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Recent advances in strategies for peripheral nerve tissue engineering

Sahba Mobini[1], Benjamin S. Spearman[1], Christopher S. Lacko[1] and Christine E. Schmidt

Abstract

Peripheral nerve injuries often result in longstanding disability with loss of motor and/or sensory function. Peripheral nerve tissue engineering researchers have been exploring strategies to replace autologous nerve grafts, the gold standard treatment for peripheral nerve injury. Currently, there is still a large technological gap between laboratory research technologies and the products used in the clinic. There are also concerns about the use of rodent models and the reliability of the treatment outcomes. In this paper, we review the most recent approaches in peripheral nerve tissue engineering and methodologies in clinical trials, preclinical studies, and *in vitro* experiments and briefly discuss future perspectives of the field. We highlight the need for improved *in vitro* modeling, including nerve-on-a-chip technology and the use of computational modeling. Progress in this area can help to optimize combinatorial treatments and accelerate clinical translation. Furthermore, we see great potential in personalized tissue-engineered scaffolds, which could incorporate patient- and injury-specific anatomy, for complex lesions that are difficult to repair using currently available options.

Addresses

J. Crayton Pruitt Family Department of Biomedical Engineering, The University of Florida, United States

Corresponding authors: Mobini Sahba J. Crayton Pruitt Family Department of Biomedical Engineering, P.O. Box 116131, The University of Florida, Gainesville, FL, 32611-6131, United States. (sahba.mobini@bme.ufl.edu); Schmidt, Christine E, J. Crayton Pruitt Family Department of Biomedical Engineering, P.O. Box 116131, The University of Florida, Gainesville, FL, 32611-6131, United States. (Schmidt@bme.ufl.edu)

[1] Equally contributing authors.

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Introduction

Approximately 200,000 peripheral nerve injury repair procedures are performed each year in the US alone [1], resulting in more than 5 million disability days each year [2]. While the peripheral nervous system is capable of endogenous regeneration because of myelinating Schwann cells, growth factors, and the biomolecules of the extracellular matrix (ECM); however, above the critical nerve-gap length (~3 cm in human), the regenerated nerve can become misdirected, or associated with neuropathic pain.

Traditional methods of peripheral nerve repair and regeneration have been reviewed at length in past [3,4]. Autologous nerve grafts (autografts) have been the standard treatment for repair of nerve injuries for decades, and remain the only clinical option for nerve injuries greater than 7 cm in length. Although autografts can be harvested from the patients' non-critical nerves, this procedure requires a secondary surgical site, associated loss of function, and increased operating time and cost. Harvesting a graft of appropriate diameter and length can pose a challenge, especially with injuries to large-diameter nerves. Furthermore, the use of primarily sensory nerves for autologous grafting has been shown to result in lower rates of regeneration for motor nerve injuries compared to motor or mixed—nerve autografts [5].

Peripheral nerve tissue engineering strategies have been explored to develop autograft alternatives in long-gap nerve injuries. One of the primary approaches in tissue engineering is mimicking the microenvironment of native tissue. Peripheral nerve microenvironment, including extracellular matrix of the nerve, has various features such as chemical composition, mechanical properties, structural organization (micro-architecture) and bioelectrical signals. The FDA has approved several nerve repair devices [6], however challenges remain and novel tissue engineering approaches continue to be evaluated in both research and clinical settings. Among the number of recent innovations for tissue-engineered devices, few technologies have successfully translated to off-the-shelf products. Here we briefly review (1) the recent devices being used in clinic, (2) recent advances in devices in preclinical trials, and (3) *in vitro* cutting-edge approaches to address the needs in both clinical and preclinical studies.

Clinical peripheral nerve tissue engineering devices

Nerve guidance conduits

Early conduit designs were made of silicone tubes, and these nerve guidance conduits (NGCs) were only capable of functional repair of nerve gaps up to 1 cm. Lack of biodegradability of silicone NGCs is cited as the primary hindrance towards regeneration in these devices, and the device's persistence can cause nerve compression and a chronic foreign body reaction inhibiting functional regeneration [7,8].

To address the problems associated with silicone NGCs, researchers developed several biodegradable nerve guidance conduits from synthetic and naturally based sources. Today, there are numerous available NGCs developed from a variety of materials such as collagen I, porcine decellularized small intestinal submucosa, polyglycolic acid, polyvinyl alcohol, and poly-lactide caprolactone. Kehoe et al. provided an excellent review of these FDA-approved devices [6]. Overall, although the introduction of resorbable, current-generation NGCs has improved upon prior silicone-based conduits, most NGCs are hollow and only capable of repairing short nerve gaps <3 cm in length. One novel conduit that received FDA 510k approval in 2014 (K130557) is the NeuraGen® 3D nerve guide matrix, Fig. 1A. This NGC is the first FDA-approved conduit to incorporate a luminal filler for three-dimensional guidance and support of regenerating axons, Schwann cells, and supportive cells. Specifically, this NGC is developed from a collagen I conduit that incorporates a luminal filler of collagen-I and the glycosaminoglycan chondroitin-6-sulfate, with axially aligned hydrogel porosity to provide topological cues for regenerating cells. This graft is indicated for nerve gaps in areas which are prone to closing with muscle and joint flexion. *In vivo* studies in a rat 10 mm sciatic nerve injury model have been published, and demonstrated significantly improved regeneration compared to an empty conduit [9]. However, regeneration was still found to be significantly lower than autograft controls.

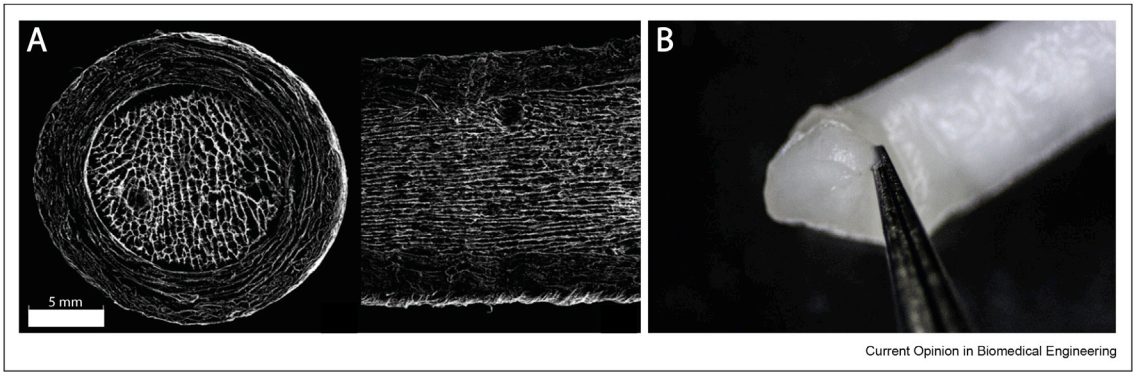
Processed nerve allografts

The Avance® nerve from AxoGen inc., Fig. 1B, was the first processed nerve allograft available in the clinic for repair of human peripheral nerve injuries. Processed nerve allografts are harvested from cadaveric nerve sources and are specially processed to remove cellular components of the tissue, including immunogenic epitopes, while maintaining the extracellular matrix architecture of native nerve, including the linear-tubule architecture of the basal lamina surrounding individual axon Schwann cell units [10]. Development of processed nerve allografts allowed for allograft nerve transplants without necessitating lifelong immunosuppression. Processed nerve allografts are indicated for longer gaps than NGCs, and are available in lengths up to 7 cm [11,12]. The improved functional recovery [13–15] induced by processed allografts is thought to be encouraged by the highly linear and biomimetic porous architecture of the nerve grafts, and native extracellular matrix present in the grafts.

Ongoing clinical trials

According to clinicaltrials.gov, there are a total of 22 registered peripheral nerve injury studies of any activity status in the United States, of which seven studies utilize tissue engineering approaches. Of these seven studies, three are focused on processed nerve allografts and post-market comparisons of currently approved devices, one is focused on electrode implantation for robotic limb control after amputation, two were on the use of autologous human Schwann cells, and only one study is focused on new biomaterial approaches for peripheral nerve repair.

Figure 1



Clinical peripheral nerve repair products with internal architecture. For products without internal architecture, see [6]. **A)** Transverse (left) and longitudinal (right) SEM micrographs of Collagen I NGC with Collagen I and glycosaminoglycan luminal filler commercialized as the NeuraGen 3D® nerve guide matrix by Integra Lifesciences [9]. **B)** Commercially available processed nerve allograft (Avance® nerve by AxoGen, [48]).

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