MATHEWS

Review Article

Mathews Journal of Pharmaceutical Science

Overcoming Challenges in Peripheral Nerve Regeneration: A Review of Pharmaceutical Scaffold Applications

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ABSTRACT

Injuries on the peripheral nerves of a patient, can affect a patient's overall quality of life and also lead to adequate loss of motor and sensory functions. Although there are various techniques that have been deployed in nerve tissue regeneration, their limitations are tied to their delayed functional recovery in patients. Some of these limitations include delayed functional independence, surgery-related complications and recovery following peripheral nerve injury. These limitations notwithstanding, techniques that could improve the peripheral nerve regeneration could be developed. Pharmaceutical scaffolds with the help of nanotechnology, have shown promising features and functional properties in nerve regeneration. Moreover, different external biophysical strategies such as electrical, magnetic and light-based stimulations can be applied to achieve even better results. The review was aimed to discuss the major factors that affect nerve recovery completely, and also throw more light on the three major biophysical strategies such as electrical, magnetic and light- based stimulations, which are currently used to improve peripheral nerve regeneration. Combination of these techniques, with pharmaceutical nanomaterial-based nerve guide conduits have shown to yield an improved nerve repair regeneration. Nanotechnology has the potential to guide regeneration of the peripheral nerve. This can be achieved by delivering bioactive molecules in a controlled manner and tuning cellular behavior. Nanoparticles and nanofibers due to their mechanical strength, serve as scaffolds for tissue and peripheral nerve regeneration.

Keywords: Injuries, Peripheral Nerve Regeneration, Stimuli, Recovery, Nanotechnology, Biophysical Strategies.

INTRODUCTION

The peripheral nervous injury (PNI) is a challenge that occurs globally, which affects atleast one million people worldwide [1]. It usually affects the sensitivity of both the motor and sensory functions. There are various

Vol No: 09, Issue: 04

Received Date: August 21, 2025

Published Date: October 31, 2025

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Citation: Ezegbe CA, et al. (2025). Overcoming Challenges in Peripheral Nerve Regeneration: A Review of Pharmaceutical Scaffold Applications. Mathews J Pharma Sci. 9(4):57.

factors that are associated with PNI. These factors include injuries that might occur physically, at construction sites or via accidents and chronic diseases such as diabetes [1]. High rise in PNI, affects the gross domestic product (GDP) of developed countries such as United States of America, Canada, Australia and developing countries, like Nigeria and Brazil [2]. Major causes of high prevalence of PNI include surgery and trauma, chronic neuropathic pain, limited time window for sufficient muscle reinnervation and regeneration rate [2]. PNI can lead to disability and neuropathic pain, resulting in a substantial economic burden [2]. PNI associated with trauma, can affect young adults negatively [3]. Regeneration in the peripheral nervous system is essential for restoring nervous system function [4]. Treatment patterns deployed in the PNI usually depends on the size of the nerve injury. In short nerve gaps, high tendency to experience a spontaneous natural regeneration occurs, while in larger gaps, there is need to incorporate a microsurgical repair [3]. Other factors that affect the repair processes in PNI include the injury site, treatment time interval, patients age and the particular affected nerve [4]. Reduced quality of life and depression can occur when there is incomplete repair [5]. Neurorrhaphy is the most commonly used approach in nerve tissue regeneration. However, large gap size is a major limitation associated with this technique. Regeneration failure is common with injuries that are greater than 0.5 cm in size [1]. In PNI repair, the current gold standard that has been deployed in treatment is the autologous graft (AG). The reason is due to the fact that it is used to treat moderate and severe injuries. For larger gaps, recommendation is usually on decellularized allografts or xenografts [6-9].

Cellular mechanisms in nerve regeneration, involves Schwann cells which play major roles in peripheral nerve regeneration. This is achieved via two major processes; the ability to myelinate axons and the ability of the cells to contribute to repair processes after injury [9]. This allows them to transit into a repair phenotype, facilitating Wallerian degeneration by clearing myelin debris, recruiting macrophages and forming Bungner bands that guide axonal regrowth [10]. Several molecular pathways regulate the nerve regeneration process, including the activation of c-Jun, which promotes the Schwann cell repair phenotype and enhances nerve regeneration. There are different developmental transitions that Schwann cells usually undergo [11]. During nerve injury, the cells exhibit remarkable plasticity, differentiating into repair Schwann cells that clear myelin debris, guide axonal regrowth and secrete neurotrophic factors essential for regeneration [10]. Biological scaffolds and stem cell therapy are both used in tissue engineering and regeneration [12]. Biological scaffolds facilitate stem cell adhesion, proliferation, differentiation and paracrine functions in wound healing [12]. This review also highlighted the light, electrical and magnetic biophysical stimuli, and how biophysical stimulation can help in nerve regeneration using pharmaceutical scaffolds.

Peripheral nerve regeneration

Regeneration of the peripheral nerve is a process that occurs in the PNS where the chances of regeneration is greater, because of the presence of Schwann cells, which facilitate repair and restore functions [10]. Factors such as inflammation, oxidative stress and excitotoxicity can influence the success of regeneration, making it essential to manage these conditions for optimal recovery [11]. The peripheral nervous system (PNS) is made up of connective tissue, blood vessels, ganglia and axons [10,11].

Peripheral nerve injuries (PNI) are associated with degeneration of the myelin sheath, leaving the endoneuria tube empty [12]. The degenerated nerve structures lead to the recruitment of macrophages and Schwann cells (SCs). Growth factors and cytokines are released by Schwann cells. This helps to regulate the regeneration of the nerve cells [13,14]. A loss of contact of the Schwann cells with the axon, leads to alteration, which resembles the precursor cells of myelinated SCs [15]. These biomolecules are maintained by the Schwann cells due to their short period of time [16,17].

During injury, there is impairment in the nerve which can only return after regeneration of the tissues. The main challenges in peripheral nerve regeneration are: duration of time taken for complete repair, regenerating nerve vascularization and immune responses control. Figure 1 represents the porous structure of peripheral nerve regeneration which consist of the axonal interruption, Wallerian degeneration, axon regeneration and terminal nerve reinnervation.

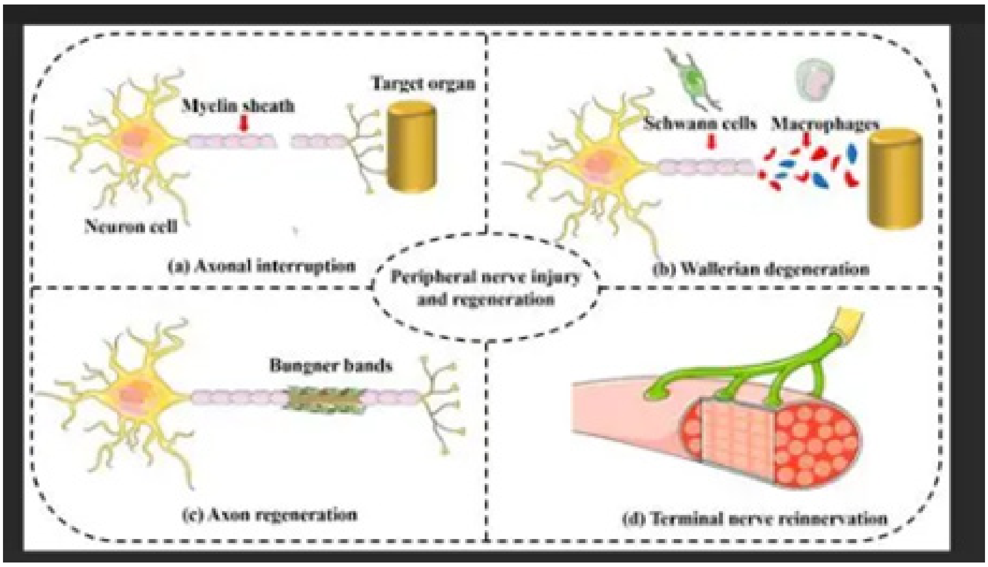

Figure 1. Porous structure of peripheral nerve regeneration [10].

ELECTRICAL STIMULATION

Electrical stimulation (ES) is a promising adjunctive therapy to peripheral nerve surgery for enhancing axonal regeneration and accelerating functional recovery that is underscored by decades of preclinical investigations and several recent prospective, randomized, clinical trials [18]. In a situation where the distance between the proximal and distal segments are long, electrical stimulation could be used to enhance the peripheral nerve regeneration [18]. The improvement in the PNR due to electrical stimulation is due to ion channel permeability [19].

There are different clinical protocols of electrical stimulation for PNR, the commonly used approach involves intraoperative procedure which deploys frequencies of 20 Hz for one hour, and this generates a good outcome [20]. Patients with cubital tunnel syndrome, a compressive neuropathy, treated by a clinical protocol (<30 V, pulse duration of 0.1 ms) had better axonal regeneration and improved grip and pinch strength [21].

Another important factor that should be considered, is the duration of time taken to ES exposure. Although brief stimulation presented a reliable result, increase in the stimulation time for more than three (3) hours exhibited results similar to the non-stimulated groups [22]. The efficiency of intermittent ES (25 Hz / 0.1 ms pulses for 30 min) in implantable devices and by the transcutaneous method in rats was investigated by Ju et al. The result obtained indicated that the group with the implantable device, capable of wireless stimulation, had a faster functional recovery with a lower sciatic functional index (SFI), having larger axon and muscle fiber diameters [23].

Figure 2 depicts the proposed mechanism of electrical stimulation enhancing regeneration versus no treatment [22,23]. They are divided into four (4) major sections: immediately after recovery, early regeneration, late regeneration and delayed regeneration.

https://doi.org/10.30654/MJPS.10057

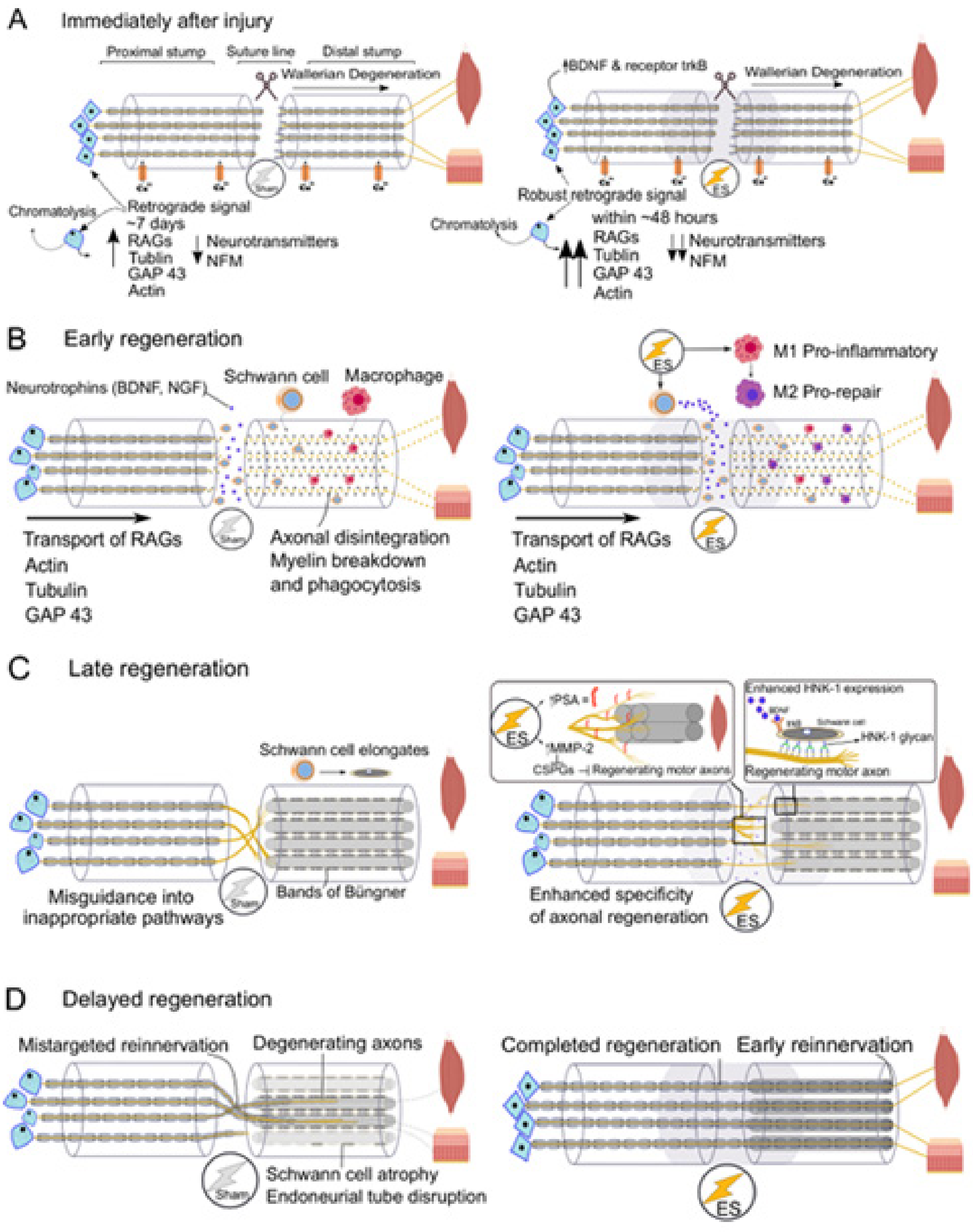

Figure 2. Proposed mechanism of electrical stimulation [23].

MAGNETIC STIMULATION

As far back as in the 1970s, especially in the healthcare sector, magnetic stimulation had played a significant role especially as a procedure used in several cell type proliferation [24-27]. Review on several studies have shown that regeneration can be improved by applying a pulsed electromagnetic field (PEMF). This procedure is based on a low-frequency electromagnetic field (0.3 to 300 mT) with a determined repetition frequency (2 to 2000 Hz) [28]. Byers et al. applied a 0.4 mT at 120 Hz in a protocol consisting of 4 hours per day, 5 days per week, for 8 weeks, to investigate the in vivo regeneration of facial nerves in mice [29].

Nanotechnology has played a key role in the amplification and enhancement of the MS effects [26]. Superparamagnetic iron oxide nanoparticles (SPIONs), are known to possess important characteristics which include biocompatibility, stability, and magnetic properties [27-30]. Superparamagnetic ion oxide nanoparticles (SPIONs) have already received approval for clinical application in other medical fields, such as ferrofluids for magnetic hyperthermia [31]. Figure 3 illustrates the schematic of the development of a double-layer conductive nerve conduit via magnetic stimulation.

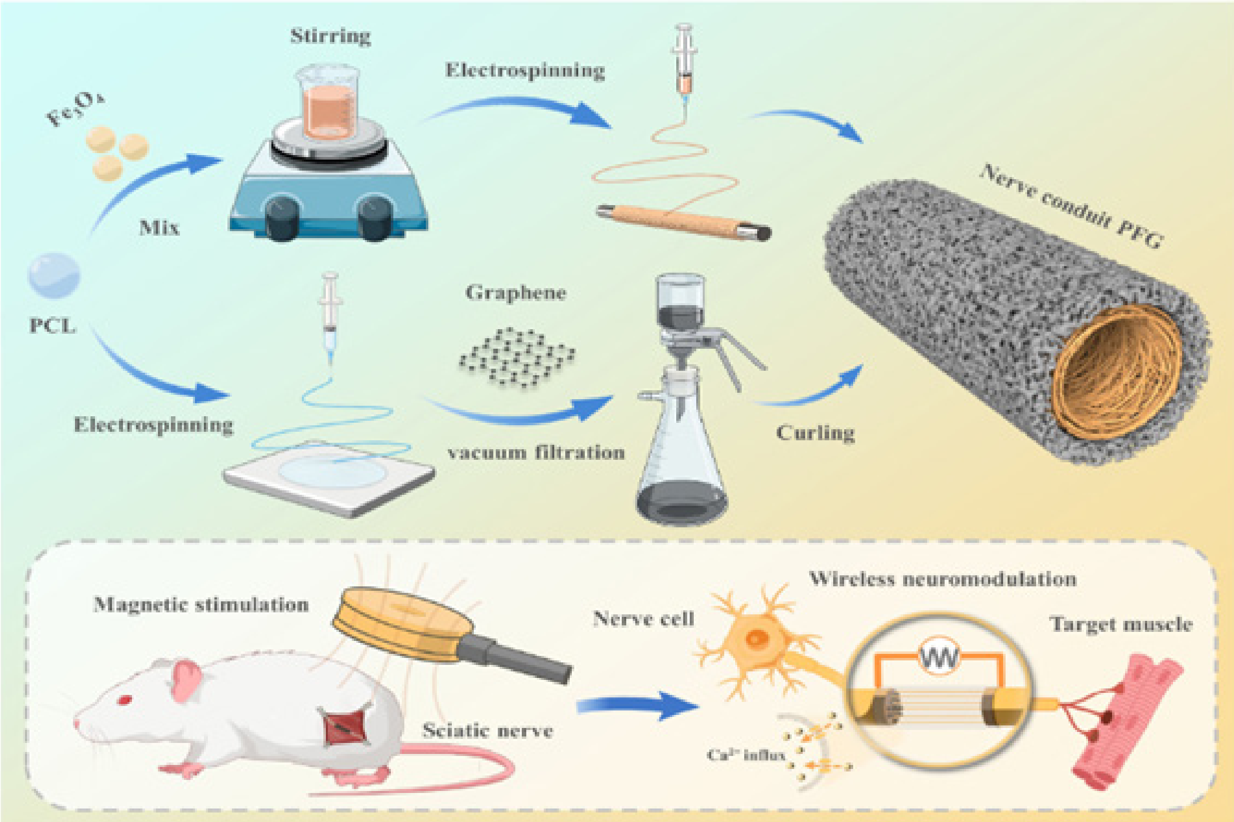

Figure 3. Schematic of the development of a double-layer conductive nerve conduit with a length and radius of 15 mm and 4 mm respectively. Graphene within the conduit generates microcurrents under the stimulation of an external alternating magnetic field at 10 V 448 KHz, promoting the proliferation and migration of Schwann cells, myelin sheath formation, and axon extension, thereby inducing peripheral nerve regeneration [33].

LIGHT STIMULATION

Since the early 1970s, and late 1980s, living tissues had been treated using light irradiation [32-34]. Macrophages rapidly accumulate in the retina after optic nerve injury and convert the non-permissive environment into a proregenerative one [35]. Oncomodulin (Ocm), a potent proregenerative factor secreted by macrophages, promotes axon regeneration in a cAMP dependent manner [34]. Overexpression of G protein-coupled receptor 3 (GPR3) further enhances inflammation-induced regeneration by elevating basal cAMP levels in RGCs [36]. According to Er-Rouassi et al. [37], they observed that the functional recovery of facial nerves in mice treated with PBMT (820 nm, twice a day for 16 days) was greatly improved, when compared to the untreated control group, which was associated with the activation of the cytochrome C oxidase.

According to Li et al. [38], they also investigated the regeneration of facial nerves with PBMT (980 nm, 30 s / 8 h for 12 days). The result obtained showed an upregulation of the phosphatidylinositol-3 kinase/protein kinase B (PI3K/Akt) signaling pathway, which lead to positive effects such as inhibition of apoptosis, increased proliferation of SCs, and improved functional recovery. Although there are some advances in comprehending the mechanism during the PBMT treatment, the effect on axonal degeneration and regeneration by stimulating mitochondrial activity still needs a deeper investigation [39-41]. Figure 4 is a representative image of advances in retinal ganglion cell (RGC)-extrinsic factors regulating optic nerve regeneration.

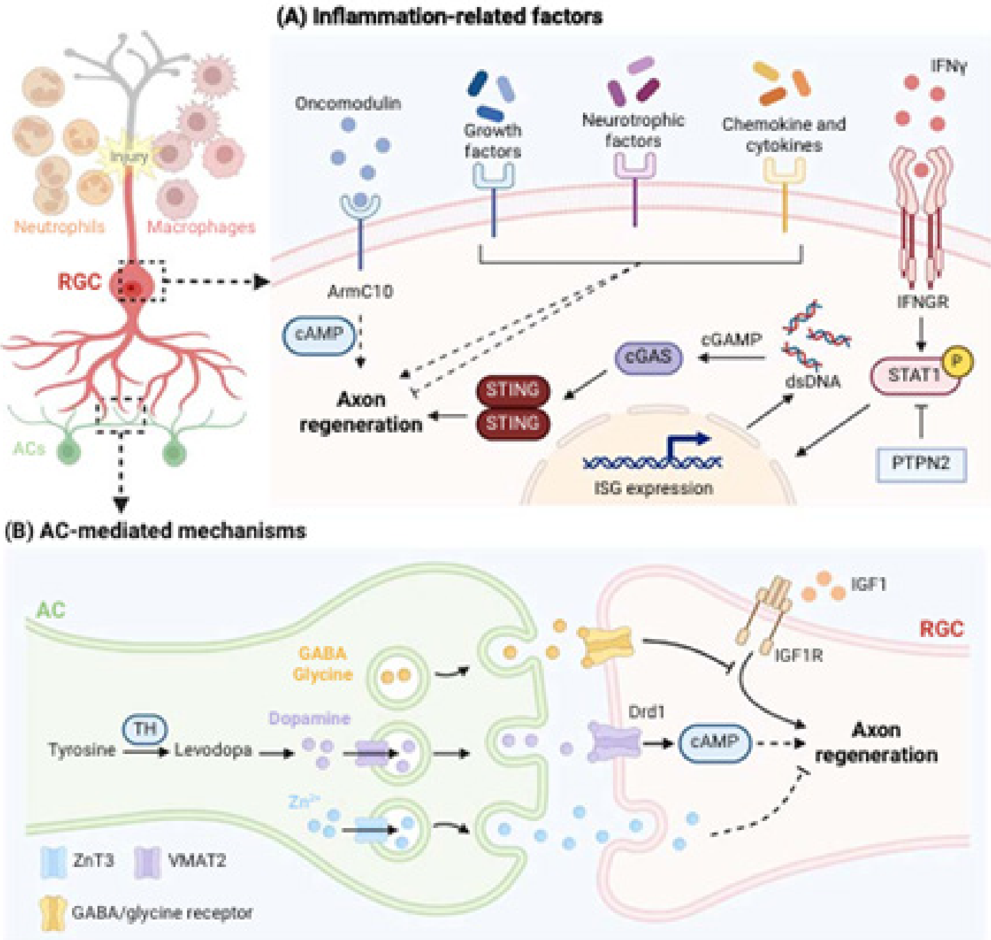

Figure 4. Advances in retinal ganglion cell (RGC)-extrinsic factors regulating optic nerve regeneration [41].

CONCLUSION AND FUTURE PERSPECTIVES

This review summarized the different techniques that could be used to enhance the regeneration of PNI. Currently, nerve guide conduits are already being used in clinical practices. However, they do not consistently outperform autologous nerve grafts. In general, the combination of NGCs, external stimulation, and nanotechnology is a revolutionary approach to PNI repair. In consideration of the current limitations and more profound knowledge of nerve regeneration mechanisms, these methods have great potential to revolutionize peripheral nerve injury treatment. Further research should be carried out to determine the usefulness of nanotechnology in humans, with studies that encompass the long-term biocompatibility and safety of nanomaterials. There is need to develop smart scaffolds that combine biophysical stimulation and pharmaceutical delivery or employing AI and machine learning for designing stimulation parameters.

ACKNOWLEDGEMENTS

None.

ETHICAL APPROVAL

Not required.

AUTHOR CONTRIBUTIONS

CAE: Formal analysis, Investigation, Methodology, Revision.

OAC: Formal analysis, Investigation, Methodology, Revision.

IJU: Formal analysis, Investigation, Methodology, Revision.

CONFLICTS OF INTEREST

No conflict of interest.

DATA AVAILABILITY

Not available.

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