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REVIEW

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Intraparenchymal stem cell transplantation for spinal cord injury: a review of clinical trials

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ABSTRACT

Traumatic spinal cord injury (SCI) results in severe and often permanent motor, sensory, and autonomic impairment, and current treatments offer limited restorative benefit. Stem-cell based approaches have been investigated to promote neural repair, but peripheral delivery is limited by poor cell localization and engraftment. Intraparenchymal (IP) transplantation, which delivers cells directly into injured spinal cord, is intended to improve local retention, survival, and integration. This review synthesizes early-phase clinical trials from the United States, Canada, Europe, and Australia, evaluating five major cell platforms: autologous olfactory-ensheathing-cells (OECs), fetal-derived neural stem cells (HuCNS-SC), embryonic stem cell derived oligodendrocyte progenitors (OPC1), fetal spinal cord derived neural progenitor cells (NSI-566), and autologous Schwann cells (ahSCs). IP delivery demonstrates convergent early-phase safety, with no recurrent cell-related severe toxicity, tumor formation, or progressive neurological deterioration attributable to the delivery platform. Functional outcomes remain heterogeneous and modest. Large, reproducible neurological recovery has not been observed, although some studies report limited sensory improvements, isolated motor gains, or electrophysiologic evidence of conduction across or below the injury. These findings support biological activity but insufficient functional efficacy under current trial designs. Future progress will require controlled efficacy studies with standardized endpoints, optimized timing and dosing, and rehabilitation or neuromodulatory integration.

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KEYWORDS
Spinal cord injury; stem cell transplantation; intraparenchymal delivery; neural repair; neural stem cells

1. Introduction

Traumatic spinal cord injury (SCI) is a severe medical condition, with ~18,000 new cases reported each year in the United States (US) [1–5]. SCI can lead to substantial deficits, including upper extremity weakness and sensory loss based on neurological level of injury as well as various degrees of autonomic, cardiovascular, and respiratory disruption [6–9].

Stem cell therapy has emerged as a promising avenue for the treatment of SCI due to its potential to promote regeneration and repair of damaged neural tissue [10]. Stem cells possess unique characteristics, including the ability to self-renew and differentiate into various specialized cell types, such as neurons and glial cells, which are essential for repairing spinal cord tissue [4]. Traditionally, stem cells have been administered peripherally, either intravenously (IV) or intrathecally (IT), allowing the cells to circulate and potentially reach the injured spinal cord. IV infusions deliver stem cells through the bloodstream to reach different areas of the body, though it faces challenges in crossing the blood–brain barrier [11]. IT injections are used to administer stem cells directly into the intrathecal space, targeting the central nervous system, however, this approach, while circulates the therapy into the CNS has restricted ability to penetrate the spinal parenchyma itself [12].

To address these challenges, intraparenchymal (IP) delivery, a direct injection of stem cells into the spinal cord tissue, has been explored as a more targeted method, aiming to enhance cell retention, survival, and integration within the injured spinal cord [13]. IP stem cell injection into the spinal cord offers targeted delivery directly to the site of injury, maximizing local therapeutic cell concentration, enhancing neuroprotection and tissue repair, and overcoming challenges of peripheral methods such as limited migration and blood – brain barrier penetration [14]. The potential for IP delivery to improve functional outcomes and accelerate recovery in spinal cord injury makes it a promising avenue for advancing therapeutic strategies. This targeted approach may significantly impact the efficacy of stem cell-based therapies by ensuring the maximum benefit is delivered to the injured spinal cord tissue, thus supporting the crucial role of intraparenchymal delivery in spinal cord injury treatment.

In this review, we examine IP stem cell transplantation for SCI, summarizing recent clinical studies, outlining proposed mechanisms of action, highlighting safety and efficacy data, and unresolved questions in the field. The scope is limited to the US, Canada, Europe, and Australia to maintain regulatory comparability and consistency in clinical trial reporting and endpoints.

2. Methods

A review of the literature was conducted using the PubMed database, maintained by the U.S. National Library of Medicine

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Article highlights

- Traumatic SCI causes severe and often permanent motor, sensory, and autonomic deficits, and current treatments offer limited restorative benefit.
- Stem cell therapies are being investigated for neural repair, but peripheral delivery routes (intravenous or intrathecal) are limited by poor localization and low engraftment in spinal cord tissue.
- IP transplantation delivers cells directly into injured spinal cord parenchyma to improve local retention, survival, and biological integration.
- This review synthesizes early-phase IP clinical trials from the United States, Canada, Europe, and Australia, evaluating five platforms: OECs, HuCNS-SC, OPC1, NSI-566, and ahSCs.
- Across cell classes, IP delivery shows a convergent early-phase safety profile, with no recurrent cell-related severe toxicity, tumor formation, syrinx development, or progressive neurological deterioration attributable to the delivery platform.
- When SAE occurred, they were more commonly related to surgical exposure or immunosuppression rather than a reproducible toxicity signal from the transplanted product.
- Functional outcomes remain modest and heterogeneous. Large, reproducible neurological recovery has not been observed, though some studies report limited sensory improvements, isolated motor gains, or electrophysiologic evidence of conduction below the lesion.
- Cross-trial efficacy comparisons are limited by heterogeneity in injury characteristics, outcome instruments, follow-up windows, rehabilitation exposure, and control conditions; AIS grade conversion is an insensitive endpoint for comparison.
- Overall, IP transplantation appears feasible and safe across diverse stem cell platforms, supporting the need for controlled efficacy trials with standardized endpoints and optimized dosing, timing, targeting, and adjunct rehabilitation/neuromodulatory strategies.

and providing access to peer-reviewed biomedical and life sciences research. The search was performed in September per 25 using the following keyword combinations and Boolean operators: "intraparenchymal" AND "stem cell" AND "spinal cord injury"; "stem cell transplantation" AND "direct injection" AND "SCI"; and "neural stem cell" OR "progenitor cell" AND "intraparenchymal" AND "spinal cord." Only articles published in English that reported clinical trials of IP stem cell delivery for SCI were included. We restricted inclusion to trials conducted in the United States, Canada, Europe, and Australia. These regions share comparable regulatory frameworks, standardized clinical trial registration, reducing regulatory and reporting heterogeneity, and allowing for more direct comparison of trial design, dosing parameters, and clinical outcomes. Reference lists of retrieved articles were screened to capture additional relevant studies. Selected publications were reviewed for details of cell type, delivery method, study design, outcomes, and reported safety or efficacy data.

3. IP stem cell types used for SCI

Various stem cell types have been investigated for IP transplantation in SCI, including neural stem cells (NSCs), oligodendrocyte progenitor cells (OPCs), olfactory ensheathing cells (OECs), fetal-derived neural cell lines such as NSI-566, and autologous Schwann cells (ahSCs). Each of these has distinct biological properties and mechanistic rationales, ranging from remyelination and axonal sprouting to modulation of the injury microenvironment, and several have advanced into early-phase clinical trials. Among the most studied are human fetal CNS-derived stem cells (HuCNS-SCs), embryonic stem cell-derived OPC1, OECs harvested from the olfactory mucosa, the fetal neural precursor line NSI-566, and autologous Schwann cells. The following sections summarize the translational rationale, trial design, safety outcomes, and preliminary efficacy signals for each of these stem cell lines in clinical use for SCI.

4. OEC

4.1. OEC preclinical rationale

Olfactory ensheathing cells (OECs) are specialized glial cells that are found within the olfactory mucosa, where they support the lifelong regeneration of olfactory receptor neurons. Sharing characteristics with Schwann cells, OECs promote axonal extension and myelination, and play a key role in bridging neural gaps and modulating glial scarring post-injury [15]. Their autologous collection from the olfactory mucosa makes them an accessible and immunologically compatible candidate for SCI transplantation. Preclinical studies in small animal models demonstrate that OECs promote axonal regeneration, restore locomotor and autonomic function, and bridge disrupted tracts [16]. In non-human primates, OEC transplantation led to remyelination and conduction recovery, providing translational evidence that directly informed the design and rationale of subsequent human clinical trials [17].

4.2. Clinical trials

4.2.1. Phase I/IIa thoracic

A Phase I/IIa, single-blind feasibility and safety trial studied the intraspinal transplantation of autologous OEC in three male patients with chronic complete thoracic (T4-T10) AIS A paraplegia 18–32 months post injury. A matched control group ($n = 3$) with comparable injuries was created for blinded assessment. OECs were harvested via an endoscopic nasal septum biopsy and enzymatically purified and expanded in vitro. Cells were injected into the injured cord and into adjacent normal cord using multiple injection sites under microscopic guidance with a purpose-designed injector system. The cell dose and injection counts varied by participant: 12 million cells/270 injections, 24 million/545 injections, and 28 million/630 injections.

The primary endpoint was procedural and long-term safety, including AE, infection, tumor or cyst formation, CSF leakage, or MRI evidence of syrin. Secondary endpoints included neurological, functional (AIS, FIM), and psychosocial assessments at baseline and periodic follow-up to 3 years.

At 1 year, there were no adverse findings, including no infection or CSF leakage, no neurological/functional deterioration, and MRI showed no evidence of cell overgrowth/mass and no post-traumatic syringomyelia/pseudomeningocele. At 3 years, the transplant recipients similarly had no adverse findings; MRIs remained unchanged from baseline and interim scans with no tumor/cyst, no post-traumatic syringomyelia, and no other adverse radiologic findings; there was no neuropathic pain and no significant functional change. One recipient showed sustained bilateral sensory improvement spanning three dermatomal levels (light touch and pinprick) over the three-year observation period. No other participant demonstrated comparable recovery in sensory or motor

scores. Quantitative AIS, FIM, and neurophysiological measures showed no consistent improvement compared to baseline or control subjects.

4.3. OEC conclusion

Across this small Phase I/IIa controlled trial, intraspinal transplantation of autologous OECs in chronic complete thoracic SCI was feasible and demonstrated no adverse findings through 3 years, including stable MRI surveillance with no tumor/cyst or post-traumatic syringomyelia and no neurological decline. Efficacy signals were limited: one participant had sustained sensory improvement, while group-level neurological and functional measures showed no significant change and no AIS A grade conversion, consistent with the small sample size and chronic injury context. Continued investigation in larger cohorts, earlier intervention windows, with refined trial designs and broader outcome measures, can improve the therapeutic potential of OECs in restoring function after SCI [18,19].

5. HuCNS-SC

5.1. HuCNS-SC preclinical rationale

HuCNS-SC are lineage-restricted, multipotent neural progenitors derived from fetal CNS tissue that can differentiate into neurons, oligodendrocytes, and astrocytes [20–23]. In mouse models of subacute and chronic contusive spinal cord injury, perilesional IP transplantation of HuCNS-SC led to engraftment, long-term survival, migration, and differentiation, accompanied by improved locomotor outcomes consistent with functional integration within the chronically injured spinal cord. These studies further showed that the reparative effects of HuCNS-SC extend into post-injury phases, supporting their relevance for patients with established chronic neurological deficits. Across these preclinical evaluations, HuCNS-SC exhibited no tumorigenicity or ectopic tissue formation and maintained a stable neural lineage identity over extended follow-up intervals [24–27]. Together, these findings established HuCNS-SC as a biologically stable and durable neural stem cell product capable of engraftment and reparative differentiation in chronic SCI, supporting clinical intramedullary transplantation in humans.

5.2. HuCNS-SC clinical trials

5.2.1. Phase I/IIa thoracic cohort (NCT01321333)

A multicenter, open-label Phase I/IIa clinical trial evaluated direct intramedullary transplantation of 20 million HuCNS-SC cells (StemCells Inc., Newark, CA) in 12 adults with chronic traumatic thoracic SCI between T3–T11, graded AIS A or B, and 5–24 months post-injury. Enrollment occurred across Zurich ($n = 9$), Calgary ($n = 2$), and Toronto ($n = 1$). The study began in 2011, with a six-year follow-up through 2020. Each participant received four ultrasound-guided intramedullary microinjections, two rostral and two caudal to the lesion, each delivering ≈70 µL, totaling 20×10^6 cells. All participants received perioperative immunosuppression consisting of tacrolimus administered for 9 months, mycophenolate mofetil for 28 days, and a short course of dexamethasone. The primary endpoint evaluated procedural and long-term safety through AE monitoring, magnetic resonance imaging (MRI), and standardized neurological exams (ISNCSCI). Secondary endpoints assessed sensory and motor recovery and functional improvement using validated pain, spasticity, and independence scales.

Participants were monitored daily the first week, then at 7-, 14-, and 28-days post-operation, then every 3 months during the first year, and at scheduled or ad-hoc intervals up to 72 months. The transplantation was well tolerated with no procedure-related mortality or neurologic deterioration. Reported short-term serious adverse events included surgery-related complications such as cerebrospinal fluid leak or pseudomeningocele, as well as rehospitalizations for medical issues (e.g., constipation, or urinary tract infection), all of which resolved without lasting sequelae. Over 6 years, recurrent AEs, UTIs, spasticity, pressure ulcers, fractures reflected typical SCI comorbidities and were unrelated to the graft.

At long-term follow-up, five of 12 participants (1 AIS A and 4 AIS B) showed reliable sensory improvement in light-touch or pinprick below the injury level – gains occurring well beyond the usual window for spontaneous recovery. Two AIS A subjects converted to AIS B; one conversion occurred immediately post-transplant and was attributed to the intervention, whereas the second occurred later and was considered unrelated. Motor recovery was not observed. MRI revealed no tumor formation, cord malformation, or lesion deterioration across 6 years [28].

5.2.2. Phase II cervical (NCT02163876)

Building on prior safety data, a multicenter phase II single-blind, randomized proof-of-concept clinical trial investigated HuCNS-SC transplantation for chronic cervical (C5-C7, AIS A/B) SCI. Cohort I ($n = 6$) was open-label and dose-escalating (15 M, 30 M, or 40 M cells), while Cohort II ($n = 6$) consisted of randomized, single-blind subjects who received a 40 M HuCNS-SC dose. Cohort I used a dose-escalation injection schema (4/6/8 injections respective to each dose), while the randomized cohort used the 40 M injection paradigm (8 injections/560 µL). The primary endpoint was motor improvement in the ISNCSCI upper extremity motor score (UEMS) at six months post-transplantation. Secondary endpoints included assessments of sensory and motor function (total ISNCSCI and GRASSP scores), spasticity via the Modified Ashworth Scale, pain, and allodynia evaluations, and MRI-based lesion length measurements.

Across both cohorts, MRI demonstrated no new spinal cord damage, syrinx formation, or hemorrhage, and mild transient T2 signal changes observed in several participants resolved by 6–12 months. Lesion lengths remained stable throughout follow-up, and there were no radiographic signs of cord edema or atrophy. Nine SAE occurred among transplanted participants and two among controls, primarily related to surgery or wound complications; none were attributed to the HuCNS-SC product. Overall, the procedure was well tolerated with no cell- or immunosuppression-related safety concerns.

At 6 months, transplanted participants demonstrated a mean UEMS gain of +2.8 compared with controls, a difference below the predefined efficacy threshold. Some individuals exhibited transient improvements in upper-limb strength and dexterity on GRASSP testing, but effects were inconsistent and not statistically significant. By 12 months, treated subjects showed mean increases of approximately 15 points in GRASSP and 16 points in ISNCSCI total scores from baseline, with no neurological decline. One AIS A subject converted to AIS B, while one AIS B subject declined to AIS A by month 9 and remained stable thereafter. MRI follow-up confirmed resolution of T2 hyperintensity and no new pathology. In total, the trial verified procedural feasibility and long-term safety but failed to demonstrate meaningful functional benefit, leading to early study termination [29,30].

5.3. HuCNS-SC Conclusion

Collectively, these studies demonstrate that IP transplantation of HuCNS-SCs is surgically feasible and biologically safe, showing no procedure-related neurological decline or long-term adverse effects. While some sensory or limited motor gains were observed, consistent functional recovery was not achieved, and efficacy remains unproven. Together, these findings establish a strong safety foundation for HuCNS-SC in chronic SCI, guiding future controlled trials aimed at optimizing dosing, timing, and outcome assessment to determine therapeutic benefit.

6. OPC1

6.1. OPC1 preclinical rationale

Oligodendrocyte progenitor cells (OPCs) derived from human embryonic stem cells (hESCs), known successively AST-OPC1, GRNOPC1, and LCTOPC1, are engineered to promote cellular repair at traumatic SCI via remyelination of denuded axons, secretion of neurotrophic factors to support neuronal survival, and modulation of the injury microenvironment to promote tissue repair [31,32]. Initial preclinical studies demonstrated that hESC-derived OPCs could differentiate into oligodendrocytes in high purity and myelinate axons in vitro [23]. In animal models of acute incomplete rat contusion injury, the transplantation of these cells led to their survival and migration to the injury site, successful remyelination of damaged axons, and subsequent improvements in locomotor function [32]. Dose scaling from animal studies indicated a human-equivalent range of $1x10^{\wedge 7}$ to $2x10^{\wedge 7}$ cells, guiding the later clinical trial design [33,34]. These preclinical findings formed the basis for FDA clearance of the first in human trial for hESC-derived cell therapy in SCI.

6.2. OPC1 clinical trials

6.2.1. Phase I thoracic (NCT01217008)

The first human trial was a Phase I multisite open label single-arm study evaluating the safety of a single dose of $2 \times 10^{\wedge 6}$ LCTOPC1 cells in five individuals with acute, complete thoracic AIS A SCI (T3–T11), 7–14 days post injury. This trial utilized the previously established surgical precedent for IP injection of stem cells caudal to the SCI epicenter. The primary endpoint was safety: frequency/severity of AEs related to product, procedure, and/or tacrolimus within 1 year. The secondary endpoint was neurological function ISNCSCI sensory and lower-extremity motor scores (LEMS), with follow up annually in person through year 5, then annual telephone follow-up through years 6–15.

Across 10 years of follow-up with 98% visit completion, there were no unanticipated SAEs related to LCTOPC1 were reported. There was no evidence of tumor formation, syrinx development, or neurological deterioration. MRI revealed no cystic enlargement or new lesions, and 80% of patients demonstrated T2 signal consistent with matrix formation at the injury site. Tacrolimus was well tolerated and discontinued at 60 days without immune rejection.

Although the trial was not powered for efficacy, modest sensory improvements were observed. Three of five participants demonstrated at least one level of improvement in their zone of partial preservation, indicating segmental sensory recovery below the original neurological level of injury. One individual with a T3 neurological level of injury demonstrated rostral improvement to T4, accompanied by bilateral sensory extension to T5–T6 at one year. Despite these localized improvements, no AIS grade conversions were observed, and LEMS remained 0/50 throughout long-term follow-up [31,35].

6.2.2. Phase I/IIa cervical (NCT02302157)

Following this successful trial, a Phase I/IIa dose-escalation study was initiated to evaluate the safety and potential efficacy of OPC1 in individuals with subacute cervical SCI (C4-C7; AIS A/B). Twenty-five participants were administered escalating doses of OPC1 ($2 \times 10^{\wedge 6}$, $1 \times 10^{\wedge 7}$, and $2 \times 10^{\wedge 7}$ cells) via a custom syringe delivery device into the lesion epicenter, treated 21–42 days post injury. The primary endpoint was safety and tolerability, AEs/SAEs attributable to cells, procedure, or tacrolimus. The secondary endpoints included change in neurological function by ISNCSCI at prespecified time points through 1 year. Participants then enter a long-term safety protocol for an additional 14 years.

The cervical trial demonstrated a favorable safety profile, with no SAEs directly attributed to the LCTOPC1 cells. Two SAEs were deemed related to the treatment: one a CSF leak from the injection procedure and the other from a bacterial infection linked to immunosuppression. Both were resolved with treatment and not linked to the OPC1 themselves. Serial MRI scans over a year of follow-up showed no evidence of tumor formation, enlarging masses, or other adverse findings. There was no immune-mediated rejection or neoplastic growth at the one year follow up.

Regarding clinical efficacy, the trial reported promising early results. At one-year follow-up, 96% (21/22) of the intention-to-treat population achieved at least a one-motor-level improvement on at least one side of their body, and 32% (7/22) recovered two or more motor levels on at least one side; 3 participants converted from AIS B→C. While the study lacked a control group and was not powered for efficacy, the reported recovery rates exceeded those of spontaneous recovery benchmarks in similar patient populations [34].

6.3. OPC1 conclusion

The outcomes of the OPC1 clinical trials provide safety data supporting the continued development of hESC-derived cell therapies for SCI. The demonstrated long-term safety of OPC1 implantation, as shown in the 10-year follow-up of the thoracic trial, marks an important longitudinal milestone. The results of the cervical trial, while preliminary, suggest a potential for neurological recovery that warrants further investigation. The research highlights the need for larger, placebo-controlled trials to definitively establish the efficacy of OPC1 and to explore optimal patient selection, dosage, and timing of intervention.

7. NSI-566

7.1. NSI-566 preclinical rationale

NSI-566 is a human spinal cord-derived NSC line obtained from a postmortem eight-week gestational age fetus with a broad multipotent ability to differentiate into new neurons, astrocytes, and oligodendrocytes using cell replacement trophic support, axonal sprouting, and overall synaptogenesis. Potential applications include regrowing disrupted neuronal microenvironments through neurotrophic secretion, remyelination, and human based neuronal circuit reintegration. Preclinical studies of L3 spinal compression rats, NSI-566 produced improvement in muscle spasticity and dysfunction, as well as ingrowth of NSI-566 cells into the rat spinal based neural circuitry [36]. In complete spinal cord transection, the grafted cells showed long distance axonal growth, functional improvements, and completely new synaptic connectivity [37]. In non-human primate models, NSI-566 demonstrated comparable efficacy signal, and minipig studies established a translational dosing platform [38].

7.2. Clinical trials

7.2.1. Phase I thoracic (NCT01772810)

To translate these findings, a first in human Phase I study enrolled four adults with chronic thoracic T2-T12 AIS-A SCI, treated >1 and <2 years post injury. The surgical protocol involved laminectomy/durotomy followed by six stereotactic intraspinal injections of NSI-566 at a dose: $2 \times 10\text{^}5$ cells per injection (total $1.2 \times 10\text{^}6$ cells/subject), placed bilaterally lateral to the injury and within medial white-matter tracts ~1 segment caudal to the lesion, under fluoroscopic guidance. No negative control group was used.

The primary endpoints were safety and tolerability, defined by the absence of SAEs, surgical complications, or new neurological deficits, with anatomical integrity confirmed on MRI and DTI. The secondary endpoints evaluated functional recovery (ISNCSCI, EMG, BMCA), quality of life (SCIM/FIM), and immunologic safety, with long-term radiologic monitoring of graft stability.

In the initial 18–27 month safety analysis, all four patients tolerated the procedure without serious surgery related AE such as infections, CSF leaks, inflammation, soft tissue edema/swelling, syrinx, or tumor formation. Additionally, there was no spontaneous or evoked pain post procedure. MRI and DTI revealed stable spinal cord architecture caudal and rostral to the injury site without evidence of tract disruption or graft-related mass effect. Anti-HLA antibodies detected in one subject (010) lacked donor specificity, confirming absence of allosensitization. Across 5 years, 65 adverse events were recorded, nonattributable to the cells or procedure. One subject (008) died from sepsis secondary to a sacral ulcer 30 months post-transplant, judged unrelated to NSI-566 or surgery. No tumors, cord edema, syrinx, enhancement, or immune rejection were observed on MRI/DTI. Pain and neuropathic scores improved in two patients, with no new or worsening pain in the others. Overall, the implantation and immunosuppression regimens remained well tolerated through 60 months.

For exploratory efficacy at 5 years, two patients (001 and 010) demonstrated durable improvement in neurological level of injury, motor, and sensory scores – each maintaining a net gain of one level relative to baseline. Subject 001's initial two-level gain declined to one by year 5, whereas subject 010's improvement remained stable. Three of four patients (001, 006, 010) exhibited new EMG or BMCA-defined electrophysiological activity below the injury site, including voluntary rectus abdominis and tibialis anterior activation at 60 months. All patients remained AIS A complete, indicating no conversion to motor incomplete status, but the electrophysiologic findings suggest persistent subclinical reinnervation five years post-grafting [39,40].

Following the initial safety data from the thoracic cohort, the trial was expanded to include cervical patients. The cervical expansion cohort (C4–C7, AIS A/B) demonstrated similar safety with no procedure-related adverse events and consistent graft stability on MRI. Early functional trends suggest a more pronounced motor signal: two patients exhibited new upper-extremity voluntary activity below the injury level, with incremental gains in shoulder abduction and elbow flexion strength persisting through 24 months. Electrophysiological studies confirmed novel motor-evoked potentials traversing the graft site, indicating partial reconstitution of descending pathways. Collectively, these results reinforce the feasibility and biologic activity of NSI-566 transplantation in higher spinal segments, warranting the ongoing multicenter Phase 2 evaluation focused on dose escalation and cervical motor recovery [41].

7.3. NSI-566 conclusion

Five-year follow-up confirms that intraspinal NSI-566 transplantation is surgically feasible, safe, and well tolerated in chronic thoracic SCI, with sustained electrophysiological and pain-related improvements in select patients. Although no subjects regained motor completeness, stable neurological and imaging profiles, and the presence of long-term voluntary motor activation signals justify continued investigation. Future studies will explore higher doses and cervical cohorts to determine whether functional connectivity can be translated into clinically meaningful recovery.

8. ahSC

8.1. ahSC preclinical rationale

Schwann cells (SCs) are the main myelinating cells of the peripheral nervous system and have long been studied for

their potential in treating SCI. After an injury, a process termed schwannosis occurs, where endogenous SCs migrate into the lesion and provide remyelination and trophic support. Preclinical transplantation studies have shown that exogenous SCs can survive in the injured central nervous system, where they preserve host neurons, remyelinate spared axons, and restore conduction in host neurons [42–45]. SCs also play a supportive role by releasing neurotrophic factors, and depositing extracellular matrix proteins like laminin and collagen, and expression of adhesion molecules that promote axonal extension [46,47]. Transplanted SCs integrate into the injury site, forming a "hybrid tissue" composed of SCs, fibroblasts, astrocytic processes, and regenerating axons, that helps stabilize the host-graft integration [47,48]. Building on this, studies in xenograft models have shown that transplanted human SCs can also survive, myelinate axons, and promote regeneration [49]. These studies establish a translational foundation for clinical human trials using ahSCs in both subacute and chronic SCI.

8.2. ahSC clinical trials

8.2.1. Phase I thoracic (NCT01739023)

In a Phase I open label, non-randomized dose escalation trial evaluated the safety and feasibility of IP ahSCs transplantation in six participants with complete thoracic AIS-A SCI 4–7 weeks post-injury. Autologous SCs were expanded ex vivo from sural nerve biopsies obtained within 5–30 days of injury and injected into the lesion epicenter with three escalating doses administered sequentially (5 M, 10 M, and 15 M cells) with standard postoperative rehabilitation. The primary endpoint was safety, assessed by absence of procedure- or cell-related adverse events, neurological deterioration, or MRI-defined structural complications at 1 year. Secondary endpoints included feasibility, stability of neurological level and AIS grade, and emergence of neuropathic pain or spasticity beyond the expected clinical course.

All six participants completed 1-year follow-up with no surgical deaths, infections, or neurological worsening. There were no SAEs attributed to the cells or procedure, and MRI scans showed no tumorigenesis, mass lesion, or new cord damage. Spasticity and neuropathic pain remained within expected post-injury ranges. Peripheral nerve harvest and cell manufacturing were completed successfully in all subjects, demonstrating the feasibility of autologous SC preparation within a subacute window.

Although this study was not powered for efficacy, participants maintained stable neurological function without deterioration. There was no significant motor or sensory decline, and MRI confirmed structural stability of the lesion site. These findings indirectly suggest that ahSC injection into the subacute cord is tolerated and does not exacerbate injury. No volitional motor recovery was reported, but preservation of baseline status supported progression to later-phase testing in chronic SCI [50].

8.2.2. Phase I thoracic/cervical (NCT02354625)

A subsequent Phase I, open label study enrolled eight participants with chronic traumatic SCI (four thoracic, four cervical AIS A-C) at least 12 months post injury [51]. Participants underwent sural nerve harvest and expansion of ahSCs, which were then injected into MRI-defined cystic cavities using a cavity-filling volume approach (up to 2 mL ≈ 200 million cells, with early participants receiving lower capped volumes). Participants completed a 10-month multimodal rehabilitation protocol (pre- and post-transplant) including functional electrical stimulation cycling, body-weight-supported locomotor training, and resistance exercise. The primary endpoint was safety and procedural feasibility. Secondary endpoints included efficacy – neurological function, motor/sensory scores, functional independence measures, and MRI-defined lesion volume change – and assessment of neuropathic pain and spasticity.

All eight participants completed the protocol without procedure-related serious AEs. No tumors, mass lesions, or cord deterioration were detected on MRI at 6–24 months. Minor AEs included urinary tract infections and skin abrasions from training. Routine labs and neuroimaging showed no evidence of systemic toxicity or cell-related complications. Long-term follow-up (over 5 years for some participants) has revealed no delayed AEs.

Although designed for safety, the trial reported preliminary efficacy results. One participant showed a 4-point motor improvement, 6-point sensory gain, and a 1-level neurological improvement. Neurophysiological recordings demonstrated the emergence of motor-evoked potentials and subclinical voluntary EMG activity below the injury level, indicating partial reconnection. MRI findings showed a transient reduction in cyst volume, most notable in cervical cohorts at 6 months. Functional indices (SCIM, SCI-FI) and quality-of-life measures remained stable or improved modestly. Collectively, these findings suggest that ahSC grafts combined with structured rehabilitation may facilitate limited functional recovery even in chronic SCI [51].

8.3. ahSC conclusion

ahSC transplantation has proven safe, feasible, and surgically reproducible across both subacute and chronic SCI. The primary advantage is the autologus nature of the stem cell line mitigates the need for transplant rejection medications. The subacute trial confirmed technical safety and stability without neurological decline, while the chronic study showed durable long-term safety and signs of neurologic gain, including improved motor and sensory scores, emergence of motor evoked potentials, and transient cyst reduction. Together, these findings establish ahSC transplantation as tolerable and procedurally reliable for future controlled trials integrating rehabilitation and neuromodulation to assess efficacy and functional impact.

9. Discussion

Across early-phase IP transplantation trials, spanning more than two decades of staggered and partially overlapping clinical programs (Figure 1), safety findings can be synthesized at the trial level because adverse events are typically reported in categorical terms (e.g., SAE vs. AE; surgical vs.

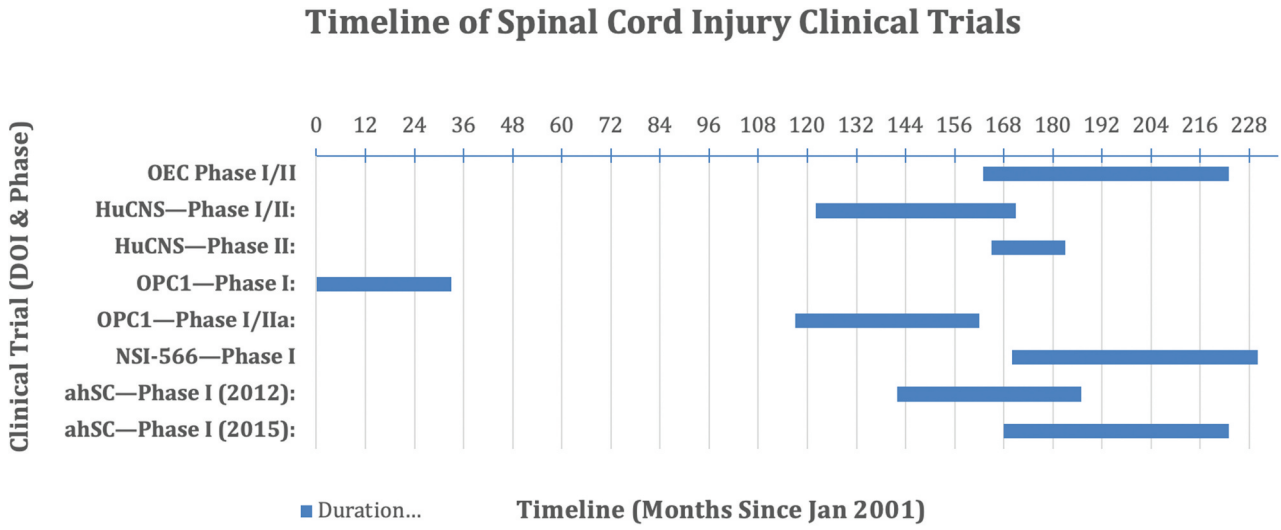

Figure 1. Timeline of intraparenchymal cell transplantation trials in spinal cord injury.

All trials are aligned to a January 2001 baseline (offset = 0). Horizontal position reflects historical sequencing by trial initiation, while bar length reflects total study duration from protocol initiation to completion or last follow-up. Trials are grouped by cell class and distinguish early feasibility studies (OEC, HuCNS-SC) from later lineage-specific products (OPC1, NSI-566, ahSC). Across studies, trial durations typically span multiple years, consistent with the demands of cell manufacturing, surgical delivery, and long-term neurological assessment. More recent lineage-specific programs show comparatively shorter enrollment-to-completion intervals, consistent with increasing procedural standardization and regulatory maturation of intraparenchymal delivery strategies.

immunosuppression vs. other attribution), and the presence/absence of specific high-concern signals (tumor formation, syrinx, progressive neurologic deterioration) is also interpretable (Figure 2). In contrast, functional outcomes are not directly comparable across trials given heterogeneity in instruments, follow-up windows, injury level/severity, chronicity, and control conditions. This functional heterogeneity is a core reason that cross-trial "ranking" is not defensible; instead, the functional figure (Figure 3) should be read as descriptive signal mapping, not comparative efficacy.

9.1. Safety

When trials are collapsed to the study level, no convergent safety signal against the IP delivery platform emerges across OEC, HuCNS-SC, OPC1s, NSI-566, and ahSCs. Across the dose

Cell Class	*Study ID*	*Trial Phase*	*Dose*	*Burden*	*Volume (μL)*	*Immun.*	*SAE Any*	*SAE Cell*	*SAE Proc.*	*SAE Immun.*	*MRI abnorm.*	*Neuro deficit*	*Neuro pain*
OEC	Mackay-Sim et al	I/IIa	12M, 24M, 28M	270, 545, 630	297, 600, 693	0	0	0	0	0	0	0	0
HuCNS-SC	NCT01321333	I/II	20M	4	280	1	1	0	1	0	0	0	0
HuCNS-SC	NCT02163876	II	15M, 30M, 40M	4, 6, 8	210, 420, 560	1	1	0	1	0	0	0	0
HuCNS-SC	NCT02163876	II	40M	8	560	1	1	0	1	1	0	0	0
OPC1	NCT01217008	I	2M	1	NA	1	0	0	0	0	0	0	0
OPC1	NCT02302157	I/IIa	2M, 10M, 20M	1, 1, 2	50, 50, 100	1	1	0	1	1	0	0	0
NSI-566	NCT01772810	I	1.2M	6	600	1	1	0	1	0	0	0	0
ahSC	NCT01739023	I	5M, 10M, 15M	NA	50, 100, 150	0	0	0	1	0	0	0	0
ahSC	NCT02354625	I	~35M *	2-3	<2 mL**	0	1	0	0	0	0	0	0

Figure 2. Safety and feasibility signals across intraparenchymal cell transplantation trial arms.

Trials are shown by cell class, study, and dose cohort, with delivery parameters (dose, injection burden, injection volume, and immunosuppression) and binary safety outcomes. Safety endpoints include the presence of any SAE, attribution of SAEs to the cell product, procedure, or immunosuppression, MRI evidence of tumor or syrinx formation, treatment-related neurologic deficit, and neuropathic pain. Binary values indicate the presence (1) or absence (0) of a given safety signal within each trial arm; no weighting by cohort size was performed.

*For ahSC NCT02354625, the reported dose reflects a range of approximately 23–75 million cells. **This trial employed a cavity-filling injection strategy with a maximum volume capped at 2 mL.

Abbreviations: Immun., immunosuppression; SAE, serious adverse event; Proc., procedure-related; MRI abnorm., MRI evidence of tumor or syrinx formation; Neuro deficit, treatment-related neurologic deterioration; Neuro pain, neuropathic pain.

and delivery intensities represented in the safety chart (Figure 4), including trials using higher cell doses (including >30 M bins) and multi-site injection strategies, there were no consistent reports of tumor formation, syrinx development, new neurological pain, or progressive neurologic decline attributed to the grafted cells. Reported SAEs, when present, were infrequent and most often aligned with (i) surgical exposure/postoperative complications or (ii) immunosuppression-related morbidity, rather than a reproducible toxicity signal from the injected product or the injection maneuver itself.

The pattern in presented in the safety chart (Figure 4) is one of convergence: across cell classes and trial timelines, serious complications do not cluster as a cell-class specific biologic toxicity signal (e.g., late mass lesion/tumor, delayed deterioration). Instead, the events that do appear are largely consistent with the expected risk profile of spinal surgery, SCI related complications, and immunosuppression exposure. This supports the interpretation that IP delivery is a procedurally feasible platform on which future trials can more credibly shift emphasis toward efficacy optimization (dose, targeting, timing, and rehabilitation pairing), while continuing structured surveillance for late-emerging structural complications.

9.2. Efficacy

Across these IP studies, the dominant clinical pattern is one of limited and inconsistent functional improvement rather than dramatic recovery. Neurological gains, when observed, are typically modest and heterogeneous, and do not follow a reproducible trajectory across trials or cell classes. Changes in AIS grade are uncommon, usually isolated to single participants, and often lack clear attribution to the intervention itself. Moreover, AIS conversion functions poorly as a comparative endpoint given its coarse categorical nature, susceptibility to baseline misclassification, and limited sensitivity to domain-specific neurological change. Functional improvements that do emerge tend to be domain-specific rather than global. Sensory changes are reported more frequently than robust motor gains and appear across multiple cell classes, but their magnitude and durability vary widely and are inconsistently linked to treatment parameters. Motor recovery signals are comparatively sparse and fail to reproduce at the trial level, while meaningful gains in independence or ambulation are largely absent. As summarized in Figure 3, these patterns suggest that functional effects, when present, remain circumscribed and do not reliably translate into higher-order functional independence.

The absence of marked recovery across trials likely reflects a convergence of biological and methodological constraints rather than a fundamental limitation of the intraparenchymal delivery platform. Most trials deliberately enrolled participants with complete or near-complete injuries, often AIS A or B, frequently in the chronic phase to avoid confounding spontaneous recovery since established tract disruption and mature glial and fibrotic scarring are known constraints on neurological recovery. Even in subacute trials (OPC1 thoracic and ahSC thoracic), transplantation typically occurs after the primary injury and early secondary injury cascades, at a point when many axons are already irreversibly lost. Under these conditions, the capacity of focal cellular grafts to generate large, measurable neurological gains is inherently constrained.

Trial design further limits the likelihood of detecting large effects. Doses and injection volumes are deliberately conservative, with grafts placed over a narrow rostrocaudal span to prioritize safety, thereby constraining the spatial reach of repair, remyelination, or relay formation. Small sample sizes, heterogeneity in injury level and chronicity, and variable rehabilitation exposure further weaken signal detection. In addition, commonly used outcome measures are relatively coarse and insensitive to modest, domain-specific change. Taken together, the functional results to date are best interpreted as the product of conservative early-phase trial design interacting with advanced

Cell Class	*Study ID*	*Trial Phase*	*Dose*	*Burden*	*Volume*	*Immunosupp.*	*AIS conversion*	*Motor recovery*	*Sensory recovery*	*Independence /ambulation*
OEC	Mackay-Sim et al.	I/IIa	12M, 24M, 28M	270, 545, 630	297, 600, 693	0	0	0	1	0
HuCNS-SC	NCT01321333	I/II	20M	4	280	1	1	0	1	0
HuCNS-SC	NCT02163876	II	15M, 30M, 40M	4, 6, 8	210, 420, 560	1	1	1	1	0
HuCNS-SC	NCT02163876	II	40M	8	560	1	1	1	1	0
OPC1	NCT01217008	I	2 M	1	NA	1	0	0	1	0
OPC1	NCT02302157	I/IIa	2M, 10M, 20M	1, 1, 2	50, 50, 100	1	1	1	1	NA
NSI-566	NCT01772810	I	1.2M	6	600	1	0	1	1	0
ahSC	NCT01739023	I	5M, 10M, 15M	NA	50, 100, 150	0	0	1	1	0
ahSC	NCT02354625	I	~35M	2-3	<2 mL	0	0	0	0	0

Figure 3. Functional outcome signals across intraparenchymal cell transplantation trial arms.

Trials are shown by cell class, study, and dose cohort, with delivery parameters and binary indicators of functional outcomes. Functional domains include AIS grade conversion, motor recovery, sensory recovery, and independence or ambulation. Binary values indicate the presence (1) or absence (0) of a reported signal within each domain, as defined by the original study authors. Outcomes were not weighted by cohort size, and heterogeneity in assessment instruments and follow-up duration precluded direct quantitative comparison across trials.

Cell Class	Cell Origin	Study ID	Trial Phase	Injury Location	Injury Severity	Chronicity	Dose	Injection Burden	Injection volume	Immuno Supp.
OEC	Autologous olfactory ensheathing cells	Mackay-Sim et al., Brain 2005–2008 (Australia, TGA-approved)	I/IIa	thoracic	AIS A	Chronic > 6 months	12M, 24M, 28M	270, 545, 630	297, 600, 693	0
HuCNS-SC	Human fetal CNS derived neural stem cells	NCT01321333	I/II	thoracic	Mixed: AIS A/B	5-24 months	20 M	4	280	1
HuCNS-SC	Human fetal CNS derived neural stem cells	NCT02163876	II	cervical	Mixed: AIS A/B	>4 months chronic	15 M, 30M, 40M	4, 6, 8	210, 420, 560	1
HuCNS-SC	Human fetal CNS derived neural stem cells	NCT02163876	II	cervical	Mixed: AIS A/B	>4 months chronic	40 M	8	560	1
OPC1	Human pluripotent stem cell derived oligodendrocyte progenitor cells	NCT01217008	I	thoracic	AIS A	Acute 7-14 days	2 M	1	NA	1
OPC1	Human pluripotent stem cell derived oligodendrocyte progenitor cells	NCT02302157	I/IIa	cervical	Mixed: AIS A/B	Subacute 21-42 days	2M, 10M, 20M	1	50, 50, 100	1
NSI-566	Human fetal spinal cord derived NSC	NCT01772810	I	thoracic	AIS A	Chronic >1 year	1.2 M	6	600	1
ahSC	Peripheral nerve derived schwann cells	NCT01739023	I	thoracic	AIS A	4-7 weeks	5M, 10M, 15M	NA	50, 100, 150	0
ahSC	peripheral nerve derived schwann cells	NCT02354625	I	mixed cervical/ thoracic	Mixed: AIS A/B/C	chronic >6 months	~35 M (23-75)	2-3 injection	cavity filling <2 mL	0

Figure 4. Overview of intraparenchymal cell-based delivery strategies and injury profiles in early-phase clinical trials for spinal cord injury.

The table summarizes Phase I – II studies across multiple cell classes (OECs, HuCNS-SC, OPC1/LCTOPC, NSI-566, and ahSC), including injury characteristics (anatomical level, baseline AIS grade, and injury chronicity) and key delivery parameters such as administered cell dose (ranges shown where dose-escalation cohorts were used), injection burden, injection volume, and use of immunosuppression. Individual dose cohorts are analyzed separately in outcome heat maps.

9.3. Limitations

Interpretation of safety and functional outcomes across IP transplantation trials is limited by substantial heterogeneity in study design and reporting. Safety events are described using non-uniform terminology, variable seriousness thresholds, and inconsistent attribution categories. Follow-up duration ranges from months to years, reducing sensitivity to late-emerging adverse signals and limiting quantitative comparison. Dose-escalation schemes, injection burdens, and targeting strategies vary widely and are often non-overlapping, precluding formal dose-risk inference.

Functional endpoints are similarly heterogeneous, with differing instruments, inconsistent follow-up windows, and frequent absence of standardized control conditions. As a result, functional outcomes cannot be meaningfully compared across studies and should be interpreted cautiously.

9.4. Synthesis of safety and functional evidence

Despite these limitations, a qualitative safety convergence emerges at the trial level. Across cell classes, IP delivery does not demonstrate recurrent cell-related severe toxicity, supporting an acceptable early-phase safety profile of the delivery platform. SAE, when present, are more often attributable to

surgical exposure or immunosuppression rather than a reproducible biologic toxicity signal.

Functional outcomes do not show comparable convergence. AIS grade conversion is an insensitive endpoint for cross-trial comparison, and the observed neurological gains are modest, heterogeneous, and domain-specific. Functional findings should therefore be interpreted descriptively rather than comparatively.

10. Conclusion

IP stem cell transplantation represents a feasible and consistently safe approach to targeted therapeutic delivery for spinal cord injury across multiple early-phase trials and diverse stem cell platforms, including OECs, HuCNS-SC, OPC1, NSI-566, and ahSCs. Although no study has demonstrated statistically significant motor recovery, several trials report modest sensory improvements, isolated motor gains, or electrophysiologic evidence of conduction below the lesion. Collectively, these findings indicate durable graft survival without tumorigenicity or progressive structural deterioration, supporting continued investigation of IP delivery as a therapeutic platform.[54]

11. Future perspective

Over the next 5–10 years, IP stem-cell transplantation is likely to transition from platform validation toward focused efficacy testing within standardized trial frameworks. Future studies will likely emphasize informed optimization of treatment timing, targeting, dose, and spatial coverage rather than conservative feasibility-driven designs. Expectations for recovery will evolve toward reproducible, domain-specific functional gains, like segmental motor activation, sensory integration, or electrophysiologic conduction.

Combination strategies integrating cellular transplantation with structured rehabilitation, neuromodulation, or biomaterial scaffolds are expected to play a larger role in improving plasticity and functional improvement. Advancements in technology may help future studies better link graft behavior to observed neurological changes. As trials expand, consistent safety, and outcome reporting and longer follow-up will be important to detect delayed AEs and allow more meaningful comparison across studies. IP delivery functioning will become one component of a broader, multimodal approach to spinal cord repair rather than as a standalone curative therapy.

Author contributions

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Karsy M, Hawryluk G. Modern medical management of spinal cord injury. Curr Neurol Neurosci Rep. 2019;19(9):65. doi: 10.1007/s11910-019-0984-1
2. Hachem LD, Ahuja CS, Fehlings MG. Assessment and management of acute spinal cord injury: from point of injury to rehabilitation. J Spinal Cord Med. 2017;40(6):665–675. doi: 10.1080/10790268.2017.1329076
3. Cadotte DW, Fehlings MG. Spinal cord injury: a systematic review of current treatment options. Clin Orthop Relat Res. 2011;469(3):732–741. doi: 10.1007/s11999-010-1674-0
4. Zipser CM, Cragg JJ, Guest JD, et al. Cell-based and stem-cell-based treatments for spinal cord injury: evidence from clinical trials. Lancet Neurol. 2022;21(7):659–670. doi: 10.1016/S1474-4422(21)00464-6
5. Kwon BK, Tetzlaff W, Grauer JN, et al. Pathophysiology and pharmacologic treatment of acute spinal cord injury. Spine J. 2004;4(4):451–464. doi: 10.1016/j.spinee.2003.07.007
6. Sahni V, Kessler JA. Stem cell therapies for spinal cord injury. Nat Rev Neurol. 2010;6(7):363–372. doi: 10.1038/nrneurol.2010.73
7. Boulis NM, Federici T, Glass JD, et al. Translational stem cell therapy for amyotrophic lateral sclerosis. Nat Rev Neurol. 2011;8(3):172–176. doi: 10.1038/nrneurol.2011.191
8. Doi D, Magotani H, Kikuchi T, et al. Pre-clinical study of induced pluripotent stem cell-derived dopaminergic progenitor cells for Parkinson's disease. Nat Commun. 2020;11(1):10 1038 41467–020–17165–. doi: 10.1038/s41467-020-17165-w
9. Chen H-X, Liang F-C, Gu P, et al. Exosomes derived from mesenchymal stem cells repair a Parkinson's disease model by inducing autophagy. Cell Death Dis. 2020;11(4):10 1038 41419–020–2473–2475. doi: 10.1038/s41419-020-2473-5
10. Abraham M, Shalom M, Gold J, et al. Stem cells in the treatment of spinal cord injury: a review of currently registered clinical trials. World Neurosurg. 2024;191:e116–e125. doi: 10.1016/j.wneu.2024.08.074
    •• **Provides the most current registry-based overview of active and completed stem cell trials in SCI, clarifying the contemporary clinical pipeline.**
11. Gabel BC, Curtis EI, Marsala M, et al. A review of stem cell therapy for spinal cord injury: large animal models and the frontier in humans. World Neurosurg. 2017;98:438–443. doi: 10.1016/j.wneu.2016.11.053
12. Bydon M, Qu W, Moinuddin FM, et al. Intrathecal delivery of adipose-derived mesenchymal stem cells in traumatic spinal cord injury: phase I trial. Nat Commun. 2024;15(1):2201. doi: 10.1038/s41467-024-46259-y
13. Upadhyayula PS, Martin JR, Rennert RC, et al. Review of operative considerations in spinal cord stem cell therapy. WJSC. 2021;13(2):168–176. doi: 10.4252/wjsc.v13.i2.168

14. Jin MC, Medress ZA, Azad TD, et al. Stem cell therapies for acute spinal cord injury in humans: a review. Neurosurg Focus. 2019;46 (3):E10. doi: 10.3171/2018.12.FOCUS18602
15. Li Y, Field PM, Raisman G. Repair of adult rat corticospinal tract by transplants of olfactory ensheathing cells. Science. 1997;277 (5334):2000–2002. doi: 10.1126/science.277.5334.2000
16. Ramón-Cueto A, Cordero MI, Santos-Benito FF, et al. Functional recovery of paraplegic rats and motor axon regeneration in their spinal cords by olfactory ensheathing glia. Neuron. 2000;25 (2):425–435. doi: 10.1016/S0896-6273(00)80905-8
17. Radtke C, Akiyama Y, Brokaw J, et al. Remyelination of the nonhuman primate spinal cord by transplantation of H-transferase transgenic adult pig olfactory ensheathing cells. Faseb J. 2004;18 (2):1–18. doi: 10.1096/fj.03-0214fje
18. Féron F, Perry C, Cochrane J, et al. Autologous olfactory ensheathing cell transplantation in human spinal cord injury. Brain. 2005;128 (12):2951–2960. doi: 10.1093/brain/awh657
19. Mackay-Sim A, Feron F, Cochrane J, et al. Autologous olfactory ensheathing cell transplantation in human paraplegia: a 3-year clinical trial. Brain. 2008;131(9):2376–2386. doi: 10.1093/brain/awn173
• **Seminal long-term clinical trial assessing feasibility and outcomes of autologous olfactory ensheathing cell transplantation in humans.**
20. Erceg S, Ronaghi M, Oria M. Transplanted oligodendrocytes and motoneuron progenitors generated from human embryonic stem cells promote locomotor recovery after spinal cord transection. STEM Cells. 2010;28(9):1541–1549. doi: 10.1002/stem.489
21. Harper JM, Krishnan C, Darman JS. Axonal growth of embryonic stem cell-derived motoneurons in vitro and in motoneuron-injured adult rats. Proc Natl Acad Sci USA. 2004;101(18):7123–7128. doi: 10.1073/pnas.0401103101
22. Kerr CL, Letzen BS, Hill CM. Efficient differentiation of human embryonic stem cells into oligodendrocyte progenitors for application in a rat contusion model of spinal cord injury. Int J Neurosci. 2010;120(4):305–313. doi: 10.3109/00207450903585290
23. Nistor GI, Totoiu MO, Haque N, et al. Human embryonic stem cells differentiate into oligodendrocytes in high purity and myelinate after spinal cord transplantation. Glia. 2005;49(3):385–396. doi: 10.1002/glia.20127
24. Cummings BJ, Uchida N, Tamaki SJ, et al. Human neural stem cells differentiate and promote locomotor recovery in spinal cord-injured mice. Proc Natl Acad Sci USA. 2005;102(39):14069–14074. doi: 10.1073/pnas.0507063102
25. Cummings BJ, Uchida N, Tamaki SJ, et al. Human neural stem cell differentiation following transplantation into spinal cord injured mice: association with recovery of locomotor function. Neurol Res. 2006;28(5):474–481. doi: 10.1179/016164106X115116
26. Hooshmand MJ, Sontag CJ, Uchida N, et al. Analysis of host-mediated repair mechanisms after human CNS-stem cell trans- plantation for spinal cord injury: correlation of engraftment with recovery. PLOS ONE. 2009;4(6):e5871. doi: 10.1371/journal.pone.0005871
27. Salazar DL, Uchida N, Hamers FP, et al. Human neural stem cells differentiate and promote locomotor recovery in an early chronic spinal cord injury NOD-scid mouse model. PLOS ONE. 2010;5(8): e12272. doi: 10.1371/journal.pone.0012272
28. Curt A, Hsieh J, Schubert M, et al. The damaged spinal cord is a suitable target for stem cell transplantation. Neurorehabil Neural Repair. 2020;34(8):758–768. doi: 10.1177/1545968320935815
29. Levi AD, Okonkwo DO, Park P, et al. Emerging safety of intramedullary transplantation of human neural stem cells in chronic cervical and thoracic spinal cord injury. Neurosurgery. 2018;82 (4):562–575. doi: 10.1093/neuros/nyx250
30. Levi AD, Anderson KD, Okonkwo DO, et al. Clinical outcomes from a multi-center study of human neural stem cell transplantation in chronic cervical spinal cord injury. J Neurotrauma. 2019;36 (6):891–902. doi: 10.1089/neu.2018.5843
•• **Early multicenter clinical outcomes data demonstrating feasibility and functional trends following human neural stem cell transplantation in chronic cervical SCI.**
31. Priest CA, Manley NC, Denham J, et al. Preclinical safety of human embryonic stem cell-derived oligodendrocyte progenitors supporting clinical trials in spinal cord injury. Regen Med. 2015;10 (8):939–958. doi: 10.2217/rme.15.57
32. Keirstead HS, Nistor G, Bernal G, et al. Human embryonic stem cell-derived oligodendrocyte progenitor cell transplants remyelinate and restore locomotion after spinal cord injury. J Neurosci. 2005;25(19):4694–4705. doi: 10.1523/JNEUROSCI.0311-05.2005
33. Manley NC, Priest CA, Denham J, et al. Human embryonic stem cell-derived oligodendrocyte progenitor cells: preclinical efficacy and safety in cervical spinal cord injury. STEM Cells Transl Med. 2017;6(10):1917–1929. doi: 10.1002/sctm.17-0065
34. Fessler RG, Ehsanian R, Liu CY, et al. A phase 1/2a dose-escalation study of oligodendrocyte progenitor cells in individuals with subacute cervical spinal cord injury. J Neurosurg: Spine. 2022;37 (6):812–820. doi: 10.3171/2022.5.SPINE22167
•• **Key dose-escalation study defining safety and dosing parameters for oligodendrocyte progenitor cell transplantation in subacute cervical SCI.**
35. McKenna SL, Ehsanian R, Liu CY, et al. Ten-year safety of pluripotent stem cell transplantation in acute thoracic spinal cord injury. J Neurosurg: Spine. 2022;37(3):321–330. doi: 10.3171/2021.12.SPINE21622
•• **Rare decade-long safety follow-up supporting long-term tolerability of pluripotent stem cell–derived therapies in SCI.**
36. Van Gorp S, Leerink M, Kakinohana O, et al. Amelioration of motor/sensory dysfunction and spasticity in a rat model of acute lumbar spinal cord injury by human neural stem cell transplantation. STEM Cell Res Ther. 2013;4(3):57. doi: 10.1186/scrt209
37. Lu P, Wang Y, Graham L, et al. Long-distance growth and connectivity of neural stem cells after severe spinal cord injury. Cell. 2012;150(6):1264–1273. doi: 10.1016/j.cell.2012.08.020
38. Rosenzweig ES, Brock JH, Lu P, et al. Restorative effects of human neural stem cell grafts on the primate spinal cord. Nat Med. 2018;24(4):484–490. doi: 10.1038/nm.4502
39. Curtis E, Martin JR, Gabel B, et al. A first-in-human, phase I study of neural stem cell transplantation for chronic spinal cord injury. Cell STEM Cell. 2018;22(6):941–950.e6. doi: 10.1016/j.stem.2018.05.014
•• **First-in-human trial establishing procedural safety and feasibility of neural stem cell transplantation in chronic SCI.**
40. Martin JR, Cleary D, Abraham ME, et al. Long-term clinical and safety outcomes from a single-site phase 1 study of neural stem cell transplantation for chronic thoracic spinal cord injury. Cell Rep Med. 2024;5(12):101841. doi: 10.1016/j.xcrm.2024.101841
41. Abraham ME, Martin J, Seaton M, et al. 2018 clinical and safety outcomes from a phase I study of neural stem cell transplantation for chronic cervical spinal cord injury. Neurosurgery. 2025;71 (Supplement_1):245–245. doi: 10.1227/neu.0000000000003360_2018
• **Updated phase I human data extending safety and durability outcomes of neural stem cell transplantation in chronic cervical SCI.**
42. Barakat DJ, Gaglani SM, Neravetla SR, et al. Survival, integration, and axon growth support of glia transplanted into the chronically contused spinal cord. Cell Transpl. 2005;14(4):225–240. doi: 10.3727/000000005783983106
43. Pearse DD, Sanchez AR, Pereira FC, et al. Transplantation of Schwann cells and/or olfactory ensheathing glia into the contused spinal cord: survival, migration, axon association, and functional recovery. Glia. 2007;55(9):976–1000. doi: 10.1002/glia.20490
44. Takami T, Oudega M, Bates ML, et al. Schwann cell but not olfactory ensheathing glia transplants improve hindlimb locomotor performance in the moderately contused adult rat thoracic spinal cord. J Neurosci. 2002;22(15):6670–6681. doi: 10.1523/JNEUROSCI.22-15-06670.2002
45. Pearse DD, Pereira FC, Marcillo AE, et al. cAMP and Schwann cells promote axonal growth and functional recovery after spinal cord injury. Nat Med. 2004;10(6):610–616. doi: 10.1038/nm1056

46. Toyota B, Carbonetto S, David S. A dual laminin/collagen receptor acts in peripheral nerve regeneration. Proc Natl Acad Sci USA. 1990;87(4):1319–1322. doi: 10.1073/pnas.87.4.1319
47. Schaal SM, Kitay BM, Cho KS, et al. Schwann cell transplantation improves reticulospinal axon growth and forelimb strength after severe cervical spinal cord contusion. Cell Transpl. 2007;16 (3):207–228. doi: 10.3727/000000007783464768
48. Guest JD, Hesse D, Schnell L, et al. Influence of IN-1 antibody and acidic FGF-fibrin glue on the response of injured corticospinal tract axons to human Schwann cell grafts. J Neurosci Res. 1997;50 (5):888–905. doi: 10.1002/(SICI)1097-4547(19971201)50:5<888::AID-JNR24>3.0.CO;2-W
49. Hill CE, Moon LDF, Wood PM, et al. Labeled Schwann cell transplantation: cell loss, host Schwann cell replacement, and strategies to enhance survival. Glia. 2006;53(3):338–343. doi: 10.1002/glia.20287
50. Anderson KD, Guest JD, Dietrich WD, et al. Safety of autologous human Schwann cell transplantation in subacute thoracic spinal cord injury. J Neurotrauma. 2017;34(21):2950–2963. doi: 10.1089/neu.2016.4895
51. Gant KL, Guest JD, Palermo AE, et al. Phase 1 safety trial of autologous human Schwann cell transplantation in chronic spinal cord injury. J Neurotrauma. 2022;39(3–4):285–299. doi: 10.1089/neu.2020.7590
• **Phase I trial demonstrating feasibility and safety of autologous Schwann cell transplantation in chronic SCI.**