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REVIEW

Advanced Nanoparticle-Engineered Platforms for Peripheral Nerve Repair: Multimodal Therapeutic Strategies and Clinical Translation

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Abstract: Peripheral nerve injuries (PNIs) remain a major clinical challenge, with current surgical interventions often falling short of restoring full function. Nanoparticle (NP)-engineered platforms are emerging as transformative tools in peripheral nerve repair by enabling multimodal therapeutic delivery, spatiotemporal control of the microenvironment, and biomimetic structural support. In this review, we summarize the recent advances in the design of inorganic, polymeric, and hybrid NPs that deliver neurotrophic factors, anti-inflammatory agents, and genetic material with high precision. Functionalization strategies—ranging from conductive and piezoelectric materials to antioxidant and immunomodulatory components—enable dynamic regulation of cellular behaviors critical for regeneration. Integration of NPs into next-generation scaffolds, including smart-responsive conduits and bioactive matrices, enhances axonal guidance and Schwann cell support. We further discuss preclinical outcomes demonstrating robust functional recovery and address translational barriers, including NP toxicity, scalable fabrication, and regulatory considerations. Finally, we outline future directions involving theranostic systems and AI-guided design for personalized nerve repair. Collectively, NP-engineered systems represent a paradigm shift in peripheral nerve regeneration, offering a multifaceted approach that bridges material science, bioengineering, and clinical translation.

Keywords: peripheral nerve injuries, nanoparticle, engineering, regeneration, translation

Introduction

Peripheral nerve injuries (PNIs) affect millions of individuals worldwide each year, leading to motor and sensory dysfunction, chronic neuropathic pain, and long-term disability. While peripheral nerves possess some intrinsic regenerative capacity, spontaneous recovery across critical-size defects (>3 cm) is often incomplete and functionally inadequate.[1,2] The current clinical gold standard—autologous nerve grafting—remains limited by donor site morbidity, restricted graft length and diameter compatibility, and the risk of neuroma formation. In response, synthetic nerve guidance conduits (NGCs) have been developed as off-the-shelf alternatives.[3,4] However, most NGCs fail to fully recapitulate the complex biochemical and biophysical cues required for orchestrated nerve regeneration, especially over long-gap defects.

To address these limitations, nanotechnology offers promising opportunities for engineering next-generation platforms that more closely mimic the native nerve microenvironment.[5] Particularly, nanoparticles (NPs) offer tunable features like size, shape, surface charge, and degradability, making them well-suited for targeted, sustained delivery of bioactive factors.[6] Beyond their drug delivery capabilities, NPs can also confer topographical, electrical, and mechanical cues to scaffold materials, influencing Schwann cell alignment, axonal guidance, and immune modulation.[7]

Of note, recent advances have led to the emergence of multimodal NP-engineered systems, which integrate therapeutic, structural, and responsive functionalities within a single platform.[8] Examples include piezoelectric hydrogels that transduce mechanical stimulation into electrical signals, magnetically responsive fibers that guide axonal extension,

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and optogenetic interfaces capable of modulating cellular activity in real-time.[8] These systems aim not only to support regeneration but to actively instruct it—adapting to the dynamic needs of the healing nerve.

Importantly, these NP-integrated strategies are not limited to nerve conduits alone. Injectable hydrogels, decellularized nerve matrices, and cell-derived exosomes can be enhanced via NP incorporation to improve bioactivity, signal delivery, and host cell interactions.[9,10] Moreover, NPs can target multiple regenerative pathways, including oxidative stress reduction, macrophage modulation, angiogenesis, and stem cell recruitment.[11] This multifunctionality supports a comprehensive, systems-level approach to neuroregeneration. Despite promising preclinical results, the path to clinical translation is complex. Key challenges include ensuring NP biocompatibility, controlling biodistribution and degradation kinetics, and achieving reproducible large-scale manufacturing under Good Manufacturing Practice (GMP) conditions. Additionally, regulatory frameworks for combination products integrating drugs, biologics, and devices remain underdeveloped.

Nowadays, several nerve guidance conduits (NeuraGen®, Neurotube®, Neurolac®, Avance®, Reaxon®) have been approved for clinical use in short-gap peripheral nerve injuries (≤3 cm in humans), but outcomes remain inferior to autograft for gaps >3 cm. Limitations include lack of intrinsic bioactivity, limited angiogenesis, and inconsistent axonal alignment. These shortcomings motivate the integration of nanoparticle-based bioactive functionalities into next-generation conduits. Therefore, this review provides a comprehensive and critical analysis of the rapidly evolving landscape of NP-based strategies for peripheral nerve repair. We first examine major NP classes and their biofunctional mechanisms, followed by strategies for their therapeutic functionalization. We then explore their integration into responsive scaffolds and bioactive matrices, with a focus on cell-instructive and clinically scalable designs. Finally, we assess preclinical outcomes, translational challenges, and future directions including intelligent theranostic systems and artificial intelligence-driven NP optimization.

Peripheral Nerve Anatomy and Mechanisms of Regeneration

Peripheral nerves form an intricate network that transmits motor, sensory, and autonomic information between the central nervous system (CNS) and peripheral tissues. Structurally, each peripheral nerve consists of axons bundled into fascicles, surrounded by three connective tissue layers: the endoneurium encasing individual axons and Schwann cells, the perineurium enclosing fascicles to maintain a protective barrier, and the epineurium providing structural support and blood supply. Schwann cells, the principal glial cells of the peripheral nervous system (PNS), play a fundamental role in myelination and axonal support, while resident macrophages, fibroblasts, and vascular elements contribute to maintaining tissue homeostasis.

Unlike the CNS, the PNS has a remarkable capacity for regeneration after injury, though functional recovery remains incomplete in many cases. Following trauma, a process termed Wallerian degeneration ensues, whereby distal axons and myelin undergo breakdown. Schwann cells rapidly dedifferentiate, phagocytose myelin debris, and adopt a repair phenotype that secretes neurotrophic factors, recruits macrophages, and guides axonal sprouting. Importantly, metabolic adaptation of Schwann cells—regulated in part by adipocyte-to-glial leptin signaling—ensures sufficient energy supply for axonal regrowth through pathways such as mitochondrial respiration and myelin autophagy.[12]

The regenerative microenvironment is orchestrated by multicellular interactions. Macrophages are central to this process, where polarization toward an M2 phenotype enhances repair. M2 macrophage-derived cathepsin S, for example, activates fibroblast–Schwann cell signaling that promotes axonal regeneration.[13] Vascularization is equally essential; endothelial cell-derived exosomes enriched in Netrin-1 construct a pre-regenerative vascular niche, fostering axonal guidance and angiogenesis.[14] Disruption of these supportive cues, however, can exacerbate neuroinflammation and degeneration, as demonstrated by Schwann cell secretion of sFRP1 that drives maladaptive macrophage responses.[15]

Design and Mechanisms

The functional diversity and structural tunability of NPs make them highly adaptable tools for modulating biological processes essential to peripheral nerve regeneration. Depending on their composition and surface chemistry, NPs can serve as carriers for bioactive molecules, physical stimuli transducers, or structural mimics of extracellular matrix (ECM) features.

Inorganic Nanoparticles

Inorganic NPs possess unique properties like magnetism, redox activity, and electrical conductivity. These features enable both passive and active modulation of the nerve injury microenvironment.[16] Magnetic nanoparticles (MNPs), particularly iron oxide-based forms like Fe_3O_4 and superparamagnetic iron oxide nanoparticles (SPIONs), have been employed to guide axonal growth through magnetically aligned scaffolds or external magnetic fields.[17] Studies by Liu et al demonstrated that MNP-functionalized conduits promote directional axonal elongation and Schwann cell migration, enabling better bridging of nerve gaps. In rodent long-gap models, Fe_3O_4-loaded conduits enhance axonal orientation and reduce muscle atrophy, but require careful control of particle dose/coating to avoid iron overload. Additionally, SPIONs can serve as MRI-visible carriers for theranostic applications.[17] Besides, SPIONs typically undergo lysosomal degradation once internalized by macrophages and reticuloendothelial cells. The iron cores dissolve gradually into Fe^{2+}/Fe^{3+} ions, which are then integrated into systemic iron pools (ferritin, transferrin) or excreted through normal iron metabolism. Clinical and preclinical evidence suggests half-lives ranging from days to weeks, depending on coating and particle size.

Cerium oxide nanoparticles (CeO_2 NPs) and carbon dots (CDs) exhibit potent antioxidant and anti-inflammatory activities by mimicking endogenous enzymes such as catalase and superoxide dismutase. These nanoparticles attenuate reactive oxygen species (ROS) accumulation and modulate macrophage phenotypes toward the pro-regenerative M2 lineage, thereby improving the inflammatory resolution phase essential for successful nerve regeneration.[18,19] Unlike SPIONs, CeO_2 displays partial biopersistence due to its crystalline structure and redox-active surface. In vivo studies show that CeO_2 can accumulate in liver, spleen, and lungs, with slow excretion (weeks to months). Reports in rodents indicate detectable cerium up to 90 days post-injection, with incomplete elimination.

Quantum dots (QDs), including black phosphorus and graphene-based nanostructures, possess high electrical conductivity and intrinsic photoluminescence. Shen et al reported that black phosphorus QDs enhance neurite outgrowth via localized electrical stimulation.[7] Together, these inorganic NPs offer multifunctional platforms for actively enhancing neural repair processes at both the cellular and systemic levels, by simultaneously guiding axonal alignment, modulating immune responses, enhancing neuroelectrical activity, and enabling real-time monitoring of regenerative progress. Their integration into nerve conduits or injectable hydrogels further amplifies their therapeutic potential, allowing for spatiotemporally controlled intervention that aligns with the dynamic stages of peripheral nerve healing.

Polymeric and Natural Nanoparticles

Biodegradable polymeric and natural NPs are well-suited for controlled therapeutic release and exhibit excellent biocompatibility, which is critical for integration into nerve tissues.

Chitosan, poly(lactic-co-glycolic acid) (PLGA), and silk fibroin-based nanoparticles have shown sustained delivery capabilities for growth factors such as NGF, BDNF, and VEGF. A nerve guidance conduit (NGC) fabricated with laminin-coated PLGA nanofibers was engineered to deliver brain-derived neurotrophic factor (BDNF) and gold nanoparticles (AuNPs) encapsulated in chitosan carriers, combined with transplantation of rat adipose-derived stem cells (r-ADSCs). This multifunctional system provided structural support while enabling controlled release of neuroprotective cues and enhancing the therapeutic effects of stem cells. In vivo evaluation in a rat sciatic nerve transection model demonstrated that PLGA conduits incorporating AuNPs- and BDNF-loaded nanoparticles significantly improved axonal regeneration, neural differentiation, and functional recovery compared to controls. Histological and immunohistochemical analyses confirmed enhanced remyelination and neurite outgrowth, while behavioral assessments supported superior motor recovery. These findings suggest that PLGA-based nanofiber conduits integrating bioactive nanoparticles and stem cells represent a promising regenerative platform for peripheral nerve injury repair.[20,21]

Lipid-based NPs and exosome-mimetic vesicles are increasingly leveraged for neurotrophic cargo delivery.[22,23] These nanocarriers can encapsulate membrane-bound proteins and RNAs while mimicking the endogenous transport systems of neural cells. Yin et al developed pericyte-derived extracellular vesicle-mimetic nanovesicles, which significantly enhanced axonal regeneration and functional recovery in a murine sciatic nerve transection model, highlighting the therapeutic efficacy of bioinspired natural NPs.[24] Similarly, Hu et al demonstrated that neural grafts incorporating exosomes derived from Schwann cell-like cells promoted robust nerve repair in a rat model of peripheral nerve injury,

emphasizing the role of cell-derived NPs in modulating the regenerative microenvironment.[25] Together, these findings underscore the translational potential of polymeric and natural nanostructures as bioactive carriers in peripheral nerve tissue engineering.

Hybrid and Composite Nanoparticles

Hybrid NPs combine distinct material classes, offering synergistic functionalities in a single construct. Core–shell systems are particularly promising for multimodal applications. For example, a previous study reported that core–shell nanospheres combined with an external magnetic field significantly promoted axonal growth and remyelination in a sciatic nerve injury mode. They introduced a multifunctional Fe_3O_4-MnO_2@Zirconium-based MOF@Retinoic acid (FMZMR) core-shell nanoparticle, which, when combined with a magnetic field (MF), enables remote-controlled drug release and enhanced Schwann cell behavior.[26] Incorporated into decellularized human umbilical artery (DHUCA) conduits with suitable mechanical properties, the FMZMR system significantly promotes Schwann cell proliferation, alignment, and neurite outgrowth (1.93-fold increase). In vivo results demonstrate improved nerve regeneration, reduced muscle atrophy, and enhanced myelination without systemic toxicity (Figure 1). These composite systems also enable independent tuning of degradation rates, release kinetics, and surface functionalization, providing a powerful platform for designing personalized and condition-specific nerve repair strategies. Giannelli et al developed a polymer-based curcumin-loaded nanoparticle designed for improved drug delivery and potential incorporation into nerve conduits, demonstrating enhanced bioavailability and suitability for localized therapeutic delivery.[27] Mechanically, hybrid NPs combine organic and inorganic components to merge complementary strengths, achieving functionalities beyond those of single-material systems. For instance, PEG, PLGA, or polysaccharide coatings shield inorganic cores (eg, Fe_3O_4, CeO_2) from aggregation and premature dissolution, which reduces ion leaching, improves circulation time, and preserves redox/magnetic activity until the NP reaches the injury site. In magnetically responsive hybrids, external magnetic fields induce localized heating or mechanical stress within the polymeric matrix, which accelerates drug diffusion or triggers on-demand release, improving spatiotemporal control compared to passive release.

Functionalization Strategies for Enhanced Regeneration

Beyond their inherent physicochemical advantages, NPs gain substantial therapeutic value through biofunctionalization, a process by which surface ligands, biomolecules, or responsive moieties are engineered onto or within the NP to achieve specific biological tasks. For peripheral nerve repair, functionalization enables targeted delivery, sustained bioactivity, and spatiotemporal modulation of cellular behavior at the injury site.

Neurotrophic Factor Delivery

Nanoparticle-mediated delivery of neurotrophic factors (NTFs) represents a promising and increasingly refined strategy for enhancing peripheral nerve regeneration.[28] Unlike traditional systemic administration, nanocarriers enable localized and sustained release of therapeutic molecules, effectively overcoming major limitations such as the short biological half-life and rapid degradation of NTFs.[29] In particular, a recent study demonstrated that dual gene delivery of plasmid-encoded vascular endothelial growth factor (VEGF) and nerve growth factor (NGF), using biodegradable polycationic vectors based on low-molecular-weight branched polyethylenimine (PEI), markedly promoted axonal regeneration in a rat sciatic nerve crush model.[30] The synergistic effect observed between VEGF and NGF highlights an important principle in nerve repair: successful regeneration not only requires neurotrophic cues but also vascular support to optimize the regenerative microenvironment.

Furthermore, sustained-release systems based on nanotechnology are critical for prolonging the bioavailability of NTFs at the injury site, thereby enhancing their regenerative efficacy while reducing dosing frequency and systemic side effects. This is particularly important in the clinical context, where achieving therapeutic concentrations of GFs in a spatially and temporally controlled manner remains a major hurdle.[31]

These findings reflect a broader trend in regenerative medicine: the shift from passive structural scaffolds to bioactive, responsive delivery systems capable of interacting with cellular and molecular pathways.[30,32] NPs not only act as delivery vehicles but also participate in modulating the biological milieu. For example, by scavenging reactive oxygen

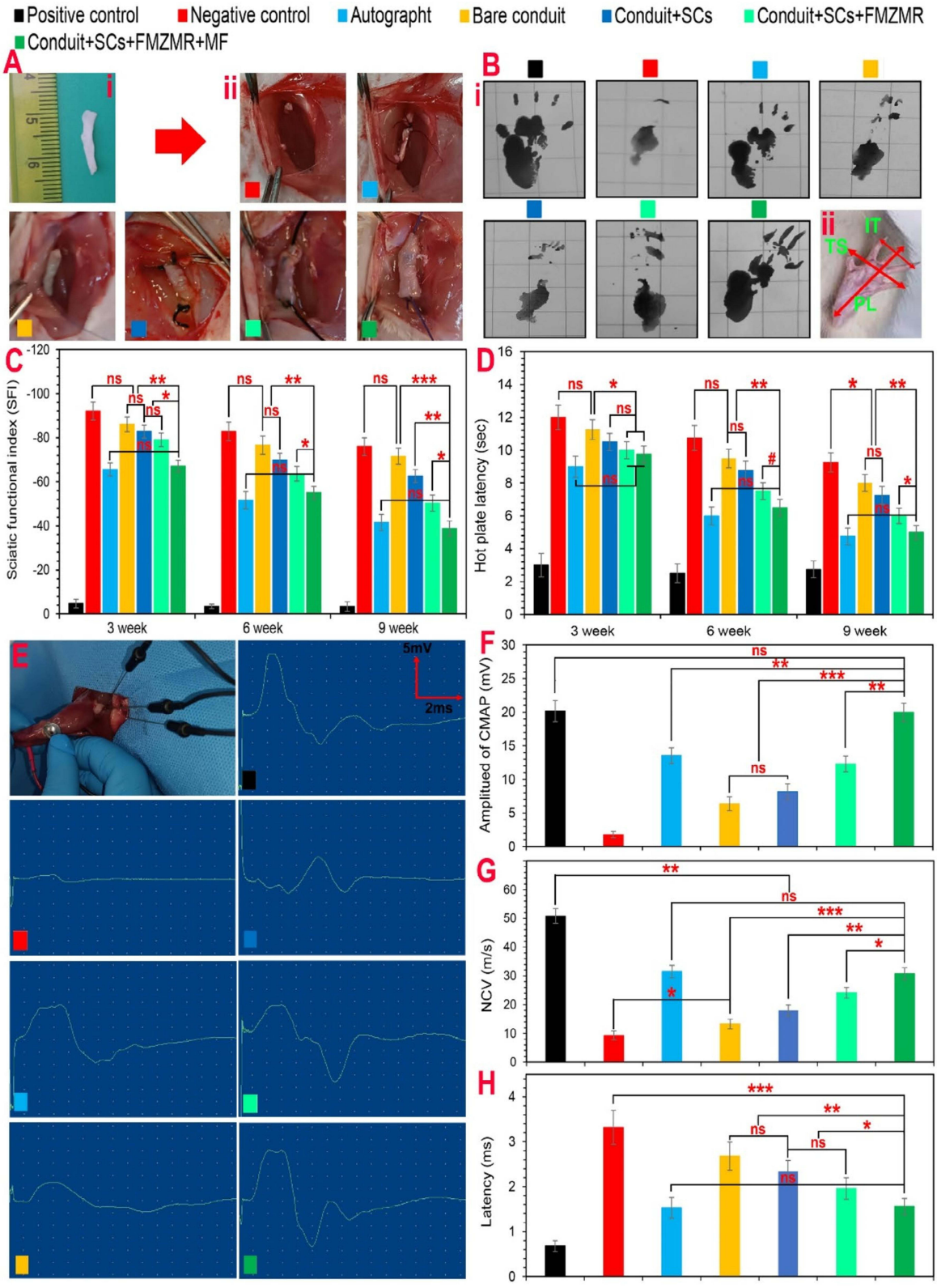

Figure 1 In vivo evaluation of DHUCA implantation and functional recovery. (**A**) (i) Schematic illustration of the DHUCA conduit and (ii) intraoperative images showing conduit implantation. (**B**) (i) Plantar view of the rat hind paw and key measurement parameters for gait analysis, and (ii) representative footprint images. (**C**) Quantitative assessment of sciatic functional index (SFI) values; data expressed as mean ± SD (n = 3). (**D**) Hot plate latency measurements at 3, 6, and 9 weeks post-surgery. (**E**) Electromyography (EMG) recordings at week 9 for each treatment group. (**F**–**H**) Comparative analysis of compound muscle action potential (CMAP) amplitude ratios, nerve conduction velocity (NCV), and latency at week 9. Statistical significance: ns = not significant, *p < 0.05, **p < 0.01, ***p < 0.001. Reprinted from Sharifi M, Salehi M, Ebrahimi-Barough S, et al. Synergic effects of core-shell nanospheres and magnetic field for sciatic nerve regeneration in decellularized artery conduits with Schwann cells. *J Nanobiotechnol.* 2024;22(1):776. Creative Commons.[26]

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species or guiding cell behavior through surface modifications. As the field advances, integrating multi-functional nanoparticles with intelligent release mechanisms could further improve outcomes.

Gene and RNA Therapeutics

Gene and RNA therapeutics are rapidly emerging as functional tools for treating PNIs by enabling precise modulation of gene expression and cellular pathways critical for nerve repair. One notable example involves the use of hypoxia-pretreated bone marrow-derived neural crest cells, which act as Schwann cell progenitors and secrete extracellular vesicles rich in miRNA-21-5p.[33] This microRNA was shown to significantly enhance axonal growth and regeneration of sensory neurons both in vitro and in vivo, as demonstrated in a rat sciatic nerve injury model. The study emphasizes the importance of extracellular vesicles as natural nanoparticle carriers that deliver functional RNA molecules to target cells, facilitating intercellular communication and creating a pro-regenerative microenvironment. The successful construction of a miRNA-21-5p-loaded neural conduit further highlights the therapeutic potential of combining RNA cargo with biomaterial scaffolds to restore motor and sensory functions after nerve injury.

In parallel, siRNA therapeutics targeting the PMP22 gene, delivered via squalene-conjugated nanoparticles, offer a promising treatment for Charcot-Marie-Tooth disease type 1A (CMT1A), an inherited peripheral neuropathy characterized by PMP22 gene overexpression.[34] The siRNA PMP22-squalene nanoparticles effectively normalized PMP22 protein levels in mouse models, leading to improved myelination, nerve conduction, and locomotor function. Importantly, the therapeutic effects were durable for several weeks and could be renewed with repeated dosing, illustrating a practical and reversible precision medicine approach to genetic nerve disorders.

These advances collectively highlight the transformative potential of gene and RNA therapeutics in peripheral nerve regeneration. By exploiting the specificity of RNA molecules and the delivery efficiency of nanocarriers, these approaches can address underlying molecular pathologies rather than merely providing symptomatic relief. Challenges remain, including optimizing delivery efficiency, minimizing immune responses, and ensuring long-term safety. However, integrating RNA therapeutics with biomaterial scaffolds and controlled-release systems could further enhance regenerative outcomes.

Conductive and Piezoelectric Nanoparticles

Conductive and piezoelectric NPs have emerged as highly promising components in the design of advanced biomaterials for peripheral nerve regeneration, owing to their unique ability to provide electrical stimulation and enhance cellular responses critical for nerve repair.[35] In one notable approach, conductive poly(3,4-ethylenedioxythiophene) (PEDOT) nanoparticles were incorporated into a biocompatible chitin hydrogel to fabricate a composite NGC.[36] The partial deacetylation of chitin improved electrostatic interactions with negatively charged PEDOT NPs and enabled functionalization with cell-adhesive peptides, thereby enhancing the mechanical properties and bioactivity of the hydrogel. This conductive chitin/PEDOT composite markedly promoted adhesion and proliferation of Schwann cells, as well as the expression of key regenerative markers including S100, NF-200, and myelin basic protein. In vivo, implantation in a rat model with a 10 mm sciatic nerve defect demonstrated functional recovery and myelinated axon regeneration comparable to that of autografts (Figure 2). These results highlight that providing electrical conductivity within a supportive hydrogel matrix not only facilitates cellular activities but also promotes angiogenesis and myelination, which are vital for successful nerve regeneration.

In parallel, biomimetic-inspired piezoelectric scaffolds combining BaTiO3 nanoparticles with ovalbumin and engineered anisotropic surface topographies have shown synergistic effects in nerve repair.[37] These scaffolds harness the piezoelectric properties of BaTiO3 to generate electrical stimulation in situ without invasive external devices. The anisotropic topography mimics the oriented architecture of native nerve tissue, guiding Schwann cell alignment and promoting DRG axon elongation. Importantly, the piezoelectric stimulation upregulated genes related to myelination and axonal growth, accelerating peripheral nerve regeneration through enhanced chemical-mechanical signal transduction. The scaffold's improved mechanical strength further supports its suitability for implantation and long-term nerve repair applications.

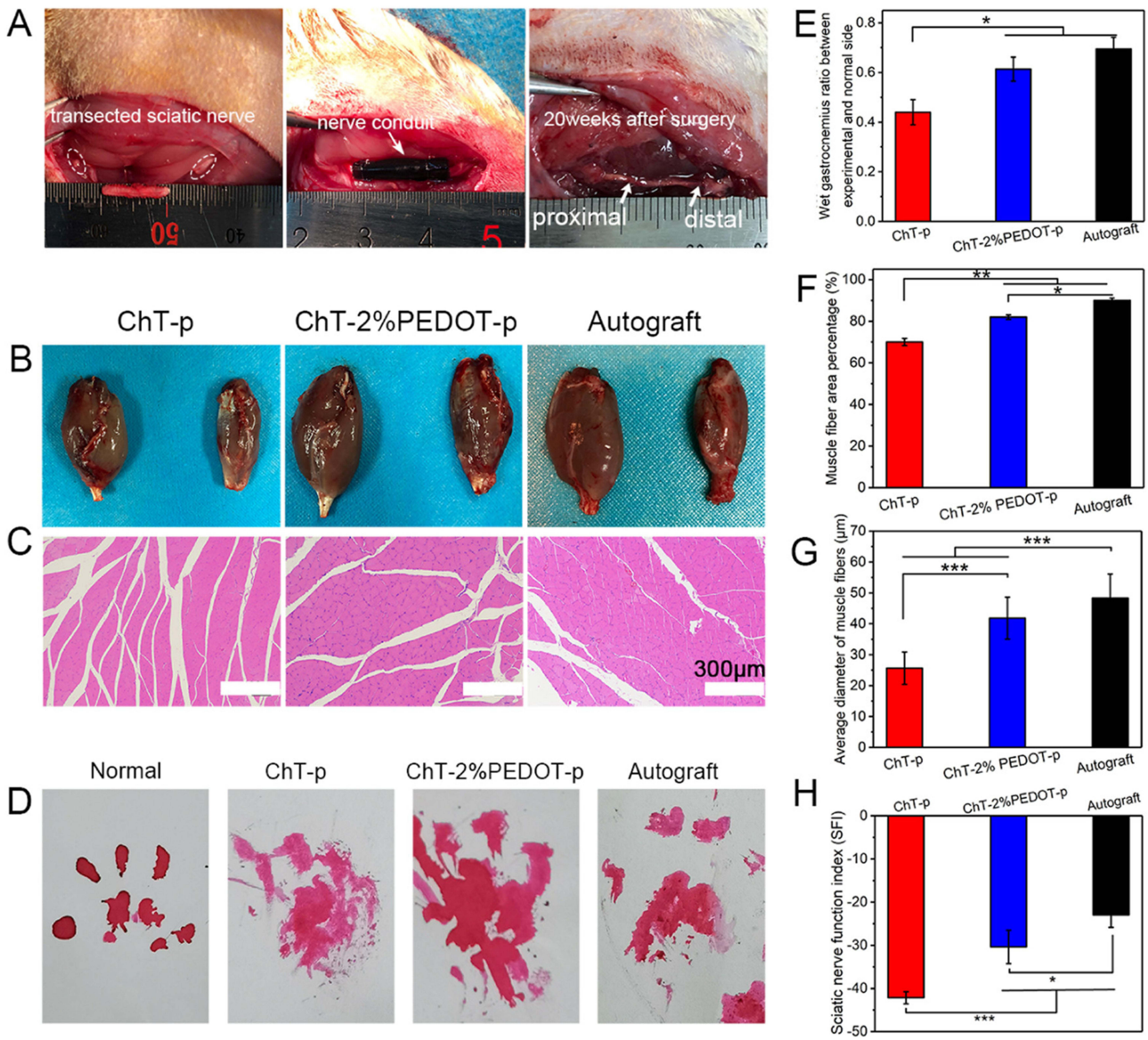

Figure 2 (**A**) Sequential images showing the rat model with a 10 mm sciatic nerve defect (left), implantation of the chitin-based nerve conduit (center), and the surgical site 20 weeks post-operation (right). (**B**) Representative images of the gastrocnemius muscle from both the uninjured (left) and operated (right) limbs. (**C**) Histological analysis using hematoxylin–eosin staining. (**D**) Footprint patterns used for gait evaluation. (**E**–**G**) Quantitative assessments of muscle recovery, including wet muscle weight ratio (**E**, $n \geq 5$, $^{*}p < 0.05$), muscle fiber area fraction (**F**, $n \geq 3$, $^{**}p < 0.01$, $^{*}p < 0.05$), and mean muscle fiber diameter (**G**, $n = 100$, $^{***}p < 0.001$). (**H**) Sciatic Functional Index (SFI) scores comparing ChT-p, ChT-2%PEDOT-p, and autograft groups ($^{***}p < 0.001$, $^{*}p < 0.05$). Data presented as mean ± standard error. Reprinted with permission from Huang L, Yang X, Deng L, et al. Biocompatible chitin hydrogel incorporated with PEDOT nanoparticles for peripheral nerve repair. *ACS Appl Mater Interfaces*. 2021;13(14):16106–16117. Copyright © 2021 American Chemical Society.[36]

Electrical stimulation is known to influence ion channel activity, intracellular signaling, and gene expression, all of which contribute to accelerated nerve repair. By embedding conductive or piezoelectric nanoparticles within biocompatible hydrogels or scaffolds, researchers can deliver controlled, localized electrical cues that synergize with topographical and biochemical signals, enhancing Schwann cell function and axonal regeneration.[35,38] However, challenges remain, such as optimizing nanoparticle dispersion, ensuring long-term biocompatibility, and scaling production for clinical translation. The immune response to novel nanomaterials also requires careful evaluation. Nonetheless, integrating conductive and piezoelectric nanotechnologies offers a versatile platform to address these issues, especially when combined with tailored surface chemistry and structural design.

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Antioxidant and Immunomodulatory NPs

NP-based antioxidant and immunomodulatory therapies have emerged as highly promising strategies for PNIs repair, offering localized, sustained release and multifunctional bioactivity. In one recent study, NO-releasing silica nanoparticles (NO-SNs) were developed to address the limited stability and short half-life of NO in vivo.[39] When delivered to crushed sciatic nerves in rats via a natural hydrogel matrix, NO-SNs facilitated early revascularization, as evidenced by increased CD34+ vessel density. This vascular support contributed to enhanced axonal regeneration, greater myelinated fiber density, and improved muscle morphology and function. The therapeutic outcomes, measured through histology, wet muscle weight, and the sciatic functional index (SFI), highlight NO's significant role in orchestrating vascular and neural repair when delivered via a stable nanocarrier.

In a complementary approach, selenium-loaded porous SiO_2 NPs (Se@SiO_2 NPs) were engineered to deliver Se in a controlled and biocompatible manner, overcoming its narrow therapeutic window.[40] Se@ SiO_2 NPs exerted potent antioxidant effects by activating the PI3K/AKT signaling pathway, as demonstrated by increased expression of antioxidative proteins (Nrf2, HO-1, SOD2) and anti-apoptotic markers (Bcl-2), along with reduced levels of ROS and pro-apoptotic proteins (Bax). In vivo studies confirmed that Se@ SiO_2 NPs significantly improved axonal regeneration, myelin thickness, gastrocnemius muscle recovery, and electrophysiological function. Notably, the administration of LY294002, a PI3K/AKT inhibitor, diminished these effects, validating the pathway-specific mechanism.

These findings collectively support the integration of redox modulation and immune regulation into the design of next-generation nanotherapeutics for PNI. The convergence of vascular support (via NO) and oxidative stress reduction (via Se) offers a synergistic opportunity. Future research should focus on co-delivery systems or multifunctional nanoplatforms that couple angiogenesis, antioxidant protection, and neurotrophic signaling, potentially in combination with bioactive scaffolds.[41,42] Such systems could provide a clinically translatable solution to promote full-scale functional nerve regeneration across complex injury environments.

NP-Integrated Scaffold Systems

While NP-based therapies demonstrate considerable potential in promoting peripheral nerve repair, their regenerative efficacy is markedly enhanced when incorporated into scaffold-based systems that offer structural integrity and spatial-temporal guidance. Emerging NP-integrated scaffolds not only facilitate controlled and localized therapeutic delivery but also provide biomechanical and bioelectrical cues that emulate the native extracellular matrix.[43] By orchestrating cell-instructive signaling, mechanical support, and responsive transduction, these multifunctional constructs recapitulate the dynamic microenvironment essential for orchestrating complex regenerative processes in peripheral nerve regeneration.[44]

Smart Responsive Conduits

Smart-responsive NGCs are redefining therapeutic strategies for PNIs by integrating biophysical stimulation with spatiotemporally controlled delivery of therapeutic agents. Traditional NGCs provide basic structural guidance, but fail to actively participate in the dynamic microenvironment required for optimal nerve regeneration. To address this, ultrasound (US)-responsive aligned piezoelectric hydrogel conduits have been engineered by incorporating barium titanate nanoparticles (BTNPs) into aligned P(VDF-TrFE) nanofibers and encapsulating neurotrophic factors within thermoresponsive hydrogel layers.[8] Upon US stimulation, the inner piezoelectric matrix generates electrical signals to promote neurite outgrowth, while the outer hydrogel contracts, triggering localized, on-demand release of nerve growth factors. In vivo studies in rat sciatic nerve defect models demonstrated accelerated axonal regeneration and improved functional outcomes, underscoring the synergistic benefits of mechanically mediated neuromodulation and programmable biodelivery. Although low-intensity US penetrates several centimeters in soft tissue, making it suitable for sciatic or femoral nerves in rodents and humans. However, attenuation occurs with depth and bone interference, meaning median or brachial plexus nerves may experience diminished intensity.

Beyond ultrasound, near-infrared (NIR)-responsive platforms offer an alternative non-invasive strategy for deep tissue intervention. A recent innovation employs a nanosystem composed of upconversion nanoparticles (UCNPs) encapsulated in ZIF-8 and loaded with photosensitive S-nitrosocysteine (CysNO), enabling NIR-triggered, spatially

confined NO release within 3D-printed poly-L-lactic acid scaffolds.[45] Upon NIR irradiation, UCNPs convert light to UV emission, cleaving S-NO bonds to release NO. The structural confinement provided by ZIF-8 ensures sustained and controllable NO kinetics, avoiding burst release. Immunofluorescence studies reveal upregulation of neural lineage markers such as Nestin and GFAP, suggesting successful neuronal differentiation via NO-enhanced calcium influx. These findings demonstrate the potential of optically responsive scaffolds to precisely modulate biochemical signaling pathways and guide stem cell fate for enhanced neuroregeneration. In addition, NIR (650–900 nm) offers deeper penetration than visible light but still only reaches 1–2 cm effectively in vivo. This is sufficient for rat sciatic nerves or superficial forearm nerves, but challenging for deep plexus injuries. Strategies to overcome this include optical fiber delivery or using second-window NIR (1000–1700 nm) with improved tissue penetration.

Further supporting this approach, ultrasound-triggered NO-releasing silicon NPs (HMSN-SNO) have been applied to noise-induced hearing loss models, revealing broader neuroprotective utility beyond peripheral nerves.[46] These nanoparticles facilitate controlled NO delivery to the cochlea, scavenging ROS and reactivating synaptogenesis between hair cells and spiral ganglion neurons through CREB/BDNF/EGR1 signaling. The observed restoration of auditory function illustrates the capacity of responsive nanotherapeutics to repair complex neural circuits by reversing adverse microenvironments and promoting axonal regeneration (Figure 3). Collectively, these studies establish smart responsive conduits as a transformative class of bioelectronic-tissue interfaces. By responding intelligently to external stimuli—such as US or NIR—they allow for precise modulation of electrical, chemical, and topographical cues, bridging the gap

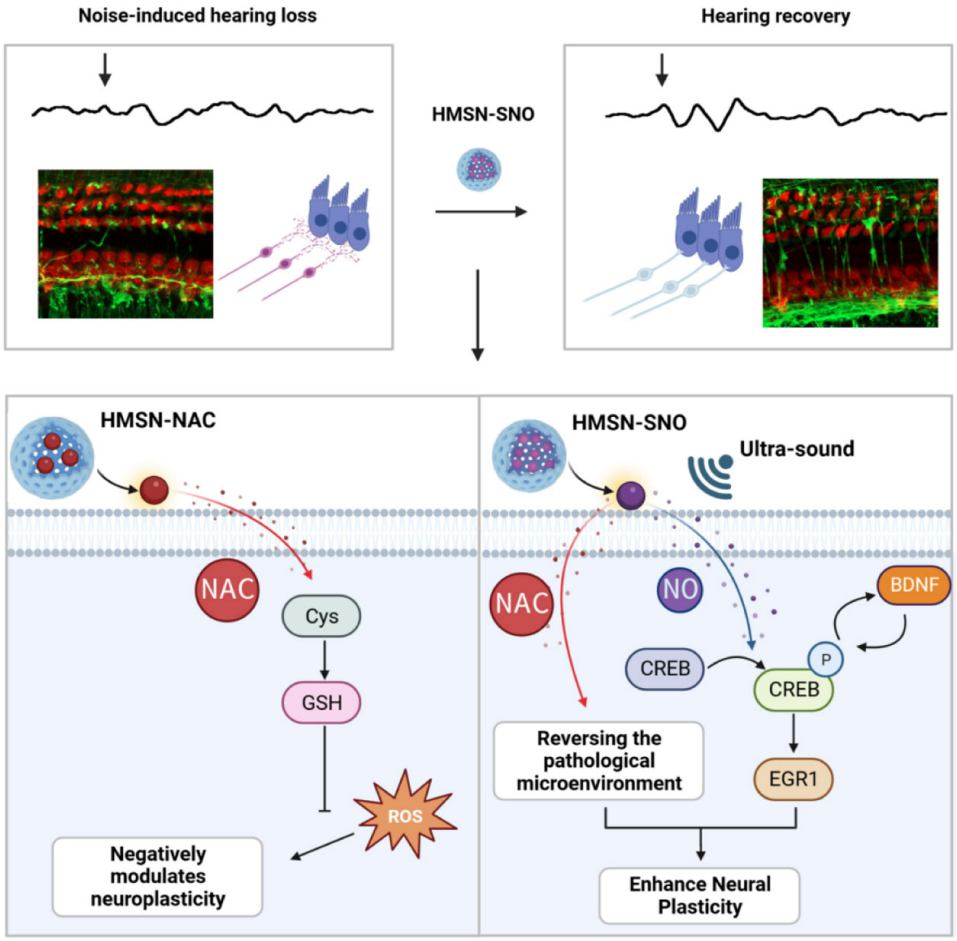

Figure 3 Schematic illustration of ultrasound-mediated neuroplasticity enhancement for the treatment of noise-induced hearing loss (NIHL). Hollow mesoporous silicon nanoparticles (HMSNs) were employed to encapsulate nitrosylated N-acetylcysteine (NAC-SNO), forming HMSN-SNO constructs capable of ultrasound-responsive release. Upon stimulation, NAC is released to mitigate oxidative stress and restore the damaged cochlear microenvironment, while NO activates the CREB/BDNF/EGR1 signaling cascade, thereby facilitating axonal regrowth and synaptic regeneration. Reprinted with permission from Chen B, Sun Y, Sun H, et al. Ultrasound-triggered NO release to promote axonal regeneration for noise-induced hearing loss therapy. *ACS Nano.* 2024;18(48):33232–33244. Copyright © 2024 American Chemical Society.[46]

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between passive scaffolding and active neuromodulation. Such multifunctional systems hold strong translational potential for treating a wide range of peripheral and central nervous system injuries through personalized and minimally invasive strategies.

Biomimetic and Bioactive Matrices

Biomimetic and bioactive matrices have become essential in advancing peripheral nerve regeneration, as they closely emulate the complex ECM microenvironment and provide critical biophysical and biochemical cues to guide cellular behaviors. Recent studies highlight the use of multifunctional hydrogels based on graphene (GR) and sodium alginate (SA) that not only replicate the native nerve growth milieu but also actively modulate inflammatory responses and neurotrophic factor expression.[47] The GR-SA composite hydrogel exhibits excellent conductivity and mechanical properties, enabling enhanced cell viability, axonal outgrowth, and functional repair both in vitro and in vivo. Its inherent electrical conductivity appears to play a pivotal role in re-establishing electrophysiological continuity across injured nerves, reflecting a promising alternative to conventional autografts.

Apart from hydrogel-based systems, nanofibrous scaffolds with tailored surface features have also demonstrated significant potential in promoting neural cell adhesion and differentiation.[48] Electrospun cellulose (EC) fibers modified with conductive polymer derivatives, such as polymers derivates (poly (N-(methacryl ethyl) pyrrole) (PMAEPy) and poly (N-(2-hydroxyethyl) pyrrole) (PHEPy), form unique surface morphologies through in situ polymerization, enhancing protein adsorption and supporting PC12 cell attachment and elongation.[49] These conductive nanofibrous substrates not only provide topographical guidance but also enable bioelectric stimulation—an emerging strategy in neural tissue engineering. Importantly, the ability to fine-tune surface conductivity and fiber architecture opens new possibilities for constructing multi-functional scaffolds that integrate mechanical support with electrical responsiveness.

In addition to material design, recent trends emphasize the integration of stem cell therapies, particularly mesenchymal stem cells (MSCs), with biomimetic scaffolds to enhance nerve repair. MSCs possess paracrine and immunomodulatory capabilities and, when combined with micro/nanostructured matrices or electrical stimulation, can significantly improve regenerative outcomes.[48] However, a key challenge remains in delineating the individual contributions of materials and cells within such combinatorial systems.[50] There is a growing consensus that future biomaterials should move beyond passive support roles, evolving into dynamic, instructive platforms capable of orchestrating cell fate decisions and guiding tissue remodeling.

Cell-Instructive Platforms

Cell-instructive platforms have garnered increasing attention in peripheral nerve regeneration, as they integrate bioactive signaling with structural cues to dynamically direct cell behavior and tissue repair.[51] One representative strategy involves pericyte-derived extracellular vesicle-mimetic nanovesicles (PC-NVs), which mimic natural extracellular vesicles to deliver neuroregenerative signals in a localized and cell-responsive manner.[24] In a mouse model of sciatic nerve transection, PC-NVs significantly enhanced early neurovascular regeneration by promoting Schwann cell recruitment, endothelial activation, and the upregulation of key neurotrophic factors via the PI3K/Akt signaling axis. Notably, this cell-instructive system also suppressed JNK signaling, associated with apoptosis and inflammation, ultimately leading to improved motor and sensory outcomes. These findings emphasize the potential of vesicle-inspired nanotherapeutics to orchestrate a pro-regenerative cellular microenvironment.

Beyond biological vesicles, engineered hybrid systems combining biochemical and biophysical signals have shown synergistic effects in restoring peripheral nerve function. In diabetic peripheral neuropathy (DPN), a degenerative condition characterized by impaired nerve conduction, the fusion of bone marrow mesenchymal stromal cell (BMSC)-derived exosomes with polypyrrole nanoparticles (PpyNPs) created a cell-instructive delivery vehicle responsive to electrical stimulation.[52] This composite system not only restored nerve conduction velocity and muscle innervation to near-normal levels, but also exerted systemic metabolic benefits, including attenuation of hyperglycemia. The dual-functionality of this platform highlights a critical direction in neural repair: the convergence of regenerative biology with nanoelectronics to guide both local tissue responses and systemic homeostasis (Figure 4).

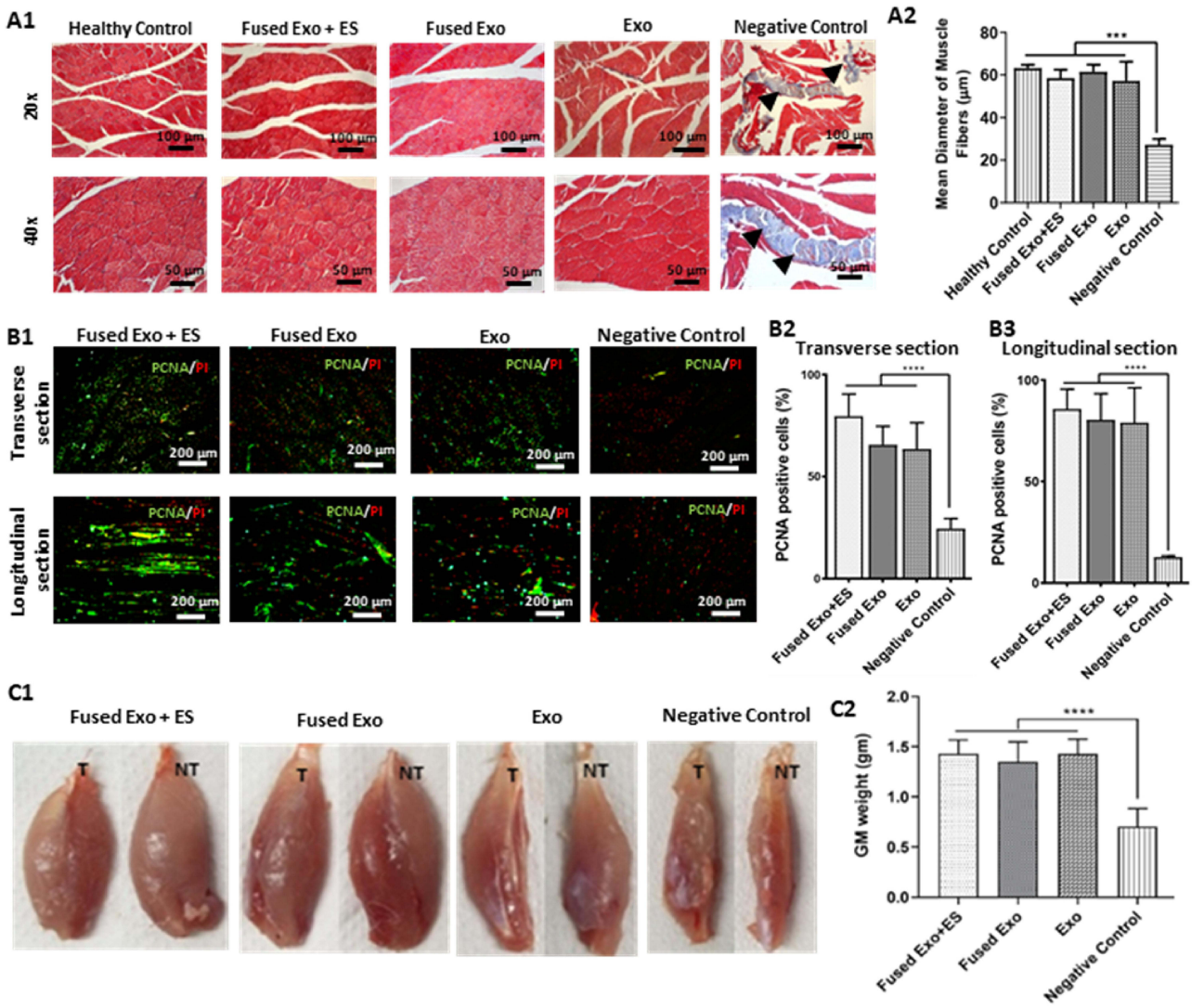

Figure 4 Exosome-based treatment enhanced gastrocnemius muscle recovery in a DPN model. (**A1**) Representative Masson's trichrome staining of gastrocnemius muscle sections from the treated limb (right side) at 8 weeks post-treatment, shown at 20× and 40× magnifications. (**A2**) Quantitative analysis of average muscle fiber diameter. (**B1**) Confocal immunofluorescence images illustrating PCNA expression in both transverse and longitudinal muscle sections across experimental groups. (**B2** and **B3**) Quantification of PCNA-positive nuclei in transverse (**B2**) and longitudinal (**B3**) views. (**C1**) Images of isolated gastrocnemius muscles from treated (T) and untreated (NT) groups. (**C2**) Measurement of muscle mass from the treated hind limb. Statistical significance: ****p ≤ 0.0001. Reprinted from Singh A, Raghav A, Shiekh PA, Kumar A. Transplantation of engineered exosomes derived from bone marrow mesenchymal stromal cells ameliorate diabetic peripheral neuropathy under electrical stimulation. *Bioact Mater.* 2021;6:2231–2249. Creative Commons.[52]

Emerging nanotechnologies also enable active modulation of cell migration and intercellular interactions—key steps in effective nerve regeneration. For example, Schwann cells magnetically transfected with ChABC-loaded superparamagnetic nanoparticles demonstrated enhanced migration across astrocytic barriers under an external magnetic field, overcoming a major limitation in glial scar-mediated inhibition.[53] These magnetically guided cell-instructive platforms provide both mechanical guidance and enzymatic remodeling of the ECM, offering a dynamic approach to unlock regenerative potential within inhibitory environments. Taken together, such strategies represent a significant shift from passive scaffolding to intelligent, responsive systems capable of real-time interaction with host tissues. However, translating these platforms from bench to bedside will require deeper understanding of their in vivo biodistribution, immunogenicity, and long-term integration.

Preclinical Outcomes and Translational Challenges

PNIs remain a substantial clinical challenge, particularly in large-gap defects or in patients with metabolic comorbidities such as diabetes. Conventional therapeutic strategies, including nerve autografts and pharmacological interventions, often

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fall short due to limited regenerative capacity and poor targeting efficiency across the blood-nerve barrier. Emerging nanomaterial-based strategies, particularly those involving NP-mediated delivery systems, have shown promise in modulating the complex nerve regeneration microenvironment. These systems aim not only to deliver bioactive molecules but also to orchestrate immune responses, reduce oxidative stress, and promote angiogenesis, thus offering a multifactorial therapeutic platform.[41,54]

One compelling example is the NO sustained-release nanoparticle system developed by Huo et al, which exemplifies the pleiotropic potential of nanomedicine in nerve repair.[55] The system comprises macromolecular NO donor nanoparticles (NO-NPs) embedded in a thermosensitive hydrogel conduit, allowing spatiotemporally controlled NO release. NO, a gaseous neurotransmitter with small molecular weight and diffusivity, is capable of penetrating physiological barriers and simultaneously modulating neuroinflammation, oxidative stress, and vascularization. In preclinical models, this platform promoted Schwann cell proliferation, axonal regrowth, and revascularization at the injury site. However, the narrow therapeutic window of NO, due to its dual roles in cytoprotection and cytotoxicity, presents a significant translational bottleneck. Careful control over release kinetics, degradation profiles of the hydrogel matrix, and long-term biosafety are essential for clinical translation.

In parallel, Zhang et al have developed an implantable, self-powered microneedle (MN) nerve conduit based on enzyme cascade reactions.[56] This unique nanotechnology-based conduit incorporates glucose oxidase and horseradish peroxidase encapsulated in ZIF-8 nanoparticles to generate localized electric currents that mimic endogenous bioelectric cues. This electroactive scaffold not only restores electrical conductivity at the lesion site but also facilitates regeneration of blood vessels, muscle tissue, and nerve fibers. The innovation here lies in its autonomy and integrative function, minimizing reliance on external stimuli or invasive electrodes. Nonetheless, the in vivo stability of ZIF-8, potential immunogenicity of enzymatic components, and scaling of microneedle fabrication remain critical hurdles for regulatory approval and clinical adoption.

Additionally, Bi et al demonstrate how neuro-immune modulation via conductive hydrogel scaffolds can significantly accelerate peripheral nerve regeneration, especially in complex pathophysiological settings such as diabetic wounds.[57] Their hydrogel system, composed of melanin-inspired nanoparticles and curcumin as an anti-inflammatory agent, exhibits near-infrared-responsive drug release and mild photothermal antibacterial effects. This approach not only fosters Schwann cell activity but also recalibrates macrophage polarization and ROS levels, highlighting the importance of synchronizing neural and immune regeneration. While promising, this multifunctional strategy faces typical challenges of complex systems—batch-to-batch reproducibility, nanoparticle clearance pathways, and the cumulative effects of multimodal stimulation should be thoroughly evaluated in larger animal models before progressing to human trials.

Taken together, the integration of nanotechnology into nerve repair offers versatility to address the multifaceted nature of peripheral nerve injury. These nanoparticle-based platforms, whether through chemical signaling (NO), electrical stimulation (enzymatic microneedles), or immunomodulation (conductive hydrogels), underscore the paradigm shift from single-target interventions to microenvironmental reprogramming. Because crush injuries, short-gap transections, and long-gap transections pose distinct pathophysiological barriers, the preclinical quantitative outcomes of using NPs in different injury types are summarized in Table 1. Despite encouraging preclinical outcomes, translation to clinical practice requires overcoming significant barriers, including manufacturing scalability, regulatory validation of complex bioactive systems, and long-term biosafety. Future efforts should focus on standardizing evaluation metrics, refining animal-to-human extrapolation models, and developing modular, adaptable delivery platforms tailored to specific injury types and patient conditions.

Future Perspectives

Conventional tracers and diagnostic tools fall short in providing real-time, high-resolution, and deep-tissue information critical for evaluating nerve regeneration. Recent advances in nanoparticle-enabled neural tracing systems present transformative opportunities. For instance, Fe_3O_4@COOH NPs conjugated with biotinylated dextran amine (BDA) represent a dual-modal tracing platform, enabling both magnetic resonance (MR) and photoacoustic (PA) imaging.[58] These multifunctional nanoparticles exhibit high tissue penetration, long-term signal stability, and minimal leakage when encapsulated in microfluidic droplets. This integrated imaging-therapeutic strategy not only facilitates precise

Table 1 Preclinical Results of NPs Functional in Different Injury Model

Injury Model	NP Functionalization	Key Quantitative	Mechanism	Reference
Crush (rat sciatic)	NO-SN (NO-releasing silica NPs)	Earlier SFI improvement at 2–4 wks vs vehicle; SFI ≈ sham by ~5 wks; improved myelinated axons, myelin thickness and tetanic force	Antioxidant/anti-inflammatory burst control speeds early functional recovery and remyelination	[35]
Crush/ transection adjunct	Se@SiO_2 (sustained antioxidant)	Improved motor function and pro-regeneration, decreased oxidative stress in vivo	ROS scavenging plus pathway modulation supports axon regrowth and function	[36]
Transection 10 mm	Conductive PEDOT-based hydrogel/conduit	Improved SFI and muscle metrics comparable to autograft; superior myelination vs non-conductive controls	Conductivity restores bioelectric cues that drive axon extension/ myelination across short gaps	[32]
Transection ≥15 mm	Magneto-responsive core–shell NPs + external MF (FMZMR)	~1.93× neurite length in vitro; decreased muscle atrophy, and increased axon/myelin metrics in vivo; no gross tissue toxicity reported	Magnetic cues provide long-range guidance; best when combined with trophic/angiogenic support	[22]

visualization of axonal regrowth but also offers localized, controlled delivery potential. Such systems may evolve into theranostic platforms capable of simultaneously tracking, modulating, and accelerating nerve regeneration in vivo.

Another exciting development lies in the realm of wireless stimulation-based nanomedicine. Bonato et al introduced a computational framework that predicts electric field distributions generated by magnetoelectric core-shell nanoparticles and nanochains under external magnetic stimulation.[59] These CFO-BTO (cobalt ferrite–barium titanate) nanostructures demonstrate significant magnetoelectric coupling, allowing remote activation of therapeutic electric fields (5–140 V/m) within neural tissue. Notably, the nanochain configuration significantly enhances field generation efficiency compared to individual particles, particularly under 3D in vivo conditions. This opens the possibility of developing wireless, non-invasive neural stimulators that can be spatially and temporally controlled by external magnetic fields. In future applications, such nanostructures could be integrated into injectable hydrogels or microneedle platforms, forming closed-loop systems that respond dynamically to injury signals or physiological stimuli.[60] Importantly, the computational modeling framework provides a quantitative design toolkit that could accelerate the translation of these advanced nanostructures into clinical-grade neurostimulation therapies.

NP-based conduits often combine device-like scaffolds with drug or biologic functionalities. Such drug–device hybrids face unique regulatory challenges because they must meet both medical device and pharmaceutical/biologic standards. Therefore, to translate these advances into clinical therapies, several critical challenges should be addressed.[61] Foremost is the need for comprehensive evaluation of biocompatibility and long-term degradation, particularly for magnetically or electrically active nanostructures, in large animal models. Equally pressing is the scalability of manufacturing architecturally defined nanoformulations with consistent quality and function, which should be complying with both device ISO standards and pharmaceutical cGMP. Furthermore, regulatory frameworks for NP-based combination products, which simultaneously serve diagnostic and therapeutic purposes, remain underdeveloped and will require adaptive, mechanism-driven clinical trial strategies.[7]

Despite these hurdles, the convergence of computational nanodesign, responsive material engineering, and real-time multimodal imaging is rapidly reshaping the landscape of neural repair. Through sustained interdisciplinary collaboration, next-generation nanoparticle systems hold the promise not only to accelerate functional nerve regeneration, but to fundamentally reimagine how neurotherapies are delivered, monitored, and personalized at the molecular scale.

Conclusion

PNIs pose significant clinical challenges, particularly in complex or chronic cases where traditional treatments fall short. NP-engineered platforms offer a transformative approach by integrating targeted delivery, immune modulation, axonal guidance, and real-time diagnostics into a single system. These multifunctional nanoparticles enable sustained, precise,

Table 2 Representative Nanoparticles and Functionalization Strategies Applied in Peripheral Nerve Regeneration

NP Type/ Functionalization	Mechanism of Action	Key Outcomes	Reference
CeO_2 antioxidant NPs	Redox cycling ($Ce^{3}+/Ce^{4}+$) scavenges ROS	Neuroprotection, improved regeneration; but partial tissue persistence	[15]
Magneto-responsive (Fe_3O_4 core–shell NPs, FMZMR)	Magnetic guidance/orientation under external field	~1.93× neurite length in vitro, improved axon/myelin regeneration, decreased muscle atrophy	[22]
PEDOT-conductive polymer NP hydrogel	Conductive cues restore bioelectric signals	SFI recovery comparable to autograft, increased myelination and muscle wet weight	[32]
Piezoelectric (eg, $BaTiO_3$ NPs in scaffold)	Converts US/mechanical forces to localized electric stimulation	Improved Axon alignment elongation and improved functional recovery	[33]
NO-releasing silica (NO-SN)	Controlled NO release to pro-regenerative signaling, ROS modulation	Faster SFI recovery (≈ sham by 5 wks), increased myelin thickness, axon counts and muscle force	[35]
$Se@SiO_2$ (antioxidant)	Sustained ROS scavenging, anti-inflammatory effects	Improved motor recovery and axon regeneration, reduced oxidative stress	[36]

and responsive interventions designed to the nerve repair microenvironment (Table 2). As the field advances toward intelligent, multimodal solutions, future success will depend on addressing biosafety, scalability, and regulatory hurdles through interdisciplinary collaboration. Ultimately, NP-based therapies have the potential to redefine peripheral nerve repair with unprecedented precision and therapeutic efficacy.

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Disclosure

The authors report no conflicts of interest in this work.

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