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# Spinal Cord Injury: Developments in Using Stem Cells and Specialised Cells in Treating Spinal Cord Injuries

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## ABSTRACT

Spinal cord injury (SCI) is a severely debilitating condition that results in irreversible neurological deficits and significantly diminishes quality of life. Traditionally, treatment has primarily focused on symptom management and has offered limited functional recovery. Recent advancements in regenerative medicine and stem cell research have presented new possibilities for SCI patients. This review discusses key developments in SCI treatment, particularly stem cell transplantation, specialised cells, and combinational therapies. Mesenchymal stem cells (MSCs), neural stem cells (NSCs), induced pluripotent stem cells (iPSCs) and olfactory ensheathing cells (OECs) have shown promise in neural repair and functional recovery. Additionally, combining stem cell therapy with rehabilitation and neurotrophic factors enhances the therapeutic potential. However, achieving consistent and substantial functional recovery remains challenging and requires further research and large-scale clinical trials. This review underscores the need to translate these scientific advancements into clinical practice to improve the quality of life of SCI patients.

**Keywords:** Stem cells, MSCs, NSCs, iPSCs, OECs, Biomaterial, Scaffold, SCIs, Neurorehabilitation, Specialised cells, Functional recovery

## Introduction

According to the World Health Organization (WHO), it is estimated that between 250,000 and 500,000 people worldwide suffer from SCI annually.<sup>1</sup> The prevalence of SCI varies widely across different regions and populations and is often influenced by factors such as traffic accidents, workplace safety, and availability of medical care.<sup>1,2</sup>

SCI damage occurs in the spinal cord, resulting in the loss of functions such as mobility or sensation. The spinal cord, a vital part of the central nervous system, comprises nerve fibres that relay signals between the brain and the body.<sup>3</sup> Damage to the spinal cord can disrupt these signals, causing significant and often permanent changes in strength, sensation, and other functions below the injury site. SCIs can be caused by traumatic events, such as motor vehicle accidents, sports injuries, falls, and violence, or by nontraumatic factors.<sup>3,4</sup> SCIs are classified as complete or incomplete injuries: a complete injury results in no function below the injury level, whereas an incomplete injury preserves some function. The severity and impact of SCI are determined by the affected spinal cord level (cervical, thoracic, lumbar, or sacral).<sup>4</sup>

SCIs significantly impact individuals, resulting in physical, psychosocial, and economic challenges.

These injuries often lead to the loss of movement and sensation, which can result in paralysis, such as tetraplegia or paraplegia.<sup>5</sup> Physical consequences may also include respiratory problems, spasticity, and persistent pain. Injuries to the cervical and thoracic regions can impede neural pathways, leading to respiratory difficulties such as ventilatory failure and pneumonia. Spasticity results in continuous muscle rigidity and hinders mobility, whereas chronic pain can manifest as neuropathic, musculoskeletal, or visceral discomfort.<sup>6–8</sup>

SCI can have a profound impact on an individual's emotional and psychological well-being, often leading to feelings of depression and anxiety as a result of sudden changes in physical capabilities. Furthermore, the financial strain caused by high medical expenses and loss of employment can exacerbate the challenges faced by individuals and their families.<sup>9</sup>

## History of Treating SCI

The treatment of SCIs with stem cells and specialised cells can be traced back to early animal studies that examined the regenerative capabilities of various stem cell types, including MSCs, NSCs, and iPSCs. These studies have revealed the potential of these cells to improve motor and sensory functions and facilitate neural repair. Initial clinical trials conducted in the early 2000s focused on the safety and feasibility of MSC transplantation, demonstrating that MSCs derived from sources such as the bone marrow and adipose tissue are safe and can modulate immune responses and promote tissue repair.<sup>10–13</sup> Advances in iPSC technology in the 2010s have enabled the reprogramming of somatic cells into pluripotent stem cells, offering new avenues for neural repair.<sup>14,15</sup> NSCs derived from foetal tissues or iPSCs have been tested for their ability to differentiate into neurons and glial cells, aiding in neural repair and functional recovery.<sup>14,16–18</sup>

Specialised cell types, such as olfactory ensheathing cells (OECs) and stem cell-derived exosomes, have also been investigated for their regenerative potential.<sup>19–22</sup> OECs are known for their ability to support axonal growth, while exosome therapy offers a cell-free therapeutic approach by carrying neuroprotective and regenerative factors to the injury site.<sup>20,21</sup>

Despite promising results, challenges such as immune rejection, tumorigenesis, and the optimisation of cell delivery methods remain.<sup>23,24</sup> Recent studies have endeavoured to enhance these therapies and establish consistent guidelines for their clinical application, which could significantly advance the treatment of SCI and promote better patient outcomes.<sup>25,26</sup>

### **Stem Cell Transplantation Mesenchymal Stem Cells (MSCs)**

MSCs possess immunomodulatory and regenerative properties. Derived from bone marrow, adipose tissue, and umbilical cord, MSCs show potential in improving motor and sensory functions in SCI patients.<sup>24,27</sup> Levi et al. demonstrated the safety and feasibility of transplanting 20 million human central nervous system stem cells (HuCNS-SC) into the thoracic spinal cord of 12 patients with chronic motor-complete and sensory-incomplete SCI in a multi-site phase I/IIa clinical trial. The six-year study revealed no severe adverse effects or tumour formation, and while sensory improvements were observed in five patients, motor function recovery was not detected, emphasising the need for further research to enhance cell engraftment and integration.<sup>28</sup> Sykova et al. illustrated that MSCs from various sources have shown promise in treating neurodegenerative diseases such as SCI and ALS, owing to their multilineage differentiation potential and immunomodulatory properties.<sup>29,30</sup> They release neuroprotective cytokines, migrate to lesion sites, and enhance neural plasticity, leading to improved function in animal models.<sup>27,31</sup> Clinical studies have confirmed the safety and modest benefits of MSCs in promoting neural repair and functional recovery, particularly umbilical cord-derived MSCs with high neurotrophic factor secretion.<sup>29,32,33,34</sup> Tahmasebi et al.'s review, reflects that although improvements in sensory and bladder functions have been noted, the effects on motor function remain unclear, requiring further research to optimise and assess the application of these therapies in humans.<sup>34</sup>

### **Neural Stem Cells (NSCs)**

NSCs can differentiate into neurons, astrocytes, and oligodendrocytes, making them suitable for repairing neural damage.<sup>35-38</sup> Additionally, it has been suggested that genetically modified NSCs could overcome certain limitations, such as low migration and survival rates, thereby enhancing their therapeutic potential.<sup>39</sup> Pre-clinical studies using NSCs derived from fetal tissues and iPSCs have shown promising results in promoting neurogenesis and functional recovery in animal models of SCI.<sup>18,40-42</sup> However, several challenges persist that must be addressed before the clinical application of this technology can be realised, including the regulation of cell differentiation and proliferation, as well as ensuring patient safety.<sup>18,43</sup> Further research is needed to optimise these therapies and ensure their efficacy and safety for potential use in humans.<sup>41,42,44</sup>

Another technology that has been explored is the conversion of human fibroblasts into NSCs using single zinc-finger transcription factors, which represents a significant advancement and provides deeper insights into neural development and potential therapeutic applications.<sup>45,46</sup> This method allows the generation of long-term self-renewable and multipotent NSCs, which are similar to control NSCs in terms of their characteristics and functionality. Induced NSCs exhibit the capacity to survive, migrate, and differentiate

into neural phenotypes post-transplantation without tumour formation, which is crucial for any therapeutic application.<sup>45</sup> However, while this advancement is promising, it is important to consider the broader context of SCI treatment and the various approaches being explored. For instance, Yu et al. and Pereira et al. elaborate on the opportunities presented by NSCs derived from iPSCs and their capacity for cell transplantation therapy aimed at addressing SCI.<sup>47,48</sup> Lu et al. and Ao et al. emphasised the survival and integration of NSCs in severe SCIs and the potential synergistic effects of co-transplanting NSCs with other cell types, such as OECs, to promote regeneration and functional reconstruction.<sup>49,50</sup> Furthermore, Kiani et al. indicated the potential of employing human-induced neural stem cells (hiNSCs) for cell-based therapy in rats with spinal cord injury (SCI), as evidenced by the enhanced cell viability and locomotor function observed following transplantation.<sup>51</sup>

### **Induced Pluripotent Stem Cells (iPSCs)**

iPSCs are a versatile source of stem cells that can be reprogrammed from somatic cells and differentiated into various cell types, including neural stem/progenitor cells (NS/PCs), which can be used for SCI treatment.<sup>52-54</sup> Research has demonstrated that iPSCs can survive, differentiate, and extend axons over long distances in the injured spinal cord, forming synapses with host neurons, which are crucial for functional recovery after SCI.<sup>55,56</sup> Recent studies have focused on preparing for first-in-human clinical trials using iPSC-derived neural stem/progenitor cells (NS/PCs) for subacute SCI.<sup>57,58</sup> These studies have addressed critical issues such as safety, tumorigenesis, and the practical challenges of cell preparation and transplantation.<sup>54,58</sup>

### **Olfactory Ensheathing Cells (OECs)**

OECs have been identified as promising agents in treating SCIs because of their unique ability to support axonal growth and facilitate neural regeneration.<sup>59,60</sup> These cells, which share characteristics with both Schwann cells and astrocytes, can migrate within the damaged spinal cord, secrete neurotrophic factors, and potentially carry exogenous genes to promote neuronal regeneration.<sup>61,62</sup> Olfactory mucosa cells have been found to be effective in restoring motor function due to their capacity to remyelinate and regenerate axons. Furthermore, they express neurotrophic factors essential for nerve tissue recovery following SCI.<sup>63</sup> Additionally, OECs have been shown to interact with astrocytes, regulate inflammatory reactions, and contribute to myelination, which is a critical process in nerve repair.<sup>59</sup>

However, there are challenges in the application of OECs, such as inconsistency in therapeutic outcomes, which may be attributed to the variability in cell populations used for transplantation.<sup>64</sup> Moreover, while OECs have demonstrated neuroprotective and repair roles, the mechanisms by which they mediate anti-inflammatory effects remain a subject of debate.<sup>65</sup> The potential of OECs is further complicated by the need

for improved purification procedures to achieve their full therapeutic potential.<sup>64</sup>

In summary, OECs offer a multifaceted approach to SCI treatment by promoting axonal regeneration, myelination, and modulation of the inflammatory response. Despite promising evidence, further research is required to standardise cell preparations and fully understand the mechanisms of OEC-mediated repair to optimise their therapeutic application.<sup>64,65</sup>

### Exosomes

Exosome therapy presents a novel cell-free approach to treating spinal cord injuries (SCIs) by capitalising on the intrinsic ability of exosomes to transport neuroprotective and regenerative factors to the site of injury. Exosomes are extracellular vesicles that facilitate intercellular communication and possess the potential to modify the injured spinal cord's environment by delivering bioactive molecules that promote neuroprotection and regeneration.<sup>20,21,66</sup> Numerous studies have demonstrated the therapeutic potential of exosomes. Zhou et al., in their study, revealed that exosomes derived from human placental MSCs possess the ability to promote recovery from SCIs by stimulating endogenous neurogenesis and improving locomotor and bladder functions via the MEK/ERK/CREB signalling pathway.<sup>67</sup> In addition, a study by Xue et al. showed that human umbilical cord mesenchymal stem cell (hUC-MSC)-derived small extracellular vesicles (sEVs) have the potential to repair disrupted blood-spinal cord barriers in SCI through the regulation of Endothelin-1 and the enhancement of tight junction proteins. These findings further support the idea that sEVs may offer a promising cell-free therapeutic strategy for treating SCI.<sup>68</sup> Another study demonstrated that exosomes derived from UC-MSCs enhanced motor function recovery and reduced inflammation by inhibiting the NF- $\kappa$ B/MAPK signalling pathway.<sup>69</sup> Lee et al. demonstrated that targeted delivery of MSC-derived nanovesicles (MF-NVs) enhances neuroprotection, anti-inflammation, and angiogenesis in SCI treatment, offering an effective cell-free therapeutic approach.<sup>70</sup> A study by Mu et al. showed that an emergency treatment strategy using MSC-derived exosomes encapsulated in fibrin glue resulted in significant functional recovery in SCI, suggesting potential benefits in urinary function recovery.<sup>71</sup>

### Combination Therapies

#### Combining Different Types of Stem Cells

Recent research has suggested that combining different stem cell types may enhance therapeutic outcomes.<sup>62</sup> Co-transplantation of NSCs and MSCs has demonstrated synergistic effects, resulting in improved motor and sensory function. Furthermore, scaffolds and growth factors facilitate stem cell transplantation by establishing a favourable microenvironment that promotes tissue regeneration.<sup>72-75</sup> Notably, while the advantages of employing a combination of stem cells have been emphasised, the literature also recognises the intricacy of spinal SCI pathophysiology and the necessity for

precision medicine approaches. This indicates that the efficacy of combined stem cell therapies may be contingent upon customised treatment to the unique features of the injury and the patient.<sup>24,76,77</sup>

### Rehabilitation and Neurotrophic Factors

Integrating stem cell transplantation with rehabilitation and neurotrophic factors has yielded encouraging outcomes.

Rehabilitation enhances the effects of cell transplantation by promoting neural plasticity and functional recovery. Studies have shown that rehabilitation when combined with stem cell transplantation, can lead to significant improvements in functional recovery, particularly when initiated during the chronic phase of SCI.<sup>78</sup> This synergistic effect is thought to be the result of the rehabilitation's capacity to facilitate neuronal plasticity within transplanted stem cells and sensorimotor circuits, which is crucial for functional recovery.<sup>79</sup> Furthermore, it has been demonstrated that the integration of rehabilitation and neural progenitor cell (NPC) transplants leads to enhanced functional results because rehabilitation promotes the growth of host corticospinal axons into grafts.<sup>78</sup> This suggests that rehabilitation not only supports the integration of transplanted cells but also enhances endogenous repair mechanisms.

The use of neurotrophic factors, such as neurotrophin-3 (NT-3), in conjunction with stem cell therapies, has been shown to improve outcomes in patients with spinal cord injuries (SCI). The combination of these two therapies has demonstrated synergistic effects, leading to improved locomotor function and reduced SCI pathology.<sup>80,81</sup> In particular, the use of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF), in conjunction with stem cell therapies has demonstrated the potential to mitigate damage and facilitate recovery in preclinical models of SCI.<sup>80</sup>

In conclusion, evidence suggests that neurotrophic factors, including NT-3, can effectively improve outcomes after SCIs when combined with stem cell treatments. This joint approach benefits from the neuroprotective and regenerative qualities of neurotrophins and the extensive therapeutic potential of stem cells, presenting a promising strategy for improving recovery in SCI.<sup>77,80,81</sup>

### Clinical Trials and Outcomes

#### Safety and Feasibility

Clinical trials have established the safety and feasibility of stem cell transplantation in SCI. Rong et al. study highlights that stem cell transplantation has been performed at various stages of SCI and is safe and feasible, with the potential to alleviate inflammation and restore the function of damaged nerve cells.<sup>82</sup> Similarly, Digma et al. reported that early clinical trials demonstrated the safety and feasibility of stem cell transplantation in patients with SCI, with observed improvements in sensory and motor functions.<sup>83</sup> Silvestro et al. also supported these findings, indicating

that clinical trials have demonstrated the safety and efficacy of stem cell therapy in patients with SCI.<sup>82-84</sup> However, despite these positive indications, challenges and limitations remain to be addressed. Agosti et al. pointed out that, while stem cell therapies show promise, some potential adverse events and limitations necessitate careful optimisation of transplantation conditions.<sup>85</sup> Moreover, there is a need for a deeper understanding of SCI pathophysiology and concerns, such as tumourigenicity and immunogenicity, before its widespread clinical adoption. Goel et al. and Kan et al. echo the sentiment that more rigorous, large-scale clinical trials are needed to fully understand the safety, efficacy, and long-term viability of stem cell therapies for SCI.<sup>85-87</sup>

### Efficacy

Although the safety of stem cell therapies has been well documented, their efficacy remains variable. The efficacy of these therapies is less consistent, as clinical studies have not always yielded encouraging results, and the translation of preclinical success to clinical practice has been challenging.<sup>88</sup> This discrepancy may be due to the heterogeneity of SCI pathophysiology, timing of intervention, and types of stem cells used.<sup>76</sup> Moreover, despite the promise shown in animal models, the limitations of preclinical data and the complexity of translating these findings into successful clinical outcomes have been acknowledged.<sup>89</sup>

Various studies have reported improvements in motor and sensory functions post-SCI have been reported in various studies, particularly with the use of MSCs and NSCs. MSCs have been shown to promote repair through immunomodulation, neuroprotection, and nerve regeneration,<sup>24</sup> whereas NSCs have demonstrated the ability to form synapses with host axons and extend new axons from the injury site.<sup>79</sup>

However, the extent of recovery is variable and dependent on factors such as the type of stem cells used, the severity of injury, and the therapeutic approach. The promising results from MSC and NSC therapies underscore the potential of stem cell-based interventions in SCI treatment, although further research is needed to optimise these therapies and understand their mechanisms of action.<sup>24,90</sup>

### Discussion

Recent advancements in SCI treatment, particularly in stem cell therapies and combinational approaches, offer new hope for improving the quality of life for individuals with SCI.<sup>76,89,91,92</sup> Significant progress has been made in developing these therapies, demonstrating their potential to repair damaged spinal cord tissues and restore lost function.<sup>22,93-95</sup> However, ongoing research and clinical trials are crucial to overcome the existing challenges and fully realise the potential of these therapies. Addressing issues such as immune rejection, precise delivery methods, and ensuring stem cell treatments' long-term safety and efficacy remain essential.

### Overcoming the Challenges

The advent of iPSC technology has mitigated ethical concerns, particularly with the use of embryonic stem cells (ESCs) and fetal tissues.<sup>40</sup> Although stem cells are not a complete solution for neural repair, their combination with other therapies, such as rehabilitation and nanotechnology, may enhance their effectiveness.<sup>96</sup>

Integrating innovative technologies and comprehensive treatment strategies is fundamental to advancing SCI treatment and achieving substantial functional recovery.<sup>97-99</sup> Technologies, such as biomaterials, scaffolding, and gene editing, are being explored to enhance the effectiveness of stem cell therapies. Biomaterials can provide a supportive environment for stem cells, promoting their survival and integration into the host tissues.<sup>74,75,99-101</sup>

Scaffolding techniques help guide the growth and organisation of new cells, whereas gene editing can be used to enhance the regenerative capacity of stem cells.<sup>44,74,93,100</sup> Moreover, integrating complementary technologies, such as neurorehabilitation, electrical stimulation, and pharmacological treatments, can maximise the benefits of stem cell therapy.<sup>102,103</sup> Neurorehabilitation can help patients relearn motor skills and improve functional outcomes. Electrical stimulation can enhance the activity of spinal circuits and promote nerve regeneration.<sup>103-105</sup> Pharmacological treatments can address inflammation and other secondary complications, creating a more favourable environment for stem cell therapy.<sup>106</sup>

### Conclusion

Stem cell therapy for SCI is a promising field with great potential for improving patient outcomes. Collaborative efforts among stakeholders, including scientists, clinicians, and regulatory bodies, are vital to address the current challenges. Advances in stem cell biology and regenerative medicine have pushed the boundaries of what is possible. Future studies should focus on optimising stem cell therapy protocols to ensure the highest safety and efficacy standards. This includes determining the best types of stem cells to use, refining delivery methods, and establishing optimal timing for intervention.

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