Stem-cell Based Therapies to Enhance Peripheral Nerve Regeneration

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Abstract

Peripheral nerve injury remains an important cause of morbidity in trauma patients. Despite advances in microsurgical techniques and improved understanding of nerve regeneration, obtaining satisfactory outcomes following peripheral nerve injury remains a tough clinical problem. There is a growing body of evidence in preclinical animal studies demonstrating the supportive role of stem cells in peripheral nerve regeneration following injury. The characteristics of both mesoderm-derived and ectoderm-derived stem cell types and their role in peripheral nerve regeneration will be discussed, specifically focusing on the presentation of both foundational laboratory studies and translational applications. The current state of clinical translation is presented, with an emphasis on both ethical considerations of using stems cells in humans, and current governmental regulatory policies. Current advancements in cell-based therapies represent an optimistic future with regards to supporting nerve regeneration and achieving significant functional recovery following debilitating nerve injuries.

KEYWORDS: nerve regeneration, stem cell, peripheral nerve injury, cellular therapy

Introduction

Peripheral nerve injury remains an important cause of morbidity in trauma patients[1]. Despite advances in microsurgical techniques and improved understanding of nerve regeneration, obtaining satisfactory outcomes following peripheral nerve injury remains a serious clinical problem[2-4]. Unfortunately, a large proportion of patients with severe peripheral nerve injuries fail to recover normal function [5,6]. Even following the most optimal surgical situation of direct nerve repair, return of motor and sensory function is slow and often incomplete[7-9].

The regeneration of damaged peripheral nerves occurs though a complex process in which Schwann cells (SC) play a crucial role[10]. Following axonal injury, SCs proliferate, phagocytose debris, and recruit macrophages[11] to help establish the optimal regenerative milieu[12]. These cells further aid in axonal regrowth by synthesizing neurotrophic factors[13-15], producing both extracellular matrix and cell adhesion molecules[16], and providing physical guidance to regenerating axons[17,18]. SC based therapies have been successfully utilized in preclinical animal models to enhance nerve regeneration[19-

[22]. However, due to the invasive nature of SC harvest[23] and the difficulty of cell expansion *in vitro*[24], there remain significant barriers to clinical use.[25]

In light of the practical limitations associated with SCs, there has been growing enthusiasm for the use of both precursor and stem cell-based therapies (we use the term "stem cell" throughout the review to maintain consistency while recognizing that few of the cell sources mentioned are true stem cells) for peripheral nerve regeneration[26-29]. We are also cognizant of the fact that embryonic stem cells generally have a higher regenerative capacity and are less lineage committed than adult precursor and/or stem cells[30,31]. There is a growing body of evidence in preclinical animal studies that show stem cells play a positive role in the regeneration of peripheral nerves after injury[32-37]. These effects are thought to be based on the ability of transplanted stem cells to promote regeneration by cell differentiation into tissue-specific cell types[38-40], signaling through cell-to-cell contact, and/or sustained release of neurotrophic factors[27,41,42]. A number of stem cell types with varying phenotypic and gene expression profiles have been investigated. This review will summarize the literature supporting the utilization of various stem cell types that have been employed to enhance peripheral nerve regeneration. A detailed list of stem cell types discussed is presented in Table 1. We will review the foundational laboratory studies for each type and then subsequently focus on translational works using human-derived cells in animals. If available, the current use of these cells in humans for the treatment of peripheral nerve conditions will also be highlighted.

1. Bone Marrow Stromal Stem Cells (BMSCs)

One of the most comprehensively studied cell types with respect to peripheral nerve regenerative potential is the bone marrow stromal stem cell (BMSC). These multipotent cells may

differentiate into mesenchymal lineages but can also be persuaded to adopt a SC phenotype *in vitro*[26]. However, their eventual fate *in vivo* may not robustly retain this differentiation[43,44].

BMSCs effectively produce and secrete numerous neurotrophins [e.g, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial-cell line derived neurotrophic factor (GDNF), ciliary neurotrophic factor (CNTF)] in peripheral nerve repair and have been previously shown to enhance regeneration[45,46]. Chen et al, convincingly showed improved walking track scores, wet muscle weights, and increased axonal counts in a 15 mm gap sciatic transection model[45] using BMSC therapy. These cells have also been tested (and found efficacious) as supplements to nerve scaffolds using inside-out arterial grafts[47], decellularized nerve grafts[48-51], and veins[52]. One study found a relative inferiority of BMSCs when directly compared against SCs for electrophysiological recovery of a sciatic transection/silicone tube model, though functionally the groups performed at equivalent levels[53]. BMSCs have also been studied in larger animal models of long-gap nerve regeneration, including rabbits[54], and non-human primates[55], and in the latter demonstrated efficacy on par with both SCs and allografts.

A further interesting observation is the ability of BMSCs to “home in’ to injured targets, where they have demonstrated this ability in CNS animal injury models when administered intravenously[56]. Although BMSCs are yet to be used in humans, the practicality of an effective systemic stem cell therapy makes these cells a prime candidate for translational study.

2. Adipose-derived Stem Cells (ADSCs)

Originally described by Zuk et al., adipose-derived stem cells (ADSCs) present a potential adjunct to improve nerve repair and are derived from adipose tissue, which in turn is derived from embryonic mesoderm[57,58]. However, they can be effectively differentiated along ectodermal lines, with

SC-like ADSCs first described in 2007 by Kingham[38]. Numerous published studies have focused on neuroregenerative effects of adipose tissue using purified, cultured, differentiated, or dedifferentiated adipose-derived tissues[59-61]. ADSCs have also been extensively investigated for use in peripheral nerve regeneration, with promising results. They produce mRNA for the growth factors BDNF, glial-growth like factor (GGF), neurogulin-1 (NRG-1), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and insulin-like growth factor (IGF) on par or greater than SCs in culture[41]. ADSCs support a robust neurite response[38] and myelinate DRG neurites *in vitro*[62]. When used in animal models, they may be superior to both SCs and mesenchymal cells for regeneration through a fibrin conduit[63]. They have also demonstrated efficacy in improving recovery in both acute and chronic sciatic denervation injury paradigms in rodents[62,64].

One benefit of ADSCs for clinical translation is the relative abundance of adipose tissue for harvest. In this regard, human adipose-derived mesenchymal cells obtained from abdominal fat improve recovery metrics when injected into a murine sciatic crush model, including the Sciatic Functional Index (SFI), and walking track analysis. Remarkably, these cells were injected systemically (IV) in this study, and were found to localize at the area of injury[65]. As a counter point, it would seem that mesenchymal cells derived from human adipose tissue may not maintain their SC-like phenotype for long when withdrawn from the permissive *in vitro* cocktail of mitogens and growth factors, as recently demonstrated in a study by Faroni et al[66]. Adult adipose mesenchymal cells also have known limitations in terms of senescence and donor-age dependent efficacy, making their specific clinical indications the subject of future research.

3. Amniotic Mesenchymal Stromal Cells (AMSCs)

Amniotic mesenchymal stromal cells (AMSCs) are derived from the avascular amniotic mesoderm, and are relatively non-immunogenic cells[67-70]. Because of this, their membrane has been investigated as a cellular scaffold both *in vivo*[71] and *ex vivo*[67]. Recently, the *in toto* amniotic membrane has been differentiated towards a SC phenotype and proposed as a scaffold alternative to autograft repair[72]. AMSCs have been compared against ADSCs in a sciatic nerve crush model, and were found to be better at improving electrophysiologic and functional recovery at 4 weeks post-injury[73]. Interestingly, the AMSCs markedly improved the overall perfusion vascularity of the injured sciatic nerve distal to the crush (Figure 1), in keeping with their known angiogenic profile[74].

AMSCs are an interesting candidate for human transplantation experiments, with their demonstrated ability to graft effectively into non-autologous environments[75,76]. Such bio-compatibility may enable allograft cell banks to be developed for immediate human use, without the need for post-transplantation immunosuppression.

4. Umbilical Cord Mesenchymal Cells

The umbilical cord is a potent source for mesenchymal stem cells, both from the Wharton's jelly[77,78] and umbilical cord blood[79-83]. These are multipotent cells that are likely of two distinct populations; one with a propensity to differentiate into neuronal ectodermal phenotypes, and another with a mesodermal lineage production[79]. These cells have been previously shown to express pluripotent stem cell markers such as Oct4, Nanog, Sox2, ABCG2, and the neuro-ectodermal marker nestin[79]. There are several potential advantages to the use of these cells which include: (1) the ease of accessibility; (2) the fact that they are immunologically inert; (3) their use bears no ethical considerations; and (4) they possess a low probability of resulting in graft versus host disease[83,84].

As peripheral nerve regeneration support cells, the therapeutic potential of human umbilical cord blood-derived stem cells (hUCBDSCs) has been investigated in studies of cavernous nerve injury, recurrent laryngeal nerve injury, optic nerve injury, and sciatic nerve injury[85-89], all with varying degrees of success. hUCBDSCs were shown to improve recovery from a rat sciatic nerve crush injury, with improved SFI over non-injured controls as well as increased expression of both BDNF and TrkB receptor mRNA. Wharton's jelly derived umbilical mesenchymal cells also seem to improve recovery from rodent sciatic nerve crush, showing improvements in SFI, myelin histology, and sensory hindlimb function[78].

5. Dental Pulp Stem Cells (DPSCs)

Thought to be an embryological derivative of the cranial neural crest[39,90], human dental pulp houses a progenitor mesenchymal population that easily differentiates into both a neural and a SC phenotype *in vitro*[91-93]. First described by Gronthos in 2000, DPSCs are self-renewing, and express numerous stem cell markers such as CD29, CD90, CD271, nestin, glial fibrillary acidic protein (GFAP), and do not express hematopoietic markers[94-97]. These cells have been shown to be able to differentiate into numerous tissue types, including neurons[98], myoctes[99], hair follicle cells[100], and hepatocytes[101]. However, previous research has shown that these cells are susceptible to cellular senescence, and that they secrete toxic factors to adjacent tissues when they develop this phenotype[102].

DPSCs have been used in experimental models of optic nerve injury, where they have been shown to promote neurotrophin mediated retinal ganglion cell (RGC) survival, and axonal regeneration following optic nerve injury[103]. When co-cultured *in vitro* with DRG cells, DPSCs displayed increased survival, neuritogenesis, and myelination when compared to undifferentiated DPSC cultures[104,92]. These cells also demonstrate myelinating capacity and improve functional recovery from rodent sciatic

nerve transection[105]. They have been shown to counterbalance peripheral nerve injury-induced oxidative stress and neuro-inflammation[106]. Interestingly, these cells may have their regenerative effects seen in crush injury enhanced by application of an external pulsed electromagnetic field[107]. Clinically, wisdom teeth may one day be a potential source of autologous donor for this particular type of stem cell to be used in treatment of peripheral nerve injuries.

6. Skeletal Muscle-Derived Stem Cells (Sk-SCs)

Isolated skeletal muscle-derived stem cells (Sk-SCs) obtained from skeletal muscle satellite cells are able to differentiate into multiple lineages including myogenic, adipogenic, osteoblastic, neuronal, and glial[42,108-110]. These cells therefore display a clonal productivity somewhere on the spectrum between ectodermal and mesodemeral[111].

In a murine model of a long nerve gap injury using an acellular scaffold, Sk-SC seeded grafts demonstrated improved histomorphological metrics of recovery versus control grafts. These cells formed SCs as well as cells of both the endo and perineurial architecture, suggesting that Sk-SCs may help in forming co-ordinated regeneration by being able to reconstitute the muscle-nerve-blood vessel unit[112]. Interestingly, the same research group also used human derived Sk-SCs in a murine sciatic graft model with similar positive results in both histological parameters as well as metrics of tibial muscle health[113].

7. Olfactory Ensheathing Cells (OECs)

This cell class originates as the myelinating cell of the olfactory bulb in fetal development[114]. These cells have demonstrated an ability to respond to injury by secretion of an extensive array of neurotrophins[115], and also act as the primary phagocytic cell of the olfactory bulb[116], clearing debris and bacteria alike[117].

Olfactory ensheathing cells (OECs) have shown great promise in restoring function and improving histological injury parameters in animal models of spinal cord injury[118-122], and they remain one of the few cell types to be utilized experimentally in clinical human spinal cord injury[123,124]. However, their utility in peripheral nerve injury remains less clear; although they integrate and may improve function after rat sciatic nerve injury[125], their efficacy in doing so may not be on par with transplanted SCs[126].

8. Hair Follicle-Associated Pluripotent Cells (HAPs)

Hair follicle-associated pluripotent cells (HAPs) are nestin expressing cells which reside in the hair follicle and are thought to be intimately involved in the formation of the hair follicle sensory nerve[127]. They are pluripotent and can differentiate into cells of both glial and neuronal lineage[128], as well as smooth muscle myocytes, keratinocytes, and melanocytes[129-131]. One challenge is that HAP cells remain pluripotent in regenerative models, transforming into both neurons and glia *in vivo*[132]. This presents a significant problem for the translatable utility of these cells clinically. It is speculated that the skin-derived precursor cell (SKP) may be one of the early fates of the HAP[133].

Newly regenerated axons from explanted hair follicles are highly enriched in HAP cells *in vitro*, with their primary *in vivo* function thought to be the caretaking of the hair follicle sensory nerve[127]. One study showed that HAP cells appear to incorporate into the regenerating microenvironment of a sciatic nerve transection injury, though robust quantitative evidence of improved regeneration was not present[134]. Further investigation into seeding HAP cells in polyvinylidene fluoride membranes for a sciatic gap injury also demonstrated good incorporation at the injury site. However, there was no additional evidence of functional benefit in walking track analysis over controls[132].

9. Neural Crest Stem Cells (NCCs)

Neural crest stem cells (NCCs) originate in embryological development as migratory progenitors that initially appear between the neural and surface ectoderm at approximately embryologic day eight[112,135]. These cells maintain their multi-potency during and after migration.[136] NCCs have been identified in both embryonic and postnatal adult tissues, including bone marrow, dorsal root ganglion (DRG), carotid body, cornea, gut, heart, sciatic nerve, and skin[137]. Neural crest cells present a promising strategical intervention for nerve repair given that they are the parent population to several peripheral nervous system lineages, including immature SC-like cells[138].

NCCs that were differentiated from human embryonic derived support cells (hESC) were shown to incorporate well into a murine model of sciatic nerve repair and convincingly demonstrate histological benefit over non-treated nerves, with more robust nerve diameter and myelination demonstrated in cell treatment groups[139]. Interestingly, medium from differentiated NSCs enhances outgrowth of dorsal root ganglion (DRG) neurites *in vitro*, while at the same time convincingly demonstrating improved regeneration of NCC/scaffold assisted sciatic nerve repair on par with a SC assisted cohort (Figure 2)[138]. Of note, these cells were derived from human embryonic stem cells, suggesting their efficacy in rodent models of peripheral nerve regeneration.

10. Skin-derived Precursor Cells (SKPs)

First isolated and characterized by Toma et al.[140], skin-derived precursor cells (SKPs) originate in dermal papilla and readily differentiate into neurons and glia, as well as smooth muscle cells[40]. Early work demonstrated the efficacy of the SKP in assuming a SC lineage (SKP-SC) when exposed to the proper mitogens[40], and extensive work has followed to investigate the role of the SKP-SC in peripheral nerve repair[141,142,27,143]. SKP-SCs have proved beneficial in sciatic nerve repair with acellular nerve grafts[142], and a delayed cross re-innervation paradigm also demonstrated an ability to improve

regeneration after chronic denervation[27]. We have previously injected lentiviral enhanced blue fluorescent protein (BFP) SCs into *Thy-1* green fluorescent protein (GFP) rats who underwent doxorubicin-induced focal myelination[144]. Our group has shown that these cells may aid regeneration through growth factor production[27], debris clearance[145], and myelination[146,144,147] (Figure 3).

In one experiment, SKP-SCs were impressively shown to improve behavioral recovery even from acute transection repair[145]. Skilled locomotor assessments such as ladder rung and tapered beam were seen to be improved in animals administered SKP-SCs after acute, chronic, and nerve graft repair[145] In addition, it has recently been shown that SKP-SC action may in part involve their local immunomodulatory effect on both neurites and macrophages, which appears to be mediated by an IL-6 dependent mechanism[148]. As a cell for translational therapy, SKP-SCs seem quite promising. Human SKP-SCs are able to be produced by differentiation of human induced pluripotent stem cells[149], while the practical expansion of clinically relevant numbers of SKP-SCs has been shown to be possible through the use of bioreactors[143].

Current State of Clinical Translation

Recent years have seen tremendous progress in precursor and stem cell biology and its application in the treatment of various neurological disorders. Clinical trials in the United States have evaluated the regenerative benefits of stem cells in the context of multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), Duchene muscular dystrophy (DMD), traumatic spinal cord injury, and other disorders of the nervous system[150,35,124]. Unfortunately, there are very few clinical trials examining the use of stem cells in the clinical treatment of peripheral nerve pathologies[151], and none specifically investigating the neuroregenerative benefits of stem cells following traumatic peripheral nerve injury[35].

While the neuroprotective and regenerative potential of stem cells in the repair of peripheral nerves has been demonstrated in both a number of *in vitro* and *in vivo* animal models, it is currently unclear when widespread clinical implementation of stem cell therapies will become a reality. Of note, none of the cell based approaches has shown clear superiority to another, and few pre-clinical studies have attempted to compare one cell type with another[152]. The literature is also limited by the lack of data on the clinical safety and efficacy of stem cell-derived therapies, with no long-term reports currently available. The clinical use and early promise of autologous SC therapies in clinical nerve repair[153,154] suggest that cell types that can be readily pre-differentiated *in vitro* to SCs (such as SKPs) or demonstrate transdifferentiation to SCs *in vivo* (such as BMSCs and ADSCs) may have the highest potential for clinical success. Levi and colleagues from the University of Miami have recently published two papers detailing the first in human use of autologous SCs to supplement sciatic nerve repair[153,154]. In these groundbreaking studies, two patients were enrolled in an FDA-approved trial to assess both the safety and ability of autologous cultured SCs to enhance regeneration through sural nerve autografts. Long-term follow up in both patients demonstrated nerve graft patency, absence of tumor formation, and significant improvements in both sensory and motor impairments compared to pre-operative values[154].

Although these initial clinical studies are encouraging, more rigorous studies examining stem cell stability, differentiation, and migration patterns are required before clinical safety is definitively established[155]. Metrics that accurately characterize the clinical efficacy of stem cell-based therapies must also be identified. Current peripheral nerve stem cell literature exhibits wide variability in animal models, nerve injury type, stem cell source, differentiation protocols, cell delivery methods, and assessment of nerve regeneration. In particular, variations in the timing of diverse outcome measures

between different stem cell treatment modalities make specific treatments difficult to assess[35,37]. These inconsistencies make it extremely difficult to establish clear conclusions about efficacy or safety in a clinical population. In addition, ethical considerations are a necessity when translating research from the bench to bedside. Furthermore, governmental restrictions and regulations may negatively affect the speed of translation of stem cell therapy into clinical practice[156-158]. Strategies to manipulate cells using genetic and viral transduction approaches *in vitro* to potentially enhance their effect *in vivo* (as recently reviewed[159]), raise additional regulatory considerations. Nevertheless, the evidence presented in this review suggests an optimistic future for stem cell-based approaches to traumatic peripheral nerve damage, though continued high quality research is essential for bench to bedside translation. Our opinion is that approaches that use stem and precursor cells akin to a SC phenotype have the greatest potential for clinical translation.

Conclusion

Peripheral nerve injuries remain a common problem with unsatisfactory functional outcomes following standard therapeutic interventions. Several stem cell-based therapies have been investigated in both *in vitro* and *in vivo* experiments to positively modulate the regenerative milieu following nerve injury. These advancements represent an optimistic future for stem cell-based approaches in enhancing regeneration and functional recovery following nerve injury.

Abbreviations

Adipose-derived Stem Cell	-	ADSC
Alzheimer's Disease	-	AD
Amniotic Mesenchymal Stromal Cell	-	AMSC
Amyotrophic Lateral Sclerosis	-	ALS
Blue Fluorescent Protein	-	BFP
Bone Marrow Stromal Cell	-	BMSC
Brain-derived Neurotrophic Factor	-	BDNF
Ciliary Neurotrophic Factor	-	CNTF
Dental Pulp Stem Cell	-	DPSC
Dorsal Root Ganglion	-	DRG
Duchene Muscular Dystrophy	-	DMD
Glial-cell Line Derived Neurotrophic Factor	-	GDNF
Glial-growth Like Factor	-	GGF
Green Fluorescent Protein	-	GFP
Hair Follicle-Associated Pluripotent Cell	-	HAP
Hepatocyte Growth Factor	-	HGF
Human Embryonic-derived Support Cell	-	hESC
Human Umbilical Cord Blood-derived Stem cell	-	hUCBDSC
Insulin-like Growth Factor	-	IGF
Interleukin-6	-	IL-6
Multiple Sclerosis	-	MS
Nerve Growth Factor	-	Nerve Growth Factor
Neural Crest Stem Cell	-	NCC
Neuroregulin-1	-	Neuroregulin-1
Olfactory Ensheathing Cell	-	OEC
Retinal Ganglion Cell	-	RGC
Schwann cell	-	Schwann cell
Sciatic Functional Index	-	SFI

Skeletal Muscle-derived Stem Cell	-	Sk-SC
Skin-derived Precursor Cell	-	SKP
Tyrosine Kinase B	-	TrkB
Vascular Endothelial Growth Factor	-	VEGF

Figure Legend

Figure 1. Amniotic membrane-derived mesenchymal stem cells (AMMs) transplantation augments blood perfusion. **A.** Representative pictures of blood perfusion in the sciatic nerve. Blood perfusion was performed at 4 weeks following the initial operation using Laser Doppler perfusion imaging (LDPI) **B.** Quantitative analysis by using LDP perfusion imaging. AMMs significantly improved blood perfusion compared to adipose-derived mesenchymal stem cells (ADM) and phosphate-buffered saline (PBS). **P < 0.01, *P < 0.05; n = 9 per group. (excerpted from Li et. Al, 2014[73]).

Laser Doppler perfusion imaging (LDPI) Blood perfusion was measured at 4 weeks after the operation as previously described [14]. Briefly, the mice were anaesthetized and placed on a heating blanket to maintain a

constant temperature. The nerves were exposed by using blunt dissection and scalpel incision. The blood flow in the sciatic nerve was examined by using LDPI (Moor Instrument, Wilmington, Delaware).

Figure 2. Differentiated neural crest cells (NCCs) enhance in vivo sciatic nerve regeneration. **A-P.** Immunohistochemical and histological analyses of longitudinal sections through transplanted biodegradable conduits seeded with control rat (a–d) Schwann cells, (e–h) human embryonic stem cells (hESCs), or (i–p) differentiated NCCs. Dashed lines mark the walls of the conduits. Asterisks represent the site of nerve transection and the beginning of the regeneration front. **Q.** Axon profile numbers beginning 1 mm distal to the proximal stump. The data represent the mean ± SD of five independent measurements from each animal and condition. Scale bars: (a, e, i, and m) 500 μm, (b, f, and j) 200 μm, (c, g, k, and n) 200 μm; (d, h, and l) 50 μm, and (o–p) 20 μm. The p values are denoted as follows: ns = not significant; **p ≤ .01, ***p ≤ .001, ****p ≤ .0001. HNA = human nuclear antigen; SC = Schwann cells (adapted from Jones et al., 2018[138]).

Figure 3. Lentiviral enhanced blue fluorescent protein (BFP) SCs injected into *Thy-1* GFP rats who underwent doxorubicin-induced focal de-myelination of the tibial nerve. Presented are high-magnification intra-vital images of BFP-positive SKP-SC myelination, including a 3-channel unmixed spectral image demonstrating live *in-vivo* myelination by SKP-SCs 27 days post-doxorubicin tibial nerve injury, 19 days after cell injection. **A.** GFP axons. **B.** Nile red myelin. **C.** BFP Schwann cells. **D.** Merge image; the arrow indicates a probable node of Ranvier, as evidenced by BFP-positive cytoplasm crossing the axon, likely in loosely packed paranodal myelin (adapted from Grochmal et al.2018[144]).

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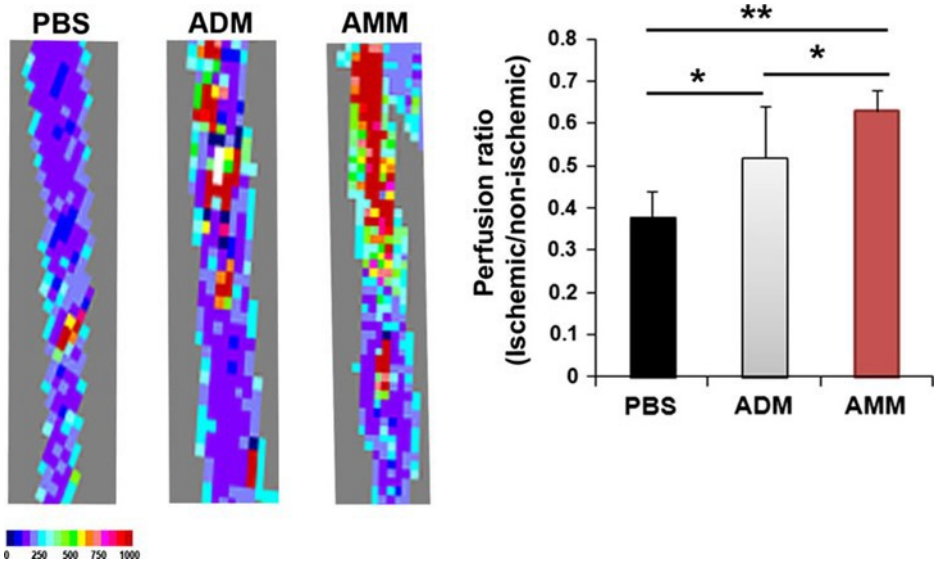

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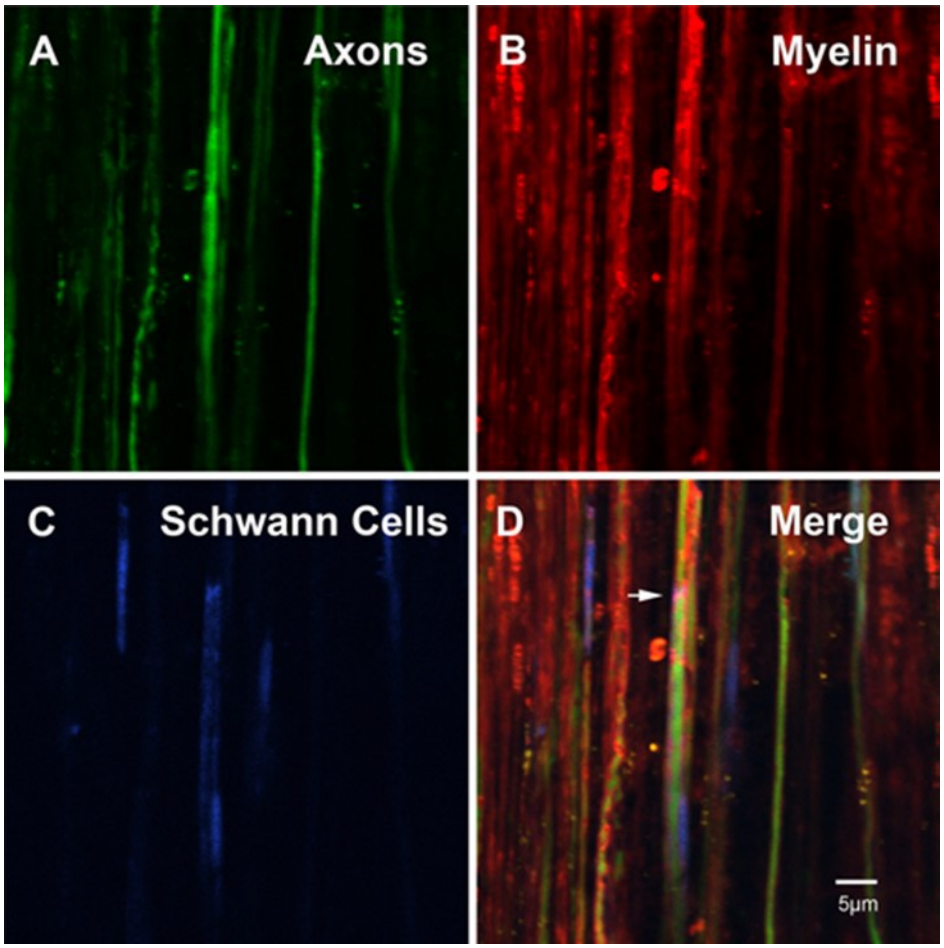

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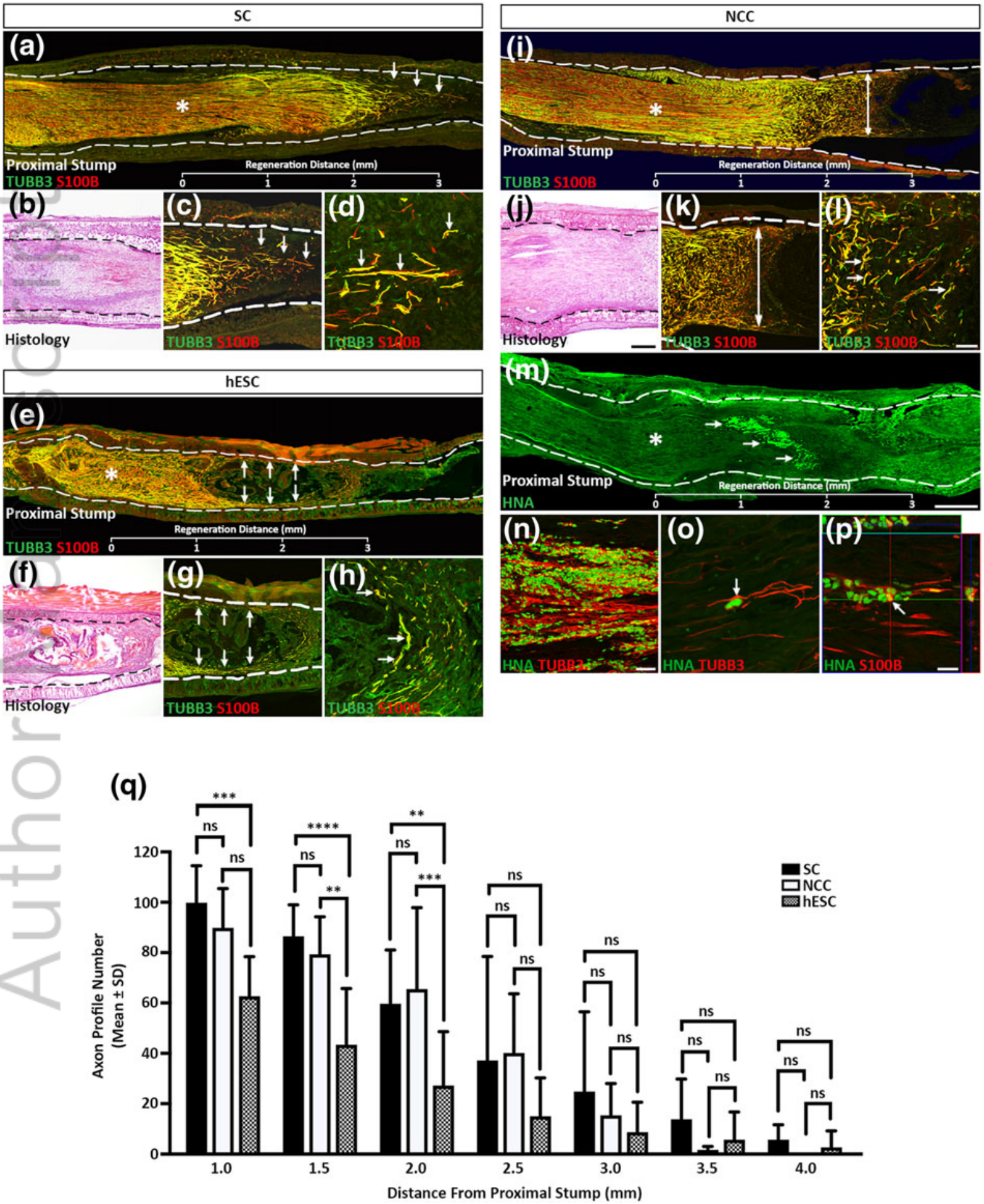

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Cheers,

Steve

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Date: Thu, Oct 31, 2019 at 8:27 AM
Subject: Fwd: Permission for article reuse
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Cc: Rajiv.Midha@albertahealthservices.ca <Rajiv.Midha@albertahealthservices.ca>, stevekemp.phd@gmail.com <stevekemp.phd@gmail.com>, Margie Shreve <margieshreve@thejns.org>, Sam Geouge <samanthageouge@thejns.org>

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Sincerely,

Gillian

Gillian Shasby | Director of Publications
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>
> Dear Margie, can you assist Joey Grochmal with the request for permission below.
> Thanks,
> Raj
>
>
> Rajiv Midha, MSc, MD, FRCSC, FAANS, FCAHS
> Professor and Head, Department of Clinical Neurosciences
> Calgary Zone, Alberta Health Services

> Scientist, Hotchkiss Brain Institute
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> Cheers,
>
> Steve
>
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> From: Joey <joeygrochmal@gmail.com<mailto:joeygrochmal@gmail.com>>
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>
> Warm regards,
> Joey Grochmal
>
>
> --
> Stephen W.P. Kemp, Ph.D
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Table 1

Stem Cell Type	Cell Description	Mechanism	Observed Outcomes	Notes	Animal Models
Bone Marrow Stromal Stem Cells (BMSCs)	Mesenchymal, multipotent	• Adopt Schwann cell phenotype[24] • Secrete neurotrophins[41-42]	• Improved walking track scores, wet muscle weights and increased axonal counts[41]	• Require an invasive procedure for autologous harvesting	• Rodent[41,43-44,48] • Rabbits[50] • Primate[45,51]
Adipose-Derived Stem Cells (ADSCs)	Mesenchymal	• Adopt Schwann cell phenotype[34] • Produce mRNA for growth factors[37]	• Improved myelination[57] • Promote neurite outgrowth *in vitro*[34] • Improved talking track scores[60]	• Available via minimally invasive harvesting with high cellular yield • Donor-age dependent efficacy	• Rodent[57,59]
Amniotic Mesenchymal Stromal Cells (AMSCs)	Mesenchymal	• Adopt Schwann cell phenotype[67]	• Improved functional recovery compared to ADSCs[68] • Exhibit strong angiogenic potential[69]	• Low immunogenicity[62-65] • Graft effectively in non-autologous environments[70-71] • Easily obtained without need for invasive procedure	• Rat[66] • Mouse[68-69]
Umbilical Cord Mesenchymal Cells	Mesenchymal, multipotent	• Adopts Schwann cell phenotype • Secretes neurotrophins	• Increased expression of neurotrophin receptor mRNA • Improved sciatic functional index scores, improved myelination, and sensory hind limb function[72]	• Likely of two distinct cell populations	• Rabbit[84] • Rat[81-83]

Dental Pulp Stem Cells (DPSCs)	Mesenchymal	• Adopts both neuronal and Schwann cell phenotypes[87-88]	• Improved myelination • Improved functional recovery[88]	• Wisdom teeth are potential source[90-91]	• Rat[89,98] • Mice[90,94]
Skeletal Muscle Derived Stem Cells (Sk-SCs)	Mesenchymal	• Capable of differentiating into multiple cell lineages[38,103-105]	• Improved histomorphic metrics of recovery	• Derived from satellite cells in skeletal muscle	• Rodent[107]
Olfactory Ensheathing Cells (OECs)	Neural Crest Derived	• Secretes neurotrophins[110] • Phagocytic[111-112]	• Improved histological parameters in spinal cord injury[113-117]	• Myelinating cell of the olfactory bulb in fetal development	• Rodent[113-117,120] • Canine[118] • Human[119]
Hair-Follice-Associated Pluripotent (HAP) Cells	Pluripotent	• Capable of differentiating into multiple cell lineages[122-126]	• Incorporation of cell at nerve injury site[129] • Quantitative evidence of improved regeneration NOT present[129]	• Cells reside in hair follicle • Thought to be involved in the formation of hair follicle sensory nerve	• Mice[127]
Neural Crest Stem Cells (NCCs)	Pluripotent	• Capable of differentiating into multiple cell lineages	• More robust nerve diameter[131] • Improved myelination[137] • Promote neurite outgrowth *in vitro*[34]	• Originate in embryological development between the neural and surface ectoderm[107,130]	• Rodent[108]
Skin-Derived Precursor Cells (SKPs)	Neural Crest Derived	• Capable of differentiating into multiple cell lineages[36] • Adopts Schwann cell phenotype[36] • Produces growth factors[27] • Phagocytic[141]	• Improved behavioral recovery[137] • Improved myelination[138-140] • Immunomodulatory effects[141]	• Originate in dermal papilla	• Rats[27,33,137,140]