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REVIEW

Nanoparticles in traumatic spinal cord injury: therapy and diagnosis [version 1; peer review: 2 approved with reservations]

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Abstract

Nanotechnology has been previously employed for constructing drug delivery vehicles, **biosensors**, solar cells, lubricants and as antimicrobial agents. The advancement in synthesis procedure makes it possible to formulate nanoparticles (NPs) with precise control over physico-chemical and optical properties that are desired for specific clinical or biological applications. The surface modification technology has further added impetus to the specific applications of NPs by providing them with desirable characteristics. Hence, nanotechnology is of paramount importance in numerous biomedical and industrial applications due to their biocompatibility and stability even in harsh environments. Traumatic spinal cord injuries (TSCIs) are one of the major traumatic injuries that are commonly associated with severe consequences to the patient that may reach to the point of paralysis. Several processes occurring at a biochemical level which exacerbate the injury may be targeted using nanotechnology. This review discusses possible nanotechnology-based approaches for the diagnosis and therapy of TSCI, which have a bright future in clinical practice.

Keywords

Nanoparticles, Neurosurgery, Spinal cord injuries, Trauma, Therapy

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Introduction

Traumatic spinal cord injuries (TSCIs) occur due to damage to the spinal cord from trauma, resulting in transient or permanent loss of motor, sensory, and autonomic functions in the parts of the body served by the spinal cord below the level of the injury.¹ Knowledge of the causes of TSCI is an essential aspect that aids in the development of modalities for prevention and treatment of the condition.² A previous study conducted in the United States to examine the specific etiologies of TSCI was carried out using data from the NSCID & NSSCID, and assessed various parameters to determine the etiology including age, sex, race, ethnicity, day and month of injury, and neurological outcomes.^{3,4} The study concluded that the most common cause of TSCI was automobile crashes. Other significant causes included falls and gunshot wounds. Another in-depth analysis of the causes showed that automobile crashes were the leading cause of TSCI until age 45 years, whereas falls were the leading cause after age 45 years. Gunshot wounds, motorcycle crashes, and diving caused more TSCIs in men than in women.⁵

Spinal cord injuries (SCIs) consist of two main stages, primary and secondary. The primary stage occurs due to the direct effect of the initial mechanical injury or infarction affecting the spinal cord,⁶ and its severity can serve as a prognostic indicator for recovery.¹ The main mechanisms of primary injury include impact with persistent compression, followed by impact with transient compression, distraction and laceration or transection.⁷ The majority of SCIs in humans were found to be contusion injuries⁶, and as a result, the most commonly used experimental animal models for studying SCIs are contusion models, followed by transection and compression models.⁸

The initial traumatic impact to the spinal cord, in the form of fracture or dislocation, causes microhemorrhages in the white and grey matter, axonal damage, and cellular membrane destruction.⁹ Following the primary injury, the more complex secondary stage, composed of a cascade of pathophysiological events, takes place within minutes to weeks following the initial injury.⁶ It has been observed that measures taken for preventing and managing this phase are critical for enabling early ambulation in patients with incomplete SCI.¹

The American Spinal Injury Association Impairment Scale (AIS) classifies SCIs into two main types: complete and incomplete. A complete SCI is the absence of all motor and sensory functions, including sacral roots, distal to the site of injury, and is designated as being Grade A. An incomplete SCI is one with some degree of retained motor or sensory function below the site of injury and is graded B through E depending on severity.¹⁰

This review aims to discuss the recent therapeutic and diagnostic options provided via the use of nanoparticles (NPs). NPs are solid colloidal particles with diameters ranging from 1–1000 nm. They are comprised of macromolecular materials that can act as therapeutic drug carriers in a variety of applications, such as drug delivery, imaging, and detection of apoptosis.¹¹ Nanotechnology could provide future potential minimally invasive management options for TSCI, which would decrease the burden that comes with managing TSCI.

Diagnosis of SCI

Physical examination

Physical examination aids in determining the affected motor and sensory levels and eventually classifying the injury according to the AIS grades.^{12,13} In patients who cannot participate in a reliable physical examination, the integrity and function of axons in the spinal cord can be measured with the use of electrophysiological recordings, such as somatosensory evoked potentials and motor evoked potentials.¹⁴ This non-invasive method can provide real-time display of nerve function, and can detect the latency and amplitude of nerves, so that the neurological function of the spinal cord can be timed for quantified evaluation, making the assessment of neurological function after SCI and intraoperative monitoring of spinal cord function possible.¹⁵

Radiological investigations

Computer tomography (CT) is used in the diagnosis of SCIs resulting from spinal fractures as well as lesions that result from ischemia and other vascular injuries.¹⁶ Traditionally, a thorough neurological examination was considered sufficient for the acute diagnosis of SCIs and assessing the severity and level of the injury.¹⁴ However, magnetic resonance imaging (MRI) has recently become the diagnostic modality of choice, especially in lesions that result from ischemia and other vascular injuries.¹⁶ A typical lesion appears spindle shaped, containing an epicenter of hemorrhage surrounded by a halo of edema on an MRI.¹⁴

Biochemical investigations

Due to the challenges accompanying the use of MRI in patients with medical implants and devices, many efforts have been made to innovate new rapid diagnostic biomarkers for SCIs. Several prognostic biomarkers in cerebral spinal fluid and blood have been identified. They include neurofilament proteins, glial fibrillary acidic protein, Tau and S100

calcium-binding protein β , as well as other cell damage-associated proteins and even microRNAs.¹⁷ A review article published in 2015 suggests that structural proteins, such as α -II spectrin breakdown products (SBDPs) and ubiquitin C-terminal hydrolase-L1 (UCH-L1), have potential as promising biomarkers in animal TSCI models and in human patients with SCIs.¹⁸

NP investigations

A study reported the use of ferumoxylol-labeled human neural progenitor cells transplanted into the porcine spinal cord for diagnostic MRI-based cellular tracking.¹⁹ Superparamagnetic iron oxide NPs are bioactive molecules that can localize inflammation and can therefore be used as contrast agents in imaging.^{20,21} Campbell *et al.* developed injectable composite of hydrogel poly(N-isopropylacrylamide) reinforced by superparamagnetic iron oxide NPs as a good contrast material for MRI.²² In addition, quantum dots have been used, which are metal-cored particles with improved photostabilizing properties that can aid in tracking specific proteins or surface antigens for molecular imaging.²⁰

TSCI therapy with NPs

The challenges in TSCI therapy are diverse. They range from psychological effects on often traumatized patients to socioeconomic effects on healthcare systems and individuals. Additional challenges are present in many countries where there is an absence of medical equipment, comprehensive rehabilitation, and lack of adequate support to allow community reintegration.²³ From a medical perspective, the main challenge for treating TSCIs is the requirement of severe intensive approaches, either to surgically remove foreign bodies in the spine or performing permanent surgical fixation, which if not applied might lead to damage and could even be fatal. Current management options for TSCI are limited. Among the most common management approaches is the use of high-dose IV methylprednisolone, which in the long run leads to a wide variety of corticosteroid-induced side effects. Given the diversity in the mechanism of action of glucocorticoids, they can cause a wide array of adverse effects ranging from mild to severe, some of which are unavoidable.²⁴ Other current treatment modalities being applied at a preclinical stage include the use of vasopressor medications for mean arterial blood pressure augmentation to improve spinal cord perfusion, and early surgical decompression and fixation for acute cases.²⁵

Below, we introduce therapies with highest potential for TSCI that involve NPs.

Natural polymeric NPs

Chitosan and its derivatives

Background to chitosan

Chitosan is a linear polysaccharide composed of *N*-acetyl-D-glucosamine and D-glucosamine linked by 1-4- β -glycosidic bonds. It is a deacetylated derivative of the naturally occurring polysaccharide chitin found in the shells of crustaceans.²⁶ Depending on the parameters during the synthesis procedure, chitosan NPs can range in size between 30 nm²⁷ to 2500 nm.²⁸ Due to its deacetylated structure, a net positive charge is imparted on its surface which enables its interaction with the negatively charged mucous membranes. As a result, chitosan is classified as a mucoadhesive compound, with the ability to pass through the otherwise impermeable blood-brain barrier.²⁹ It is water insoluble at physiologic conditions, as a result, chitosan derivatives, such as quaternized chitosan may be used to produce injectable formulas, as was experimented using quaternized chitosan, gelatin and dopamine to produce hydrogels for localized drug delivery.³⁰ Chitosan NPs are nontoxic, biocompatible, biodegradable and have antimicrobial activity,²⁹ with potential antioxidant properties.³¹ Other important properties are their high drug entrapment efficiency³¹ and sustained drug release.³²

Chitosan NPs in TSCI models

In a new published study, valproic acid labeled chitosan NPs (VA-CN) were evaluated for use in targeted delivery of the drug to injured spinal cord. Spinal cord contusion was induced to the exposed spinal cord of Sprague-Dawley rats after performing a laminectomy at the level of 10th thoracic vertebra. To compare the concentration of VA-CN NPs against that of plain valproic acid, both structures were labelled by Cy5.5 to detect fluorescence intensities.³³ Following intravenous injection, the results indicated a significant increase in the effectiveness and maintenance of drug delivery to injured spinal cord when using the NP compared to the drug alone. In addition, to evaluate the tissue and function repair, Basso, Beattie and Bresnahan (BBB) scale scores, void frequency, void volume, and residual urine volume in rats were compared using VA, CN and VA-CN. Again VA-CN revealed early and higher BBB scores and void frequency, and lower void volume and residual urine volume compared to the others. VA-CN also reduced astrocytic reactivity (based on percentage of GFAP+ nestin+ cells produced). In addition, the treatment promoted neuroprotection by decreasing the numbers of microglia and enhanced NF160 immunoreaction, reducing inflammation by lowering IL-1 β , IL-6 and TNF- α expression compared to VA alone. Lesion cavity volume was significantly decreased, and the integrity of the

blood-spinal cord barrier was enhanced after treatment with VA-CN based on higher Claudin-5, and lower albumin and IgG marker levels. Finally, no histological changes were seen between the organs of control rats and treated injured rats, suggesting the lack of systemic adverse effects of VA-CN.³³

In a compression mouse model of SCI, following a bilateral hemilaminectomy at the lower thoracic region, the spinal cord was crushed to 10% of its original width using compression forceps. Then the spinal cord was injected using antibody conjugated siRNA-chitosan NP solutions and layers were sutured. After 24 hours, the mice were euthanized, and the injured cord segments removed for examination. Results demonstrated both a reduction in iNOS expression and nitric oxide levels, reduced pro-apoptotic Bax expression, and a two-fold increase in the anti-apoptotic Bcl-2 protein expression, leading to an overall inhibition of cellular apoptosis.³⁴

Another study employed the use of tubular chitosan scaffolds filled with neurotrophin-3-releasing chitosan carriers (C-NT3 implant) to investigate tissue formation, neurogenesis, electrophysiology, and hind limb function in a complete spinal cord transection model using female Wistar rats. Results suggest that the C-NT3 implants elicits endogenous neurogenesis and supports its potential for tissue modeling in the injured adult spinal cord.³⁵

Another study loaded chitosan scaffolds with strontium-doped hydroxyapatite NPs, creating nanocomposites to be used for drug delivery in SCIs. Results revealed that the use of these materials lead to the formation of functional neurons decreasing the gap in the injured area, with more synaptic connections formed among them via myelination, in addition to hindered growth of scar-like tissue, which can be beneficial for the effective treatment of SCIs.³⁶

Moreover, a study developed chitosan/polyvinyl alcohol (PVA) nanofiber scaffolds loaded with genistein. Following laminectomy at the level of T9-10 in female Sprague Dawley rats, a right lateral hemi-section SCI was induced using micro iris scissors to create the spinal injury model. This was followed by the application of the nanofibers with or without genistein on the injured area. Results revealed increased activity of super oxide dismutase and higher levels of IL-10, while nitric oxide levels, lipid peroxidation, and TNF α were lower in both nanofiber treated groups compared to the control groups, although nanofiber+genistein revealed slightly better results.³⁷

A study investigating the *in vitro* profiles of dexamethasone sodium phosphate (DEXP)-loaded chitosan NPs embedded in a poly- ϵ -caprolacton (PCL)/gelatin nanofiber scaffold demonstrated them to have good mechanical properties, hydrophilicity, as well as controlled release of dexamethasone. This may be used as a bridging biomaterial construct that allows the axons to grow while avoiding glial scar formation by inhibiting astrocyte proliferation and reducing the oligodendrocyte apoptosis for the repair of SCIs.³⁸

One study utilized chitosan and gelatin NPs to produce a composite hydrogel, which was then loaded with endometrial stem cells. This biomimetic hydrogel composite was then transplanted in the spinal cord of T9 dorsally hemisected male Wistar rat followed by Atorvastatin injection. Locomotor function assessed using the BBB scale revealed over three-fold higher advancement in motor function in this group compared to the control. In addition, histopathological study using hematoxylin & eosin (H&E) stain revealed axonal remyelination and neuronal regeneration.³⁹

On the other hand, a study evaluated and compared the use of cerium oxide (CeO₂) NPs and CeO₂/chitosan nanocomposites for SCI. The *in vitro* drug release tests revealed the chitosan loaded NPs to provide more sustained release (drug release rate 28%) compared to the bare CeO₂ NP (45%). When cell viability tests were conducted using spinal cord cells from euthanized rats, CeO₂/chitosan nanocomposite led to lower cell death. As a result, it was concluded that loading CeO₂ NPs with chitosan enables them to behave as an effective biocompatible material causing enhanced antioxidant properties, and auto regenerative and neuroprotective activity in spinal cord regeneration.⁴⁰

Another paper investigated the *in vitro* protective effects of quercetin encapsulated in chitosan-alginate NPs against oxidative stress injury in neuronal SH-SY5Y cells. The results revealed that the highest protective effects were registered with quercetin loaded in the positively charged NPs that were formulated with a higher concentration of chitosan.⁴¹

Another study employed chitosan NPs to encapsulate nerve growth factor (NGF). Canine bone marrow derived mesenchymal stem cells were used to evaluate the effect of these NPs on the delivery of NGF to these cells and its influence on their differentiation into neuronal cells. Results obtained were promising and can enable opportunities for the use of these NPs for targeted differentiation of stem cells for *in vitro* and *in vivo* nerve tissue regeneration in the future.⁴²

In another study, chitosan-dextran sulfate NPs were used to study its neuroprotective effect on BV-2 mouse microglia treated with H₂O₂ (to mimic acute post-SCI H₂O₂ release). Cell viability measured by Trypan blue showed lower cell death in chitosan NP preserved cells than those without.⁴³

A paper published in 2019 proposed an experimental protocol for inducing transgene expression in neural stem cells obtained from the brain of the mouse embryo through chitosan NPs loaded with pDNA. Hyaluronic acid is used as a ligand for neuronal cell receptor attachment. This protocol can be utilized for investigating its efficiency in treating SCI.⁴⁴

Synthetic polymeric NPs

Poly (lactic-co-glycolic acid) (PLGA)

Background to PLGA

PLGA is a member of polyesters, being the copolymer of lactide and glycolide⁴⁵ whose degradation produces lactic acid and glycolic acid as a result of spontaneous ester chain hydrolysis.⁴⁶ As a copolymer, PLGA inherits the intrinsic properties of poly (glycolic acid) which is a crystalline, hydrophilic polymer with low water solubility and fast degradation rate under physiological conditions, and poly (lactic acid) which is a stiff, hydrophobic polymer with low mechanical strength.⁴⁷ This also explains why the rate at which PLGA degrades is influenced by its lactic acid to glycolic acid ratio.⁴⁶

Depending on the parameters used during the synthesis procedure, PLGA NPs can range in size between 100 to 5000 nm.⁴⁸ However, the average size varies between 107.7 nm and 245.7 nm for effective intracellular delivery.⁴⁹ Due to PLGA's hydrophobic nature, surface modification using polymers such as polyethylene glycol (PEG), PVA, and d- α -tocopheryl PEG 1000 succinate plays an important role with respect to targeting strategy, biocompatibility, and blood half-life.⁵⁰ PLGA NPs are nontoxic, biocompatible, biodegradable,⁴⁷ and produce minimal inflammatory response in the body.⁴⁶

PLGA NPs in TSCI models

The intravenous administration of PLGA NPs has been investigated in spinal cord contusion models. In one study, Sprague-Dawley rats and female Yucatan miniature pigs were used, where following a laminectomy, spinal cord contusion was performed at the level of 10th thoracic vertebra using an impactor. Then, to see the effects of therapeutic delay after the SCI, the BSA-containing PLGA nanoparticle formulation was injected at 6 hours, 1, 2 and 4 weeks to four different SCI rat groups beside the control group without an SCI injected at 6 hours.⁵¹

Additionally, the porcine SCI model groups were injected at 30 minutes and 3 hours post-SCI. Following euthanasia, the animals' spinal cords were harvested. Results for nanoparticle dose localization revealed more NPs at the lesion site in both rat and porcine SCI models, while the control group animals showed a bimodal distribution in the thoracic and lumbar enlargement regions. Regarding delay in administration after SCI, localization of NPs at the site of injury decreased with delayed administration, but despite this, there was an increase in the uptake of NPs in the entire spinal cord, probably due to the sustained release properties of PLGA NPs and the blood-spinal cord barrier at the lesion site being accessible to NPs for longer.⁵¹

In a similar study, PLGA NPs loaded with the two antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT), named nano-SOD/CAT, were evaluated for their neuroprotective quality in SCIs via intravenous route, specifically on their ability to protect mitochondria from oxidative stress, neuronal cell apoptosis, and hence secondary SCI. Results demonstrated that treatment with nano-SOD/CAT protects the mitochondria, reduces reactive oxygen species activity, prevents the release of cytochrome c, and inhibits activation of caspase-3.⁵²

One paper describes the production of immune-modifying NPs (IMPs) using PLGA NPs. A laminectomy was performed on C57BL/6 mice, followed by induction of a contusion SCI using an impactor. The IMPs were then injected intravenously at 2, 24 and, 48 hours post-SCI. It was observed that IMPs decrease inflammatory cells infiltration into the injured spinal cord without altering the number of microglia, as well as lower the chances of chronic fibrotic scarring after SCI substantially. Behavioral scoring based on Basso Mouse Scale (BMS) open field scoring was also done at 24 hours, with the IMP-treated group demonstrating significant and sustained behavioral improvement and recovery in comparison to the control group. So, it was concluded that IMPs may provide a practical and easily translatable means of improving outcome after SCI.⁵³

Another study developed PLGA-g-PEI (PgP) polymeric micelle NPs and assessed their use in the treatment of SCIs by loading them with the drug Rolipram. The effect of PgP on cultured rat primary cerebellar granular neurons in hypoxia condition did not show any cytotoxicity, but there was a slight increase in cAMP levels and neurite length compared to the untreated group. Furthermore, the rat clip compression SCI model (dorsal T9 spinal cord) was employed using Sprague Dawley rats in hypoxia condition. Rolipram-loaded PgP NPs were then injected into the spinal cord in the area of injury.

The data demonstrated a prolonged therapeutic effect of the drug with sustained release, a feature that may improve patient compliance. It was also found that this formulation can affect important aspects of secondary SCI such as restoring cAMP levels and decreasing apoptosis and inflammatory response.⁵⁴

The use of PLGA nanospheres modified using 3 β -[N-(N',N' - dimethylaminoethane) carbamoyl] cholesterol (DC-Chol) for gene delivery (in this case being the luciferase pDNA (pSV-Luc)) in comparison to polyethyleneimine (PEI) complex has also been demonstrated. *In vitro* investigations revealed these NPs underwent sustained drug release with a minimum release period of 20 days and there was no difference in the structural integrity of the released pDNA compared to unencapsulated pDNA. Also, tests for cellular uptake of the NPs using mouse neural stem cells shows that these NPs localize more in the nuclei and cytoplasm and are less toxic than the PEI complex. Additionally, *in vivo* investigations were performed on SCI model using Sprague-Dawley rats, with PLGA/DC-Chol nanosphere being injected into their injured spinal cords. Apoptosis based on TUNEL staining was shown to be reduced with NP usage, while luciferase gene expression was detected in both neurons and astrocytes in the spinal cord. In addition, rats injected with PLGA/DC-Chol/VEGF or PLGA/VEGF showed better recovery of locomotor function compared with rats not treated with NPs.⁵⁵

Neuregulin-1 (Nrg-1) and Nrg-1-encapsulated PLGA NPs were evaluated for intrathecal vs intraspinal delivery, respectively, in a model of severe clip-compression SCI at T6-8 using adult female Sprague Dawley. In this study, the group that received intraspinal PLGA-Nrg-1 microparticles showed a significantly higher level of Nrg-1 compared to the group receiving intraspinal bolus of Nrg-1, which indicates the importance of PLGA encapsulation. On the other hand, the group undergoing intrathecal infusion of Nrg-1 using an osmotic pump showed less improvement compared to the PLGA-Nrg-1 microparticles group, but better results in comparison to the bolus group.⁵⁶

In another study, resveratrol and puerarin-loaded PLGA NPs were prepared to enhance the oral bioavailability of the drugs resveratrol and puerarin, then examined both *in vitro* and *in vivo* using male Wistar rats. Results indicated high entrapment efficiency of 74.85% drug loading capacity of 15.50% for this 1:3 drug-polymer formulation, in addition to slower drug release rates compared to the plain resveratrol and puerarin solutions. Moreover, for the *in vivo* studies, surgery where a small aneurysm clip used to cause ischemia was performed, followed 48 hours later by ischemia-reperfusion treatment. Then blood samples and L3-5 spinal cord segments were collected. It was then observed that the plasma nitrite/nitrate level were lower in the SCI rats when using NPs. Also, there was lowering of increased levels of iNOS protein expression to normal levels, decreased levels of Malondialdehyde and AOPP, and increased antioxidant activity of GSH, SOD and CAT. These findings suggest the protective property of using PLGA NPs in human spinal cord reperfusion injuries.⁵⁷

Furthermore, resveratrol loaded PLGA NPs coated with chitosan were synthesized to test for its effectiveness when employed in treating SCI in female adult Sprague-Dawley rat. The drug release profiles were measured to be 44.4% for coated and 79.9% for the uncoated NPs, indicating prolonged availability of the drug when using chitosan coating. In addition, following laminectomy at the 9th thoracic vertebra, a 2 mm piece of spinal cord was dissected to mimic spinal contusion injury. This was followed by intraperitoneal injection of the resveratrol solution or resveratrol NPs in rats of different groups. Regarding the behavioral changes observed via grid and beam walking, there was significant improvement in the groups treated with both coated and uncoated NPs, however coated drug revealed slightly better results. ELISA was used to test for the anti-inflammatory potential of the NPs, and results revealed significant reduction in the level of IL-1 β and TNF- α and significant increase in the level of IL-10 in animals treated with both NPs, however, chitosan-coated particles were found to be more efficacious in the reduction of the level of these cytokines.⁵⁸ On histopathological examination, efficient re-establishment of the spinal cord integrity was observed with significant reduction in the area of pseudocyst, intensity of the cell infiltration and hemorrhage.⁵⁸

Another identical study was performed using chitosan to stabilize PLGA NPs loaded with methylprednisolone and minocycline and coupled with albumin acting as a ligand of gp60 receptors. Injury was induced at the 11th thoracic vertebra to investigate the utility of the ligand-based polymeric NPs in the simultaneous delivery of methylprednisolone and minocycline when injected intravenously for the treatment of SCI.⁵⁹

Another study compared the use of PLGA NPs loaded with the natural antioxidant α -Tocopherol with that of pure antioxidant drug solution for treatment against oxidative stress in SCIs. Human astrocyte-spinal cord cells were used to test for *in vitro* toxicity and antioxidant activity. Results demonstrated that the NPs were less toxic and had a two-fold antioxidant activity compared to the pure drug.⁶⁰

Four similar studies investigated the benefit of PLGA NPs for alleviating pain in rat models of spinal nerve ligation (performed at L5) using Sprague-Dawley rats, by loading PLGA NPs with Foxp3 plasmid,⁶¹ p66shc siRNA,⁶²

p38 siRNA⁶³ and encapsulating PLGA with CX3CR1 siRNA,⁶⁴ respectively. All four studies indicated that the use of the aforementioned PLGA NPs effectively reduced neuropathic pain in SNL-induced rats by reducing microglial activity and expression of proinflammatory mediators.

PLGA NPs have been used in the form of nanocomposite hydrogels made in combination with sodium hyaluronate and methylcellulose. Female Sprague Dawley rats were used as compression models of SCI using the clip compression method following a laminectomy at the level of T2. Then the PLGA hydrogel, HAMC hydrogel and artificial cerebrospinal fluid were then injected intrathecally in three different groups, after which the overlying muscles and fascia were sutured closed. Open field locomotor function was assessed using the BBB scoring, which revealed slight improvement of motor function in all three groups with no significant difference between them. Similarly, the parasagittal sections of the spinal cord stained with Luxol fast blue (LFB)/H&E to assess cavity shape, another stained using ED-1 for assessing inflammation and a third series stained with GFAP for astrogliosis assessment showed no significant difference between the three groups, hence supporting the safety and biocompatibility of PLGA hydrogels as a platform for sustained combination therapy in SCIs.⁶⁵

Similarly, another study utilized PLGA NPs dispersed in a HAMC hydrogel as a local drug delivery system for NT-3 and anti-NogoA into the injured spinal cord. Moderate impact/compression injury was induced in female Sprague-Dawley rats following a laminectomy at T1-2 level using a modified aneurysm clip. Immediately after inducing the SCI, the hydrogel solution was injected intrathecally at the site of injury, and the overlying muscles and fascia were sutured closed. Locomotor function was then assessed using the ladderwalk task, BBB score, and the BBB motor subscore, all showing significant improvement. This nanocomposite enabled the sustained co-delivery of the two factors to the injured area, which led to increased axonal density, however tissue sparing and cavitation after injury were not affected.⁶⁶

Previous studies focus on drug release profiles of PLGA NPs based on degradation or erosion of PLGA encapsulating the drug, or on the diffusion of the drug through it. However, a recently published study demonstrated the possibility of eliminating the need for encapsulating drugs in PLGA NPs, instead, simply mixing in the drug with the NPs in a hydrogel solution. This study was based on the adsorption of drug on the PLGA nanoparticle via electrostatic interactions in the hydrogel. Results obtained for drug release profiles in both PLGA-encapsulated and PLGA-mixed protein formulations were remarkably similar for the three proteins (stromal cell-derived factor 1a (SDF), neurotrophin-3 (NT-3), and brain-derived neurotrophic factor (BDNF)) tested.⁶⁷

In another study, crosslinked methylcellulose hydrogel loaded with chondroitinase ABC and stromal cell-derived factor 1 α in addition to PLGA NPs were evaluated against its counterpart hydrogel containing no NPs.⁶⁸ Similar to Elliott *et al.*,⁶⁶ after a laminectomy at the level of T1-2, a moderate impact/compression injury was induced in female Sprague-Dawley rat, after which the hydrogel was injected intrathecally. Despite improvement with both formulation, better results were obtained when using PLGA NPs in the hydrogel, since the transient electrostatic interaction between PLGA and SDF allow the controlled release of bioactive SDF without encapsulation, as explained by Pakulska *et al.*⁶⁷

Alginate hydrogel embedded with minocycline and paclitaxel-loaded PLGA microspheres embedded in a minocycline-loaded alginate hydrogel were utilized for dual drug delivery in a left lateral hemisection model of SCI using male Wistar rats in which the hydrogels were injected into the spinal cord at the site of injury. The ED1 level of Gel/MH and the Gel/MH.PTX groups used for monitoring inflammatory responses was lower than the untreated group, in addition to a reduction in the immune response, and reduced expression of caspase-3. Cell density used to assess tissue scar formation was shown to be lower in the rats receiving Gel/MH.PTX or Gel/MH, and neural regeneration in the microenvironment of the damaged tissue based on NF200-positive cells density was high in Gel/MH.PTX and Gel/PTX. BBB locomotor score, BBB sub-score and footprint analysis also indicated better results with Gel/MH.PTX.⁶⁹

Another study fabricated electrospun graphene oxide-PLGA hybrid nanofiber immobilized with IGF-1 and BDNF for use as scaffolds in the local delivery of said factors in a rat spinal cord hemisection model. After inducing the injury at the level of T9-10 in female Sprague Dawley rats, a piece of the nanofiber mat was placed, covering the hemisected area. Motor function evaluated via BBB scale and motor function regeneration assessed according to MEP amplitude revealed significantly increased BBB scores and MEP amplitude, respectively. H&E staining of the longitudinal spinal cord sections also showed decreased cavity size in the injured area. *In vitro* investigations on neural stem cells isolated from the cerebral cortex of embryonic mice were also performed to study their possible effect on endogenous stem cells, with results revealing good neural stem cell proliferation, survival and neuronal differentiation on the PLGA/GO nanofibers.⁷⁰

In another study, electrospun PLGA scaffolds were modified to carry FTY720 and neural stem cells. Results suggest that the local application of PLGA/FTY720 scaffolds can be used in treating SCIs due to their positive effects on neural stem

cell proliferation and differentiation. In the T9 spinal cord transection model using female Sprague Dawley rats, the implanted scaffold effectively promoted nerve function recovery. Moreover, the immobilization of neural stem cells on electrospun PLGA/FTY720 scaffolds may have potential applications as a nerve implant for treating SCIs.⁷¹

Furthermore, hyaluronic acid-based hydrogel scaffolds modified with anti-Nogo receptor antibody were implanted with PLGA microspheres loaded with BDNF and VEGF to treat T9-10 dorsal hemisection rat model. Injury repair was observed to be markedly enhanced by displaying excellent biocompatibility, inhibiting inflammation, and promoting angiogenesis.⁷²

Moreover, another study produced novel PLGA scaffolds inoculated with olfactory ensheathing cells, which were then implanted in a complete spinal cord transection rat model. Results of this study showed improved locomotor function recovery, as well as neuroprotection and enhanced remyelination, which suggests their potential success in human SCIs.⁷³

A study prepared PDA-PLGA scaffolds with NGF immobilized on them. These scaffolds were then implanted into a rat spinal cord transection model which revealed their ability to promote nerve function recovery by sustained release of the growth factor.⁷⁴

Since published reports demonstrated that without proper scaffolding, human mesenchymal stem cells (hMSCs) or neural stem cells would quickly die in the lesion gap of an SCI model, PLGA-polylysine nanofiber scaffolds seeded with human mesenchymal stem cells were produced for implanting in male Sprague Dawley rats with T9-10 level hemisection model. In this study both hard and soft scaffolds were used for evaluating the effect of scaffold stiffness on SCI recovery. Motor function test using the BBB scale and downward-facing inclined plane performance indicated better results when using soft scaffolds in comparison to hard scaffolds. Spinal cord reflexes and nociceptive withdrawal reflex were also better in groups implanted with soft PLGA-scaffolded hMSCs, in addition to less neuropathic pain. There was also smaller cavity area indicating less tissue loss and more interneuron sparing in the soft scaffold groups, while hard scaffold groups showed the worst tissue loss at the epicenter region. It was also observed that hard PLGA scaffolds diminished the anti-inflammatory and anti-oxidative properties of hMSCs, further supporting the use of soft PLGA scaffolds with stem cells.⁷⁵

In addition, several papers published over the years investigated PLGA-based scaffolds used in association with stem cells for promoting their neuronal differentiation.⁷⁶ Kim *et al.* seeded NSCs into a PLGA scaffold, which was then implanted into canine hemisection models, which promoted the recovery of neural function.⁷⁷ Pritchard *et al.* reported a similar result in a primate model.⁷⁸ Subsequently, Liu *et al.* observed restoration of the continuity of the spinal cord and reduced cavity formation following the implantation of a PLGA/PEG scaffold loaded with NSCs.⁷⁹

Polycaprolactone (PCL)

Background to PCL

PCL is a synthetic polyester that is partially crystalline, having a low melting point of 60°C and a glass transition temperature of -60°C. It is made by ring-opening polymerization of ϵ -caprolactone.⁸⁰ PCL is degraded by hydrolysis of its ester linkages in physiological conditions and has therefore received a great deal of attention for use as an implantable biomaterial. Also, a variety of drugs have been encapsulated within PCL beads for controlled release and targeted drug delivery.⁸¹

PCL NPs in TSCI models

A study investigated the use of minocycline-loaded PCL NPs injected into the site of injury in a compression model of SCI using C57BL/6J mice or B6.129PCx3cr1tm1Litt/J mice. Results were compared to those obtained from intraperitoneal injection of the drug alone. It was revealed that only early treatment with the NPs was able to improve behavioral outcome assessed using the BMS score while intraperitoneal injection did not cause any improvement. Furthermore, it was demonstrated that microglia inhibitory treatment delivered immediately after injury induces a significant long-lasting recovery up to 63 days post-injury.⁸²

Another study fabricated biodegradable monomethyl poly (ethylene glycol)poly(ϵ -caprolactone) (MPEG-PCL) nanomicelles as a drug delivery vehicle for dexamethasone acetate (DA). Following a laminectomy at the level of T9-10, a spinal cord hemisection was induced, succeeded by intravenous injection of the DA-loaded nanomicelles (DA-M). Motor function was evaluated by means of serial BBB score analysis which showed significantly higher values than the blank

micelle group, free DA group and normal saline group. In addition, histopathological examination using H&E staining revealed that administration of DA-M possessed the ability to significantly reduce the volume of the spinal cord lesion and cavity formation in injury site as compared to the other treated groups.⁸³

To overcome the high incidence of adverse effects upon systemic administration of methylprednisolone, a study embedded methylprednisolone sodium succinate-loaded PCL-based NPs in an implantable fibrin gel, which was then tested in male Wistar rats with a spinal cord contusive injury for localized drug delivery. Results showed that IL-1 β , IL-6 and caspase-3 levels were significantly lowered in the group treated with these NPs, showing a similar decrease with 25-fold lower dose of drug compared to intraperitoneally administered drug.⁸⁴

Once study also embedded minocycline-loaded PCL NPs in an agarose hydrogel and implanted this into the site of the contusion. Results demonstrated that a selective microglia treatment with minocycline-loaded PCL NPs, only when administered immediately after injury before macrophage infiltration, reduced the proinflammatory response, maintained a pro-regenerative milieu and ameliorated the behavioral outcome up to 63 days post injury.⁸⁵

A study fabricated polycaprolactone/polysialic acid (PCL/PSA) hybrid nanofiber scaffold loaded with the drug methylprednisolone. This was then transplanted in a T10 complete spinal cord transection model using female Sprague Dawley rats to evaluate its efficacy in comparison to PCL scaffold loaded with methylprednisolone (MP). Motor function was assessed using BBB scores, which revealed blank PCL nanofiber scaffold to have limited therapeutic effects, with the addition of PSA leading to slightly better results, while the PCL/PSA/MP nanofiber scaffold group had the best BBB scores out of all groups. An array of stains was also used for histopathological investigations of tissue sections for the rat groups including H&E, which showed the lesion cavity and glial scarring in PCL/PSA/MP nanofiber scaffold group to be absent similar to the control group, LFB stains (together with transmission electron microscopy), which revealed more myelin sheaths number and more intact myelin structure, and immunofluorescence staining, which showed enhanced therapeutic effects towards axonal survival and reactive astrocytes inhibition in the PCL/PSA/MP group compared to the others groups.⁸⁶

Another study, incorporated NT-3 and miR-222 into PCLEEP nanofibers distributed within a collagen hydrogel for use in a C5 hemi-section model using female Sprague Dawley. This hybrid scaffold was implanted into the site of injury such that the nanofibers were aligned to the longitudinal axis of the spinal cord. The scaffold was shown to provide localized and sustained release of drugs and nucleic acid molecules for non-viral transfection to enhance axon regeneration and remyelination *in vivo*, besides demonstrating good host-implant integration.⁸⁷

One study employed the use of PCL/gelatin nanofibrous scaffolds seeded with human endometrial stem cells cocultured with human Schwann cells to evaluate its regenerative potential in a T9 dorsal hemisection model of male Sprague Dawley rats. This method was based on the finding that coculturing of these stem cells with Schwann cells led to their differentiation into nerve-like cells. Following induction of injury, the scaffolds were implanted into the spinal cord. Hindlimb function recovery based on the BBB score demonstrated that implanting of these scaffolds showed the most promising recovery compared to the other animals in the study, in addition to regeneration assessed using immunohistochemical staining against neuronal marker NF-H, which revealed increased density of NF-H positive neural fibers.⁸⁸

Carbon nanotubes (CNTs)

Background to CNTs

CNTs are hollow cylinders made of graphene sheets rolled in on themselves to form a tube.^{89,90} They have a great role in the advancement of nanotechnology due to their unique architecture with high aspect ratio, high surface area, rich surface chemistry, small size, cell membrane penetrability and size alterability. They are also non-immunogenic, nontoxic, photostable, ultra-lightweight and biocompatible.⁹¹ CNTs possess excellent electrical and mechanical properties, such as neutral electrostatic potential, extremely high drug cargo ability, ultimate electrical and thermal conductivities making them an attractive tool for biomedical applications which is useful in the detection and treatment of neurological diseases.^{89,91} Due to their various thermal, optical, electrical, mechanical and chemical characteristics, CNTs have potential applications in different fields of nanomedicine, drug delivery, biosensors, energy storage and neural prosthetics.⁹¹

CNTs in TSCI models

In a study, nano-scaffolds of nonwoven PCL generated by electrospinning and carbon nanomaterials were created. The carbon nanomaterials in nanofibers was confirmed by Fourier transform infrared spectroscopy. This design of nanofibers

ensures therapeutic cell delivery to a neural lesion with excellent electrical conductivity suitable for cell adhesion and neural tissue regeneration in traumatic brain and SCI. The study indicated the nano-scaffolds were biocompatible to the cells. To generate nanomaterials scaffold that resemble the extracellular matrix, the artificial PCL scaffolds encapsulating CNTs were successfully fabricated. The diameters of the nanofibers (80 to 200 nm) were close to the actual architecture within the central nervous system (CNS). Under this fabrication the diameters of PCL-CNT were higher than those of PCL nanofibers. The alamarBlue assay' bioanalysis showed the PCL nanofibers were not toxic to the astrocytes grown on the scaffolds. The nano-scaffolds showed growth of multiple processes of the glial fibrillary acidic protein (GFAP) positive astrocytes.⁹²

In another study, vertically super-aligned MWCNTs (VA-MWCNTs) were manufactured using chemical vapor deposition to create nanoelectrodes for diagnosis of diseases and for the development of the nanocarrier to deliver drugs to the diseased site in various neurological disorders. VA-MWCNTs were purified with HCl, carboxylated with H₂SO₄: HNO₃ and acylated with SOCl₂. After purification and functionalization, they became highly hydrophilic, electrically conductive, highly stable and reduced in size for use in biomedical application. Specific VA-MWCNTs grown on silicon wafer were incorporated in epoxy resin to develop an application in diagnosing neurological disorders such as ischemic stroke.⁹¹

In SCI excessive glutamate concentration abnormally increases around the synaptic cleft leading to the apoptosis of neuron.⁹³ Chemically functionalized water-soluble single walled-CNT (SW-CNT)-PEG (carboxyl group) 5 µg/ml increases GFAP immunoreactivity and glutamate transporter expressions in astrocytes and upregulates the uptake of glutamate by astrocytes. Astrocyte plated into well-plates with SW-CNT-PEG 5 µg/ml for four days also enhanced the uptake of glutamate. Therefore, the reduction of extracellular glutamate leads to decreased excitotoxicity. The increase in GFAP immunoreactivity decreases tissue damage and neuronal loss and demyelination. These results suggest that functionalized CNTs play a role in various brain disease therapies.⁸⁹ Another study shows that SW-CNT-PEG solute causes a reduction in the ATP-induced glutamate release but does not affect the intracellular Ca²⁺ elevations in astrocytes.⁹⁴

In a study, self-standing 3D meshes of interconnected MWCNTs were manufactured. Such three-dimensional (3D) mesh of pure carbon nanotubes can open new horizons in treating injured CNS tissues, such as the spinal cord. MWCNTs – based 3D structure was interfaced *in vitro* with long-term, cocultured pairs of mouse organotypic spinal cord explants that led to the development of spinal networks over extended periods. For the first time the study also reported *in vivo* implantation of 3D carbon nanotube frame materials in four adults male Wistar rats led to tissue reaction and glial scar formation.⁹⁵

In a study neurite outgrowth from primary dorsal root ganglia (DRG) was evaluated in the presence or absence of electrical stimulation and SWCNT were selected as model nanofiller to manipulate the electrical properties of a collagen type I-10% Matrigel™ composite hydrogel. DRG were encapsulated within SWCNT-collagen I-10% Matrigel™ composite hydrogel (20-100-µg/ml) and nanomaterial-free collagen I-10% Matrigel™. The nanofillers influence on neurite outgrowth, with or without electrical stimulation. Neurite outgrowth were measured in response to both nanomaterials loading and electrical stimulation. Increased SWCNT loading (10-100-µg/ml) resulted in great bulk conductivity up to 1.7-fold whereas neurite outgrowth increases 3.3-fold in 20-µg/ml SWCNT loaded biomaterials. Electrical stimulation of SWCNT-free control resulted in a 2.9-fold increase in outgrowth. In concurrent electrical stimulation of SWCNT-loaded with biomaterials resulted in a 7.0-fold increase in outgrowth relative to unstimulated nanofiller- free controls. Therefore, SWCNT-composite hydrogels do enhance neuronal outgrowth, and with combination of electrical stimulation a further increase to neurite extension is expected.⁹⁶

CNTs can accumulate due to consequent reduction in size leading to multifunctional defects in organ systems, particularly hearts and lungs. Metal traces available in nanotubes can also cause toxicity. SWCNTs affect the spinal cord or DSR due to high degree of accumulation, reduces the DNA content in the cells and causes ultrastructural and morphological changes in cultured skin cells.⁸⁹

MWCNTs are more toxic as compared to SWCNTs. MWCNT toxicity causes loss of cell viability through programmed cell death thus having genotoxicity effects leading to mutations. Recently, researchers have warranted of nonoxidative stress-mediated pathway of cellular damage.⁸⁹ A study has reported that environmental and occupational exposure to respirable particulates such as MWCNT can induce acute neuroinflammation.

Pulmonary interactions of MWCNTs can generate secondary bioactive factors that enter the systemic circulation and causes Cerebrovascular inflammation leading to loss of blood brain barrier and neuroinflammation. The mechanism and potential intermediate drivers of such neuroinflammatory outcomes remains unclear.⁹⁷

The current data of CNT toxicity is inadequate and contradictory, therefore extensive research is required on toxicity, safety, and efficacy studies on animal models, including humans.⁸⁹

Iron oxide NPs (IONPs)

Background to IONPs

Generally, there are three IONPs available: magnetite (Fe_3O_4), hematite ($\alpha\text{-Fe}_2\text{O}_3$) and maghemite ($\gamma\text{-Fe}_2\text{O}_3$). However, due to their superparamagnetic property, where no magnetism remains after removal of the magnetic field, Fe_3O_4 nanoparticles are used in clinical applications.⁹⁸ Hence the name, superparamagnetic iron oxide nanoparticles (SIONPs).

IONPs in TSCI models

The use of IONPs and magnetic fields for alleviating pain in SCI was studied on male CD1 mice in which an inflammatory pain condition was induced using Complete Freund's Adjuvant. Then, the nonsteroidal anti-inflammatory drug Ketorolac was conjugated with IONPs, dissolved in PBS, injected intrathecally into the mice's spinal cord, and a neodymium magnet was placed at the lumbar spine level for 30 minutes. Then, the analgesic effect of the drug was evaluated. The results obtained from this experiment deduced that different polarity alignments can significantly affect the analgesic effect of Ketorolac-SIONPs.⁹⁹

A study conducted on female Wistar rats employed the use of IONPs and exposure to magnetic field to evaluate their efficacy in treating SCI. This experiment was performed on six groups of rats, with every two groups undergoing 50%, 80% and complete spinal cord transection via a laminectomy at T9/T10 vertebrae. Then each three corresponding groups were divided into study and control groups, with study groups being administered a suspension of IONPs intrathecally via a polyethylene catheter and exposed to electromagnetic field. Behavioral assessment based on the BBB score and electrophysiological assessment evaluated using compound motor evoked potential (MEP) testing revealed marked improvement in the IONP-treated groups with 50% and 80% transection over the course of four weeks, but no significant improvement in the remaining four groups. Regarding histopathological examination, there were greater viable motor neuron counts and thicker myelinated fibers in the IONP-treated groups. In addition, measurement of the cavity area was revealed to be smaller in the 50% transection group, with lower collagen content despite pronounced glial reactions in the areas next to the lesions in the same group.¹⁰⁰

Another similar study was performed on male Wistar rats, where following a bilateral laminectomy, their spinal cord was completely transected at the level of the 11th thoracic vertebra (13th spinal segment). Then, immediately, IONPs embedded in agarose hydrogel was implanted at the site of SCI via intrathecal injection. Eventually, motor responses to stimulation of nociceptive afferents, beside somatosensory evoked potential and MEP were assessed, with the group treated with both IONPs and magnetic field (MF) having the most favorable results such as recovery of the extensive movements of all three joints of hindlimb, plantar placement of paw with no weight support, in addition to complete recovery of autonomic and partial recovery of locomotor function. On histological analysis, IONPs concentration near the site of TSCI was greater in the IONP and IONP+MF groups, suggesting their diffusion from the agarose hydrogel into the spinal cord as well as their intracellular localization in the motor neurons and their axons. Myelination was also higher in the IONP+MF group, besides more intense expression of GAP-43 at week 5, indicating spinal cord regeneration. It was also observed that the use of magnetic field with IONPs enhanced the latter's antioxidant effect, thereby decreasing secondary injury cascades after SCIs.¹⁰¹

IONPs were utilized by a study for labelling porcine mesenchymal stem cells and canine glial restricted progenitors. These labelled cell type groups were then individually embedded in a hyaluronic acid-based hydrogel which was then intrathecally injected under the guidance of MRI into the porcine and canine animal models. Dynamic imaging following hydrogel injection showed signal stability indicating cells remained at the injection site within the intrathecal space, unlike stem cells embedded in PBS in which the injected cells rapidly disperse, quickly becoming undetectable by MRI. This approach can potentially show success when used for treating SCIs.¹⁰²

One paper investigated the magnetic targeting ability of SIONPs *in vitro* using D1 mouse bone marrow-derived mesenchymal stem cells. The NPs used in this case were oleic acid-coated SIONPs, which were further surface modified with dopamine, rendering them hydrophilic and amine-functionalized. Transmission electron microscopy analysis showed that the cellular uptake of SIONPs was mediated by endocytosis, placing them in the cytoplasm of the MSCs as SIONP-containing vesicles, mostly seen close to the cell membrane, nuclear membrane, and some even in the nucleus. Then, these SIONP-labeled D1 MSCs were further labeled with a fluorescent marker. After exposure to magnetic field, fluorescence signals were detected, showing a migration value of over 95% at 30 min. Furthermore, the D1 MSCs were

induced to undergo nerve cell differentiation, and it was confirmed that SIONPs were not lost after differentiation. Results obtained from this study indicate that we can target damaged neural tissue for promoting tissue regeneration potentially by influencing endogenous stem cells to undergo neuronal differentiation using this strategy.¹⁰³ Another study made use of a similar principle to study the effect of magnetic field on the migration of Schwann cells containing chondroitinase ABC-loaded SIONPs across the astrocytes *in vitro*.¹⁰⁴ Also, in a third study, poly-L-lysine (PLL) coated SIONPs were loaded into Schwann cells (also by endocytosis) and under the influence of magnetic field, their migration across the astrocyte boundary and intermingling with astrocytes was investigated.¹⁰⁵ These results can potentially open doors for the use of magnetically-driven migration of cells *in vivo*, and further work is necessary to validate these findings using animal models of SCI.

One study treated human mesenchymal stem cells with IONPs to produce IONP-incorporated exosome-mimetic nanovesicles (NV-IONP). Then upon *in vitro* investigations, it was deduced that NV-IONPs had the ability to induce angiogenesis, were antiapoptotic, neuroprotective, and had anti-inflammatory properties, all which are involved in TSCI repair. Moreover, in spinal cord injured mice, the use of magnetic field was found to markedly enhance the targeting efficacy of intravenously injected NV-IONP towards the injured spinal cord, as well as alleviate spinal cord damage and improve spinal cord function.¹⁰⁶

It was found that the cytotoxicity of PLL-SIONPs was both time and dose dependent following the co-incubation of PLL-SIONPs with Schwann cells.¹⁰⁵

In another study performed on male Wistar rats, injury was inflicted via a longitudinal incision into the right dorsal horn of the T10–11 segment of the spinal cord. Then, to investigate the influence of IONPs on the pathophysiology of SCI, a suspension of IONPs in Tween 80 solution was administered intravenously. It was observed that IONPs can induce mild damage in the blood-spinal cord barrier permeability after 24 hours of injury, as well as a mild increase in neuronal damage and astrocyte release. However, these changes were not seen with the non-SCI control group and the use of cerebrolysin as adjunct therapy appeared to markedly attenuate the aggravation of SCI-induced cord pathology on IONP administration and induce significant neuroprotection. This study also directs attention towards the importance of surface modifications of IONPs.¹⁰⁷

Table 1 demonstrates the challenges faced PLGA and iron oxide nanoparticles.

Exosomes

Background to exosomes

Exosomes are single-membrane vesicles released from various cell types including mesenchymal stem cells, with diameters ranging from approximately 30 to 200 nm and containing a wide variety of membrane-associated proteins, soluble proteins, nucleic acids, lipids, and glycoconjugates, giving them an otherwise unremarkable morphology compared to a cell. Once released, exosomes can perform activities such as remodeling the extracellular matrix and transporting different molecules such as coding or noncoding RNA, antigen presentation molecules, DNA, and proteins¹⁰⁹ between cells, which can play important roles in many aspects of human health.¹¹⁰

Due to their ability to cross the blood-spinal cord barrier and migrate to the spinal cord, exosomes can offer the potential for noninvasive, rapid, cell-free, lesion-specific, and effective treatment strategies for SCI. Exosomes can be promising nanocarriers for drug delivery and targeted therapy, as well as alternatives to stem cell therapy.¹¹¹

Table 1. Challenges faced when using nanoparticles for treating TSCIs.

Nanoparticle	Challenges
PLGA	Higher concentration of drug required in comparison to intraspinal injection, potentially leading to systemic toxicity and side effects. ⁵⁶ Chronic catheter implantation poses the risk of meningeal fibrotic scarring and further spinal cord injury. ⁵⁶ Overtime collapse/breakdown of tubes hindered axon survival. ¹⁰⁷
Iron Oxide	It was found that the cytotoxicity of PLL-SPIONs was both time and dose dependent following the co-incubation of PLL-SPIONs with Schwann cells. ¹⁰⁸ IONPs can induce mild damage in the blood-spinal cord barrier permeability after 24 hours of injury, as well as a mild increase in neuronal damage and astrocyte release. However, the use of cerebrolysin as adjunct therapy can markedly attenuate the aggravation of SCI-induced cord pathology on IONP administration and induce significant neuroprotection. ¹⁰⁷

Exosomes in TSCI models

The most common experimental use of exosomes in SCI models involve gene delivery (mainly RNAs) and different growth factors since their levels and target-regulated pathways have been found to be directly associated with the pathophysiology of SCI. One study showed that serum exosomal miR-130a-3p, miR-152-3p, and miR-125b-5p are specific and easily detectable diagnostic markers in acute SCI,¹¹² while a second study demonstrated that some serum miRNAs (such as miR-30b-5p, miR-152-3p, miR-200c-3p, miR-125b and miR-124-3p)¹¹³ in cerebrospinal fluid and serum could reflect injury severity in TSCI, indicating their use as targets for treatment and markers for diagnosis and prognosis.¹¹⁴ Another study demonstrated that reactive astrocytes increased proNGF expression after SCI, suggesting the involvement of exosome-like proNGF transport or release in triggering neuronal apoptosis and aggravating progression of SCI.¹¹⁵ Furthermore, the mRNA and protein expression levels of Nogo-A in spinal cord after injury are upregulated moderately, and the proteolyzed exosomal Nogo-A fragment called reticulon-4A can potentially inhibit axon regeneration.¹¹⁶

One study investigated the potential therapeutic effect of human umbilical cord mesenchymal stem cells-derived exosomes in a contusion model of SCI using C57BL/6 mice. The prepared exosomes were injected intravenously, and functional recovery was evaluated through behavioral testing using BMS scoring and CatWalk-assisted gait analysis which showed significant improvement in locomotor function, electrophysiological assessment which also showed an increase in peak-to-peak amplitude, histopathological study, which revealed decreased cavity volume. In addition, the use of hucMSC-derived exosomes led to the polarization of macrophages *in vitro* and reduced the pro-inflammatory cytokines levels while increasing anti-inflammatory cytokines levels.¹⁰⁹

Surprisingly, phosphatase and tensin homolog siRNA-loaded mesenchymal stem cell-derived exosomes administered intranasally in a complete spinal cord transection rat model demonstrated neuroinflammation-attracted migration of the exosomes to neurons in the lesioned area. Results showed significant motor function and sensory recovery, and faster urinary reflex restoration, in addition to decreased inflammation and gliosis, increased axonal regeneration and angiogenesis, and structural and electrophysiological improvements.¹¹¹

Bone mesenchymal stem cell-derived exosomes injected intravenously in a contusion rat model was also shown to remarkably decrease inflammation, tissue loss, glial scar formation, and effectively protected cells from apoptosis after spinal cord trauma, while angiogenesis and axonal regeneration were promoted, in addition to significant improvement in the BBB locomotor score. The underlying mechanism in this case was thought to be the suppression of the activation of A1 neurotoxic reactive astrocytes by these exosomes.¹¹⁷ Another identical study supports the aforementioned data, proposing a slightly more in depth mechanism which suggests that the decrease in A1 astrocytes occurs due to bone mesenchymal stem cell-derived exosomes inhibiting nuclear translocation of NF- κ B p65 to exert their anti-inflammatory and neuroprotective effects.¹¹⁸ Moreover, another similar study reported that intravenously administered exosomes trafficked to the lesion sites, but not uninjured spinal cord, and were specifically taken up by macrophages expressing the M2 marker CD206, but not by macrophages expressing the M1 marker iNOS, suggesting that MSC-derived exosomes may exert their therapeutic effects by regulating the actions of macrophages within the lesion.¹¹⁹ Furthermore, bone marrow mesenchymal stem cell-derived exosomes were found to also inhibit complement activation by suppressing complement mRNA synthesis and release and by inhibiting SCI-activated NF- κ B by binding to microglia.¹²⁰ In addition, GIT1-overexpressing bone marrow mesenchymal stem cell-derived exosomes were also shown to promote recovery in a contusive injury rat model.¹²¹ Also, one study provided the first evidence that bone marrow mesenchymal stem cell-derived exosomes can effectively inhibit the migration of pericytes, thereby maintaining the integrity of the blood-spinal cord barrier following injury.¹²² Another study demonstrated that these exosomes attenuate neuronal apoptosis by promoting autophagy.¹²³

On the other hand, exosomes derived from pericytes were also shown to promote blood flow, improve endothelial function, protect the blood-spinal cord barrier, alleviate the apoptotic response, thus promoting functional and behavioral recovery after injury.¹²⁴

The use of neural stem cell-derived exosomes have also shown favorable results including microvascular regeneration, reduced the spinal cord cavity, and improved the BMS scores in SCI mice, suggesting an underlying mechanism of neural stem cell-derived exosome-mediated angiogenesis.¹²⁵ Another study using neural stem cell-derived exosomes demonstrated that upon their exposure to insulin-like growth factor-1, inflammation and apoptosis were suppressed, while nerve regeneration was enhanced via an miR-219a-2-3p-dependent mechanism after the SCI.¹²⁶

Exosomes derived from lncGm37494-overexpressing adipose tissue-derived mesenchymal stem/stromal cells have also been studied as a potential therapeutic for SCI due to its ability to shift microglial M1/M2 polarization.¹²⁷

Table 2. Summary of the routes of administration for the nanoparticles in this review paper with their respective references.

Route	Nanoparticle	Reference
Intraspinal	PLGA	54, 55, 56
	Chitosan	34
Intravenous	PLGA	51, 52, 53, 59
	Iron Oxide	106
	Chitosan	33
	Exosomes	109, 117-128
	PCL	83
Intrathecal	PLGA	56
	Iron Oxide	99-102
Oral	PLGA	57
Intraperitoneal	PLGA	58
Intranasal	Exosomes	111

Human placenta amniotic membrane mesenchymal stem cell-derived exosomes adhered on a peptide-modified hyaluronic acid-based hydrogel (Exo-pGel) were presented in one study. These materials were then implanted in a long-span spinal cord transection model. Results revealed that implanted Exo-pGel exhibited high efficiency in nerve tissue repair and functional restoration. The findings were also compared to results obtained from the intravenous injection of the exosome alone, which indicated implantation to produce better results than systemically administered exosomes.¹²⁸

Furthermore, several studies have investigated the use of exosomes containing miRNAs such as miR-133b,¹²⁹ miR-126,^{130,131} miR-216a-5p,¹³² miR-544,¹³³ microRNA-124-3p,¹³⁴ miR-25,¹³⁵ miR-21^{136,137} and siRNA.¹³⁸⁻¹⁴⁰ Results all favor the use of these miRNAs and siRNA for SCI recovery.

Table 2 demonstrates the summary of the routes of administration studied for each NP for treating TSCIs.

Conclusion

In conclusion, traumatic SCIs can have devastating outcomes on patients due to the challenges in the healing process resulting from the complex secondary stage of injury. However, the field of nanotechnology has shined light on potential treatment options utilizing natural and synthetic NPs and exosomes. These are excellent candidates for drug delivery due to their ability to bypass the blood-brain barrier, and can even be used as diagnostic modalities for other central nervous system disorders

Data availability

No data is associated with this article.

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The article does a great job summarizing many relevant experiments and investigations done regarding various nanoparticle applications to SCI. Where it falls short for the reviewer is the lack of an overarching theme or main point.

After summarizing the relevant data from various experiments, the paper fails to bring it together to talk about the relevance (why this is important) or specific pros and cons of each nanoparticle type discussed. The authors just simply summarized the many previous studies using NPs. What are the underlying mechanisms of NPs for SCI? How are they taken up by cells? Are they employed as a drug delivery vehicle? Or Immunomodulatory factors? What are the effects of physicochemical properties for each of the polymeric NPs on SCI (i.e., size, surface charge, and molecular weight - If the author could provide the table for this it would be helpful)?. The authors mentioned only chitosan and chitosan-related NPs in the natural polymeric NPs section. Is this the only natural polymeric NPs for SCI (one or two additional natural polymeric NP would be helpful)? What are the pros and cons of utilizing natural polymeric NPs and polymeric NPs for SCI treatments?

If the paper could bring all the information together after each section and in the conclusion to talk more about why these developments are innovative or how they could lead to a new SCI treatment, the reviewer would have no reservations.

Is the topic of the review discussed comprehensively in the context of the current literature?

Partly

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Immunoengineering, nanoparticles, gene delivery, spinal cord injury, inflammation

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Reviewer Report 01 February 2022

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Ilya Klabukov

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1. The presented review paper "Nanoparticles in Traumatic Spinal Cord Injury: Therapy and Diagnosis" contains many up-to-date ideas for diagnosing and treating Traumatic Spinal Cord Injury. The primary approach is believed that nanoparticles suggest a promising methodology for the target delivery of materials and biomolecules.
2. At the same time, it seems that the paper's theme is speculative. To avoid any awkwardness, authors have used mainly PubMed sources. This is a very fruitful approach, but this is not enough, and I recommend using ONLY PubMed-indexed sources. Therefore, only 118 existing PubMed sources plus Statistics resources are recommended to be left in the Reference list.
3. The authors use statistics based on 2010 and 2011 sources. Statistic sources should be updated, if possible.
4. The References list needs to be updated by papers published in 2021, some are presented in the following citations:
 - Javdani *et al.* (2021¹)

- Rong *et al.* (2021²)
- Zhang *et al.* (2021³)
- Lin *et al.* (2021⁴)
- Wang *et al.* (2021⁵)

5. The paper should be shortened, especially the details of research on laboratory animals. Abstracts of original articles should be critically discussed, not retold.

6. I recommend adding a subsection on Complications for the use of nanoparticles. Injection of nanoparticles can lead to multiple complications, such as aggregation in tissues, nonspecific binding, and a systemic immunological response. The real and potential risks of using nanoparticles should be disclosed in the manuscript.

7. The paper has no references both to Preclinical and Clinical trials. It should be taken into account that clinical trials will be a challenge for nanoparticle-based drugs, and these trials need to be noted in the manuscript in Table form.

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Is the topic of the review discussed comprehensively in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Regenerative medicine and Tissue engineering

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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