as melanocytes, craniofacial cartilage, bone and connective tissue, smooth muscle of vasculature, endocrine cells, and neurons and glial cells of the autonomic and peripheral nervous system^[115]. Neuregulin is known to promote proliferation and differentiation of SCs from embryonic neural crest precursors^[115-117] and is also believed to be mediate SC proliferation during Wallerian degeneration^[118]. When cultured with neuregulin-1 β , rodent and human SKPs express markers consistent with functioning SCs^[115-120]. Exogenous neureglins and heregulin-1 β may also improve *in vivo* viability by reducing apoptosis^[22].

Both undifferentiated and differentiated SKPs (SKP-SCs) have been shown to have positive effects on regeneration. In rodent models, SKP-SCs have been shown to maintain differentiation and viability, myelinate axons, and exhibit superior outcomes following de-myelination and crush injury^[117,120], acute and chronic transection injury^[22,120-122] and following implantation into ANAs^[122-124].

Hair follicle stem cells: Hair follicles are dynamic dermal appendages and are abundant and readily accessible sources of pluripotent stem cells. The hair follicle is derived from the neural crest and harbors NCSC-like cells^[125]. Hair follicle stem cells (HFSCs) were discovered following the detection of nestin, a marker for neural progenitor cells, in the cells of the hair follicle bulge in mice^[126] and humans^[127]. They are readily expanded in culture, although, as with SKPs, clinical applicability may be limited by prolonged periods of cell expansion. HFSCs are positive for ESC transcription factors Nanog, Oct4 and nestin, and have the ability to differentiate into adipocytes, smooth muscle cells, melanocytes, neurons and glial cells^[116,128,129]. Differentiation into epithelial and vascular cells emphasizes the important role HFSCs have in vascularizing the skin and dermis^[130-132].

A small number of studies have reported the use of undifferentiated HFSCs in murine models of sciatic and tibial nerve crush and transection injuries^[133-135]. HFSCs were found to differentiate into glial fibrillary acidic protein positive SC-like cells and participated in myelination. Functional outcomes were significantly improved in those nerves receiving HFSCs. The efficacy of differentiated HFSCs seeded into acellular xenografts has also been investigated^[136]. Cells were able to maintain differentiation long term and the number of regenerated axons and myelination in cell-supplemented xenografts was higher than cell-free xenografts.

Dental pulp stem cells: Dental pulp is neural crest-derived tissue that can be harvested from exfoliated deciduous teeth and arguably represents the most convenient source of multipotent stem cells. As with fetal tissue, widespread application of autologous cells would require harvest and storage of teeth at an early age. Although experience is limited with this newly described population of cells,

evidence shows that these cells may have a role in supporting peripheral nerve regeneration. In avian embryonic models, dental pulp stem cells (DPSCs) have been shown to chemo-attract trigeminal ganglion axons^[137]. DPSCs have also been shown to successfully differentiate into SCs *in vitro* and were able to support DRG neurite outgrowth^[138]. When implanted into a collagen gel matrix, DPSCs were able to form aligned columns and had the ability to guide and myelinate neurites^[138]. Rat DPSCs have also been shown to provide axonal support following hemisection of the spinal cord^[139,140].

Induced pluripotent stem cells: In 2006, Takahashi *et al.*^[141] described the derivation of induced pluripotency in somatic mouse cells following ectopic co-expression of transcription factors^[141]. This ability to reprogram cells questioned the stability of cellular identity and injected new optimism into the quest to develop a patient specific pluripotent stem cell that could circumvent the limitations of ESCs. Although multiple similarities between ESCs and induced pluripotent stem cells (iPSCs) exist, subtle differences have also been detected^[142]. Currently it is believed that these cells are neither identical nor distinct populations and instead represent cells with overlapping identity. These differences do not abrogate their potential. Since their discovery, iPSCs have furthered the understanding of many disease mechanisms and have advanced *in vitro* drug screening and the assessment of therapeutic efficacy following pharmaceutical and cell-based interventions^[142].

In addition to differentiation into various somatic cell lines, established protocols now exist for the *in vitro* differentiation of iPSCs along neural lineages^[143,144]. Although evidence suggests that differentiation occurs with reduced efficiency and increased variability^[145], iPSCs have been shown to have a pro-regenerative effect in small animal models of central and peripheral nervous system injury^[146-149].

These cells possess several advantages over embryonic sources such as the avoidance of ethical and immunosuppressive issues. However, concerns surrounding these cells exist. Retained epigenetic “memory” from their somatic cells of origin, coupled with chromosomal aberrations resulting from re-programming, can render these cells even more tumorigenic than ESCs^[150].

The preferred option: Adipose derived stem cells represent the most practical source of cells for transplantation. In light of easier harvest, superior stem cell fraction, differentiation potential and proliferation capacity, they have supplanted bone marrow derived cells. Other alternatives such as fetal, hair follicle and tooth pulp have great potential but are currently limited by the lack of autogenous supply and the requirements for cell expansion. Whether these cells are best differentiated prior to transplantation is a contentious issue although the use of undifferentiated cells obviates the requirement for *in vitro* differentiation. The beneficial effect of these cells on regeneration has been widely reported

and, until clear evidence emerges that differentiation is superior, the use of undifferentiated cells is the most pragmatic and clinically translatable option. Optimizing the effect of the preferred option is heavily reliant on appropriate delivery and support.

Cell scaffolds and methods of delivery

Cell scaffolds aim to maintain cell viability, support proliferation and permit intercellular communication and growth factor elution. N-methacrylate glycol chitosan, alginate, hyaluronic acid, polyethylene glycol, fibrin and Matrigel have all been shown to successfully fulfill these requirements^[151-157]. In addition to their supportive role, scaffolds also help prevent unwanted cell dissipation from the site of injury and, when used in combination with nerve conduits, have emerged as useful adjuncts for improving the delivery of cells.

In cases where nerves are repaired primarily or when autograft or allograft nerve is going to be used, stem cells can be delivered by a variety of different methods (Figure 2). Cells suspended in culture medium can be microinjected into nerve ends or grafts (Figure 2A)^[28,29,32,40,158-160]. Although this delivers cells directly to the site of injury, the process of micro-injection can be traumatic to the delicate intra-neural architecture and can result in unpredictable cell distribution. Evidence suggests that intra-neural injection may be unnecessary. Cells suspended in fibrin matrix that were injected around repair sites maintained neurotrophic factor secretion and cell migration and resulted in outcomes that were not significantly different in comparison to injected nerves (Figure 2B)^[160].

Cells can be injected within the lumen of a conduit (Figure 2C) or can be seeded onto conduit matrix (Figure 2D). Natural conduits including vein and artery grafts are rich in ECM proteins such as collagen and laminin and provide a useful substrate for cell adhesion, though only at the periphery of the constructs^[33,34 37,161-163]. Vessels can remain empty or can be pre-filled with tissue such as muscle to support axonal guidance^[36]. Commercially available natural conduits are usually composed of ECM components such as collagen^[38] and fibrin^[28]. Synthetic materials include polyglycolic acid^[57], Poly(lactic-co-glycolic) acid^[164], silicone tube^[39,43], polyhydroxybutyrate^[20], polytetrafluoroethylene^[24] silk fibroin^[42] and chitosan^[91,165]. The degradation profile of conduits must be carefully considered when used with cell therapy. Natural conduits tend to degrade in a predictable, non-toxic fashion, though the rate of degradation may not be sufficiently slow in some cases to allow for adequate regeneration time. Some synthetic polymers can acidify the microenvironment during degradation and can have a detrimental impact on cellular activity^[166].

In recognition of the importance of basal lamina and other ECM framework for axonal guidance, conduits with internal structure have become more popular than hollow, single lumen tubes. These structures may be organized arrangements of multiple fibers^[23,164,165] or less orderly structures such as collagen sponge^[24]. However,

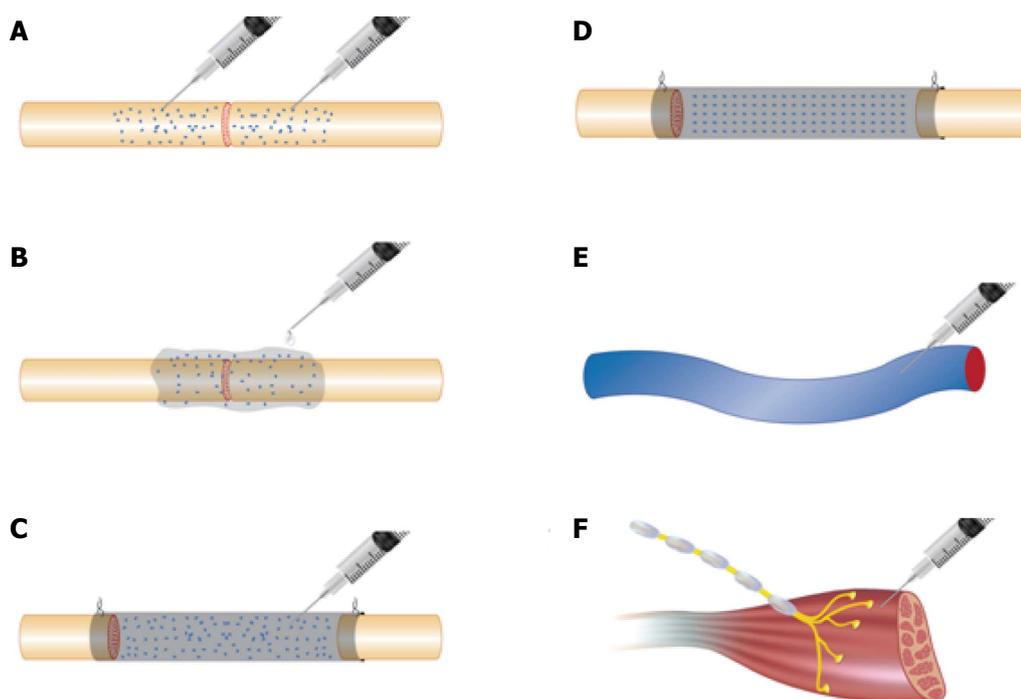


Figure 2 Methods of stem cell delivery. A: Direct injection into nerve ends or bridging nerve graft; B: Injection of cells suspended in matrix around nerve rather into the substance of the nerve; C: Nerve gap model using a conduit as the bridging method. Conduit lumen can be injected and filled with cells suspended in scaffold; D: Nerve gap model using conduit as bridging method. Conduit has been cultured and seeded with stem cells. Lumen of conduit may also be filled with cells. Hollow conduits may have internal framework added. This framework may also be seeded with cells; E: Systemic injection of cells. Stem cells have been shown to home to the site of injury; F: Cells may also be injected into neuromuscular junctions of peripheral muscles.

in the absence of cells, attempts to replicate the structural complexity of the nerve have led to disappointing results.

Recent evidence exists that systemic administration of stem cells following peripheral nerve injury can be efficacious (Figure 2E)^[5,114]. With further refinement, it may become possible to sustain regenerative support through regular systemic dosing. There is also evidence that stem cells may be efficacious when administered at the level of neuromuscular junction (NMJ) (Figure 2F) or when distributed within denervated muscle^[76,77,167].

Future

Nerve regeneration and re-innervation is a protracted and dynamic process. Any attempts to improve the speed and integrity of this process must be equally enduring and migratory. Local delivery of biochemical mediators to the site of repair is a common approach, though this provides only finite support that is unable to follow the advancing growth cone, not to mention recapitulate the elegant temporal coordination of myriad different factors. Development of systemic administration and cell homing to bring these cells to the advancing neural growth cone and the regenerating axons may help sustain regenerative support.

A fusion of cell based therapy and optogenetics may also hold promise by restoring motor function in those that have lost central control. Murine embryonic stem cell derived motor neurons have been induced to express the light-sensitive ion channel channelrhodopsin-2. When engrafted into mouse sciatic nerve, not only did axons re-

innervate hind limb muscles, but function was restored in a controllable manner through optical stimulation and did not require connection to the central nervous system^[168].

CONCLUSION

Despite *in vitro* and pre-clinical success, the application of stem cells to peripheral nerve repair has yet to make an impact in the clinical arena. Translation is currently limited by justified concerns regarding genetic manipulation, cell instability and the risks of tumorigenesis. However, perhaps the most pertinent issue is that despite great effort to manipulate the regenerative process, the use of stem cells simply has not led to outcomes that significantly and consistently surpass those achieved with conventional techniques. Augmentation of peripheral nerve repair with stem cells must consider stem cell type, differentiation, cell scaffold and method of delivery in order to offer effective new therapies. These factors, in addition to animal and injury models, vary widely in the current literature, making it very difficult to draw definitive conclusions as to which combination is most efficacious.

The ideal strategy would involve administration of stem cells immediately, or as soon as possible, following injury and for this to be sustained throughout the period of regeneration and recovery. This may require a shift away from the development of methods of local delivery and a re-focus on developing cells that can be administered systemically and that have the ability to specifically target and support not only the migrating growth cone, but also

centrally located cell bodies and peripherally located NMJs.

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