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# Frontier Integration in Spinal Cord Injury Repair: Engineering-Driven Mechanistic Exploration and a New Paradigm for Clinical Translation

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ABSTRACT

Spinal cord injury (SCI) is a devastating traumatic disorder of the central nervous system that severely impairs sensory, motor, and autonomic functions, placing heavy burdens on patients, families, and society. This review summarizes engineering advances in SCI repair, emphasizing neuromodulation therapies, surgical approaches, cell therapy, pharmacological and gene therapies, and biomaterial-based tissue engineering. It also discusses challenges in clinical translation, such as ethical considerations, multimodal technology integration, and interindividual variability. The review underscores the importance of strengthening interdisciplinary collaboration to integrate multiple-model treatments and accelerate their clinical application.



## 1. Introduction

Spinal cord injury (SCI) is a severe central nervous system (CNS) disorder that causes profound sensory, motor, and autonomic dysfunctions, resulting in paralysis, sensory loss, and autonomic dysregulation. An estimated 0.57 million new SCI cases occurred in 2021 [1]. Etiologically, SCI is classified into traumatic (tSCI) and non-traumatic SCI (non-tSCI); tSCI accounts for over 90% of cases and mainly results from falls, traffic accidents, and other violent injuries that cause partial or complete neural circuit disruption and functional loss below the lesion site [2]. Tumors are the leading cause of non-tSCI [3]. Pathophysiological changes involve primary mechanical and secondary cascading injuries. The primary injury, induced by abrupt external force, damages neural tissue and vasculature, causing hemorrhage, inflammatory mediator leakage [4], and microglial activation that triggers secondary injury. The secondary cascade progresses dynamically: the acute phase features blood–spinal cord barrier (BSCB) disruption, cytokine storms, and oxidative stress; the subacute phase involves immune cell phenotypic shifts and disordered tissue repair; and the chronic phase forms glial and fibrotic scars that inhibit axonal regeneration [5].

Conventional treatments inadequately address the complex pathology of SCI. High-dose methylprednisolone (MP) sodium succinate may reduce inflammation and delay degeneration, but has a narrow therapeutic window and serious side effects, including gastrointestinal bleeding, hyperglycemia, and infection [6]. Surgical decompression cannot mitigate secondary cascades, highlighting the urgent need for new therapies. Recent research has introduced engineering innovations, such as tissue engineering and neuromodulation, as promising interventions. Engineered biologics, through strategic modification of cytokines and bioactive molecules, modulate immune responses and promote axonal regeneration. These engineering-driven advances transcend conventional therapeutic limits, offering novel solutions for SCI recovery. This review consolidates progress in engineering-based SCI repair and advocates the combined use of multimodal approaches in clinical translation.

## 2. Search strategy

A comprehensive literature search was conducted using the PubMed, ScienceDirect, and Google Scholar databases. Articles

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and studies were eligible for inclusion if they met the following criteria: published between 2015 and 2025, written in English, and focused on clinical trials, fundamental experimental research, or advancements in pharmacology, surgical techniques, or biomaterials for SCI. The search terms included "spinal cord injury," "biomaterials," "stem cell transplantation," "rehabilitation therapy," "pharmacological therapy," "gene therapy," "neuromodulation," and "spinal cord stimulation," along with relevant medical subject headings. Keywords were combined using Boolean operators "AND" and "OR." The search was conducted from June to July 2025. After duplicate removal, titles and abstracts were screened to exclude irrelevant studies, yielding a total of 657 eligible articles (Fig. 1).

## 3. Pathophysiological mechanisms of SCI

It is worth emphasizing that the core pathological process of tSCI is mainly divided into the primary mechanical injury and secondary cascade injury phases [7]. Following direct mechanical trauma to spinal cord tissue by external forces, the body initiates a series of endogenous repair mechanisms to mitigate damage and maintain microenvironmental homeostasis. However, these secondary cascade reactions frequently impede neurological recovery (Fig. 2).

### 3.1. Primary mechanical injury

In the initial stage, sudden external impacts cause vertebral fractures or dislocations, resulting in primary mechanical damage to the spinal cord. Bone fragments and ligament displacement accompanying this process further exacerbate structural disruption of the spinal cord, with the severity of injury serving as a critical determinant of functional prognosis [8]. From a biomechanical perspective, primary injury mainly arises from characteristic external force modes such as impact combined with sustained compression, transient compression impact, traction, and tearing. Among these, impact combined with sustained compression is the most common, often caused by burst fractures or vertebral dislocations [9]. As the initiating event in the pathological cascade of SCI, primary injury irreversibly damages local neurons, resident glial cells, and vascular structures. Vascular rupture induces intramedullary hemorrhage and hematoma formation, facilitating the massive infiltration of monocytes, neutrophils, and related inflammatory mediators into the spinal cord parenchyma, thereby disrupting local microenvironmental stability [10]. This imbalance rapidly activates resident microglia, recruiting circulating monocytes to the injury site through the secretion of chemokine ligand 2 (CCL2) and polarizing them toward pro-inflammatory (M1-type) macrophages [11]. This process marks the explosive initiation of the secondary cascade injury, which progressively invades adjacent normal spinal cord tissue, thereby aggravating neurological dysfunction [12].

### 3.2. Secondary cascade injury

Secondary injury is a dynamically evolving process involving multiple factors, with core mechanisms including apoptosis and necrosis, cytokine storm, oxidative stress, ion imbalance, tissue fibrosis, and scar formation. These pathological processes interact, collectively creating a pathological microenvironment that is highly inhibitory to nerve regeneration [13,14]. It is important to note that both the pathological features and microenvironmental composition undergo significant temporal changes, typically divided into the acute, subacute, and chronic phases.

#### 3.2.1. Acute phase

In the acute phase, mechanical trauma disrupts the integrity of the BSCB, leading to the rapid infiltration of peripheral immune cells and damage-associated molecular patterns (DAMPs) into the

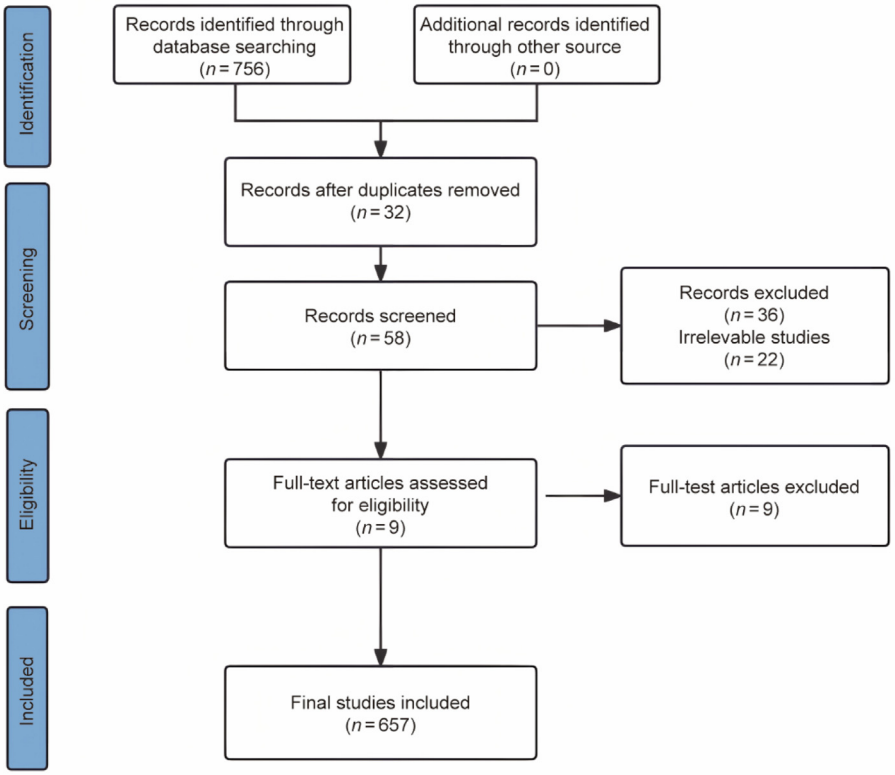


**Fig. 1.** Flowchart of eligible study selection. The diagram summarizes the literature screening and inclusion process for SCI studies.

injury site [15]. During this stage, resident microglia are the first to become activated, recognizing and binding DAMPs through pattern recognition receptors and triggering the release of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1α (IL-1α), IL-1β, and IL-6, forming a "cytokine storm" that recruits neutrophils and monocytes/macrophages. The levels of these cytokines typically peak within 6–12 h post-injury and remain elevated for up to 4 d [16]. Thus, the acute immune microenvironment is characterized by an excessive pro-inflammatory state. Although some studies suggest that early infiltration of inflammatory cells and related cytokines may facilitate debris clearance and tissue repair [17], when local pro-inflammatory mediators accumulate to toxic levels, they induce various forms of programmed cell death, including autophagy, necroptosis, and ferroptosis. These processes exacerbate neuronal and oligodendrocyte injury and are a major cause of functional deficits after SCI [18]. Additionally, infiltrating phagocytic immune cells release large quantities of reactive oxygen species (ROS), triggering severe oxidative stress that damages DNA, proteins, and lipids. This process results in delayed neuronal necrosis and apoptosis, representing a substantial obstacle to subsequent neural repair [19].

#### 3.2.2. Subacute phase

The subacute phase usually occurs days to weeks after injury and marks the onset of spinal cord repair. However, delayed restoration of the BSCB leads to persistent abnormal infiltration of immune cells, accompanied by impaired clearance of myelin debris and apoptotic cells, resulting in a "pro-inflammatory/anti-inflammatory imbalance" of the microenvironment [20]. Microglia and infiltrating macrophages, as core immune effectors, undergo dynamic phenotypic shifts. Pro-inflammatory M1 populations continuously secrete pro-inflammatory factors, while anti-inflammatory M2 populations gradually increase, releasing IL-4, IL-10, and transforming growth factor-β (TGF-β), and expressing nerve growth factor (NGF) and neurotrophin-3 (NT-3), which promote phagocytosis and suppress excessive inflammation [21]. Notably, M2 macrophages also secrete C–X3–C motif ligand 1 (CX3CL1) to polarize microglia toward the repair phenotype [22]. Similarly, T lymphocyte subsets exhibit functional duality. T helper 1 (Th1) cells secrete pro-inflammatory mediators such as interferon-γ (IFN-γ) and chemokines, including CCL2 and CCL5, affecting neuronal survival and promoting microglia/macrophage polarization toward the M1 phenotype. In contrast, Th2 cells and regulatory T cells (Tregs) mediate immunosuppression by upregulating IL-10 and TGF-β, reducing ROS production, and enhancing M2 polarization, thereby exerting neuroprotective effects [23,24]. Pro-fibrotic factors, particularly TGF-β, are mainly produced by M2 macrophages, infiltrating fibroblasts, and activated astrocytes. Despite its anti-inflammatory effects, TGF-β might paradoxically promote fibroblast proliferation, migration, and excessive deposition of extracellular matrix (ECM) components such as type I and III collagen and fibronectin, accelerating fibrotic scar formation and hindering axonal regeneration [25]. Additionally, reactive astrocyte proliferation occurs in the injury border zone, forming early glial scar structures through tight junctions, isolating the injury core, and restricting inflammation to protect adjacent healthy tissue [26]. Overall, the subacute immune microenvironment in SCI exhibits complex pathological features characterized by dynamic immune cell phenotype transitions and active tissue remodeling.

#### 3.2.3. Chronic phase

The injury microenvironment transitions to an immunosuppressive state during the chronic phase, which generally occurs months to years after injury. Key features of this state include a gradual decline in inflammation and a reduced number of microglia/macrophages within the injured region [27]. However, several studies indicate that abnormal microglial activation may persist for months or even years, representing a major mechanism of chronic neurodegeneration [28]. A defining pathological feature of this phase is the formation of mature glial scars composed of microglia/macrophages, reactive astrocytes, and ECM molecules [29]. Activated astrocytes continuously secrete large quantities of inhibitory molecules such as chondroitin sulfate proteoglycans (CSPGs) and Tenascin-C, impeding axonal growth [30], while persistent myelin-derived inhibitors such as myelin-associated glycoprotein and oligodendrocyte myelin glycoprotein (OMgp), induce growth cone collapse and neurite retraction of regenerating axons. Simultaneously, fibrotic scars mature into cystic or solid structures rich in dense collagen, encapsulating cavities formed after the inflammatory storm. These two scar types together act as physical and chemical barriers to axonal regeneration [31]. Although scarring restricts inflammation, it also severely obstructs neural circuit reconstruction, posing a core challenge for tissue-engineered scaffold design. Another key feature of the chronic phase is the slow initiation of endogenous repair mechanisms. Residual neurons gradually lose function due to axonal transection and limited neurotrophic support, while neural stem cells (NSCs)/neural progenitor cells (NPCs) in the perilesional area may become activated, proliferate, and differentiate. However, they often struggle to migrate to the injury core or achieve functional integration [32]. Furthermore, expression of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) increases in the injury microenvironment to support neuronal survival and axonal growth. Nevertheless, these endogenous repair processes remain largely insufficient, underscoring the need for exogenous interventions and providing a theoretical foundation for SCI repair through tissue-engineered delivery of neurotrophic factors or supportive cells.

## 4. Neurostimulation and neuromodulation therapy

A key reason neurostimulation and neuromodulation therapies play a pivotal role in engineering-based treatments is their ability to address the shortcomings of traditional intervention methods. Beyond the conventional emphasis on repairing damaged neural tissues, these therapies directly address core functional impairments following SCI, such as motor, sensory, and urinary-bowel dysfunctions, by modulating neural signal transmission, activating residual neuronal networks, and promoting neural circuit remodeling. Moreover, these emerging strategies provide promising opportunities for restoring functional recovery even in patients with long-term paralysis.

### 4.1. Electrical stimulation

#### 4.1.1. Spinal cord stimulation (SCS)

Epidural SCS (ESCS) was initially developed as a surgical intervention for drug-resistant chronic neuropathic pain [33,34]. The system comprises one or more leads implanted in the epidural space and connected to an implantable pulse generator, with its primary mechanism believed to align with the gate control theory of pain. Following initial success in treating drug-refractory neuropathic pain, ESCS has increasingly gained attention for its potential to promote neurological recovery in patients with SCI [35]. In 2012, Harkema et al. [36] reported that a patient with incomplete SCI (American Spinal Injury Association (ASIA) B, $C_7$-$T_1$) could consciously control leg movements during stimulation. Subsequent studies have shown that ESCS can also enhance hemodynamic stability [37] and modulate respiratory patterns

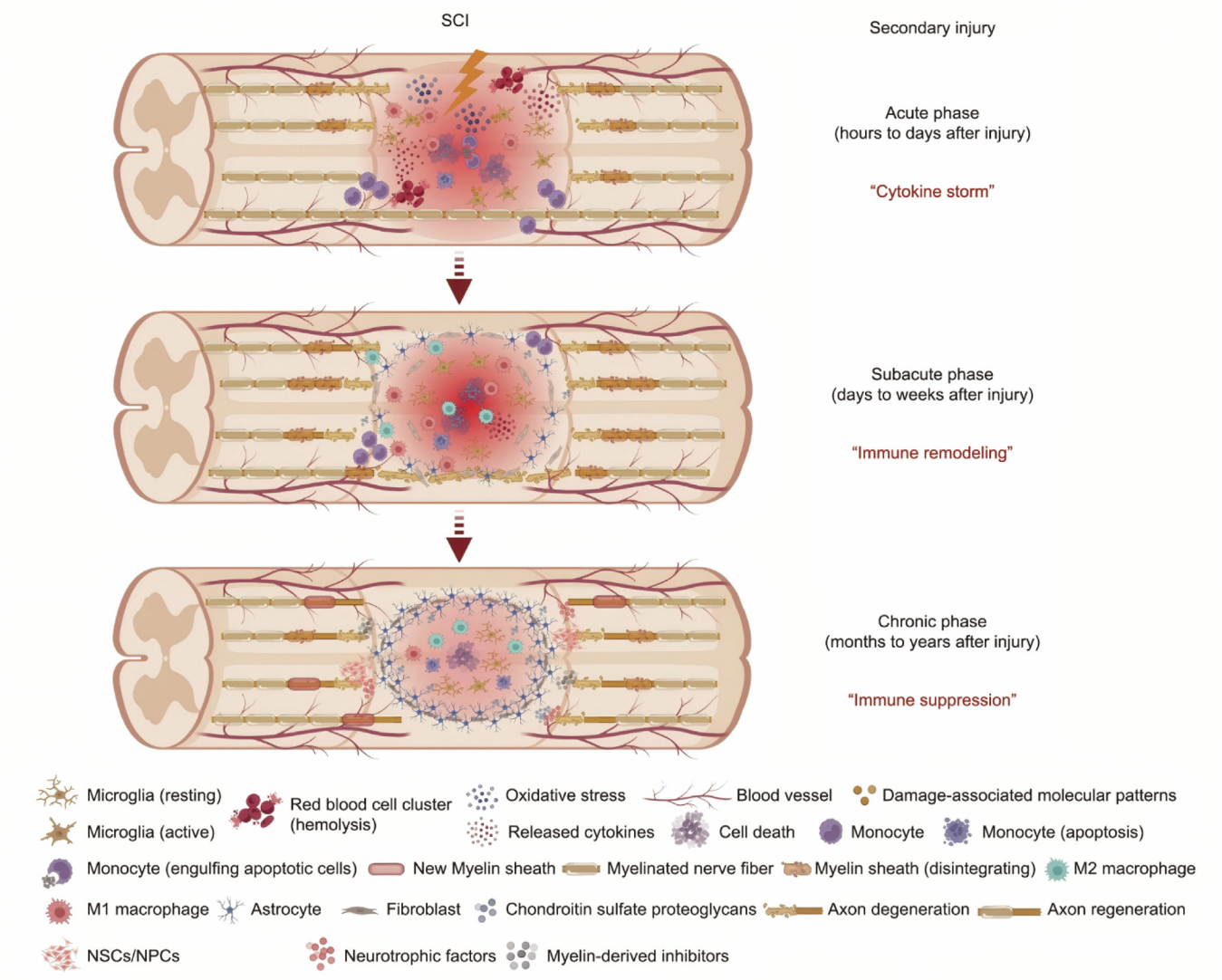


**Fig. 2.** Temporal pathological evolution and salient features of the secondary injury phase after SCI. The illustration depicts acute, subacute, and chronic phases following SCI, showing cellular and molecular changes including inflammation, scar formation, and limited endogenous repair.

[38,39], establishing it as the most widely applied technique in SCS therapies and demonstrating its strong potential to improve quality of life in individuals with neurological impairments [40]. A meta-analysis including 64 studies and 306 patients, using different stimulation devices, parameters, and rehabilitation methods, revealed significant motor improvements, with 44% of patients achieving assisted or independent standing and walking. Furthermore, ESCS has been found to improve autonomic functions, including bladder and sexual function, airway pressure, and defecation [41]. Studies indicate that ESCS current does not directly stimulate neurons [42], rather, it propagates through the cerebrospinal fluid, causing depolarization of large-diameter afferent fibers. Owing to their relatively low impedance, these fibers are more susceptible to depolarization, particularly at the dorsal root entry zone. Alternatively, stimulation may activate motor neurons directly or indirectly by recruiting large-diameter afferent fibers, facilitating a shift in spinal circuitry from a dormant to an excitable state [43].

In recent years, to further enhance the therapeutic efficacy of SCS in SCI, researchers have explored innovative multidisciplinary integration strategies. Some have proposed combining ESCS with muscle stimulation to develop a dual-stimulation system designed to simulate feedforward and feedback electrical signaling within the spinal sensorimotor circuit. Zhou et al. [44] demonstrated that reconstructing spinal sensorimotor pathways depends on specific signal inputs, and this dual-stimulation mode not only activates genes associated with axonal regeneration but also enhances spinal neuron excitability, offering new potential for improving motor recovery in patients with SCI. In treating a 16-year-old patient with complete SCI, investigators combined epidural electrical stimulation (EES) with exoskeleton-assisted rehabilitation. An SCS device was implanted at the $T_{11}$-$L_1$ level, and an innovative algorithm integrating spatiotemporal SCS with real-time triggered exoskeleton training (EXS-SCS) was employed. Sequential stimulation with precise timing activated target neurons at specific movement phases, thereby amplifying neuromuscular responses. After one month of treatment, the patient's iliopsoas and quadriceps strength significantly improved to grades 3–4 [45]. Hodgkiss et al. [46] compared ESCS with transcutaneous SCS (TSCS) to assess the effects of ESCS on cardiovascular modulation and upper-body exercise performance in patients with SCI. Their similar endurance-enhancing outcomes suggested that both methods could effectively improve exercise tolerance and reduce daily fatigue in patients with SCI.

With advancing clinical practice (Table 1 [45–52]), researchers have increasingly emphasized quantitative analyses of SCS therapeutic efficacy and optimization of stimulation protocols, leading to systematic investigations aimed at improving treatment outcomes. SCI involves complex pathology and marked interindividual variability, rendering a single stimulation protocol insufficient. Consequently, individualized precision therapy is essential for enhancing SCS performance. Rowald et al. [47] and Herrity et al. [53] employed 3D spinal model libraries derived from human imaging data, integrated with electric field simulations, to develop electrode design principles that maximize the transverse electrode diameter and minimize non-target nerve root recruitment near the midline. Wagner et al. [54], seeking to map afferent fiber projection areas, augmented muscle spindle afferent signals through tendon vibration to enhance proprioceptive input, and then monitored spinal blood oxygen changes verified at the ankle, knee, and hip levels. A correlation between spinal oxygenation and afferent activity confirmed that these responses were restricted to one or two spinal segments. Optimizing electrode spatial resolution improves motor neuron targeting, while individualized spinal models integrated with computational simulation allow precise activation of 3D motor pools and refined nerve root recruitment across axial and transverse planes. These findings on segmental response specificity provide crucial anatomical and physiological insight for advancing neural stimulation precision [55]. Liu et al. [48] released an open-access magnetic resonance imaging (MRI) dataset offering detailed depictions of spinal nerve roots, captured via multi-sequence imaging of 14 healthy adults to enhance root resolution. The dataset includes anatomical markers and reconstructed 3D spinal models to support future epidural electrode array optimization and targeting accuracy. Because conventional wired stimulation can induce secondary injury, inflammation, pain, and infection, researchers have proposed graphite nanosheet-based ESCS patches. Utilizing the high conductivity and electromagnetic induction properties of graphite, these patches generate wireless pulsed electrical signals under a rotating magnetic field for SCI treatment, with output controllable by adjusting rotation speed [56].

Previous SCS strategies often overlooked the critical role of command signals originating from higher neural centers. Intelligent closed-loop stimulation systems are anticipated to establish a digital interface linking supra- and infra-lesional regions [57], effectively converting motor cortical signals into task-specific electrical stimulation. Additionally, enabling patients to engage in personalized adaptive programming provides real-time feedback on stimulation effectiveness and allows selection of activity-specific modes for daily use [49]. In the future, intelligent SCS platforms are expected to detect neural discharges more precisely above the lesion, analyze signal conduction through residual neural pathways, and decode patients' voluntary motor intentions. When combined with EMG feedback from target muscles, this approach would permit fine-tuned modulation of spinal motor neurons.

#### 4.1.2. Cortical and subcortical electrical stimulation

Cerebral neural circuits are modulated through cortical and subcortical stimulation techniques, and functional recovery after SCI is facilitated by influencing descending pathways. Major approaches include deep-brain stimulation (DBS) [58], transcranial direct current stimulation (tDCS) [59], and transcranial alternating current stimulation (tACS) [60]. Current evidence shows that repeated activation of the motor cortex via electrical stimulation enhances activity-dependent growth of corticospinal tract (CST) projections [61,62]. Other studies indicate that activation of cortical circuits triggers downstream signaling through brainstem neurons, which retain extensive projections below the injury site, reinforcing residual brain–spinal connections [42].

Courtine's group [63] investigated brain regions responsible for gait recovery after incomplete SCI to enhance targeted rehabilitation. Using 3D imaging methods (iDISCO+ and CLARITY), they created spatiotemporal maps of transcriptionally active, spinal-projecting neurons and identified a neuronal population associated with brain-mediated gait recovery. Activation of the lateral hypothalamus via DBS markedly improved gait in two clinical patients with long-term incomplete SCI. Researchers also found that tDCS induced notable alterations in the morphology and activity of cortical microglia in mice [64]. Accordingly, Oishi et al. [59] analyzed neuronal activity in layer 5 (L5) of the primary motor cortex (M1) in SCI mice following tDCS, revealing that tDCS promoted favorable microglial morphology, suppressed activation, and reduced microglia–pyramidal tract axon interactions. They further determined that this interaction depended on synchronized neuronal activity.

### 4.2. Ultrasound neuromodulation

Current research on ultrasound in clinical neuroscience encompasses focused tissue ablation, neuromodulatory brain stimulation, and targeted opening of the blood–brain barrier (BBB) [65,66]. Unlike other neuromodulation methods, ultrasound offers advantages such as noninvasiveness, strong directionality, deep tissue penetration, and precise controllability. Thus, compared with invasive interventions, it is expected to enable more accurate and non-invasive rehabilitation for patients with SCI.

In a clinical trial involving 62 healthy adults, researchers applied low-intensity (2.5 $W{\cdot}cm^{-2}$) and high-intensity (10 $W{\cdot}cm^{-2}$) ultrasound. The results confirmed that spinal cord ultrasound stimulation modulates corticospinal excitability in a parameter-dependent manner, with inhibition occurring mainly at higher intensities and pulse repetition frequencies [67]. Experimental studies have further shown that low-intensity pulsed ultrasound (LIPUS) yields promising outcomes in neural repair following traumatic brain and peripheral nerve injuries. Ahmed et al. [68] reported that combining LIPUS with buspirone, a 5-hydroxytryptaminergic agonist, synergistically improved forelimb recovery in rats after cervical SCI. Our lab demonstrated that bone marrow stem cells (BMSCs) treated with LIPUS exhibited superior viability and neurotrophic factor expression compared with untreated cells, leading to better motor recovery and reduced cavity formation after transplantation [69]. Similar findings were reported by Liao et al., [70] who observed that NSCs subjected to LIPUS showed increased neurogenic marker and neurotrophic factor expression while reducing glial fibrillary acidic protein levels and preventing apoptosis after SCI. Studies have also explored optimal parameters for direct spinal LIPUS stimulation. Hong et al. [71] demonstrated that a 5% duty cycle significantly reduced macrophage and microglial activation and infiltration compared with a 40% cycle. Addressing complications secondary to SCI, Zamarioli et al. [72] applied LIPUS to treat femoral fractures in rats with severe osteoporosis induced by SCI, finding that LIPUS mitigated bone loss by enhancing bone formation while suppressing resorption.

Recent studies have explored how the cavitation effect of low-intensity focused ultrasound (LIFU) modulates BBB permeability. Using real-time magnetic resonance temperature monitoring, researchers demonstrated that LIFU directly opened the BSCB in rats without causing significant tissue damage [73,74]. Consequently, LIFU-induced BSCB opening has been proposed in combination with ultrasound-guided delivery strategies. Cationic nanobubbles loaded with BDNF [75] and poly(lactic-*co*-glycolic acid) (PLGA) nanobubbles expressing NGF [76], have been used to transfect target neurons via ultrasound-mediated nanobubble destruction, effectively inhibiting neuronal apoptosis in injured spinal tissue. Although no direct clinical studies have yet applied

**Table 1**
Summary of trials for SCS.

| Reference | Institute | Country | Study type | Patient type (acute/sub-acute/chronic) | AIS grade | Intervention | Number of enrolled patients | Outcomes | Effectiveness and significant findings |
|---|---|---|---|---|---|---|---|---|---|
| [45] | Department of Neurosurgery, Xuanwu Hospital | China | Case report | Chronic (1 year after injury, T12) | A | Spatiotemporal SCS with real-time triggered exoskeleton training (EXS-SCS) | One patient | After one month of treatment, patient gained improvement in iliopsoas and quadriceps femoris muscle strength to grades 3–4 | Spatiotemporal SCS + real-time exoskeleton training promises to restore SCI walking ability, aiding brain-spinal-muscle coordination and motor recovery |
| [46] | University of Birmingham | Canada | Case series | Chronic (≥ 1 year after injury, ≥ T6) | A–B | Cardiovascular-optimized ESCS, cardiovascular-optimized TSCS | Seven participants recruited, 4 completed the study (2 ESCS, 2 TSCS) | Cardiovascular function improved (blood pressure, cardiac contractility, stroke volume), alongside increased exercise endurance and peak oxygen pulse, and reduced perceived exertion | This study indicates that SCS has applications beyond enhancing motor function, particularly in improving cardiovascular function |
| [47] | Swiss Federal Institute of Technology | Switzerland | Prospective clinical feasibility study | Chronic (individuals with traumatic thoracic SCI, with injury levels including T4, T5/T6, and T6/T7) | A–B | Electrical stimulation is delivered to the dorsal roots of the lumbosacral spinal cord via an implanted new paddle lead, whose electrode arrangement is optimized to target the ensemble of dorsal roots involved in leg and trunk movements. It is combined with a computational framework to guide surgical positioning, and software is developed to rapidly configure activity-specific stimulation programs that simulate the activation pattern of motor neurons during natural movements | Three patients | Activity-specific stimulation programs let participants do key movements, boosting trunk control significantly | The new paddle lead outperforms original pain electrodes by targeting dorsal roots more precisely, enhancing stimulation selectivity and coverage. With personalized computational tools, it rapidly sets up activity-specific programs to simulate natural motor neuron activation, improving treatment efficiency |
| [48] | Fudan University | China | Experimental | — | — | Acquisition of MRI datasets for the lumbosacral spine with improved resolution of spinal nerve roots | Fourteen healthy adults (2 females, 12 males) | An open-access MRI dataset with detailed anatomical annotations, including nerve roots and 3D models of the lumbosacral spine | This high-res, open-access spinal nerve root dataset advances SCI rehabing nerve roots and 3D models of the lumbosacral spine, supports machine learning detection, and boosts clinical translation via anatomical data |
| [49] | Department of Neurosurgery, National Neuroscience Institute | Singapore | A preliminary study | Chronic (greater than 1 year, T1-L1) | A–B | The spinal cord stimulator (SCS) electrode array is surgically implanted on the dorsal epidural surface of the spinal cord. Mental imagery training is rehearsed at home and during rehabilitation sessions. The EksoGT robotic exoskeleton is used for overground gait training | Two patients | Both participants regained volitional motor control below the injury level, achieved independent overground walking with aids, and showed improved sEMG results and functional scores | The multimodal combined therapy is feasible and safe in improving volitional motor control and walking ability in patients with chronic complete SCI. |
| [50] | University of Washington | USA | Prospective, single-arm, multicenter, open-label, non-significant risk trial | Chronic (C2–C8), injury duration of more than 12 months. | B–D | Using the ARC$^{EX}$device, two surface electrodes were placed in intervertebral spaces above/below the cervical injury, and two large return electrodes over iliac crests or clavicles. Stimulation (30 Hz, 10 kHz carrier with 10e electrodes were placed in intervertebral spaces above/below the cervical injury, and two large return electrodes over iliac crests recovery | Sixty-five patients | Sixty-five patients enrolled, 60 completed the trial. 5 withdrew: 1 pre-procedure, 2 in rehabilitation-only (unrelated), 2 in therapy | First prospective multicenter trial: non-invasive cervical spinal cord stimulation (ARC$^{EX}$ therapy) + structured rehabilitation boosts arm/hand function in chronic cervical SCI. Seventy-two percent had meaningful strength/functional improvements, a new option for these patients |

**Table 1** (*continued*)

| Reference | Institute | Country | Study type | Patient type (acute/sub-acute/chronic) | AIS grade | Intervention | Number of enrolled patients | Outcomes | Effectiveness and significant findings |
|---|---|---|---|---|---|---|---|---|---|
| [51] | Tim and Caroline Reynolds Center for Spinal Stimulation | USA | Randomized controlled clinical trial | Chronic (C3–C8) | A–C | Electrical stimulation is delivered to the lumbosacral spinal cord via a 16-electrode array (5–6-5 Specify; Medtronic) and an Intellis™ neurostimulator implanted in the L1-S1 spinal segments | Thirty patients | Twenty-seven out of the 30 patients achieved a certain degree of ability to maintain proper trunk posture without external assistance | It demonstrates that even patients with severe motor complete injuries (such as AIS grade A) can significantly recover standing-related motor functions |
| [52] | Faculty of Physiotherapy and Nursing of Toledo | Spain | Double-blind randomized controlled clinical trial | Subacute incomplete injury (C2-T11) | C–D | Lokomat training combined with TSCS | Twenty-seven patients | Both groups improved significantly vs baseline, but the tSCS group had all functional outcomes enhanced post-intervention and at follow-up, while the sham group lacked improvement in post-intervention WISCI-II | tSCS + robotic-assisted gait training was well-tolerated and safe: only mild adverse effects (transient skin redness, lower limb paraesthesia, etc.) were reported, with no severe events |

AIS: American Spinal Injury Association Impairment Scale.

transcranial ultrasound stimulation (TUS) to human SCI, Blackmore J et al. [77] reported its safety and efficacy in 2019. Their systematic review of 35 studies involving 677 participants, including healthy individuals and patients with chronic pain, dementia, epilepsy, traumatic brain injury, and depression, found no serious adverse reactions. TUS altered short-term brain excitability and connectivity, induced long-term plasticity, and modulated behavior, providing a foundation for future SCI applications.

Current limitations include small sample sizes, variable patient responses, and strong placebo effects [65]. Moreover, ultrasound neuromodulation studies differ across multiple parameters, including duty cycle, energy level, pulse duration, pulse configuration, and total sonication time. Future work requires standardized protocols and comprehensive evaluation systems to accurately assess TUS efficacy in SCI.

### 4.3. Magnetic stimulation

Transcranial magnetic stimulation (TMS) is a noninvasive neuromodulation technology increasingly used in rehabilitation to induce neuroplasticity [78]. During TMS, a figure-of-eight coil combined with electric field navigation delivers magnetic pulses to the motor cortex, eliciting motor evoked potentials (MEPs) in the contralateral hand or lower limb. Clinically, single-pulse TMS is often applied to assess CST integrity by recording MEPs, providing objective indicators of injury severity and prognosis [79]. Various treatment coils, stimulation protocols, and outcome measures have been developed for TMS in SCI rehabilitation [80] (Table S1 in Appendix A). Magnetic stimulation acts on neurons by generating induced currents in nerve cells [81]. The resulting action potentials propagate through cortical current bundles, promoting cumulative therapeutic effects. Repeated stimulation strengthens synaptic efficacy, facilitates neuronal development, axonal branching, and myelination, thereby enhancing cortical–spinal connectivity [82,83]. TMS applications in SCI are based on its regulation of neuroplasticity. Repetitive TMS (rTMS) exerts frequency-dependent modulation: high-frequency stimulation (5–20 Hz, typically 10 Hz) enhances motor cortex excitability and reorganizes neural circuits below the lesion [84], whereas low-frequency stimulation (1 Hz or lower) inhibits hyperactivity in pain-related cortical areas, alleviating neuropathic pain in SCI [85]. Benito et al. [86] conducted a randomized, double-blind trial assessing high-frequency rTMS in 17 patients with motor incomplete SCI (ASIA grade D). The intervention group showed significant improvements in the modified ashworth scale (MAS), 10-meter walk test (10MWT), and other gait measures. Nogueira et al. [87] combined rTMS with body-weight-supported treadmill training (BWSTT), finding greater walking independence in the real stimulation group after six sessions. After 12 sessions, the lower extremity motor score and spinal cord independence measure III (SCIM-III) mobility score significantly improved, with no change in other indicators. These findings suggest that rTMS combined with BWSTT enhances gait in chronic SCI, consistent with animal studies [88]. Mechanistically, rTMS may downregulate autophagic flux and upregulate mammalian target of rapamycin (mTOR), phosphorylated mTOR (p-mTOR), and phosphorylated ribosomal protein S6 (p-S6) expression, activating the mTOR pathway and restoring hindlimb motor function in SCI mice, thereby reducing neuronal autophagy and promoting recovery [89]. rTMS also shows potential in regulating respiratory function after SCI. Patients with high cervical injuries often experience severe respiratory muscle paralysis due to disrupted respiratory pathways, accompanied by weak cough reflexes and impaired mucociliary clearance, which can result in pulmonary infections and respiratory failure [55,90,91]. Animal studies have shown that cervical spinal cord magnetic stimulation in

rats across acute, subacute, and chronic phases activates residual phrenic motor circuits and the diaphragm [92].

Researchers have also applied TMS directly to injured spinal regions with favorable results. In one case, a patient received ultra-early single-point TMS (25 Hz, 20 stimuli per 0.8 s, 15 s intervals, 76 repetitions, 1520 total stimuli), resulting in rapid recovery of motor and sensory functions, marking a successful in-situ magnetic stimulation intervention for SCI [93]. Another pilot study on patients with incomplete chronic spinal cord injury showed that after applying 2.5-mA transcutaneous spinal direct current stimulation in combination with intermittent theta-burst repetitive transcranial magnetic stimulation (iTBS), MEP assessments at 4 and 8 weeks demonstrated that the combined application could enhance corticospinal excitability and muscle activity. This is likely due to the synergistic activation of broader neural pathways [94].

### 4.4. Light-based modulation

#### 4.4.1. Photobiomodulation (PBM)

PBM therapy is a noninvasive treatment with anti-inflammatory properties and minimal side effects (Table S2 in Appendix A). It uses light of specific wavelengths to irradiate the injured site, modulating cellular functions through photobiological interactions to promote tissue repair and functional recovery [95,96]. Animal studies show that early PBM after SCI significantly reduces edema and hemorrhage, decreases neuronal necrosis and axonal degeneration, and notably inhibits secondary injury processes such as inflammation and oxidative stress [96–98]. Zhu Z et al. [99] demonstrated that PBM improves SCI prognosis by enhancing neuronal mitochondrial bioenergetics. The mechanism involves restoring mitochondrial respiratory chain activity, increasing ATP synthesis, and reducing neuronal apoptosis. Follow-up studies confirmed that PBM attenuates M1 macrophage polarization via the miR-330-5p–signal transducer and activator of transcription 3 (STAT3) pathway, providing theoretical support for its reparative potential [100]. Stevens et al. [101] examined transcriptomic changes in a rat SCI model and found that PBM induced significant enrichment of key repair pathways. On day 3 post-injury, gene set enrichment analysis revealed upregulation of Notch homolog 3 (Notch3), slit guidance ligand 1 (Slit1)/roundabout guidance receptor 2 (Robo2), and semaphorin 3 g (Sema3g) signaling, alongside suppression of apoptotic pathways. Other studies also showed that PBM acts on the nuclear factor kappa B (NF-κB) pathway to modulate C–X–C motif ligand 10 (CXCL10) secretion by astrocytes, thereby alleviating neuropathic pain following SCI [102]. A randomized clinical trial targeting patients with acute or subacute incomplete SCI (C3-L5 segments, ASIA grades B–D) demonstrated that those receiving PBM therapy—with parameters including a wavelength of 808 nm, a spectral bandwidth of 10 nm, continuous wave mode, and an average radiant energy of 120 mW—exhibited improvements in light touch/pinprick sensitivity, muscle strength, muscle contraction perception [103]. In contrast, a single-center observational study focusing on patients with acute thoracic SCI (ASIA grade B) found that 12 patients treated with laser therapy (wavelength 810 nm, power 300 mW, 30 min of irradiation daily for 7 consecutive days) showed no significant changes in vital signs or ASIA sensory/motor scores during treatment, and the slight improvement observed at the three-month follow-up was unrelated to PBM. Currently, the clinical application of PBM still necessitates the standardization of stimulation parameters [104].

#### 4.4.2. Optogenetics

Optogenetics centers on introducing genes encoding light-sensitive proteins into specific cells, which activate related ion channels under targeted light stimulation, promoting neuronal excitation or inhibition [105]. This precise regulation of neuronal activity provides a powerful tool for studying neural circuit function. In SCI research, this capability enables selective manipulation of distinct neural populations, allowing investigation of their roles in recovery and aiding the development of novel therapeutic strategies. Studies have shown that optogenetic stimulation facilitates regeneration of damaged axons in neural pathways such as the CST. Activation of neurons in the CST promotes axonal regeneration via the Janus kinase 2 (JAK2)/STAT3 signaling pathway [106]. Other studies indicate that neuron-specific optogenetic SCS significantly increases expression of regeneration-related proteins growth associated protein 43 (GAP-43) and laminin [107]. Deng et al. [108] used optogenetics to selectively activate glutamatergic neurons in the primary motor cortex of rats. Their findings demonstrated that this activation enhanced motor function scores, shortened motor evoked potential (MEP) latency, and increased motor potential amplitude.

### 4.5. Brain–computer interface (BCI)

BCI technology converts brain activity into commands to control external devices, offering innovative treatment and rehabilitation strategies for neurological disorders [109]. As a leading frontier technology, it is considered one of the most promising approaches for achieving functional recovery in patients with SCI (Table S3 in Appendix A). BCIs have also been widely applied in ischemic stroke [110,111], amyotrophic lateral sclerosis (ALS) [112], Parkinson's disease [113], and various cognitive and psychiatric disorders [114,115]. The core of BCI lies in real-time acquisition of brain electrical signals and their translation into executable commands for external devices. This process includes several stages: signal acquisition [116,117], preprocessing, feature extraction, classification, interface control, and feedback. BCI systems differ primarily in the use of invasive versus noninvasive inputs. At present, most rely on electroencephalography (EEG), a noninvasive method that records electrical brain activity via scalp electrodes [118]. With advantages such as noninvasiveness and high temporal resolution, EEG is suitable for real-time applications, though its spatial resolution and ability to detect deep brain signals remain limited [119]. To address this, researchers advocate techniques offering greater depth and precision in brain signal capture. Electrocorticography (ECoG), a semi-invasive method in which electrodes are placed directly on the cortical surface, provides clearer, higher-resolution signals [120,121], but requires surgical implantation and is typically restricted to clinical use. Other technologies, such as functional MRI (fMRI), indirectly measure neural activity through blood oxygenation changes, offering detailed anatomy and deep-brain functional mapping with relatively high spatial resolution [122].

Lorach et al. [123] reported that combining EES with a BCI created a digital bridge between the brain and spinal cord. ECoG signals from the sensorimotor cortex were transmitted in real time to a portable base station and processing unit via a high-frequency antenna (402–405 MHz). Decoded motor intentions were converted into stimulation commands, transmitted to custom software, and delivered to an implantable pulse generator. Currently, multiple studies involving institutions from various countries have been carried out. By combining technologies such as functional electrical stimulation (FES), virtual reality (VR), and microelectrode arrays with BCI, these studies have achieved varying outcomes in motor function, sensory function, and quality of life. Meanwhile, they also reflect that further exploration is still needed in aspects like the standardization of stimulation parameters and the limitations of technical applications [124–128].

In 2024, Levett's team conducted a systematic review of implantable closed-loop neural interface systems for SCI repair.

Across 19 clinical studies involving 21 patients with cervical SCI, results showed that despite variations in interface design, algorithms, and modulation protocols, all participants demonstrated sustained motor improvement during task performance, confirming the strong potential of BCIs in this field [129]. In the work of Oliveria et al. [128], a noninvasive neural interface was used in eight patients with motor-complete cervical SCI (C5–C6 segment injury), allowing modulation of spinal motor neuron populations with residual pathways. Signals from spared motor neurons under voluntary control were captured by wearable muscle sensors and mapped to a real-time controllable virtual hand. Patients utilized surviving neurons to enhance motor recovery when integrated with assistive devices.

Future integration of BCIs with artificial intelligence (AI), machine learning, neural networks, and virtual reality (VR) is expected to greatly improve system adaptability and performance. AI can learn individual brain patterns, process large-scale data to enhance precision, and perform real-time adaptive optimization, while VR facilitates immersive, task-specific neurorehabilitation. The therapeutic targets, mechanisms, and limitations of various current neurostimulation and neuromodulation techniques are summarized in Table S4 in Appendix A.

## 5. Rehabilitation training

Rehabilitation training for SCI requires a long-term, comprehensive plan that integrates medical care, exercise therapy, psychological support, and social assistance. For patients, rehabilitation should focus on restoring or compensating for functional deficits, preventing complications, and improving quality of life [130]. Common rehabilitation approaches include exoskeleton-assisted walking (EAW), VR applications [131], psychological counseling [132], and active or passive exercise training.

Early rehabilitation is vital for preventing joint contractures, muscle atrophy, loss of bone mineral density, and maintaining respiratory and digestive function. It is now recognized that SCI rehabilitation should continue throughout the entire treatment process. During the acute phase, patients with complete SCI are prone to joint stiffness and contracture, requiring high-intensity lower limb range-of-motion training: at least once daily during spinal shock, increasing to 2–3 times daily after spasticity develops [133]. Proper joint positioning must be maintained. Bedridden patients should be repositioned every 2–3 h, with attention to pressure-prone areas such as the sacrum and ischium. Patients should actively participate in repositioning and maintain skin hygiene. Regular prone rest and full range-of-motion training help reduce hip flexor tone, while ankle joint exercises prevent foot contracture. In the chronic phase, the primary goal is to help patients achieve independent mobility. Walking potential is influenced by injury level and age; generally, the lower the injury, the better the walking ability.

In recent years, several studies have examined optimal parameter protocols for EAW in specific indications. Evidence-based recommendations suggest conducting three 60 min sessions per week for nine weeks to guide overground exoskeleton training in patients with SCI and disease [134]. A study of 161 veterans with SCI found no significant difference in health outcomes between those using EAW and those receiving standard care. However, two cases of foot fractures associated with EAW use and nine unrelated fractures were reported, highlighting that adverse outcomes may stem from insufficient supervision or inadequate training [135]. Furthermore, a randomized crossover trial by McKenzie et al. [136] showed that combining acute intermittent hypoxia, TSCS, and locomotor training yielded greater improvements in functional measures, including the timed up-and-go assessment and preferred walking speed, than individual or placebo interventions. Similarly, Tsai et al. [137] reported that patients with acute SCI demonstrated significantly higher scores on the International Standards for Neurological Classification of Spinal Cord Injury and improved motor and sensory assessments compared with their acute rehabilitation outcomes.

Depression and psychiatric comorbidities are notably prevalent among patients with SCI; suicide remains a leading cause of death in individuals younger than 55 years, and post-traumatic stress disorder occurs in about 17% of cases. Prompt psychiatric consultation is essential if such symptoms develop [132]. In the future, rehabilitation programs for individuals with SCI should adopt an interdisciplinary collaborative model to optimize recovery outcomes.

## 6. Surgical intervention

### 6.1. Surgical decompression

Early surgical decompression after SCI alleviates sustained spinal cord compression, improves local blood supply, and limits secondary injury progression. The timing of decompression in acute traumatic SCI remains one of the most urgent clinical decisions [138]. The theoretical basis for early surgery lies in promptly relieving mechanical compression and restoring microcirculation [139], allowing oxygen and nutrients to reach neurons, thereby maintaining cellular metabolism and reducing ischemic and hypoxic neuronal death [140,141].

Currently, no universally accepted definition exists for "early decompression." Most studies classify surgeries within 24–72 h post-injury as early, though others refine this window for precision. A 2021 pooled analysis in *The Lancet Neurology* by Badhiwala et al. [145] included 1548 patients from four multicenter datasets who underwent decompressive surgery for acute SCI. Patients were grouped by timing, early (< 24 h) or late SCI. Patients in the early group achieved significantly greater motor-score improvements, with benefits declining after 24 h and plateauing beyond 36 h. These findings suggest that decompression within 24 h optimizes neurological recovery, with the 24–36 h period representing a critical therapeutic window [142]. In analyses of central cord syndrome (CCS), 186 patients were divided equally into early and late surgery groups. Early decompression markedly improved upper-limb motor function, whereas lower-limb gains were modest. Subgroup analysis showed similar outcomes between groups in patients with American Spinal Injury Association Impairment Scale (AIS) grade D, but those with grade C benefited significantly from early surgery in both upper and lower limbs [143]. Although early decompression surgery has several theoretical advantages, it still faces substantial challenges in clinical practice. Differences in patient selection, surgical approaches, and postoperative evaluation methods among studies limit comparability. For instance, some researchers have suggested using intraoperative ultrasound (IOUS) to assess decompression effectiveness. Chryssikos et al. [144] evaluated the accuracy of IOUS in determining real-time spinal cord decompression adequacy after cervical laminectomy by comparing it with postoperative MRI and computed tomography (CT) myelography. IOUS immediately identified 9.8% of cases requiring further decompression, while postoperative imaging confirmed adequate decompression in 43 cases (84.31%).

Based on current evidence, the guideline development team explicitly recommended that surgical decompression within 24 h post-injury be considered a preferred treatment for SCI, with stronger endorsement than in the 2017 edition. This guideline

emphasized the critical role of early decompression in SCI management and provided key evidence for elevating its recommendation grade in clinical practice [145].

### 6.2. Hemodynamic management and expansile duraplasty

Spinal cord hypoperfusion is a major contributor to secondary injury, exacerbating neuronal ischemia and necrosis and worsening neurological outcomes. Thus, hemodynamic management has become a central strategy for maintaining spinal cord perfusion and reducing secondary injury, drawing increasing focus in both clinical and experimental SCI research. Current management primarily targets mean arterial pressure (MAP) and spinal cord perfusion pressure (SCPP) [146]. Numerous studies have confirmed that the spinal cord is highly sensitive to perfusion changes [147] and extremely vulnerable to reduced blood pressure and perfusion. Blood pressure instability within 7 d of injury is a critical prognostic factor. Neurogenic and hypovolemic shock often cause abrupt MAP declines [148], aggravating ischemia. Present clinical approaches emphasize determining optimal MAP targets and maintenance duration [149]. Although studies have not fully established a consistent relationship between MAP and neurological recovery [149,150], the association appears individually variable, influenced by injury level, severity, and comorbidities [151]. Further personalized research is needed to validate these links. Future efforts should focus on developing non-invasive SCPP monitoring techniques to replace current invasive methods.

tSCI leads to persistent bleeding, edema, and inflammatory responses that cause swelling of the spinal cord tissue. This swelling compresses the surrounding dura mater, elevating intraspinal pressure [152,153], impairing perfusion, and worsening secondary neurological injury. Although traditional decompression surgery relieves external compression, it is less effective in improving pressure dynamics within the intrathecal space. As an extended decompression technique, expansile duraplasty offers a new treatment approach for SCI by enlarging the dural sac, lowering intraspinal pressure, and enhancing spinal cord perfusion [154].

A single-center retrospective study by Robinson et al. [155] reported that patients with tSCI who underwent expansile duraplasty achieved significantly greater ASIA motor score improvement at rehabilitation discharge than those who did not undergo duraplasty. Telemacque et al. [156] reviewed the outcomes of durotomy and myelotomy for SCI, finding that 92.3% of human studies and 83.3% of animal studies reported positive neurological effects. A phase II multicenter randomized controlled trial is currently enrolling 222 adults with acute, severe cervical tSCI (ASIA grades A, B, or C), randomized 1:1 to bony decompression alone or decompression plus duraplasty. The primary outcome is motor score change at six months, with secondary outcomes including functional recovery, quality of life, complications, reoperation rates, and mortality at 6 and 12 months. This trial is expected to clarify the efficacy and safety of expansile duraplasty and provide high-level evidence for its clinical application [157].

### 6.3. Nerve bypass and transfer surgery

Recent years have seen nerve bypass and nerve transfer emerge as two innovative neural reconstruction techniques that repair and compensate for disrupted neural pathways through distinct mechanisms, offering new possibilities for SCI repair. In spinal cord reconstruction via nerve bypass surgery, proximal peripheral nerves are typically relocated to spinal cord segments below the injury level [158,159]. This approach spans the SCI segment to reconstruct neural continuity above and below the lesion. The procedure involves connecting proximal and distal nerves through direct relocation or grafts to form a "bridge" that bypasses the injured area. Hsueh et al. [160] evaluated the feasibility and clinical efficacy of nerve bypass surgery in patients with complete thoracic SCI. Among eight participants, six showed motor and overall functional improvements, with ASIA scores increasing by an average of 10 points in motor function and 28.25 points in sensory function. The remaining two had no motor recovery but showed distal sensory extension, with ASIA scores rising by 16 points. Xiang et al. [161] systematically reviewed advances in nerve transposition for functional restoration after CNS injury. Their findings showed that, in patients with SCI, target muscle strength increased by an average of 3.13 grades on the Medical Research Council scale, and 15 of 20 cases exhibited a reduction in residual urine volume exceeding 100 mL. By constructing a "signal bypass" that enhances neural plasticity, nerve transposition significantly improves limb sensorimotor and bladder functions, providing a promising surgical strategy for SCI rehabilitation.

Nerve transfer involves redirecting a healthy nerve to a target organ that has lost its innervation, aiming to reestablish direct neural input to the affected muscle or organ. In SCI, peripheral nerves above the lesion level are typically selected as donors, and their original conduction function is "grafted" to muscles or organs below the injury. Berger et al. [162] assessed nerve transfer efficacy in patients with high-level SCI by measuring compound muscle action potential (CMAP) from the ulnar nerve at the abductor digiti minimi, showing that hand function improved after the procedure. A research team from the University of Alberta conducted a population-based analysis of patients with tSCI, including 709 cases, of which 224 (32%) met screening criteria with injuries between C1 and T1. Ultimately, 108 patients (15% of the total cohort and 48% of cervical tSCI cases) were deemed suitable candidates for nerve transfer (NT). These findings suggest that a substantial number of patients with cervical tSCI may benefit from this intervention. [15]. Additionally, Italian investigators examined upper limb nerve transfer in 12 patients with tSCI (AIS grade A or B) and neurological levels between C4 and C7. The results showed improvements in Medical Research Council (MRC) muscle strength scale scores, upper limb function, and independent living ability, as assessed by the grasp-and-release test. [163].

## 7. Cytotherapy

Cell transplantation has been recognized as a highly promising therapeutic strategy for SCI [164]. Transplanted cells promote neural repair through multiple mechanisms, including replacing apoptotic neurons, stimulating axonal regeneration, and modulating the immunosuppressive microenvironment.

### 7.1. Engineered strategies for transplanted cells

*In vitro* cell modification involves pre-transplant manipulation to enhance post-implantation survival, integration, and repair efficacy. Core strategies include genetic engineering, pre-activation or pre-differentiation, and pharmacological preconditioning. These approaches collectively overcome the limitations of native cells, forming a key direction for efficient and controlled cell-based SCI therapies. Genetic engineering modifies gene expression *in vitro* using viral vectors (lentiviruses, adeno-associated viruses, and non-integrating vectors) or non-viral methods (electroporation and nanoparticles) [165]. For example, overexpression of neurotrophic factors (vascular edothelial growth factor (VEGF), BDNF, NT-3, and GDNF), anti-apoptotic proteins (Bcl-2 and Akt), pro-regenerative molecules (L1 cell adhesion molecule (L1CAM) and integrins), or immune modulators (heme oxygenase-1 (HO-1) and IL-10) enhances the pro-repair and anti-inflammatory capacity of transplanted cells in SCI [166]. Pre-activation or pre-differentiation stimulates stem or progenitor cells with specific

factors before transplantation, guiding differentiation into therapeutically potent phenotypes. NSCs can be induced into functional neurons, and quiescent macrophages polarized into anti-inflammatory M2 states. This pre-specification process improves targeting precision, efficacy, and therapeutic outcome. Pharmacological preconditioning refers to a preprocessing method in which cells are exposed to pharmaceutical agents or modified culture environments prior to transplantation. [167]. This approach enhances the tolerance of cells to harmful microenvironmental stresses, improves survival rates, or optimizes beneficial paracrine functions. By altering the profile or levels of secreted factors, it can indirectly enhance the repair ability of cells at the injury site [168].

### 7.2. Types of cells available for transplantation

A growing body of clinical research has evaluated various cell types for SCI therapy, including NSCs, mesenchymal stem cells (MSCs), olfactory ensheathing cells (OECs), and Schwann cells (SCs). These studies collectively demonstrate a consistent safety profile and preliminary evidence of functional recovery in selected patients. Table 2 [169–182] summarizes representative clinical trials of cell-based therapies for SCI, outlining cell type, delivery route, study design, and major outcomes. This overview provides a framework for understanding the translational potential of each cell source before discussing specific categories such as stem cells.

#### 7.2.1. Embryonic stem cells (ESCs)

Derived from the inner cell mass of the blastocyst, ESCs possess high pluripotency and can differentiate into nearly any somatic cell type. However, direct ESC transplantation carries a significant risk of teratoma formation, severely limiting clinical use [181]. Therefore, ESC-based applications require *in vitro* pre-differentiation into specific functional cell types, such as neurons or NPCs, before transplantation. In a rat thoracic contusion model, Kim et al. [182] transplanted 100 000 human ESC-derived NPCs expressing the polysialylated neural cell adhesion molecule (PSA-NCAM) marker (hNPCs PSA-NCAM$^+$) via microinjection into the lesion at 7 d post-injury. Results showed successful differentiation of hNPCs PSA-NCAM$^+$ into neural cells, integration into host tissue, improved motor function, and no tumorigenicity. Similarly, Jones et al. [183] transplanted ESC-derived neural crest cells, capable of neuronal differentiation, into acute and chronic rat cervical SCI models, observing enhanced axonal remodeling and forelimb motor recovery.

#### 7.2.2. Induced pluripotent stem cells (iPSCs)

iPSCs, characterized by unlimited self-renewal while preserving the patient's genetic background, serve as crucial tools bridging basic research and clinical application. However, direct iPSC transplantation remains limited by uncontrolled differentiation. Pre-transplant strategies, such as *in vitro* directed differentiation, are therefore essential to enhance precision and efficiency toward target cell types, improving therapeutic efficacy [184]. Gong et al. [185] transplanted iPSCs into the spinal cord, followed by pharmacological induction toward gamma-aminobutyric acid-ergic (GABAergic) inhibitory neurons, which integrated into host circuits and significantly reduced post-SCI spasticity. Wertheim et al. [186] encapsulated iPSCs in an ECM-mimetic hydrogel replicating the embryonic spinal microenvironment. This engineered construct, designed with defined structural and functional properties, markedly enhanced therapeutic outcomes and translational potential in acute and chronic SCI models. Wu et al. [187] generated NSC-like cells from iPSCs *in vitro* and integrated them into functional neural networks using biomaterial scaffolds. This composite promoted neuronal regeneration, synaptogenesis, and improved the pathological microenvironment within the lesion.

#### 7.2.3. NSCs/NPCs

As multipotent stem cells capable of self-renewal, NSCs differentiate into neurons, astrocytes, and oligodendrocytes. Although widely studied in SCI therapy, unmodified NSC transplantation shows limited efficacy [188]. A major challenge is the hostile post-injury microenvironment, where ROS and pro-inflammatory cytokines bias NSC differentiation toward astrocytes rather than neurons, impeding neural circuit reconstruction [189–191]. To counter this, Li et al. [192] used biomimetic nanoscaffolds with NSC transplantation to guide cell alignment and promote neuronal differentiation, significantly enhancing axonal reinnervation and remyelination in rat SCI models. Another innovative study employed a modular tissue-engineering approach: white matter-like tissue containing ciliary neurotrophic factor (CNTF)-overexpressing oligodendrocytes and gray matter-like tissue with NT-3/tropomyosin receptor kinase C (TrkC)-overexpressing neurons were co-cultured and assembled into spinal cord-like tissue. When transplanted into a rat spinal transection model with modulated medium-frequency tail nerve stimulation, this construct effectively reconstructed neural circuitry and restored motor function [193]. Notably, Wang et al. [194] showed that astrocytes derived from oligodendrocyte transcription factor 2 (Olig2)-GFP-labeled progenitors (Olig2PC-Astros) reprogrammed lesion-associated microglia toward an anti-inflammatory phenotype via IL-4 signaling, facilitating repair. Collectively, these studies highlight that engineered strategies regulating NSC/NPC differentiation and function enable precise interventions in diverse pathological processes of SCI.

#### 7.2.4. Mesenchymal stromal cells (MSCs)

MSCs originate from diverse sources, including BMSCs, adipose tissue MSCs (AT-MSCs), umbilical cord MSCs (UC-MSCs), and dental pulp MSCs (DP-MSCs) [195]. As multipotent stem cells, MSCs self-renew and differentiate into various cell types [196,197]. Their therapeutic value arises mainly from paracrine actions, secreting factors such as colony-stimulating factors (CSFs), stem cell factor, and NGF [198] to promote neurogenesis and neural pathway reconstruction. MSCs also modulate the lesion immune microenvironment and provide neurotrophic support [199]. However, short transplant survival substantially limits efficacy. Yang et al. [200] used a hyaluronic acid (HA)-scaffold system to enhance adhesion and proliferation of human MSCs in rat SCI models, prolonging survival and identifying IL-10 as a core regulator in MSC-mediated repair. Subsequent studies show that MSC preconditioning augments efficacy. Liang et al. [201] demonstrated that hypoxia-preconditioned MSCs, by upregulating miR-146a-5p, reprogrammed lesion macrophages toward an anti-inflammatory phenotype, reducing inflammation and secondary injury.

#### 7.2.5. Olfactory ensheathing cells

OECs, specialized glia present in both the peripheral and central nervous systems, possess strong regenerative and protective properties [202]. Zhang et al. [203] reported that transplanted OECs respond to pro-inflammatory mediators released by activated microglia at the injury site, secreting IL-1 receptor antagonist (IL-1Ra) to suppress neuroinflammation. Jiang et al. [204] found that curcumin-preconditioned OECs more effectively modulate microglial polarization toward anti-inflammatory states, markedly reducing inflammatory cascades and promoting functional recovery.

#### 7.2.6. Schwann cells

As essential structural elements of the peripheral nervous system, SCs establish a permissive microenvironment for axonal regeneration by secreting neurotrophic factors and depositing pro-neural growth proteins (e.g., laminin and fibronectin) in the

**Table 2**
Summary of representative clinical trials of cell-based therapies for SCI.

| Reference | Institute | Country | Study type | Patient type (acute/sub-acute/ chronic) | AIS grade | Intervention | Number of enrolled patients | Outcomes |
|---|---|---|---|---|---|---|---|---|
| [169] | Department of Neurological Surgery, University of California | USA | Phase I study | Chronic SCI | A | Six bilateral injections; 2 × 10 bilateral injection | Four patients | Sensory and motor gains in three of four patients |
| [170] | Department of Neurological Surgery, University of California | USA | Single-site phase 1 study | Chronic thoracic SCI | A | Removal of spinal instrumentation; laminectomy and durotomy; Bilateral injections of NSI-566 cells | Four patients | Sustained sensory and motor gains up to five years |
| [171] | Department of Neurological Surgery, Mayo Clinic | USA | Phase I trial | Six cervical-level and four thoracic-level SCI | A and B | Adipose-derived mesenchymal stem cells (AD-MSCs) are isolated and expanded to 100 million cells, and then injected into patients intrathecally | Ten patients | AIS grade improvement in seven of ten patients |
| [172] | Shahid Beheshti University of Medical Sciences | Iran | A phase II randomized active-controlled trial | Chronic SCI | A | A mixture containing MSCs ($5 \times 10^5$ cells per mL) and scs (SCs, $5 \times 10^5$ cells per mL) was suspended in 6 mL of normal saline | Thirty-seven patients | Reduced neuropathic pain |
| [173] | Sapporo Medical University School of Medicine | Japan | Phase II study | Chronic cervical SCI | A and B | Intravenous infusion of 1.0 ative Medicine, Resea | Thirteen patients | AIS grade and SCIM improved in 12 of 13 |
| [174] | Department of Neurosurgery, Çorlu Reyap Hospital, | Turkey | Phase I study | Chronic complete SCI | A | Wharton's jelly mesenchymal stromal cells (WJ-MSCs) were administered twice monthly for two months, with each route receiving a dose of $1 \times 10^6$ cells·kg$^{-1}$ | Six patients | ASIA motor improved |
| [175] | Department of Neurosurgery, N.V. Sklifosovsky Research Institute of Emergency Care | Russia | Phase 1/2a pilot clinical study | Severe acute contusion SCI | A and B | Patients were treated with four infusions of group-matched and rhesus-matched cord blood samples after primary surgery within 3 d after SCI | Ten patients | Lower-limb motor scores improved |
| [176] | Stem Cell & Translational Neurosciences Lab | India | A randomized placebo-controlled trial | Acute complete SCI | A | After sufficient surface at the contusion site was exposed, 300 μL aliquots of cells (with a total volume of 1.8 mL) were injected into six separate positions surrounding the lesion site (to cover the maximum cord volume as much as possible), with an injection depth of 5 mm from the ventral surface and 5 mm lateral from the midline; $2 \times 10^8$ cells were injected at a rate of 300 μL·min$^{-1}$ | Twenty-seven patients | 85% AIS grade and bladder improved |
| [177] | Shahid Beheshti University of Medical Sciences | Iran | A randomized, open-label, phase II clinical trial | Chronic cervical SCI | A | A mixture of SCs and MSCs (with a concentration of $5 \times 10^6$ cells per mL for each cell type) was suspended in 6 mL of normal saline and used for intrathecal injection | Thirty-two patients | Improvement of neurogenic bladder dysfunction |
| [178] | Fundación Institut Guttmann | Spain | A randomized controlled study | Chronic thoracic SCI | A | Single intrathecal infusion of *ex vivo* expanded WJ-MSCs derived from human umbilical cord ($10 \times 10^6$ cells) | Ten patients | Pinprick sensation improved vs placebo |
| [179] | The Miami Project to Cure Paralysis, University of Miami | USA | Phase 1 study | Chronic thoracic SCI | A–C | Soft medical grade tubing (inner diameter 0.31 mm, outer diameter 0.62 mm) was inserted into the cavity via myelotomy. The tubing, pre-filled with cells, was connected to an insulin syringe loaded with ahSCs (100 000 cells·μL$^{-1}$). Initially, the injection proceeded at a rate of less than 50 μL·min$^{-1}$ | Eight patients | Motor and sensory gain and MRI cavity reduced |
| [180] | University of Tsukuba | Japan | Prospective, multicenter, nonrandomized, nonblinded, single-arm study | Chronic cervical SCI | A and B | The participants were administered $15 \times 10^6$ Muse cells ($2.1 \times 10^6$–$2.7 \times 10^6$ cells·kg$^{-1}$ of body weight) in normal saline via intravenous drip infusion | Ten patients | Motor and ADL improved |

ECM [205]. However, direct SC transplantation results in substantial cell loss. Marquardt et al. [206] developed an injectable hydrogel SC carrier that markedly reduced cell loss and enhanced SC-mediated functional recovery. To further improve efficacy, Du et al. [207] transplanted GDNF-overexpressing SCs (SCs-GDNF) into SCI lesions, reconstructing axon growth-permissive pathways and promoting local axonal regeneration. David et al. [208] reported that hypoxia- or deferoxamine-preconditioned Schwann cells transiently upregulated hypoxia-inducible factor-1α (HIF-1α) and its target genes, reduced oxidative stress, and enhanced

vascularization in the injured cord. However, this approach did not significantly improve long-term graft survival or functional recovery.

#### 7.2.7. Astrocytes

Providing crucial trophic and metabolic support for neuronal regeneration, astrocyte transplantation remains a promising SCI therapy [209]. Chang et al. [210] generated A1 and A2 astrocyte phenotypes *in vitro* and transplanted them into murine SCI lesions. Compared with A1 astrocytes, A2 astrocyte transplantation significantly improved motor recovery, reduced glial scarring, and enhanced neurofilament formation at the lesion site.

#### 7.2.8. Macrophages and microglia

As principal immune regulators after SCI, macrophage and microglial polarization toward pro-inflammatory (M1) or anti-inflammatory (M2) phenotypes determines both secondary damage and neural repair outcomes. Han et al. [211] showed that tauroursodeoxycholic acid (TUDCA)-induced M2 macrophage transplantation into the lesion core reduced neuroinflammation and improved motor recovery. Kobashi et al. [212] generated M1 and M2 microglia using granulocyte macrophage colony stimulating factor (GM-CSF) or IL-4 *in vitro* and transplanted them into SCI mice. Compared with control or M1 microglia groups, M2 microglia transplantation significantly improved motor recovery and restored retrograde axonal transport between neuromuscular junctions and the injured cord.

#### 7.2.9. T cells

T cells exert vital immunomodulatory effects after SCI. Single-cell RNA sequencing confirmed clonal T cell expansion in both mice and humans. Notably, murine $CD4^+$ T cell clones displayed antigen specificity toward myelin- and neuron-derived peptides. To mitigate sustained autoreactive activation, Gao et al. [213] engineered transient autoimmune T cells via messenger RNA (mRNA)-based T cell receptor (TCR) recombination technology for controlled immune modulation. Transplantation into SCI lesions produced notable neuroprotection mediated through IFN-$\gamma$-dependent regulation of myeloid cell activity.

## 8. Biomaterials

In the field of biomaterials for SCI repair, the conventional classification into natural and synthetic materials reflects their sources but does not fully capture their functional orientation or translational relevance in therapeutic contexts. To emphasize the clinical applicability and translational significance of biomaterials in SCI repair, this paper departs from the traditional natural/synthetic distinction and categorizes materials into five groups—hydrogel, 3D-printed scaffolds, nanomaterials, microspheres, and responsive materials—based on morphology, structure, and mechanisms of action in key clinical applications (Table S5 in Appendix A). This framework better addresses the practical requirements of spinal cord repair, clarifying application contexts and guiding material selection from experimental design to clinical translation.

### 8.1. Hydrogel

Hydrogel—3D polymeric network materials with excellent biocompatibility—serve as biomimetic platforms that replicate native extracellular matrices. They integrate seamlessly into lesion sites, optimizing the microenvironment and establishing favorable conditions for neural regeneration [214,215]. Hydrogels also act as delivery vehicles for stem cells, therapeutic agents, and growth factors [216]. By modulating release kinetics, spatial distribution, and the transplanted cell niche, hydrogel-based systems enhance therapeutic strategies for spinal cord microenvironmental repair (Table S5).

Based on material origin, hydrogels are classified as natural or synthetic. Natural hydrogels, derived from biogenic macromolecules, mimic ECM functions to support cell proliferation and differentiation [217]. They include protein- and polysaccharide-based types. Collagen and its derivative gelatin are the main protein hydrogels, shown to suppress glial scar formation and promote axonal regeneration in SCI rat models [218,219]. Recombinant proteins provide programmable alternatives for constructing matrices tailored for spinal repair. Wei et al. [220] engineered a self-assembling recombinant CsgA hydrogel that reduced neuroinflammation and enhanced regeneration, resulting in notable locomotor recovery in SCI rats. HA, a vital extracellular component, forms the basis of polysaccharide hydrogels [221]. Owing to its chemical versatility and high drug-loading capacity, HA hydrogels are widely applied in SCI therapy. Tan et al. [222] synthesized dopamine-grafted HA (HADA) and combined it with a designer peptide (HRR) to form HADA/HRR hydrogel, which modulated fibroblast activity, reduced scarring, and enabled axonal regrowth across lesions.

Synthetic hydrogels, built from polymers with defined molecular weights and repetitive monomers, allow tailored control of degradation, elasticity, and pore structure. Polyethylene glycol (PEG) and poly(vinyl alcohol) (PVA) are primary examples. Liu et al. [223] created an aligned PVA hydrogel system in which tetramethylpyrazine (TMP) was encapsulated during gelation, overcoming TMP hydrophobicity and low drug-loading efficiency. A newer category maintains hydrogel fundamentals but optimizes specialized properties, such as injectability, conductivity, and anisotropic architecture [224]. Wu et al. [225] designed a conductive chitosan/gelatin hydrogel doped with black phosphorus nanosheets (BPNSs). Under high-frequency electrical fields, the scaffold generated alternating current via capacitive coupling, enabling wireless *in situ* stimulation for SCI treatment.

In recent years, hydrogels have demonstrated strong potential in SCI therapy due to their ECM-like structure and high water content, which allow lesion filling, axonal support, and controlled drug or cell delivery. Research trends emphasize enhancing natural hydrogels through molecular modification and refining synthetic ones via structural design. Both approaches regulate local regeneration by releasing bioactive cues, and some composites have achieved tissue integration in large animal models. Nonetheless, challenges persist: limited mechanical strength, incomplete degradation–drug release synchronization, reduced efficacy in compression versus transection models, and lack of standardized production and safety systems hinder clinical translation. Future directions include reinforcing mechanical stability through composite design [226,227], developing multifunctional and personalized platforms, and establishing standardized manufacturing and multicenter clinical trials to ensure long-term safety and cross-scale translation.

### 8.2. 3D-printed material

Conventional bioscaffold fabrication often fails to replicate the complex architecture, tissue-specific properties, and physiological functions of the native spinal cord. 3D bioprinting overcomes these limitations through structural biomimicry, functional integration, and customized design, offering superior precision, reproducibility, and efficiency. These advantages establish it as a transformative approach in regenerative medicine and tissue engineering [228]. 3D bioprinting strategies for spinal cord scaffolds generally fall into two categories. A cellular 3D scaffold printing employs bio-inks to

produce structurally defined, cell-free constructs. Cell/factor-scaffold co-bioprinting homogenizes bio-inks with cells or bioactive agents before printing, generating scaffolds embedded with biological components [229]. Liu et al. [230] developed a supramolecular bio-ink combining gelatin methacryloyl (GelMA) and acrylated β-cyclodextrin (Ac-β-CD) to fabricate 3D-printed neural scaffolds with spinal-cord-like architecture. These constructs, co-loaded with NSCs and an O-GlcNAc transferase inhibitor (OSMI-4), markedly improved hind-limb motor recovery in SCI rats. Jiu et al. [231] designed a mechanoresponsive stem-cell complex (MRSCC) via 3D bioprinting using gelatin microcarriers encapsulating MSCs. The MRSCC established an optimized mechano-microenvironment that activated piezo-type mechanosensitive ion channel component 1 (Piezo1) channels and yes-associated protein 1 (YAP) signaling, upregulating neurogenic genes and enhancing paracrine effects.

Because the spinal cord's gray and white matter differ biomechanically, replicating this stiffness gradient is vital. Tran et al. [232] introduced a modified digital-light-processing technique to print scaffolds with programmable mechanical heterogeneity mimicking white/gray-matter contrasts. *In vivo*, these heterogeneous scaffolds promoted robust axonal regrowth. Bai et al. [233] fabricated a multidimensional biomimetic spinal-cord-like scaffold (MBSLS) from silk fibroin and decellularized umbilical cord using dual-network crosslinking and laser processing. The MBSLS exhibited hierarchical gray/white-matter channels and micropores that precisely guided neural regeneration. Given the architectural complexity of the CNS, spatial cellular heterogeneity governs neural-pathway reconstruction. Accordingly, 3D-printed scaffolds must reproduce this zonation [234]. Joung et al. [235] engineered a dual-zonal scaffold with BMSCs patterned peripherally and SCs aligned axially. This spatial organization induced BMSC neurogenesis and SC-mediated myelination, accelerating signal conduction. Despite promising outcomes, deeper insight into scaffold–cell molecular crosstalk remains crucial for clinical translation.

Presently, 3D printing in SCI repair emphasizes developing biocompatible, degradable polymer scaffolds, typically blends of silk fibroin, collagen, or alginate. Tuning their mechanical and biological properties enhances neural regeneration. Integrating cell carriers and neurotrophic factors further optimizes the microenvironment, yet challenges persist: limited vascularization, insufficient host–tissue integration, and poor long-term stability. Future directions include improving vascular support, refining cell-carrier functionality, and enhancing tunable composite design to enable durable functional recovery.

### 8.3. Stimuli-responsive smart biomaterials

In recent years, stimuli-responsive smart biomaterials have gained prominence in SCI repair due to their manipulability, biosafety, therapeutic efficacy, and multifunctionality. These materials uniquely simulate the lesional microenvironment across multiple scales while dynamically responding to pathological cues, ROS, enzymatic activity, and pH fluctuations, and external stimuli such as temperature, ultrasound, and electromagnetic fields. This enables precise spatiotemporal control of functional transitions to remodel the damaged spinal cord niche [236–238].

Oxidative stress arising from disrupted homeostasis between ROS production and clearance plays a central role in secondary SCI pathology. ROS-responsive smart materials activate upon exposure to elevated ROS concentrations, releasing encapsulated therapeutics and bioactive factors to modulate ROS levels and suppress oxidative stress [239]. Eldahan et al. [240] isolated extracellular vesicles from MSCs and encapsulated dexamethasone (Dxm) to create drug-loaded vesicles termed 3EVs-Dxm. The vesicle surface was modified with *O*-dihydroxyl groups (–2OH), allowing covalent conjugation with phenylboronic acid-modified HA (HA-PBA) via phenylboronate ester bonds and crosslinking with tannic acid (TA) to form an injectable ROS-responsive hydrogel (3EVs-Dxm-Gel). Dynamic cleavage of phenylboronate bonds enabled precise, on-demand 3EVs-Dxm release at lesion sites, mitigating oxidative stress and neuroinflammation during acute SCI [241].

Sequential stimulus-responsive materials differ from conventional single-stimulus systems by responding to multiple triggers through programmed activation sequences, producing progressive functional transitions under dynamic conditions. Chen et al. [242] designed a dual-responsive hydrogel sensitive to ROS and matrix metalloproteinases (MMPs) for spatiotemporally controlled release of CNT@$MnO_2$ nanodrugs and VEGF. The hydrogel responds to pathological ROS by deploying nanodrugs that initiate ROS-scavenging cascades to protect neurons in the acute phase, while subsequent MMP activity releases VEGF, promoting angiogenesis and NSC differentiation during subacute repair.

Beyond endogenous pathological cues—such as ROS accumulation, MMP dysregulation, and pH imbalance—exogenous physical stimuli, including electric, magnetic, and ultrasonic fields, serve as targeted interventions to activate therapeutic functions of smart materials. Shi et al. [243] engineered piezoelectric nanomaterials functionalized with gold nanoparticles (Au@barium titanate (Au@BT)), where Schottky heterojunction design enhanced piezocatalytic hydrogen-generation capacity. Under ultrasonic excitation, this metal–semiconductor composite exhibited strong redox potential via continuous hydrogen production, demonstrating promise as a nanoprodrug for anti-inflammatory therapy in acute SCI. Likewise, the electroconductive hydrogel created by Luo et al. [217] generated programmable alternating current under high-frequency electric fields through capacitive coupling, enabling wireless *in situ* electrostimulation in rat SCI models that improved axonal regeneration and locomotor recovery. Future work on smart responsive materials for SCI should prioritize biosafety, advanced bionic architecture, and integration of multistimuli-responsive systems to accelerate clinical translation.

Current challenges include limited long-term stability, incomplete degradation control, suboptimal biocompatibility and cell support, and inconsistent responsiveness tuning. Upcoming studies should therefore emphasize multifunctional, durable materials with optimized biological performance and adaptability to clinical environments.

### 8.4. Microspheres

Microspheres are spherical or near-spherical polymer particles from the nanoscale to hundreds of micrometers with high surface-area-to-volume ratios, porous architectures, and tunable surface functionalization. By morphology, they are classified as porous, multilayered, non-spherical, and hollow microspheres [244].

Porous architectures provide platforms for stem cell transplantation, supporting activation and lineage commitment essential for SCI repair. Feng et al. [245] integrated PLGA microspheres with spinal cord ECM to create bioengineered microspheres (BEMs). Transplanting MSC-loaded BEM (BEM@MSC) in T10-contused rats suppressed reactive astrogliosis, biased transplanted MSCs toward neuronal differentiation, improved host–graft integration, and enhanced electrophysiological conduction. Wang et al. [246] fabricated laminin-modified porous GelMA microspheres loaded with NSCs; laminin-functionalized pGelMA (Lam-pGelMA) established biomimetic 3D microniches, increased NSC survival, and raised neuronal/oligodendroglial differentiation ratios, improving histology and function in SCI rats.

Microspheres can also serve as carriers for drugs and bioactive factors, demonstrating significant advantages in SCI therapy,

including strong storage stability, high drug-loading capacity, and excellent controlled release kinetics. By programming the drug release profile to match the pathological progression after injury, synergistic therapeutic efficacy can be achieved while reducing the incidence of adverse effects. Ai et al. [247] engineered dual-layer core–shell hydrogel microspheres (PC-GEN): the shell rapidly released cerium oxide nanoparticles (CONPs) during early SCI to dampen inflammation, while the core sustained spinal cord white-matter ECM (swm-ECM) and NGF through intermediate/late phases to drive axonal regeneration. Liu et al. [248] similarly engineered core–shell chimeric hydrogel microspheres composed of an outer $Mg^{2+}$-crosslinked GelMA layer and an inner PLGA core encapsulating $Zn^{2+}$. The outer layer enables controlled early-stage $Mg^{2+}$ release to mitigate inflammatory responses, while subsequent $Zn^{2+}$ release promotes neural cell proliferation and axonal regeneration. Despite advances in microsphere fabrication, persistent challenges include complex operational procedures and difficulties in optimizing process parameters, often resulting in heterogeneous size distributions and inconsistent encapsulation efficiency. Manufacturing stability is particularly demanding for architecturally complex microspheres with specialized surface topographies. Moreover, current microsphere systems fail to dynamically synchronize with evolving SCI pathophysiology, underscoring the need for smart, responsive microsphere platforms that can adaptively modulate drug release according to microenvironmental cues, thereby overcoming the inherent limitations of static release kinetics.

Present challenges in applying microsphere materials to SCI include the absence of convenient, efficient large-scale fabrication methods, despite structural diversity, and the limited responsiveness of current microspheres to injury-induced microenvironmental changes. Future studies should deepen understanding of microsphere–host microenvironment interactions, foster multidisciplinary integration to optimize material design, and ultimately facilitate translation from basic research to clinical therapy.

### 8.5. Nanomaterials

Nanomaterials (1–100 nm in diameter) have become pivotal in biomedical research due to their unique size effects, multifunctionality, and biocompatibility [249]. Leveraging their BSCB penetrability, these materials act as high-efficiency drug carriers that optimize bioavailability and pharmacokinetics, offering innovative strategies for SCI repair [250]. After SCI, BSCB disruption and ROS overproduction allow targeted nanodrug accumulation at lesion sites, where ROS-triggered release scavenges excess ROS and suppresses neuroinflammation. To overcome reduced nicotinamide adenine dinucleotide (NADH) instability, Gao et al. [251] engineered degradable diselenium-bridged silica nanovectors that stabilize NADH and degrade under pathologically high ROS, enabling precise NADH release and potent anti-inflammatory and antioxidant activity.

Although conventional nanomaterials face challenges—short half-life, immunogenicity, and poor targeting—cell membrane-coated nanoparticles (CMNPs) offer a biomimetic solution. These nanovehicles preserve nanoparticle tunability while inheriting membrane-derived biological functions. Sun et al. [252] designed neutrophil membrane-coated quercetin nanoparticles that enhance delivery efficiency and reprogram lesional microglia toward anti-inflammatory phenotypes, with the coating enabling lesion targeting and neutralization of inflammatory mediators. Similarly, bacterial outer membrane coatings simulate immune cell phagocytosis, guiding nanomaterials to lesions. Kondiles et al. [253] created biomimetic bacterial outer membrane nanoparticles (BM-NPs) integrating detoxified outer membrane vesicles (dOMVs) with liposomes for precise targeting and high drug-loading capacity. In acute phases, neutrophils transport BM-NPs to injury sites, releasing drugs via neutrophil extracellular trap (NET) formation; in subacute phases, macrophages sustain release, synchronizing with the evolving immune microenvironment to suppress foam-cell formation, limit neuroinflammation, and enhance neurofunctional recovery.

Despite advances in nanocarrier design, clinical translation remains constrained by complex synthesis, high cost, and limited delivery efficiency. Future work should refine nanocarrier engineering to improve biocompatibility, stability, and functionality. Intravenously delivered nanomaterials still accumulate off-target, mainly in the liver and spleen, necessitating high doses that raise toxicity risks. Thus, next-generation nanomaterials must combine multifunctionality with cell-specific tropism to achieve precise, safe, and effective SCI therapeutics.

### 8.6. Current clinical and preclinical applications for biomaterials

The progress of biomaterials in clinical trials for SCI shows several defining characteristics. First, material types are diverse, spanning natural and synthetic systems. Natural materials such as collagen scaffolds (NCT03966794 and NCT02510365) are widely used as carriers for cells or biological factors due to their strong biocompatibility, while synthetic materials like poly(lactic acid-*co*-glycolic acid)-*b*-polylysine scaffolds (NCT02138110 and NCT03762655) target thoracic SCI repair through controlled degradability. Self-assembling peptide nanofiber hydrogels (NCT05967325), which recruit stromal vascular elements by mimicking ECM architecture, are currently in participant recruitment. Amr et al. [254] also reported using chitosan–laminin scaffolds with peripheral nerve grafts and BMSCs in 14 chronic patients with SCI, achieving partial neural regeneration but with complications such as postoperative seroma. Secondly, "biomaterials + combina tion therapy" has become a core strategy. To overcome the limitations of single-material approaches, clinical trials frequently combine "biomaterials + stem cells, physical field stimulation, and biological factors" to target multiple aspects of the SCI microenvironment, including inflammation, glial scarring, and vascular injury. For example, the NeuroRegen scaffold (NCT02352077, NCT02688049, and NCT02688062), combined with BMSCs or NSCs, not only provides a scaffold for engraftment but also modulates local inflammation through material degradation and molecular signaling. Collagen scaffolds (NCT03966794) combined with EES enhance the reconstruction of neural conduction pathways. A series of studies on the NeuroRegen scaffold have shown that in patients with chronic complete SCI, some exhibited measurable improvements in lower-limb motor function one year or more after surgery [255–257]. Thirdly, most trials remain in early stages, primarily verifying biomaterial safety and preliminary efficacy. Many are phase I or phase I/II studies. The three NeuroRegen scaffold trials (NCT02352077, NCT02688049, and NCT02688062) mainly assess tissue compatibility post-implantation, including inflammatory or scarring responses. The phase I collagen scaffold trial (NCT02510365) focuses on postoperative adverse events in cervical–thoracic patients with SCI, forming the basis for phase II optimization.

## 9. Pharmacological repair strategy

In recent years, drug therapy has focused on the dynamic pathology of SCI, aiming to mitigate secondary injury and promote neural repair. Most studies have examined specific molecular pathways, designing interventions tailored to the pathological stages after injury, leading to notable advances in small-molecule drugs and drug delivery systems. Current drug strategies for SCI fall into

three main categories: anti-inflammatory therapy, neuroprotection, and axon regeneration promotion.

Acute neuroinflammation is the principal driver of secondary injury. MP has shown efficacy in preclinical models by modulating immune responses and improving motor function through inhibition of inflammatory factor release and T cell activation. However, high-dose MP can cause complications such as allergic reactions and fungal infections [258]. Recently, research has shifted from nonspecific anti-inflammatory drugs like MP to targeted neuroprotective agents that act on injured neurons and the BSCB, providing mitochondrial protection, oxidative stress reduction, and microcirculation enhancement. For instance, Wang et al. [259] demonstrated that bexarotene regulates nuclear translocation of transcription factor E3 through the adenosine monophosphate-activated protein kinase (AMPK)–S-phase kinase-associated protein 2 (SKP2)–coactivator-associated arginine methyltransferase 1 (CARM1) and AMPK–mTOR signaling pathways, promoting autophagy, reducing ROS, and inhibiting pyroptosis, thereby improving motor function in SCI mice. Wu et al. [260] showed that 20-deoxyginkgol (20-DOI) activates transcription factor EB (TFEB) to induce mitophagy, inhibit apoptosis, and restore motor function in SCI rats. Additionally, valproic acid (VPA), beyond alleviating neuropathic pain, exhibits neuroprotective potential: VPA-labeled chitosan nanoparticles inhibit neuroinflammation, reduce BSCB disruption by upregulating claudin-5, and enhance neuronal survival after SCI [261]. Simmons et al. [262] reported that lasmiditan, a 5-hydroxytryptamine 1F receptor (5-$HT_1F$) agonist, induces mitochondrial biogenesis, promotes angiogenesis, and preserves BSCB integrity. Food and Drug Administration (FDA) approval positions it as a promising candidate for restoring motor function after SCI.

Regarding axon regeneration, drugs targeting inhibitory signaling pathways have also shown encouraging therapeutic potential. For instance, amino acid (AA)-Nogo receptor (NgR) (310) ecto-Fc blocks Nogo-A receptor 1 (NgR1) signal transduction. Animal experiments demonstrated that it improves neurological recovery in rats with chronic SCI and in non-human primate hemisection models, while promoting axonal growth of specific conduction tracts. Wang et al. [263] and Maynard et al. [264] investigated a soluble Nogo receptor-Fc antagonist, AXER-204, in patients with chronic cervical SCI. Early clinical data confirmed that it achieved the target cerebrospinal fluid concentration without inducing severe adverse events.

Beyond these categories, small-molecule compounds can activate neural regeneration and repair pathways by mediating intercellular signaling. Our group demonstrated that a glutathione peroxidase 4 (GPX4) activator, PKUMDL-LC–102, promotes motor recovery in SCI rats by enhancing neuronal survival and suppressing neuroinflammation [265]. Chen et al. [266] further reported that a potassium–chloride cotransporter-2 (KCC2) agonist, CLP290, restores motor function in paralyzed mice by reducing hyperexcitability of spinal inhibitory interneurons.

Although numerous pharmacological agents exhibit potential for SCI treatment, clinical application remains constrained by issues such as delivery route, dosage optimization, and therapeutic timing. Future pharmacological strategies should integrate stem cell bioengineering and biomaterials science, advancing toward clinical translation through multidisciplinary collaboration.

## 10. Gene therapy

Gene therapy is widely recognized as a promising strategy for SCI treatment, as it modulates gene expression in the injured spinal cord, reconstructs a regenerative microenvironment, and facilitates neural tissue remodeling. Viral vectors remain the principal carriers for gene delivery, primarily including adenovirus (Ad), adeno-associated virus (AAV), and lentivirus (LV).

Davleeva et al. [267] developed a chimeric adenoviral (Ad5/35) delivery method carrying recombinant complementary DNA (cDNA) to transduce autologous leukocyte concentrates *in vitro*, enabling targeted gene delivery. Using a minipig model of moderate SCI, they evaluated intravenous infusion of autologous gene-modified leukocytes co-expressing VEGF, GDNF, and NCAM, demonstrating significant molecular and cellular remodeling at the lesion site. This intervention in the acute phase effectively promoted neural tissue repair.

Similarly, Leibinger et al. [268] achieved unilateral transduction of cortical motor neurons using AAV expressing hyper-interleukin-6 (hIL-6), which markedly enhanced hindlimb motor recovery in mice with severe SCI. As an engineered cytokine, hIL-6 activates the JAK/STAT3 signaling cascade, thereby driving axonal regeneration. However, Anderson et al. [269] found that although regenerating fibers extended within structurally preserved spinal regions, functional recovery remained limited. To address this, the team later identified a subset of key neurons essential for motor restoration after incomplete SCI and developed a lentiviral therapy for sustained GDNF delivery. This approach guided long-distance axonal regrowth by recapitulating developmental mechanisms [270].

Furthermore, Qu et al. [271] combined gene therapy and cytotherapy in a thoracic SCI rat model. Lentiviral delivery of the chondroitinase *ABC* gene to the rostral and caudal margins of the lesion reduced inhibitory matrix accumulation, while Schwann cells transplantation amplified the neuroregenerative response. This combined approach significantly enhanced tissue remodeling and functional recovery.

Recent studies have advanced vector design and introduced gene-editing systems such as clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9), achieving efficient, targeted *in vivo* gene transfer and upregulation of pro-regenerative promoters [272]. These innovations have strengthened the precision and biosafety of gene therapy, providing a key technological foundation for translating regenerative strategies into clinical SCI applications (Fig. 3).

## 11. Current status of translational research and prospects

With the interdisciplinary integration of bioactive materials, neuromodulation devices, and cell-based therapies, tissue-engineering strategies for SCI have progressed from single-technology applications to multi-modal regenerative systems.

Although basic research has achieved important advances, clinical translation still encounters significant barriers. Key issues include performance limitations of engineered constructs, challenges in patient-specific adaptation, difficulties in achieving multi-technology synergy, and the absence of standardized evaluation and regulatory frameworks.

### 11.1. Clinical translation of biomaterials

Although bioactive materials show great promise in SCI repair, major barriers to clinical translation remain, particularly biocompatibility and functional durability after implantation. Natural hydrogels such as collagen, fibrin, and alginate exhibit excellent cellular compatibility and controllable degradation, inhibiting glial scar formation and promoting axonal regeneration. However, their limited mechanical strength and rapid degradation in MMP-rich microenvironments hinder long-term neural support and restrict clinical application. Conversely, synthetic hydrogels such as PEG and PVA offer tunable mechanical strength and degradation via molecular design, though with somewhat reduced biocompatibility.

Composite biomaterials like GelMA and PLGA hydrogels balance mechanical and biological properties through synergistic composition and remain a major research focus [272]. For instance, supramolecular bioinks based on GelMA and acrylated β-cyclodextrin have been used to 3D-print scaffolds mimicking spinal cord architecture. Their porous topology facilitates neuronal communication and directional differentiation within the lesion microenvironment. Simultaneously, engineered scaffolds form axonal guidance channels, enabling linear axon crossing through the lesion and preventing misdirected growth. Kim et al. [273] assessed the safety and neurological outcomes of a highly porous, absorbable polymer neurospinal scaffold (NSS) implanted within 4 d post-injury in patients with AIS grade A, T2-12 SCI. This prospective, multicenter, open-label, single-arm study confirmed the safety of intraspinal NSS implantation during decompression and stabilization surgery for complete thoracic SCI, supporting further randomized trials. In another study, Tang et al. [257] implanted collagen scaffolds loaded with autologous bone marrow mononuclear cells or human umbilical cord mesenchymal stem cells (hUCMSCs) into patients with SCI. Among 15 acute and 51 chronic complete SCI cases followed for 2–5 years, patients with acute SCI regained neural conduction and partial independent ambulation, while those with chronic SCI showed sensory recovery and improved reflexive defecation. Long-term follow-up suggested that functional scaffold transplantation may represent a viable therapeutic strategy for complete SCI.

However, several challenges persist in the clinical translation of these materials. For instance, some composite scaffolds degrade too slowly, leading to prolonged retention within the body that interferes with neuronal regeneration and ECM remodeling. Their degradation byproducts can trigger inflammatory responses, further disrupting the regenerative microenvironment. Additionally, bio-inks remain costly, making large-scale manufacturing economically unfeasible and limiting clinical accessibility. Moreover, the absence of standardized evaluation frameworks complicates cross-comparison of biological properties among materials, reducing research reproducibility. Consequently, injectable biopolymers must still demonstrate long-term safety and therapeutic efficacy through comprehensive, multicenter clinical trials.

### *11.2. Clinical translation of cell transplantation*

In translating stem cell transplantation into clinical therapy for SCI, several major challenges persist: low post-transplant cell survival, uncontrolled differentiation, limited efficacy in chronic injury stages, difficulty balancing safety and efficacy across delivery routes, lack of standardized protocols, and risks of immune rejection.

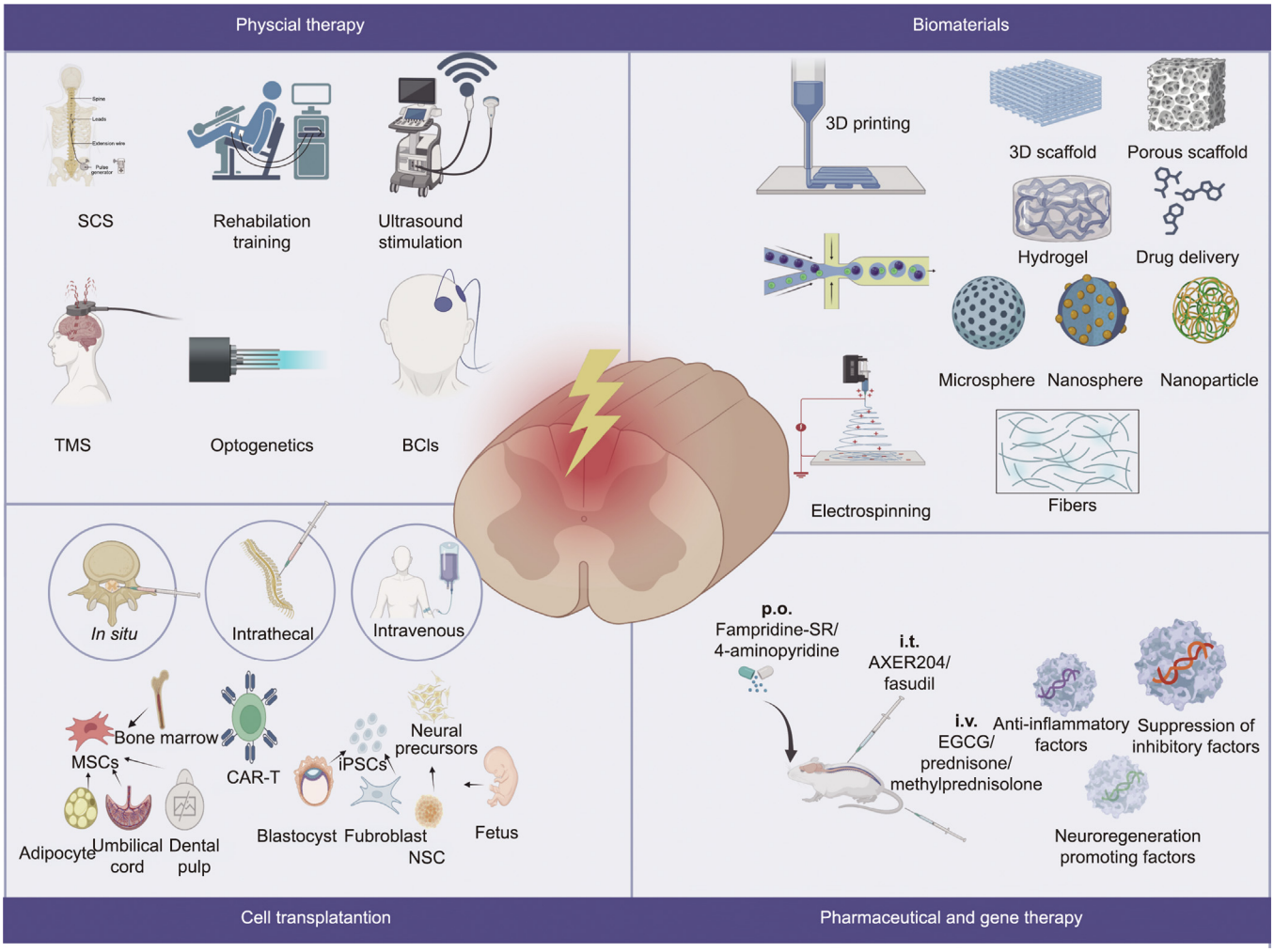


**Fig. 3.** Emerging clinical engineering therapeutic strategies for SCI. The figure outlines four major engineering-based therapeutic domains: physical stimulation, biomaterial technology, cell transplantation, and pharmaceutical or gene therapy, highlighting how these approaches promote neural repair and regeneration. p.o.: per os; i.t.: intrathecal; i.v.: intravenous; SR: sustained release.

Extensive studies and clinical trials have explored strategies to address these translational barriers. Phase I trials have confirmed the feasibility and safety of intralesional transplantation. Anderson et al. [274] conducted a phase I trial of autologous human SC (ahSC) transplantation for SCI and confirmed its safety and preliminary efficacy in patients with subacute injury. Gant et al. [179] evaluated the therapeutic effect of ahSCs transplantation combined with rehabilitation training on patients with chronic SCI through an open-label, non-randomized phase I clinical trial. It was found that the sensory and motor functions of the patients, as well as the level of nerve injury, were all improved. It was worth emphasizing that Bydon et al. [171] conducted a phase I clinical trial, enrolling ten patients with tSCI at AIS grade A or B. After intrathecal delivery of *in vitro*-expanded AD-MSCs, it was found that seven of these patients showed functional improvement during the follow-up period. They further pointed out that combining cell therapy with novel therapies such as gene therapy or biomaterials further enhanced the therapeutic effect. However, reproducible clinical efficacy remains unproven, as trials often show small effect sizes and limited sensitivity in study design. Persistent challenges include low cell survival due to the hostile post-injury microenvironment, uncontrolled differentiation into neurons or glia, immune rejection, and insufficient extracellular support for neurite extension [275]. Bini et al. [276] further reported that simple cell transplantation without mechanical or matrix support leads to tissue collapse around grafts, restricting axonal elongation and synaptic integration. To overcome these limitations, engineered strategies now combine genetic or epigenetic cell modifications with optimized biomaterial microenvironments, significantly enhancing graft survival, integration, directed differentiation, and functional repair [277–279].

### 11.3. Clinical translation of neuromodulation devices

Neuromodulation techniques such as ESCS, tDCS, DBS, and rTMS reconstruct neural conduction pathways from the central to peripheral nervous system through electrical stimulation, aiding respiration, voluntary lower-limb movement, and bladder control [280,281]. Their mechanism primarily relies on neural plasticity, promoting axonal regeneration, collateral sprouting, and new synaptic connectivity, thereby enhancing residual fiber activity and remyelination [282]. Despite progress, clinical translation faces significant barriers. ESCS requires electrode implantation on the dorsal spinal surface. Devices using silicon or carbon fiber microelectrodes precisely enhance excitability, but long-term implantation induces glial scarring, signal loss, and reduced stimulation efficacy. Additionally, vascular damage from implants can activate coagulation cascades [283]. Electrode stability, corrosion resistance, and transmission efficiency still need optimization [284].

Compared with conventional implants, nanoelectrode arrays offer higher efficiency, smaller size, and reduced inflammation [285]. DBS targeting subcortical motor regions has improved hindlimb function in rats [286], yet its long-term efficacy in SCI remains uncertain. Future work should refine DBS parameters and improve implant durability. Non-invasive approaches such as rTMS and spinal stimulation also show promise. One study enhanced hand motor control by pairing auditory clicks with biceps stimulation in healthy adults [287], inspiring wearable designs for SCI therapy [288]. The ARC–EX, the first FDA-approved non-invasive spinal stimulation system, restored partial hand motor and sensory function in chronic SCI [289]. Adeel et al. [290] found multimodal neuromodulation (rTMS-iTBS/transcutaneous spinal direct current stimulation (tsDCS) and rTMS-20 Hz/tsDCS) improved MEP amplitude and lower-limb motor scores in chronic SCI. Additionally, magnetically guided nanoparticle-loaded stem cells increased cell retention and repair efficiency [291]. Yet, standardized stimulation parameters and targets are still lacking, and large-scale trials are required to confirm safety and efficacy. The mechanisms through which TMS alters CNS plasticity also remain unclear, demanding further research for clinical adoption.

BCI technology, an advanced form of neuromodulation, enables control of external prosthetics or motor output via functional electrical stimulation. However, implementation requires sophisticated equipment and remains partially wired [292]. Integrating BCIs with AI, machine learning, neural networks, and VR could enhance adaptability and precision. AI can decode brain signals, improve feedback speed, and adjust outputs in real time, while VR provides immersive rehabilitation. Long-term implant biocompatibility and material risk assessment remain essential [293]. Continuous refinement of safety standards and testing protocols is needed to ensure reliable clinical use of next-generation neural interface materials [294].

### 11.4. Synergistic application of multi-modal technologies

Functional repair of SCI requires overcoming the limitations of single-modality treatments through coordinated multimodal strategies for engineered neural reconstruction. Clinically used drugs such as erythropoietin, naloxone, and MP reduce secondary injury by suppressing inflammatory cytokines and inhibiting lipid peroxidation. However, conventional delivery routes like oral or intravenous administration restrict drug penetration across the BSCB, limiting therapeutic concentration at the lesion. Thus, biomaterial scaffolds or cell-based therapies can serve as adjuncts to enhance drug efficacy [295–298]. Wang et al. [299] developed a PEG-modified maghemite nanosystem for tacrolimus delivery that reduced oxidative stress, promoted macrophage polarization from M1 to M2, and markedly improved motor recovery in SCI rats. Nanosystems also augment the bioactivity of regeneration-related growth factors. Biomaterials play versatile roles in growth-factor delivery and cellular support. Oudega et al. [300] demonstrated that chitosan implants releasing NT-3 promoted spinal cord tissue remodeling. Hydrogels and scaffolds not only act as sustained-release carriers for bioactive agents but also provide substrates for transplanted cells and regenerating axons, facilitating neural repair, angiogenesis, and inflammation modulation after SCI [301]. However, early post-transplantation cell survival within biomaterials often declines due to poor local perfusion, reducing therapeutic benefit. To address this, Winter et al. [302] engineered a tubular hydrogel–collagen microcolumn that enabled astrocytes to self-assemble into a 3D scaffold network. This structure improved neuronal co-culture viability and guided neurite extension along astrocyte bundles. Moreover, early administration of engineered exosomes has been shown to modulate inflammation, stimulate axonal growth and angiogenesis, and suppress glial proliferation [303]. Although peripheral delivery of exosomes provides a non-invasive route, most vesicles are metabolized by peripheral organs before reaching the injured spinal cord, thereby limiting therapeutic efficacy. Studies have shown that using 3D GelMA hydrogels as an exosome delivery system (GelMA-Exo) can fill the spinal cavity and enable sustained release [304]. Moreover, stimuli-responsive biomaterials achieve precise spatiotemporal release of therapeutic agents by reacting to endogenous pathological cues such as ROS and MMPs, or to exogenous physical stimuli, including electrical, magnetic, or ultrasonic signals [305]. Huang et al. [279] reported that MSC transplantation combined with pulsed electromagnetic fields promoted axonal regeneration in SCI mice by elevating neurotrophic factor expression. The electromagnetic stimulation also enhanced BDNF and VEGF levels in MSCs via the Wnt/β-catenin pathway. Collectively, these studies demonstrate that integrating tissue-engineering technologies raises demands for technical coordination and operational preci-

sion while accelerating the clinical translation of novel multimodal therapies for SCI.

### 11.5. Prospects of the translational pathway in SCI research

In the future, the translational research pathway for SCI treatment holds broad potential but also faces challenges. Technically, advances in precision medicine, such as personalized cell therapy and targeted biomaterial design, may revolutionize SCI management. This includes applying single-cell sequencing and developing humanized animal models to better analyze human SCI pathology and improve understanding of its pathophysiological mechanisms. Integrating cutting-edge imaging technologies enables real-time, high-resolution monitoring of tissue regeneration and treatment response in both preclinical models and clinical trials.

At the collaborative level, stronger partnerships among laboratories, industry, and regulatory agencies will streamline translation. Expanding funding for multi-institutional and interdisciplinary research consortia can accelerate resource and data sharing, reduce redundant efforts, and hasten therapy validation (Fig. 4).

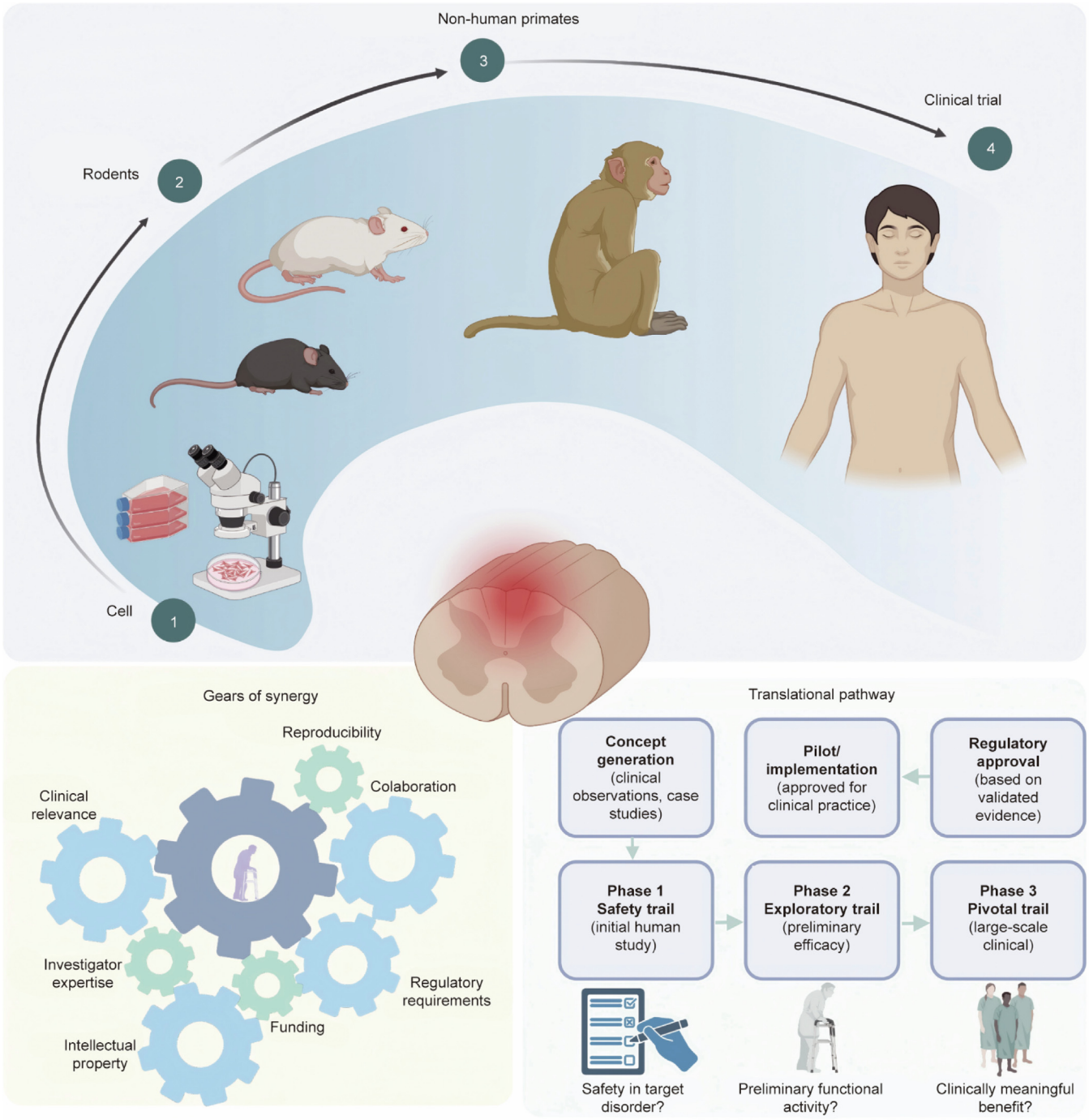


**Fig. 4.** Translational pathway for SCI research. This schematic illustrates the continuum from preclinical studies (cellular, rodent, and non-human primate models) to clinical trials, emphasizing key collaborative, regulatory, and technical milestones in SCI translational research.

From a regulatory standpoint, developing flexible and adaptive frameworks is vital to keep pace with rapid technological advances. Establishing clear guidelines for evaluating the safety and efficacy of emerging therapies will help ensure timely patient access to promising treatments. Ultimately, the success of SCI translational research depends on aligning technical, collaborative, and regulatory progress to move innovative therapies efficiently from bench to bedside, bringing new hope to patients with SCI.

## 12. Conclusion

After SCI, patients experience irreversible functional loss across multiple systems and lifelong disability. Integration between medicine and engineering has generated promising preclinical results, with several clinical trials underway. Although many interventional strategies have encountered setbacks, they have yielded valuable insights, emphasizing the importance of understanding pathological mechanisms to guide more effective therapies. Individualized treatments targeting single mechanisms are evolving into elements of a broader multimodal approach. Advances in spatiotemporal mapping, scar formation biology, neural pathway imaging, and biomarker identification are collectively accelerating the development of such therapies.

Overall, SCI treatment and rehabilitation are progressing toward a comprehensive, precise, multidisciplinary, and personalized model emphasizing functional recovery and social reintegration. Through sustained interdisciplinary collaboration and method integration, the search for more effective therapeutic and rehabilitative strategies continues.

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## CRediT authorship contribution statement

**Mi Zhou:** Conceptualization, Writing – review & editing. **Xue Yao:** Writing – review & editing, Funding acquisition, Conceptualization. **Boya Huang:** Data curation. **Jie Ren:** Methodology. **Haiwen Feng:** Visualization. **Shiqing Feng:** Funding acquisition, Writing - review & editing, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eng.2025.11.012.

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