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Engineered Tools to Advance Cell Transplantation in the Nervous System Towards a Clinical Reality

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Abstract

Purpose of the Review The goal of this review is to highlight engineered tools for overcoming challenges in cell survival and engraftment for tissue regeneration and mitigation of neuropathic pain following cell transplantation for neural applications.

Recent Findings There is a growing body of evidence supporting the safety of cell transplantation for the treatment of injuries to the brain, spinal cord, and peripheral nerves. However, the efficacy of these cell therapies is inconclusive, and the path forward remains unclear due to a lack of evidence of transplant survival and engraftment. Engineered biomaterials offer promising pre-clinical evidence of enhanced survival and engraftment of cells transplanted within the nervous system. Biomaterials have been used alone or in combination with drug and gene delivery to direct cell transplant outcomes and represent a future direction for clinical evaluation given pre-clinical survival rates that may eliminate reliance on systemic immunosuppression.

Summary Biomaterial approaches under pre-clinical evaluation can support cell survival, localize cells in the injured tissue where they are needed, and enable tissue engraftment, yet have not advanced towards the clinic. Existing biomaterials provide passive support of survival during delivery and/or place a premium on supporting cell engraftment, but active remediation of tissue-local inflammation that inhibits transplant survival and leads to neuropathic pain has seen very little advancement in recent years. Combinatorial approaches capable of addressing challenges in both survival and engraftment of cell transplants in the nervous system represent an area for significant growth in the coming years.

Keywords Neural stem cells · Schwann cells · Spinal cord injury · Traumatic brain injury · Peripheral nerve injury

Introduction

Traumatic injury to the nervous system has a profound impact on an individual's mobility, cognition, perception, and, ultimately, their independence. Given the young median age at which injuries are sustained and the long-term survival rates following traumatic injuries to the nervous system, there is a growing population of people suffering from chronic injuries to the nervous system [1, 2]. For injuries to the central nervous system (CNS), including the brain and spinal cord, there is no cure to fully restore motor, sensory, and autonomic function due to the robust barriers to regeneration in these tissues following injury [3]. Injuries in the peripheral nervous system (PNS) have limited treatment options to repair tissues, yet complete restoration of motor and sensory function following large gap injuries is still out of reach for patients due to limited regenerative potential [4]. To alleviate the rising healthcare costs and restore neurological function lost to injury, many pre-clinical approaches advancing towards clinical trials aim to increase spared tissue after the initial injury, increase plasticity of intact neural circuits, repair damaged neural tissue, and regenerate new neural tracts [3, 5–7]. One area of particular interest is the use of cell transplantation techniques that have the potential to improve tissue sparing, plasticity, repair, and regeneration to treat injuries in the brain, spinal cord, and peripheral nervous system, which has been reviewed by others [8–14].

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The safety and efficacy of cell transplantation for spinal cord injuries has been well established in pre-clinical models, including rodents, porcine, and non-human primate models [15], with preliminary efficacy demonstrated in rodent models of traumatic brain injury [16]. However, only recently have clinical trials demonstrated the safety of cell transplantation for neural applications with stem cells and differentiated cells from neural, mesenchymal, and hematopoietic lineages [8, 14, 17]. While many have demonstrated feasibility and safety of transplanted cells, a consensus on efficacy remains elusive. The goal of cell transplantation for neural applications includes neural repopulation, immune modulation, reparative biomolecular secretion, tissue remodeling, and pain management. While many of these goals can be best achieved through localized administration within the injury, intravenous and intrathecal dosing have been used widely to achieve immune modulation [8, 14]. Figure 1 summarizes the tissue lineage source, administration routes, and therapeutic goals explored in recent clinical trials. Focusing on the safety of transplantation directly into the nervous system, clinical trials have demonstrated that transplantation of neural stem cells (NSCs), Schwann cells, and bone marrow-derived stem cells within sites of spinal cord injury can be safely achieved without severe adverse effects or tumorigenicity [14]. Similarly, NSCs, hematopoietic stem cells, mesenchymal stem cells (MSCs), and other glial progenitors have demonstrated safety in clinical trials for neurodegenerative diseases, including amyotrophic lateral sclerosis and Parkinson's disease [10]. Meanwhile, only bone marrow-derived and umbilical cord-derived stem cells have demonstrated safety for use in treating traumatic brain injury when transplanted via intravenous and intrathecal routes [8]. Table 1 summarizes clinical trials involving the use of cell transplants for spinal cord, brain, or peripheral nerve injuries that are completed or active, whereas clinical trials that were terminated or have unknown status were excluded from this cohort of trials.

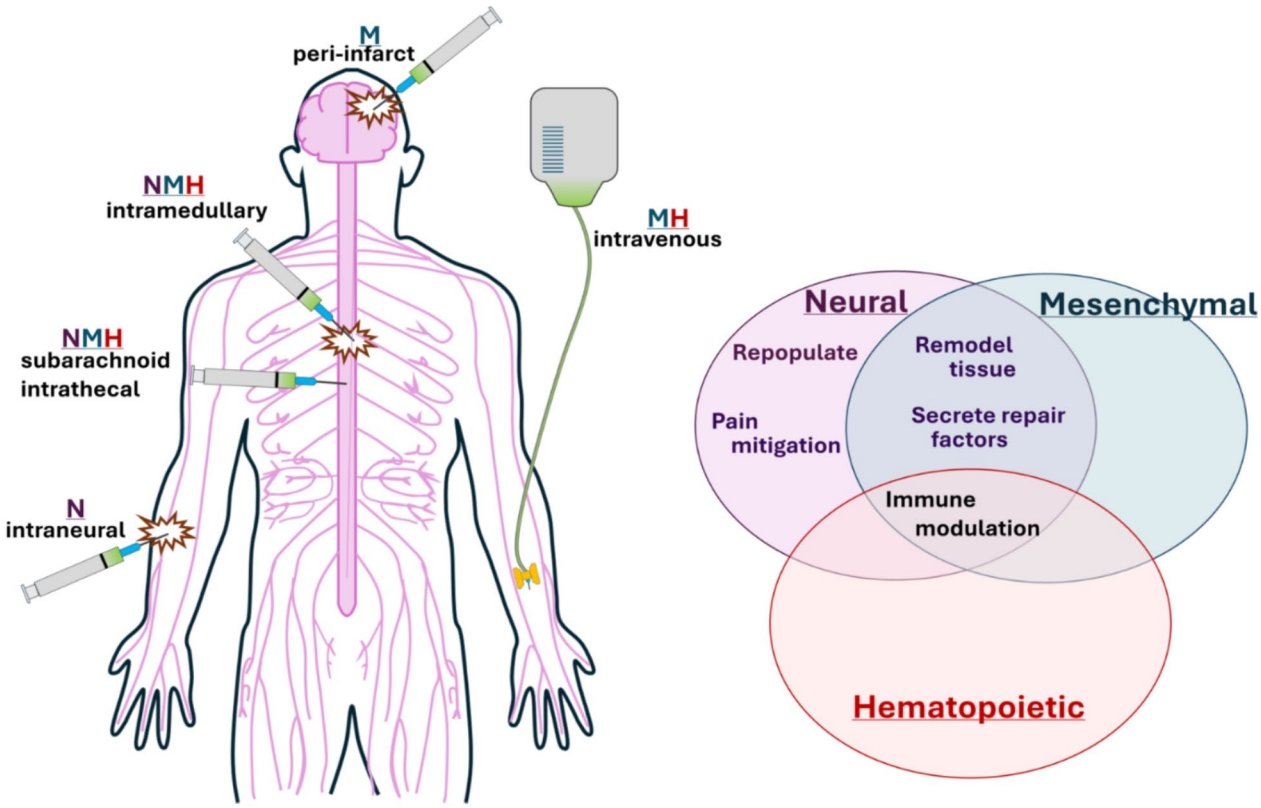

Fig. 1 Cell therapies for the treatment of injuries to the brain, spinal cord, and peripheral nerves have been administered in clinical trials via multiple routes, including intravenous, intramedullary, peri-infarct, subarachnoid, intrathecal, and intraneural. Cells isolated from the neural (N), mesenchymal (M), and hematopoietic (H) tissue sources are indicated for each route of administration. Each cell source offers its own unique benefits, which have been primarily demonstrated in pre-clinical studies

Table 1 Completed and active clinical trials for cell transplantation following injury to the nervous system. Clinical trials with the same sponsor, but differ in inclusion criteria are grouped together

Clinical Trial	Cell Type	Route	Phase	Dose (Cells)	Follow-up (Months)	Enrollment (#)	Completion (Year)
SPINAL CORD INJURY							
Autologous cell source							
NCT01739023 [18]	Schwann cells	intramedullary	I	5, 10, or 15 E6	12	9	2016
NCT02354625 [19]	Schwann cells	Intramedullary	I	5, 10, or 15 E6	6	8	2019
NCT00816803 [20]	BM	Intrathecal	I/II	2 E6 /kg	18	80	2008
NCT04205019	BM stem cells	Intrathecal	I	not reported	3	10	2023
NCT03935724	BM stem cells	Intrathecal	II/III	not reported	12	16	*2024*
NCT02152657 [21]	BM MSC	Intramedullary	--	2 E7	6	5	2016
NCT01325103 [22]	BM MSC	Intramedullary	I	5 E6/cm3 lesion	6	14	2012
NCT01186679	BM MSCs	Intrathecal, intramedullary	I	not reported	18	12	2010
NCT02570932 [23]	BM MSCs	Intramedullary	II	3×100 E6	24	10	2017
NCT02165904 [24]	BM MSCs	Subarachnoid	I	3×30 E6	12	10	2016
NCT01909154	BM MSCs	Intramedullary subarachnoid	I	100 E6 30 E6	12	12	2015
NCT02482194 [25]	BM MSCs	Intrathecal	I	2–3×1.2 E6/kg	12	9	2016
NCT04288934 [26]	BM MSCs vs. WJ-MSC	Intrathecal	I	6×1.2 E8	12	20	2020
NCT02981576	BM MSC vs. AD MSC	Intrathecal	I/II	not reported	12	14	2019
NCT03308565 [27]	AD MSCs	Intrathecal	I	100 E6	1	10	2021
NCT04520373	AD MSCs	Intrathecal	II	not reported	12	40	*2024*
NCT01769872	AD MSCs		I/II	2 E8, 5 E7, or 2 E7	8	15	2016
NCT01274975 [28]	AD MSCs	Intravenous	I	4 E8	3	8	2010
NCT01624779	AD MSCs	Intrathecal	I	3×9 E7	6	15	2014
NCT04812431	PSA-NCAM + NSCs	Intrathecal	I/IIa	5,4 E7	18	5	*2028*
NCT01321333 [29]	NSCs	Intramedullary	I/II	15–40 E6	12	12	2015
NCT01217008 [30]	OPCs	Intramedullary	I	2 E6	12	5	2013
NCT02302157 [31]	OPCs	intramedullary	I/IIa	2 E6, 1 E7,or 2E7	12	25	2018
NCT05054803	WJ-MSCs	intrathecal	I/II	2×1 E6/kg	12	18	*2024*
NCT03003364 [32]	WJ- MSCs	intrathecal	I/IIa	10 E6	12	10	2020
NCT05152290	UC-MSCs	intravenous, intrathecal	I	100 E6	48	20	*2026*
NCT01873547	UC-MSCs	subarachnoid	III	not reported	12	300	2015
NCT03979742	UC-BMNC	subarachnoid	II	6.4 E6	12	18	*2027*
NCT05693181	UC-BMNC	intravenous	I/II	500 E6	12	80	*2025*
NCT04331405	UC-BMNC	intravenous	I/II	1200 E6	12	20	2018
NCT01471613	UC-BMNC	Intramedullary	I/II	6.4 E6	12	16	2014
NCT01354483	UC-BMNC	intramedullary	I/II	1.6, 3.2, or 6.4 E6	12	20	2013
NCT02481440 [33]	UC-BMNC	intrathecal	I/II	4×1 E6	12	102	2020
TRAUMATIC BRAIN INJURY							
Autologous cell source							
NCT01575470	BMMCs	intravenous	I/II	6, 9, or 12 E6/kg	6	25	2015
NCT02525432	BMMCs	intravenous	II	6 or 9 E6/kg	6	37	*2024*
NCT01851083 [34]	BMMCs	intravenous	II	6 or 10 E6/kg	12	47	2020
NCT04063215	AD-MSCs	intravenous	I/II	3×2 E8	12	24	*2024*
NCT05951777	AD-MSCs	intravenous	Iia	3×2 E8	12	51	*2026*
Allogenic cell source							
NCT02416492 [35]	MSCs	peri-infarct	II	2.5, 5, or 10 E6	12	63	2019
NCT06163833	MSCs	Intravenous	II	80 or 160 E6	12	78	*2026*
PERIPHERAL NERVE INJURY							

Table 1 (continued)

Clinical Trial	Cell Type	Route	Phase	Dose (Cells)	Follow-up (Months)	Enrollment (#)	Completion (Year)
Autologous cell source							
NCT03999424	Schwann cells	Intraneural	I	not reported	24	10	*2025*
NCT05541250	Schwann cells	Intraneural	I	80–100 E6	24	30	*2026*
NEUROPATHIC PAIN							
Allogeneic cell source							
NCT05152368	UC-MSCs	intravenous	I	100 E6	48	20	*2026*

Bone marrow (BM), mesenchymal stem cell (MSC), neural stem cell (NSC), polysialylated-neural cell adhesion molecule (PSA-NCAM), oligodendrocyte progenitor cell (OPC), adipose derived (AD), Wharton's jelly (WJ), umbilical cord (UC), bone marow mononuclear cells (BMMC), blood mononuclear cells (BMNC)

While safety and feasibility of cell transplantation within the nervous system has begun to be demonstrated, therapeutic efficacy remains a challenge due to a lack of standardization of transplantation methods and patient assessments across individual injury types. As the field works towards a consensus on cell delivery and standardized assessments across studies, there remains a significant challenge in transplant survival and engraftment that persists and requires new tools to resolve. The purpose of this review is to highlight engineered tools to couple with cell transplantations to overcome poor survival and engraftment for CNS injury, PNS injury, and neuropathic pain reported in preclinical models that have resulted in little evidence of cell transplant survival and engraftment in clinical trials.

Enabling Robust Stem Cell Survival in the CNS

Stem cell transplantation into the CNS is subject to many of the same barriers that plague cell transplantation approaches in other parts of the body. Survival is predicated on the transplantation method, cell sourcing and expansion methods, and the engraftment microenvironment [12, 36]. Location of implantation, cell dose density, and timing are also important influencers of cell survival and efficacy with trade-offs including lower survival when cells are transplanted intralesional compared to higher survival in distal implantation sites [37–39]. Yet even if each of these criteria is addressed, survival in pre-clinical studies remains low [40], and stem cell survival in clinical trials has not been well-documented [14].

Biomaterials are a high potential tool in promoting stem cell transplantation survival. Alone, biomaterials can reduce secondary injury, guide repair processes, and limit scar formation in the CNS [41–43]. Yet, when used as a vehicle for cell transplantation, these outcomes can be synergistically enhanced, in part through improved cell survival and engraftment [40]. Biomaterials can reduce stem cell loss during surgical transplantation and improve transplant localization within the injury, where the stem cell transplantation has the highest potential to improve patient outcomes [38]. Previously, we have reviewed biomaterial techniques to bolster cell survival and localization for treatment of spinal cord injury [40], with many of the guiding principles being applicable to other nervous system transplants sites. To that end, we will focus on recent advances in the past three years, highlighting the role biomaterials can play as a tool to improve survival of stem cell transplantation in the CNS.

Initial cell loss during implantation is due to the high shear forces exerted on the cells resulting in cell membrane damage and rupture during the injection process. Strategies that implant stem cells on scaffolds are one way to alleviate cell loss due to these high forces. In this scenario, cells are loaded into a scaffold through a variety of means, including bioprinting. The cells are allowed to attach, proliferate, and produce cell networks that can enhance activation of pro-survival pathways [44, 45]. The stem cell laden scaffold is then surgically implanted, thereby eliminating the need to use traditional injection methods. Transplantation of stem cells in this manner allows for high precision of stem cell organization and structural guidance cues. One challenge to this approach is that the biomaterial typically accounts for a high percentage of the lesion volume compared to the stem cell transplants, as the scaffold stiffness is needed for handling and surgical implantation compared to injectable approaches. A recent study overcame this issue, using a core-sheath scaffold extrusion method that is comprised of an NSC-rich core surrounded by a thin-coat of acellular electrospun polymeric fibers that provides sufficient rigidity to improve surgical implantation, while also providing protection of the NSCs from the surgical implantation process [46].

While cell-seeded scaffolds are a promising approach to improve cell survival, these strategies are limited to large defect injuries. To that end, the Heilshorn lab has developed an injectable biomaterial method to reduce cell loss that occurs due to the high shear forces present with injectable strategies. The resulting injectable hydrogels undergo on-demand dynamic modifications of the matrix leading to

shear forces being exerted on the biomaterial matrix, rather than the cells [47]. Use of these injectable hydrogels can be tuned for individual cell types to include cell adhesion molecules and selective reactivity dependent on the delivery method and implant environment. By eliminating shear forces exerted on the cells during injection and including cell adhesion molecules to prevent anoikis, cell transplantation survival from injection alone can be dramatically improved by almost half for more sensitive cells, such as induced pluripotent stem cell derived deep cortical neurons [48].

In addition to overcoming stem cell loss due to the method of delivery, the transplanted cells then undergo a biochemical assault due to the heightened inflammation associated with injury, which can limit survival and/or result in differentiation into less desirable glial phenotypes. To bolster stem cell transplant survival, immunosuppressants are used to dampen inflammation that accompanies CNS injuries, however, immunosuppressants can result in severe complications in CNS injured patients, such myopathies [49], pneumonia, sepsis, and death [50–52]. These outcomes are associated with the high doses necessary to access the brain and spinal cord, given the low permissiveness of the blood-brain barrier and blood-spinal cord barrier [49, 51, 53, 54]. Moreover, commonly used immunosuppressant drugs can hamper NSC transplant proliferation needed for recovery [52]. Other immunomodulatory agents are in the pre-clinical pipeline, however, the systemic administration and high doses continue to present translational challenges even when used alone [55]. However, one group has found a promising immunosuppressant drug cocktail has shown promise in increasing NSC transplant survival and engraftment without reported toxicity [56].

While there are several local immunomodulatory strategies to treat inflammation, there is a scarcity of studies that utilize these techniques with stem cell transplantation approaches in the nervous system, even though biomaterial platforms can potentially overcome translational challenges. Biomaterials can provide local, tunable release of immunosuppressant and immunomodulatory agents, thus improving cell transplant survival and reducing toxicity associated with high, systemic drug administration [49, 51, 53, 54]. In the case of SCI, we have delivered anti-inflammatory cytokines through lentiviral-mediated over-expression, from biomaterials to locally reduce acute inflammation [57]. Overexpression of anti-inflammatory interleukin-10 mediated by lentivirus loaded into hydrogel tubes resulted in a 1.9-fold increase in NSC transplant survival compared to the biomaterial alone, and a 11.6-fold fold increase compared to NSCs delivered independent, thus demonstrating the importance of using combinatorial biomaterial strategies for stem cell transplantation into the CNS. There is a paucity of studies combining local strategies to mitigate inflammation associated with poor cell transplant survival, yet there are several combinatorial strategies seeking to improve engraftment and differentiation of transplanted stem cells for CNS repair and regeneration [58]. Future work that addresses temporal needs of cell transplants may build on these past works to achieve a truly tunable cell transplantation approach for the CNS to overcome current translational obstacles. For example, biomaterial systems that provide local, modular drug delivery [59] could be designed to delivery of early immune modulation and subsequent regenerative cues that could guide cell transplant-mediated regeneration. Such an approach would provide protection for transplanted stem cells, as well as provide additional instructional cues to modulate differentiation of transplanted stem cells to repopulate lost or damaged tissue.

Enabling Robust Schwann Cell Engraftment in the Spinal Cord and PNS

Schwann cells have emerged as a pivotal therapeutic strategy for promoting axon regeneration and myelination, not only within the PNS but also within the spinal cord as highlighted in Table 1. Pioneering research conducted by the Bunge Laboratory laid the groundwork for further exploration supported by in vitro observations demonstrating the independent survival and growth stimulation of Schwann cells by molecules bound to axon membranes [60]. Recent investigations utilize the NeuraGen collagen conduits seeded with autologous Schwann cells resulted in strong Schwann cell engraftment and regenerative efficacy in a critical gap peripheral nerve injury rat model [61]. Importantly, the use of an autologous cell source capable of regeneration, represents a potent cell therapy that can mitigate the need for immune suppressing/modulating drugs. An ongoing clinical trial for the transplantation of autologous Schwann cells is under investigation for large gap peripheral nerve injuries [17, 62]. Several million Schwann cells are transplanted on an autologous nerve graft within the injury, resulting in repair-activated Schwann cells that guide and biochemically support regenerative processes. While promising, this approach requires secondary surgeries to harvest nerves for isolating and expanding patient-specific Schwann cells, as well as a second nerve to serve as a nerve autograft and provide structural cues to instruct repair across the injury [17]. Without guided repair, axon regrowth across large-gap nerve damage can result in synkinesis and muscle atrophy due to lack of innervation for prolonged periods, thus a bridging material is essential. To that end, we anticipate the next major advance will be a combinatorial clinical trial integrating autologous Schwann

cells with synthetic biomaterial conduits, not unlike those currently under investigation in pre-clinical studies [63, 64].

Within the CNS, endogenous Schwann cells migrate into the spinal cord after injury. Building on this phenomenon, there has been a push to explore Schwann cell transplantation for spinal cord repair. Phase I trials have tested the safety and feasibility of autologous Schwann cell transplantation for both subacute and chronic SCI [65]. These trials have demonstrated the safety and feasibility of obtaining and delivering autologous Schwann cells into the injury epicenter, with promising evidence of motor and sensory function improvement in select participants. Given the small sample size and inherent patient variability, further studies are needed to assess Schwann cell engraftment and efficacy of this method.

As described in the PNS, Schwann cell engraftment into the spinal cord could also be enhanced using engineered biomaterials. Once again, the novel class of materials pioneered by the Heilshorn lab can be applied, but in this instance they can minimize Schwann cell loss during injection, mitigate cell membrane damage, prevent reflux from the spinal cord, and address rapid post-injection cell death [66]. Using a novel bioengineered injectable material modified specifically for Schwann cells the survival, engraftment, and therapeutic efficacy of transplanted Schwann cells was significantly improved [66]. By effectively addressing these critical challenges, this approach aims to bolster Schwann cell retention while diminishing spinal cord cavitation, thereby underscoring the significance of biomaterial tools to advance Schwann cell transplantation delivery for spinal cord treatment.

Tools for Transplanted Cell Engraftment to Overcome Neuropathic Pain

Much of the focus of cell transplantation into the nervous system is to regain motor function and independence for those suffering from nerve injuries. However, a secondary complication that occurs after injury to the nervous system is chronic neuropathic pain (NP) due to the cascade of neuroinflammation stimulated during injury. The complex pathophysiology associated with NP makes it difficult to treat effectively [67]. NP severely affects a patient's quality of life and poses a tremendous burden on the healthcare system [68]. Over 50% of patients suffering from NP do not receive sufficient pain relief due to the longevity and severity of symptoms, emphasizing the urgent need for new therapeutic strategies [9]. Some of the major contributors to the sensitization that causes pain stimuli are intracellular interactions, molecular signaling, and the structural changes of cells to harmful phenotypes [68]. While many are trying to understand the complex mechanisms behind NP to improve treatments, one potentially effective therapeutic approach is cell transplantation therapy. In several prior studies, cell-based therapeutics have been shown to provide neurorestoration through the regeneration of neurological networks, leading to both motor functional improvements and sensory impairment improvements [13, 69]. In this section, we will discuss the results and efficacy of several pre-clinical and clinical studies for cell transplantations, specifically NSCs, chromaffin cells, and GABAergic precursor cells.

NSCs are a popular candidate for cell therapy due to their neuroprotective and immunomodulatory properties in reducing neuroinflammation, potentially leading to the alleviation of NP [70]. The role of NSCs in pain alleviation has been measured through their interaction with cells within the damaged injury microenvironment. Local transplantation of NSCs into an injured rodent spinal cord resulted in regulation of NP signaling, indicating an improvement in the inflammatory microenvironment and a reduction in NP [71]. Within the PNS, NSC-laden scaffolds improved motor function and mitigated peripheral nerve injury-induced NP through nerve repair [72], suggesting NSC-mediated repair can alleviate NP throughout the nervous system.

More recently, the mechanism of human NSC-mediated modulation of NP via the secretome has been investigated in a rodent model of spinal cord injury. The hNSC-secretome decreased antioxidants, reduced matrix degradation, and modulated transforming growth factor (TGF)-β and brain-derived neurotrophic factor (BDNF) secretion, ultimately improving functional recovery and pain management [73]. Due to the anatomical and immunological differences in rodents and primates, it is important to look at the effectiveness of NSCs in larger animal models. Common marmosets with contusive SCI were grafted with embryonic stem cell-derived NSCs. Behavioral, histological, and immunoelectron microscopy analyses showed improved functional recovery in transplanted primates [74]. Although there have been successes in several rodent and primate models for functional recovery and mitigation of NP by transplanted NSCs, further studies must be conducted with larger sample sizes. Transplanted NSCs have also been shown to induce forelimb allodynia due to the differentiation into maladaptive structures [75]. A possible solution to this mechanism is the combination of NSCs with neurotrophins such as glial-derived neurotrophic factor (GDNF), vascular endothelial growth factor (VEGF), or BDNF, which may provide an analgesic effect in lessening allodynia [70, 75, 76]. Another limitation of NSCs is invasive cell grafting directly into the spinal parenchyma during transplantation, offering the potential for further injury and disruption of the microenvironment [77].

A potential cell transplantation type that may address translational obstacles of NSCs for NP is chromaffin cells.

The production of high levels of catecholamines and opioid peptides increases their role in the reduction of pain sensitivity [78]. Unlike many other administered therapeutics for chronic pain, chromaffin cell transplantation would not require the build-up of tolerance to these released factors. Pre-clinical trials demonstrated the lack of neurotoxicity and long-lasting analgesic effects of these biological "mini pumps" after injection into the spinal subarachnoid space [79]. Adrenal medullary allografts have also demonstrated success in clinical studies for managing pain in acute and chronic pain not associated with nervous system injury. A phase II clinical study performed on 15 patients with cancer pain looked at the stabilization of opioid dosage and intrathecally administered morphine to determine the analgesic effect of these allografts on pain progression. The study demonstrated the safety and feasibility of grafting human chromaffin cells into cerebrospinal fluid for chronic cancer pain and showed promising results with significant reduction or stabilization of opioid and morphine usage after cell transplant [80].

A more recent clinical study looked at two patients suffering from chronic neuropathic pain after spinal cord injury and the effect of an intrathecal injection of chromaffin cells. Six months after injection, the patient's pain had reduced significantly, providing preliminary evidence of the therapeutic efficacy for severe central NP [81]. Studies in animal models have also shown the reduction of both forelimb and hindlimb mechanical and thermal allodynia in rodents after adrenal medullary transplants [82]. Due to the sustained secretion of a synergistic cocktail of analgesic agents and the ability to non-invasively transplant into the subarachnoid space, chromaffin cells may be a unique therapeutic option for chronic pain management. However, the primary drawback to most further advancements is the lack of a sufficient and feasible clinical cell source due to limited human donor sources or the immune rejection from xenogeneic alternatives. Chromaffin-like cells from human induced pluripotent stem cells (hiPSCs) have recently been developed, offering a solution for sufficient cell sourcing without the need for immunosuppression [83]. Moreover, biomaterial tools described in prior sections of this review have not been evaluated to address chromaffin cell transplantation challenges, thus offering an attractive area for future investigation utilizing what is already well-established for biomaterial mediated cell transplantation into the CNS and PNS.

Another novel alternative currently being considered is GABAergic precursor/progenitor cells to reduce and manage chronic pain by restoring the important neurotransmitter, γ-aminobutyric acid (GABA) [84]. A primary cause of persistent pain is the decrease in GABAergic inhibition, leading to increased neurotransmission [85]. Pharmaceuticals such as gabapentin and benzodiazepines have aimed to target the GABAergic system and restore healthy levels, but many side effects have limited their clinical efficacy [86]. Animal models have demonstrated the preliminary efficacy of GABAergic cells in alleviating chronic NP [87, 88]. Mouse embryonic stem cell-derived NSCs differentiated into GABAergic neurons were intrathecally transplanted in a rat model 21 days after spinal cord injury and chronic NP attenuation was evaluated. The results found that the GABAergic neurons significantly attenuated chronic pain levels and cell survival for at least 7 weeks post-transplantation [87]. Transplanted pluripotent stem cell-derived GABAergic interneurons also indicated significant relief from injury-induced NP and long-term survival at the spinal transplantation site [88]. Overall, GABAergic precursor cell transplantations in rat models have demonstrated preliminary evidence of the ability to mitigate allodynia, however larger animal and human studies are still necessary to verify the efficacy of this therapeutic strategy [89].

Conclusions

Biomaterials afford improved cell transplant survival, injury localization, and engraftment within the CNS and PNS in pre-clinical models, but have not yet been used in clinical trials for nervous system injuries. Given the high prevalence of clinical trials for cell transplantation into patients with spinal cord injuries and of biomaterial approaches to enhance cell transplantation in pre-clinical spinal cord injury models, the use of a combinatorial biomaterial-cell transplant approach for treatment of spinal cord injury and its associated NP is not unfounded. The question remains, which biomaterial option is optimal for translating to patients? This is not an easy question to answer, given each biomaterial targets a different cell transplant need, or in many cases the biomaterial is designed to support endogenous repair and does not apply cell transplant design considerations. Nevertheless as the field moves forward, a robust approach that alleviates cell death during delivery, remediates inflammation, and guides regeneration will be needed to address the challenges that plague cell transplantation following spinal cord injury and facilitate translation to patients. Conversely, the use of biomaterials for cell delivery following traumatic brain injury appears to be a more distant future given that MSCs are systemic administered to remediate inflammation and would not necessarily benefit from a biomaterial approach. Implantation local to the sites of traumatic brain injury have also shown to be safe for MSC administration [35] and could potentially benefit from a biomaterial to maintain MSCs local to the injury, but further safety and efficacy testing of these two administration modalities would be needed to assess whether a biomaterial

is necessary in this particular injury paradigm. Lastly, the use of cells, tissue grafts, or acellular biomaterials have been explored in the clinic for tissue repair after injury to the PNS, where Schwann cells and topographical guidance are essential for rapid recovery necessary to reinnervate distal tissue targets. Given that the researchers leading clinical trials for the use of autologous Schwann cells are exploring the use of collagen scaffolds or autologous nerve grafts in combination with these cells [17, 62], it is possible that the first cell transplant with an engineered biomaterial into the nervous system might be close at hand.

Key References

- Zipser CM, Cragg JJ, Guest JD, Fehlings MG, Jutzeler CR, Anderson AJ, et al. Cell-based and stem-cell-based treatments for spinal cord injury: evidence from clinical trials. Lancet Neurol. 2022;21(7):659–70. https://doi.org/10.1016/S1474-4422(21)00464-6.
  - ○ Detailed overview of clinical trials for spinal cord injury.
- Finnerup NB, Kuner R, Jensen TS. Neuropathic Pain: from mechanisms to treatment. Physiol Rev. 2021;101(1):259–301. https://doi.org/10.1152/physrev.00045.2019.
  - ○ Comprehensive review of diagnosis, mechanisms, and treatment of neuropathic pain.
- Saboori M, Riazi A, Taji M, Yadegarfar G. Traumatic brain injury and stem cell treatments: a review of recent 10 years clinical trials. Clin Neurol Neurosurg. 2024;239:108219. https://doi.org/10.1016/j.clineuro.2024.108219.
  - ○ Detailed overview of clinical trials for traumatic brain injury.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

References

1. Haarbauer-Krupa J, Pugh MJ, Prager EM, Harmon N, Wolfe J, Yaffe K. Epidemiology of Chronic effects of Traumatic Brain Injury. J Neurotrauma. 2021;38(23):3235–47. https://doi.org/10.1089/neu.2021.0062.
2. Barbiellini Amidei C, Salmaso L, Bellio S, Saia M. Epidemiology of traumatic spinal cord injury: a large population-based study. Spinal Cord. 2022;60(9):812–9. https://doi.org/10.1038/s41393-022-00795-w.
3. Zheng B, Tuszynski MH. Regulation of axonal regeneration after mammalian spinal cord injury. Nat Rev Mol Cell Biol. 2023;24(6):396–413. https://doi.org/10.1038/s41580-022-00562-y.
4. Singh VK, Haq A, Tiwari M, Saxena AK. Approach to management of nerve gaps in peripheral nerve injuries. Injury. 2022;53(4):1308–18. https://doi.org/10.1016/j.injury.2022.01.031.
5. Pearn ML, Niesman IR, Egawa J, Sawada A, Almenar-Queralt A, Shah SB, et al. Pathophysiology Associated with Traumatic Brain Injury: current treatments and potential Novel therapeutics. Cell Mol Neurobiol. 2017;37(4):571–85. https://doi.org/10.1007/s10571-016-0400-1.
6. Ramer LM, Ramer MS, Bradbury EJ. Restoring function after spinal cord injury: towards clinical translation of experimental strategies. Lancet Neurol. 2014;13(12):1241–56. https://doi.org/10.1016/S1474-4422(14)70144-9.
7. Loane DJ, Faden AI. Neuroprotection for traumatic brain injury: translational challenges and emerging therapeutic strategies. Trends Pharmacol Sci. 2010;31(12):596–604. https://doi.org/10.1016/j.tips.2010.09.005.
8. Saboori M, Riazi A, Taji M, Yadegarfar G. Traumatic brain injury and stem cell treatments: a review of recent 10 years clinical trials. Clin Neurol Neurosurg. 2024;239:108219. https://doi.org/10.1016/j.clineuro.2024.108219.
9. Basbaum AI, Braz JM. Cell transplants to treat the disease of neuropathic pain and itch. Pain. 2016;157(Suppl 1):S42–7. https://doi.org/10.1097/j.pain.0000000000000441.
10. Fan Y, Goh ELK, Chan JKY. Neural cells for neurodegenerative diseases in clinical trials. Stem Cells Transl Med. 2023;12(8):510–26. https://doi.org/10.1093/stcltm/szad041.
11. Monje PV, Deng L, Xu XM. Human Schwann Cell Transplantation for Spinal Cord Injury: prospects and challenges in Translational Medicine. Front Cell Neurosci. 2021;15:690894. https://doi.org/10.3389/fncel.2021.690894.

12. Tetzlaff W, Okon EB, Karimi-Abdolrezaee S, Hill CE, Sparling JS, Plemel JR, et al. A systematic review of cellular transplantation therapies for spinal cord injury. J Neurotrauma. 2011;28(8):1611–82. https://doi.org/10.1089/neu.2009.1177.
13. Willison AG, Smith S, Davies BM, Kotter MRN, Barnett SC. A scoping review of trials for cell-based therapies in human spinal cord injury. Spinal Cord. 2020;58(8):844–56. https://doi.org/10.1038/s41393-020-0455-1.
14. Zipser CM, Cragg JJ, Guest JD, Fehlings MG, Jutzeler CR, Anderson AJ, et al. Cell-based and stem-cell-based treatments for spinal cord injury: evidence from clinical trials. Lancet Neurol. 2022;21(7):659–70. https://doi.org/10.1016/S1474-4422(21)00464-6.
15. Assinck P, Duncan GJ, Hilton BJ, Plemel JR, Tetzlaff W. Cell transplantation therapy for spinal cord injury. Nat Neurosci. 2017;20(5):637–47. https://doi.org/10.1038/nn.4541.
16. Chang J, Phelan M, Cummings BJ. A meta-analysis of efficacy in pre-clinical human stem cell therapies for traumatic brain injury. Exp Neurol. 2015;273:225–33. https://doi.org/10.1016/j.expneurol.2015.08.020.
17. Gersey ZC, Burks SS, Anderson KD, Dididze M, Khan A, Dietrich WD, et al. First human experience with autologous Schwann cells to supplement sciatic nerve repair: report of 2 cases with long-term follow-up. Neurosurg Focus. 2017;42(3):E2. https://doi.org/10.3171/2016.12.FOCUS16474.
18. Anderson KD, Guest JD, Dietrich WD, Bartlett Bunge M, Curiel R, Dididze M, et al. Safety of Autologous Human Schwann Cell Transplantation in Subacute thoracic spinal cord Injury. J Neurotrauma. 2017;34(21):2950–63. https://doi.org/10.1089/neu.2016.4895.
19. Maher JL, Anderson KD, Gant KL, Cowan RE. Development and deployment of an at-home strength and conditioning program to support a phase I trial in persons with chronic spinal cord injury. Spinal Cord. 2021;59(1):44–54. https://doi.org/10.1038/s41393-020-0486-7.
20. El-Kheir WA, Gabr H, Awad MR, Ghannam O, Barakat Y, Farghali HA, et al. Autologous bone marrow-derived cell therapy combined with physical therapy induces functional improvement in chronic spinal cord injury patients. Cell Transpl. 2014;23(6):729–45. https://doi.org/10.3727/096368913X664540.
21. Larocca TF, Macedo CT, Souza BSF, Andrade-Souza YM, Villarreal CF, Matos AC, et al. Image-guided percutaneous intralesional administration of mesenchymal stromal cells in subjects with chronic complete spinal cord injury: a pilot study. Cytotherapy. 2017;19(10):1189–96. https://doi.org/10.1016/j.jcyt.2017.06.006.
22. Mendonca MV, Larocca TF, de Freitas Souza BS, Villarreal CF, Silva LF, Matos AC, et al. Safety and neurological assessments after autologous transplantation of bone marrow mesenchymal stem cells in subjects with chronic spinal cord injury. Stem Cell Res Ther. 2014;5(6):126. https://doi.org/10.1186/scrt516.
23. Vaquero J, Zurita M, Rico MA, Aguayo C, Bonilla C, Marin E, et al. Intrathecal administration of autologous mesenchymal stromal cells for spinal cord injury: safety and efficacy of the 100/3 guideline. Cytotherapy. 2018;20(6):806–19. https://doi.org/10.1016/j.jcyt.2018.03.032.
24. Vaquero J, Zurita M, Rico MA, Bonilla C, Aguayo C, Fernandez C, et al. Repeated subarachnoid administrations of autologous mesenchymal stromal cells supported in autologous plasma improve quality of life in patients suffering incomplete spinal cord injury. Cytotherapy. 2017;19(3):349–59. https://doi.org/10.1016/j.jcyt.2016.12.002.
25. Satti HS, Waheed A, Ahmed P, Ahmed K, Akram Z, Aziz T, et al. Autologous mesenchymal stromal cell transplantation for spinal cord injury: a phase I pilot study. Cytotherapy. 2016;18(4):518–22. https://doi.org/10.1016/j.jcyt.2016.01.004.
26. Jamali F, Alqudah M, Rahmeh R, Bawaneh H, Al-Shudifat A, Samara O, et al. Safe reversal of motor and sensory deficits by repeated high doses of mesenchymal stem cells in a patient with chronic complete spinal cord Injury. Am J Case Rep. 2023;24:e938576. https://doi.org/10.12659/AJCR.938576.
27. Bydon M, Qu W, Moinuddin FM, Hunt CL, Garlanger KL, Reeves RK, et al. Intrathecal delivery of adipose-derived mesenchymal stem cells in traumatic spinal cord injury: phase I trial. Nat Commun. 2024;15(1):2201. https://doi.org/10.1038/s41467-024-46259-y.
28. Ra JC, Shin IS, Kim SH, Kang SK, Kang BC, Lee HY, et al. Safety of intravenous infusion of human adipose tissue-derived mesenchymal stem cells in animals and humans. Stem Cells Dev. 2011;20(8):1297–308. https://doi.org/10.1089/scd.2010.0466.
29. Ghobrial GM, Anderson KD, Dididze M, Martinez-Barrizonte J, Sunn GH, Gant KL, et al. Human neural stem cell transplantation in chronic cervical spinal cord Injury: functional outcomes at 12 months in a phase II clinical trial. Neurosurgery. 2017;64(CNsuppl1):87–91. https://doi.org/10.1093/neuros/nyx242.
30. McKenna SL, Ehsanian R, Liu CY, Steinberg GK, Jones L, Lebkowski JS, et al. Ten-year safety of pluripotent stem cell transplantation in acute thoracic spinal cord injury. J Neurosurg Spine. 2022;1–10. https://doi.org/10.3171/2021.12.SPINE21622.
31. Fessler RG, Ehsanian R, Liu CY, Steinberg GK, Jones L, Lebkowski JS, 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):812–20. https://doi.org/10.3171/2022.5.SPINE22167.
32. Albu S, Kumru H, Coll R, Vives J, Valles M, Benito-Penalva J, et al. Clinical effects of intrathecal administration of expanded Wharton jelly mesenchymal stromal cells in patients with chronic complete spinal cord injury: a randomized controlled study. Cytotherapy. 2021;23(2):146–56. https://doi.org/10.1016/j.jcyt.2020.08.008.
33. Yang Y, Pang M, Du C, Liu ZY, Chen ZH, Wang NX, et al. Repeated subarachnoid administrations of allogeneic human umbilical cord mesenchymal stem cells for spinal cord injury: a phase 1/2 pilot study. Cytotherapy. 2021;23(1):57–64. https://doi.org/10.1016/j.jcyt.2020.09.012.
34. Cox CS Jr., Notrica DM, Juranek J, Miller JH, Triolo F, Kosmach S, et al. Autologous bone marrow mononuclear cells to treat severe traumatic brain injury in children. Brain. 2024. https://doi.org/10.1093/brain/awae005.
35. Kawabori M, Weintraub AH, Imai H, Zinkevych I, McAllister P, Steinberg GK, et al. Cell therapy for chronic TBI: interim analysis of the Randomized Controlled STEMTRA Trial. Neurology. 2021;96(8):e1202–14. https://doi.org/10.1212/WNL.0000000000011450.
36. Iyer NR, Wilems TS, Sakiyama-Elbert SE. Stem cells for spinal cord injury: strategies to inform differentiation and transplantation. Biotechnol Bioeng. 2017;114(2):245–59. https://doi.org/10.1002/bit.26074.
37. Piltti KM, Avakian SN, Funes GM, Hu A, Uchida N, Anderson AJ, et al. Transplantation dose alters the dynamics of human neural stem cell engraftment, proliferation and migration after spinal cord injury. Stem Cell Res. 2015;15(2):341–53. https://doi.org/10.1016/j.scr.2015.07.001.
38. Piltti KM, Salazar DL, Uchida N, Cummings BJ, Anderson AJ. Safety of epicenter versus intact parenchyma as a transplantation site for human neural stem cells for spinal cord injury therapy. Stem Cells Transl Med. 2013;2(3):204–16. https://doi.org/10.5966/sctm.2012-0110.
39. Piltti KM, Salazar DL, Uchida N, Cummings BJ, Anderson AJ. Safety of human neural stem cell transplantation in chronic spinal

cord injury. Stem Cells Transl Med. 2013;2(12):961–74. https://doi.org/10.5966/sctm.2013-0064.
40. Tejeda G, Ciciriello AJ, Dumont CM. Biomaterial strategies to bolster neural stem cell-mediated repair of the Central Nervous System. Cells Tissues Organs. 2023;1–15. https://doi.org/10.1159/000515351.
41. Vijayavenkataraman S. Nerve guide conduits for peripheral nerve injury repair: a review on design, materials and fabrication methods. Acta Biomater. 2020;106:54–69. https://doi.org/10.1016/j.actbio.2020.02.003.
42. Chen K, Yu W, Zheng G, Xu Z, Yang C, Wang Y, Zhihao Y, Yuan W, Hu B, Chen H. Biomaterial-based regenerative therapeutic strategies for spinal cord injury. Npg Asia Mater. 2024;16:5.
43. Maclean FL, Horne MK, Williams RJ, Nisbet DR, Review. Biomaterial systems to resolve brain inflammation after traumatic injury. APL Bioeng. 2018;2(2):021502. https://doi.org/10.1063/1.5023709.
44. Stukel JM, Willits RK. Mechanotransduction of neural cells through cell-substrate interactions. Tissue Eng Part B Rev. 2016;22(3):173–82. https://doi.org/10.1089/ten.TEB.2015.0380.
45. Marquardt LM, Heilshorn SC. Design of Injectable materials to improve stem cell transplantation. Curr Stem Cell Rep. 2016;2(3):207–20. https://doi.org/10.1007/s40778-016-0058-0.
46. Zhang J, Li X, Guo L, Gao M, Wang Y, Xiong H, et al. 3D hydrogel microfibers promote the differentiation of encapsulated neural stem cells and facilitate neuron protection and axon regrowth after complete transactional spinal cord injury. Biofabrication. 2024. https://doi.org/10.1088/1758-5090/ad39a7.
47. Madl CM, Heilshorn SC. Bioorthogonal Strategies for Engineering Extracellular matrices. Adv Funct Mater. 2018;28(11). https://doi.org/10.1002/adfm.201706046.
48. Doulames VM, Marquardt LM, Hefferon ME, Baugh NJ, Suhar RA, Wang AT, et al. Custom-engineered hydrogels for delivery of human iPSC-derived neurons into the injured cervical spinal cord. Biomaterials. 2024;305:122400. https://doi.org/10.1016/j.biomaterials.2023.122400.
49. Qian T, Guo X, Levi AD, Vanni S, Shebert RT, Sipski ML. High-dose methylprednisolone may cause myopathy in acute spinal cord injury patients. Spinal Cord. 2005;43(4):199–203. https://doi.org/10.1038/sj.sc.3101681.
50. Hurlbert RJ. Methylprednisolone for acute spinal cord injury: an inappropriate standard of care. J Neurosurg. 2000;93(1 Suppl):1–7. https://doi.org/10.3171/spi.2000.93.1.0001.
51. Hurlbert RJ. Strategies of medical intervention in the management of acute spinal cord injury. Spine. 2006;31(11):S16–21. https://doi.org/10.1097/01.brs.0000218264.37914.2c. discussion S36.
52. Schroter A, Lustenberger RM, Obermair FJ, Thallmair M. High-dose corticosteroids after spinal cord injury reduce neural progenitor cell proliferation. Neuroscience. 2009;161(3):753–63. https://doi.org/10.1016/j.neuroscience.2009.04.016.
53. Hurlbert RJ. Methylprednisolone for acute spinal cord injury: an inappropriate standard of care. J Neurosurg. 2000;93(1):1–7. https://doi.org/10.3171/spi.2000.93.1.0001.
54. Suberviola B, Gonzalez-Castro A, Llorca J, Ortiz-Melon F, Minambres E. Early complications of high-dose methylprednisolone in acute spinal cord injury patients. Injury. 2008;39(7):748–52. https://doi.org/10.1016/j.injury.2007.12.005.
55. Kwon BK, Okon E, Hillyer J, Mann C, Baptiste D, Weaver LC, et al. A systematic review of non-invasive pharmacologic neuroprotective treatments for acute spinal cord injury. J Neurotrauma. 2011;28(8):1545–88. https://doi.org/10.1089/neu.2009.1149.
56. Guo B, Zhao X, Zou Y, Cheng X, Sun Z, Xue X, Yin M, Jin C, Chen Z, Quan R, Liu W, Chen B, Xiao Z, zhao Y, Gu R, Dai J. Evaluation of benefits and risks of immunosuppressive drugs in biomaterial-based neural progenitor cell transplantation for spinal cord injury repair. Chem Eng J. 2024;487:150404.
57. Ciciriello AJ, Smith DR, Munsell MK, Boyd SJ, Shea LD, Dumont CM. IL-10 lentivirus-laden hydrogel tubes increase spinal progenitor survival and neuronal differentiation after spinal cord injury. Biotechnol Bioeng. 2021;118(7):2609–25. https://doi.org/10.1002/bit.27781.
58. Fuhrmann T, Anandakumaran PN, Shoichet MS. Combinatorial therapies after spinal cord Injury: how can Biomaterials help? Adv Healthc Mater. 2017;6(10). https://doi.org/10.1002/adhm.201601130.
59. Ciciriello AJ, Surnar B, Medy GD, Su X, Dhar S, Dumont CM. Biomaterial-targeted precision nanoparticle delivery to the injured spinal cord. Acta Biomater. 2022;152:532–45. https://doi.org/10.1016/j.actbio.2022.08.077.
60. Levi AD, Bunge RP, Lofgren JA, Meima L, Hefti F, Nikolics K, et al. The influence of heregulins on human Schwann cell proliferation. J Neurosci. 1995;15(2):1329–40. https://doi.org/10.1523/JNEUROSCI.15-02-01329.1995.
61. Burks SS, Diaz A, Haggerty AE, Oliva N, Midha R, Levi AD. Schwann cell delivery via a novel 3D collagen matrix conduit improves outcomes in critical length nerve gap repairs. J Neurosurg. 2021;135(4):1241–51. https://doi.org/10.3171/2020.8.JNS202349.
62. Dietrich WD. Safety and efficacy of autologous human Schwann cell (ahSC) augmentation in severe peripheral nerve injury (PNI). (2023). Accessed 2023.
63. Fadia NB, Bliley JM, DiBernardo GA, Crammond DJ, Schilling BK, Sivak WN, et al. Long-gap peripheral nerve repair through sustained release of a neurotrophic factor in nonhuman primates. Sci Transl Med. 2020;12(527). https://doi.org/10.1126/scitranslmed.aav7753.
64. Fregnan F, Muratori L, Bassani GA, Crosio A, Biagiotti M, Vincoli V, et al. Preclinical validation of SilkBridge(TM) for peripheral nerve regeneration. Front Bioeng Biotechnol. 2020;8:835. https://doi.org/10.3389/fbioe.2020.00835.
65. Gant KL, Guest JD, Palermo AE, Vedantam A, Jimsheleishvili G, Bunge MB, et al. Phase 1 Safety Trial of Autologous Human Schwann Cell Transplantation in chronic spinal cord Injury. J Neurotrauma. 2022;39(3–4):285–99. https://doi.org/10.1089/neu.2020.7590.
66. Marquardt LM, Doulames VM, Wang AT, Dubbin K, Suhar RA, Kratochvil MJ, et al. Designer, injectable gels to prevent transplanted Schwann cell loss during spinal cord injury therapy. Sci Adv. 2020;6(14):eaaz1039. https://doi.org/10.1126/sciadv.aaz1039.
67. Matsuda M, Huh Y, Ji RR. Roles of inflammation, neurogenic inflammation, and neuroinflammation in pain. J Anesth. 2019;33(1):131–9. https://doi.org/10.1007/s00540-018-2579-4.
68. Finnerup NB, Kuner R, Jensen TS. Neuropathic Pain: from mechanisms to treatment. Physiol Rev. 2021;101(1):259–301. https://doi.org/10.1152/physrev.00045.2019.
69. Chakravarthy K, Chen Y, He C, Christo PJ. Stem cell therapy for chronic Pain Management: review of uses, advances, and adverse effects. Pain Physician. 2017;20(4):293–305.
70. Guo W, Liu K, Wang Y, Ge X, Ma Y, Qin J, et al. Neurotrophins and neural stem cells in posttraumatic brain injury repair. Anim Model Exp Med. 2024;7(1):12–23. https://doi.org/10.1002/ame2.12363.
71. Du XJ, Chen YX, Zheng ZC, Wang N, Wang XY, Kong FE. Neural stem cell transplantation inhibits glial cell proliferation and P2X receptor-mediated neuropathic pain in spinal cord injury rats. Neural Regen Res. 2019;14(5):876–85. https://doi.org/10.4103/1673-5374.249236.
72. Zhang Y, Xu X, Tong Y, Zhou X, Du J, Choi IY, et al. Therapeutic effects of peripherally administrated neural crest stem cells

on pain and spinal cord changes after sciatic nerve transection. Stem Cell Res Ther. 2021;12(1):180. https://doi.org/10.1186/s13287-021-02200-4.
73. Semita IN, Utomo DN, Suroto H, Sudiana IK, Gandi P. The mechanism of human neural stem cell secretomes improves neuropathic pain and locomotor function in spinal cord injury rat models: through antioxidant, anti-inflammatory, anti-matrix degradation, and neurotrophic activities. Korean J Pain. 2023;36(1):72–83. https://doi.org/10.3344/kjp.22279.
74. Iwai H, Shimada H, Nishimura S, Kobayashi Y, Itakura G, Hori K, et al. Allogeneic neural Stem/Progenitor cells derived from embryonic stem cells promote functional recovery after transplantation into injured spinal cord of Nonhuman Primates. Stem Cells Transl Med. 2015;4(7):708–19. https://doi.org/10.5966/sctm.2014-0215.
75. Macias MY, Syring MB, Pizzi MA, Crowe MJ, Alexanian AR, Kurpad SN. Pain with no gain: allodynia following neural stem cell transplantation in spinal cord injury. Exp Neurol. 2006;201(2):335–48. https://doi.org/10.1016/j.expneurol.2006.04.035.
76. Lee HL, Lee HY, Yun Y, Oh J, Che L, Lee M, et al. Hypoxia-specific, VEGF-expressing neural stem cell therapy for safe and effective treatment of neuropathic pain. J Control Release. 2016;226:21–34. https://doi.org/10.1016/j.jconrel.2016.01.047.
77. Bonner JF, Blesch A, Neuhuber B, Fischer I. Promoting directional axon growth from neural progenitors grafted into the injured spinal cord. J Neurosci Res. 2010;88(6):1182–92. https://doi.org/10.1002/jnr.22288.
78. Chabot-Dore AJ, Millecamps M, Naso L, Devost D, Trieu P, Piltonen M, et al. Dual allosteric modulation of opioid antinociceptive potency by alpha2A-adrenoceptors. Neuropharmacology. 2015;99:285–300. https://doi.org/10.1016/j.neuropharm.2015.08.010.
79. Wang H, Sagen J. Optimization of adrenal medullary allograft conditions for pain alleviation. J Neural Transpl Plast. 1994;5(1):49–64. https://doi.org/10.1155/NP.1994.49.
80. Lazorthes Y, Sagen J, Sallerin B, Tkaczuk J, Duplan H, Sol JC, et al. Human chromaffin cell graft into the CSF for cancer pain management: a prospective phase II clinical study. Pain. 2000;87(1):19–32. https://doi.org/10.1016/S0304-3959(00)00263-3.
81. Chen L, Xi HT, Xiao J, Chen D, Huang HY. Chromaffin cell transplantation for neuropathic pain after spinal cord injury: a report of two cases. J Neurorestoratology. 2016;5.
82. Hains BC, Chastain KM, Everhart AW, McAdoo DJ, Hulsebosch CE. Transplants of adrenal medullary chromaffin cells reduce forelimb and hindlimb allodynia in a rodent model of chronic central pain after spinal cord hemisection injury. Exp Neurol. 2000;164(2):426–37. https://doi.org/10.1006/exnr.2000.7439.
83. Abu-Bonsrah KD, Zhang D, Bjorksten AR, Dottori M, Newgreen DF. Generation of adrenal chromaffin-like cells from human pluripotent stem cells. Stem Cell Rep. 2018;10(1):134–50. https://doi.org/10.1016/j.stemcr.2017.11.003.
84. Yin Q, Zou T, Sun S, Yang D. Cell therapy for neuropathic pain. Front Mol Neurosci. 2023;16:1119223. https://doi.org/10.3389/fnmol.2023.1119223.
85. Dugan EA, Jergova S, Sagen J. Mutually beneficial effects of intensive exercise and GABAergic neural progenitor cell transplants in reducing neuropathic pain and spinal pathology in rats with spinal cord injury. Exp Neurol. 2020;327:113208. https://doi.org/10.1016/j.expneurol.2020.113208.
86. Cerne R, Lippa A, Poe MM, Smith JL, Jin X, Ping X, et al. GABAkines - advances in the discovery, development, and commercialization of positive allosteric modulators of GABA(A) receptors. Pharmacol Ther. 2022;234:108035. https://doi.org/10.1016/j.pharmthera.2021.108035.
87. Hwang I, Hahm SC, Choi KA, Park SH, Jeong H, Yea JH, et al. Intrathecal Transplantation of embryonic stem cell-derived spinal GABAergic neural precursor cells attenuates Neuropathic Pain in a spinal cord Injury Rat Model. Cell Transpl. 2016;25(3):593–607. https://doi.org/10.3727/096368915X689460.
88. Manion J, Khuong T, Harney D, Littleboy JB, Ruan T, Loo L, et al. Human induced pluripotent stem cell-derived GABAergic interneuron transplants attenuate neuropathic pain. Pain. 2020;161(2):379–87. https://doi.org/10.1097/j.pain.0000000000001733.
89. Askarian-Amiri S, Maleki SN, Alavi SNR, Neishaboori AM, Toloui A, Gubari MIM, et al. The efficacy of GABAergic precursor cells transplantation in alleviating neuropathic pain in animal models: a systematic review and meta-analysis. Korean J Pain. 2022;35(1):43–58. https://doi.org/10.3344/kjp.2022.35.1.43.