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I. Koxholt · J. Mey
Institut für Biologie II, RWTH Aachen, Aachen

Artificial implants for the regeneration of peripheral nerves

Introduction

Peripheral nerves control our muscles and transmit somatosensory information to the central nervous system. If an injury to the face or limbs severs a peripheral nerve, we lose these functions. In contrast to the largely degenerative processes after spinal cord lesions, axons are able to regenerate in the peripheral nervous system (PNS). The cell somata of PNS neurons are not localized in the periphery but in the ventral horn of the spinal cord (motorneurons), the dorsal root ganglia (sensory neurons), or in the sympathetic chain ganglia close to the spinal column (neurons of the autonomic nervous system). Neurons innervating the face are found in brain stem nuclei. Thus, if peripheral nerve fibers are cut, the nerve cells activate a growth program such that their axons can regenerate, provided they find a growth permissive substrate. For this reason, peripheral nerves can be surgically repaired after lesions. When the gap between disrupted nerve stumps is too large, the surgeon transplants an autologous nerve that is taken from elsewhere in the patient; often the sural nerve is used for this purpose. Yet, since this operation results in sensory loss at the donor site, alternatives for autologous nerve transplantation have been investigated for more than 25 years. One approach is the development of artificial implants made of natural or synthetic materials (**Box. 1**).

Regeneration in the peripheral nervous system

A look at the processes of peripheral nerve regeneration reveals the requirements that artificial nerve constructs must meet in order to substitute autologous transplants (**Fig. 1**). Peripheral nerve injury causes degeneration of the distal nerve stump, referred to as Wallerian degeneration. Since axons are disconnected from their cell somata, they will eventually die. The cytoskeleton and cell membranes of neurites break up into their molecular constituents, Schwann cells, the peripheral glia cells, shed their myelin, and the debris is removed by macrophages. At the same time, the severed axons in the proximal nerve stump form growth cones and activate a physiological program of regeneration. In a growth permissive environment, e.g., if the connection to the distal nerve stump is maintained, axons elongate in contact with longitudinal structures of perineurium and proliferating Schwann cells, the so-called bands of Büngner [22]. Regeneration reaches velocities of several millimeters per day. Injured peripheral nerves, especially the basement membranes that are formed by the glia cells, provide an excellent growth substrate for axonal regeneration. Subsequently, the Schwann cells remyelinate the regenerated axons. Axonal growth is stimulated by various paracrine factors, which are mainly secreted by the Schwann cells as well [2]. If axons reach their peripheral targets they may form new synapses or end organs, and function can be restored.

Requirements for artificial nerve implants

This description illustrates the functions that artificial implants must fulfill, if they are to allow successful nerve regenera-

Box 1: Nerve implants

Autologous nerve transplants are considered the gold standard in the clinical therapy of nerve injury. Disadvantages are the necessity of a second operation and loss of sensory function at the donor site.

Nonautologous grafts are derived from tissue of another conspecific, xenotransplants are from another species. Immunosuppression is necessary. Using freeze-thaw cycles, chemical treatment or radioactive irradiation, implants can be rendered cell-free to reduce their immunogenicity. However, this treatment also damages the extracellular matrix (ECM).

Transplants from other tissues that have been investigated include muscle fibers, tendons, blood vessels, and submucosa of the small intestine.

Artificial implants may consist of *natural materials*. Most frequently, ECM proteins are used, especially laminin, collagen, and fibronectin. Other natural materials for the construction of nerve bridges are hyaluronic acid, fibrin, and the polysaccharides agarose, alginate, and chitosan (derived from chitin by deacetylation). Structures can be improved by cross linking or the combination of different substances.

Artificial implants made from *synthetic materials* are well suited for peripheral nerve repair because their chemical and physiological properties can be designed in a controlled manner. The most important materials are listed in **Box. 2**, their structures are depicted in **Fig. 3a**.

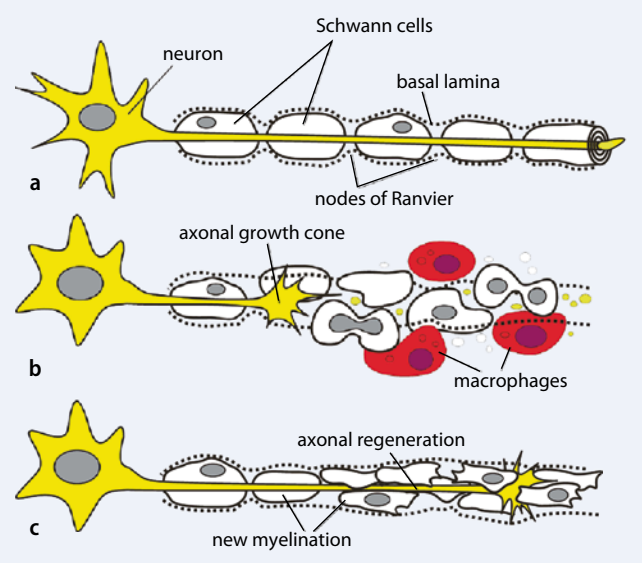

Fig. 1 ▲ Peripheral nerve regeneration. **a** Neurons of the PNS are located in the ventral horns of the spinal cord (motor neurons), the dorsal root ganglia (sensory neurons) or the sympathetic chain ganglia (autonomic nervous system). Axons are myelinated by Schwann cells. **b** After nerve injury, myelin sheaths and axons degenerate distal to the lesion site. Schwann cells proliferate; macrophages remove the debris of degenerating fibers. **c** At the lesion site neurons form axonal growth cones, and axons are able to regenerate along longitudinal bands of glia and ECM. Subsequently, Schwann cells re-myelinate the new axons

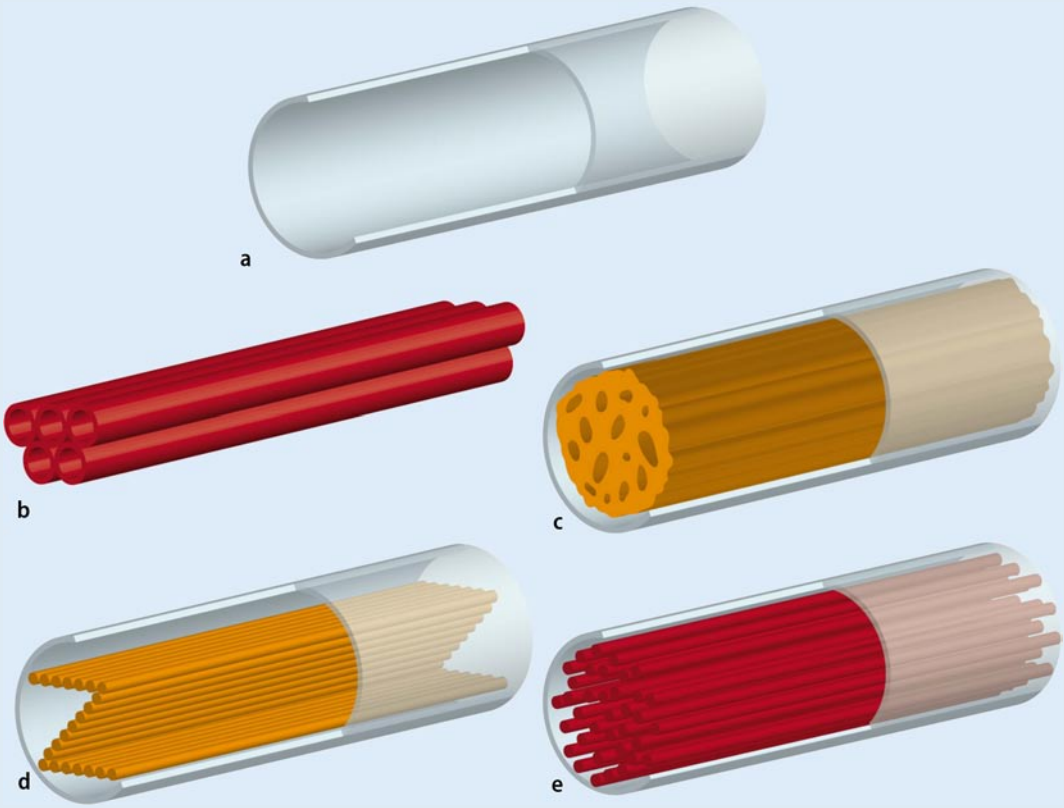

Fig. 2 ◀ Construction strategies for artificial nerve implants. a Hollow tubes for the connection of severed peripheral nerves are the basis of most implants. b Artificial nerve bridge consisting of several empty tubes attached to each other [10]. c With directional freezing, gels are produced that contain oriented channels to receive regenerating fibers [3]. d Parallel microfibers on films are arranged within the lumen of a tube implant [5]. e Electrospun fibers can be collected in three-dimensional arrays and contained in hydrogels within tubular nerve implants (Rumman and Mey, unpublished data)

Box 2: Synthetic materials for artificial nerve bridges

Poly(α–hydroxy acids) (**Fig. 3a**). For nerve regeneration poly(hydroxy acids) are spun to fibers that can be functionalized with natural proteins or peptides. The most important examples are poly(lactic acid) (PLA, with stereoisomers PLLA, PDLA), poly(lactic-co-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL), and poly(hydroxybutyric acid) (PHB). Fibers and tissues consisting of these materials have multiple applications in tissue engineering, e.g., as scaffolds and suture materials.

Polyethylene glycol (PEG; **Fig. 3a**). This polymer, which is non-adhesive to cells, is used to produce gels, matrices, or serves as a linker for proteins. From PEG the star-shaped NCO-poly(ethylene glycol)-*stat*-poly(propylene glycol) (sPEG) with a backbone of 80% ethylene oxide and 20% propylene oxide is synthesized. The reactive isocyanate end groups provide a basis for covalent modification (**Fig. 3d**).

Hydrogels, e.g., poly(2-hydroxyethyl methacrylate) (pHEMA), have a very high water content after polymerization. They can be used to make scaffolds with structured channels or to encapsulate functional molecules such as neurotrophins.

Non-degradable polymers that have been used in nerve implants include silicone, poly(urethane), poly(tetrafluoroethylene) (PTFE), and oxidized poly(pyrrole). The electrically conducting polymer poly(pyrrole) is interesting for neural applications because electrical stimulation can influence axonal growth.

tion in vivo [6]. In general, the implanted construct must be biocompatible, that is, it does not induce inflammatory reactions and is not rejected or encapsulated by scar tissue. In addition to biochemical signals, mechanical properties are important here because irritation of the tissue, e.g., due to stiffness of the material, may cause inflammation. Swelling of the implant would reduce its lumen, thereby, exerting pressure against the regenerating fibers [7]. Furthermore, it is desirable that the bridge between nerve stumps remains in the body until axonal regeneration is completed. Then, however, the material should be gradually degraded without the release of toxic products. The implanted structure should be permeable for the exchange of gases, water, and biological signals such as hormones or neurotrophins. Blood vessels that normally supply the nerve might be induced to grow. The central function of the implant remains: the guidance of regenerating axons from the proximal to the distal nerve segment. Consequently, the growth cones have to recognize physical guidance structures, which promote axonal elongation by activating specific receptors on the cell membrane. Similar molecular interactions should allow migration of Schwann cells from the host into the nerve bridge. Schwann cells are indispensable not only for the process of axonal regeneration but also for the subsequent myelination and maintenance of physiological function.

Bioengineering strategies for artificial nerve implants

Hollow tubes

The type of implant which has been tested by far most often in vivo is the hollow tube. In the simplest case, the tube consists of only one material, e.g., chitosan, collagen (natural materials, **Box. 1**), or silicon, PLA, PLGA, and PCL (synthetic materials, **Box. 2**). Hollow tubes are also the only nerve guide design that is used in clinical studies [18]. In animal experiments, grafts are primarily tested as bridges of the rat sciatic nerve. In these experiments, the nerve lesions rarely exceed 20 mm. Frequently, empty tubes serve to assess the biocompatibility of the material or as basis and reference structures for more complicated constructs. The lumen can be structured with gels, fibers, or scaffolds, or the material can be modified chemically to provide biological signals.

Structured implants: gels, fibers, and scaffolds

Mechanical guidance structures in the interior of artificial nerve bridges are intended to provide a surface for the attachment of growth cones and thereby direct elongation towards the peripheral end of the implant. The construction of three-dimensional guidance structures remains a technical challenge (**Fig. 2**). Different strategies are illustrated here with the example of electrospun nano- and microfibers. Using the method of electrospinning, parallel fibers of diameter from less than 100 nm to more than 5 µm can be produced from various synthetic polymers. These fibers have a high surface to volume ratio and mimic aspects of biological fibers in the nerve [21]. Since they can provide a growth substrate for migrating Schwann cells and regenerating axons, electrospun fibers are the basis of many artificial implant designs.

In one study microfibers of poly(glycolic acid) had been incorporated in a chitosan tube. This implant was used to bridge 30 mm long gaps in the sciatic nerve of beagles. The dogs, which were investigated after 6 months, recovered function of the operated nerves. Skeletal muscles were re-innervated, and the artificial constructs were completely degraded within the half year time frame of the study [24]. A different research team stacked films of parallel fibers consisting of poly(acrylonitrile-co-methylacrylate) inside a polysulfone tube. These constructs were implanted in rats to bridge sciatic nerve gaps of 17 mm. Sixteen weeks after surgery target muscles were found to be innervated again, and regeneration of sensory and motor nerve fibers could be demonstrated [13]. In another study, electrospun fiber films were used to subdivide a nerve conduit in two or three longitudinal compartments (**Fig. 2d**). In the rat, sciatic nerve gaps of 14 mm could be bridged in 3 months [5].

An alternative to electrospun fibers consists in the fabrication of gel scaffolds with longitudinal channels (**Fig. 2c**). A promising technique to achieve this goal is controlled freeze drying of collagen suspensions. When solvent freezes from one side of the solutions collagen is displaced to the side, thus resulting in longitudinal walls of orientated guidance channels. With this method, three-dimensional constructs were produced, seeded with Schwann cells and are now being tested in animal experiments [3].

Most likely, the development of suitable physical structures will not be sufficient to reach artificial implants that are as good as autologous nerve transplants. Chemical functionalization of the implant material with biological signals might achieve this.

Functionalization with molecules of the extracellular matrix

The purpose of functionalization is to activate endogenous cells (neurons, Schwann cells, endothelial cells) by the implanted material in a way that promotes nerve regeneration (**Fig. 3b,c,d**). Two fundamental approaches can be distiguished, (1) presentation of molecules of the extracellular matrix (ECM) and (2) controlled release of soluble growth factors.

The use of ECM molecules from the PNS is suggested because axons regenerate naturally along the basal lamina of Schwann cells. Thus, ECM proteins or peptides are coupled to synthetic polymers either by blending, adsorption, or covalent binding [15]. This should promote cells to migrate into the artificial implant and close the gap between the nerve stumps. The main components of the basement membrane are laminins. Laminins are trimeric proteins (α-, β- plus γ-chain) that have long been used to coat cell culture dishes, and therefore these are most often selected. Collagen is a major component of the ECM of peripheral nerves. Thus, electrospun fibers of collagen blends with synthetic polymers also induce axonal growth and Schwann cell migration [21]. Instead of whole ECM proteins, which are extracted from biological material, specific peptide sequences from laminin, fibronectin, or collagen can be synthesized [6, 23]. Their design was made possible by the knowledge of specific amino acid sequences in the ECM which bind to integrin receptors of Schwann cells and neurons. These peptides are adhesive because of the intracellular connection of integrins to the cytoskeleton. In addition, they activate a number of signal transduction cascades in the cells [9]. So far, peptides with the amino acid sequences RGD, YIGSR, IKVAV, and longer versions of those have been successfully applied. We showed, for instance, that covalent binding of GRGDS to electrospun nanofibers of PCL improves their ability to guide axonal growth [14]. Several functionalization strategies with ECM molecules are also being tested *in vivo*: the interior surface of a chitosan tube was modified with various laminin peptides. As an artificial bridge of the rat sciatic nerve, the tube with one of

Abstract · Zusammenfassung

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Abstract

Axonal regeneration is possible in the peripheral nervous system. Therefore, nerve lesions can be cured by suturing the dissociated nerve stumps or by grafting an autologous nerve. Since nerve transplantations cause a sensory deficit at the donor site, it is desirable to develop artificial implants for nerve regeneration. Artificial implants have to promote and guide axonal growth, the migration of Schwann cells and must not cause inflammation. Hollow tubes as nerve bridges are already used in the clinic. However, with these it is not possible to achieve nerve regeneration over distances much longer than 30 mm. For this purpose, a number of natural and synthetic materials have already been tested. Biocompatible tubes are being developed which contain orientated fibers or gels with longitudinal channels. In addition, artificial guidance materials are endowed with specific biological functions. Most frequently, extracellular matrix proteins or synthetic peptides that activate integrin receptors are coupled to the materials. Other approaches use gradients of neurotrophins or incorporate living cells. In the long run, a major goal of research is to develop cell-free artificial implants which allow a similar degree of regeneration as is possible with autologous nerve transplants.

Keywords

Peripheral nerves · Nerve regeneration · Biocompatible materials · Bioprosthesis · Electrospinning

Künstliche Implantate für die Regeneration peripherer Nerven

Zusammenfassung

Da im peripheren Nervensystem axonale Regeneration möglich ist, lassen sich Verletzungen durch Vernähen durchtrennter Nerven oder durch Nerventransplantationen heilen. Für Transplantationen verwendet man sensorische Nerven, z. B. den N. suralis. Da an der Entnahmestelle ein sensorischer Funktionsverlust entsteht, sind künstliche Nervenimplantate wünschenswert. Sie sollten die axonale Regeneration und die Migration von Schwann-Zellen fördern und dürfen keine Entzündungsreaktion hervorrufen. Leere Röhren zur Verbindung von Nervenstümpfen werden schon heute klinisch eingesetzt, es ist allerdings nicht möglich, mit diesen Brücken Distanzen >30 mm durch Regeneration zu überwinden. Um das zu erreichen, wurden eine Reihe natürlicher wie synthetischer Materialien getestet und verschiedene Konstruktionsstrategien erprobt. Verwendet werden biokompatible Röhren mit interne Leitstrukturen, für die parallele Fasern durch Elektrospinnen oder longitudinale Kanäle durch Gefriertrocknung von Gelen hergestellt werden. Daneben werden Implantatmaterialien mit biochemischen Funktionalitäten versehen; dies sind vor allem Proteine der extrazellulären Matrix oder kurze synthetische Peptide, die zelluläre Integrine aktivieren. Andere Ansätze verwenden Gradienten neurotropher Faktoren oder inkorporieren regenerationsfördernde Zellen. Fernziel ist jedoch die Entwicklung zellfreier künstlicher Nervenbrücken, die eine genau so gute Regeneration ermöglichen, wie sie in autologen Nerventransplantaten erreicht werden kann.

Schlüsselwörter

Periphere Nerven · Regeneration · Biomaterialien · Bioprothesen · Elektrospinnen

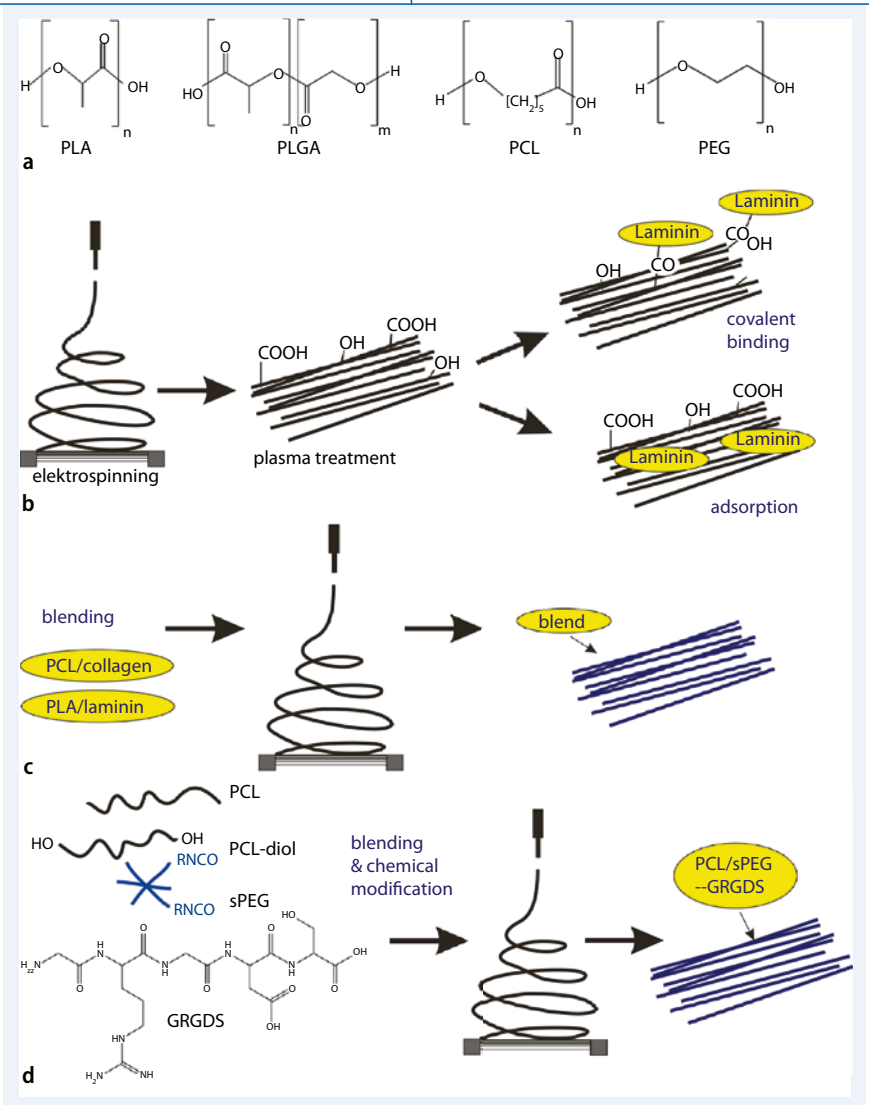

Fig. 3 ▲ Functionalization of guidance structures for nerve regeneration. a Structural formulae of synthetic polymers, which are used in the construction of artificial nerve implants (cf. ◘ **Box. 2**). b Functionalization with adsorption or covalent binding of ECM molecules to electrospun polymer fibers [15]. c Functionalization by blending of ECM molecules with synthetic polymers before electrospinning [21]. d Functionalization by chemical bulk modification of the electrospinning solution [14]

these sequences promoted regeneration to a similar degree as a transplanted nerve, although not as good as autologous implants do [23]. In addition to ECM proteins, the cell adhesion molecules (CAM, an important example for nerve regeneration is L1) constitute another group of surface bound signals that can induce axonal growth. These transmembrane proteins, which are exposed on cell membranes and not parts of the ECM, are also being considered for functionalization [26].

In conclusion, the chemical functionalization of synthetic materials with ECM molecules was an important step in the development of artificial implants with biological activities. Such signals are always fixed to surfaces. Apart from these, peripheral nerve regeneration in vivo depends on a number of small proteins that are usually secreted from Schwann cells or the neurons themselves.

Controlled release of growth factors

To study such factors in vivo the implanted devices are filled with a solution of the growth factor or, in a more sophisticated manner, with carriers that gradually release the active molecules. The latter method allows a better regulation and can be used to produce gradients, to attract axonal elongation toward the distal end of the implant. Several problems have yet to be solved. For instance, the biological activity should be present for a long time (several weeks to months), especially in the case of longer nerve lesions. Also, sterilization should be possible without compromising the function of the signals [7]. The effect of growth factors was studied in several experiments. In one study, 40 mm nerve gaps in the peroneal nerve of rabbits could be repaired in a time of 2 months using glial growth factor (GGF) [19]. This was one of the largest gaps that could so far be bridged successfully with artificial implants. In a different study, the glial derived neurotrophic factor (GDNF) was released from electrospun fibers. These fibers were lining the inside of implanted tubes, which supported functional regeneration over 15 mm in the sciatic nerve of rats [4]. Growth factors have also been combined with ECM proteins. Dodla and colleagues devised an agarose gel to apply a gradient of nerve growth factor (NGF) and laminin. Both gradients had a positive effect on nerve regeneration [8]. Since, unfortunately, there are few studies that would compare different strategies of functionalization, it is at this moment not possible to decide which molecules should be preferred in the future and which, while having effects in vitro, are less suitable.

Implantation of cells with the artificial nerve bridge

The closest thing to real nerve transplants are artificial constructs that are pre-seeded with growth-promoting cells. These cells may derive from the host organism itself or from cultures. They are intended to release physiological signals, many of which may be unknown and, thus, cannot be mimicked with chemical modification of the implant material.

Best suited for this purpose are Schwann cells because they naturally populate the PNS. As alternatives for Schwann cells, olfactory ensheathing cells, mesenchymal stem cells or genetically modified cells are being tested [20]. The majority of studies on PN regeneration have used Schwann cells. They support nerve regen-

eration in various ways, for instance, by forming the bands of Büngner that serve as guidance structures for axonal growth cones. In addition, Schwann cells synthesize ECM molecules and secrete several growth factors, including neurotrophins, CNTF, GDNF, and TGFβ [2]. Unfortunately, the implantation of foreign cells is not without complications. First, the purity of the Schwann cell primary culture is essential because it must not be contaminated with fibroblasts. Second the source of the cells is an issue. Heterologous transplantation between inbred strains of mice and rats is less of a problem, but this would require immune suppression in humans. For a potential therapy of CNS lesions, one strategy is already the preparation of olfactory ensheathing cells from the human olfactory epithelium. In many physiological respects, these glial cells are similar to Schwann cells [12]. Perhaps this will be explored as a possibility to also produce better implants for peripheral nerves. Nonetheless, because of the fundamental difficulties of immune rejection when foreign tissues are implanted, we consider the development of cell-free artificial nerve bridges as important.

Clinical studies with artificial nerve implants

To date, several types of tubes are already approved for implantation in humans [18]. They have been tested with several hundreds of patients. *NeuraGen*, consisting of type I collagen, is produced by Integra Neuroscience (http://www.integrals.com). In the largest study so far, *NeuraGen* implants were used mostly for bridging sensory nerves of the arms. A total of 26 patients were evaluated quantitatively to assess functional recovery of nerve transmission. In 45% of the patients, an improvement of sensory functions was observed [25]. *Neurotube* is a PGA implant, produced by Synovis Life Technologies Inc. (http://www.synovismicro.com). It has been tested in several clinical studies. In one of these, a group of 24 patients received *Neurotube* implants for lesions of nerves innervating the hand, while autologous nerves were transplanted in 74 patients. Lesions ranged between 2 mm and 12 mm. Rehabilitation training was performed in all cases. Although 18 patients had complications due to the implants, about 9/10 of the grafts resulted in successful regeneration [27]. The third artificial implant is *Neurolac*, produced by Polyganics Inc. (http://www.polyganics.com). It consists of a PLA/PCL blend. So far, two clinical studies have been published with a total of 36 patients. While in the first report from 2003, no nerve re-

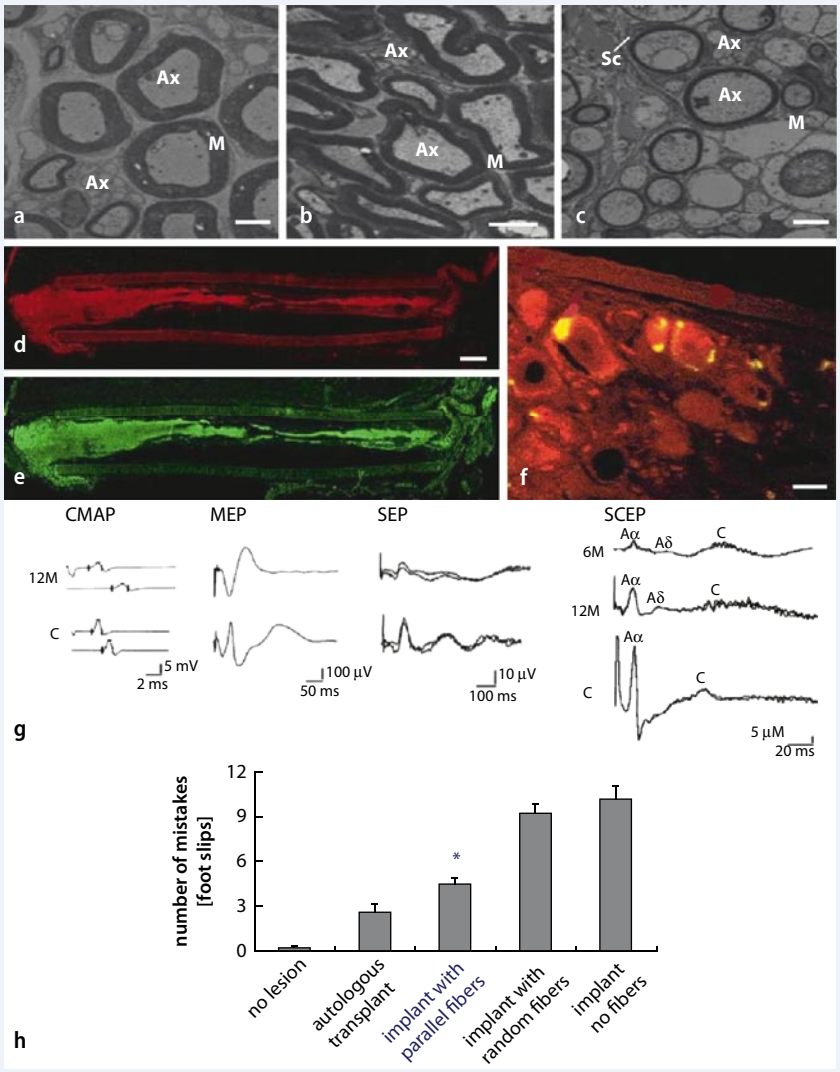

Fig. 4 ▲ Experimental results with artificial nerve implants. **a**,**b**,**c** Electronmicroscopy of transverse sections, scale bar 2 µm: **a** non-lesioned sciatic nerve of the rat; **b** regeneration in an autologous nerve transplant; **c** in an implant with gradients of NGF and laminin, after 4 months, distance 10 mm from the transection site; *Ax* axons, *M* myelin sheaths, *Sc* Schwann cell [8] (©Elsevier Publisher); **d**,**e** regenerated axons in an implant with electrospun microfibers; rat sciatic nerve, after 4 months, immunohistochemical staining of longitudinal sections; *above* (red): neurofilament, axons; *below* (green): S100, Schwann cells [13] (©Elsevier Publisher); **f** retrograde tracing with FluoroGold from the distal end of a chitosan/PGA implant shows axonal regeneration of sensory neurons from the dorsal root ganglion; dogs, 6 months after implantation [24] (©Guarantors of Brain); **g** electrophysiological recordings to assess functional regeneration across a gap of 80 mm, dogs, after 12 months; collagen tubes with laminin coated fibers were implanted into the peroneal nerve: compound muscle action potential (CMAP) of the anterior tibialis muscle after stimulation of the sciatic nerve; motor evoked potentials (MEP) in the tibialis muscle after electrical stimulation of the motor cortex; somatosensory evoked potentials (SEP) recorded from the cerebral cortex after muscle stimulation and spinal cord evoked potentials (SCEP) with stimulation of the nerve stump distal to the graft [17] (©Guarantors of Brain). **h** Functional demonstration of regeneration (through the implants shown in **d**,**e**) in rats. In the grid walking test the number of mistakes are counted while the rat walks across a grid. Implants with fibers orientated in parallel (*) achieved better results than implants without or with non-orientated fibers, yet autologous nerve transplants were still better [13] (©Elsevier Publisher)

generation was found, the second study reported functional regeneration similar to results with autologous nerve transplants [1].

Another type of nerve bridge has been developed in Japan, but so far is not approved in the US or Europe. This structure consists of PGA implants with collagen scaffolds. In the most recent study from 2007, excellent recovery was achieved in two patients who suffered injuries to the facial nerve [11].

Problems and perspectives

In contrast to long distance connections within the CNS such as the optic nerve or spinal cord, peripheral nerves already provide an area of successful projects for neuronal tissue engineering (**Fig. 4**). A fair number of biocompatible materials have been developed, which offer great potential for therapies of peripheral nerve injury. Nevertheless several issues present technical or scientific challenges today.

Standardized efficiency control: Many experiments with different biomaterials are not compatible because different cell cultures, animal models, or criteria of success were used. In general, we observe that a considerable proportion of publications with innovative materials use poor standards when it comes to the biological tests. Inflammatory reactions, effects on gene expression and long-term results are rarely investigated. Clearly, systematic comparisons of the different materials for artificial nerve conduits are needed.

Structured three-dimensional implants: So far most studies of PN regeneration in vivo have only implanted hollow tubes, where axons start to grow on the inner surface of the implant. Thus, a major technical challenge is the construction of three-dimensional nerve bridges with internal structures that guide axonal growth and migration of the endogenous Schwann cells. Promising approaches are the integration of microfibers in parallel orientation [13, 16] and the production of orientated channels in collagen gels [3].

Biomimetic functionalization of implants: With the use of proteins and peptides derived from ECM of the PNS, artificial implants already mimic the signals that regenerating axons encounter naturally in lesioned peripheral nerves. However, the targeted use of factors that specifically activate Schwann cells, sensory or motor neurons is still in its infancy. In addition to the selection of the right molecular signals, it remains a challenge to find the specific temporal and spatial patterns of activity that promote axonal growth through the entirety of an implant and into the target tissue. Neurotrophic signals might be required for several months and with increasing gradients towards the distal end of the implant.

The thirty millimeter mark: Most animal studies demonstrate that peripheral nerve regeneration through artificial implants can cover distances of up to 30 mm but not beyond. Since larger gaps must occasionally be bridged in cases of human nerve injury, the usefulness of future constructs will be judged by their ability to support regeneration over long distances, and here experiments with the rat sciatic nerve come to their limits. We are convinced that results from basic research on mechanisms of axonal growth in combination with engineering methods like electrospinning, freeze-drying, and chemical functionalization will result in further progress with the development of artificial nerve implants. There is hope that these approaches will provide the neurosurgeon with suitable cell-free implants that can be stored and used on demand.

Corresponding address

I. Koxholt
Institut für Biologie II, RWTH Aachen
Mies-van-der-Rohe-Str. 15, 52074 Aachen
mey@bio2.rwth-aachen.de

I. Koxholt. studied history and biology at the RWTH Aachen, Germany. She has been working on the development of a three-dimensional nerve conduit since 2009.

Prof. Dr. rer. nat. J. Mey
Institut für Biologie II, RWTH Aachen
Mies-van-der-Rohe-Str. 15, 52074 Aachen
mey@bio2.rwth-aachen.de

J. Mey. studied history and biology at the Universities of Freiburg, Germany, St. Catharines, Canada, and Tübingen, Germany. His PhD thesis at the University Eye Hospital, Tübingen and Max-Planck Institute of Developmental Biology focused on regeneration of retinal ganglion cells. After his postdoctoral years at the Shriver Center/Harvard Medical School, Boston, he moved to the Institute of Zoology and Neuroscience, RWTH Aachen, where he has been a professor since 2007. In addition to the project on artificial nerve implants, his group investigates retinoid signaling in the nervous system.

Conflict of interest. The corresponding author states that there are no conflicts of interest.

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