International Journal of Nanomedicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Nanoparticle-Facilitated Therapy: Advancing Tools in Peripheral Nerve Regeneration

Shaoyan Shi, Xuehai Ou, Deliang Cheng

Department of Hand Surgery, Honghui Hospital, Xi'an Jiaotong University, Xi'an Honghui Hospital North District, Xi'an, Shaanxi, 710000, People's Republic of China

Correspondence: Deliang Cheng, Department of Hand Surgery, Honghui Hospital, Xi'an Jiaotong University, Xi'an Honghui Hospital North District, Xi'an, Shaanxi, 710000, People's Republic of China, Tel +86 18740308729, Email chengdeliang2003@163.com

Abstract: Peripheral nerve injuries, arising from a diverse range of etiologies such as trauma and underlying medical conditions, pose substantial challenges in both clinical management and subsequent restoration of functional capacity. Addressing these challenges, nanoparticles have emerged as a promising therapeutic modality poised to augment the process of peripheral nerve regeneration. However, a comprehensive elucidation of the complicated mechanistic foundations responsible for the favorable effects of nanoparticle-based therapy on nerve regeneration remains imperative. This review aims to scrutinize the potential of nanoparticles as innovative therapeutic carriers for promoting peripheral nerve repair. This review encompasses an in-depth exploration of the classifications and synthesis methodologies associated with nanoparticles. Additionally, we discuss and summarize the multifaceted roles that nanoparticles play, including neuroprotection, facilitation of axonal growth, and efficient drug delivery mechanisms. Furthermore, we present essential considerations and highlight the potential synergies of integrating nanoparticles with emerging technologies. Through this comprehensive review, we highlight the indispensable role of nanoparticles in propelling advancements in peripheral nerve regeneration.

Keywords: nanoparticle, nanomedicine, biomaterials, nerve regeneration, tissue

Introduction

Peripheral nerve injuries, stemming from a variety of causes such as trauma, compression, and diseases, present a multifaceted challenge.[1] Traumatic injuries may result from accidents, falls, or surgical procedures, whereas compression-related conditions, like carpal tunnel syndrome, manifest due to prolonged pressure on nerves.[2] Diseases such as diabetes can contribute to peripheral neuropathy, adding to the diverse etiology of these injuries. The epidemiology of peripheral nerve injuries varies based on the underlying causes, with traumatic incidents often associated with specific events and neuropathies linked to diseases demonstrating a more widespread prevalence.[3] The consequences of peripheral nerve injuries extend beyond the physical realm, encompassing symptoms like pain, numbness, weakness, and impaired motor function. The impact is not solely confined to the affected body part but can significantly influence an individual's overall quality of life and mental well-being.

In the realm of treatments, current therapeutic approaches for peripheral nerve injuries encompass a spectrum of interventions.[3,4] These include physical therapy, pain management strategies, and, in certain instances, surgical procedures. Medications, such as pain relievers and anti-inflammatory drugs, are commonly prescribed to alleviate symptoms and manage the condition. However, these conventional treatments have their limitations, including systemic side effects, restricted drug penetration into affected nerve tissues, and the necessity for frequent administrations. This suggests the burgeoning demand for alternative drug delivery systems tailored to address these shortcomings. Innovative approaches, such as targeted nanoparticles or sustained-release formulations, offer the promise of more effective and patient-friendly treatment options.

Received: 1 October 2023
Accepted: 21 December 2023
Published: 3 January 2024

Understanding the regulatory network of peripheral nerves is crucial to appreciate the significance of these injuries and the need for advanced drug delivery methods. Peripheral nerves, extending from the spinal cord throughout the body, comprise sensory and motor nerves.[4,5] Sensory nerves convey signals from sensory organs to the brain, enabling the perception of touch, temperature, and pain. On the other hand, motor nerves transmit signals from the brain to muscles, facilitating voluntary movements.

During the past decades, the convergence of cutting-edge nanotechnology and the expansive domain of regenerative medicine has spurred a considerable development in peripheral nerve repair therapeutics.[6] Notably, nanoparticles, enriched with distinct attributes stemming from their complicated nanoscale structure, have emerged as noteworthy candidates for potential therapy, offering the capacity to intricately enhance the multi-faceted process of peripheral nerve repair (Figure 1).[7,8] Nanoparticles, often crafted from a composite of diverse materials engineered at the nanometer scale, harness their exceptional versatility to potentially address the challenges associated with peripheral nerve restoration.[9] Their diminutive dimensions grant nanoparticles a unique capability to interface with biological structures at a scale that aligns harmoniously with the complexities of the cellular milieu. This interaction can extend to the facilitation of cellular communication, the beneficial modulation of molecular cascades, and the orchestration of regenerative processes. Furthermore, the remarkable adjustability inherent in nanoparticles' physicochemical properties has unlocked potentials for customizing their behavior, including their interactions with nerve cells, growth factors, and the neighboring biomaterial milieu.[7,10]

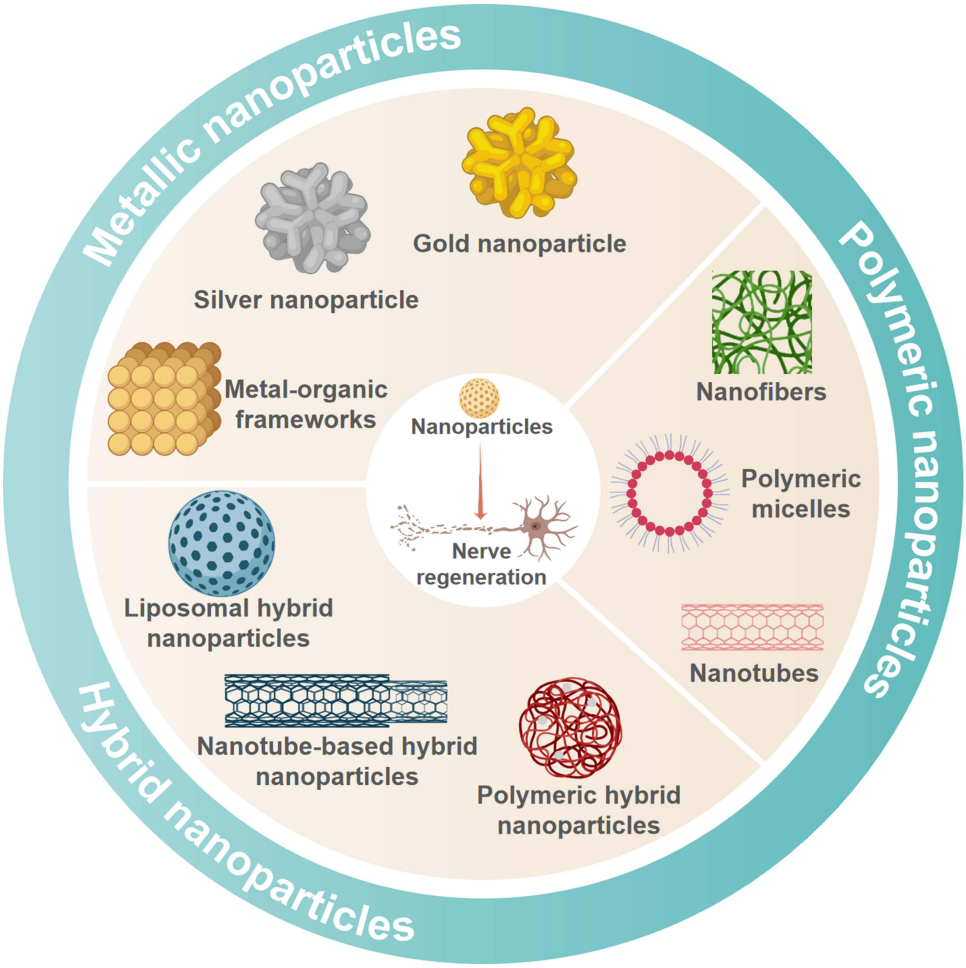

Figure 1 The outline of the nanoparticle-enabled therapies in promotion of peripheral nerve regeneration. Created with Medpeer (https://www.medpeer.cn/).

Nevertheless, further comprehensive investigations are imperative to unveil the mechanistic underpinnings that substantiate the advantageous contributions of nanoparticle-enabled therapy in nerve regeneration.

Through a comprehensive exploration of nanoparticles' role as transformative therapeutic entities, this review extensively scrutinizes the potential of nanoparticles as pioneering therapeutic agents primed to accelerate the process of peripheral nerve repair. We engage in a comprehensive discussion and summarization of the classifications and synthesis methodologies of nanoparticles, elucidating their multifaceted capabilities, which encompass neuroprotection, facilitation of axon growth, and proficient drug delivery mechanisms. By identifying the complicated structural attributes and multifaceted functional capacities inherently possessed by nanoparticles, we aim to unveil their profound and transformative potential in the facilitation of peripheral nerve repair.

Diverse Nanoparticle Typologies and Synthesis Modalities

Nanoparticles, providing a potential approach characterized by elevated therapeutic precision in peripheral nerve repair, span a wide range of typologies and synthesis methodologies.[11] One critical direction of investigation involves utilizing nanoparticles as carriers for neurotrophic and growth factors, enhancing their targeted delivery to injured nerve sites and fostering neuronal survival and axonal outgrowth.[12] Concurrently, conductive nanoparticles, such as carbon nanotubes and graphene, have demonstrated promise in providing a supportive environment for nerve cell growth, mimicking the natural cues of the nervous system.[13] These materials, whether integrated into nerve scaffolds or used independently, contribute to the facilitation of nerve regeneration. Additionally, nanoparticles have been explored for their immune-modulating properties, playing a role in minimizing inflammation at the injury site and creating a conducive environment for successful nerve repair.[14] The synthesis of these diverse studies suggests the versatile and transformative potential of nanoparticles in peripheral nerve regeneration, offering innovative solutions to address nerve injuries and enhance functional recovery.

Classification of Nanoparticles

The field of nanoparticles unfolds as a diverse landscape, characterized by a wide array of compositions, each endowed with distinct capabilities in peripheral nerve repair (Table 1).[15] Among which, metallic nanoparticles, notably exemplified by gold and silver variants, offer a range of exceptional attributes.[16,17] These include enhanced electrical conductivity and the phenomenon of surface plasmon resonance. Such inherent characteristics endow metallic nanoparticles with significant versatility, thereby substantiating their utility in a wide range of applications including nerve stimulation and regeneration.[18]

Furthermore, polymeric nanoparticles assume a pivotal role as carriers for therapeutic agents.[19] This significant function indicates their potential for orchestrated and precise payload delivery, thereby providing opportunities for

Table 1 Types of Nanoparticles, Methods for Preparation, Characteristics, Advantages, and Disadvantages in the Context of Nanomedicine for Peripheral Nerve Injury

Nanoparticle Type	Method for Preparation	Characteristics	Advantages	Disadvantages
Liposomes	Lipid film hydration method	Biocompatible, versatile, drug encapsulation	Targeted drug delivery, reduced side effects	Limited drug payload, potential instability
Polymeric Nanoparticles	Emulsion polymerization	Controlled drug release, customizable polymers	Sustained release, enhanced bioavailability	Biodegradation variability, potential toxicity
Dendrimers	Divergent or convergent synthesis	Well-defined structure, multivalent drug loading	Precise drug delivery, low systemic toxicity	Complex synthesis, potential immunogenicity
Nanofibers	Electrospinning	High surface area, tunable mechanical properties	Mimics natural extracellular matrix	Limited drug loading, challenging scalability
Quantum Dots	Colloidal synthesis	Size-dependent fluorescence, versatile applications	Imaging, real-time tracking	Toxicity concerns, long-term effects unclear

neuroprotection and growth modulation.[20,21] The intrinsically compatible nature of these polymeric architectures offers an environment favorable for sustaining and restoring compromised neural substrates.[22]

The nanoparticle innovation extends further into the domain of hybrid nanoparticles, where the combination of diverse material components gives rise to entities endowed with multifaceted functionalities.[23,24] The deliberate integration of metallic and polymeric domains within these hybrid constructs results in the convergence of distinctive attributes.[21,25] This combination synchronizes electrical conductivity with precisely controlled release mechanisms. This emerging synergy not only broadens the spectrum of therapeutic possibilities but also holds the potential for heightened efficacy in strategies aimed at nerve regeneration and recuperation.

The use of nanoparticles in nerve repair, however, is hindered by significant concerns related to toxicity. An essential factor in understanding nanoparticle toxicity is the material composition.[26] Nanoparticles can be constructed from a diverse range of materials, including lipids, polymers, metals, and quantum dots. Each material introduces unique properties, influencing how nanoparticles interact with biological systems.[27] Understanding these interactions is fundamental to predicting potential adverse effects. Additionally, the size of nanoparticles plays a crucial role.[28] Smaller particles may exhibit higher reactivity and cellular uptake, impacting their biological fate. Surface characteristics, such as charge and coating, further modulate these interactions. These factors collectively contribute to the overall biocompatibility of nanoparticles and their subsequent impact on cellular functions. Studies focused on elucidating the intricate relationship between material properties and biological responses are essential for developing nanoparticles that minimize toxicity while maximizing therapeutic efficacy.[26,28]

Furthermore, biodistribution and accumulation patterns of nanoparticles within the body are critical aspects of their toxicological role.[29] Prolonged accumulation in specific organs may lead to toxicity over time. Investigating inflammatory responses is equally important, as nanoparticles can trigger immune reactions that may affect their overall safety profile. Assessing cytokine release, immune cell activation, and inflammatory markers provides insights into the potential immunotoxicity of nanoparticles.[30] A holistic understanding of these factors requires not only in vitro studies but also in vivo investigations using animal models. These studies help simulate systemic responses and evaluate the long-term effects of nanoparticle exposure.[30,31] Considering the ethical considerations and species-specific differences is imperative for translating findings from preclinical studies to human applications.

In the pursuit of a comprehensive toxicological assessment, a variety of screening methods are employed. In vitro studies using cell culture models are foundational, enabling researchers to evaluate cytotoxicity, cell viability, and morphological changes in response to nanoparticle exposure.[32] These studies provide an initial understanding of the potential risks associated with specific nanoparticles. Moving to more complex in vivo studies, researchers assess biodistribution, organ toxicity, and long-term effects using animal models. This multifaceted approach helps bridge the gap between cellular responses and systemic effects, providing a more holistic perspective on nanoparticle toxicity.[27,33] Biocompatibility assessments and immunotoxicity testing further contribute to the comprehensive screening process, ensuring that nanoparticles do not elicit adverse reactions from the immune system.

Incorporating advanced imaging techniques into nanoparticle toxicity screening enhances our ability to visualize and understand the in vivo behavior of nanoparticles. Techniques such as electron microscopy, magnetic resonance imaging (MRI), and positron emission tomography (PET) allow researchers to track the distribution of nanoparticles within tissues and organs.[3,34] This not only aids in confirming the success of targeted delivery but also provides crucial information on potential off-target effects and accumulation in non-target organs. Integrating these advanced techniques with traditional toxicity screening methods creates a robust framework for evaluating the safety profile of nanoparticles in the landscape of nanomedicine and nerve repair.

Diverse Nanoparticle Synthesis Methods

The functional arrangement of nanoparticles emphasizes the essential need for a critical need of synthesis techniques.[35,36] This exploration extends along a binary axis, encompassing the realms of both bottom-up and top-down strategies, each imbued with distinct properties and applications.[37,38] The inception of bottom-up strategies transpires at the molecular scale, affording the meticulous construction of nanoparticles, atom by atom, and molecule by molecule.[39] In the micro-level exploration, the classification of nanoparticles takes center stage, primarily based on their composition and

structure. Metal nanoparticles, crafted through chemical synthesis, offer unique optical and electrical properties, exemplified by gold and silver nanoparticles, which can be harnessed for targeted drug delivery and imaging in nerve repair.[40] Similarly, polymeric nanoparticles, created through bottom-up techniques like emulsion polymerization or self-assembly, provide controlled release properties ideal for encapsulating neurotrophic factors crucial for nerve regeneration.[41] Another avenue involves lipid-based nanoparticles, synthesized through techniques such as thin-film hydration, serving as carriers for bioactive molecules and facilitating their transport across the blood-brain barrier for enhanced nerve repair. Beyond composition, the functionalization and surface modifications of nanoparticles at the atomic or molecular level play a critical role. Bottom-up surface engineering enables the attachment of peptides or proteins, improving biocompatibility and cellular uptake.[42] Responsive nanoparticles, engineered through self-assembly, respond to stimuli such as pH or temperature, ensuring the controlled release of therapeutic agents at the site of injury.[41,42] This hierarchical classification extends to therapeutic applications, with intracellular nanoparticles designed for cellular uptake, interacting nanoparticles tailored for the extracellular matrix, and multifunctional nanoparticles combining diagnostic and therapeutic capabilities. Ultimately, the bottom-up approach provides effective control over the properties and functions of nanoparticles, offering a targeted strategy for neural regeneration at the cellular and molecular levels.

In contrast, top-down strategies intricately fabricate nanoparticles from larger source materials, constructing them through controlled fragmentation or etching processes. Approaches such as lithography and laser ablation epitomize the finesse of top-down methodologies, adroitly carving nanoparticles possessing bespoke dimensions from bulk materials.[40,43] This wide-ranging spectrum of synthesis modalities encapsulates the core of nanoparticle origination, wherein innovative capacity at the atomic and molecular levels enhances the foundation of the promising therapeutic potential.

The complex structures of nanoparticles play a pivotal role in elucidating their behavior within the complicated environment of the nervous system, particularly when it comes to targeted therapy. One crucial aspect is the structural design of polymeric nanoparticles.[44] These structures can be engineered with a high degree of precision, allowing for the creation of nanoparticles with specific shapes, sizes, and surface properties. These factors collectively influence the circulation time in the bloodstream, cellular uptake, and overall biodistribution. For instance, tailoring the polymer structure can result in nanoparticles with prolonged circulation times, increasing the likelihood of reaching the target site within the neural tissue.[45]

Furthermore, the incorporation of stimuli-responsive elements into the nanoparticle structure adds another layer of complexity.[46] Responsive nanoparticles can alter their physicochemical properties in response to specific cues present in the microenvironment of the injured nerves. This responsiveness can be achieved through the integration of pH-sensitive, temperature-responsive, or enzymatically degradable components.[47] Such functional control over the nanoparticle structure enables them to release therapeutic agents in a spatiotemporally controlled manner, precisely at the site of neural injury, optimizing the therapeutic effect and minimizing off-target effects.

In terms of surface modifications, a detailed examination of ligand conjugation is essential. Ligands, such as peptides or antibodies, can be strategically attached to the nanoparticle surface using bottom-up approaches. This enables the nanoparticles to recognize and bind to specific receptors on the surface of neural cells, enhancing their cellular uptake and internalization. The molecular specificity conferred by these ligands ensures targeted delivery, a critical factor in the success of nerve repair therapies.[13] This targeted approach minimizes systemic exposure and potential side effects, focusing the therapeutic intervention on the affected neural tissues.

Moreover, the exploration of multifunctional nanoparticles reveals how the integration of various components within the complex structure can synergistically enhance targeting.[13]

Neuroprotective Efficacy of Nanoparticles

The beneficial role of nanoparticles acting in peripheral nerve repair transcends the confines of structural reinforcement, deeply exploring the orchestration of neuroprotective cues.[48]

The size of nanoparticles assumes an important role, influencing cellular interactions and tissue penetration. Nanoparticles within particular size ranges exhibit enhanced cellular uptake, facilitating the targeted delivery of bioactive molecules crucial for promoting regeneration at injured nerve sites.[49] Moreover, the size of nanoparticles dictates their

diffusion properties, directly affecting their ability to permeate nerve tissue and offer an environment conducive to regeneration.[49] Chemistry, as another critical attribute, shapes the surface properties of nanoparticles. Surface functionalization with bioactive molecules, growth factors, or neurotrophic agents enhances biological compatibility, fostering advantageous interactions with nerve cells.[50] Tailoring nanoparticle chemistry allows for precise modulation of cellular responses, a key determinant in the overall success of peripheral nerve regeneration. Additionally, surface charge emerges as a pivotal factor influencing cellular uptake and intracellular signaling. Positively or negatively charged nanoparticles elicit different interactions with the cell membrane, subsequently affecting internalization and cellular responses.[51] By elucidating the intricate interplay of specific nanoparticle characteristics, encompassing size, chemistry, and surface charge, a deeper comprehension of their contributions to enhanced peripheral nerve regeneration comes to light.

Nanoparticles' Multifunctional Role as Antioxidants and Anti-Inflammatory Agents in Nerve Repair

The intricate milieu of nerve regeneration is besieged by an array of challenges, chief among them being oxidative stress and the cascades of inflammation that pose existential threats to neuronal integrity. Nanoparticles, owing to their intrinsic ability to scavenge free radicals and deftly modulate inflammatory responses, emerge as vanguards of protection against these pernicious forces.[52,53] Their capacity as antioxidants stands resolute as a protective bulwark against cellular damage, a sentinel that decisively mitigates the perils posed by oxidative stress, thereby mitigating its corrosive impact on regenerative processes.[54] For instance, Liu et al synthesized superparamagnetic iron oxide nanoparticles (mSPIONs) coated with mannose to alleviate the over-generated reactive oxygen species (ROS) around the injured nerves.[55] The results revealed a substantial reduction in ROS levels both in vitro and in vivo due to the administration of mSPIONs. Moreover, the application of mSPIONs induced a specific reduction in interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) levels in macrophages localized in the vicinity of the sciatic nerve, consequently alleviating peripheral neuropathic pain. These findings introduce a novel strategy for mitigating overloaded oxidative stress and inflammation through the utilization of nanoparticles, as exemplified by the mSPIONs employed in this study.

Furthermore, nanoparticles exert attributes that extend into the domain of anti-inflammation, effectively quelling the tempestuous storm of inflammatory responses and thereby fostering an environment conducive to repair. By orchestrating the regulated release of inflammatory mediators and adeptly modulating immune responses, these nanoparticles serve to pacify the tumultuous waves of inflammation. In so doing, they beneficially constructed an environment that significantly promote the process of neuronal recovery.

Nanoparticles Enhance Neuronal Viability via Mitigating Oxidative Stress

Oxidative stress, a critical factor that impairs neuronal survival, encounters a formidable adversary of its own in nanoparticles. Equipped with the remarkable ability to neutralize reactive oxygen species, these nanoscale entities actively counteract oxidative insults that act as formidable barriers to the regenerative process.[56,57] Functionally, through their strategic intervention, nanoparticles serve as effective protectors of neuronal viability, thus establishing a conducive milieu wherein damaged neurons are afforded the opportunity to repair and regenerate.[58–60] For instance, cerium oxide nanoparticles, recognized for their potent capacity to scavenge free radicals, were employed as carriers for the encapsulation of dl-3-n-butylphthalide (NBP-CeO2 NPs). NBP-CeO2 NPs effectively mitigated the presence of ROS within murine brain microvascular endothelial cells and hippocampal neurons subjected to oxygen-glucose deprivation/reoxygenation. In a murine model, NBP-CeO_2 NPs demonstrated remarkable ROS scavenging capabilities, affording considerable protection to mitochondrial architecture.[61] These effects collectively culminated in a suppression of neuroinflammatory processes, and inhibition of neuronal apoptosis. By concomitantly mitigating oxidative stress and inflammation around neural cells, these nanoparticles present a versatile and promising approach in protecting neuronal viability.

The orchestration of nanoparticle-mediated neuroprotection extends well beyond the confines of mere preservation, promoting the remarkable augmentation of neuronal vitality.[60] By combating against oxidative stress, nanoparticles provide an environment wherein neurons are not merely shielded from harm, but are, in fact, empowered to flourish. This complicated interplay between nanoparticle-mediated neuroprotection and the resultant enhancement of neuronal

resilience represents a predominant demonstration to the transformative potential of nanotechnology.[58] The multifaceted role of nanoparticles as neuroprotective agents in the context of peripheral nerve repair provides a promising approach wherein therapeutic interventions transcend conventional structural support. The roles they undertake as antioxidants and potent anti-inflammatory agents reflect the body's inherent defense mechanisms, magnified through the precision of the nanoscale.

Facilitating Axonal Growth and Myelination

Nanoparticles emerge as profound conductors in enhancement of nerve repair, their influence extending beyond neuronal protection to encompass the dynamic facilitation of axonal growth and myelination. In this section, we introduce the interplay between nanoparticles and the regenerative intricacies associated with guided neurite elongation and the reconstruction of myelin sheaths.

Surface Modification of Nanoparticles for Enhanced Guided Neurite Elongation

Central to the process of nerve regeneration resides the critical necessity for axonal extension, wherein the orchestrated elongation of guided neurites navigates the intricate terrain of compromised tissue. Nanoparticles, through strategic surface modification, assume the role of trailblazers, functionally guiding axons along predetermined trajectories.[50] By engineering nanoparticles with cues that emulate the native topography of the extracellular matrix (ECM), researchers harness their innate ability to offer tactile guidance, thereby steering emerging axons with precision toward their intended destinations.[62]

Nanoparticle surface modification embodies a form of regenerative strategy, where each functional alteration contributes intricately to the elaborate fabric of neural repair.[50,62] The strategic alignment of nanoparticles with regenerating neurites introduces innovative avenues for orchestrating directional growth. The integration of purpose and alignment in this manner serves to elevate the regenerative process, akin to the orchestrated cues observed in natural developmental processes.[62] In a recent study, Hu et al unveiled a promising approach centered around a conductive topological scaffold for nerve restoration.[63] This scaffold is fabricated through the incorporation of reduced graphene oxide (rGO) nanosheets and methacrylated gelatin (GelMA) hydrogel onto Morpho butterfly wing surfaces, all while encapsulating BDNF. By harnessing GelMA hydrogel's biocompatibility, the electrical conductivity of rGO, and the inherent parallel nanoridge structures of butterfly wing scales, the modified wing engenders amplified neurite length in PC12 cells and neural stem cells. Moreover, this scaffold effectively steers cellular orientation, augmenting the overall regenerative potential. Employing a manual rolling technique, this ingenious approach yields nerve guidance conduits (NGCs) derived from the aforementioned scaffolds. The NGCs exhibit robust effectiveness in rectifying 10 mm sciatic nerve defects in rats. Notably, the in vitro outcomes suggest the remarkable viability of electrically conductive NGCs fashioned through the integration of rGO/BDNF/GelMA onto Morpho butterfly wing constructs. Specifically, the wet weight ratio of the gastrocnemius muscle exhibited similarity between the Wing+rGO+BDNF+GelMA group and the Autograft group. Since sciatic nerve regeneration and functional recovery coincide with muscle regeneration, hematoxylin and eosin (HE) staining was conducted on muscle fibers to assess their sizes. The muscle fiber diameters in the Autograft group measured 35.64 ± 1.05 μm, while those in the Wing+rGO+BDNF+GelMA group were 32.97 ± 0.78 μm —both significantly larger than the native Wing group, which recorded 21.12 ± 0.60 μm (Figure 2). These NGCs manifest functionality as conduits facilitating nerve regeneration, thereby harboring considerable promise in the realm of peripheral nerve injury mitigation.

Nanoparticles' Profound Contributions to Enhance Myelin Sheath Reconstruction

Peripheral nerve regeneration encompasses not only the regrowth of axons but also the reconstruction of myelin sheaths, essential insulating layers that facilitate efficient nerve signal propagation. In this process, nanoparticles emerge as pivotal protagonists, playing a critical role in orchestrating myelin sheath reconstruction.[64] Through their function as scaffolds and guidance cues, nanoparticles foster a nurturing environment where Schwann cells—the architects of myelin —can functionally weave their regenerative tapestry.

Nanoparticles, endowed with the capacity to secrete growth factors and modulate cellular behavior, amplify the cues that underlie myelination.[65] Their presence harmonizes the delicate interplay between Schwann cells and axons,

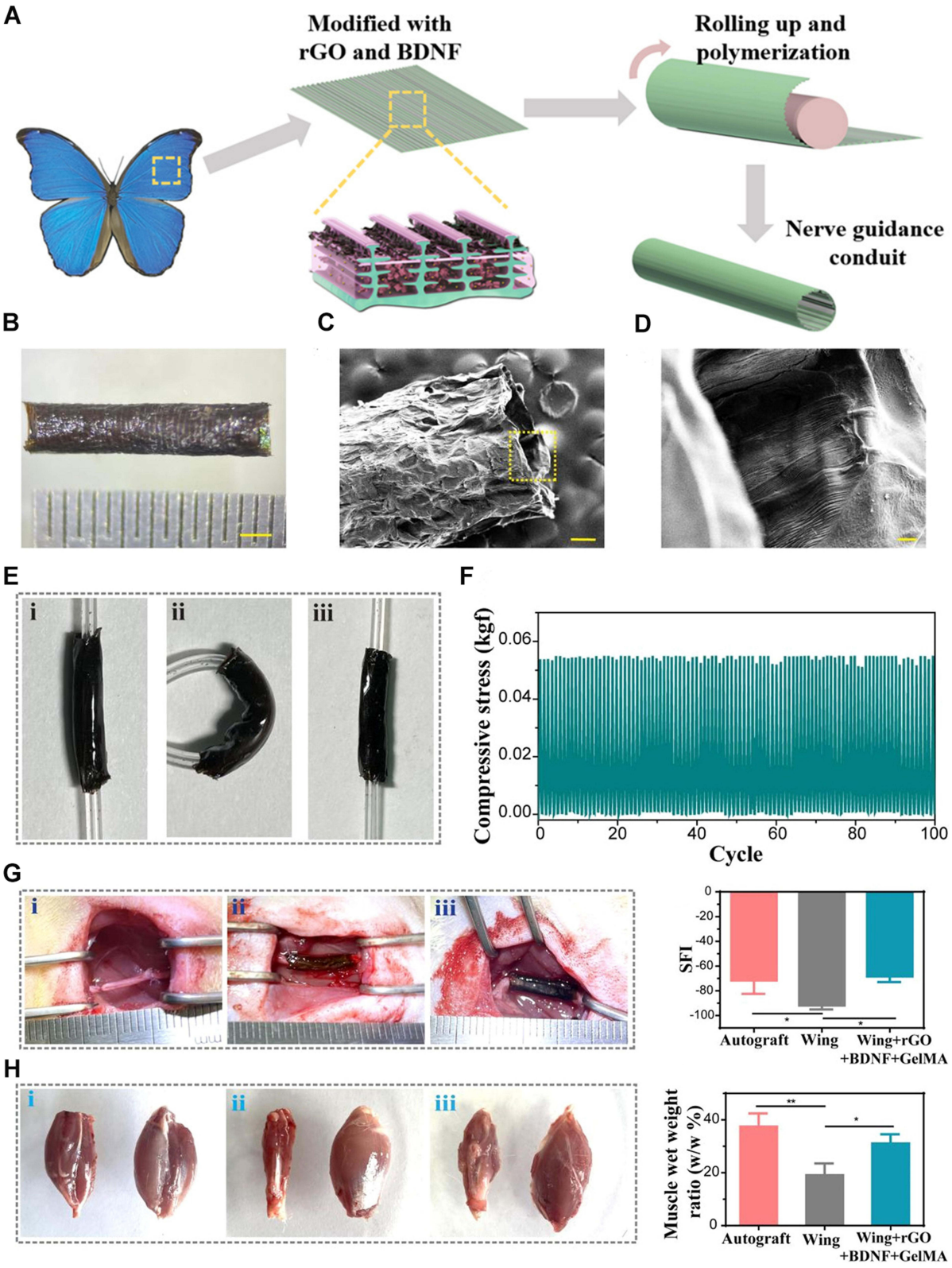

Figure 2 (**A**) Schematic illustration of the conductive NGC based on the integration of rGO and BDNF onto the wing of Morpho menelaus butterfly, designed for peripheral nerve regeneration. (**B**) Photograph showing an NGC founded on the integration of rGO/BDNF onto the wing of Morpho menelaus butterfly. (**C**) SEM images of the fabricated NGC, presented in both low and high magnifications. (**D**) Photographs capturing the NGC in different states of bending, emphasizing its flexibility and adaptability. (**E**) illustration a cyclic fatigue test involving the prepared NGC, showing its durability and ability to withstand repetitive stress and deformation. (**F**) Conducting a cyclic fatigue test using the prepared NGC. (**G**) Photographs depicting NGCs implanted in Autograft (i), Wing (ii), and Wing+rGO+BDNF+GelMA (iii) groups. And the SFI evaluation for rats across various groups at 8 weeks. (**H**) Images capturing muscle conditions, and the muscle wet weight ratio analysis in Autograft (i), Wing (ii), and Wing+rGO+BDNF+GelMA (iii) group. Reproduced with permission from Hu Y, Chen Z, Wang H, et al. Conductive nerve guidance conduits based on morpho butterfly wings for peripheral nerve repair. ACS Nano. 2022;16(2):1868–1879.[63] Copyright 2022, American Chemical Society.

culminating in the reestablishment of functional neural conduits. The contribution of nanoparticles to the reconstruction of myelin sheaths stands as a testament to their multifaceted roles in the orchestration of nerve repair, wherein they embrace the mantle of regenerative maestros.[66] For instance, Lopes et al introduced novel polymeric nanoparticles formulated from thiolated trimethyl chitosan (TMCSH), designed to facilitate precise gene delivery to peripheral neurons.[21] This delivery modality is achieved through a minimally invasive intramuscular administration, thus optimizing peripheral accessibility. Notably, these nanoparticles are bioengineered with a grafting of the non-toxic carboxylic fragment of the tetanus neurotoxin (HC), affording neuron-specific targeting capabilities. The core of this study revolves around the utilization of these engineered nanoparticles as carriers for plasmid DNA, specifically encoding the brain-derived neurotrophic factor (BDNF), a pivotal neurotrophic agent. Upon treatment with TMCSH-HC/BDNF nanoparticles, a remarkable outcome was observed by the release and substantial expression of BDNF within neural tissues. A distinctive attribute of the proposed neuron-targeted nanoparticle intervention was its correlation with an elevated density of myelinated axons in the distal segment of injured nerves. More importantly, the treatment also yielded the preservation of density among unmyelinated axons, serving to differentiate it from the control counterparts. Remarkably, a protective influence was found in muscles subjected to injury-denervation dynamics, effectively counteracting denervation effects (Figure 3). These results indicate the substantial potential inherent in TMCSH-HC nanoparticles as carriers for therapeutic gene delivery to peripheral neurons.

Strategies for Nanoparticle-Mediated Drug Delivery

Nanoparticles, characterized by their adaptability as therapeutic carriers, transcend their roles as structural entities to embrace a pivotal mission: delivering potent neuroactive agents to precise targets. This section elucidates the intricacies of nanoparticle-mediated drug delivery—an arena where these nanosize carriers hold the potential to reshape the landscape of therapeutic interventions.

Neuroactive Agent Encapsulation Within Nanoparticulate Matrices

The interplay between nanoparticles and therapeutic agents establishes a function characterized by unrivaled precision, where these minuscule carriers assume the role of custodians for the essence of healing.[48] Yet, this encapsulation surpasses the mere confinement of physical boundaries; it blossoms into a strategic alliance, endowing heightened stability, prolonged and controlled release kinetics, and a magnified therapeutic efficacy upon these agents.[49,67]

The composition of nanoparticulate matrices, whether stemming from polymeric, lipid-based, or hybrid origins, intricately reflects the landscape of the therapeutic agents they encapsulate. The orchestrated interplay that unfolds between these nanoparticle carriers and the encapsulated agents generates a dynamic synergy that culminates in a paradigm of therapeutic precision. Within the sphere of encapsulation, therapeutic interventions undergo a profound metamorphosis, evolving from transient actions into orchestrated and sustained endeavors.[10,48] This transformative shift gives rise to a regenerative milieu adeptly fostering and guiding the complicated processes of healing.

A pertinent example lies in the work of Hanwright et al, who ingeniously formulated biodegradable nanoparticles encompassing insulin-like growth factor 1 (IGF-1) within dextran sulfate polyelectrolyte complexes.[10] Employing the flash nanoprecipitation technique, they carefully chose this method to uphold IGF-1's bioactivity and optimize encapsulation efficiency. Results from both in vitro and in vivo assessments illuminated the profound impact of IGF-1 nanoparticles. This treatment manifested in substantially enhanced forepaw grip strength recovery, effectively counteracting the muscle atrophy triggered by denervation, reducing senescence in Schwann cells (SCs), and fostering an environment conducive to heightened neuromuscular reinnervation (Figure 4). These findings resoundingly underscore the remarkable potential of IGF-1 nanoparticle-based intervention. The strategic administration of IGF-1 through this nanoparticle delivery system holds the key to achieving superior motor recovery outcomes.

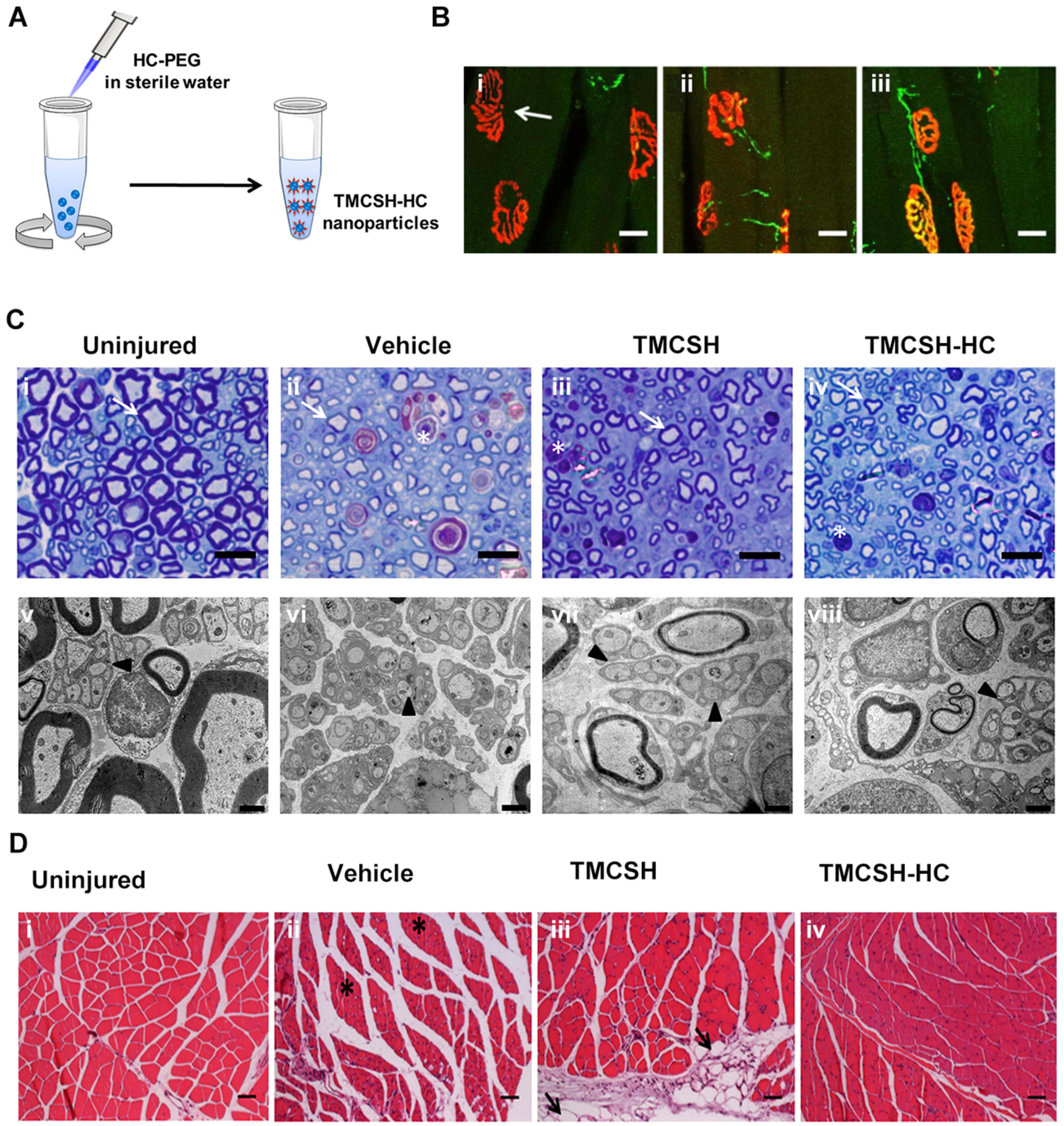

Figure 3 (**A**) Schematic illustration delineating the sequential steps involved in the preparation of TMCSH-based nanoparticles. (**B**) Illustrative images depicting denervated (i, indicated by arrows), partially innervated (ii), and fully innervated (iii) neuromuscular junctions (NMJs) in the gastrocnemius muscle are presented. The labeling was achieved using the NF200 marker (in green) and the postsynaptic marker alpha-bungarotoxin (in red) 21 days post-injury. The scale bar indicates 20 μm. (**C**) Illustrative images featuring semi-thin transverse sections of the sciatic nerve: (i) Uninjured nerves (contralateral), (ii) Vehicle group, (iii) TMCSH group, and (iv) TMCSH-HC group. Arrows are used to highlight myelinated axons, while asterisks (*) denote degenerating axons. The scale bar corresponds to 25 μm. Furthermore, the exemplar images displaying ultra-thin transverse sections of the sciatic nerve: (v) Uninjured nerves (contralateral), (vi) Vehicle group, (vii) TMCSH group, and (viii) TMCSH-HC group. Arrowheads are utilized to indicate Remak bundles. The scale bar corresponds to 1 μm. (**D**) Representative images of gastrocnemius muscles sourced from different experimental groups: (i) Uninjured nerves (contralateral), (ii) Vehicle group, (iii) TMCSH group, and (iv) TMCSH-HC group. *Depicts groups of atrophic muscle fibers; Arrows indicate the presence of adipocytes. Scale bar 50 μm. Reproduced from Biomaterials, Volume 121, Lopes CDF, Goncalves NP, Gomes CP, Saraiva MJ, Pego AP. BDNF gene delivery mediated by neuron-targeted nanoparticles is neuroprotective in peripheral nerve injury, pages 83–96, Copyright 2017, with permission from Elsevier.[21]

Augmented Drug Bioavailability and Targeted Delivery

The robust potency of therapeutic agents often grapples with the complexities of limited bioavailability and the looming specter of off-target effects. In this context, nanoparticles emerge as a transformative force, endowed with the remarkable

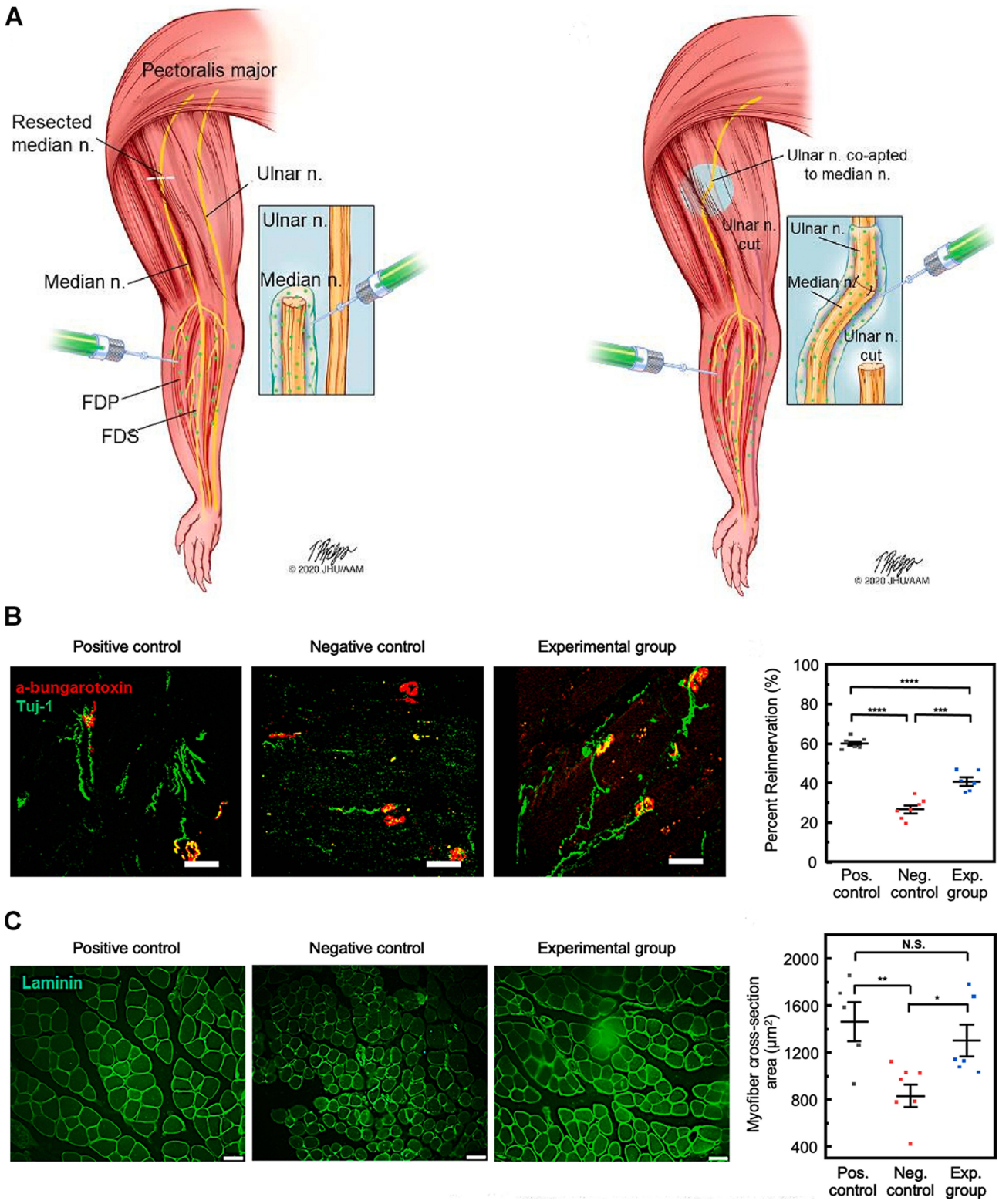

Figure 4 (**A**) Illustration of a median nerve transection, accompanied by the administration of nanoparticles around the distal nerve and within the denervated muscle compartment. And the illustration of the second surgical step in the second phase of the study. This step involves an ulnar-to-median nerve transfer, alongside the re-administration of nanoparticles. (**B**) Representative staining applied to longitudinal muscle sections, taken 15 weeks after nerve repair. This staining technique focuses on capturing the details of neuromuscular junctions, shedding light on their structural characteristics and interactions. (**C**) Representation of laminin staining applied to cross-sections of muscle tissue, taken at the 15-week mark following nerve repair. This staining method is utilized to highlight and visualize the presence and distribution of laminin, a structural protein that plays a crucial role in maintaining the integrity of the muscle basement membrane and facilitating neuromuscular connections. Reproduced from Biomaterials, Volume 280, Hanwright PJ, Qiu C, Rath J, et al, Sustained IGF-1 delivery ameliorates effects of chronic denervation and improves functional recovery after peripheral nerve injury and repair, page 121244, Copyright 2022, with permission from Elsevier.[10]

capability to surmount biological barriers and pinpoint specific anatomical locales. These nanoscale entities stand as robust amplifiers of therapeutic payloads, accentuating the impact of treatment interventions.[68]

Through the strategic implementation of functional surface modifications, nanoparticle carriers adeptly navigate the complex network of biological pathways with exceptional precision. This strategic navigation endows them with the ability to evade premature degradation and efficiently deliver therapeutic payloads to the designated sites of therapeutic necessity.[69]

A defining attribute of nanoparticle carriers lies in their capacity for site-specific delivery, a facet that exerts a transformative influence on the therapeutic landscape.[70] This hallmark characteristic significantly bolsters the therapeutic index by minimizing undue impact on healthy tissue. The delivery of neuroactive agents to the targeted sites of nerve injury emerges as a highly promising endeavor. In this context, nanoparticles demonstrate their excellent function in guiding these agents to the core of regenerative necessities. Lopes et al constructed a nonviral neurotropic nanoparticle based on poly(ethylene imine), which demonstrates the capability to facilitate neuron-specific transfection following subcutaneous injection.[71] The targeting of nanoparticles to peripheral neurons is achieved using the neurotropic carboxylic fragment of the tetanus toxin (HC), which not only exhibits neurotropic properties but can also be retrogradely transported from neuron terminals to cell bodies. Following subcutaneous injection in the footpad of Wistar rats, the results obtained after five days reveal that 56% and 64% of L4 and L5 dorsal root ganglia neurons, respectively, exhibited expression of the reporter protein. Importantly, the delivery facilitated by HC-functionalized nanoparticles displayed spatially confined transgene expression when compared to the control groups. Detailed histological assessment indicated no significant adverse effects associated with the proposed delivery system.

Perspectives and Challenges

The neuroprotective efficacy of nanoparticles in the context of peripheral nerve injury involves mechanisms aimed at mitigating damage and fostering a regenerative microenvironment.[6] One key facet of their neuroprotective role is their inherent antioxidant properties, acting as scavengers of ROS to counteract oxidative stress.[72] Additionally, nanoparticles exhibit anti-inflammatory effects by modulating immune responses, attenuating inflammation, and thereby reducing damage to neural tissues. Another crucial facet is the delivery of neurotrophic factors, where nanoparticles are engineered to release these factors directly at the injury site, promoting the survival and growth of neurons.[21] Transitioning to their role in facilitating axonal growth, nanoparticles act as guidance cues through surface modifications that mimic the extracellular matrix, providing a supportive substrate for directed axonal regeneration. Furthermore, nanoparticles encapsulate growth-promoting drugs, fostering controlled release and creating a conducive biochemical environment for axonal outgrowth. In myelination support, nanoparticles influence oligodendrocyte differentiation, crucial for the formation of myelin sheaths around regenerating axons.[48] They also contribute to sustained release of myelin-related factors, expediting and enhancing the efficiency of myelin formation. This multifaceted approach shows the potential of nanoparticles not only in neuroprotection but also in actively promoting axonal growth and facilitating myelination.

One of the most advantageous properties of nanoparticles is their potential to revolutionize drug delivery precision, particularly to the precise sites of nerve injury.[73] With their remarkable ability to traverse biological barriers, these nanoparticles assume the role of therapeutic couriers, delivering their cargo directly to the sites in need. This targeting capacity holds the promise of minimizing off-target effects, consequently mitigating potential harm to surrounding healthy tissues.

Furthermore, the controlled and sustained release manner of nanoparticles becomes an indispensable virtue.[74] Nanoparticles, with their capacity to functionally regulate the release kinetics of neuroactive agents, offer a pivotal solution. This orchestrated release not only ensures sustained therapeutic levels within the system but also obviates the need for frequent interventions, thereby optimizing efficacy and patient compliance.The utilization of nanoparticles is extended through their incorporation in the realm of co-delivery. This excellent advance facilitates the implementation of synergistic therapeutic strategies, wherein a multitude of therapeutic agents, each possessing distinct mechanisms of action, harmoniously collaborate.[73,74] The coordinated interplay of these agents not only augments the processes of nerve repair but also introduces heightened efficacy in terms of regeneration promotion and inflammation attenuation.

Moreover, the realm of nanoparticles unveils opportunities for personalized medicine. The capability to customize nanoparticles in dimensions, composition, and surface attributes introduces a revolution where therapeutic formulations are designed to harmonize with the distinct attributes of individual patients and the precise profiles of their nerve injuries. This individualized approach stands as a testament to the transformative potential of nanoparticles in fostering patient-centric healing.

Nevertheless, critical challenges accompany this transformative potential. The intricate interplay between nanoparticles and biological systems necessitates a comprehensive understanding of their biocompatibility and long-term safety. Rigorous assessment to preclude unintended immune responses or toxicity is of paramount importance to safeguard against adverse effects.

While nanoparticles excel in improving targeting precision, attaining the required degree of delivery accuracy for optimal nerve repair remains a challenge.[75] Moreover, the intricate intricacies of nanoparticle biodistribution, tissue interactions, and eventual clearance assume critical importance.[35] Ensuring that nanoparticles do not inadvertently accumulate in unintended organs or tissues beyond their designated target is essential to preclude unforeseen consequences. Finally, nanoparticle accumulation's long-term effects in the body requires comprehensive examination. The assurance that nanoparticles do not engender unintended chronic effects or accumulate over time becomes pivotal to ensuring the long-term safety and viability of nanoparticle-based therapies.

Conclusion

The emergence of nanoparticles-enabled pharmacotherapy marks a transformative trend in peripheral nerve repair. This innovative approach leverages the unique attributes of nanoparticles to revolutionize therapeutic interventions, promising enhanced precision, sustained release, and synergistic therapies. However, this advanced strategy is not without its challenges, necessitating comprehensive considerations of biocompatibility, regulatory navigation, targeting precision, biodistribution, and long-term effects. The potential to redefine healing modalities and offer personalized, patient-centric interventions is profound.

As interdisciplinary research and clinical exploration continue to unravel the interplay between nanoparticles and nerve repair, the prospect of ushering in a new era of regenerative medicine becomes increasingly tantalizing. With each stride made in understanding and overcoming these challenges, the landscape of peripheral nerve repair stands on the brink of a transformative modality shift. This shift holds the potential to not only ameliorate but also revolutionize the lives of numerous individuals grappling with the repercussions of nerve injuries.

Acknowledgments

The authors would like to thank Medpeer software (https://www.medpeer.cn/) for its picture source assistance during the Figure 1 preparation of this manuscript.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Barnes SL, Miller TA, Simon NG. Traumatic peripheral nerve injuries: diagnosis and management. *Curr Opin Neurol*. 2022;35(6):718–727. doi:10.1097/WCO.0000000000001116
2. Lopes B, Sousa P, Alvites R, et al. Peripheral nerve injury treatments and advances: one health perspective. *Int J Mol Sci*. 2022;23(2):918. doi:10.3390/ijms23020918
3. Rahman M. Magnetic resonance imaging and iron-oxide nanoparticles in the era of personalized medicine. *Nanotheranostics*. 2023;7(4):424–449. doi:10.7150/ntno.86467
4. Olivo R, Tsao B. Peripheral nerve injuries in sport. *Neurol Clin*. 2017;35(3):559–572. doi:10.1016/j.ncl.2017.03.010
5. Modrak M, Talukder M, Gurgenashvili K, Noble M, Elfar JC. Peripheral nerve injury and myelination: potential therapeutic strategies. *J Neurosci Res*. 2020;98(5):780–795. doi:10.1002/jnr.24538
6. Carvalho CR, Silva-Correia J, Oliveira JM, Reis RL. Nanotechnology in peripheral nerve repair and reconstruction. *Adv Drug Deliv Rev*. 2019;148:308–343. doi:10.1016/j.addr.2019.01.006
7. Sharifi M, Farahani MK, Salehi M, et al. Exploring the physicochemical, electroactive, and biodelivery properties of metal nanoparticles on peripheral nerve regeneration. *ACS Biomater Sci Eng*. 2023;9(1):106–138. doi:10.1021/acsbiomaterials.2c01216
8. Soto PA, Vence M, Pinero GM, et al. Sciatic nerve regeneration after traumatic injury using magnetic targeted adipose-derived mesenchymal stem cells. *Acta Biomater*. 2021;130:234–247. doi:10.1016/j.actbio.2021.05.050

9. Jin Y, Zhang W, Zhang Y, et al. Multifunctional biomimetic hydrogel based on graphene nanoparticles and sodium alginate for peripheral nerve injury therapy. *Biomater Adv*. 2022;135:212727. doi:10.1016/j.bioadv.2022.212727
10. Hanwright PJ, Qiu C, Rath J, et al. Sustained IGF-1 delivery ameliorates effects of chronic denervation and improves functional recovery after peripheral nerve injury and repair. *Biomaterials*. 2022;280:121244. doi:10.1016/j.biomaterials.2021.121244
11. Das S, Sharma M, Saharia D, Sarma KK, Muir EM, Bora U. Electrospun silk-polyaniline conduits for functional nerve regeneration in rat sciatic nerve injury model. *Biomed Mater*. 2017;12(4):045025. doi:10.1088/1748-605X/aa7802
12. Lackington WA, Raftery RM, O'brien FJ. In vitro efficacy of a gene-activated nerve guidance conduit incorporating non-viral PEI-pDNA nanoparticles carrying genes encoding for NGF, GDNF and c-Jun. *Acta Biomater*. 2018;75:115–128. doi:10.1016/j.actbio.2018.06.014
13. 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. doi:10.1021/acsami.1c01904
14. Sun X, Bai Y, Zhai H, et al. Devising micro/nano-architectures in multi-channel nerve conduits towards a pro-regenerative matrix for the repair of spinal cord injury. *Acta Biomater*. 2019;86:194–206. doi:10.1016/j.actbio.2018.12.032
15. Amini S, Saudi A, Amirpour N, et al. Application of electrospun polycaprolactone fibers embedding lignin nanoparticle for peripheral nerve regeneration: in vitro and in vivo study. *Int J Biol Macromol*. 2020;159:154–173. doi:10.1016/j.ijbiomac.2020.05.073
16. Das S, Sharma M, Saharia D, et al. In vivo studies of silk based gold nano-composite conduits for functional peripheral nerve regeneration. *Biomaterials*. 2015;62:66–75. doi:10.1016/j.biomaterials.2015.04.047
17. Ding T, Lu WW, Zheng Y, Li Z, Pan H, Luo Z. Rapid repair of rat sciatic nerve injury using a nanosilver-embedded collagen scaffold coated with laminin and fibronectin. *Regener Med*. 2011;6(4):437–447. doi:10.2217/rme.11.39
18. Pop NL, Nan A, Urda-Cimpean AE, et al. Chitosan functionalized magnetic nanoparticles to provide neural regeneration and recovery after experimental model induced peripheral nerve injury. *Biomolecules*. 2021;11(5):676. doi:10.3390/biom11050676
19. Zhan Y, Zhou Z, Chen M, Gong X. Photothermal treatment of polydopamine nanoparticles@hyaluronic acid methacryloyl hydrogel against peripheral nerve adhesion in a rat model of sciatic nerve. *Int J Nanomed*. 2023;18:2777–2793. doi:10.2147/IJN.S410092
20. Ebrahimi-Zadehlou P, Najafpour A, Mohammadi R. Assessments of regenerative potential of silymarin nanoparticles loaded into chitosan conduit on peripheral nerve regeneration: a transected sciatic nerve model in rat. *Neurol Res*. 2021;43(2):148–156. doi:10.1080/01616412.2020.1831341
21. Lopes CDF, Goncalves NP, Gomes CP, Saraiva MJ, Pego AP. BDNF gene delivery mediated by neuron-targeted nanoparticles is neuroprotective in peripheral nerve injury. *Biomaterials*. 2017;121:83–96. doi:10.1016/j.biomaterials.2016.12.025
22. Harrison J, Bartlett CA, Cowin G, et al. In vivo imaging and biodistribution of multimodal polymeric nanoparticles delivered to the optic nerve. *Small*. 2012;8(10):1579–1589. doi:10.1002/smll.201102648
23. Xiong Y, Feng Q, Lu L, et al. Metal-organic frameworks and their composites for chronic wound healing: from bench to bedside. *Adv Mater*. 2023: e2302587. doi:10.1002/adma.202302587
24. Zhang Y, Khalique A, Du X, et al. Biomimetic design of mitochondria-targeted hybrid nanozymes as superoxide scavengers. *Adv Mater*. 2021;33(9): e2006570.
25. Xiong Y, Lin Z, Bu P, et al. A whole-course-repair system based on neurogenesis-angiogenesis crosstalk and macrophage reprogramming promotes diabetic wound healing. *Adv Mater*. 2023;35(19):e2212300. doi:10.1002/adma.202212300
26. Buchman JT, Hudson-Smith NV, Landy KM, Haynes CL. Understanding nanoparticle toxicity mechanisms to inform redesign strategies to reduce environmental impact. *Acc Chem Res*. 2019;52(6):1632–1642. doi:10.1021/acs.accounts.9b00053
27. Zhang YN, Poon W, Tavares AJ, Mcgilvray ID, Chan WCW. Nanoparticle-liver interactions: cellular uptake and hepatobiliary elimination. *J Control Release*. 2016;240:332–348. doi:10.1016/j.jconrel.2016.01.020
28. Lewinski N, Colvin V, Drezek R. Cytotoxicity of nanoparticles. *Small*. 2008;4(1):26–49. doi:10.1002/smll.200700595
29. Bobo D, Robinson KJ, Islam J, Thurecht KJ, Corrie SR. Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date. *Pharm Res*. 2016;33(10):2373–2387. doi:10.1007/s11095-016-1958-5
30. Casals E, Zeng M, Parra-Robert M, et al. Cerium oxide nanoparticles: advances in biodistribution, toxicity, and preclinical exploration. *Small*. 2020;16(20):e1907322. doi:10.1002/smll.201907322
31. Khlebtsov N, Dykman L. Biodistribution and toxicity of engineered gold nanoparticles: a review of in vitro and in vivo studies. *Chem Soc Rev*. 2011;40(3):1647–1671. doi:10.1039/C0CS00018C
32. Joris F, Manshian BB, Peynshaert K, De Smedt SC, Braeckmans K, Soenen SJ. Assessing nanoparticle toxicity in cell-based assays: influence of cell culture parameters and optimized models for bridging the in vitro-in vivo gap. *Chem Soc Rev*. 2013;42(21):8339–8359. doi:10.1039/c3cs60145e
33. Chrishtop VV, Mironov VA, Prilepskii AY, Nikonorova VG, Vinogradov VV. Organ-specific toxicity of magnetic iron oxide-based nanoparticles. *Nanotoxicology*. 2021;15(2):167–204. doi:10.1080/17435390.2020.1842934
34. Chakravarty R, Hong H, Cai W. Positron emission tomography image-guided drug delivery: current status and future perspectives. *Mol Pharm*. 2014;11(11):3777–3797. doi:10.1021/mp500173s
35. Angelova A, Angelov B, Drechsler M, Lesieur S. Neurotrophin delivery using nanotechnology. *Drug Discov Today*. 2013;18(23–24):1263–1271. doi:10.1016/j.drudis.2013.07.010
36. Singh D, Singh D, Zo S, Han SS. Nano-biomimetics for nano/micro tissue regeneration. *J Biomed Nanotechnol*. 2014;10(10):3141–3161.
37. Guo S, Perets N, Betzer O, et al. Intranasal delivery of mesenchymal stem cell derived exosomes loaded with phosphatase and tensin homolog siRNA repairs complete spinal cord injury. *ACS Nano*. 2019;13(9):10015–10028. doi:10.1021/acsnano.9b01892
38. Khare P, Dave KM, Kamte YS, Manoharan MA, O'donnell LA, Manickam DS. Development of Lipidoid Nanoparticles for siRNA Delivery to Neural Cells. *AAPS J*. 2021;24(1):8. doi:10.1208/s12248-021-00653-2
39. Lacko CS, Singh I, Wall MA, et al. Magnetic particle templating of hydrogels: engineering naturally derived hydrogel scaffolds with 3D aligned microarchitecture for nerve repair. *J Neural Eng*. 2020;17(1):016057. doi:10.1088/1741-2552/ab4a22
40. Farokhzad OC, Langer R. Impact of nanotechnology on drug delivery. *ACS Nano*. 2009;3(1):16–20. doi:10.1021/nn900002m
41. Gaspar VM, Lavrador P, Borges J, Oliveira MB, Mano JF. Advanced bottom-up engineering of living architectures. *Adv Mater*. 2020;32(6): e1903975. doi:10.1002/adma.201903975
42. Martynenko IV, Ruider V, Dass M, Liedl T, Nickels PC. DNA origami meets bottom-up nanopatterning. *ACS Nano*. 2021;15(7):10769–10774. doi:10.1021/acsnano.1c04297

43. Fu X, Cai J, Zhang X, Li WD, Ge H, Hu Y. Top-down fabrication of shape-controlled, monodisperse nanoparticles for biomedical applications. *Adv Drug Deliv Rev*. 2018;132:169–187. doi:10.1016/j.addr.2018.07.006
44. Kamaly N, Xiao Z, Valencia PM, Radovic-Moreno AF, Farokhzad OC. Targeted polymeric therapeutic nanoparticles: design, development and clinical translation. *Chem Soc Rev*. 2012;41(7):2971–3010. doi:10.1039/c2cs15344k
45. Masood F. Polymeric nanoparticles for targeted drug delivery system for cancer therapy. *Mater Sci Eng C Mater Biol Appl*. 2016;60:569–578. doi:10.1016/j.msec.2015.11.067
46. Xie F, Wang M, Chen Q, et al. Endogenous stimuli-responsive nanoparticles for cancer therapy: from bench to bedside. *Pharmacol Res*. 2022;186:106522. doi:10.1016/j.phrs.2022.106522
47. Krishnan N, Fang RH, Zhang L. Engineering of stimuli-responsive self-assembled biomimetic nanoparticles. *Adv Drug Deliv Rev*. 2021;179:114006. doi:10.1016/j.addr.2021.114006
48. Yu X, Yang Z, Zhang Y, et al. Lipid nanoparticle delivery of chemically modified NGF(R100W) mRNA alleviates peripheral neuropathy. *Adv Healthc Mater*. 2023;12(3):e2202127. doi:10.1002/adhm.202202127
49. Tao J, Zhang J, Du T, et al. Rapid 3D printing of functional nanoparticle-enhanced conduits for effective nerve repair. *Acta Biomater*. 2019;90:49–59. doi:10.1016/j.actbio.2019.03.047
50. Jin B, Yu Y, Lou C, et al. Combining a density gradient of biomacromolecular nanoparticles with biological effectors in an electrospun fiber-based nerve guidance conduit to promote peripheral nerve repair. *Adv Sci*. 2023;10(4):e2203296. doi:10.1002/advs.202203296
51. Xue J, Xie J, Liu W, Xia Y. Electrospun nanofibers: new concepts, materials, and applications. *Acc Chem Res*. 2017;50(8):1976–1987. doi:10.1021/acs.accounts.7b00218
52. De Logu F, Nassini R, Hegron A, et al. Schwann cell endosome CGRP signals elicit periorbital mechanical allodynia in mice. *Nat Commun*. 2022;13(1):646. doi:10.1038/s41467-022-28204-z
53. Jin L, Ding M, Oklopcic A, et al. Nanoparticle fullerol alleviates radiculopathy via NLRP3 inflammasome and neuropeptides. *Nanomedicine*. 2017;13(6):2049–2059. doi:10.1016/j.nano.2017.03.015
54. Kim Y, Kong SD, Chen LH, Pisanic TR, Jin S, Shubayev VI. In vivo nanoneurotoxicity screening using oxidative stress and neuroinflammation paradigms. *Nanomedicine*. 2013;9(7):1057–1066. doi:10.1016/j.nano.2013.05.002
55. Liu H, Qing X, Peng L, et al. Mannose-coated nanozyme for relief from chemotherapy-induced peripheral neuropathic pain. *iScience*. 2023;26(4):106414. doi:10.1016/j.isci.2023.106414
56. Ding JY, Chen MJ, Wu LF, et al. Mesenchymal stem cell-derived extracellular vesicles in skin wound healing: roles, opportunities and challenges. *Mil Med Res*. 2023;10(1):36. doi:10.1186/s40779-023-00472-w
57. Lopes D, Lopes J, Pereira-Silva M, et al. Bioengineered exosomal-membrane-camouflaged abiotic nanocarriers: neurodegenerative diseases, tissue engineering and regenerative medicine. *Mil Med Res*. 2023;10(1):19. doi:10.1186/s40779-023-00453-z
58. Brenza TM, Ghaisas S, Ramirez JEV, et al. Neuronal protection against oxidative insult by polyanhydride nanoparticle-based mitochondria-targeted antioxidant therapy. *Nanomedicine*. 2017;13(3):809–820. doi:10.1016/j.nano.2016.10.004
59. Li C, Zhao Z, Luo Y, et al. Macrophage-disguised manganese dioxide nanoparticles for neuroprotection by reducing oxidative stress and modulating inflammatory microenvironment in acute ischemic stroke. *Adv Sci*. 2021;8(20):e2101526.
60. Malko P, Jiang LH. TRPM2 channel-mediated cell death: an important mechanism linking oxidative stress-inducing pathological factors to associated pathological conditions. *Redox Biol*. 2020;37:101755. doi:10.1016/j.redox.2020.101755
61. Li X, Han Z, Wang T, et al. Cerium oxide nanoparticles with antioxidative neurorestoration for ischemic stroke. *Biomaterials*. 2022;291:121904. doi:10.1016/j.biomaterials.2022.121904
62. Yang S, Wang C, Zhu J, et al. Self-assembling peptide hydrogels functionalized with LN- and BDNF- mimicking epitopes synergistically enhance peripheral nerve regeneration. *Theranostics*. 2020;10(18):8227–8249. doi:10.7150/thno.44276
63. Hu Y, Chen Z, Wang H, et al. Conductive nerve guidance conduits based on morpho butterfly wings for peripheral nerve repair. *ACS Nano*. 2022;16(2):1868–1879. doi:10.1021/acsnano.1c11627
64. Wu C, Shi L, Ma Y, et al. Construction and optimization of a coculture system of mouse brain microvascular endothelial cells and myelin debris. *Neurosci Lett*. 2023;811:137345. doi:10.1016/j.neulet.2023.137345
65. Boutary S, Caillaud M, El Madani M, et al. Squalenoyl siRNA PMP22 nanoparticles are effective in treating mouse models of Charcot-Marie-Tooth disease type 1 A. *Commun Biol*. 2021;4(1):317. doi:10.1038/s42003-021-01839-2
66. Dolkhani S, Najafpour A, Mohammadi R. Fabrication and transplantation of chitosan-selenium biodegradable nanocomposite conduit on transected sciatic nerve: a novel study in rat model. *Neurol Res*. 2020;42(6):439–450. doi:10.1080/01616412.2019.1709143
67. Giannaccini M, Calatayud MP, Poggetti A, et al. Magnetic nanoparticles for efficient delivery of growth factors: stimulation of peripheral nerve regeneration. *Adv Healthc Mater*. 2017;6(7). doi:10.1002/adhm.201601429
68. Goncalves NP, Oliveira H, Pego AP, Saraiva MJ. A novel nanoparticle delivery system for in vivo targeting of the sciatic nerve: impact on regeneration. *Nanomedicine*. 2012;7(8):1167–1180. doi:10.2217/nnm.11.188
69. Roversi K, Tabatabaei M, Desjardins-Lecavalier N, et al. Nanophotonics enable targeted photothermal silencing of nociceptor neurons. *Small*. 2022;18(14):e2103364. doi:10.1002/smll.202103364
70. Zhang Y, Zhang W, Johnston AH, Newman TA, Pyykko I, Zou J. Targeted delivery of Tet1 peptide functionalized polymersomes to the rat cochlear nerve. *Int J Nanomed*. 2012;7:1015–1022. doi:10.2147/IJN.S28185
71. Lopes CD, Oliveira H, Estevao I, Pires LR, Pego AP. In vivo targeted gene delivery to peripheral neurons mediated by neurotropic poly(ethylene imine)-based nanoparticles. *Int J Nanomed*. 2016;11:2675–2683. doi:10.2147/IJN.S104374
72. Du Z, Li M, Ren J, Qu X. Current strategies for modulating abeta aggregation with multifunctional agents. *Acc Chem Res*. 2021;54(9):2172–2184. doi:10.1021/acs.accounts.1c00055
73. Kargozar S, Singh RK, Kim HW, Baino F. "Hard" ceramics for "Soft" tissue engineering: paradox or opportunity? *Acta Biomater*. 2020;115:1–28. doi:10.1016/j.actbio.2020.08.014
74. Paviolo C, Stoddart PR. Gold nanoparticles for modulating neuronal behavior. *Nanomaterials*. 2017;7(4):92. doi:10.3390/nano7040092
75. Escobar A, Reis RL, Oliveira JM. Nanoparticles for neurotrophic factor delivery in nerve guidance conduits for peripheral nerve repair. *Nanomedicine*. 2022;17(7):477–494. doi:10.2217/nnm-2021-0413