Peripheral Nerve Healing: So Near and Yet So Far

Aslan Baradaran, MD, MSc[1] Hassan El-Hawary, MD, MSc[1] Johnny Ionut Efanov, MD, PhD, FRCSC[2] Liqin Xu, MD, MSc, FRCSC[1]

[1] Division of Plastic and Reconstructive Surgery, Montreal General Hospital, McGill University, Montreal, Quebec, Canada
[2] Division of Plastic and Reconstructive Surgery, Centre Hospitalier de l'Université de Montréal, Montreal, Quebec, Canada

Address for correspondence Liqin Xu, MD, MSc, FRCSC, Division of Plastic and Reconstructive Surgery, Department of Surgery, Montreal General Hospital, 1650 Cedar Avenue L9-317, Montreal, Quebec, H3G 1A4, Canada (e-mail: liqin.xu@mcgill.ca).

Semin Plast Surg 2021;35:204–210.

Abstract

Peripheral nerve injuries represent a considerable portion of chronic disability that especially affects the younger population. Prerequisites of proper peripheral nerve injury treatment include in-depth knowledge of the anatomy, pathophysiology, and options in surgical reconstruction. Our greater appreciation of nerve healing mechanisms and the development of different microsurgical techniques have significantly refined the outcomes in treatment for the past four decades. This work reviews the peripheral nerve regeneration process after an injury, provides an overview of various coaptation methods, and compares other available treatments such as autologous nerve graft, acellular nerve allograft, and synthetic nerve conduits. Furthermore, the formation of neuromas as well as their latest treatment options are discussed.

Keywords
- peripheral nerve
- injury
- repair
- review

Peripheral nerve injury (PNI) is a common condition that often affects a younger and otherwise healthy individual, with 83% of the patients being under 55 years old and an equal male to female ratio.[1] It is estimated that approximately 5% of all patients admitted to a Level I trauma center have a PNI.[2] Common etiologies include penetrating trauma, crush, ischemia, and traction, while injuries from electric shock and vibration are less frequent.[3] Their typical symptoms are sensory/motor function deficits that could result in the development of intractable neuropathic pain, with devastating impacts on patients' quality of life. Multiple factors predict the outcome after a peripheral nerve repair including age, gender, materials utilized, repair time, type of nerve injured, defect size, and duration of follow-up.[4]

The peripheral nervous system has regenerative potential. However, for optimal healing to occur, an appropriate environment must be provided physiologically or surgically. In this article, we review the peripheral nervous system response to injury, and discuss surgical repair options and their applications.

Peripheral Nerve Injury Classification

Classically, after a focal injury to the peripheral nerve, one of two consequences to the axon is observed: conduction block or axonal degeneration.[5] In the former, the axon remains anatomically intact; the conduction of action potentials is blocked in the zone of injury, while it persists distal to it. In this case, if the underlying cause (i.e., ischemia, traction) is removed, spontaneous recovery is expected. On the other hand, in a nerve transection, axonal degeneration happens through Wallerian degeneration,[6,7] a rapid and active process which takes place in the distal nerve stump secondary to separation of the nerve axon from its cell body. Nerve recovery in a degenerative lesion depends on the basal lamina preservation. In other words, if the basal lamina remains intact, the proximal axon may grow in an organized fashion into the distal tube once the insulting injury is eliminated. However, when there is an interruption in the basal lamina, spontaneous regeneration will not be organized or may not occur at all.

In 1943, Seddon et al proposed three fundamentally distinct groups of PNIs. He coined the terms neurapraxia, axonotmesis, and neurotmesis. Neuropraxia refers to a nerve conduction block, axonotmesis refers to a degenerative injury with an intact continuous basal lamina, and neurotmesis indicates nerve injury leading to disruption of the basal lamina.[8] In 1951, Sunderland[9] refined this classification and introduced five types of PNI based on increasing

Issue Theme Healing, Inflammation, and Fibrosis; Guest Editor: Joshua Vorstenbosch, MD, PhD, FRCSC

Thieme Medical Publishers, Inc., 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA

DOI https://doi.org/10.1055/s-0041-1731630.
ISSN 1535-2188.

Table 1 Classification of nerve injuries

Seddon	Sunderland	Injury	Recovery	Need for surgical repair
Neuropraxia	Type 1	Focal demyelination and conduction block. No WD	Complete	No
	Type 2	Axonal discontinuity + WD	Complete - up to 12 wk	No
Axonotmesis	Type 3	Axonal and endoneurial disruption + WD	Partial - up to 12 wk	Yes/No
	Type 4	Perineurial rupture with fascicle disruption + WD	None	Yes
Neurotmesis	Type 5	Nerve truck discontinuity + WD	None	Yes
	Mackinnon Type 6	Mixed	Some	Yes

Abbreviation: WD, Wallerian degeneration.

severity of damage to the nerve structure. Mackinnon and Dellon[10] introduced a sixth injury pattern that combines any of the Sunderland's classes and therefore variable degrees of recovery is witnessed (►**Table 1**). A Type 2 or greater Sunderland PNI presents a diagnostic and decision-making challenge, as Wallerian degeneration and subsequent nerve scarring begins within 48 to 72 hours following injury.[11,12] For a nerve to fully regenerate, axons are required to grow in an antegrade fashion within the endoneurial tube. However, in the presence of excessive intraneural fibrosis, normal neural migration and growth can be delayed or diverted.[11,13]

While crush and traction injuries may leave nerves in continuity, penetrating injuries can be more complex. They can present as isolated nerve transection, or be associated with crush and traction. These mixed lesions may obscure the diagnosis. While Sunderland introduced an elaborate system of classifying injury, clinically, it is simpler to categorize the injury to "degenerative" and "nondegenerative," as this is the more important question that should be initially answered by the peripheral nerve surgeon.

Repair Cascade

When the continuity of a peripheral nerve is interrupted, its distal and proximal ends retract, and Schwann cells in both stumps orchestrate an inflammatory response that clears the debris and begins the process of neuronal remodeling.[14]

Proximal to the injury, Schwann cells de-differentiate and transform from a myelinating supporting role to a progenitor-like cell and become repair cells.[15] These cell changes, characterized by the downregulation of the myelin protein, and upregulation of growth-promoting factors,[16–18] are triggered by the injury signal[19] or by axonal signal loss.[20] A retrograde signal is sent to the nucleus to stimulate the transcription factors in the injured neuron.[21] In particular nerves, the length of axons presents a special challenge, as these signals have to travel more than 50 cm to reach the nucleus.[20]

On the other end, tube-like structures (bands of Büngner) are formed at the distal stump, which act as "channels" to direct the regenerating axons back to their original targets. In the case of a transection, however, guidance of axons into the bands of Büngner will be more complex.[22] The two stumps are joint by a "bridge" of inflammatory cells and matrix,[23] which does not provide sufficient directional capacity for axonal regrowth. Schwann cells become responsible for guiding the axons across this bridge region.[24] While Schwann cells from both proximal and distal nerve stumps migrate until they bridge the gap, Schwann cells from the proximal stump attract the growing axons. Fibroblasts organize this migration at the wound level, via ephrinB/EphB2 signaling, which gives Schwann cells an adhesive behavior necessary for their orchestrated migration.[24] Macrophages respond to the hypoxia created within the bridge and secrete vascular endothelial growth factor A, which triggers vascularization within the bridging zone.[23] This neovascularization acts as tracks, guiding Schwann cells to cross the bridge, directing the sprouting axons to the distal stump. With vascularization begins a crucial part that guides Schwann cell migration; when this system is disrupted, the blood vessels may misdirect Schwann cells to grow into surrounding tissues, and suboptimal healing inevitably occurs.[23,24]

Muscle Reinnervation and Motor Unit Territories

Cross-section of motor nerves branching is similar to cross-section of a tree and its roots. Motor nerves begin to branch within the intramuscular nerve sheath of their destined skeletal muscle.[25] This branching takes the nerve to various muscle fascicles. Motor units are territories of all muscle fibers that are innervated by one motor neuron. These spatial territories specify the number of muscle fibers reinnervated by a nerve after injury.[26–28] The number of muscle fibers in each motor unit has a direct correlation with the size of the

unit territory; in a muscle cross-section, this territory can take up to 30% of the surface area.[26]

If reinnervation is provided shortly postinjury, motor units will not significantly reduce in number.[15] On the other hand, if a muscle suffers from prolonged denervation, the number of motor units will drastically drop, affecting the structure and function of the reinnervated muscle.[29] In chronic denervation, the intramuscular portion of the nerve sheath can no longer support the regenerating axons.[15] Other contributing factors have been recognized, namely reduced number of Schwann cells and failure to maintain their regenerative role, disintegration of muscle spindles,[30] irreversible atrophy, and muscle fiber necrosis.[31,32] All these factors contribute to unsatisfactory functional recovery.

Functional Recovery after Nerve Injury

A functional recovery signifies a nerve has regained its physiologic state preinjury. This is largely dependent on three major factors: reinnervation of the end organ, timing of the injury, and distance to target organ.

To facilitate reinnervation, a nerve repair must primarily guide the regenerating axons to their original endoneurial tubes.[33] Motor and sensory nerves can find their correct path to a motor unit or sensory dermatome, respectively. Despite this capacity, motor fibers occasionally fail to follow their respective pathway and, consequently, fibers never meet the preinjury target organ.[34] This misdirection can happen even after surgical repair of a nerve, which poses a major long-term functional deficit.[35,36]

Although sensory nerves reinnervate their specific organs, it is unlikely for them to reach their original mechanoreceptor. With a portion of healing consisting of misguided afferent fibers, misinterpretation of tactile stimuli and poorly localized sensation may occur. This is observed in patients with severe brachial plexus injury, in particular patients who report "wrong-way" sensation.[37] Similarly, the efferent motor fibers may reinnervate a different muscle. This has a particular clinical importance following complete transection of large mixed sensory and motor nerves. Random reinnervation was observed in patients' hand muscles after surgical approximation of a transected ulnar nerve at the wrist, and result in simultaneous antagonistic muscles contractions.[38]

While the regeneration of sensory nerves can still happen with delayed repairs over months to years,[39] the timing of reinnervation is particularly important for motor nerves, as the regenerated nerve must make contact with its denervated target (i.e., motor endplate) in a timely manner.[15,40] In motor nerves, a significant delay in regeneration becomes a major challenge to functional recovery.[15,40,41] In chronic denervation, newly generated axons approach the motor endplate of the target muscle, but cannot form functional connections or synapses.[42] This is possibly due to the irresponsive Schwann cells in the end plate that no longer support reinnervation. This is observed clinically in patients with complete brachial plexus palsy with almost no functional recovery in repairs delayed beyond 12 months following injury, whereas patients with an operative delay of 6 months or less have significantly better return of biceps function.[43] Delayed presentation further complicates the clinical assessment and decision-making for the appropriate treatment course. The current consensus is that if reinnervation is not expected to have occurred within 12 to 18 months postinjury, the neuromuscular junctions degenerate, precluding any future reinnervation.[3,44–47] It is generally recommended to consider functional reconstruction for patients presenting after this cutoff and to avoid nerve repair since reports have clearly demonstrated its dismal outcomes.[48] The distance to target organ reinnervation goes hand-in-hand with the timing of reinnervation and plays another important role in functional recovery. Axons regenerate at a relatively constant rate of 1 mm per day, or one inch per month, and usually can be followed clinically with an advancing Tinel sign.[49] Hence, in a proximal motor nerve injury (e.g., above-elbow ulnar nerve laceration) where the distance to motor target reinnervation exceeds the estimated 12 months period, other strategies such as distal baby sitter nerve transfers (e.g., anterior interosseous to distal ulnar nerve transfer) may be needed to maintain muscle stimulation pending reinnervation from the proximal original nerve repair.[50] Alternatively, a functional distal nerve transfer (e.g., Oberlin transfer) can be employed to restore a specific motor deficit.[51] Specific well-documented examples of functional transfers form a whole topic on its own, and are beyond the scope of this article.

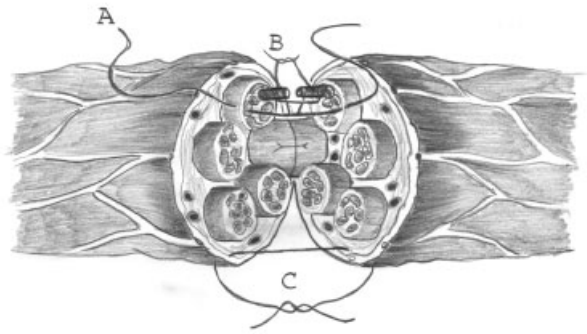

Fig. 1 Schematic presentation of proximal and distal nerve stumps: (**A**) grouped fascicular repair, suture coapting the corresponding a group of fascicles using the perineurium; (**B**) fascicular repair; and (**C**) standard epineural repair, stumps are aligned based on the anatomy of vessels.

Primary Nerve Coaptation

The ideal nerve repair occurs after trimming the proximal and distal nerve ends to healthy fascicular structures. The topographic anatomy must be restored to decrease the risk of aberrant reinnervation.[52] This can be achieved by realigning the vasa nervorum, and by visually identifying known fascicular groups within the nerve. Whenever possible, a tension-free, precisely aligned, and atraumatic primary neurorrhaphy is favored.[53,54] ►**Fig. 1** describes three main categories of primary direct nerve repair and their

subcategories. Although there is theoretical advantage of precisely realigning each fascicle in interfascicular neurorrhaphy, the formation of excessive internal scarring has proven to adversely affect the clinical outcome of such repair. Today, the epineural repair is the mainstay of primary neurorrhaphy.[55]

Fibrin glue is sometimes used instead of standard microsurgical suturing.[56,57] The first commercially available fibrin sealant was introduced in the 1970s, and since then, its use in nerve repair has increased.[58] Potential benefits of fibrin glue utilization are: shorter procedure time, reduced recovery time, possible barrier to invading scar tissue, minimal trauma and scarring, and subsequently decreasing fibrosis and inflammation.[56,59] The main disadvantage of this technique is its inferior holding strength.[58] Currently, most available studies are from animal models and a well-controlled human study is lacking. Most of this literature demonstrates similar clinical outcomes for fibrin glue and microsutures in small diameter peripheral nerve coaptations.[56,59–61] Fibrin glue can also be used as an adjunct to microsuturing to reduce the total number of sutures, thus theoretically reducing the chance of suture-induced fibrosis.[62,63] That being said, there is a dichotomy in the evidence, while some works show the ease of use and noninferiority of fibrin glue to suturing, others show that it can lead to an inflammatory response and a high degree of scarring. This paucity in strong literature and human studies, warrants further studies to better investigate their comparative efficacy.[64]

Even when optimal end-to-end microsurgical coaptation is done, scar tissue formation postoperatively can lead to excessive collagen deposition, fibrosis of the epineurium, and nerve compression that eventually impedes regeneration.[11] Pathophysiology of epineural scarring and compression are due to three main reasons: (1) vascular compromise, (2) tethering forces, and (3) direct nerve compression.[65] Few of the regenerating axons may escape the coaptation and create a neuroma.[45] To prevent this, nerve wraps were introduced to support repairs and minimize fibrosis and scarring. Wraps potentially offload tension from the repair site and distribute it across a larger length of the nerve. They can also act as a barrier and reduce axonal escape.[66] Currently, different nerve wraps are being utilized with autologous veins being the most common; mainly the great saphenous vein.[67] Several other types are namely: local and free flaps, autograft, allograft, and xenograft wraps. In a recent review, improvement in subjective and objective outcomes were drawn across all studies using vein autografts and despite a paucity of clinical and experimental data, many surgeons tend to use nerve wraps to protect the repair.[68]

Nerve Defects

To overcome a nerve gap and to achieve a tension-free repair, interpositional nerve grafts or conduits can be used. The gold standard for such a repair is an autologous nerve graft.[69] Nerve grafts can be single, cable, trunk, and interfascicular, to provide a proper size match with the recipient nerve.[62] The ideal donor is a dispensable nerve, salvaged from spare part surgery, or from an easily accessible sensory nerve that does not result in a critical sensory deficit. Common autograft donors include the sural nerve, medial antebrachial cutaneous nerve, and lateral antebrachial cutaneous nerve, with the sural nerve offering up to 40 cm of graft length from each leg.[70] When possible, an autograft 10 to 20% longer than the measured defect length should be harvested to ensure a tension-free repair and to avoid future shortening.[71]

While nerve repair using autografts is a valuable surgical reconstructive option, it can be limited by tissue availability, donor site morbidity, or when a major size discrepancy exists between the donor and recipient.[72,73] Alternatives to nerve autografts include the use of autologous or synthetic conduits, nerve allograft, and xenograft.

Nerve conduits guide and facilitate axonal regeneration across segmental nerve defects, mimicking the natural structure of the nerve pathway. Natural material such as skeletal muscle tissue or vessels,[74] nondegradable materials such as silicone, and more recently biodegradable materials such as collagen,[75] have been widely investigated. Autologous vein grafts impart minimal donor site morbidity, and serve as a conduit that facilitates cellular migration between the cut nerve ends, bridging gaps up to 3 cm.[76] The advantages of synthetic nerve conduits include no donor site morbidity and the elimination of donor size discrepancy. However, they are limited to the defect size, with defects >2 cm are better treated with autologous nerve grafting.[77] Processed allograft is a decellularized and sterile extracellular matrix obtained from human peripheral nerve tissue which requires no immunosuppressive therpay.[78,79] Clinical data support their use in noncritical nerve defects up to 5 cm.

Neuroma Formation

In situations where regenerating axons cannot successfully reenter the distal stump, the biologic response of the proximal stump leads to neuroma formation. This swelling of the terminal bulb of the proximal stump contains Schwann cells, fibroblasts, blood vessels, and most importantly, regenerating axons.

Severe neuropathic pain is normally not provoked if a main nerve fiber is cut sharply. Nonetheless, significant pain is almost always unavoidable after accidental damage to the terminal branch of the same type of cutaneous nerve. Some susceptible cutaneous sensory branches are: medial cutaneous nerve of the forearm, superficial radial nerve, sural nerve, and the long saphenous nerve. As the name implies, in complete neuromas (fully transected), the nerve trunk has been divided, whereas partial neuromas (neuroma in continuity) contain a portion of intact fibers.

The most commonly performed treatment of a neuroma is excision and anastomosis of the two ends.[80] Recent studies have compared various surgical options including: excision alone, traction neurectomy, excision and cap, excision and transposition, excision and repair with allograft or autograft,[81] and neurolysis and coverage, showing no superiority of one to another.[82,83] The current concept supports the shift to attempt to heal rather than hide the injured nerves.[84]

A neuroma that has no distal nerve stump for a reconstruction of the resected nerve segment with a graft can be treated with a regenerative peripheral nerve interface or targeted muscle reinnervation (TMR). The former involves wrapping the cut nerve end with a small free muscle graft, which allow nerve ingrowth and innervation. In TMR, the nerve stump is coapted to a small target motor nerve within a nearby muscle. In both modalities, the goal is to create a new functioning nerve–muscle interface for the transected nerve to innervate, thereby conferring it a new "job" to facilitate normal nerve healing and to prevent its dysregulated growth into a painful neuroma. TMR, in particular, has been shown in randomized controlled trials to decrease the incidence of postamputation neuroma pain and phantom limb pain compared with traditional traction neurectomy.[80]

Strategies to Enhance Nerve Healing

There are several strategies to improve functional recovery after a nerve injury. As previously mentioned, a distal babysitting nerve transfer was initially proposed by Terzis and Tzafetta.[85] To decrease the risk of muscle atrophy and endplate loss in a high motor nerve injury, the procedure utilizes an end-to-side neurorrhaphy between a healthy donor located close to the motor target and the distal injured nerve to rapidly restore efferent stimuli to the denervated muscles, thereby preventing irreversible atrophy. This method has multiple applications, for instance, ipsilateral hypoglossal to facial nerve transfer is performed with cross-facial nerve grafting, anterior interosseous nerve to distal motor branch of the ulnar nerve transfer is done with high ulnar nerve laceration repair, and many other.

Emerging evidence demonstrates accelerated axon outgrowth across injury sites with brief electrical stimulation.[86] Electrical stimulation of the injured nerve can enhance the functional recovery even after delayed surgical repair.[87] A more recent study also supported the accelerating effect of immediate electrical stimulation in TMR with daily stimulation right after denervation.[88] These promising findings anticipate more rigorous clinical studies regarding their practicality and application. If proven to be clinically successful, intraoperative and postoperative brief electrical stimulation may become the standard of practice.

Low-intensity pulsed ultrasound (LIPUS) has demonstrated some benefit in different therapeutic applications such as pseudarthrosis, bone fractures, and various soft tissue conditions.[89] Although further studies are required to clearly demonstrate clinical efficacy, there are some promising reports on animal models indicating that LIPUS use accelerates peripheral nerve regeneration.[90]

One of the most recent biologic agents administered to assist nerve regeneration is FK506, a Food and Drug Administration approved immunosuppressant. While FK506 has proven to enhance nerve regeneration, side effects of the systemically delivered FK506 has averted clinicians from its routine use. The current research is focused on developing innovative routes of local medication delivery such as using a fibrin gel matrix to significantly reduce the biodistribution, thereby reducing the chance of FK506 systemic toxicity.[91] Until this milestone is reached, its wide use in nerve repairs is unlikely.

Conclusion

During the last several decades, our knowledge of peripheral nerve pathophysiology has expanded drastically, and parallel to our refined microsurgical skills, we have discovered strategies to enhance its healing. We have become more consistent in achieving satisfactory reinnervation and functional outcomes in short nerve gap reconstructions, and recently have found new venues to repair larger defect. Future approaches should focus on new methods to improve the outcome in more challenging scenarios such as chronic injuries and delayed nerve repairs, for the aim of offering a better quality of life to a large portion of our trauma patients.

Conflict of Interest
None declared.

References

1 Taylor CA, Braza D, Rice JB, Dillingham T. The incidence of peripheral nerve injury in extremity trauma. Am J Phys Med Rehabil 2008;87(05):381–385
2 Noble J, Munro CA, Prasad VS, Midha R. Analysis of upper and lower extremity peripheral nerve injuries in a population of patients with multiple injuries. J Trauma 1998;45(01): 116–122
3 Robinson LR. Traumatic injury to peripheral nerves. Muscle Nerve 2000;23(06):863–873
4 He B, Zhu Z, Zhu Q, et al. Factors predicting sensory and motor recovery after the repair of upper limb peripheral nerve injuries. Neural Regen Res 2014;9(06):661–672
5 Thomas P, Holdorff B. Neuropathy due to physical agents. Peripheral Neuropathy. 1993;2:1948
6 Waller AV. Experiments on the section of the glossopharyngeal and hypoglossal nerves of the frog, and observations of the alterations produced thereby in the structure of their primitive fibres. Philos Trans R Soc Lond 1850;(140):423–429
7 Zochodne DW. Neurobiology of Peripheral Nerve Regeneration. Cambridge University PressCambridge, UK2008
8 Seddon HJ, Medawar PB, Smith H. Rate of regeneration of peripheral nerves in man. J Physiol 1943;102(02):191–215
9 Sunderland S. A classification of peripheral nerve injuries producing loss of function. Brain 1951;74(04):491–516
10 Mackinnon S, Dellon A. Classification of nerve injuries as the basis for treatment. In: Surgery of the Peripheral Nerve. New York: Thieme; 1988:35–63
11 Atkins S, Smith KG, Loescher AR, et al. Scarring impedes regeneration at sites of peripheral nerve repair. Neuroreport 2006;17 (12):1245–1249
12 Chen P, Piao X, Bonaldo P. Role of macrophages in Wallerian degeneration and axonal regeneration after peripheral nerve injury. Acta Neuropathol 2015;130(05):605–618
13 Carriel V, Garzón I, Alaminos M, Campos A. Evaluation of myelin sheath and collagen reorganization pattern in a model of peripheral nerve regeneration using an integrated histochemical approach. Histochem Cell Biol 2011;136(06):709–717
14 Napoli I, Noon LA, Ribeiro S, et al. A central role for the ERK-signaling pathway in controlling Schwann cell plasticity and

peripheral nerve regeneration in vivo. Neuron 2012;73(04): 729–742
15 Fu SY, Gordon T. Contributing factors to poor functional recovery after delayed nerve repair: prolonged denervation. J Neurosci 1995;15(5 Pt 2):3886–3895
16 Höke A, Gordon T, Zochodne DW, Sulaiman OA. A decline in glial cell-line-derived neurotrophic factor expression is associated with impaired regeneration after long-term Schwann cell denervation. Exp Neurol 2002;173(01):77–85
17 Chen Z-L, Yu W-M, Strickland S. Peripheral regeneration. Annu Rev Neurosci 2007;30:209–233
18 Rahmatullah M, Schroering A, Rothblum K, Stahl RC, Urban B, Carey DJ. Synergistic regulation of Schwann cell proliferation by heregulin and forskolin. Mol Cell Biol 1998;18(11): 6245–6252
19 Murinson BB, Archer DR, Li Y, Griffin JW. Degeneration of myelinated efferent fibers prompts mitosis in Remak Schwann cells of uninjured C-fiber afferents. J Neurosci 2005;25(05):1179–1187
20 Scheib J, Höke A. Advances in peripheral nerve regeneration. Nat Rev Neurol 2013;9(12):668–676
21 Lu P, Wang Y, Graham L, et al. Long-distance growth and connectivity of neural stem cells after severe spinal cord injury. Cell 2012;150(06):1264–1273
22 Nguyen QT, Sanes JR, Lichtman JW. Pre-existing pathways promote precise projection patterns. Nat Neurosci 2002;5(09): 861–867
23 Cattin AL, Burden JJ, Van Emmenis L, et al. Macrophage-induced blood vessels guide Schwann cell-mediated regeneration of peripheral nerves. Cell 2015;162(05):1127–1139
24 Parrinello S, Napoli I, Ribeiro S, et al. EphB signaling directs peripheral nerve regeneration through Sox2-dependent Schwann cell sorting. Cell 2010;143(01):145–155
25 Lu J, Tapia JC, White OL, Lichtman JW. The interscutularis muscle connectome. PLoS Biol 2009;7(02):e32
26 Gordon T, de Zepetnek JET. Motor unit and muscle fiber type grouping after peripheral nerve injury in the rat. Exp Neurol 2016;285(Pt A)24–40
27 Gordon T, Tyreman N. Sprouting capacity of lumbar motoneurons in normal and hemisected spinal cords of the rat. J Physiol 2010; 588(Pt 15):2745–2768
28 Rafuse VF, Gordon T. Self-reinnervated cat medial gastrocnemius muscles. II. analysis of the mechanisms and significance of fiber type grouping in reinnervated muscles. J Neurophysiol 1996;75 (01):282–297
29 Willand MP, Holmes M, Bain JR, de Bruin H, Fahnestock M. Sensory nerve cross-anastomosis and electrical muscle stimulation synergistically enhance functional recovery of chronically denervated muscle. Plast Reconstr Surg 2014;134(05):736e–745e
30 Elsohemy A, Butler R, Bain JR, Fahnestock M. Sensory protection of rat muscle spindles following peripheral nerve injury and reinnervation. Plast Reconstr Surg 2009;124(06):1860–1868
31 Schmalbruch H, al-Amood WS, Lewis DM. Morphology of long-term denervated rat soleus muscle and the effect of chronic electrical stimulation. J Physiol 1991;441:233–241
32 Veltri K, Kwiecien JM, Minet W, Fahnestock M, Bain JR. Contribution of the distal nerve sheath to nerve and muscle preservation following denervation and sensory protection. J Reconstr Microsurg 2005;21(01):57–70, discussion 71–74
33 Brushart TM, Mesulam MM. Alteration in connections between muscle and anterior horn motoneurons after peripheral nerve repair. Science 1980;208(4444):603–605
34 Gillespie MJ, Gordon T, Murphy PR. Motor units and histochemistry in rat lateral gastrocnemius and soleus muscles: evidence for dissociation of physiological and histochemical properties after reinnervation. J Neurophysiol 1987;57(04):921–937
35 Alant JD, Senjaya F, Ivanovic A, Forden J, Shakhbazau A, Midha R. The impact of motor axon misdirection and attrition on behavioral deficit following experimental nerve injuries. PLoS One 2013;8(11):e82546
36 de Ruiter GC, Spinner RJ, Verhaagen J, Malessy MJ. Misdirection and guidance of regenerating axons after experimental nerve injury and repair. J Neurosurg 2014;120(02):493–501
37 Htut M, Misra P, Anand P, Birch R, Carlstedt T. Pain phenomena and sensory recovery following brachial plexus avulsion injury and surgical repairs. J Hand Surg [Br] 2006;31(06):596–605
38 Thomas CK, Stein RB, Gordon T, Lee RG, Elleker MG. Patterns of reinnervation and motor unit recruitment in human hand muscles after complete ulnar and median nerve section and resuture. J Neurol Neurosurg Psychiatry 1987;50(03):259–268
39 Lee SK, Wolfe SW. Peripheral nerve injury and repair. J Am Acad Orthop Surg 2000;8(04):243–252
40 Gordon T. The role of neurotrophic factors in nerve regeneration. Neurosurg Focus 2009;26(02):E3
41 Gordon T, Tyreman N, Raji MA. The basis for diminished functional recovery after delayed peripheral nerve repair. J Neurosci 2011;31 (14):5325–5334
42 Anzil AP, Wernig A. Muscle fibre loss and reinnervation after long-term denervation. J Neurocytol 1989;18(06):833–845
43 Bentolila V, Nizard R, Bizot P, Sedel L. Complete traumatic brachial plexus palsy. Treatment and outcome after repair. J Bone Joint Surg Am 1999;81(01):20–28
44 Tötösy de Zepetnek JE, Zung HV, Erdebil S, Gordon T. Innervation ratio is an important determinant of force in normal and reinnervated rat tibialis anterior muscles. J Neurophysiol 1992;67 (05):1385–1403
45 Grinsell D, Keating CP. Peripheral nerve reconstruction after injury: a review of clinical and experimental therapies. BioMed Res Int 2014;2014:698256
46 Moore AM, Novak CB. Advances in nerve transfer surgery. J Hand Ther 2014;27(02):96–104, quiz 105
47 Boyd KU, Nimigan AS, Mackinnon SE. Nerve reconstruction in the hand and upper extremity. Clin Plast Surg 2011;38(04):643–660
48 Gregory J, Cowey A, Jones M, Pickard S, Ford D. The anatomy, investigations and management of adult brachial plexus injuries. Orthop Trauma 2009;23(06):420–432
49 Burnett MG, Zager EL. Pathophysiology of peripheral nerve injury: a brief review. Neurosurg Focus 2004;16(05):E1
50 Novak CB, Mackinnon SE. Distal anterior interosseous nerve transfer to the deep motor branch of the ulnar nerve for reconstruction of high ulnar nerve injuries. J Reconstr Microsurg 2002; 18(06):459–464
51 Oberlin C, Béal D, Leechavengvongs S, Salon A, Dauge MC, Sarcy JJ. Nerve transfer to biceps muscle using a part of ulnar nerve for C5-C6 avulsion of the brachial plexus: anatomical study and report of four cases. J Hand Surg Am 1994;19(02):232–237
52 Watchmaker GP, Gumucio CA, Crandall RE, Vannier MA, Weeks PM. Fascicular topography of the median nerve: a computer based study to identify branching patterns. J Hand Surg Am 1991;16 (01):53–59
53 Diao E, Vannuyen T. Techniques for primary nerve repair. Hand Clin 2000;16(01):53–66, viii viii.
54 Siemionow M, Tetik C, Ozer K, Ayhan S, Siemionow K, Browne E. Epineural sleeve neurorrhaphy: surgical technique and functional results–a preliminary report. Ann Plast Surg 2002;48(03):281–285
55 Levinthal R, Brown WJ, Rand RW. Comparison of fascicular, interfascicular and epineural suture techniques in the repair of simple nerve lacerations. J Neurosurg 1977;47(05):744–750
56 Ornelas L, Padilla L, Di Silvio M, et al. Fibrin glue: an alternative technique for nerve coaptation–Part I. Wave amplitude, conduction velocity, and plantar-length factors. J Reconstr Microsurg 2006;22(02):119–122
57 Sames M, Blahos J Jr, Rokyta R, Benes V Jr. Comparison of microsurgical suture with fibrin glue connection of the sciatic nerve in rabbits. Physiol Res 1997;46(04):303–306

58 Isaacs JE, McDaniel CO, Owen JR, Wayne JS. Comparative analysis of biomechanical performance of available "nerve glues". J Hand Surg Am 2008;33(06):893–899
59 Martins RS, Siqueira MG, Da Silva CF, Plese JP. Overall assessment of regeneration in peripheral nerve lesion repair using fibrin glue, suture, or a combination of the 2 techniques in a rat model. Which is the ideal choice? Surg Neurol 2005;64(Suppl 1):S1, 10–16, discussion S1, 16
60 Nishimura MT, Mazzer N, Barbieri CH, Moro CA. Mechanical resistance of peripheral nerve repair with biological glue and with conventional suture at different postoperative times. J Reconstr Microsurg 2008;24(05):327–332
61 Félix SP, Pereira Lopes FR, Marques SA, Martinez AM. Comparison between suture and fibrin glue on repair by direct coaptation or tubulization of injured mouse sciatic nerve. Microsurgery 2013; 33(06):468–477
62 Colen KL, Choi M, Chiu DTW. Nerve grafts and conduits. Plast Reconstr Surg 2009;124(06):e386–e394
63 Terzis JK, Kostopoulos VK. Vascularized nerve grafts and vascularized fascia for upper extremity nerve reconstruction. Hand (N Y) 2010;5(01):19–30
64 Cruz NI, Debs N, Fiol RE. Evaluation of fibrin glue in rat sciatic nerve repairs. Plast Reconstr Surg 1986;78(03):369–373
65 McCall TD, Grant GA, Britz GW, Goodkin R, Kliot M. Treatment of recurrent peripheral nerve entrapment problems: role of scar formation and its possible treatment. Neurosurg Clin N Am 2001; 12(02):329–339
66 Hanwright PJ, Rath JB, von Guionneau N, et al. The effects of a porcine extracellular matrix nerve wrap as an adjunct to primary epineurial repair. J Hand Surg Am 2021:S0363-5023(20)30741-3
67 Kokkalis ZT, Jain S, Sotereanos DG. Vein wrapping at cubital tunnel for ulnar nerve problems. J Shoulder Elbow Surg 2010;19(02):91–97
68 Thakker A, Sharma SC, Hussain NM, Devani P, Lahiri A. Nerve wrapping for recurrent compression neuropathy: a systematic review. J Plast Reconstr Aesthet Surg 2020
69 Jiang X, Lim SH, Mao H-Q, Chew SY. Current applications and future perspectives of artificial nerve conduits. Exp Neurol 2010; 223(01):86–101
70 Siemionow M, Brzezicki G. Chapter 8: Current techniques and concepts in peripheral nerve repair. Int Rev Neurobiol 2009; 87:141–172
71 Thorne CH, Chung KC, Gosain AK, et al. Grabb and Smith's plastic surgery: Seventh edition. Wolters Kluwer Health Adis (ESP)'. 2013
72 Nichols CM, Brenner MJ, Fox IK, et al. Effects of motor versus sensory nerve grafts on peripheral nerve regeneration. Exp Neurol 2004;190(02):347–355
73 Gu X, Ding F, Yang Y, Liu J. Construction of tissue engineered nerve grafts and their application in peripheral nerve regeneration. Prog Neurobiol 2011;93(02):204–230
74 Schmidt CE, Leach JB. Neural tissue engineering: strategies for repair and regeneration. Annu Rev Biomed Eng 2003;5:293–347
75 Pierucci A, de Duek EAR, de Oliveira ALR. Peripheral nerve regeneration through biodegradable conduits prepared using solvent evaporation. Tissue Eng Part A 2008;14(05):595–606
76 Strauch B, Ferder M, Lovelle-Allen S, Moore K, Kim DJ, Llena J. Determining the maximal length of a vein conduit used as an interposition graft for nerve regeneration. J Reconstr Microsurg 1996;12(08):521–527
77 Kehoe S, Zhang XF, Boyd D. FDA approved guidance conduits and wraps for peripheral nerve injury: a review of materials and efficacy. Injury 2012;43(05):553–572
78 Jones LL, Oudega M, Bunge MB, Tuszynski MH. Neurotrophic factors, cellular bridges and gene therapy for spinal cord injury. J Physiol 2001;533(Pt 1):83–89
79 Whitlock EL, Tuffaha SH, Luciano JP, et al. Processed allografts and type I collagen conduits for repair of peripheral nerve gaps. Muscle Nerve 2009;39(06):787–799
80 Lanier ST, Jordan SW, Ko JH, Dumanian GA. Targeted muscle reinnervation as a solution for nerve pain. Plast Reconstr Surg 2020;146(05):651e–663e
81 Souza JM, Purnell CA, Cheesborough JE, Kelikian AS, Dumanian GA. Treatment of foot and ankle neuroma pain with processed nerve allografts. Foot Ankle Int 2016;37(10):1098–1105
82 Poppler LH, Parikh RP, Bichanich MJ, et al. Surgical interventions for the treatment of painful neuroma: a comparative meta-analysis. Pain 2018;159(02):214–223
83 Ives GC, Kung TA, Nghiem BT, et al. Current state of the surgical treatment of terminal neuromas. Neurosurgery 2018;83(03): 354–364
84 Wolvetang NHA, Lans J, Verhiel SHWL, Notermans BJW, Chen NC, Eberlin KR. Surgery for symptomatic neuroma: anatomic distribution and predictors of secondary surgery. Plast Reconstr Surg 2019;143(06):1762–1771
85 Terzis JK, Tzafetta K. The "babysitter" procedure: minihypoglossal to facial nerve transfer and cross-facial nerve grafting. Plast Reconstr Surg 2009;123(03):865–876
86 Al-Majed AA, Neumann CM, Brushart TM, Gordon T. Brief electrical stimulation promotes the speed and accuracy of motor axonal regeneration. J Neurosci 2000;20(07):2602–2608
87 Elzinga K, Tyreman N, Ladak A, Savaryn B, Olson J, Gordon T. Brief electrical stimulation improves nerve regeneration after delayed repair in Sprague Dawley rats. Exp Neurol 2015; 269:142–153
88 Willand MP, Chiang CD, Zhang JJ, Kemp SW, Borschel GH, Gordon T. Daily electrical muscle stimulation enhances functional recovery following nerve transection and repair in rats. Neurorehabil Neural Repair 2015;29(07):690–700
89 Jiang X, Savchenko O, Li Y, et al. A review of low-intensity pulsed ultrasound for therapeutic applications. IEEE Trans Biomed Eng 2019;66(10):2704–2718
90 Jiang W, Wang Y, Tang J, et al. Low-intensity pulsed ultrasound treatment improved the rate of autograft peripheral nerve regeneration in rat. Sci Rep 2016;6(01):22773
91 Tajdaran K, Chan K, Shoichet MS, Gordon T, Borschel GH. Local delivery of FK506 to injured peripheral nerve enhances axon regeneration after surgical nerve repair in rats. Acta Biomater 2019;96:211–221