NEURAL REGENERATION RESEARCH
Volume 7, Issue 29, October 2012
www.nrronline.org

doi:10.3969/j.issn.1673-5374.2012.29.004 [http://www.crter.org/nrr-2012-qkquanwen.html]
Geuna S, Tos P, Battiston B. Emerging issues in peripheral nerve repair. Neural Regen Res. 2012;7(29):2267-2272.

Special Issue

Emerging issues in peripheral nerve repair☆

Stefano Geuna[1], Pierluigi Tos[2], Bruno Battiston[2]

1 *Neuroscience Institute of the "Cavalieri Ottolenghi" Foundation (NICO) & Department of Clinical and Biological Sciences, University of Turin, Torino 10043, Italy*
2 *Department of Traumatology, Microsurgery Unit, C.T.O. Hospital, Torino 10126, Italy*

Abstract
It is today widely acknowledged that nerve repair is now more than a matter of perfect microsurgical reconstruction only and that, to further improve clinical outcome, the involvement of different scientific disciplines is required. This evolving reconstructive/regenerative approach is based on the interdisciplinary and integrated pillars of tissue engineering such as reconstructive microsurgery, transplantation and biomaterials. In this paper, some of the most promising innovations for the tissue engineering of nerves, emerging from basic science investigation, are critically overviewed with special focus on those approaches that appear today to be more suitable for clinical translation.

Key Words
nerve reconstruction; tissue engineering; cell and tissue transplantation; gene therapy; biomaterials; peripheral nervous system; microsurgery; artificial hollow tubes; muscle-vein-combined tubes; non-nervous guides; neural regeneration

Research Highlights
(1) The most promising innovations for nerve repair and tissue engineering are reviewed and discussed critically with special focus on those approaches that appear to be suitable of clinical translation and spread among surgeons in the near future.
(2) It is expected that in the forthcoming years, a number of new regenerative tools will enrich our possibilities for repairing the damaged peripheral nerves, making nerve reconstruction no more only a matter of microsurgical repair, but rather an integrated regeneration strategy based on the contribution of several different scientific disciplines.

Abbreviations
CNS, central nervous system; PNS, peripheral nervous system

Stefano Geuna☆, M D., Associate professor, Neuroscience Institute of the "Cavalieri Ottolenghi" Foundation (NICO) & Department of Clinical and Biological Sciences, University of Turin, Torino 10043, Italy

Corresponding author: Setfano Geunea, Neuroscience Institute of the "Cavalieri Ottolenghi" Foundation (NICO) & Department of Clinical and Biological Sciences, University of Turin, Torino 10043, Italy
stefano.geuna@unito.it

Received: 2012-05-11
Accepted: 2012-07-10
(NY20120409010/ZLJ)

INTRODUCTION

Although in the adult central nervous system (CNS) some potential for neurogenesis (in the gray matter) and axonal regrowth (in the white matter) exists, the response to stimulation (neuroplasticity) and injury (neuroregeneration) in the CNS is mainly based on a synaptic reorganization of the existing/surviving neurons and nerve fibers to cope with the new environmental conditions. By contrast, in the adult peripheral nervous system (PNS), adaptive neuroplasticity and axonal regeneration potential is much higher[1-2] and is at the basis of the usually higher degree of recovery after peripheral nerve trauma (in comparison to CNS) provided that the continuity of the nerve is either maintained or, if lost, adequately reconstructed[3-4]. However, complete recovery is only occasionally achieved after a nerve lesion and in many cases the clinical outcome is frankly unsatisfactory[5]. The lack of optimal clinical

outcome thus represents the rationale for further in-depth investigation aimed at identifying new effective strategies which might improve nerve regeneration and, eventually, functional recovery after nerve reconstruction, especially in case of severe nerve lesions. Today, there is a growing consensus that further improvements of peripheral nerve repair and regeneration are no more a matter of developing new microsurgical tools and techniques, but rather a matter of a multi-translational regenerative medicine approach aimed at reaching a new level of innovation which brings together the various disciplines of tissue engineering[6]. In this review, we will focus on some of the most promising innovations emerging from recent advancements originating from basic science research and that appear to be close to jumping to clinical employment.

MICROSURGICAL RECONSTRUCTION

Although other disciplines have enriched the world of tissue engineering, the microsurgical act still plays a key role in peripheral nerve reconstruction. This is true not only because microsurgery represents a key link in the chain which connects innovative research to the development of new treatment strategies to the patient but also because the role of the microsurgeon is fundamental in the proper design of the basic science experiments. The involvement of microsurgeons in all stages of study design helps in optimizing the entire research and development process and, eventually, facilitates the reaching of the ultimate translational and clinical goals[6].

Microsurgical techniques for nerve reconstruction, which find their roots in ancient times[7] have much improved over the last fifty years[5] and today direct suture for repairing a damaged nerve can be performed in many trauma centers worldwide. Besides end-to-end neurorrhaphy, among the other microsurgical techniques that have been successfully introduced to the clinical practices, particular mention is deserving to nerve transfers[8-10] which have a great spread over the last few years and have significantly increased the range of surgical options in the reconstruction of very severe nerve traumas such as brachial plexus lesions. Another technique that is slowing spreading among surgeons is direct muscle neurotization, *i.e*. the direct implantation of motor nerve fascicles in a denervated skeletal muscle. This technique prevents muscle atrophy and may allow partial degree of motor recovery and it is thus used particularly after severe traumas when no other option of nerve reconstruction is possible[11-12].

The history of the last decades tells us that progress in nerve reconstruction technique might derive not only from completely new methods but also from revisiting and/or modifying an old (and maybe abandoned) technique, rather than by a complete innovation. End-to-side neurorrhaphy is a clear example. When experimental and preliminary clinical experiences using end-to-side nerve repair were reported by Viterbo and co-workers in early nineties[13], it was considered a great innovation in nerve microsurgery. However, it was then reported that a similar technique was already described, both in experimental models and with patients, in the eighteen century[14]. Although studies in experimental animals have shown the effectiveness of this technique for nerve reconstruction[15-18], its clinical use is still below expectations. It appears thus that more basic science data (elucidating the mechanisms that regulate lateral axonal sprouting and describing effective additional strategies for promoting the regeneration process) is needed before clinical use of end-to-side neurorrhaphy might spread among nerve surgeons.

Besides the discovery and/or re-discovery of new microsurgical approaches, technical advances in nerve repair might still be expected based on the development of new technologies. Two innovations appear to be in the pipeline for being spread in the clinical practice based on the very good results obtained in experimental research. The first is the use of glue, instead of nerve micro-suturing, the clinical employment of which is still very limited. However, a body of experimental studies indicate that the performance of glue is equal, if not superior, to micro-suture[19] and it may be predicted that its use will continuously grow in the future considering also that it may represent an important alternative to suture repair especially in the setting of a surgeon relatively inexperienced with microsurgery[20].

The second is robot-assisted microsurgery. Although robotics has recently spread over many surgical fields, its use in peripheral nerve surgery is still low and basically limited to urology-related reconstructions[21-23]. However, it can be expected that once robot-assisted technologies become simpler and cheaper it will spread much more among peripheral nerve surgeons since results from experimental studies are encouraging[24].

TRANSPLANTATION

Transplantation strategies are progressively evolving from whole organ transplantation to more sophisticated forms of tissue engineering based on the employment of only parts (tissue transplantation), or even single cellular (cell transplantation) or sub-cellular constituents (gene transfer), of an organ.

In the case of peripheral nerve substance loss requiring

transplantation, the present gold standard strategy is represented by the transplantation of an autologous nerve segment taken from another “less precious nerve”[5]. This technique finds its roots in the pioneering work of Hanno Millesi who, in the early 1970s[25-26], showed that grafting an autogenous nerve segment to bridge a nerve defect is much better that suturing the nerve stumps under tension and opened the possibility to successfully treat a number of complex nerve lesions that before were almost not treatable at all.

Several other transplantation approaches are being tentatively translated to the patient.

A very promising emerging transplantation approach using processed nerve allografts is receiving much attention because of the ability of these conduits to bridge large nerve defects[27-28]. Allografts are prepared from donated human peripheral nerve tissue by a process that selectively removes cellular components and debris and induces pre-wallerian degeneration to cleave growth inhibitors. Very recently[29], the results of the first large scale clinical trial have been published showing that this reconstructive approach performed well in sensory, mixed and motor nerve defects between 5 mm and 50 mm leading to a functional recovery comparable to traditional nerve autograft and higher than non-nervous guides. Thus, although their high costs raise concern, processed nerve allografts for nerve gap reconstruction hold promise as a successful alternative to traditional nerve autografts.

Another interesting approach is represented by the use of veins for bridging short nerve defects. This technique had been introduced as early as 1909 by Wrede[30] who reported functional recovery after repairing the median nerve by means of a 45-mm-long vein tube. The interest in this surgical technique revived with the clinical studies by Walton *et al* [31] and Chiu and Strauch[32] who showed that sensory nerve repair by vein autografts may lead to satisfactory return of sensibility comparable to the nerve grafting technique and, since then, vein conduits have a discrete spread among nerve surgeons[33].

However, their effectiveness is limited to short-gap repair because long vein segments tend to collapse[6]. Thus several authors have explored the possibility of filling up vein tubes with other tissues, the most promising approach being the use of skeletal muscle fibers[34]. This muscle-vein-combined technique for nerve reconstruction has been extensively investigated in experimental models[6, 35-38] and papers reporting on its successful clinical employment in both sensory and mixed nerves (also in cases of gaps longer than 30 mm) have already been published[39-42]. It can thus be expected that its use in patients will increase over the next several years.

Also the use of skeletal muscle autografts alone has been explored[43-44] and several authors have also proposed to perform predegeneration of the muscle fiber in order to avoid the presence of impeding material[45]. Although the published clinical studies showed that this technique can work well in patients[46-48], it did not spread among nerve microsurgeons and it appears that nowadays it is almost abandoned.

In more recent years, cell transplantation has attracted much attention also in peripheral nerve reconstruction. Among the various cell types that have been investigated, there are great expectations for Schwann cells[49] since these cells are known to play a major role in promoting peripheral nerve regeneration[3]. The other cell type that has received particular attention among nerve regeneration researchers is mesenchymal stem cells since they can be easily obtained from the same subject and can be expanded in culture offering a potentially unlimited source of cells for tissue engineering[50]. They can be derived from various stem cell niches in adult tissues such as bone marrow, adipose tissue, umbilical cord blood, and tooth pulp[51]. The demonstration that, *in vitro*, they can be differentiated in Schwann cells[52-53] and that when transplanted in the injured peripheral nerve can be effective in promoting nerve regeneration open very interesting perspectives in the view of clinical employment. However, no clinical trial has been carried out since safety issues still raise some concerns that should be properly addressed before translation to patients. The same is true for gene transfer for local growth factor delivery[54-56]. This approach holds great promises based on studies in animal models that have shown that peripheral nerve regeneration can be improved by transferring single genes (*e.g.* fibroblast growth factor 2) directly into the nerve and/or into Schwann cells[57-58]. Since the new generation of viral vectors (especially adeno-associated vectors) have been shown to be safe[55], it can be expected that gene transfer-based strategies for nerve regeneration promotion might be translated to patients earlier than cell transplantation-based strategies.

BIOMATERIALS: ARTIFICAL NERVE PROSTHESES

The investigation on the use of biomaterials for peripheral nerve repair has un doubtfully seen a tremendous expansion over the last 15 years and an enormous body of experimental research has been published[59]. Up to now, several artificial peripheral nerve substitutes have been translated to clinical employment[60]. In all cases so far, nerve prostheses for clinical applications are represented by hollow

tubes. Although the employment of artificial hollow tubes for nerve reconstruction has proven to lead to successful functional recovery in selected clinical cases, it appears that surgeons are now waiting for a new generation of nerve guides that may guarantee similar (or even better) results in comparison to traditional nerve autografts.

The considerable progress in material science of the recent years[59] has stimulated the design and experimental testing of a considerable number of new nerve guides[61-62]. While biomaterials for tissue engineering can be classified using various parameters[59, 62], we propose a simple three-category classification which, in our opinion, fits well with the three main generations of biomaterials that have signified scientific and technological progress in nerve reconstruction approaches.

The first generation is represented by non-absorbable synthetic materials. The first, and unsuccessful, attempts to implant synthetic conduits (made of polyethylene, polyvinyl, rubber, tantalum metal) for bridging a nerve gap in patients were reported in the middle of the past century[63-64]. More recently, the extensive work of Dahlin and Lundborg showed the effectiveness for short gaps of silicone tubes[65-66]. Among the other attempts to use nonabsorbable tubes in patients, expanding polytetrafluoroethylene led to satisfactory functional outcome in upper extremity nerve defect repair[67] while Gore-Tex led to poor results for reconstruction of inferior alveolar and lingual nerves[68].

The second generation is represented resorbable synthetic materials that have been developed since an employment of nonresorbable synthetic material might lead to complications due to local fibrosis, triggered by the implanted material, and nerve compression[69]. Among the first materials adopted and by far the one that has seen higher clinical employment is polyglycolic acid [40, 70-71]. However, concerns have been raised as to the possibility of foreign body reaction, thus opening the door to the third generation that is represented by resorbable biomimetic materials that are made of substances that are derived from animal tissues and thus are expected to better integrate with the biological tissues of the host patient. Within this category, chitosan, a partially deacetylated polymer of acetyl glucosamine obtained from chitin, attracts considerable attention among basic and clinical scientists because of its strong effectiveness in promoting nerve regeneration as well as its high biocompatibility and biodegradability, and its low toxicity and cost[72-74].

CONCLUSION

Clinicians agree that although considerable progress has been achieved over the last decades, the clinical outcome after peripheral nerve injury and repair is still far from being satisfactory for most patients[5].

This evidence calls for more basic science on nerve regeneration as well as for optimized translation of basic science results towards clinical applications. In this paper, we have overviewed some of the most promising new approaches for nerve repair and regeneration that are emerging from basic science results and that might be suitable for clinical translation and spread among reconstructive surgeons in the near future.

What is needed to achieve better functional outcome after nerve reconstruction? Various factors can hinder optimal clinical outcome in patients including limited number of regenerating axons and failure to achieve a sufficient length of axon regeneration and/or a sufficient degree of myelination. In addition, impairment of proximal neuronal circuitries (motor and sensory) and of peripheral targets (muscle fibers and sensory receptors) might also interfere with overall functional recovery. Therefore, although microsurgical techniques for nerve reconstruction have reached a high level of effectiveness and reliability today, it is clear that further improvement to nerve repair will not only depend on the implementation of the surgical techniques but rather on their combination with other synergistic regeneration strategies. Yet, future progress in nerve tissue engineering will most probably not develop from the optimization of a single regenerative strategy but rather from the optimized combination of different strategies. An interdisciplinary approach appears thus to be the main challenge in peripheral nerve repair and regeneration and it is expected that it might lead to significant clinical advances in the forthcoming years.

Funding: This study was supported by *San Paolo Bank Foundation* and *Piemonte Region*.

Author contributions: Stefano Geuna conceived and designed the paper, retrieved the references and wrote the manuscript. Pierluigi Tos and Bruno Battiston retrieved the references and critically revised the manuscript.

Conflicts of interest: None declared.

REFERENCES

[1] Geuna S, Borrione P, Fornaro M, et al. Adult stem cells and neurogenesis: historical roots and state of the art. Anat Rec. 2001;265:132-141.

[2] Geuna S, Fornaro M, Raimondo S, et al. Plasticity and regeneration in the peripheral nervous system. Ital J Anat Embryol. 2010;115:91-94.

[3] Geuna S, Raimondo S, Ronchi G, et al. Histology of the peripheral nerve and changes occurring during nerve regeneration. Int Rev Neurobiol. 2009;87:27-46.
[4] Raimondo S, Fornaro M, Di Scipio F, et al. Chapter 5: Methods and protocols in peripheral nerve regeneration experimental research: part II-morphological techniques. Int Rev Neurobiol. 2009;87:81-103.
[5] Siemionow M, Brzezicki G. Current techniques and concepts in peripheral nerve repair. Int Rev Neurobiol. 2009;87:141-172.
[6] Battiston B, Raimondo S, Tos P, et al. Tissue engineering of peripheral nerves. Int Rev Neurobiol. 2009;87:227-249.
[7] Battiston B, Papalia I, Tos P, et al. Peripheral nerve repair and regeneration research: a historical note. Int Rev Neurobiol. 2009;87:1-7.
[8] Teboul F, Kakkar R, Ameur N, et al. Transfer of fascicles from the ulnar nerve to the nerve to the biceps in the treatment of upper brachial plexus palsy. J Bone Joint Surg (Am). 2004;86:1485-1490.
[9] Tung TH, Mackinnon SE. Nerve transfers: indications, techniques, and outcomes. J Hand Surg (Am). 2010;35: 332-341.
[10] Zhang CG, Gu YD. Contralateral C7 nerve transfer-Our experiences over past 25 years. J Brachial Plex Peripher Nerve Inj. 2011;6:10.
[11] Terzis JK, Karypidis D. Outcomes of direct muscle neurotization in pediatric patients with facial paralysis. Plast Reconstr Surg. 2009;124:1486-1498.
[12] Terzis JK, Karypidis D. Outcomes of direct muscle neurotization in adult facial paralysis. J Plast Reconstr Aesthet Surg. 2011;64:174-184.
[13] Viterbo F, Trindade JC, Hoshino K, et al. End-to-side neurorrhaphy with removal of the epineurial sheath: an experimental study in rats. Plast Reconstr Surg. 1994;94:1038-1047.
[14] Papalia I, Geuna S, D'Alcontres FS, et al. Origin and history of end-to-side neurorrhaphy. Microsurgery. 2007;27:56-61.
[15] Papalia I, Geuna S, Tos PL, et al. Morphologic and functional study of rat median nerve repair by terminolateral neurorrhaphy of the ulnar nerve. J Reconstr Microsurg. 2003;19:257-264.
[16] Papalia I, Cardaci A, d'Alcontres FS, et al. Selection of the donor nerve for end-to-side neurorrhaphy. J Neurosurg. 2007;107:378-382.
[17] Sakalidou M, Leibig N, Boyle V, et al. Interleukin-10 and regeneration in an end-to-side nerve repair model of the rat. J Peripher Nerv Syst. 2011;16:334-340.
[18] Haastert K, Joswig H, Jäschke KA, et al. Nerve repair by end-to-side nerve coaptation: histologic and morphometric evaluation of axonal origin in a rat sciatic nerve model. Neurosurgery. 2010;66:567-576.
[19] Sameem M, Wood TJ, Bain JR. A systematic review on the use of fibrin glue for peripheral nerve repair. Plast Reconstr Surg. 2011;127:2381-2390.
[20] Whitlock EL, Kasukurthi R, Yan Y, et al. Fibrin glue mitigates the learning curve of microneurosurgical repair. Microsurgery. 2010;30:218-222.
[21] Zorn KC, Bernstein AJ, Gofrit ON, et al. Long-term functional and oncological outcomes of patients undergoing sural nerve interposition grafting during robot-assisted laparoscopic radical prostatectomy. J Endourol. 2008;22:1005-1012.
[22] Nectoux E, Taleb C, Liverneaux P. Nerve repair in telemicrosurgery: an experimental study. J Reconstr Microsurg. 2009;25:261-265.
[23] Liverneaux P, Nectoux E, Taleb C. The future of robotics in hand surgery. Chir Main. 2009;28:278-285.
[24] Latif MJ, Afthinos JN, Connery CP, et al. Robotic intercostal nerve graft for reversal of thoracic sympathectomy: a large animal feasibility model. Int J Med Robot. 2008;4:258-262.
[25] Millesi H. Interfascicular nerve grafting. Orthop Clin North Am. 1970;2:419-435.
[26] Millesi H, Meissl G, Berger A. The interfascicular nerve-grafting of the median and ulnar nerves. J Bone Joint Surg[Am]. 1972;54:727-750.
[27] Neubauer D, Graham JB, Muir D. Chondroitinase treatment increases the effective length of acellular nerve grafts. Exp Neurol. 2007;207:163-170.
[28] 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: 787-799.
[29] Brooks DN, Weber RV, Chao JD, et al. Processed nerve allografts for peripheral nerve reconstruction: a multicenter study of utilization and outcomes in sensory, mixed, and motor nerve reconstructions. Microsurgery. 2012;32:1-14.
[30] Wrede L. Uberbrueckung eines Nervendefektes mittels Seidennaht und leben Venenstueckes. Dtsch Med Wochenschr. 1909;35:1125-1160.
[31] Walton RL, Brown RE, Matory WE Jr, et al. Autogenous vein graft repair of digital nerve defects in the finger: a retrospective clinical study. Plast Reconstr Surg. 1989;84: 944-949.
[32] Chiu DT, Strauch B. A prospective clinical evaluation of autogenous vein grafts used as a nerve conduit for distal sensory nerve defects of 3 cm or less. Plast Reconstr Surg. 1990;86:928.934.
[33] Colen KL, Choi M, Chiu DT. Nerve grafts and conduits. Plast Reconstr Surg. 2009;124:386-394.
[34] Brunelli G, Battiston B, Vigasio A, et al. Bridging nerve defects with combined skeletal muscle and vein conduits. Microsurgery. 1993;14:247-251.
[35] Geuna S, Tos P, Battiston B, et al. Morphological analysis of peripheral nerve regenerated by means of vein grafts filled with fresh skeletal muscle. Anat Embryol. 2000;201: 475-482.
[36] Geuna S, Raimondo S, Nicolino S, et al. Schwann-cell proliferation in muscle-vein combined conduits for bridging rat sciatic nerve defects. J Reconstr Microsurg. 2003;19: 119-123.
[37] Geuna S, Tos P, Battiston B, et al. Bridging peripheral nerve defects with muscle-vein-combined guides. Neurol Res. 2004;26:139-144.
[38] Tos P, Battiston B, Nicolino S, et al. Comparison of fresh and predegenerated muscle-vein-combined guides for the repair of rat median nerve. Microsurgery. 2007;27:48-55.

[39] Battiston B, Tos P, Cushway T, et al. Nerve repair by means of vein filled with muscle grafts. I. Clinical results. Microsurgery. 2000;20:32-36.
[40] Battiston B, Geuna S, Ferrero M, et al. Nerve repair by means of tubulization: literature review and personal clinical experience comparing biological and synthetic conduits for sensory nerve repair. Microsurgery. 2005;25: 258-67.
[41] Marcoccio I, Vigasio A. Muscle-in-vein nerve guide for secondary reconstruction in digital nerve lesions. J Hand Surg (Am). 2010;35:1418-1426.
[42] Tos P, Battiston B, Ciclamini D, et al. Primary repair of crush nerve injuries by means of biological tubulization with muscle-vein-combined grafts. Microsurgery. 2012.
[43] Keynes RJ, Hopkins WG, Huang LH. Regeneration of mouse peripheral nerves in degenerating skeletal muscle: guidance by residual muscle fibre basement membrane. Brain Res. 1984;295:275-281.
[44] Fawcett JW, Keynes RJ. Muscle basal lamina: a new graft material for peripheral nerve repair. J Neurosurg. 1986;65: 354-363.
[45] Meek MF, Den Dunnen WFA, Schakenraad JM, et al. Evaluation of several techniques to modify denatured muscle tissue to obtain a scaffold for peripheral nerve regeneration. Biomaterials. 1999;20:101-108.
[46] Norris RW, Glasby MA, Gattuso JM. Peripheral nerve repair in humans using muscle autografts: a new technique. J Bone Joint Surg[Br]. 1988;70:530-533.
[47] Pereira JH, Palande DD, Subramanian A, et al. Denatured autologous muscle graft in leprosy. Lancet. 1991;338: 1239-1240.
[48] Rath EM. Skeletal muscle autograft for repair of the human inferior alveolar nerve: a case report. J Oral Maxillofac Surg. 2002;60:330-334.
[49] Schmitte R, Tipold A, Stein VM, et al. Genetically modified canine Schwann cells--In vitro and in vivo evaluation of their suitability for peripheral nerve tissue engineering. J Neurosci Methods. 2010;186:202-208.
[50] Caplan AI, Dennis JE. Mesenchymal stem cells as trophic mediators. J. Cell Biochem. 2006.98;1076-1084.
[51] Alhadlaq A, Mao JJ. Mesenchymal stem cells: isolation and therapeutics. Stem Cells Dev. 2004;13:436-448.
[52] Kingham PJ, Kalbermatten DF, Mahay D, et al. Adipose-derived stem cells differentiate into a Schwann cell phenotype and promote neurite outgrowth in vitro. Exp Neurol. 2007;207:267-274.
[53] Mantovani C, Mahay D, Kingham P, et al. Bone marrow- and adipose-derived stem cells show expression of myelin mRNAs and proteins. Regen Med. 2010;5:403-410.
[54] Haastert K, Grothe C. Gene therapy in peripheral nerve reconstruction approaches. Curr Gene Ther. 2007;7: 221-228.
[55] Zacchigna S, Giacca M. Gene therapy perspectives for nerve repair. Int Rev Neurobiol. 2009;87:381-392.
[56] Pereira Lopes FR, Lisboa BC, Frattini F, et al. Enhancement of sciatic nerve regeneration after vascular endothelial growth factor (VEGF) gene therapy. Neuropathol Appl Neurobiol. 2011;37:600-612.
[57] Haastert K, Lipokatic E, Fischer M, et al. Differentially promoted peripheral nerve regeneration by grafted Schwann cells over-expressing different FGF-2 isoforms. Neurobiol Dis. 2006;21:138-153.
[58] Hoyng SA, Tannemaat MR, De Winter F, et al. Nerve surgery and gene therapy: a neurobiological and clinical perspective. J Hand Surg Eur Vol. 2011;36:735-746.
[59] Williams DF. On the nature of biomaterials. Biomaterials. 2009;30:5897-5909.
[60] Kehoe S, Zhang XF, Boyd D. FDA approved guidance conduits and wraps for peripheral nerve injury: A review of materials and efficacy. Injury. 2012;43:553-572.
[61] Siemionow M, Bozkurt M, Zor F. Regeneration and repair of peripheral nerves with different biomaterials: review. Microsurgery. 2010;30:574-588.
[62] Pfister BJ, Gordon T, Loverde JR, et al. Biomedical engineering strategies for peripheral nerve repair: surgical applications, state of the art, and future challenges. Crit Rev Biomed Eng. 2011;39:81-124.
[63] Garrity RW. The use of plastic and rubber tubing in the management of irreparable nerve injuries. Surg Forum. 1955;6:517-520.
[64] Ducker TB, Hayes GJ. Experimental improvements in the use of Silastic cuff for peripheral nerve repair. J Neurosurg. 1968;28:582-587.
[65] Dahlin LB, Anagnostaki L, Lundborg G. Tissue response to silicone tubes used to repair human median and ulnar nerves. Scand J Plast Reconstr Surg Hand Surg. 2001;35: 29-34.
[66] Lundborg G, Rosen B, Dahlin L, et al. Tubular repair of the median or ulnar nerve in the human forearm: a 5-year follow-up. J Hand Surg[Br]. 2004;29:100-107.
[67] Stanec S, Stanec Z. Reconstruction of upper-extremity peripheralnerve injuries with ePTFE conduits. J Reconstr Microsurg. 1998;14:227-232.
[68] Pitta MC, Wolford LM, Mehra P, et al. Use of Gore-Tex tubing as a conduit for inferior alveolar and lingual nerve repair: experience with 6 cases. J Oral Maxillofac Surg. 2001;59:493-496.
[69] Merle M, Dellon AL, Campbell JN, et al. Complications from silicone polymer intubulation of nerves. Microsurgery. 1989;10:130-133
[70] Dellon AL, Mackinnon SE. An alternative to the classical nerve graft for the management of the short nerve gap. Plast Reconstr Surg. 1988;82:849-856.
[71] Weber RA, Breidenbach WC, Brown RE, et al. A randomized prospective study of polyglycolic acid conduits for digital nerve reconstruction in humans. Plast Reconstr Surg. 2000;106:1036-1045.
[72] Freier T, Montenegro R, Shan Koh H, et al. Chitin-based tubes for tissue engineering in the nervous system. Biomaterials. 2005;26:4624-4632.
[73] Ishikawa N, Suzuki Y, Ohta M, et al. Peripheral nerve regeneration through the space formed by a chitosan gel sponge. J Biomed. Mater Res A. 2007;83:33-40.
[74] Amado S, Simoes MJ, Armada da Silva PA, et al. Use of hybrid chitosan membranes and N1E-115 cells for promoting nerve regeneration in an axonotmesis rat model. Biomaterials. 2008;29;4409-4419.

(Edited by Himes BT, Martin J/Zhao LJ/Song LP)