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Stem Cell–Based Therapies for Spinal Cord Injury: Biology, Evidence, Clinical Status, and Future Directions

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ABSTRACT

Spinal cord injury (SCI) causes permanent neurological disability through primary mechanical damage followed by secondary cascades involving inflammation, demyelination, vascular disruption, and glial scarring. Because standard care rarely restores lost neural circuitry, stem cell–based therapies have emerged as promising regenerative strategies. This review summarizes the biological rationale, major cell sources, mechanisms of action, preclinical evidence, clinical status, and future directions of stem cell therapy for SCI. Cell platforms discussed include embryonic stem cell-derived oligodendrocyte progenitor cells, induced pluripotent stem cell-derived neural stem/progenitor cells, mesenchymal stromal/stem cells, Schwann cells, and olfactory ensheathing cells. Across preclinical models, these therapies demonstrate neuroprotection, immunomodulation, remyelination, trophic support, and, in selected platforms, relay-like circuit reconstruction. Early clinical studies generally support short-term feasibility and acceptable safety, but efficacy signals remain heterogeneous and are limited by small cohorts, nonrandomized designs, variable rehabilitation exposure, and inconsistent manufacturing and delivery protocols. Emerging advances include combinatorial strategies integrating cells with biomaterials, extracellular matrix modulation, neuromodulation, and cell-free secretome or extracellular vesicle platforms. Overall, stem cell therapy for SCI is biologically compelling but not yet definitively efficacy-established. Progress toward clinical translation will require rigorous manufacturing, harmonized trial design, structured rehabilitation, mechanistic biomarkers, and long-term safety surveillance.

Keywords: Spinal cord injury; Stem cell therapy; Mesenchymal stromal cells; Induced pluripotent stem cells; Regenerative medicine.

INTRODUCTION

Spinal cord injury (SCI) causes lifelong neurological deficits and a range of secondary complications. Beyond the initial mechanical insult, secondary processes including ischemia, excitotoxicity, inflammation, demyelination, and glial scarring further hinder tissue repair and functional recovery. Standard clinical care, such as acute decompression, hemodynamic

stabilization, complication management, and rehabilitation, can improve outcomes but rarely restores full neurological function.[1-3] Stem cell–based therapies offer complementary strategies by promoting neuroprotection, remyelination, neuronal and glial replacement, immune modulation, and microenvironment remodeling.[4,5] This review summarizes the biological rationale, preclinical and clinical evidence, delivery considerations, safety and regulatory requirements, and emerging directions in stem cell therapy for SCI.

LITERATURE REVIEW

PATHOPHYSIOLOGY OF SCI AND RATIONALE FOR CELL THERAPY

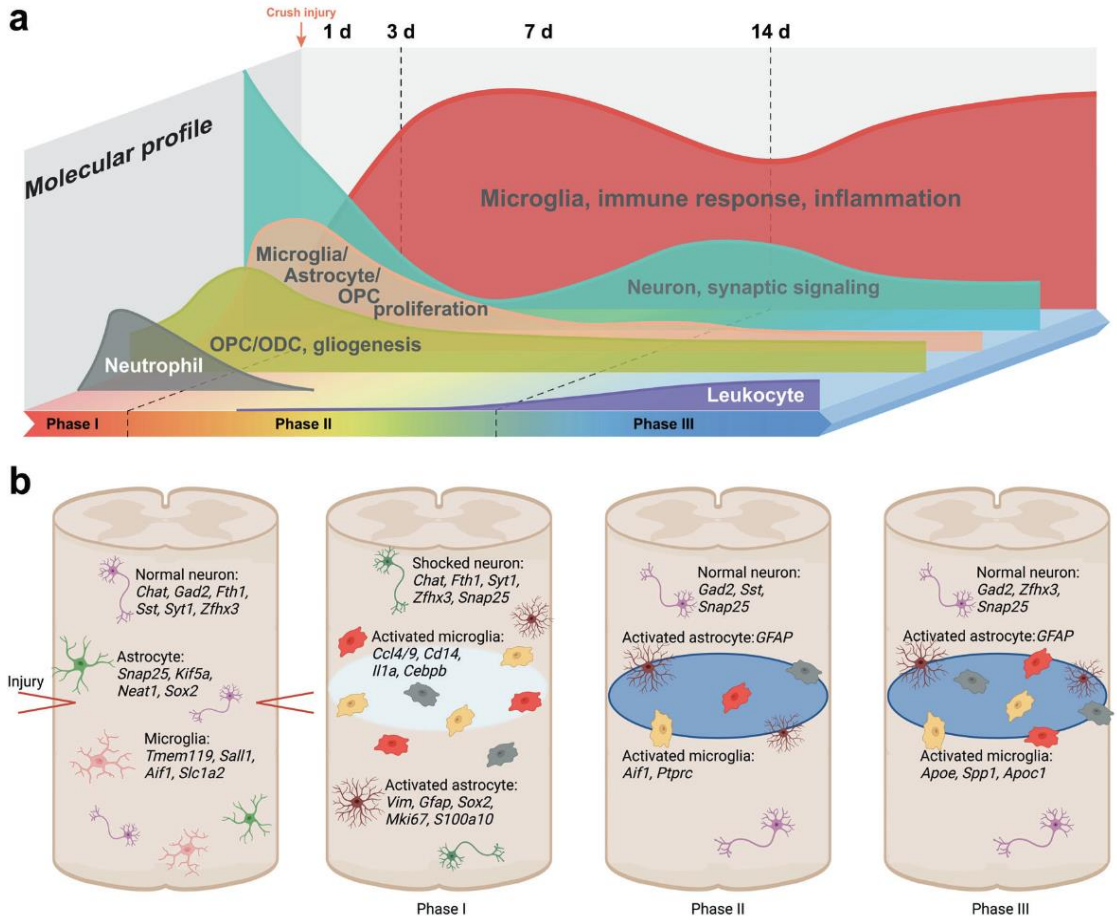


Figure 1. Schematic illustration of secondary injury in molecular (a) and cellular (b) level [6]

Secondary injury and barriers to regeneration

Following primary trauma in SCI, a destructive secondary cascade unfolds, including edema, oxidative stress, blood-spinal cord barrier disruption, leukocyte infiltration, and apoptosis or necrosis of neurons and oligodendrocytes. [6,7] As illustrated in Figure 1, these secondary injury processes evolve dynamically across molecular and cellular levels, with temporally shifting inflammatory, glial, and neuronal responses that contribute to progressive tissue damage after the initial insult. These processes enlarge the lesion, worsen demyelination, impair axonal conduction, and amplify neurological dysfunction.[6,8] Concurrently, the regenerative environment becomes strongly inhibitory after injury.[9,10] Myelin-associated inhibitors such as Nogo-A, MAG, and OMgp restrict axonal extension, while reactive astrocytes and associated stromal elements form a CSPG-rich glial scar that limits axon penetration and synaptic integration.[9-11] In chronic SCI,

cystic cavitation and dense astroglial/fibrotic interfaces create additional structural discontinuities that further impede regeneration.[10,11] Taken together, these mechanisms explain why spontaneous recovery is limited and why regenerative strategies must address both cell loss and the hostile lesion microenvironment.[6,8]

Targetable mechanisms with cell therapy

Cell-based therapies for SCI provide multimodal effects that include paracrine neuroprotection, immune modulation, support of remyelination, and, in selected platforms, structural repair. [4,12,13] In Figure 2, the post-injury spinal cord environment is shaped by interaction of inflammatory, vascular, glial, and extracellular matrix components, which cell-based therapies may target for reconstruction. Paracrine and immunomodulatory signaling, not lasting engraftment, may provide most of the therapeutic effect from MSC-based therapies.[12,14] Transplanted MSCs, NS/PCs, and iPSC-derived progenitors improve neurotrophic signaling, minimize inflammatory damage, and reduce apoptosis .[12,13] Schwann cells, oligodendrocyte progenitor cells, and iPSC-derived oligodendroglial-lineage products may increase axonal conduction and remyelination.[5,13] Preclinically, NS/PCs and chosen pluripotent stem cell-derived neuronal grafts can stretch axons, integrate with host tissue, and create relays across lesion sites.[13,15] Cells can also promote reparative macrophage polarization, stabilize the vascular and blood–spinal cord barrier, and alter inhibitory extracellular matrix signaling after injury. [12,14] In difficult lesion situations, chondroitinase ABC with cell transplantation may increase graft migration, axonal penetration, and functional recovery.[16] Thus, cell therapy in SCI is based on a platform strategy that includes neuroprotection, remyelination, circuit restoration, and microenvironmental modification. [4,13]

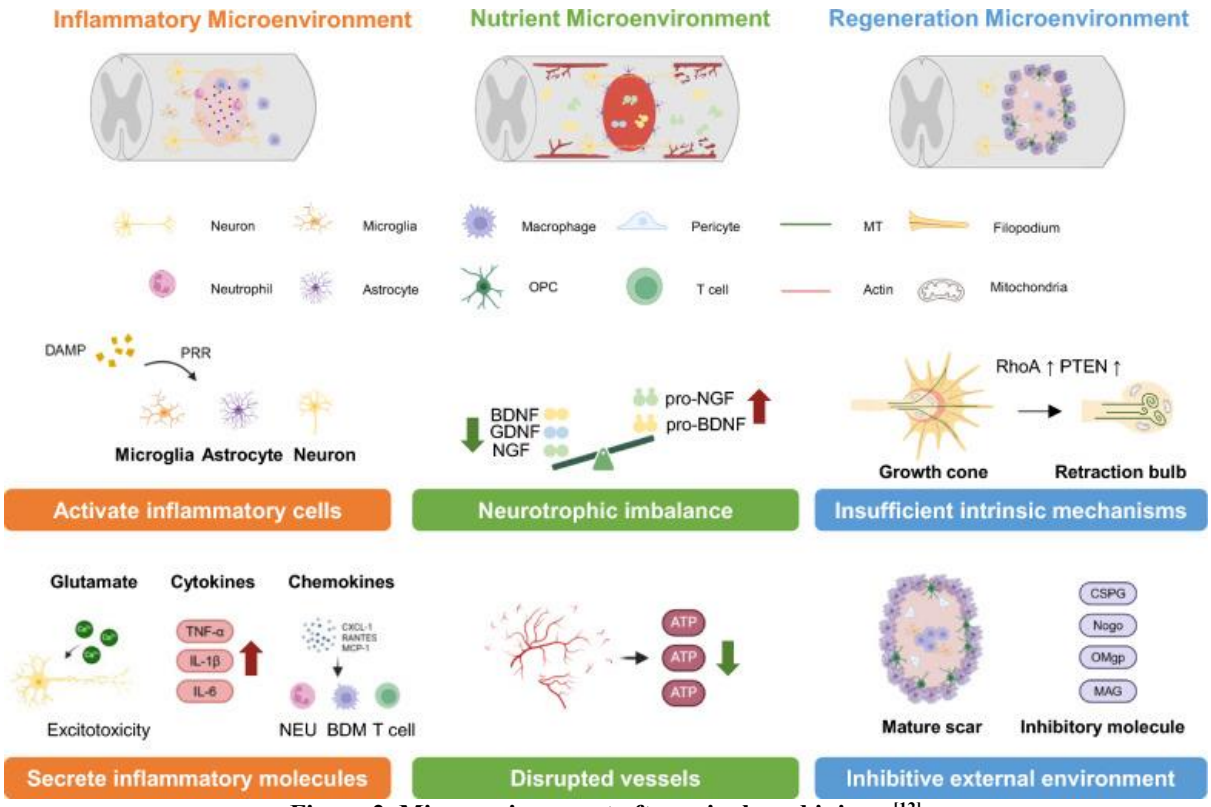


Figure 2. Microenvironment after spinal cord injury [12]

CELL SOURCES, PROPERTIES, AND MANUFACTURING

Embryonic stem cell (ESC)–derived products

ESCs are pluripotent, with unlimited self-renewal and the capacity to differentiate into any somatic lineage, making them attractive for standardized and scalable manufacturing.[5,17] ESCs can be directed into specific neural lineages, such as oligodendrocyte-lineage products, making them interesting for remyelination-focused SCI techniques.[4,5] Controlled differentiation procedures and standardized master cell banks may increase batch uniformity, quality control, and translational reproducibility.[17] Due to embryonic source, ESC-derived therapies create ethical difficulties despite their benefits.[5] Since most ESC-derived products are allogeneic, immunogenicity and transient immunosuppression remain translational concerns.[4,17] If undifferentiated pluripotent cells remain in the product, tumorigenicity is a major safety risk.[17] Instead of differentiation alone as a safety guarantee, ESC-derived clinical products require strict purification, release testing, and long-term surveillance.[5,17]

Induced Pluripotent Stem Cell (iPSCs)–Derived Ns/Pcs

iPSCs generate pluripotent cells from adult somatic tissues, supporting autologous and allogeneic therapies. [18,19] Figure 3 shows that diverse transplanted cell types can have complimentary therapeutic benefits following spinal cord damage, with NS/PCs being best suited to replace tissue and repair structures and provide regenerative support. HLA-matched haplobanks, which reduce immunologic mismatch and increase off-the-shelf access, are a translational benefit of iPSC platforms.[19] Avoiding embryonic tissue procurement makes iPSCs more ethical and allow for international adoption.[18] They also aid illness modelling, lineage optimisation, and advanced manufacturing pipelines.[17,18] However, genetic anomalies, variable differentiation efficiency, and production timetables that may conflict with the subacute SCI intervention window remain problems for iPSC-derived NS/PCs.[13,18] Genomic screening, tumorigenicity tests, potency assays, and tight manufacturing and release standards are essential to clinical translation of iPSC-derived products.[13,17]

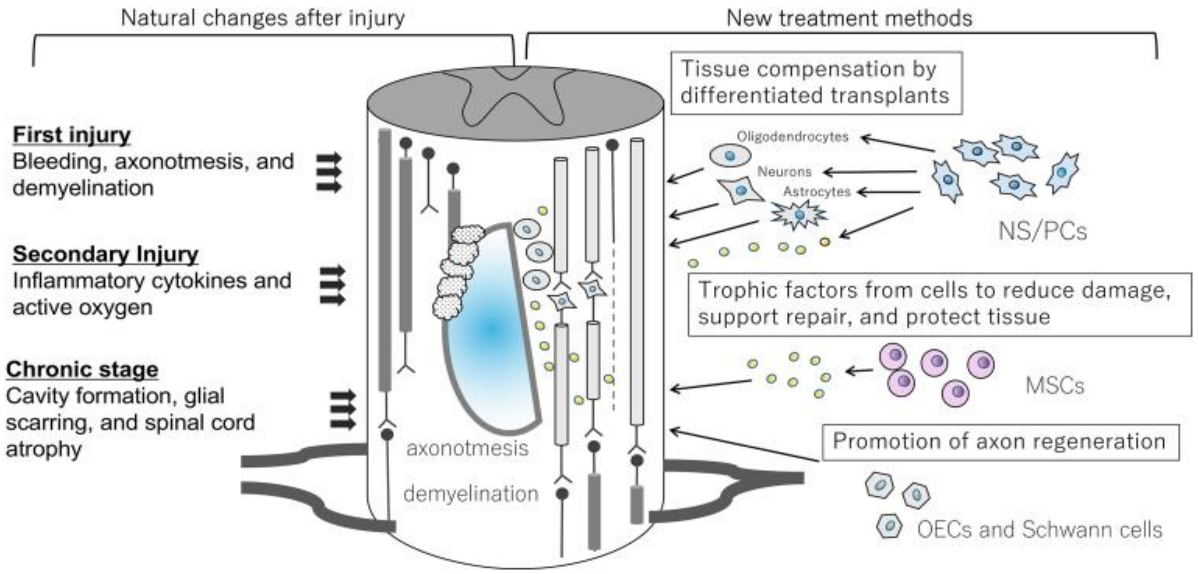


Figure 3. Therapeutic effects from different cell types transplantations in spinal cord injury [18]

Mesenchymal stromal/stem cells (MSCs)

MSCs are widely studied in SCI because they are relatively accessible, have extensive clinical experience across regenerative medicine, and can be obtained from bone marrow, adipose tissue, and

perinatal tissues such as umbilical cord.[4,5] These tissue sources differ in proliferation profile, secretory behavior, immunomodulatory characteristics, and manufacturing scalability.[12] In SCI, MSCs appear to act predominantly through paracrine mechanisms, including secretion of anti-inflammatory cytokines, growth factors, and extracellular vesicles that support neuroprotection, angiogenesis, tissue preservation, and modulation of the secondary injury microenvironment.[12,14] Their relatively low tumorigenic risk and favorable safety profile make them attractive for minimally invasive delivery and clinical-scale manufacturing.[4,5] However, MSCs have limited capacity for direct neuronal replacement, and donor-related variability, source heterogeneity, and product inconsistency can all affect potency and reproducibility.[4,12] Accordingly, stronger characterization standards and mechanism-based potency assays are needed if MSC products are to move from "promising" to reliably comparable clinical platforms.[12,17]

Neural stem/progenitor cells (NS/PCs, fetal or pluripotent-derived)

NS/PCs from foetal tissue or pluripotent stem cells are fundamentally neuroectodermal and can differentiate into neurones, oligodendrocytes, and astrocytes, offering them promising options for SCI-related cellular loss and demyelination.[4,13] NS/PC transplants can survive, move, and assume region-appropriate phenotypes in the damaged cord, according to preclinical investigations.[13] Axonal extension, synaptic integration, and relay-like circuit creation have also been linked to functional improvement in preclinical platforms, depending on graft type, time, and host environment.[13,15] NS/PCs may assist the lesion microenvironment with trophic and immunomodulatory support in addition to structural repair.[13] Combinatorial techniques using biomaterials, growth-promoting cues, or rehabilitation may improve graft survival and integration, depending on the host environment.[13,20] Many clinical NS/PC products are allogeneic, therefore immunological management and longitudinal surveillance are essential to translation.[17,18] Timing, immunological management, product quality, and follow-up are essential for long-term integration and recovery.[13,18]

Schwann cells and olfactory ensheathing cells (OECs)

OECs and Schwann cells are suitable for SCI repair since they are glial populations with innate regenerative characteristics.[21,22] Axonal regeneration, remyelination, and neurotrophic support in damaged spinal cord tissue are supported by Schwann cells.[22] OECs may direct axons across damage surfaces and promote a more favorable repair environment through neuroprotective and immunomodulatory actions.[21,23] Because harvesting, expansion, purity, and transplantation processes vary between investigations, preclinical and clinical outcomes vary.[4,22,23] Autologous Schwann cell procurement may cause donor-site morbidity and logistical issues.[22] Tissue-source variability, contamination risk, and inconsistent phenotypic characterisation hamper OEC isolation.[21,23] Due to poor controlled evidence and unstandardized methodologies, OEC clinical translation is sluggish.[23] Standardized manufacturing, rigorous phenotypic validation, and harmonized trial design are needed before these glial cell platforms may be clinically viable.[4,22]

GMP manufacturing and quality

Successful clinical translation of cell-based SCI treatments requires rigorous product characterisation, release testing, and mechanism-aligned potency assessment.[13,17] Before clinical usage, identity, purity, contamination, and differentiation stability must be verified.[17] Release characteristics including viability, sterility, endotoxin burden, and mycoplasma status affect safety and repeatability.[5,17] Potency assays should reflect the expected

mechanism of action, not only be lab checks.[17] Potency testing should highlight lineage fidelity and meaningful functional differentiation for pluripotent stem cell-derived brain progenitors or oligodendrocyte-lineage products.[13,17] Potency testing for MSC-based products should emphasize trophic and immunomodulatory function.[12] Genetic stability and tumorigenicity are key considerations for ESC- and iPSC-based therapies, therefore remnant undifferentiated cells must be eliminated, differentiation controlled, and long-term monitoring are necessary.[5,17] Standardized cryopreservation, thawing, transport, and bedside handling are scientifically crucial because inconsistent handling can turn a "good" made product into a bad delivered product.[17] HLA-matched iPSC banking shows how manufacturing strategy and immunologic planning increasingly overlap in clinical-grade product development.[17,19]

MECHANISMS OF ACTION

Cell-based therapies in SCI exert benefits through both paracrine signaling and structural repair.[4,13] Transplanted cells such as MSCs and neural progenitors can secrete neurotrophic and immunomodulatory factors, including BDNF, GDNF, NT-3, VEGF, IGF-1, and anti-inflammatory mediators that support neuronal survival, angiogenesis, and attenuation of secondary injury.[12,13] Extracellular vesicles and exosomes are also thought to participate in intercellular communication within the injured microenvironment, particularly in MSC-based approaches.[12] Remyelination-oriented approaches using oligodendrocyte-lineage cells or Schwann cells may improve axonal conduction and circuit stability, although the degree of functional translation depends on cell type and lesion context.[13,22] Pluripotent stem cell-derived neural progenitors have also shown preclinical capacity to extend axons, establish synaptic connections, and contribute to relay formation across lesion sites.[13,15] MSCs additionally modulate the lesion environment by reducing pro-inflammatory signaling and promoting more reparative immune phenotypes.[12] Combination strategies that incorporate extracellular matrix remodeling, such as CSPG-directed approaches, may further enhance graft migration, axonal penetration, and neural reconnection.[16] Overall, these mechanisms support cell therapy as a multimodal platform for neuroprotection, remyelination, microenvironmental modulation, and, in selected settings, circuit reconstruction.[4,13]

PRECLINICAL EVIDENCE

Preclinical studies in rodent SCI models consistently show functional improvement after transplantation of ESC- and iPSC-derived neural cells, MSCs, Schwann cells, and OECs, but reproducibility is stronger at the broad trend level than exact effect size.[4,13] Locomotor scores, electrophysiological conduction, lesion burden, tissue sparing, axonal density, and remyelination or white matter preservation are reported advantages.[13,22] The extent of effect varies greatly across studies depending on damage model, severity, cell source, manufacturing technique, transplantation timing, and additional therapy.[4,20] Acute-to-subacute settings are better for graft survival and integration than chronic scarred lesions, therefore transplantation timing is crucial.[13,20] Chronic-stage repair is possible, but it often needs combinatorial techniques to target the resistant lesion microenvironment.[16,20] Biomaterial scaffolds, trophic support, and rehabilitation may improve graft survival, neurite extension, and activity-dependent plasticity.[13,20]

Illustrative studies

Recent preclinical work has strengthened the argument that some grafts can contribute to circuit reconstruction rather than neuroprotection alone.[13,15] Human iPSC- and ESC-derived pyramidal neuronal precursors have shown safety and efficacy signals in rat SCI models, including graft

survival, axonal projection, and functional improvement.[15] MSC-based strategies appear to complement this paradigm by limiting inflammatory injury, preserving tissue, and supporting angiogenic and trophic repair rather than replacing complex neural circuitry directly.[12] These mechanistic differences matter, because they suggest that "cell therapy" in SCI is not one intervention class but several biologically distinct platforms with different strengths and limitations.[4,13] Together, these findings highlight the importance of cell type, delivery strategy, timing, and microenvironmental support in optimizing regenerative outcomes after SCI.[13,20]

CLINICAL EVIDENCE

As summarized in Table 1, the current clinical landscape of stem cell–based therapies for SCI includes multiple platforms, such as ESC-derived OPCs, iPSC-derived neural progenitors, MSCs, Schwann cells, and OECs, with substantial variation in trial phase, route of administration, dosing strategy, and reported efficacy signals.

ESC-derived OPCs (e.g., AST-OPC1)

A multicenter, open-label Phase I/IIa dose-escalation research in subacute cervical traumatic SCI investigated embryonic stem cell-derived oligodendrocyte progenitor cells for clinical translation.[24] Between 21 and 42 days following injury, 25 subjects with C4-7 AIS A/B injuries received a single intraparenchymal dosage of 2×10^6, 1×10^7, or 2×10^7 cells.[24] Low-dose tacrolimus was given until day 60 to meet the immunologic needs of an allogeneic pluripotent-derived product.[24] All patients suffered adverse events at 1-year follow-up, but most were expected SCI problems rather than product-specific toxicities.[24] Two grade 3 significant adverse events were attributed to injections or temporary immunosuppression.[24] MRI showed no growing mass, injection-related spinal cord injury, inflammatory lesions, or ventricular masses.[24] At 1 year, 21 of 22 intention-to-treat patients recovered at least one neurological level on one side.[24] Because the trial was limited, uncontrolled, and not designed for conclusive benefit assessment, these data support procedural feasibility and short-term safety but not efficacy.[18,24]

iPSC-derived NS/PCs

Early-phase clinical programs in Japan, particularly those associated with the Keio group, are evaluating iPSC-derived NS/PCs for SCI.[18] These programs place strong emphasis on genomic screening, tumorigenicity assessment, and product-quality control before transplantation.[17,18] At present, the human literature for iPSC-derived SCI therapy remains predominantly early phase and safety focused.[18] Accordingly, robust efficacy data have not yet been established, and it would be premature to present this platform as clinically validated.[4,18] Even so, iPSC-derived NS/PCs remain among the most promising platforms because they combine strong mechanistic support from preclinical studies with increasingly sophisticated manufacturing and release criteria.[13,17,18] HLA-matched banking strategies further strengthen the translational appeal of this platform by improving the feasibility of semi-universal allogeneic products.[17,19]

Mesenchymal stromal/stem cells

MSCs from bone marrow, umbilical cord, or adipose tissue are the most investigated SCI cell therapy platform.[4,18] Most clinical investigations use intrathecal delivery, however intraparenchymal and intravenous methods have been investigated.[4,18] Recent clinical evidence supports a good short-term safety profile, although efficacy signals are inconsistent.[4,18] Ten patients with traumatic SCI and AIS grade A or B received intrathecal autologous adipose-derived MSCs in the 2024 CELLTOP Phase I study.[25] Manufacturing and delivery were effective in all patients, and headache and musculoskeletal pain were the most common adverse effects.[25] Nothing significant occurred. From injection to final

follow-up, seven patients improved AIS grade.[25] Without a control arm, the neurological improvements cannot be attributed to the cell product alone.[4,25] Broader evaluations also find MSC therapy safe and viable, but variables in source tissue, dose, route, timing, rehabilitation, and outcome assessment restrict judgments concerning benefit size and durability. [4,18]

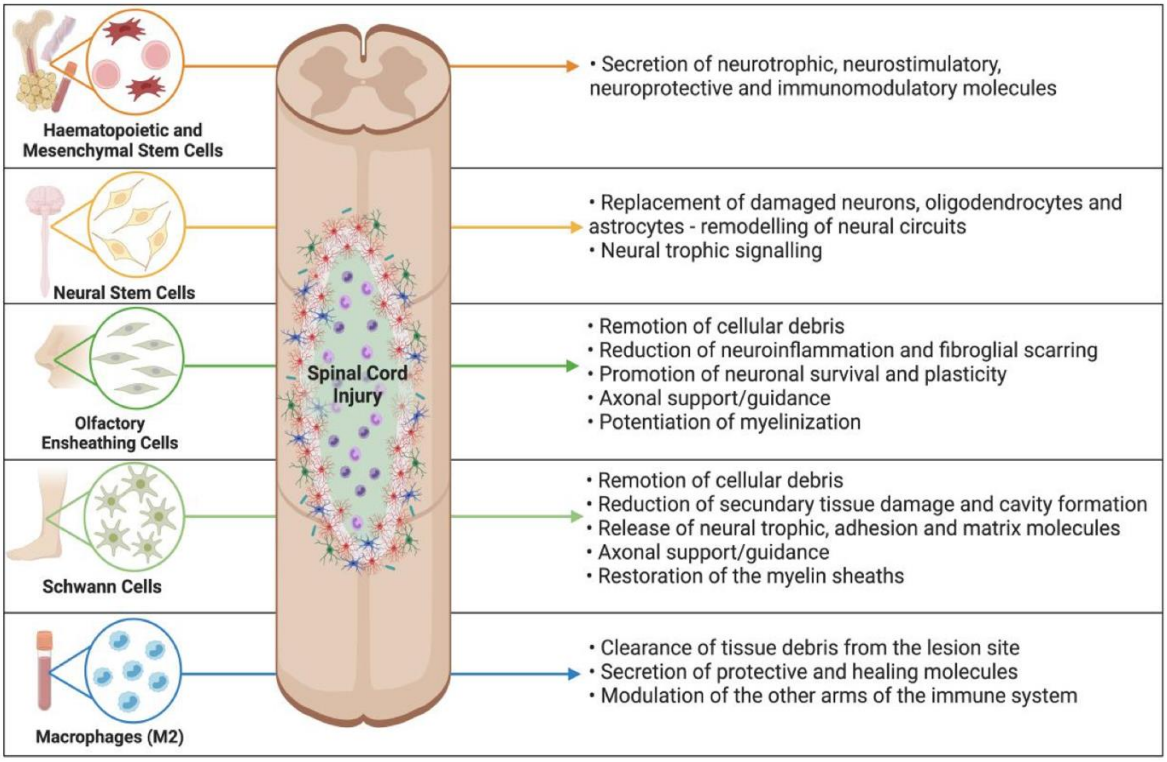


Figure 4. Therapeutic potential of various cell types [4]

Neural stem/progenitor cells (fetal or pluripotent-derived)

Early-phase clinical studies using fetal-derived or pluripotent stem cell-derived neural progenitors have demonstrated procedural feasibility and acceptable short-term safety in small SCI cohorts. [4,18] As illustrated in Figure 4, neural stem/progenitor cells are part of a broader regenerative cell-therapy landscape in SCI, with therapeutic potential that includes neural cell replacement, neural circuit remodeling, and trophic support within the injured spinal cord microenvironment. These products are typically delivered intraparenchymally into or around the lesion, with follow-up based on neurological examination and imaging surveillance.[4,18] Reported functional gains have been variable and generally modest.[4] Interpretation is further complicated by small sample size, open-label design, inconsistent rehabilitation exposure, and the absence of controlled comparators in much of the literature.[4,18] For reviewer-proof wording, it is more accurate to describe this field as "promising but not yet efficacy-established" rather than "clinically effective".[4,18] Future studies will need harmonized outcomes, tighter trial control, and structured neurorehabilitation frameworks to determine true therapeutic value more definitively.[13,18]

Schwann cells and OECs

Autologous Schwann cell transplantation and OEC grafting have been evaluated in small Phase I/II clinical studies across multiple centers.[4,22,23] Current evidence supports overall feasibility and an acceptable short-term safety profile.[4,22] Therapeutic efficacy, however, remains

inconsistent and not yet proven in a way that would justify routine clinical adoption.[4,23] For Schwann cells, limitations include variability in harvest technique, expansion, survival after transplantation, and host-graft integration.[22] For OECs, recent reviews explicitly emphasize stagnation in clinical translation because of persistent issues with cell purity, heterogeneity, protocol variability, and insufficient controlled evidence.[23] These observations support the need for standardized manufacturing, delivery protocols, and better-controlled multicenter studies before either glial cell-based strategy can be considered an established clinical option.[4,22,23]

DELIVERY, DOSING, AND PERIOPERATIVE MANAGEMENT

Routes and dosing

The route of cell administration in spinal cord injury critically influences both therapeutic effect and procedural risk.[4,18] Intraparenchymal transplantation places cells directly into or adjacent to Cithe lesion and is therefore the most suitable strategy when the intended mechanism involves local remyelination, relay formation, or tissue integration, but it requires spinal surgery and carries risks such as hemorrhage, additional cord manipulation, and procedure-related morbidity.[4,24] Intrathecal delivery is less invasive and has been used most commonly for MSC-based products, where the expected effect is mainly trophic and immunomodulatory rather than direct structural replacement[4,25] Intravenous infusion is technically the simplest approach, but a substantial fraction of administered cells is distributed outside the spinal cord, so any benefit is generally thought to reflect systemic or paracrine signaling rather than durable local engraftment.[4,18]

Cell dose is also platform-dependent.[4,18] In the LCTOPC1/AST-OPC1 dose-escalation study, participants with subacute cervical SCI received a single intraparenchymal administration of 2×10^6, 1×10^7, or 2×10^7 cells between 21 and 42 days after injury.[24] By contrast, intrathecal MSC trials generally use doses in the 10^7 to 10^8 cell range per treatment, sometimes with repeat administration depending on the protocol and product type.[18,25] Because potency may vary by cell source, viability after thaw, manufacturing process, and route of administration, dose should not be interpreted as a simple cross-platform numeric equivalent.[4,17]

Immunosuppression and rehabilitation

Allogeneic ESC- and iPSC-derived neural products generally require systemic immunosuppression to reduce graft rejection risk, although the optimal regimen and duration remain product-specific rather than standardized across the field.[17,18,24] In the LCTOPC1 study, patients received low-dose tacrolimus until day 60, showing that some pluripotent-derived neural cell regimens use immunosuppression.[24] Even though early SCI trials have not reported treatment-related neoplasia, pluripotent-derived products raise concerns about delayed immune rejection, ectopic tissue formation, and tumorigenicity, making long-term surveillance crucial.[17,18]

Many MSC-based therapies do not require systemic immunosuppression since these cells are immunomodulatory and low in immunogenicity.[4,25] However, repeated dosage, allogeneic products, and inflammatory host settings warrant cautious monitoring for infusion-related or delayed immune reactions.[4,18] Because activity-dependent plasticity may affect graft maturation, host-graft connectivity, and recovery of trained functions, rehabilitation is a key determinant of functional outcome after transplantation.[20,26] Task-specific and rigorous rehabilitation is biologically feasible as a synergistic partner to cell therapy, although its timing, intensity, and content vary between studies.[18,20,26]

COMBINATORIAL AND NEXT-GENERATION STRATEGIES

Cell transplantation alone may be limited by poor graft survival, limited retention, hostile

extracellular signaling, and inadequate long-distance axonal organization after SCI.[20,27] Figure 5 shows how hydrogels, aligned conduits, and extracellular matrix-mimetic materials can increase cell retention, physical guiding, and lesion microenvironment modulation to promote regeneration.[27] Due to their potential to affect activity-dependent circuit refinement after grafting, neuromodulatory and regenerative-rehabilitation techniques are becoming complimentary.[20,26,27] Thus, a multimodal platform that integrates cells with biomaterials, rehabilitation, and other targeted pro-regenerative therapies is the most promising future direction.[18,27]

Next-generation stem-cell platforms are also being developed using cell-free methods including extracellular vesicles and secretome-based products [4,18]. These approaches to SCI may replicate some of the paracrine effect of live-cell therapy while avoiding some issues about uncontrolled proliferation or long-term graft permanence, but they are still in development.[18]

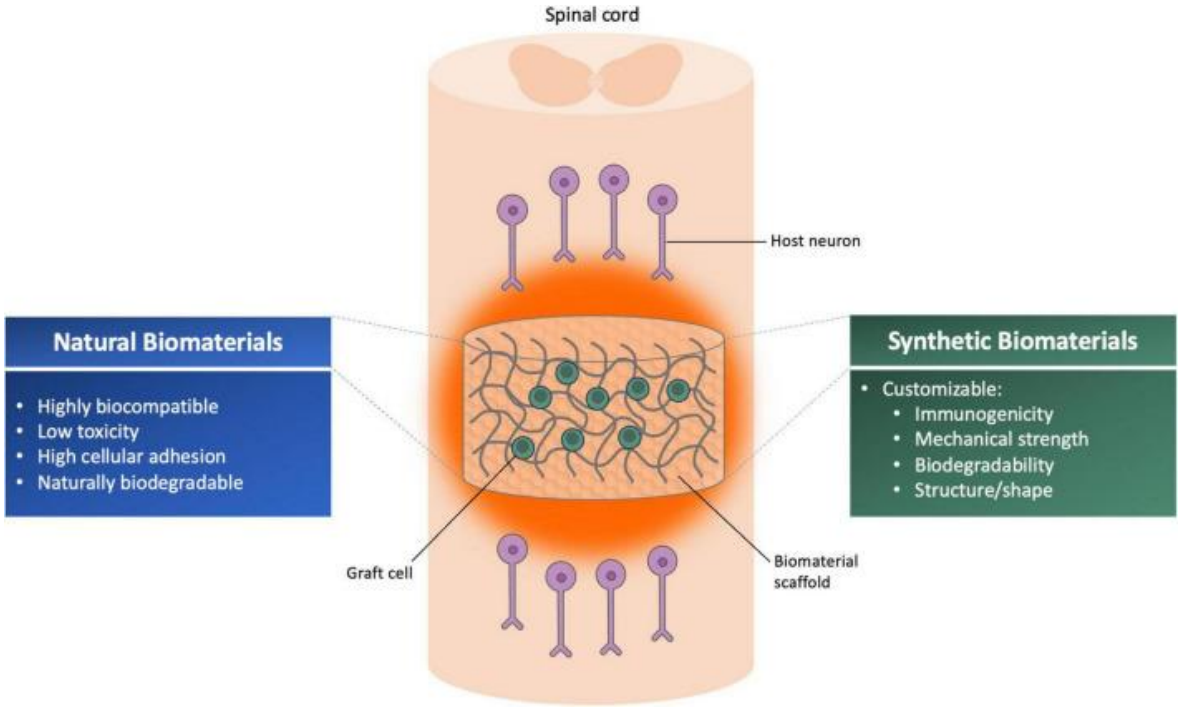


Figure 5. Combination of biomaterial scaffolds with cell transplantation therapy [27]

SAFETY, ETHICS, AND REGULATORY CONSIDERATIONS

Cell therapy for SCI carries both procedural risks and product-specific biological risks.[5,18] Even with good safety in early-phase trials, intraparenchymal administration may cause CSF leakage, infection, bleeding, transitory neurological deterioration, neuropathic pain, or stiffness.[4,24] Translational initiatives include genetic screening, lineage purification, release testing, MRI surveillance, and long-term follow-up for pluripotent-derived products since tumorigenicity remains a theoretical issue.[17,18]

Quality manufacturing is as crucial as clinical safety.[17] Pluripotent-derived products must be produced under GMP-aligned conditions and tested for identification, purity, viability, sterility, and potency.[17] Genomic stability and remnant undifferentiated cells must also be controlled.[17] Patient enrollment in registered, regulator-reviewed studies with explicit consent processes, realistic uncertainty disclosure, and protection against treatment misconception or commercial exploitation is ethical and

regulatory.[28] Especially in regenerative medicine, where "pay-to-participate" or poorly regulated clinics can outpace evidence.[28]

LIMITATIONS OF CURRENT EVIDENCE

Despite strong biological rationale, the current clinical evidence base remains fragmented.[4,18] Studies differ substantially in injury level, AIS grade, chronicity, cell source, manufacturing process, timing of administration, route of delivery, rehabilitation exposure, and outcome assessment, which makes cross-trial comparison difficult.[4,5] Many small, open-label, early-phase trials are useful for feasibility and short-term safety but underpowered for efficacy claims.[18,24,25] Thus, neurological improvement should be taken as positive but provisional, especially when spontaneous recovery, selection bias, and rehabilitation heterogeneity cannot be totally separated from treatment impact.[4,18]

FUTURE DIRECTIONS AND RESEARCH PRIORITIES

Future progress in SCI cell therapy will likely depend on better trial rigor rather than simple expansion of the same small single-arm designs.[4,18] Multicenter randomized trials with harmonized rehabilitation, imaging, and electrophysiological objectives are needed to determine efficacy and which patient subgroups benefit most.[18,26] Mechanism-based potency testing and stricter release requirements are needed to match manufacturing quality with biological function.[17]

HLA-matched iPSC banking, tighter pluripotent-cell management, and tailored safety features are being developed to lower immunologic and tumorigenic risk while keeping scalability.[17] Blood, CSF, and advanced imaging biomarkers may improve patient classification and objective outcome tracking more than neurological evaluation alone.[29] Short follow-up cannot address delayed complications, response durability, and real-world reproducibility, therefore long-term registries and post-trial surveillance are needed.[18,28]

Table 1. Summary of Representative Clinical Trials of Stem Cell–Based Therapies in Spinal Cord Injury

Product / Cell Type	Sponsor / Lead	Phase / Design	Sample / Population	Route / Dose	Primary Endpoints	Headline Outcomes	Reference / ID
ESC-derived oligodendrocyte progenitor cells (AST-OPC1)	Asterias/Freedom; academic collaborators	Phase I/IIa; open-label; dose-escalation	~25 participants; subacute traumatic cervical SCI (AIS A/B), 14–30 days post-injury	Intraparenchymal; 2–20 million cells	Safety/feasibility; UEMS; imaging	Acceptable safety; several participants achieved clinically meaningful UEMS gains; no product-related tumors reported to date	[24]; ClinicalTrials.gov: NCT02302157
iPSC-derived neural stem/progenitor	Keio University, gritjpan (Okano/Nori/Tsuji)	Early Phase I/II; prospective; safety-focused	Very small cohorts; subacute/chronic	Intraparenchymal; stringent genomic-release criteria	Safety; long-term tumor surveillance;	Ongoing trials; safety frameworks	[18,19,30]

cells (NS/PCs)			cervical or thoracic SCI		neurological assessments	established; efficacy yet to be determined	
Autologous bone marrow–derived MSCs (intrathecal)	Multiple academic centers (India, China, Europe, others)	Phase I/II; open-label and some controlled studies	Dozens per study; subacute and chronic SCI; cervical/thoracic	Intrathecal; 10–100 million cells per dose; some repeated dosing	Safety; ASIA motor/sensory; bladder/urodynamic measures; pain	Generally safe; meta-analyses report modest motor/sensory and bladder improvements in subsets; high heterogeneity	[4,31]
Umbilical cord–derived MSCs (UC-MSCs)	Various academic/industry groups	Phase I/II; some randomized controlled trials vs rehabilitation/placebo	Tens to low hundreds across trials; subacute/chronic SCI	Intrathecal or intravenous; repeat dosing common	Safety; ASIA/SCIM; urodynamics; QoL	Acceptable safety; several studies report SCIM or bladder improvements; mixed results across centers	[18,31,32]
Adipose-derived MSCs (AD-MSCs)	Multiple institutions (Spain, Korea, others)	Phase I/II; open-label or controlled	Dozens; subacute/chronic SCI; cervical/thoracic	Intrathecal; often repeated courses	Safety; ASIA/SCIM; pain/spasticity scales	Favorable safety; some sensory/motor or spasticity improvements; significant variability	[25,31]
Human fetal/ESC-derived neural progenitors (various)	Multiple academic centers	Early Phase I; open-label feasibility	Small cohorts; subacute/chronic SCI; cervical/thoracic	Intraparenchymal; variable dosing and lesion targeting	Safety/feasibility; neurological and imaging measures	Generally safe; sporadic functional gains; need for standardized controlled trials	[4,13]
Schwann	The Miami	Phase I;	Small	Intraparenchy	Safety;	Feasible	[4,22]

cell autografts	Project and collaborators	open-label feasibility	cohorts; subacute/chronic SCI	mal placement into/around lesion cavity	neurological outcomes; MRI	and generally safe; functional signals inconsistent; technique- and center-dependent	
Olfactory ensheathing cells (OECs)	Multiple international centers	Phase I/II; open-label; some controlled	Small to moderate cohorts; chronic/subacute SCI	Intraparenchymal/lesion cavity; sometimes with scaffolds	Safety; motor/sensory; gait; bladder	Mixed efficacy; substantial center-to-center variability; careful selection and standardization advised	[4,23]
Neural progenitors with biomaterial scaffolds (combinatorial)	Various academic–industry collaborations	Early Phase I; feasibility	Small cohorts; subacute/chronic SCI	Intraparenchymal grafting within hydrogel/scaffold	Safety; engraftment (imaging); functional scales	Procedurally feasible; acceptable safety; preliminary efficacy signals; controlled trials pending	[13,27]

CONCLUSION

Stem cell–based therapies for SCI have advanced from compelling preclinical proof-of-concept to early clinical feasibility with reassuring short-term safety across several platforms. While consistent, large-magnitude functional restoration has not yet been demonstrated in adequately powered randomized settings, converging evidence supports biologically meaningful effects, particularly through paracrine immunomodulation, tissue preservation, and remyelination, with growing promise for neuronal relay reconstruction in selected platforms. Translation will depend on rigorous manufacturing, careful patient selection, standardized rehabilitation, and well-powered trials that incorporate mechanistic biomarkers and long-term safety surveillance. The most plausible path forward is multimodal: integrating cells with biomaterials, targeted molecular cues, and neuromodulation to pursue durable, clinically meaningful recovery.

Declaration by Authors

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REFERENCES

1. Fehlings MG, Tetreault LA, Wilson JR, et al. An update of a clinical practice guideline for the management of patients with acute spinal cord injury: recommendations on the role and timing of decompressive surgery. *Global Spine Journal*. 2024;14(3 Suppl):174S-186S.
2. Kwon BK, Badhiwala JH, Ahuja CS, et al. A clinical practice guideline for the management of patients with acute spinal cord injury: recommendations on hemodynamic management. *Global Spine Journal*. 2024;14(3 Suppl):187S-211S.
3. Zipser CM, Curt A. Disease-specific interventions using cell therapies for spinal cord disease/injury. *Handbook of Clinical Neurology*. 2024; 205:263-282.
4. Ribeiro BF, da Cruz BC, de Sousa BM, et al. Cell therapies for spinal cord injury: a review of the clinical trials and cell-type therapeutic potential. *Brain*. 2023;146(7):2672-2693.
5. Agosti E, Zeppieri M, Pagnoni A, et al. Current status and future perspectives on stem cell transplantation for spinal cord injury. *World Journal of Transplantation*. 2024;14(1):89674.
6. Hu X, Xu W, Ren Y, et al. Spinal cord injury: molecular mechanisms and therapeutic interventions. *Signal Transduction and Targeted Therapy*. 2023;8(1):245.
7. Hellenbrand DJ, Quinn CM, Piper ZJ, et al. The secondary injury cascade after spinal cord injury: an analysis of local cytokine and chemokine regulation. *Neural Regeneration Research*. 2024;19(6):1308-1317.
8. Khaing ZZ, Milman BD, Vanscoy JE, et al. Clinical trials targeting secondary damage after traumatic spinal cord injury. *International Journal of Molecular Sciences*. 2023;24(4):3824.
9. Shafqat A, Albalkhi I, Yaqinuddin A. Tackling the glial scar in spinal cord regeneration: new discoveries and future directions. *Frontiers in Cellular Neuroscience*. 2023; 17:1180825.
10. Clifford T, Finkel Z, Rodriguez B, et al. Current advancements in spinal cord injury research-glial scar formation and neural regeneration. *Cells*. 2023;12(6):853.
11. Elmalky MI, Alvarez-Bolado G, Younsi A, et al. Axonal regeneration after spinal cord injury: molecular mechanisms, regulatory pathways, and novel strategies. *Biology (Basel)*. 2024;13(9):703.
12. Liu Y, Zhao C, Zhang R, et al. Progression of mesenchymal stem cell regulation on imbalanced microenvironment after spinal cord injury. *Stem Cell Research & Therapy*. 2024;15(1):343.
13. Hosseini SM, Borys B, Karimi-Abdolrezaee S. Neural stem cell therapies for spinal cord injury repair: an update on recent preclinical and clinical advances. *Brain*. 2024;147(3):766-793.
14. Nakazaki M, Loayza Sanchez NA, Kwon H, et al. Mesenchymal stem cells and their extracellular vesicles: therapeutic mechanisms for blood-spinal cord barrier repair following spinal cord injury. *International Journal of Molecular Sciences*. 2024;25(24):13460.
15. Li M, Qi B, Li Q, et al. Human induced pluripotent stem cell/embryonic stem cell-derived pyramidal neuronal precursors show safety and efficacy in a rat spinal cord injury model. *Cellular and Molecular Life Sciences*. 2024;81(1):318.
16. Qu W, Hill CE, Joosten EAJ, et al. Chondroitinase ABC combined with Schwann cell transplantation enhances restoration of neural connection and functional recovery following acute and chronic spinal cord injury. *Neural Regeneration Research*. 2025;20(5):1467-1482.
17. Kirkeby A, Main H, Carpenter M. Pluripotent stem-cell-derived therapies in clinical trial: a 2025 update. *Cell Stem Cell*. 2025;32(1):10-37.
18. Sugai K, Nakamura M, Okano H, et al. Stem cell therapies for spinal cord injury in humans: a review of recent clinical research. *Brain and Spine*. 2025; 5:104207.
19. Yoshida S, Kato TM, Sato Y, et al. A clinical-grade HLA haplobank of human induced pluripotent stem cells matching approximately 40% of the Japanese population. *Med (N Y)*. 2023;4(1):51-66. e10.

20. Tashiro S, Nakamura M, Okano H. Regenerative rehabilitation and stem cell therapy targeting chronic spinal cord injury: a review of preclinical studies. *Cells*. 2022;11(4):685.
21. Liao JX, Liang YT, Sun XH, et al. The role of olfactory ensheathing cells in the repair of nerve injury. *European Journal of Pharmacology*. 2024; 963:176269.
22. Lu MF, Liu JP, Xu YS, et al. Application and challenge of Schwann cell transplantation in spinal cord injury and clinical trial. *International Journal of Surgery*. 2025;111(11):8284-8300.
23. Huang HY, Xiong MJ, Pu FQ, et al. Application and challenges of olfactory ensheathing cells in clinical trials of spinal cord injury. *European Journal of Pharmacology*. 2024; 963:176238.
24. 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. *Journal of Neurosurgery: Spine*. 2022;37(6):812-820.
25. Bydon M, Qu W, Moinuddin FM, et al. Intrathecal delivery of adipose-derived mesenchymal stem cells in traumatic spinal cord injury: Phase I trial. *Nature Communications*. 2024;15(1):2201.
26. Tashiro S, Nakamura M, Okano H. Current progress of rehabilitative strategies in stem cell therapy for spinal cord injury: a review. *NPJ Regenerative Medicine*. 2021;6(1):81.
27. Jagrit V, Koffler J, Dulin JN. Combinatorial strategies for cell transplantation in traumatic spinal cord injury. *Frontiers in Neuroscience*. 2024; 18:1349446.
28. Jayaram P, Danilkowicz RM, Yuan X. Ethical and regulatory considerations related to regenerative medicine. *HSS Journal*. 2025;21(3):531-538.
29. Schading S, Emmenegger TM, Freund P. Improving diagnostic workup following traumatic spinal cord injury: advances in biomarkers. *Current Neurology and Neuroscience Reports*. 2021;21(9):49.
30. Tsuji O, Sugai K, Yamaguchi R, et al. Concise review: laying the groundwork for a first-in-human study of an induced pluripotent stem cell-based intervention for spinal cord injury. *Journal of Clinical Medicine*. 2020;9(5):1435.
31. de Araújo LT, de Souza JS, de Carvalho PP, et al. Clinical trials using mesenchymal stem cells for spinal cord injury: challenges in generating evidence. *Cells*. 2022;11(6):1019.
32. Hussein M, Gibran S, El Masry M, et al. Advancing regenerative therapies with umbilical cord-derived mesenchymal stem cells for spinal cord injury. *Cytotherapy*. 2025.

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