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Leiden  
The Netherlands

## Peripheral nerve graft architecture affects regeneration

Vleggeert-Lankamp, Carmen Lia Anne-Marie

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## **CHAPTER 1**

### **Introduction**



## Introduction

Depending on the nature and severity of impact, peripheral nerve injury can vary from a temporary block of nerve conduction at the site of injury without loss of axon continuity to injury in which axons are severed or damaged to a degree that results in their disintegration. Some axons in the proximal stump degenerate totally, but the majority degenerate up to the first node of Ranvier proximal to the injury. Axons in the distal stump are doomed to die since they have lost contact with their cell bodies and cannot be supplied adequately [3]. Such disintegration also concerns the axons' myelin sheath at the site of the injury and below, also known as Wallerian degeneration [3]. After completion of Wallerian degeneration, the architecture of the distal nerve stump is reduced to empty tubes formed by the basal lamina that previously surrounded the myelinated axons. The Schwann cells remain present in these basal lamina scaffolds, though in a different axon-independent mode [1].

Recovery from nerve injury is considered to be dependent on the continuity of the axon, the myelin sheath and the basal lamina scaffold. In order to categorise nerve injuries and to predict recovery, Seddon classified nerve injuries into three categories, i.e. neurapraxia, axonotmesis and neurotmesis [2]. Sunderland distinguished five categories of nerve injury, the first degree corresponding to neurapraxia, the fifth to neurotmesis [3]. If the continuity of the axons is preserved, local changes are of a minor nature and full recovery of function can occur, usually within weeks ('neurapraxia'). If only the axons are interrupted, Wallerian degeneration will take place while the basal lamina scaffold persists. Schwann cells within the basal lamina scaffold will form Büngner bands along which the regenerating axons can grow out and the axons will eventually be led to their original target ('axonotmesis'). In most cases not all axons will regenerate, and consequently functional recovery will be incomplete. In this respect the distance between injury site and target organ is an important factor. Given an average growth of regenerating nerve fibres of 1 mm per day, the time to recovery can be estimated. If the basal lamina scaffolds are damaged and their continuity cannot be preserved, the regenerating axons will not be guided to the distal nerve stump and no recovery of function will take place ('neurotmesis').

Surgical repair is only indicated after neurotmesis in order to restore the anatomical continuity which enables the regenerating nerve fibres to reach the distal nerve stump. This can be done by either direct coaptation of the nerve stumps, or by the interposition of an autologous nerve graft ('autograft') between the stumps. After approximately one week, Wallerian degeneration in the autograft will have caused the axons and surrounding myelin sheaths to disintegrate, and the autografts will consist of empty tubes formed by the basal lamina scaffolds, filled with Schwann cells. Regenerating axons are able to grow through these scaffolds and they may regain contact with their target organs. However, both after direct coaptation and after autografting the basal lamina scaffold will be interrupted, and notwithstanding the restoration of continuity, it is highly likely that the proximal and distal scaffolds will be misaligned. Therefore the regenerating axon in the proximal basal lamina scaffold has

a very low chance to enter the original matching distal basal lamina scaffold. Misrouting is the term used for the outgrowth of nerve fibres towards a wrong target. Since in autografting two instead of one coaptation sites have to be bridged, the chance of misrouting is increased, and it is therefore not surprising that the functional outcome after autografting is usually worse in comparison to direct coaptation. Additional problems of autografting are donor site morbidity related to the harvesting of the autografts, and the prolonged surgical procedure [4, 5]. Theoretically it is also possible that the supply of autograft material is too limited, especially after extensive brachial plexus lesions.

The poor recovery after autografting motivated the search for alternative tools to bridge nerve defects, and the manufacture of a synthetic nerve graft is one of the avenues under investigation. A synthetic nerve graft is a hollow tube that merely guides the regenerating nerve fibres from the proximal to the distal nerve stump. In order to optimize the synthetic nerve graft, the fabrication of the tube material can be changed, it can be filled with a nerve growth promoting factor, and the architecture of the graft can be varied.

A very popular experimental model to investigate peripheral nerve repair was and is the rat sciatic nerve model. Using this model a wide range of synthetic nerve grafts has been studied. However, making progress in this particular field of research is hampered somewhat by the fact that the outcome of peripheral nerve regeneration through a particular synthetic nerve graft is difficult to distinguish from other grafts, especially across laboratories. An inherent drawback of the field of synthetic nerve graft research is the comparative approach; novel devices are compared against a previous device, or against an autograft. Consequently there has been little systematic research into the properties that a synthetic nerve graft should ideally have in order to support regenerating nerve fibres optimally.

### **Aims and outline of this study:**

- 1) It is important to adequately evaluate peripheral nerve regeneration in order to qualify a new synthetic nerve graft. The first aim of this study is to summarize the evaluation methods that are described in literature and to score their (in)ability to statistically differentiate between grafted nerves. These results will allow us to establish what evaluation methods should preferably be used by us to adequately quantify nerve regeneration (chapter 2).
- 2) Methods that give comprehensive information about the electrophysiological functioning of regenerated nerve fibres are only sporadically present in literature concerning nerve regeneration. The second aim of this study is to develop an electrophysiological evaluation method with a low signal to noise ratio in order to be able to measure small differences between responses. Furthermore we intend to couple electrophysiological to nerve morphometrical results to gain insight in the processes that play a role in peripheral nerve regeneration (chapter 3).

- 3) Although a lot of papers are published on the implantation and subsequent evaluation of synthetic nerve grafts, papers concerning preferable properties of those nerve grafts are remarkably scarce. The third aim of this study is to investigate the influence of porosity (chapter 4 and 5) and degradability (chapter 6) of a synthetic nerve graft on peripheral nerve regeneration.
- 4) The (mal)functioning of the target organs of regenerated peripheral nerves is considered to be the most important evaluation tool. However, it is intricate to properly investigate the functioning of the motor and sensory target organs. Since we consider the functioning of the muscle to be closely related to its morphology, we want to study morphological changes that take place in muscles that are reinnervated by regenerated nerve fibres. The fourth aim of this study is to compare the morphology of muscles distal to a nerve gap bridged by an autograft or by a synthetic nerve graft (chapter 7).
- 5) Schwann cells will inevitably be present in synthetic nerve guides, either by their migration from the proximal and distal nerve stump, or by the application of cultured Schwann cells in nerve grafts, which is done to improve nerve regeneration. The fifth aim of this study will be to test the interaction of Schwann cells with potential graft biomaterials (chapter 8) and matrices to fill the synthetic nerve guides with (chapter 9).

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