

## Review Article

# Cell Therapy Augments Functional Recovery Subsequent to Spinal Cord Injury under Experimental Conditions

Vikram Sabapathy,<sup>1</sup> George Tharion,<sup>2</sup> and Sanjay Kumar<sup>1</sup>

<sup>1</sup>Centre for Stem Cell Research, Christian Medical College, Bagayam, Vellore, Tamil Nadu 632002, India

<sup>2</sup>Department of Physical Medicine and Rehabilitation, Christian Medical College, Vellore, Tamil Nadu 632002, India

Correspondence should be addressed to Sanjay Kumar; [skumar@cmcvellore.ac.in](mailto:skumar@cmcvellore.ac.in)

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The spinal cord injury leads to enervation of normal tissue homeostasis ultimately leading to paralysis. Until now there is no proper cure for the treatment of spinal cord injury. Recently, cell therapy in animal spinal cord injury models has shown some progress of recovery. At present, clinical trials are under progress to evaluate the efficacy of cell transplantation for the treatment of spinal cord injury. Different types of cells such as pluripotent stem cells derived neural cells, mesenchymal stromal cells, neural stem cells, glial cells are being tested in various spinal cord injury models. In this review we highlight both the advances and lacuna in the field of spinal cord injury by discussing epidemiology, pathophysiology, molecular mechanism, and various cell therapy strategies employed in preclinical and clinical injury models and finally we discuss the limitations and ethical issues involved in cell therapy approach for treating spinal cord injury.

## 1. Introduction

Spinal cord injury (SCI) is a serious debilitating disorder that results in complete or partial loss of motor/sensory neuronal functions due to mechanical damage of the spinal cord [1]. Overall analysis of the incidence report suggests that extent of patients suffering from spinal cord injury might approximately vary from 8 to 83 cases per million factoring into account diversities in geographical and socio-economic and political conditions [2–4]. The spinal cord injury can be broadly classified into two groups: traumatic and nontraumatic [3]. Traumatic spinal cord injury results from contusion, compression, and stretch of the spinal cord [5]. Trauma related injury is the most prevalent among SCI cases majorly involving road traffic accidents, especially in case of young adults between age group of 15 and 29 years and accidental falls in case of aged people (>65 years) [6, 7]. Nontraumatic related injury mainly consists of vertebral spondylosis, tumor compression, vascular ischemia, and congenital and inflammatory spinal cord disorders [8]. Several different treatment strategies such as drug intervention (steroidal/nonsteroidal), growth factors, cellular

metabolites (cAMP/GTPases), small molecules, extracellular matrices, and cellular therapy involving pluripotent stem cells/mesenchymal stem cells (MSCs)/neural progenitor cells (NPCs/NSCs) are being tested for successful therapeutic intervention [9]. Incidentally, various therapeutic strategies exist to alleviate the symptoms/complications but there is no proper treatment available to completely cure spinal cord injury.

## 2. Physiological Complications due to Spinal Cord Injury

The pathophysiological stages after spinal cord injury can be classified into primary and secondary phases [10, 11]. The primary phase is the phase at the moment of aberration in spinal cord structure due to mechanical forces. The spinal cord at the time of injury may be subjected to hyperbending, overstretching, twisting, or laceration [12]. The complications arising in the secondary phase are directly proportional to the extent of injury in the primary phase. The secondary phase can be in turn classified into three different subphases such as acute phase (2 hours to 2 days), subacute phase

(days to weeks), and chronic phase (months to years) [13–15]. The inflammatory response mediated by convoluted cellular and molecular interactions after spinal cord trauma forms the core of secondary injury phase. The acute phase is characterized by edema, ischemia, hemorrhage, reactive oxygen species (ROS) production, lipid peroxidation, glutamate mediated excitotoxicity, ionic dysregulation, blood-spinal cord barrier permeability, inflammation, demyelination, neuronal cell death, and neurogenic shock. The subacute phase is comprised of activation and recruitment of microglial cells, astrocytes, monocytes, T lymphocytes, and neutrophils, macrophage infiltration, scar formation, and initiation of neovascularization. The chronic phase exhibits neuronal apoptosis, retraction and demyelination of axons, loss of sensorimotor functions, Wallerian degeneration, glial scar maturation, cyst and syrinx formation, cavity formation, and Schwannosis [16, 17] (Figure 1). The subacute phase after spinal injury provides optimal time frame for therapeutic interventions [18].

### 3. Molecular Mechanism of Spinal Cord Injury

The trauma of spinal cord injury results in an irreversible and progressive degeneration of neuronal tissue. After spinal cord injury, the acute and chronic phases are accompanied by various molecular changes leading to inflammation, loss in biochemical homeostasis, and degeneration of neurofilaments, higher ROS (reactive oxygen species) levels and apoptosis [1]. During the onset of spinal cord injury various injury genes are activated. Based on the meta-analysis of the previous reports, these genes can be broadly classified into early and late injury genes depending upon the phase of activation or downregulation [1]. The first 24–48 hours refers to early injury phase and late phase represents 1 week after injury. Molecular cascade after spinal cord injury results in the activation of genes responsible for inflammatory pathway, apoptosis, cell cycle and oxidative stress, and downregulation of genes involved in energy metabolism, lipid metabolism, neurotransmission, and cytoskeleton [1]. Inflammation is a convoluted process. It can be broadly classified into acute and chronic inflammatory. Immediately after spinal cord injury, the proinflammatory cytokines such as IL6, TNF $\alpha$ , and IL1 $\beta$  are activated and expressed multifold [90, 91]. Apoptosis refers to programmed cell death. As a result of spinal cord injury, it has been observed that there is significant increase in the proapoptotic genes such as Bad, Bax, p53, AFAP1, caspase 3, and caspase 9, during the early phase of injury and significant decrease in antiapoptotic genes like Bag1 and Bcl2 during late phase of injury [90, 92, 93]. Following spinal cord injury there is elevation of cell cycle associated genes such as PCNA, cyclin D1, cdk4, cyclin G, Rb, E2F5, c-Myc, and Gadd45a which might support the neuronal cell death [94]. Further, reports suggest that spinal cord injury results in the redox imbalance in the tissues leading to increased reactive oxygen species (ROS) levels and oxidative stress. Consequently, upregulation of Hspb1 [90] and Hspa4 [95] genes involved in regulating oxidative stress was observed during the early phase of injury. Lipid metabolism in general involves lipogenesis and fatty acid oxidation. It is required to

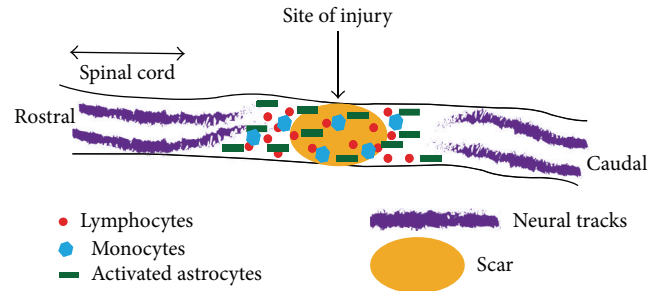


FIGURE 1: Mechanism of spinal cord injury.

maintain the tissue homeostasis. During the later phase of injury it is observed that genes involved in lipid biosynthesis such as Gpd1 and Alox12 required for lipooxygenase are effectively downregulated [92]. Most importantly, genes involved in neural excitation such as Kcnh2/k1/c1, Scn1a/8a, Gria3, and Grm3, neurotransmission related genes like Gabra5/b1, synapse associated genes like Slc6a1, and genes required to maintain electrochemical gradient such as Atp1a3 and Atp2a1/b2 are found to be markedly downregulated during both early and late phases of spinal cord injury [95, 96]. Also cytoskeleton-scaffolding proteins like Nefl required for maintenance of axonal cytoskeleton and Map2 involved in microtubule assembly are notably downregulated [95].

### 4. Cell Therapy

Currently, there are limited therapeutic interventions and no proper cure for effective treatment of spinal cord injury but recent preliminary studies have indicated that cell therapy may help. For effective functional recovery, the transplanted cells have to reduce the inflammatory response, inhibit neuronal apoptosis/necrosis, enhance neuronal regeneration, and promote axonal regeneration and remyelination [97]. Cell transplantation augments the neuronal regeneration after spinal cord injury through secretion of paracrine factors, acting as a scaffold for axonal regrowth and replacing the lost neurons or neural progenitor cells [98]. Based on the choice of the cells used for transplantation, cellular based therapy can be broadly classified into pluripotent stem cells, fetal stem cells, progenitor cells, and differentiated cells. Further, the cells can be genetically engineered to enhance the therapeutic functionality of the cells. Various gene therapy approaches have been reported for treating spinal cord injury. Some of the notable genes overexpressed include transcription factors (Ngn2), neurotrophic factors (NT3, BDNF, GDNF, and MNTS1), growth factors (bFGF, HGF), receptor tyrosine kinases (TrKC), and cell adhesion molecule (LICAM) (Table 7).

### 5. Animal Models and Preclinical/Nonclinical Studies

Various types of animal models such as mouse, rat, dogs, and nonhuman primates, such as marmoset, have been employed to undertake preclinical studies. A recent review

TABLE 1: Preclinical spinal cord injury trials using induced pluripotent stem cells (iPSCs)/embryonic stem cells (ESCs).

Transplanted cell type	SCI model	Neuronal regeneration	Functional recovery	Inflammation repression	Reference
mESCs	Mice, T8, contusion	—	Yes	Yes	[19]
mESCs + mMSCs	Mice, T9-10, contusion	Yes	—	—	[20]
mESCs-neurosphere	Mice, T10, contusion	Yes	Yes	—	[21]
hiPSCs-neuroepithelial cells	Mice, T10, contusion	Yes	Yes	—	[22]
hiPSCs-neural cells	Marmoset, C5, contusion	Yes	Yes	—	[23]
L1-mESCs-neural cells	Mice, T9, compression	Yes	Yes	Yes	[24]
Ngn2-hESCs	Rats, T9, compression	Yes	Yes	—	[25]
hESCs-NPCs	Rats, T10, hemisection	Yes	Yes	—	[26]
hESCs-NPCs + SCs	Rat, T9, contusion	Yes	Yes	—	[27]
hESCs-MPCs	Rat, C5-C6, contusion	Yes	Yes	—	[28]
hESCs-OPCs	Rat, T10, contusion	Yes	Yes	—	[29]
hESCs-OPCs	Rat, T9, contusion	Yes	Yes	—	[30]
hESCs-OPCs	Rat, C5, contusion	Yes	Yes	Yes	[31]
hESCs-MPCs/OPCs	Rat, T8, complete transection	Yes	Yes	—	[32]
hESCs-MPCs + OECs	Rat, T9, complete transection	Yes	Yes	—	[33]
mESCs-GABAergic	Rat, T13, lateral hemisection	Yes	Yes	—	[34]

Mouse embryonic stem cells (mESCs); human embryonic stem cells (hESCs); human induced pluripotent stem cells (hiPSCs); neural progenitor cells (NPCs); Schwann cells (SCs); neurogenin 2 (Ngn2); motoneuron progenitor cells (MPCs); oligodendrocyte progenitor cells (OPCs); olfactory ensheathing cells (OECs).

after systematic meta-analysis of the animal studies points out that stem cell therapy might offer some hope for cure in spinal cord injury [99]. The pluripotent stem cells like embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) are the type of cells that possess the ability to give rise to all the three germ layers [100, 101]. Recent studies have demonstrated that pluripotent stem cells alone or in combination with other cell types might help in augmenting the recovery from spinal cord injury (Table 1). Bottai et al. directly transplanted mESCs into the lesion immediately after injury and observed that significant function BBB score in the transplanted mice [19]. Nevertheless, there is significant risk of teratoma formation in transplanting the undifferentiated pluripotent cells [102]. Hence the pluripotent stem cells are differentiated into neuronal progenitors, motor neurons, oligodendrocyte progenitor cells, and olfactory ensheathing cells *in vitro* prior to *in vivo* transplantation. Kumagai et al. observed that transplantation of ESCs derived neurospheres in mouse model increased the functional recovery following spinal cord injury [21]. With the help of improved neuronal differentiation protocol Fujimoto et al. showed that transplantation of hiPSCs derived neural epithelial cells resulted in improved axonal regeneration and remyelination [22]. Okano's lab has shown that human iPSCs derived neural cells promote functional recovery after spinal cord injury using nonhuman primate marmoset model [23]. Transplantation enhanced increased axonal regeneration, myelination, and angiogenesis with complete absence of teratomas. An intriguing study by Matsuda et al. has shown that c-transplantation of ESCs with MSCs resulted in no teratoma formation [20]. It has been suggested that MSCs might propel the undifferentiated ESCs to neural cell lineage through mediation of the neurotrophic factors released by

them. Additionally, previous data had revealed that neural cell adhesion molecule L1 is reported to promote survival and axonal growth [103] (Table 7). Transplantation of L1 expressing mESC differentiated into neurons significantly improved the motor function and increased cell survival [24]. Neurogenin 2 (Ngn2) is a transcription factor involved in CNS development [104]. Ngn2 expressing hESCs differentiated neural cells significantly restored the motor functions of the SCI rat model [25]. Combinatorial therapy of hESCs derived neural cells embedded along with collagen scaffold promoted locomotory recovery and prolonged the survival of the graft [26]. Niapour et al. combined hESCs derived neural progenitor cells along with Schwann cells (SCs) to rescue SCI in rat contusion model and observed significant improvement motor functional improvement [27]. The motoneuron progenitor cells (MPCs) [28] and oligodendrocyte progenitor cells (OPCs) [29–31] derived from hESCs have been successfully transplanted in SCI rat models, resulting in significant improvement in functional neuronal regeneration and reduced acute inflammation. Effective promotion of functional recovery and axonal remyelination was observed in transplantation of hESCs derived MPCs along with OPCs [32] and olfactory ensheathing cells (OECs) [33]. Kim et al. reported improved mechanical sensitivity in rat SCI hemisection models after transplantation of mESCs dedifferentiated GABAergic neurons [34].

Mesenchymal stromal cells (MSCs) are a kind of mesodermal stem cells that exhibit plasticity to give rise to cells from all the three germ layers under *in vitro* condition. The ease of availability [105], rapid expansion [106], cryopreservation [107], and subtle immunological complications makes the cells ideal candidates for cellular therapy [108, 109]. Previous preclinical studies have indicated that utilization of MSCs

TABLE 2: Preclinical spinal cord injury trials using mesenchymal stromal cells (MSCs).

Transplanted cell type	SCI model	Neuronal regeneration	Functional recovery	Inflammation repression	Reference
r-BMMSCs	Rat, compression/contusion	Partial	Yes	Yes	[35–42]
m-BMMSCs	Mice, T9, compression	Partial	Yes	—	[43]
h-BMMSCs	Rat, T8-T9, complete transection	Yes	Yes	Yes	[44, 45]
h-UCMSCs	Dog, L2-3, compression	Yes	Yes	—	[46]
r-BMMSCs-NPCs	Rat, T8-T9, contusion/compression	Yes	Yes	—	[47, 48]
Canine-aMSCs-NPCs	Dogs, L2-3, compression	Yes	Yes	Yes	[49]
h-BMMSCs-NPCs	Rats, T9, contusion	Yes	Yes	—	[50]
r-BMMSCs-bFGF	Rats, T9, contusion	Yes	Yes	—	[51]
r-BMMSCs-NT3	Rats, T9, ethidium bromide induced demyelination	Yes	Yes	—	[52]
r-BMMSCs-NT3	Rats, T9, contusion	Yes	Yes	—	[53]
h-BMMSCs-HGF	Rats, C4, hemisection	Yes	Yes	Yes	[54]
h-BMMSCs-BDNF	Rats, T9, transection	Yes	Yes	—	[55]
r-BMMSCs-GDNF	Rats, T9, contusion	Partial	—	—	[56]
r-BMMSCs-MNTS1	Rats, T8, contusion	Yes	Yes	Yes	[57]
r-BMMSCs-TrkC	Rats, T10, complete transection	Yes	Yes	—	[58]

Rat bone marrow MSCs (rBMMSCs); human umbilical cord MSCs (hUCMSCs); basic fibroblast growth factors (bFGF); neurotrophin 3 (NT3); hepatocyte growth factor (HGF); brain derived neurotrophic factor (BDNF); glial cell line derived neurotrophic factor (GDNF).

for treatment of spinal cord injury resulted in reduction in demyelination, suppression of neuroinhibitory molecules, and promoting axonal regeneration [110] (Table 2). Transplantation of bone marrow derived MSCs (BMMSCs) derived from rats into SCI rat models revealed slight improvement in neural regeneration with significant restoration of motor functions and attenuation of inflammatory response was found [35–42]. Similar observations were recorded after transplantation of mice BMMSCs into spinal cord injury mouse models [111]. Injection of human BMMSCs [44, 45] and human UCMSCs [46] into the SCI animal models effectively promoted the functional recovery following spinal cord injury. Differentiation of rat [47, 48], canine [49], and human MSCs [112] into neuronal cells prior to transplantation has shown to significantly augment neural regeneration and motor functional recovery with reduction in inflammatory cells. Cotransplantation of r-BMMSCs [77] and h-BMMSCs [113] with Schwann cells (SCs) into SCI rat models resulted in increased axonal remyelination and motor function along with reduced scar formation. Transplantation of genetically modified MSCs expressing growth factors such as bFGF [51] and neurotrophin 3 (NT3) [52, 53] has been shown to improve neuronal functions. Hepatocyte growth factor (HGF) is a paracrine factor secreted by the MSCs. It is a morphogenetic factor that helps in growth and survival of cells [114]. A specific study has observed that transplantation of human BMMSCs expressing HGF in rat hemisection SCI model reduced the glial scar formation by repressing the astrocyte activation and ameliorated the functional recovery of forepaw [54]. Brain-derived neurotrophic factor (BDNF) is a neurotrophic factor encoded by BDNF gene. It has been shown to enhance the neuronal regeneration capabilities in the corticospinal tracks [115]. Grafting of hBMMSCs expressing BDNF in rat SCI model helped in regaining

the locomotory function [55]. Glial cell line derived neurotrophic factor (GDNF) is a secretory protein encoded by GDNF gene. GDNF is necessary for normal neuromuscular development [116]. Further, it has been shown that it helps in the survival of motor neurons [117]. Assessment of rat SCI transplanted with rBMMSCs expressing GDNF indicated moderate neural regeneration [56]. MNTS1 is a multineurotrophin that binds and autophosphorylates Trk receptor tyrosine kinases (TrkA/TrkB/TrkC) and p75 neurotrophin receptor (p75 NTR) [118]. Kumagai et al. observed that transplantation of rBMMSCs expressing MNTS1 resulted in suppression of inflammation, reduction in cavity size, and improved neuronal regeneration [57]. Trk family [119] and p75 NTR [120] have been extensively associated with neuronal survival. Improvement in functional motor recovery was observed after transplantation of rBMMSCs expressing TrkC proteins in SCI rat models [58].

The existence of neural progenitor cells (NPCs) was first identified, isolated, and cultured from subventricular zone of the mouse [121, 122]. These NPCs have the ability to differentiate into neurons, astrocytes, and oligodendrocytes under both *in vitro* and *in vivo* conditions. Multiple studies have shown that transplantation of NPCs derived from fetal sources (human/rat/mice) into SCI models has resulted in efficient regeneration of neural structures with function recovery and reduced inflammatory response [59–63] (Table 3). Åkesson et al. observed that human neurospheres obtained from the spinal cord tissue facilitated neuronal regeneration after transplantation into rat spinal cord lesion [64]. The differentiation of NPCs into oligodendrocyte progenitor cells (OPCs) has shown to significantly increase axonal remyelination with better motor and sensory recovery [112]. Further combinatorial studies have indicated that cotransplantation of NPCs with OECs has promoted



TABLE 3: Preclinical spinal cord injury trials using neural stem cells (NSCs)/neural progenitor cells (NPCs).

Transplanted cell type	SCI model	Neuronal regeneration	Functional recovery	Inflammation repression	Reference
Fetal-mNSCs	Mice, T10, contusion	Yes	Yes	—	[59]
Fetal-rNSCs	Rats, C4, dorsal hemisection	No	Partial	—	[60]
Fetal-hNSCs	Rats/mice, contusion/avulsion	Yes	Yes	—	[61–63]
Spinal cord-hNPCs	Rats, T8, compression	Yes	—	—	[64]
Fetal-hNPCs-OPCs	Rats, T8, compression	Yes	Yes	—	[50]
Fetal-hNSCs-Olig2	Rats, T9-10, contusion	Yes	Yes	—	[65]
Fetal-rNSCs + OECs	Rats, T8, compression	Yes	Yes	—	[66]
rNSCs-TrkC + NT-3	Rats, T10, transection	Yes	Yes	—	[67]

Oligodendrocyte progenitor cells (OPCs); olfactory ensheathing cells (OECs).

TABLE 4: Preclinical spinal cord injury trials using olfactory ensheathing cells (OECs).

Transplanted cell type	SCI model	Neuronal regeneration	Functional recovery	Inflammation repression	Reference
rOECs	Rats, contusion/compression/ Transection/hemisection	Yes	Yes	—	[68–71]
rOECs + motor neurons	Rat, T9, transection	Yes	Yes	—	[33]
rOECs + MSCs	Rat, T8, compression	Yes	Partial	—	[72]
rOECs-NT3	Rat, T8, compression	—	Partial	—	[73]

Neurotrophin 3 (NT3).

functional recovery [66]. Hwang et al. reported that transplantation of Olig2 expressing NPCs enhances the locomotory recovery with increase in myelination and reduction in lesion cavity [65]. Genetically modified NSCs expressing TrkC gene along with gelatin sponge scaffold seeded with NT3 helped in bridging the injury site, promoted axonal regeneration, and promoted partial locomotory functional recovery [67].

Olfactory ensheathing cells (OECs) are a class of glial cells that are found in both PNS and CNS [123] (Table 4). Tharion's lab [70] and others [68, 69, 71] have shown that transplantation of rat OECs and mouse OECs into SCI models has shown satisfactory process in the functional recovery and neural tissue restoration. Cotransplantation of OECs with motor neurons [33] yielded significant progress in regeneration capabilities displaying synergistic effect when compared to results obtained from transplantation of OECs with MSCs [72]. Injection of NT3 expressing OECs into rat SCI lesion resulted in neural stimulation and longer survival of the graft with significant increase in motor functional recovery [73].

Schwann cells are the type of glial cells that are associated with myelination of the axonal structures. After SCI, transplantation of Schwann cells has been observed to result in axonal regeneration and remyelination [124] (Table 5). These cells further secrete neurotrophic factors such as nerve growth factor (NGF), brain-derived neurotrophic factors (BDNF), and ciliary neurotrophic factors (CNTF), extracellular matrix proteins that mainly include laminin and collagens, and upregulate cell adhesion molecules like integrins, N-cadherins, N-CAM, LI, and contactins [124–126].

Transplantation of SCs into the SCI lesion has shown to augment the neuronal functional regeneration capabilities along with improved axonal myelination [74–76]. Additionally, cotransplantation of MSCs [77, 78] and NSCs [79] along with SCs has been shown to reduce scar formation and restore the neural functional potential.

## 6. Clinical Trials

The success of the cellular transplantation studies at the preclinical levels resulted in extrapolating a similar therapeutic strategy at the clinical levels (Table 6, Figure 2). In 2009, Geron Corporation was the first to get FDA approval to initiate clinical transplantation of ESCs derived OPCs (GRNOPC1) on spinal cord injury patients [17]. The Phase I clinical trial data did not indicate any improvement in therapeutic potential. However, there are no reported adversities till date following transplantation. In 2011, Geron abruptly ended its clinical trial citing financial limitations. Nevertheless, initiation of the study paved the way for regularizing the following stem cell studies. Unlike the ESCs/iPSCs derived cells, other cell types such as MSCs, NSCs/NPCs, OECs, and SCs exhibit higher safety standards. In a transplantation study involving 171 patients, Huang et al., in 2003, reported functional recovery after transplantation of olfactory ensheathing cells [80]. Further, in 2005, a study by Kang et al. has shown that transplantation of MSCs from human umbilical cord blood into 37-year-old spinal cord injury patient resulted in the functional recovery [81]. Cotransplantation of umbilical cord derived MSCs (UCMSCs) and CD34+ HSCs (UCHSCs) on a 29-year-old L1 SCI American Spinal Injury Association

TABLE 5: Preclinical spinal cord injury trials using Schwann cells (SCs).

Transplanted cell type	SCI model	Neuronal regeneration	Functional recovery	Inflammation repression	Reference
rSCs	Rats, contusion/compression/hemisectomy	Yes	Yes	—	[74–76]
rSCs + MSCs	Rat, contusion/4 mm spinal cord removal	Yes	Yes	—	[77, 78]
rSC + NSCs	Rat, T8-9, transection	Yes	Partial	—	[79]

TABLE 6: Clinical spinal cord injury trials using cell therapy.

Transplanted cell type	SCI model	Safety	Neuronal Regeneration and functional recovery	Inflammation repression	Reference
ESCs-OPCs	Phase 1, ASIA Scale Type A	Yes	—	—	[17]
OECs	171 Patients	Yes	Yes	—	[80]
UCMSCs	1, T11-12, ASIA Scale Type A	Yes	Yes	—	[81]
UCMSCs + CD34 <sup>+</sup> HSCs	L1, ASIA Scale Type A	Yes	Yes	—	[82]
BMMSCs	ASIA Scale Type A	Partial (spasticity/ neuropathic pain)	Yes	Partial	[83]
BMMSCs	ASIA Scale Type A/B/C	Yes	Yes	Partial	[84–86]
SCs	ASIA Scale Type A/B/C	Partial	Yes	—	[87–89]

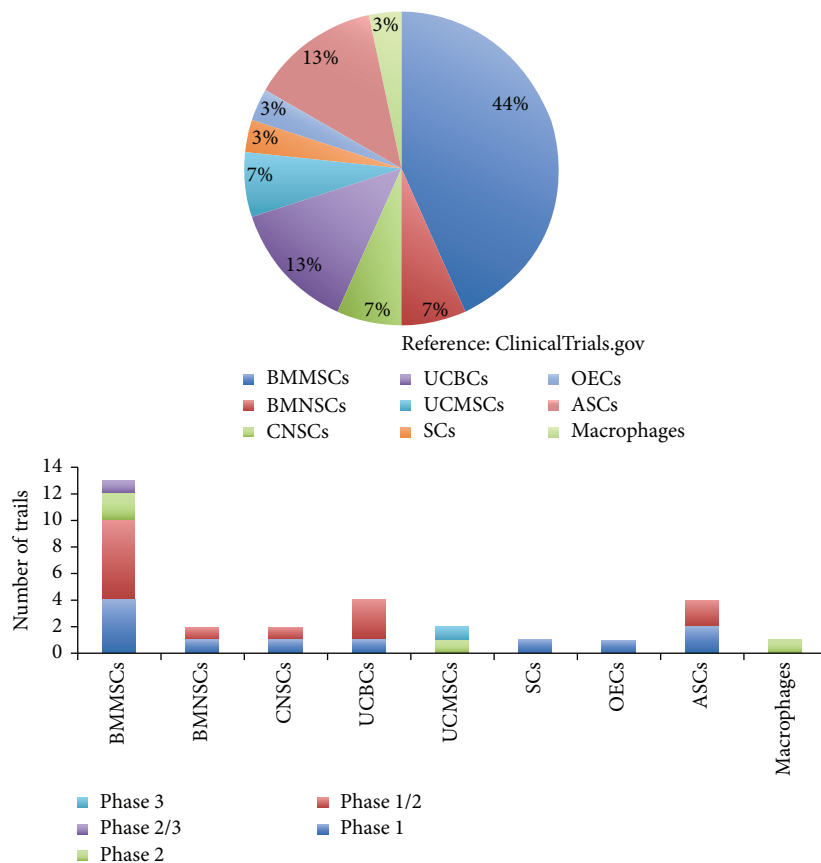


FIGURE 2: Clinical trials in spinal cord injury using cell therapy. Bone marrow MSCs (BMMSCs), bone marrow mononuclear cells (BMNSCs), central nervous system cells (CNSCs), umbilical cord blood cells (UCBCs), umbilical cord blood MSCs (UCBMSCs), Schwann cells (SCs), olfactory ensheathing cells (OECs), and adipocyte stem cells (ASCs).

TABLE 7: Genes used for engineering cells.

Genes	Carrier	Reference
LI	Electroporation	[24]
Ngn2	Lentivirus	[25]
Olig2	Retrovirus	[65]
bFGF	Transfection	[51]
HGF	Lentivirus	[54]
NT3	Adenovirus	[52]
BDNF	Adenovirus	[55]
GDNF	Retrovirus	[56]
MNTS1	Lentivirus	[57]
TrkC	Adenovirus	[58]

(ASIA) Scale Type A patient resulted in noted recovery of muscle, bowel, and sexual function [82]. There were no reported adversities during the study and ASIA Scale was reduced to Type D. A critical study including 64 patients by Kishk et al. observed limited progress after autologous intrathecal transplantation of BMMSCs [83]. The ASIA Scales of the patients were rated down from Type A to Type B. However some of the patients exhibited complications such as cell induced spasticity, neuropathic pain, and development of encephalomyelitis. Bhanot et al. reported that transplantation of autologous MSCs on 13 SCI patients (ASIA Scale Type A) at the site of the lesion resulted in sensory functional recovery in 2 patients and motor function recovery in only one patient [84]. In a similar study involving 10 SCI patients, transplantation of autologous BMMSCs showed significant improvement in motor/sensory functional recovery in 6 patients [86]. Moreover, MRI studies indicated neurogenesis and decrease in the cavity size, and electrophysiological analysis indicated improved functional potential. There were no reported complications. Karamouzian et al. demonstrated that transplantation of autologous BMMSCs via lumbar puncture into CSF in 11 SCI patients resulted in borderline functional recovery in 5 patients [85]. In a study involving Schwann cells (SCs), Saberi et al. reported that transplantation of autologous SCs into 4 SCI patients resulted in marginal functional improvement in only one patient [87]. No complications were reported in any of the patients. In a follow-up study involving 33 patients, 16 patients ASIA Scale Type A and 17 patients ASIA Scale Type B, upon transplantation of SCs, up to 6 patients had shown progress in bladder and bowel control [88]. Some of the patients had exhibited some function recovery, which was not very significant. In another study, Zhou et al. described that injection of the autologous SCs in 6 SCI patients led to moderate improvement in all of the treated patients in terms of anatomical, motor, and sensory functions after follow-up of 5 years [89].

## 7. Limitations and Ethical Concerns

Although the various strategies are employed for the treatment of spinal cord injury, until now there is no proper

cure that is safe and effective for spinal cord injury patients [17]. Although cell based interventions hold a great promise in the treatment of spinal cord injury, it is at its nascent stages; still a lot of multicentric studies are required as there are variations in treatment regime from one clinical setting to another. Further questions like type of cell to be used, site of transplantation, dosage, and number of cells are not properly standardized. The mechanisms governing injury and regeneration are not properly understood. There are very limited preclinical and clinical studies reported at present. Due to poor regulations, there are a lot of unethical practices associated with stem cell transplantation. The 2003 transplantation study reported by Huang et al. was received with skepticism and ethical concerns [127–129]. Still a lot of research has to be carried out at preclinical levels, which include screening using small animal models (rats and mice), large animal models (cats, dogs, rabbit, and primates), and clinical levels to optimize various parameters until it becomes standard of care [130]. The propensity of tumor development after transplantation is significantly higher in case of pluripotent stem cells derived neural cells. Transplantation of hESCs derived NPCs into spinal cord of SCID mice has been shown to result in teratoma [131]. Hence pluripotent stem cell derived neural cells sources have to be subjected to rigorous selection before transplantation.

## 8. Conclusion

Currently, very few places have spinal cord injury registry. Hence maintenance of spinal cord injury registry has to be promoted in order to properly take care and evaluate spinal cord injury patients. Currently, there is no proper cure for SCI therapy. The current preclinical and clinical data indicate that cell therapy may hold key to future regenerative medical applications. There are lots of animal models and clinical data that are incompletely evaluated leading towards utter confusion in the field. The researchers working in spinal cord injury have to communicate, coordinate, and conduct multicentric clinical trials in order to generate some meaning of full consensus with respect to cell therapy in the field of spinal cord injury. Moreover, cellular therapy can be combined with genetic modification or small molecules as a combinatorial approach to deliver the cure. Our current goal should be to regain some functional recovery and neuronal regeneration. We cannot expect the injured person to get up and start walking. Still a lot of questions like the type of cell, number of cells, and region of transplant have to be answered. At present, it is difficult to ascertain the fate of the cells. Further, *in vivo* tracking technology of the cells is at its nascent stages. Hence, development of *in vivo* tracking has to be given due importance.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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