REVIEW
NEUROSCIENCES

Diseases & Research

Advances in Stem Cell-Based Therapies with Involved Mechanisms for Neurological Disorders

Surajit Hansda[1], Akash Naik[1], Hiranmoy Das[1,#]

[1] Department of Pharmaceutical Sciences, Jerry H. Hodge School of Pharmacy, Texas Tech University Health Sciences Center, Amarillo, Texas 79106, USA

Abstract: Neurological disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), ischemic stroke, multiple sclerosis (MS), neuropathic pain (NP), and temporal lobe epilepsy (TLE) pose major healthcare challenges due to their progressive nature and limited treatment options. Stem cell-based therapies have been emerging as a promising approach to repair or replace damaged neural tissues and restore functions. This review discusses types of stem cells and their therapeutic applications in neurological diseases. Special focus is given to emphasize the cellular microenvironment and immune system interactions that influence stem cell behavior and treatment outcomes. Advances in gene-modified stem cells, synthetic biology, and the development of organoids, brain-on-a-chip, and 3D models have improved preclinical evaluation and safety testing. Furthermore, the use of biomaterials and scaffolds has further enhanced cell delivery and integration and is also included in this review. Personalized and precision medicine approaches are also explored, along with current clinical trial outcomes. Despite advances, significant challenges, including limited cell survival and integration, immune rejection, risks of tumorigenicity or inappropriate differentiation, lack of standardized protocols, ethical considerations, and insufficient long-term clinical data, remain. Addressing these limitations will be essential for improving success in translation and advancing stem cell-based therapies toward routine clinical application in neurological disorders.

Keywords: Stem cell; Stem cell therapy; Neurologic disorders; Neuroregeneration; Personalized medicine.

Introduction

The human nervous system, a marvel of biological complexity, controls our thoughts, movements, memories, and emotions. However, when affected by disease or injury, this complex network often shows its vulnerability and limited ability to repair itself[1]. Neurological disorders, which include conditions like Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), spinal cord injury (SCI), and traumatic brain injury (TBI), are among the most difficult to treat[2]. These disorders impact millions around the world, causing progressive disability, loss of independence, and significant societal and economic challenges.

Despite significant progress in neurobiology and pharmacology, managing most neurological disorders remains mostly palliative[3]. Current treatments typically aim to relieve symptoms or slow disease progression but often cannot stop or reverse neuronal loss and disruption of neural circuits, which are key features of many neurodegenerative and neuroinflammatory diseases. The adult central nervous system (CNS) has limited natural ability to regenerate after injury, and therapies that can cross the blood-brain barrier (BBB) and target complex, multifactorial diseases are rare[1]. Therefore, there is a pressing need to develop interventions that not only protect neurons but also replace or repair damaged neural tissue.

In this context, stem cell-based therapies have become one of the most promising areas in regenerative neurology[4-6]. Stem cells, having the ability to self-renew, differentiate, and release paracrine signals, provide a flexible toolkit for tackling both cellular and molecular aspects of neurological diseases. From embryonic stem cells (ESCs) and neural stem cells (NSCs) to adult-derived mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs), different cell types have been studied for their capacity to reduce neuroinflammation, replace lost neurons and glia, and activate the body's natural repair processes. Positive results from preclinical studies have shown improved functional recovery, neurogenesis, and synaptic integration after stem cell transplantation[7,8].

Additionally, advances in gene editing, biomaterial scaffolds, and cell delivery techniques are improving the effectiveness and safety of these therapies[9]. Gene-modified stem cells, nanoparticle-assisted targeting, and hydrogel encapsulation systems are actively being developed to address challenges like immune rejection, limited engraftment, and the difficult post-injury environment of the CNS. As stem cell therapies move from research to clinical application, early-phase trials are beginning to offer important insights into their feasibility, tolerability, and potential benefits for various neurological conditions[3].

Correspondence: Hiranmoy Das. E-mail: hiranmoy.das@ttuhsc.edu. Address: Department of Pharmaceutical Sciences, Jerry H. Hodge School of Pharmacy, Texas Tech University Health Sciences Center, ARB Suite 2116, 1406 South Coulter Street, Amarillo, Texas 79106, USA.

Received 22 November 2025; Revised 19 December 2025; Accepted 25 December 2025; Available Online 6 February 2026
DOI: 10.54457/DR.202504007

Despite the promise of stem cell therapies, the translation from bench to bedside remains complex and multifaceted[6]. In basic research, significant advances have been made in elucidating the molecular and cellular mechanisms by which stem cells exert neuroprotective, immunomodulatory, and regenerative effects. These include paracrine signaling pathways, mitochondrial transfer, exosome-mediated intercellular communication, and modulation of neuroinflammation. Such insights have deepened our understanding of how stem cells interact with the neural microenvironment and have guided the design of preclinical studies. Translational research has bridged the gap between laboratory findings and human application by refining cell sourcing, manufacturing protocols, and delivery strategies. However, clinical implementation continues to face substantial hurdles, including variability in cell behavior, limited survival and engraftment after transplantation, immune compatibility concerns, and risks of tumorigenicity or ectopic tissue formation[6]. Additionally, regulatory, ethical, and logistical challenges further complicate large-scale, standardized therapeutic deployment. Rigorous clinical trials are ongoing, yet heterogeneity in patient selection, disease stage, outcome measures, and trial design has made it difficult to establish definitive efficacy and safety profiles. Addressing these barriers will require an integrated, multidisciplinary approach involving clinicians, basic scientists, and regulatory agencies to refine stem cell interventions and translate their potential into safe, effective, and scalable treatments for patients with debilitating neurological disorders.

This review aims to provide a comprehensive and critical synthesis of current research on stem cell-based therapies for neurological disorders. We will explore the biological properties and therapeutic mechanisms of various stem cell types, review preclinical and clinical evidence, and discuss emerging strategies that aim to overcome translational hurdles. By highlighting both the promise and the limitations of this rapidly evolving field, we seek to inform and inspire further interdisciplinary collaboration in the quest to restore neural function and improve outcomes for patients suffering from neurological disease.

Stem cell classifications and therapeutic applications

Stem cells are undifferentiated cells that can self-renew and differentiate into various specialized cell types[10]. Based on their origin and differentiation capacity, stem cells are classified into four main types: ESCs, NSCs, mesenchymal stem cells (MSCs), and induced pluripotent stem cells (iPSCs).

Embryonic stem cells

ESCs are derived from the inner cell mass of the blastocyst and are pluripotent, meaning they can differentiate into cells of all three germ layers: ectoderm, mesoderm, and endoderm[11]. Consequently, they become the subject of studies as a remedy for various neurological disorders. Post-transplantation, they can develop into neurons and glial cells, demonstrating long-term stability that enables them to merge with the neurological circuitry. ESCs have been used in models of spinal cord injury, Parkinson's disease, and macular degeneration due to their high regenerative capacity[6]. However, ethical concerns and the risk of teratoma formation limit their clinical use[12].

Neural stem cells

NSCs are multipotent cells found in the developing and adult brain. Primarily arise from the subventricular zone and sub-granular zone of the hippocampal dentate gyrus. During the embryonic development of the central nervous system, NSCs produce neurons, astrocytes, and oligodendrocytes. Furthermore, derived neurons can be sustained for extended culture with the assistance of growth factors like epidermal growth factor, fibroblast growth factor-2, and brain-derived neurotrophic factor (BDNF). They give rise to neurons, astrocytes, and oligodendrocytes[13-15]. NSCs have shown promise in treating CNS injuries and neurodegenerative diseases like Alzheimer's and multiple sclerosis[16]. For example, NSC transplantation in animal models has improved motor and cognitive function after brain damage[17].

Mesenchymal stem cells

MSCs are adult stem cells typically isolated from bone marrow, adipose tissue, and umbilical cord[18]. They are multipotent and can differentiate into bone, cartilage, and fat cells. MSCs are widely studied for their immunomodulatory and anti-inflammatory properties[19,20]. Researchers found that MSCs are capable of differentiating into cell types from all three germ layers. This positions MSCs as a treatment option for multiple neurological disorders. Their properties related to neurogenesis and immune modulation render them an appropriate treatment for various neurological conditions. Certainly, MSCs offer numerous benefits: readily available, no tumor development, and no ethical concerns about their clinical application. Additional significant benefits include the ability of MCSs to not only draw in other MSCs and move towards the site of brain lesions, but also to trigger signaling pathways that enhance the paracrine release of cytokines and growth factors. Additionally, because of their immune-suppressing properties, one should not anticipate any immunological rejection, along with their capacity to be transplanted across the allogeneic barrier. Clinically, MSCs are being used in trials for osteoarthritis, graft-versus-host disease, myocardial infarction, and Crohn's disease[21]. Their low immunogenicity makes them suitable for allogeneic transplantation[22]. Moreover, bone marrow MSCs play a role in anti-inflammation and immunomodulation. Nonetheless, there is presently no proof that transplanted MSCs, even when transdifferentiated into neurons, can assimilate into the neuronal networks of the recipient nervous system.

Induced pluripotent stem cells

iPSCs are generated by reprogramming adult somatic cells into a pluripotent state through the expression of transcription factors such as Oct4, Sox2, Klf4, and c-Myc[23]. Although iPSCs have many characteristics in common with ESCs, they are distinct. iPSCs behave like ESCs and can differentiate into any cell type. They are being used for disease modeling, drug testing, and potential regenerative therapies without the ethical concerns associated with ESCs[24]. iPSC-derived cardiomyocytes, neurons, and retinal cells are under clinical investigation[25]. The availability of iPSCs from individuals with a specific neurological disorder is currently enhancing the creation of improved disease models. A model utilizing iPSCs for neurodegenerative disorders like Alzheimer's disease has been created, and iPSC derivatives have been employed to explore the mechanisms behind retinal degen-

erative diseases. However, safety issues like genetic instability and tumorigenesis still need to be addressed[26].

Emerging tools and applications

Extracellular vesicles (EVs) derived from stem cells gained attention for their ability to mediate tissue repair and cell signaling without the risks of cell transplantation-mediated complications[27]. Stem cell-based therapies are also being enhanced by combining biomaterials, scaffolds, and gene editing technologies, like clustered regularly interspaced short palindromic repeats- CRISPR-associated protein (CRISPR-Cas9)[28]. These strategies aim to improve the safety, efficiency, and precision of regenerative interventions.

Microenvironment-targeted stem cell therapies

The therapeutic efficacy of stem cells depends not only on their intrinsic properties but also on the tissue microenvironment[29]. The microenvironment, often referred to as the 'stem cell niche', comprises the extracellular matrix (ECM), soluble factors, immune cells, endothelial cells, and mechanical cues that regulate stem cell survival, migration, differentiation, and integration[30]. Injury or disease disrupts this niche, creating a hostile environment that can impair stem cell function[31]. Therefore, targeting or modifying the microenvironment has emerged as a promising strategy to enhance the outcomes of stem cell therapy[32].

The success of the hematopoietic stem cell (HSC) transplantation largely depends on the bone marrow microenvironment. Preconditioning the niche using agents like granulocyte colony-stimulating factor (G-CSF) or by modulating chemokine receptor type 4 (CXCR4)/ C-X-C motif chemokine ligand 12 (CXCL12) signaling improves HSC homing and engraftment[33]. Mesenchymal stem cells (MSCs) have also been co-transplanted to restore niche support[34]. MSCs are highly sensitive to inflammatory cues. In inflamed or fibrotic tissues, the secretion of tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and interleukin-1 beta (IL-1β) can impair their survival[35]. Strategies such as preconditioning MSCs with hypoxia or growth factors, including transforming growth factor beta (TGF-β) and platelet-derived growth factor (PDGF), help them better adapt and restore damaged niches[36]. Additionally, MSCs modulate the immune microenvironment through paracrine signals, which is critical in treating graft-versus-host disease (GVHD) and autoimmune disorders[20]. In neurodegenerative diseases, the brain microenvironment often contains elevated reactive oxygen species (ROS), glial scarring, and proinflammatory cytokines that limit NSC integration[37]. Antioxidant preconditioning and the use of biomaterials mimicking brain ECM have been shown to improve NSC survival and differentiation in such settings. When iPSC-derived cells are transplanted, they often encounter fibrotic or hypoxic microenvironments. This can reduce their function or lead to aberrant differentiation. Microenvironmental support using scaffolds, ECM proteins, or oxygen-releasing biomaterials helps improve therapeutic integration and stability[38]. Co-transplantation with supportive stromal cells is found to create a favorable microenvironment. In cancer therapy, targeting the cancer stem cells (CSC) microenvironment is crucial to prevent recurrence. Stromal signals, hypoxia, and immune evasion support CSC survival[39,40]. Therapies combining stem cells with inhibitors of tumor ECM components or immune checkpoint blockers aim to remodel this microenvironment for better outcomes[41]. Stem cell-derived EVs carry bioactive molecules that can modulate the tissue microenvironment without the risks of whole-cell transplantation[27]. EVs influence immune responses, reduce fibrosis, and promote angiogenesis, especially in cardiac and renal injury models[27]. Biomaterials such as hydrogels, decellularized matrices, and nanofibers mimic native ECM and provide mechanical and biochemical cues that recreate favorable niches[42]. These scaffolds are used to deliver stem cells more efficiently and improve retention, especially in orthopedic and neural applications[43]. Microenvironment-targeted approaches are critical to enhancing stem cell survival, function, and therapeutic efficiency. By modifying or mimicking the stem cell niche using preconditioning, biomaterials, co-transplantation, or EVs, hostile environments can be changed to promote better regeneration.

Dynamic crosstalk with the immune system in neurological diseases

The CNS was long considered immune-privileged; however, it is now clear that dynamic crosstalk exists between the CNS and the immune system, especially during neurological diseases[44]. This interaction involves resident immune cells (like microglia), peripheral immune cells, cytokines, and signaling pathways that affect disease onset, progression, and healing[45]. Microglia are the brain's resident macrophages and provide the first line of immune defense. They play a key role in synaptic pruning, debris clearance, and surveillance[13,46]. In diseases like Alzheimer's, microglia become chronically activated and release inflammatory mediators, such as IL-1β and TNF-α, contributing to neurodegeneration[47]. Although BBB restricts immune cell entry to the brain, its integrity is often compromised during pathogenesis. This allows T cells, B cells, and monocytes to infiltrate the CNS[48]. In multiple sclerosis (MS), autoreactive $CD4^+$ and $CD8^+$ T cells cross the BBB, triggering demyelination and axonal damage[49]. Cytokines such as IL-6, IFN-γ, and IL-17 are elevated in neuroinflammatory diseases and amplify immune activation and glial cell responses[50]. Chemokines like CXCL10 and C-C motif chemokine ligand 2 (CCL2) promote leukocyte migration into the CNS, as seen in MS and viral encephalitis[51]. In AD, amyloid-β (Aβ) aggregates activate microglia and astrocytes via Toll-like receptors (TLRs), leading to sustained inflammation and neuronal injury[52]. NLR family pyrin domain-containing 3 (NLRP3) inflammasome activation in microglia also promotes the release of IL-1β, exacerbating disease pathology[53]. In PD, α-synuclein aggregates stimulate microglia and infiltrating T cells, creating a pro-inflammatory environment[54]. This leads to the loss of dopaminergic neurons in the substantia nigra area, as elevated TNF-α and IFN-γ levels were frequently observed in patient brains[55]. After ischemic stroke, damage-associated molecular patterns (DAMPs) released from dying neurons activate microglia and infiltrating immune cells[56]. This secondary immune response can expand the injury if not properly regulated. Targeting immune cells post-stroke is now being evaluated in clinical trials[57]. Emerging evidence shows that gut microbiota shape neuroimmune responses. Short-chain fatty acids (SCFAs) from gut microbes modulate microglial function, while dysbiosis can exacerbate inflammation in diseases like MS and PD[58]. Experimentally, it was shown that the germ-free mice show impaired

microglial maturation, suggesting a strong gut-immune-brain connection[59]. Regulatory T cells (Tregs) also play an important role in limiting CNS inflammation and promoting healing. In stroke and MS models, Tregs suppress effector T cells and modulate microglial activity to reduce damage[60]. Enhancing Treg function is being considered as a potential therapeutic strategy[61]. The immune system plays both damaging and protective roles in neurological diseases. A deeper understanding of immune-CNS interactions is essential for developing therapies that modulate inflammation without impairing defense or repair mechanisms (Fig. 1).

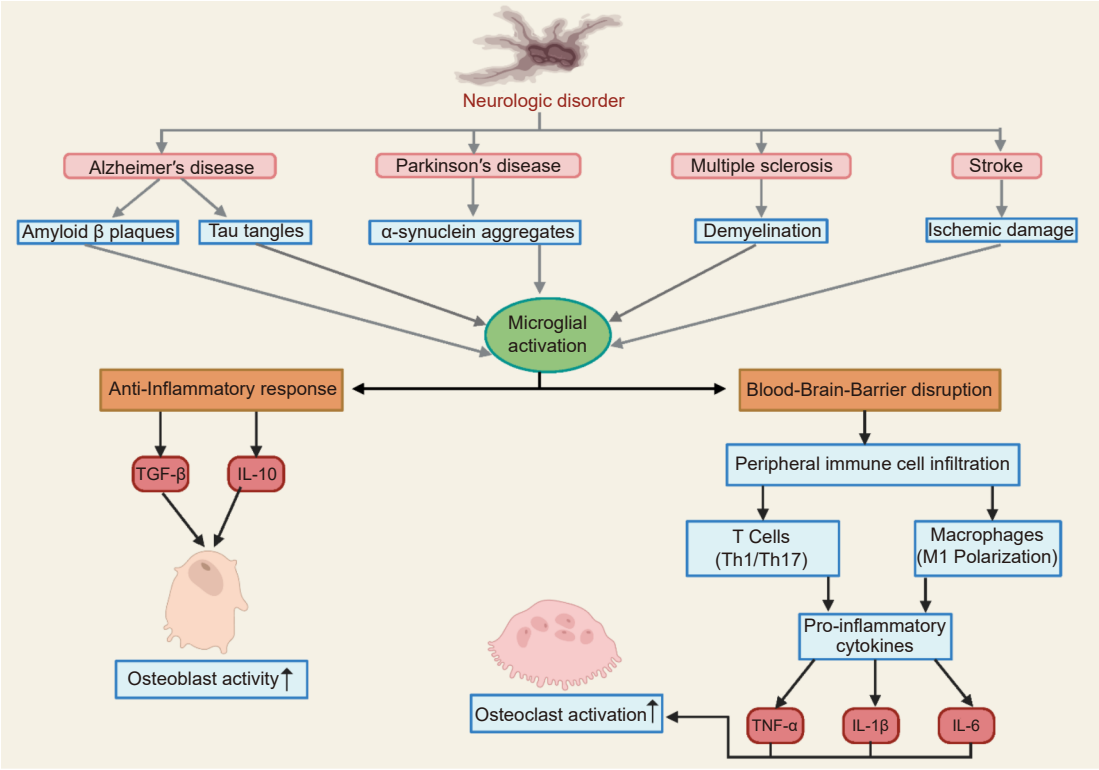

Fig. 1. The dynamic crosstalk between the immune system and neurological diseases.

Neurodegenerative and neuroinflammatory diseases including Alzheimer's disease, Parkinson's disease, multiple sclerosis, and stroke, induce microglial activation through the accumulation of pathological proteins (amyloid-β plaques, tau tangles, α-synuclein aggregates), demyelination, and ischemic injury. Activated microglia orchestrate both anti-inflammatory and pro-inflammatory signaling cascades. The anti-inflammatory response, mediated by cytokines such as TGF-β and IL-10, promotes osteoblast activity and tissue homeostasis. Conversely, microglial-driven BBB disruption facilitates peripheral immune cell infiltration, including Th1/Th17 T cells and M1-polarized macrophages, which release pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), contributing to osteoclast activation and neuroinflammatory damage. This integrated network highlights the bidirectional interaction between neuroinflammation and bone remodeling pathways.

Stem cell therapy in Alzheimer's Disease

AD is a progressive neurodegenerative disorder marked by cognitive decline, formation of amyloid-beta (Aβ) plaques, hyperphosphorylation of tau protein, synaptic loss, and development of neuroinflammation. Stem cell therapy is emerging as a promising approach to counteract the pathology associated with AD and restore cognitive function. Preclinical studies have demonstrated that neural stem/progenitor cells (NSPCs) can reduce the formation of amyloid plaques and accumulation of tau protein while promoting synaptic density and expression of neurotrophic factors such as BDNF. Transplanted NSPCs also integrate into damaged regions, support endogenous neurogenesis, and improve memory performance in animal models of AD[62-64]. MSCs, derived from bone marrow or umbilical cord, are also extensively studied in AD models. These cells also reduce Aβ plaque burden and tau hyperphosphorylation by activating microglial phagocytosis and secreting anti-inflammatory cytokines[65,66]. MSC transplantation has been shown to enhance the expression of synaptic proteins such as synapsin-1 and dynamin-1, leading to improved learning and memory in APP/PS1 mice. Combining MSCs with immune regulatory cells, like Tregs, further augments Aβ clearance and modulates neuroinflammation. Early clinical studies involving intrathecal or intravenous administration of MSCs have shown safety and potential benefits in slowing cognitive decline in patients with mild AD. Human neural stem cells (hNSCs) derived from fetal or pluripotent sources have shown therapeutic effects when transplanted into the hippocampus of AD mouse models. These hNSCs promote synaptic repair, enhance neuronal connectivity, and partially reverse metabolic deficits[65,67]. In some studies, they also activate microglia to clear Aβ deposits, although effects on tau pathology are less consistent. Importantly, patient-derived iPSCs allow for personalized neural models and potential autologous therapy. iPSC-derived neural progenitors transplanted into triple-transgenic AD mice lead to

reduced amyloid pathology, improved synaptic function, and better cognitive outcomes. Recently, induced neural stem cells (iNSCs), reprogrammed directly from somatic cells, have shown promise in AD models. These cells differentiate into neurons and glia, integrate into the host brain, restore synaptic function, and enhance memory performance. EVs derived from MSCs or hNSCs are also gaining attention as a cell-free therapeutic strategy. EVs carry neuroprotective factors and microRNAs, reduce Aβ deposition and inflammation, and improve cognition in preclinical models[68,69]. Overall, stem cell therapy addresses multiple aspects of AD pathology through cell replacement, neurotrophic support, immunomodulation, and stimulation of endogenous repair. While preclinical data are encouraging, human studies remain in early stages[70-73]. NSPCs transplanted into AD rodent models reduce Aβ and tau burdens, increase synaptic density, and elevate BDNF, leading to improved learning and memory[64,74]. *In vitro* co-cultures of NSPCs with Aβ-exposed neurons reveal enhanced neuronal survival and decreased apoptosis, demonstrating neuroprotective paracrine effects[64]. Bone marrow-derived MSCs added to microglia neuron cultures reduce inflammatory cytokines, such as IL-1β and TNF-α, and promote Aβ clearance[74,75]. Similarly, MSCs increase synaptic proteins like synapsin-1 and dynamin-1 in neuron cultures, a change linked to improved synaptic function[76]. Small-scale human trials using intrathecal or intravenous MSC administration in early-stage AD patients have reported safety, tolerability, and potential slowing of cognitive decline. A phase-I study of intravenous MSCs showed stabilization of Mini-Mental State Examination (MMSE) scores at 6 months post-treatment, with no serious adverse events[77]. Ongoing clinical trials are also evaluating MSC-derived exosomes as a cell-free approach, aiming to harness immunomodulatory and neuroprotective effects[64,71,73,78]. Key challenges include optimizing delivery methods, selecting the most effective cell type (NSPCs, MSCs, iPSC derivatives), ensuring long-term survival and integration, and minimizing risks such as tumor formation and immune rejection. Optimization of delivery methods, cell sources, and long-term safety assessment is critical for translating these therapies into clinical practice.

Stem cell therapy in Parkinson's Disease

Stem cell therapy offers a promising approach to address dopaminergic neuron loss, the hallmark of Parkinson's disease (PD). *In vitro* studies using patient-derived iPSC models have generated dopaminergic (DA) neurons exhibiting PD-related phenotypes, such as oxidative stress and dopamine synthesis deficits, which are useful for disease modeling and drug screening[79]. Preclinical studies in rodent models show that neural NSPC transplantation consistently improves motor function and increases tyrosine hydroxylase-positive dopaminergic neurons in the substantia nigra and striatum region of the animals[80]. A meta-analysis confirmed significant reductions in rotational behavior and enhancements in limb function and dopaminergic cell density when using unmodified NSPCs. MSCs also show beneficial effects in rats and monkeys, where MSC administration reduced neuroinflammation, promoted neuro-regeneration, differentiated into dopaminergic-like neurons, and enhanced motor performance[81,82]. Nonhuman primate studies using iPSC-derived DA neurons demonstrated functional integration into the striatum region of the animal, leading to sustained motor improvement and increased dopamine uptake over periods up to more than a year, without evidence of tumor formation or inflammatory rejection[83]. In particular, autologous iPSC-derived grafts outperform allogeneic ones, highlighting the importance of immune compatibility. Clinically, the first-in-human trial where 2.4 million DA neurons derived from iPSCs were transplanted into a PD patient in 2018, with no serious adverse effects observed during initial follow-up[84]. A separate autologous iPSC-based trial reported robust graft survival and stabilization of motor symptoms at 18–24 months post-transplant, without immunosuppression[84,85]. Additionally, clinical trials using fetal DA neuron grafts and MSC therapies have shown varied motor response benefits and modest improvement of total symptoms; however, dyskinesia and dopamine dysregulation remain potential side effects[86]. Together, these findings indicate that stem cell therapies can significantly restore dopaminergic functions; however, mechanisms such as neuronal replacement, trophic factor release, immune modulation, and synaptic reinnervation remain to be defined. Still, key challenges remain, including ensuring graft purity, avoiding teratoma formation, optimizing delivery methods, and scaling up manufacturing under GMP standards.

Recent advances in Huntington's disease (HD) highlight the therapeutic promise of stem cell-based approaches aimed at replacing lost medium spiny neurons and modulating the neuroinflammatory microenvironment. Preclinical studies using iPSC-derived neural progenitors, MSCs, and gene-corrected patient-specific iPSCs have demonstrated improved motor function, reduced striatal degeneration, and enhanced synaptic connectivity, supporting the feasibility of regenerative and personalized stem cell therapeutic strategies for HD[87].

Stem cell therapy in ischemic stroke

MSCs have consistently shown improved outcomes for ischemic stroke using various animal models. *In vitro*, MSCs enhance angiogenesis, synaptogenesis, and neuronal survival by releasing cytokines and growth factors that modulate apoptosis and inflammation while improving BBB integrity. Rodent and other primate models reveal that MSC transplantation reduces infarct size, enhances neurogenesis, promotes vascular remodeling, and improves sensorimotor function. Meta-analyses of preclinical data confirm large effect sizes, supporting the translation potential of MSC therapy for stroke. Additionally, comparisons with brain-derived injury-activated stem cells suggest even greater functional recovery and promotion of endogenous neural stem/progenitor cell activation in murine stroke models[88-91]. Clinically, randomized controlled trials (RCTs) and non-randomized studies involving MSCs, bone marrow mononuclear cells (BMMNCs), and other progenitors have enrolled over 1,200 patients. Meta-analyses show that stem cell therapy modestly improves neurological deficits (NIHSS), daily living activities (modified Rankin scale and Barthel Index), and reduces mortality without increasing adverse events[92]. Phase I/II trials demonstrate safety for both autologous and allogeneic MSC treatments. One intravenous study in chronic stroke patients found significant gains in the Barthel Index at six and twelve months, with only mild side effects like fever and headache. Intracerebral transplantation of modified MSCs (SB623) into chronic stroke patients also showed no cell-

related serious adverse events over a two-year follow-up period[93,94]. Timing of administration appears crucial; earlier (within 1 month) stem cell delivery is associated with better outcomes, highlighting the importance of addressing inflammation and engraftment early. However, an RCT using intravenous bone marrow stromal cells in the subacute phase showed safety but no significant neurological improvement, emphasizing the influence of timing, dose, and patient selection. Cell-free approaches are also emerging, while MSC-derived EVs show promise in preclinical models by modulating inflammation and promoting repair, and early clinical trials are underway. Overall, this body of evidence indicates that stem cell therapies in ischemic stroke are safe and show functional benefit. However, heterogeneity in cell types, delivery methods, timing, and small sample sizes limits definitive conclusions.

Stem cell therapy in Multiple Sclerosis

MS is an autoimmune disease in which the immune system attacks the myelin sheath of nerve fibers, leading to neurological symptoms, progressive disability, and demyelination. Stem cell-based therapies offer a new frontier for treating by modulating the immune response and promoting nerve repair. Studies show that the MSCs derived from bone marrow or umbilical cord demonstrate immunomodulatory properties, such as reducing inflammatory T-cell activity, suppressing cytokine release, and supporting the survival of neural support cells such as microglia and oligodendrocytes[95]. In animal models of MS, these MSCs improve motor function, reduce immune cell infiltration into the spinal cord, and stimulate endogenous repair of myelin, even without direct differentiation into nerve cells[95]. Early-stage clinical trials, using both intravenous and direct spinal (intrathecal) infusion of MSCs or MSC-derived neural progenitors (MSC-NPs), demonstrate excellent safety with only mild side effects such as headache or fever. In progressive MS patients, those receiving MSC-NPs showed sustained improvements in mobility, bladder function, and reductions in neurodegeneration biomarkers (CCL2, MMP9) over periods of up to two years[96,97]. A comprehensive meta-analysis showed that about 40% of treated patients improve, 32% remain stable, and fewer than 20% worsen, with no major safety concerns[95]. Autologous hematopoietic stem cell transplantation (aHSCT), a more aggressive approach that resets a patient's immune system, has shown profound benefits in relapsing-remitting MS, with up to 83% remaining free of disease activity for two years, and many experience long-term remission[95,98-101]. Stem cell therapies, particularly MSCs and MSC-derived neural progenitors, show promise for progressive MS by modulating inflammation and supporting repair without major risks. Meanwhile, aHSCT offers a potent immune reset in aggressive relapsing-remitting MS. However, larger, controlled trials are needed to define optimal cell type, delivery route, dosing, and long-term effectiveness before these treatments can become mainstream options (Fig. 2).

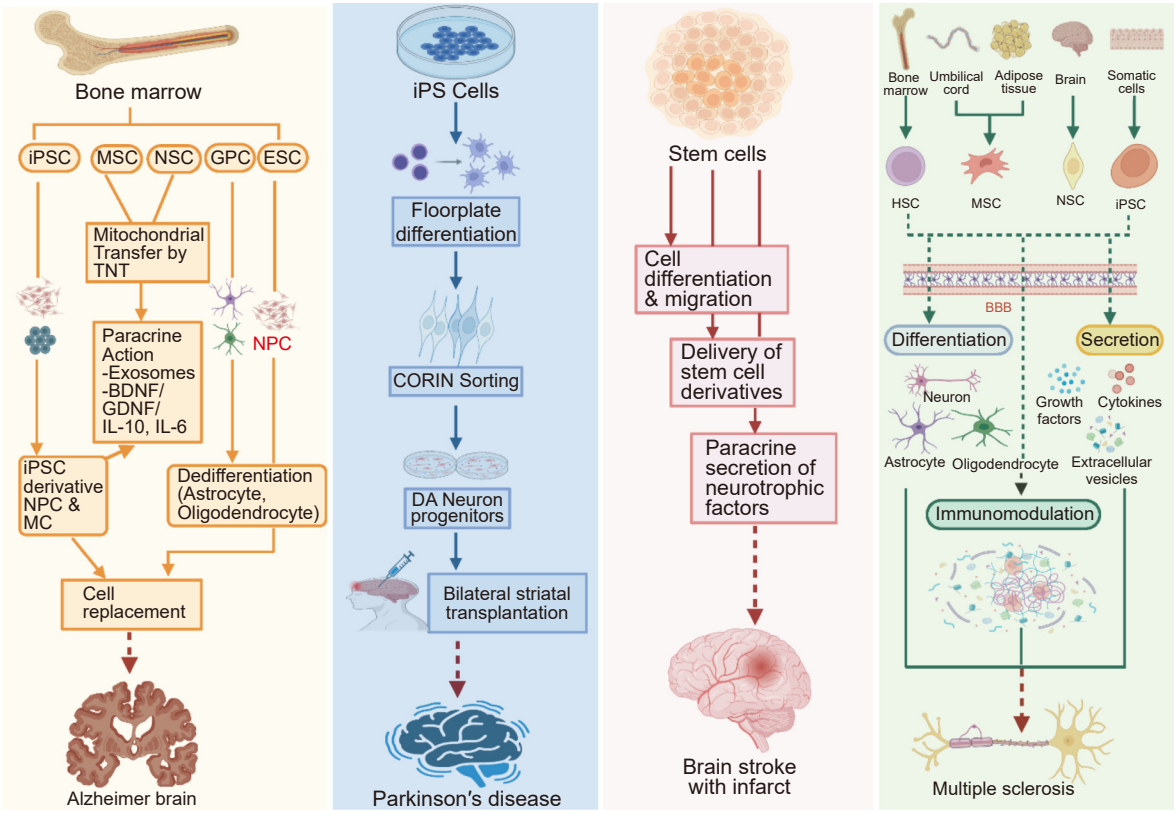

Fig. 2. The therapeutic potential of stem cells and the proposed mechanisms for Alzheimer's disease, Parkinson's Disease, stroke, and Multiple Sclerosis. Mesenchymal stem cells (MSCs), neural stem cells (NSCs), glial progenitor cells (GPCs), neural progenitor cells (NPCs), embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), tunneling nanotube (TNT), mesenchymal cells (MC), BDNF, glial cell line-derived neurotrophic factor (GDNF), interleukin (IL), dopaminergic (DA), HSC, blood-brain barrier (BBB).

Stem cell therapy in temporal lobe epilepsy

Epilepsy is a neurological condition that impacts around 70 million individuals globally. Temporal lobe epilepsy (TLE) is the most common form of epilepsy, marked by recurrent seizures originating in the temporal lobe structures, including the amygdala and hippocampus. TLE often resists drug treatment, with persistent seizures and cognitive decline. Stem cell therapy offers promise for restoring inhibitory neural circuits and reducing seizure activity. NSPCs, expanded as neurospheres, differentiate into neurons, glia, and GABAergic interneurons in culture. When grafted into the hippocampus of rodent TLE models, these cells release gamma-aminobutyric acid (GABA), significantly reducing seizure duration and frequency[102]. Similarly, iPSC-derived medial ganglionic eminence (MGE) interneuron progenitors engraft into the hippocampus and restore inhibitory signaling. They markedly reduce spontaneous seizures, abate aberrant neurogenesis and mossy fiber sprouting, and improve cognition and mood[103]. Adipose-derived mesenchymal stem cells (ADSCs) have also demonstrated therapeutic efficacy in kainic-acid-induced TLE models. Intracerebral or intrathecal ADSC transplantation reduced seizure frequency, preserved blood-brain barrier integrity, and improved cognitive function. These benefits were mediated via secretion of neurotrophins such as BDNF, neurotrophin-3 (NT-3), neurotrophin-4 (NT-4), and reduction of inflammatory cytokines[83,104]. Moreover, reprogramming reactive glial cells into interneurons via gene delivery, like achaete-scute homolog 1 (Ascl1) and distal-less homeobox 2 (Dlx2) expression, reduced seizure burden in mice with chronic TLE and integrated new GABAergic neurons into existing hippocampal circuits[105]. Clinical experience remains limited. A few small trials using autologous bone marrow mononuclear cells or MSCs in children and adults with drug-resistant epilepsy have demonstrated safety and feasibility, with minimal reductions in seizure frequency[106]. However, these were non-controlled studies, and rigorous randomized trials are still lacking. In early phase human regenerative studies, embryonic stem cell-derived interneurons are being implanted intracerebrally in patients with unilateral mesial TLE. Preliminary results from clinical-research efforts (such as NRTX-1001) indicate seizure reduction of up to 95% in two treated individuals without serious adverse effects[107]. Preclinical studies across species consistently demonstrate that stem cell therapies, whether NSPCs, iPSC-derived interneurons, MSCs, or glia to neuron reprogramming, can reduce seizures, restore inhibitory circuitry, and support cognitive recovery in TLE models. Clinical translation is still in early stages, with promising safety data but limited efficacy evidence.

Stem cell therapy in neuropathic pain

Neuropathic pain (NP) is very common and typically arises in diabetic individuals, with a higher prevalence in females. Regrettably, existing pharmacological treatments for neuropathic pain are primarily symptomatic, not entirely effective, and come with numerous side effects. Medications such as pregabalin (Lyrica), tricyclic antidepressants, and opioids are included in this group. Stem cell therapy, including MSCs and their secretome, suppresses pro-inflammatory cytokines and microglial activation while enhancing anti-inflammatory signaling[108,109]. They also promote neurotrophic support, angiogenesis, and modulation of endogenous opioid signaling. Conditioned medium derived from MSCs demonstrates acute antinociceptive effects in pain models, comparable to standard analgesics[109]. Bone marrow-derived MSCs (BM-MSCs) reduce mechanical allodynia in rodent models of neuropathic pain, though their effect on thermal hyperalgesia is seen only when administered within days of injury[110]. In peripheral nerve injury models, MSCs consistently alleviate both mechanical and thermal pain regardless of timing or route of administration. Genetic enhancement with factors such as fibroblast growth factor and glial-derived neurotrophic factor significantly enhances efficacy[111]. Exosomes from BM-MSCs carrying miR-150-5p reduce pain in spinal nerve ligation models by inhibiting microglial neurogenic locus notch homolog protein 2 (NOTCH2) signaling and neuroinflammation[112]. Umbilical cord MSCs (UC-MSCs), administered intrathecally after nerve injury, also reduce mechanical allodynia and thermal hyperalgesia by suppressing activated microglia and astrocytes, reducing IL-1β and IL-17A, and increasing IL-10[113]. Multilineage-differentiating stress-enduring cells also demonstrate analgesic effects in chronic neuropathy models through the secretion of anti-inflammatory mediators like TGF-β and IL-10[114]. An early open-label study of autologous adipose-derived MSCs injected into trigeminal nerve pain fields showed safety and reduced pain scores at six months, where average pain dropped from 7.5 to 4.3, and the need for medication decreased[115]. Patients experienced no serious adverse events. Human studies remain limited, and larger randomized controlled trials are needed to confirm efficacy and long-term safety.

Preclinical evidence strongly supports MSC-based therapies and MSC-derived exosomes as effective for reducing mechanical allodynia and, in some cases, thermal hyperalgesia in neuropathic pain models. These therapies act via anti-inflammatory, neurotrophic, and immunomodulatory mechanisms. Clinical data are promising but preliminary, emphasizing the need for well-designed trials to establish optimal cell types, administration protocols, and long-term outcomes before broader clinical adoption.

Modified stem cell therapy

Gene editing tools like CRISPR/Cas9, transcription activator-like effector nucleases (TALENs), and zinc-finger nucleases enable to precise integration or correction of genes in stem cells[116]. Hematopoietic stem and progenitor cells (HSPCs) edited with CRISPR can correct monogenic disorders like sickle-cell disease and β-thalassemia in preclinical models[117]. However, long-term engraftment remains challenging, as persistence of edited HSPCs often declines after transplantation[118]. Designer stem cells with synthetic gene circuits have been created to deliver anti-inflammatory proteins in response to disease signals[119]. For example, iPSCs engineered to express IL-1 receptor antagonist under inflammatory control have shown therapeutic efficacy in arthritis models[119]. MSCs have been modified to secrete therapeutic cytokines (IL-2, IL-12, IL-21, IFN-α, TRAIL), enabling targeted cancer immunotherapy in preclinical studies. These engineered MSCs can home to tumors and deliver cytokines locally, effectively suppressing tumor growth in mice[120]. Gene-modified epi-

dermal stem cells have been used to correct genetic skin disorders such as recessive dystrophic epidermolysis bullosa (RDEB) and junctional epidermolysis bullosa (JEB) by restoring key proteins like collagen type VII alpha 1 chain (Col7A1) and laminin subunit beta 3 (LAMB3)[121]. Prime editing in pluripotent stem cells allows precise placement of disease mutations, such as Parkinson's and their reversal, enabling accurate disease modeling[122]. Synthetic biology approaches have generated 'smart' cells such as chimeric antigen receptor T-cell (CAR-T) and chimeric antigen receptor-natural killer (CAR-NK) cells equipped with logic circuits to improve targeting and safety in cancer therapy[123]. CAR-NK-92, an off-the-shelf cell line engineered with chimeric antigen receptors, is advancing through clinical trials for solid tumors[124]. Synthetic gene circuits can program cells to sense biomarkers and release therapeutic proteins in a controlled, spatiotemporal manner[125]. Delivery of CRISPR components via plasmids, viral vectors, or ribonucleoprotein particles (RNPs) influences editing efficiency and safety, with RNPs offering lower off-target risks[126]. Stem-cell therapies for diseases like hemophilia use MSCs edited to express clotting factors (e.g., coagulation factor IX and coagulation factor VIII) from safe loci in the genome[120]. Despite progress, challenges remain, such as off-target editing, immunogenicity, engraftment variability, and manufacturing complexity[120]. Future directions include improving gene circuit design, enhancing *in vivo* control of cell therapies, and scaling production for clinical use[123].

Stem cell-based models for preclinical evaluation

Brain organoids, derived from human pluripotent stem cells, self-organize into 3D structures resembling developing brain architecture and are used to model neurological disorders[127,128]. Perfusable organ-on-a-chip systems enhance organoid development through fluid mechanics, improving neural differentiation and cortical layer formation[128]. Organoids have replicated key disease hallmarks such as amyloid-β and tau accumulation in Alzheimer's disease and dopaminergic neuron loss in Parkinson's disease[127]. Patient-specific iPSC-derived organoids allow modeling of genetic disorders like Timothy syndrome and autism, facilitating personalized drug testing[127,129]. Brain-on-a-chip platforms combine microfluidics and 3D cultures to model the BBB, neurovascular interfaces, and shear stress effects. These systems enable high-throughput drug screening, evaluating toxicity, and biomarker discovery under conditions closer to *in vivo* physiology[130]. Vascularized organoids created by co-culturing endothelial cells show improved cell viability and offer more realistic disease models. 3D bioprinting of iPSC-derived neural tissue permits precise patterning for modeling diseases such as multiple sclerosis[131]. Fused organoid systems, including neuromuscular junction models, successfully replicate motor neuron pathology and are used to evaluate candidate therapeutics[132]. Preclinical studies using organoid-grafted animal models demonstrate functional integration and potential therapeutic efficacy in epilepsy and schizophrenia[128]. Despite fetal-like immaturity, these models are advancing through maturation protocols and computational tools like AI-assisted structural design[20]. However, limitations remain, including a lack of full BBB components, immune cells, and adult-level functional maturity[127]. Overall, these 3D stem cell platforms provide powerful tools for mechanistic studies and drug evaluation in neurological disorders, bridging the gap between 2D cultures and animal models[127,129]. Beyond therapeutic applications, advances in anatomical and experimental modeling are increasingly influencing stem cell research and translational neuroscience. Studies focus on the growing use of alternative anatomical teaching and experimental models, as well as refined animal-based platforms, to improve biological understanding, reproducibility, and ethical compliance in biomedical education and preclinical research[133-135]. These approaches complement stem cell-based neurological research by supporting accurate anatomical interpretation and enhancing translational relevance to reduce the use of animals in research.

Biomaterials in stem cell therapy

Biomaterial scaffolds mimic the ECM and provide structural, biochemical, and mechanical support to transplanted stem cells. Natural polymers like collagen, hyaluronic acid, fibrin, chitosan, and urinary bladder ECM hydrogels enhance survival, differentiation, and integration of neural progenitors after CNS injury[136]. Porous collagen-based scaffolds carrying NSCs promote neuronal differentiation, axon growth, reduced gliosis, and restore motor function in spinal cord injury models. Porous collagen-glycosaminoglycan scaffolds deliver embryonic NSCs, improve neuronal integration, and restore locomotion in mice. Covalent immobilization of neurotrophins (BDNF, GDNF) onto electrospun nanofiber scaffolds supports long-term neural progenitor survival and enhances differentiation in vitro and *in vivo*. Injectable thermo-responsive hydrogels (methylcellulose, chitosan/GP) conform to lesion cavities, deliver NSCs, and improve cell adhesion while minimizing inflammation. Implantable scaffolds with anisotropic porosity and conductive properties help guide axonal alignment and transmission, aiding regeneration after stroke, TBI, and spinal cord injury. Combinatorial scaffolds (collagen/heparin with vascular endothelial growth factor, gelatin + polydopamine + GDNF) modulate inflammation, promote M2 microglial phenotype, neuronal survival, and myelination. 3D bio-printed scaffolds (Gelatin methacryloyl, collagen/silk fibroin) allow precise cell placement, reduce scarring, and restore function in spinal cord injury. Nanofiber scaffolds patterned with laminin or graphene oxide direct neurite extension and glial differentiation, improving tissue guidance and integration. Hybrid scaffolds combining stem cells, exosomes, nanoparticles, and growth factors such as MSC-derived exosomes enhance neural regeneration and immunomodulation in TBI. Meta-analysis shows combined scaffolds and MSCs outperform individual treatments, improving motor recovery in preclinical spinal cord injury models[137,138]. Biomaterial scaffolds greatly enhance stem cell therapies for neurological disorders by providing structural support, localized delivery of cells and bioactive cues, and immune modulation[139]. These combinatorial approaches consistently improve cell survival, integration, and functional recovery in preclinical models, representing a promising translational strategy.

Personalized and precision stem cell therapies

Personalized stem cell therapies use a patient's own cells to min-

imize immune rejection and maximize specificity[140]. iPSCs are commonly generated from patient somatic cells and reprogrammed to develop personalized neural cells for therapy and disease modeling[141]. Patient-derived iPSC models have been used to replicate genetic neurological diseases like Parkinson's, Alzheimer's, amyotrophic lateral sclerosis (ALS), and ischemic stroke *in vitro*[141,142]. For example, iPSC-derived dopaminergic progenitors were implanted in patients with Parkinson's disease, demonstrating safety and stable graft survival in a phase I or II trial[6]. Autologous iPSC-derived neural cell therapies are advancing through investigational new drug application (IND) clearance and early-stage clinical studies[22,143]. Brain-on-a-chip platforms with patient-specific iPSC neurons provide personalized drug screening under physiologically relevant conditions[141]. ESC and iPSC-derived neural grafts in spinal cord injury show improved motor function and integration in preclinical rodent models[142,143]. MSCs, harvested from a patient's bone marrow or adipose tissue, are used for personalized immunomodulatory therapies in multiple sclerosis and stroke. Gene editing (CRISPR) in patient-specific iPSCs enables correction of disease mutations before neural differentiation and transplantation[142]. Biomarkers and omics profiling of patient-derived stem cells allow stratification of subpopulations and tailoring of therapeutic cell batches. Challenges include iPSC heterogeneity, genetic/epigenetic drift during culture, tumorigenicity risk, scalability, and high production costs. Precision approaches such as sorting dopaminergic precursors (CORIN sorting) reduce tumor risks and improve treatment specificity[144]. Deep phenotyping and AI in personalized stem cell therapies help to predict differentiation fate and therapeutic potential. Future directions focus on integrating gene correction, microenvironment engineering, and bioengineering to enhance the safety and efficacy of personalized neural cell therapy[142,145]. Recent advances in single-cell transcriptomics and spatial omics have further refined patient-specific stem cell characterization, enabling the identification of responder versus non-responder cell populations before transplantation. In addition, the development of cell-free personalized therapies, such as patient-matched stem cell secretomes and extracellular vesicles, offers a precision alternative that retains therapeutic efficacy while reducing immunogenicity and tumorigenic risk[146]. Future directions focus on integrating gene correction, microenvironment engineering, and bioengineering to enhance the safety and efficacy of personalized neural cell-based therapy.

A first-in-human study conducted in Japan demonstrated the feasibility of personalized stem cell therapy using autologous iPSCs. In this study, patient-derived iPSCs were differentiated into dopaminergic progenitor cells and transplanted into the putamen of individuals with PD. The treatment showed long-term graft survival, no tumor formation, and sustained dopamine production with improvement in motor symptoms, confirming both safety and therapeutic potential of autologous iPSC-based precision therapy[147,148]. This trial highlighted the advantage of personalized approaches in minimizing immune rejection while maintaining functional integration. Patient-derived iPSC neurons from individuals with familial and sporadic AD have been used to recapitulate disease-specific phenotypes, including amyloid-β accumulation, tau hyperphosphorylation, and synaptic dysfunction. These personalized therapies enabled screening of candidate therapeutics under patient-specific genetic backgrounds, revealing differential drug responsiveness and emphasizing the need for precision medicine approaches in neurodegenerative disorders[149,150].

Clinical trials

Clinical trials of stem cell therapy in neurological disorders have shown encouraging but varied outcomes. In MS, studies using MSCs or neural progenitor cells demonstrated safety and modest improvements in mobility, inflammation, and brain atrophy[97,151]. Meta-analyses of randomized trials also reported improved scores of disabilities and reduced lesion volumes in MS patients[152]. In ischemic stroke, trials involving intravenous infusion of MSCs or bone marrow cells in over 700 patients revealed functional gains and reduced disability with minimal side effects[153]. In amyotrophic lateral sclerosis (ALS), a phase III trial using MSCs engineered to release neurotrophic factors did not meet primary efficacy endpoints but showed benefit in patients with milder disease[154]. Overall, these therapies appear to be safe, and early-phase trials support their biological activity. However, most trials remain small, and early-stage and large-scale phase III trials are still needed to confirm long-term efficacy, optimize cell types, and define standardized delivery protocols[155]. As of 2023, over 500 clinical trials in neurological disorders are registered globally, reflecting the growing interest and potential of stem cell-based interventions.

Limitations and challenges

Despite its potential, stem cell therapy for neurological disorders faces several limitations and challenges. One major issue is the limited survival and integration of transplanted cells into the host brain due to the hostile inflammatory environment and scar formation[6]. Immunological rejection remains a concern, especially with allogeneic transplantation, requiring immunosuppression that can pose health risks and side effects[156]. Another challenge is the risk of tumor formation or inappropriate differentiation, particularly with pluripotent stem cells[157]. Standardizing protocols for cell sourcing, preparation, and delivery remains a challenge, which affects reproducibility and scalability across clinical centers. Additionally, ethical concerns and the long-term safety and efficacy of therapies further complicate clinical translation[158]. Limited large-scale clinical trials with long follow-up periods also hinder definitive conclusions about therapeutic benefits. Moreover, regulatory, financial, and logistical barriers continue to slow progress toward routine clinical use in neurological diseases.

Conclusion and future directions

Stem cell-based therapies offer transformative potential for the treatment of neurological disorders, many of which lack curative options. This review explored the wide range of roles of stem cells, spanning from their classifications to their therapeutic applications in complex disorders such as AD, PD, stroke, MS, NP, and TLE. Emerging approaches that target the neuroinflammat-

ory microenvironment, as well as the dynamic crosstalk between stem cells and the immune system, underscore the importance of personalized and precision interventions. Innovations like gene-modified stem cells, synthetic biology tools, brain organoids, and 3D culture models have significantly enhanced understanding of disease mechanisms and improved the fidelity of preclinical evaluation. The integration of biomaterials and scaffolds further supports cell survival and functional recovery. In the context of current literature, this review consolidates emerging evidence that the therapeutic benefits of stem cell-based interventions in neurological disorders are driven less by direct cell replacement and more by paracrine signaling, immune modulation, and microenvironmental remodeling. While earlier studies emphasized neuronal engraftment as the primary mechanism, recent preclinical and clinical findings increasingly support secretome-mediated neuroprotection, anti-inflammatory signaling, and vascular stabilization as dominant contributors to functional recovery. Our studies highlight a paradigm shift toward acellular and precision-based stem cell strategies, aligning with growing reports advocating secretome-, exosome-, and biomaterial-assisted approaches to overcome limitations of cell survival, immune rejection, and scalability. Importantly, by integrating data across multiple neurological disorders, this review identifies convergent molecular pathways such as oxidative stress regulation, mitochondrial homeostasis, and neuroimmune crosstalk that represent shared therapeutic targets across disease contexts. Despite the progress, several challenges remain, including poor engraftment, limited cell survival, immune rejection, and safety concerns in clinical applications. Future investigations need to be focused on improving delivery strategies, optimizing host-graft interactions, and enhancing *in vivo* tracking of the transplanted cells. Additionally, expanding well-controlled, long-term clinical trials and integrating omics-based data for better patient stratification will be critical. With continued interdisciplinary collaboration, stem cell therapy holds promise to revolutionize the landscape of neuro-regenerative medicine and will lead to more effective, individualized precision therapy for debilitating neurological diseases.

Abbreviations

Aβ, Amyloid-β; AD, Alzheimer's disease; ADSCs, Adipose-derived mesenchymal stem cells; ALS, Amyotrophic lateral sclerosis; APP, Amyloid Precursor Protein; aHSCT, Autologous hematopoietic stem cell transplantation; Ascl1, Achaete-scute homolog 1; BBB, Blood-brain barrier; BDNF, Brain-derived neurotrophic factor; BMMNCs, Bone marrow mononuclear cells; CAR-NK, Chimeric antigen receptor-natural killer; CAR-T, Chimeric antigen receptor T-cell; Cas9, CRISPR-associated protein 9; CCL2, C-C motif chemokine ligand 2; CD4, Cluster of differentiation 4; CD8, Cluster of differentiation 8; CNS, Central nervous system; Col7A1, Collagen type VII alpha 1 chain; CRISPR, Clustered regularly interspaced short palindromic repeats; CXCL10, C-X-C motif chemokine ligand 10; CXCL12, C-X-C motif chemokine ligand 12; CXCR4, Chemokine receptor type 4; DAMPs, Damage-associated molecular patterns; Dlx2, Distal-less homeobox 2; ECM, Extracellular matrix; ESCs, Embryonic stem cells; EVs, Extracellular vesicles; GABA, Gamma-aminobutyric acid; G-CSF, Granulocyte colony-stimulating factor; GDNF, Glial cell line-derived neurotrophic factor; GVHD, Graft-versus-host disease; HD, Huntington's disease; HSC, Hematopoietic stem cell; hNSCs, Human neural stem cells; IFN-γ, Interferon-gamma; IL, Interleukin; IL-1β, Interleukin-1 beta; IND, Investigational new drug application; iNSCs, Induced neural stem cells; iPSCs, Induced pluripotent stem cells; JEB, Junctional epidermolysis bullosa; Klf4, Kruppel-like factor 4; LAMB3, Laminin subunit beta 3; MGE, Medial ganglionic eminence; MMP9, Matrix metalloproteinase-9; MS, Multiple sclerosis; MSC-NPs, MSC-derived neural progenitors; MSCs, mesenchymal stem cells; NLRP3, NLR family pyrin domain-containing 3; NOTCH2, Notch homolog protein 2; NP, Neuropathic pain; NSCs, Neural stem cells; NSPCs, Neural stem/progenitor cells; NT-3, Neurotrophin-3; NT-4, Neurotrophin-4; Oct4, Octamer-binding transcription factor 4; PD, Parkinson's disease; PDGF, Platelet-derived growth factor; PS1, Presenilin 1; RCTs, Randomized controlled trials; RDEB, Recessive dystrophic epidermolysis bullosa; RNA, Ribonucleic acid; ROS, Reactive oxygen species; SCFAs, Short-chain fatty acids; SCI, Spinal cord injury; Sox2, SRY-box transcription factor 2; TALENs, Transcription activator-like effector nucleases; TBI, Traumatic brain injury; TGF-β, Transforming growth factor beta; TLE, Temporal lobe epilepsy; TLRs, Toll-like receptors; TNF-α, Tumor necrosis factor-alpha; TRAIL, TNF-related apoptosis-inducing ligand; Tregs, Regulatory T cells; UC-MSCs, Umbilical cord MSCs.

Funding

Funded by a grant from the Brain Drug Discovery Center, Department of Pharmaceutical Sciences, School of Pharmacy, Texas Tech University Health Sciences Center, and a grant from Harrington Cancer and Health Foundation, Amarillo, Texas.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' contributions

This review topic was conceptualized and designed by SH and HD. SH and AN: Literature Reading and Recording Summary. SH: Writing- original draft. HD and SH: Writing- review & editing.

References

[1] Fawcett JW, Asher RA. The glial scar and central nervous system repair. Brain Res Bull, 1999, 49(6): 377-391.

[2] Feigin VL, Nichols E, Alam T, et al. Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol, 2019, 18(5): 459-480.

[3] Olanow CW, Kordower JH, Lang AE, et al. Dopaminergic transplantation for Parkinson's disease: current status and future prospects. Ann Neurol, 2009, 66(5): 591-596.

[4] Abusalah MAH, Priyanka, Abd Rahman E, et al. Evolving trends in stem cell therapy: an emerging and promising approach against

various diseases. Int J Surg, 2024, 110(11): 6862-6868.

[5] Hansda S, Das H. Tissue Regeneration: Cellular and Molecular Mechanisms. In: Tissue Repair and Regeneration: Elucidating Cellular and Molecular Mechanisms with Therapeutic Implications. Springer: Berlin, Germany, 2025; 491-524.

[6] Trounson A, McDonald C. Stem Cell Therapies in Clinical Trials: Progress and Challenges. Cell Stem Cell, 2015, 17(1): 11-22.

[7] Rolph DN, Deb M, Kanji S, et al. Ferutinin directs dental pulp-derived stem cells towards the osteogenic lineage by epigenetically regulating canonical Wnt signaling. Biochim Biophys Acta Mol Basis Dis, 2020, 1866(4): 165314.

[8] Lindvall O, Kokaia Z. Stem cells for the treatment of neurological disorders. Nature, 2006, 441(7097): 1094-1096.

[9] Madl CM, Heilshorn SC, Blau HM. Bioengineering strategies to accelerate stem cell therapeutics. Nature, 2018, 557(7705): 335-342.

[10] Weissman IL. Stem cells-scientific, medical, and political issues. N Engl J Med, 2002, 346(20): 1576-1579.

[11] Thomson JA, Itskovitz-Eldor J, Shapiro SS, et al. Embryonic stem cell lines derived from human blastocysts. Science, 1998, 282(5391): 1145-1147.

[12] Ben-David U, Benvenisty N. The tumorigenicity of human embryonic and induced pluripotent stem cells. Nat Rev Cancer, 2011, 11(4): 268-277.

[13] Prateeksha P, Howlader MSI, Hansda S, et al. Secretome of Dental Pulp-Derived Stem Cells Reduces Inflammation and Proliferation of Glioblastoma Cells by Deactivating Mapk-Akt Pathway. Dis Res, 2023, 3(2): 74-86.

[14] Hansda S, Prateeksha P, Das H. Krüppel-like factor 2 (KLF2), a potential target for neuroregeneration. Neural Regen Res, 2024, 19(11): 2327-2328.

[15] Gage FH. Mammalian neural stem cells. Science, 2000, 287(5457): 1433-1438.

[16] Willis CM, Nicaise AM, Peruzzotti-Jametti L, et al. The neural stem cell secretome and its role in brain repair. Brain Res, 2020, 1729: 146615.

[17] Zhang SC, Wernig M, Duncan ID, et al. In vitro differentiation of transplantable neural precursors from human embryonic stem cells. Nat Biotechnol, 2001, 19(12): 1129-1133.

[18] Pittenger MF, Mackay AM, Beck SC, et al. Multilineage potential of adult human mesenchymal stem cells. Science, 1999, 284(5411): 143-147.

[19] Hansda S, Das H. Unraveling the Bone–Brain Communication Network. Biology, 2025, 14(9): 1279.

[20] Uccelli A, Moretta L, Pistoia V. Mesenchymal stem cells in health and disease. Nat Rev Immunol, 2008, 8(9): 726-736.

[21] Squillaro T, Peluso G, Galderisi U. Clinical Trials with Mesenchymal Stem Cells: An Update. Cell Transplant, 2016, 25(5): 829-848.

[22] Le Blanc K, Frassoni F, Ball L, et al. Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study. Lancet, 2008, 371(9624): 1579-1586.

[23] Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell, 2006, 126(4): 663-676.

[24] Bellin M, Marchetto MC, Gage FH, et al. Induced pluripotent stem cells: the new patient? Nat Rev Mol Cell Biol, 2012, 13(11): 713-726.

[25] Mandai M, Watanabe A, Kurimoto Y, et al. Autologous Induced Stem-Cell-Derived Retinal Cells for Macular Degeneration. N Engl J Med, 2017, 376(11): 1038-1046.

[26] Zhao T, Zhang ZN, Rong Z, et al. Immunogenicity of induced pluripotent stem cells. Nature, 2011, 474(7350): 212-215.

[27] Phinney DG, Pittenger MF. Concise Review: MSC-Derived Exosomes for Cell-Free Therapy. Stem Cells, 2017, 35(4): 851-858.

[28] Zakrzewski W, Dobrzyński M, Szymonowicz M, et al. Stem cells: past, present, and future. Stem Cell Res Ther, 2019, 10(1): 68.

[29] Discher DE, Mooney DJ, Zandstra PW. Growth factors, matrices, and forces combine and control stem cells. Science, 2009, 324(5935): 1673-1677.

[30] Scadden DT. The stem-cell niche as an entity of action. Nature, 2006, 441(7097): 1075-1079.

[31] Gattazzo F, Urciuolo A, Bonaldo P. Extracellular matrix: a dynamic microenvironment for stem cell niche. Biochim Biophys Acta, 2014, 1840(8): 2506-2519.

[32] Murry CE, Keller G. Differentiation of embryonic stem cells to clinically relevant populations: lessons from embryonic development. Cell, 2008, 132(4): 661-680.

[33] Lapidot T, Petit I. Current understanding of stem cell mobilization: the roles of chemokines, proteolytic enzymes, adhesion molecules, cytokines, and stromal cells. Exp Hematol, 2002, 30(9): 973-981.

[34] Le Blanc K, Tammik C, Rosendahl K, et al. HLA expression and immunologic properties of differentiated and undifferentiated mesenchymal stem cells. Exp Hematol, 2003, 31(10): 890-896.

[35] Waterman RS, Tomchuck SL, Henkle SL, et al. A new mesenchymal stem cell (MSC) paradigm: polarization into a pro-inflammatory MSC1 or an Immunosuppressive MSC2 phenotype. PLoS One, 2010, 5(4): e10088.

[36] Hu C, Li L. Preconditioning influences mesenchymal stem cell properties in vitro and in vivo. J Cell Mol Med, 2018, 22(3): 1428-1442.

[37] Martino G, Pluchino S. The therapeutic potential of neural stem cells. Nat Rev Neurosci, 2006, 7(5): 395-406.

[38] Rowe RG, Daley GQ. Induced pluripotent stem cells in disease modelling and drug discovery. Nat Rev Genet, 2019, 20(7): 377-388.

[39] Hansda S, Ghosh G, Ghosh R. 9-phenyl acridine photosensitizes A375 cells to UVA radiation. Heliyon, 2020, 6(9): e04733.

[40] Plaks V, Kong N, Werb Z. The cancer stem cell niche: how essential is the niche in regulating stemness of tumor cells? Cell Stem Cell, 2015, 16(3): 225-238.

[41] Batlle E, Clevers H. Cancer stem cells revisited. Nat Med, 2017, 23(10): 1124-1134.

[42] Timmers L, Lim SK, Arslan F, et al. Reduction of myocardial infarct size by human mesenchymal stem cell conditioned medium. Stem Cell Res, 2007, 1(2): 129-137.

[43] Lutolf MP, Hubbell JA. Synthetic biomaterials as instructive extracellular microenvironments for morphogenesis in tissue engineering. Nat Biotechnol, 2005, 23(1): 47-55.

[44] Galea I, Bechmann I, Perry VH. What is immune privilege (not)? Trends Immunol, 2007, 28(1): 12-18.

[45] Ransohoff RM, Brown MA. Innate immunity in the central nervous system. J Clin Invest, 2012, 122(4): 1164-1171.

[46] Paolicelli RC, Bolasco G, Pagani F, et al. Synaptic pruning by microglia is necessary for normal brain development. Science, 2011, 333(6048): 1456-1458.

[47] Heneka MT, Carson MJ, El Khoury J, et al. Neuroinflammation in Alzheimer's disease. Lancet Neurol, 2015, 14(4): 388-405.

[48] Varatharaj A, Galea I. The blood-brain barrier in systemic inflammation. Brain Behav Immun, 2017, 60: 1-12.

[49] Dendrou CA, Fugger L, Friese MA. Immunopathology of multiple sclerosis. Nat Rev Immunol, 2015, 15(9): 545-558.

[50] Sospedra M, Martin R. Immunology of multiple sclerosis. Annu Rev Immunol, 2005, 23: 683-747.

[51] Sørensen TL, Sellebjerg F, Jensen CV, et al. Chemokines CXCL10 and CCL2: differential involvement in intrathecal inflammation in multiple sclerosis. Eur J Neurol, 2001, 8(6): 665-672.

[52] Calsolaro V, Edison P. Neuroinflammation in Alzheimer's disease: Current evidence and future directions. Alzheimers Dement, 2016, 12(6): 719-732.

[53] Heneka MT, Kummer MP, Stutz A, et al. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. Nature, 2013, 493(7434): 674-678.

[54] Tansey MG, Goldberg MS. Neuroinflammation in Parkinson's disease: its role in neuronal death and implications for therapeutic intervention. Neurobiol Dis, 2010, 37(3): 510-518.

[55] Brochard V, Combadière B, Prigent A, et al. Infiltration of CD4 + lymphocytes into the brain contributes to neurodegeneration in a mouse model of Parkinson disease. J Clin Invest, 2009, 119(1): 182-192.

[56] Iadecola C, Anrather J. The immunology of stroke: from mechanisms to translation. Nat Med, 2011, 17(7): 796-808.

[57] Chamorro Á, Meisel A, Planas AM, et al. The immunology of acute stroke. Nat Rev Neurol, 2012, 8(7): 401-410.

[58] Sharon G, Sampson TR, Geschwind DH, et al. The Central Nervous System and the Gut Microbiome. Cell, 2016, 167(4): 915-932.

[59] Erny D, Hrabě de Angelis AL, Jaitin D, et al. Host microbiota constantly control maturation and function of microglia in the CNS. Nat Neurosci, 2015, 18(7): 965-977.

[60] Liesz A, Dalpke A, Mracsko E, et al. DAMP signaling is a key pathway inducing immune modulation after brain injury. J Neurosci, 2015, 35(2): 583-598.

[61] Korn T, Bettelli E, Oukka M, et al. IL-17 and Th17 Cells. Annu Rev Immunol, 2009, 27: 485-517.

[62] Barthels D, Prateeksha P, Nozohouri S, et al. Dental Pulp-Derived Stem Cells Preserve Astrocyte Health During Induced Gliosis by Modulating Mitochondrial Activity and Functions. Cell Mol Neurobiol, 2023, 43(5): 2105-2127.

[63] Howlader MSI, Prateeksha P, Hansda S, et al. Secretory products of DPSC mitigate inflammatory effects in microglial cells by targeting MAPK pathway. Biomed Pharmacother, 2024, 170: 115971.

[64] Blurton-Jones M, Kitazawa M, Martinez-Coria H, et al. Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease. Proc Natl Acad Sci, 2009, 106(32): 13594-13599.

[65] Regmi S, Liu DD, Shen M, et al. Mesenchymal stromal cells for the treatment of Alzheimer's disease: Strategies and limitations. Front Mol Neurosci, 2022, 15: 1011225.

[66] Ager RR, Davis JL, Agazaryan A, et al. Human neural stem cells improve cognition and promote synaptic growth in two complementary transgenic models of Alzheimer's disease and neuronal loss. Hippocampus, 2015, 25(7): 813-826.

[67] Li X, Zhu H, Sun X, et al. Human Neural Stem Cell Transplantation Rescues Cognitive Defects in APP/PS1 Model of Alzheimer's Disease by Enhancing Neuronal Connectivity and Metabolic Activity. Front Aging Neurosci, 2016, 8: 282.

[68] Gonzalez R, Hamblin MH, Lee JP. Neural Stem Cell Transplantation and CNS Diseases. CNS Neurol Disord Drug Targets, 2016, 15(8): 881-886.

[69] Khan MI, Jeong ES, Khan MZ, et al. Stem cells-derived exosomes alleviate neurodegeneration and Alzheimer's pathogenesis by ameliorating neuroinflamation, and regulating the associated molecular pathways. Sci Rep, 2023, 13(1): 15731.

[70] Zhang W, Uyemura R, Zhong K, et al. Current Advances and Future Perspectives on Mesenchymal Stem Cell-Derived Extracellular Vesicles in Alzheimer's Disease. Aging Dis, 2024, 15(5): 2015-2027.

[71] Ocansey DKW, Pei B, Yan Y, et al. Improved therapeutics of modified mesenchymal stem cells: an update. J Transl Med, 2020, 18(1): 42.

[72] Cui Y, Ma S, Zhang C, et al. Human umbilical cord mesenchymal stem cells transplantation improves cognitive function in Alzheimer's disease mice by decreasing oxidative stress and promoting hippocampal neurogenesis. Behav Brain Res, 2017, 320: 291-301.

[73] Matsumoto T, Kano K, Kondo D, et al. Mature adipocyte-derived dedifferentiated fat cells exhibit multilineage potential. J Cell Physiol, 2008, 215(1): 210-222.

[74] Guo Z, Zhang L, Wu Z, et al. In vivo direct reprogramming of reactive glial cells into functional neurons after brain injury and in an Alzheimer's disease model. Cell Stem Cell, 2014, 14(2): 188-202.

[75] Ma T, Gong K, Ao Q, et al. Intracerebral transplantation of adipose-derived mesenchymal stem cells alternatively activates microglia and ameliorates neuropathological deficits in Alzheimer's disease mice. Cell Transplant, 2013, 22 Suppl 1: S113-S126.

[76] Doshmanziari M, Shirian S, Kouchakian MR, et al. Mesenchymal stem cells act as stimulators of neurogenesis and synaptic function in a rat model of Alzheimer's disease. Heliyon, 2011, 7(9): e07996.

[77] Wilson JG, Liu KD, Zhuo H, et al. Mesenchymal stem (stromal) cells for treatment of ARDS: a phase 1 clinical trial. Lancet Respir Med, 2015, 3(1): 24-32.

[78] Shah S, Mansour HM, Aguilar TM, et al. Mesenchymal Stem Cell-Derived Exosomes as a Neuroregeneration Treatment for Alzheimer's Disease. Biomedicines, 2024, 12(9).

[79] Martínez-Morales PL, Liste I. Stem cells as in vitro model of Parkinson's disease. Stem Cells Int, 2012, 2012: 980941.

[80] Zheng Y, Zhou J, Wang Y, et al. Neural Stem/Progenitor Cell Transplantation in Parkinson's Rodent Animals: A Meta-Analysis and Systematic Review. Stem Cells Transl Med, 2022, 11(4): 383-393.

[81] Shastry S, Hu J, Ying M, et al. Cell Therapy for Parkinson's Disease. Pharmaceutics, 2023, 15(12).

[82] Politis M, Lindvall O. Clinical application of stem cell therapy in Parkinson's disease. BMC Med, 2012, 10: 1.

[83] Zayed MA, Sultan S, Alsaab HO, et al. Stem-Cell-Based Therapy: The Celestial Weapon against Neurological Disorders. Cells, 2022, 11(21).

[84] Song B, Cha Y, Ko S, et al. Human autologous iPSC-derived dopaminergic progenitors restore motor function in Parkinson's disease models. J Clin Invest, 2020, 130(2): 904-920.

[85] Zhang J, Wang X, Li J, et al. The Preclinical Research Progress of Stem Cells Therapy in Parkinson's Disease. Biomed Res Int, 2016, 2016: 5683097.

[86] Brundin P, Barker RA, Parmar M. Neural grafting in Parkinson's disease Problems and possibilities. Prog Brain Res, 2010, 184: 265-294.

[87] Shah S, Mansour HM, Lucke-Wold B. Advances in Stem Cell Therapy for Huntington's Disease: A Comprehensive Literature Review. Cells, 2025, 14(1).

[88] Hansda S, Das H. Insights into Cancer-Associated thrombosis leading towards ischemic stroke. Biology, 2025, 14(1): 50.

[89] Levy ML, Crawford JR, Dib N, et al. Phase I/II Study of Safety and Preliminary Efficacy of Intravenous Allogeneic Mesenchymal Stem Cells in Chronic Stroke. Stroke, 2019, 50(10): 2835-2841.

[90] Sarmah D, Agrawal V, Rane P, et al. Mesenchymal Stem Cell Therapy in Ischemic Stroke: A Meta-analysis of Preclinical Studies. Clin Pharmacol Ther, 2018, 103(6): 990-998.

[91] Xiong Y, Guo X, Gao W, et al. Efficacy and safety of stem cells in

the treatment of ischemic stroke: A meta-analysis. Medicine, 2024, 103(12): e37414.

[92] Shen Z, Tang X, Zhang Y, et al. Efficacy and safety of mesenchymal stem cell therapies for ischemic stroke: a systematic review and meta-analysis. Stem Cells Transl Med, 2024, 13(9): 886-897.

[93] Chan HH, Wathen CA, Ni M, et al. Stem cell therapies for ischemic stroke: current animal models, clinical trials and biomaterials. RSC Adv, 2017, 7(30): 18668-18680.

[94] Steinberg GK, Kondziolka D, Wechsler LR, et al. Two-year safety and clinical outcomes in chronic ischemic stroke patients after implantation of modified bone marrow-derived mesenchymal stem cells (SB623): a phase 1/2a study. J Neurosurg, 2019, 131(5): 1462-1472.

[95] Islam MA, Alam SS, Kundu S, et al. Mesenchymal Stem Cell Therapy in Multiple Sclerosis: A Systematic Review and Meta-Analysis. J Clin Med, 2023, 12(19).

[96] Harris VK, Stark JW, Yang S, et al. Mesenchymal stem cell-derived neural progenitors in progressive MS: Two-year follow-up of a phase I study. Neurol Neuroimmunol Neuroinflamm, 2020, 8(1): e928.

[97] Harris VK, Stark J, Williams A, et al. Efficacy of intrathecal mesenchymal stem cell-neural progenitor therapy in progressive MS: results from a phase II, randomized, placebo-controlled clinical trial. Stem Cell Res Ther, 2024, 15(1): 151.

[98] Jasim SA, Yumashev AV, Abdelbasset WK, et al. Shining the light on clinical application of mesenchymal stem cell therapy in autoimmune diseases. Stem Cell Res Ther, 2022, 13(1): 101.

[99] Berard JA, Freedman MS, Marrie RA, et al. Mesenchymal stem cell therapy and cognition in MS: Preliminary findings from a phase II clinical trial. Mult Scler Relat Disord, 2022, 61: 103779.

[100] Zeng L, Liu C, Wu Y, et al. Efficacy and safety of mesenchymal stromal cell transplantation in the treatment of autoimmune and rheumatic immune diseases: a systematic review and meta-analysis of randomized controlled trials. Stem Cell Res Ther, 2025, 16(1): 65.

[101] Liu S, Mao X, Hou Z, et al. Multiple transplantation of mesenchymal stem cells in a patient with active progressive multiple sclerosis: Long term therapeutic outcomes. Clin Neurol Neurosurg, 2022, 223: 107475.

[102] Lee H, Yun S, Kim IS, et al. Human fetal brain-derived neural stem/progenitor cells grafted into the adult epileptic brain restrain seizures in rat models of temporal lobe epilepsy. PLoS One, 2014, 9(8): e104092.

[103] Upadhya D, Hattiangady B, Castro OW, et al. Human induced pluripotent stem cell-derived MGE cell grafting after status epilepticus attenuates chronic epilepsy and comorbidities via synaptic integration. Proc Natl Acad Sci, 2019, 116(1): 287-296.

[104] Tesiye MR, Gol M, Fadardi MR, et al. Therapeutic Potential of Mesenchymal Stem Cells in the Treatment of Epilepsy and Their Interaction with Antiseizure Medications. Cells, 2022, 11(24).

[105] Lentini C, d'Orange M, Marichal N, et al. Reprogramming reactive glia into interneurons reduces chronic seizure activity in a mouse model of mesial temporal lobe epilepsy. Cell Stem Cell, 2021, 28(12): 2104-2121. e10.

[106] Aligholi H, Safahani M, Asadi-Pooya AA. Stem cell therapy in patients with epilepsy: A systematic review. Clin Neurol Neurosurg, 2021, 200: 106416.

[107] Alayli A, Lockard G, Gordon J, et al. Stem Cells: Recent Developments Redefining Epilepsy Therapy. Cell Transplant, 2023, 32: 9636897231158967.

[108] Joshi HP, Jo HJ, Kim YH, et al. Stem cell therapy for modulating neuroinflammation in neuropathic pain. Int J Mol Sci, 2021, 22(9): 4853.

[109] Gama KB, Santos DS, Evangelista AF, et al. Conditioned Medium of Bone Marrow-Derived Mesenchymal Stromal Cells as a Therapeutic Approach to Neuropathic Pain: A Preclinical Evaluation. Stem Cells Int, 2018, 2018: 8179013.

[110] Hosseini M, Yousefifard M, Aziznejad H, et al. The Effect of Bone Marrow-Derived Mesenchymal Stem Cell Transplantation on Allodynia and Hyperalgesia in Neuropathic Animals: A Systematic Review with Meta-Analysis. Biol Blood Marrow Transplant, 2015, 21(9): 1537-1544.

[111] Wang Q, He H, Xie S, et al. Mesenchymal Stem Cells Transplantation for Neuropathic Pain Induced By Peripheral Nerve Injury in Animal Models: A Systematic Review. Stem Cells Dev, 2020, 29(22): 1420-1428.

[112] Li S, Huang C, Tu C, et al. Bone marrow mesenchymal stem cell-derived exosomes shuttling miR-150-5p alleviates mechanical allodynia in rats by targeting NOTCH2 in microglia. Mol Med, 2022, 28(1): 133.

[113] Chen C, Chen F, Yao C, et al. Intrathecal Injection of Human Umbilical Cord-Derived Mesenchymal Stem Cells Ameliorates Neuropathic Pain in Rats. Neurochem Res, 2016, 41(12): 3250-3260.

[114] Zhao Y, Fei Y, Cai Y, et al. Multilineage-differentiating stress-enduring cells alleviate neuropathic pain in mice by secreting TGF-b and IL-10. arXiv, 2025, 2501: 11291.

[115] Vickers ER, Karsten E, Flood J, et al. A preliminary report on stem cell therapy for neuropathic pain in humans. J Pain Res, 2014, 7: 255-263.

[116] Shui B, Matias LH, Guo Y, et al. The rise of CRISPR/Cas for genome editing in stem cells. Stem Cells Int, 2016, 2016: 8140168.

[117] Frangoul H, Altshuler D, Cappellini MD, et al. CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β-Thalassemia. N Engl J Med, 2021, 384(3): 252-260.

[118] Maganti HB, Bailey AJM, Kirkham AM, et al. Persistence of CRISPR/Cas9 gene edited hematopoietic stem cells following transplantation: A systematic review and meta-analysis of preclinical studies. Stem Cells Transl Med, 2021, 10(7): 996-1007.

[119] Lach MS, Rosochowicz MA, Richter M, et al. The Induced Pluripotent Stem Cells in Articular Cartilage Regeneration and Disease Modelling: Are We Ready for Their Clinical Use? Cells, 2022, 11(3).

[120] Yeganeh P, Forghani S, Pouresmaeil L, et al. Targeted cytokine delivery for cancer therapy through engineered mesenchymal stem cells. Gene Rep, 2025: 102199.

[121] Kikuchi Y, Tamakoshi T, Ishida R, et al. Gene-Modified Blister Fluid-Derived Mesenchymal Stromal Cells for Treating Recessive Dystrophic Epidermolysis Bullosa. J Invest Dermatol, 2023, 143(12): 2447-2455. e8.

[122] Yao B, Lei Z, Gonçalves MA, et al. Integrating Prime Editing and Cellular Reprogramming as Novel Strategies for Genetic Cardiac Disease Modeling and Treatment. Curr Cardiol Rep, 2024, 26(11): 1197-1208.

[123] Clubb JD, Gao TA, Chen YY. Synthetic Biology in the Engineering of CAR-T and CAR-NK Cell Therapies: Facts and Hopes. Clin Cancer Res, 2023, 29(8): 1390-1402.

[124] Zhang C, Oberoi P, Oelsner S, et al. Chimeric Antigen Receptor-Engineered NK-92 Cells: An Off-the-Shelf Cellular Therapeutic for Targeted Elimination of Cancer Cells and Induction of Protective Antitumor Immunity. Front Immunol, 2017, 8: 533.

[125] Cimino A, Pat F, Oyebamiji O, et al. Dual-responsive synthetic gene circuit for dynamic biologic drug delivery via inflammatory and circadian signaling pathways. J Biol Eng, 2025, 19(1): 47.

[126] Lino CA, Harper JC, Carney JP, et al. Delivering CRISPR: a review of the challenges and approaches. Drug Deliv, 2018, 25(1): 1234-1257.

[127] Smirnova L, Hartung T. The promise and potential of brain organoids. Adv Healthc Mater, 2024, 13(21): 2302745.

[128] Wang Y, Wang L, Guo Y, et al. Engineering stem cell-derived 3D brain organoids in a perfusable organ-on-a-chip system. RSC Adv, 2018, 8(3): 1677-1685.

[129] Chen X, Birey F, Li MY, et al. Antisense oligonucleotide therapeutic approach for Timothy syndrome. Nature, 2024, 628(8009): 818-825.

[130] Yao Y, Coleman HA, Meagher L, et al. 3D Functional Neuronal Networks in Free‐Standing Bioprinted Hydrogel Constructs. Adv Healthc Mater, 2023, 12(28): 2300801.

[131] Chen EP, Toksoy Z, Davis BA, et al. 3D Bioprinting of Vascularized Tissues for in vitro and in vivo Applications. Front Bioeng Biotechnol, 2021, 9: 664188.

[132] Babcock CD, Hamilton LD, Lykidis A, et al. Neuromusculoskeletal Modeling and Force Prediction: Verification Through Experimental Neuromuscular Dynamics. Ann Biomed Eng, 2025, 53(10): 2489-2502.

[133] Choudhary OP, Sarkar R. Animal Anatomical Teaching Models for Enhanced Veterinary Anatomy Education and Learning. Pak Vet J, 2025, 9.

[134] Choudhary OP, Infant SS, As V, et al. Exploring the potential and limitations of artificial intelligence in animal anatomy. Ann Anat, 2025, 258: 152366.

[135] Choudhary OP. Animal models for surgeries and implants: a vital tool in medical research and development. Ann Med Surg, 2025, 87(7): 4090-4095.

[136] Giorgi Z, Veneruso V, Petillo E, et al. Biomaterials and Cell Therapy Combination in Central Nervous System Treatments. ACS Appl Bio Mater, 2024, 7(1): 80-98.

[137] Mili B, Choudhary OP. Advancements and mechanisms of stem cell-based therapies for spinal cord injury in animals. Int J Surg, 2024, 110(10): 6182-6197.

[138] Shang Z, Wang R, Li D, et al. Spinal Cord Injury: A Systematic Review and Network Meta-Analysis of Therapeutic Strategies Based on 15 Types of Stem Cells in Animal Models. Front Pharmacol, 2022, 13: 819861.

[139] Shrestha B, Coykendall K, Li Y, et al. Repair of injured spinal cord using biomaterial scaffolds and stem cells. Stem Cell Res Ther, 2014, 5(4): 91.

[140] Kirkeby A, Main H, Carpenter M. Pluripotent stem-cell-derived therapies in clinical trial: A 2025 update. Cell Stem Cell, 2025, 32(1): 10-37.

[141] Valadez-Barba V, Cota-Coronado A, Hernández-Pérez OR, et al. iPSC for modeling neurodegenerative disorders. Regen Ther, 2020, 15: 332-339.

[142] Man Y, Liu Y, Chen Q, et al. Organoids-On-a-Chip for Personalized Precision Medicine. Adv Healthc Mater, 2024, 13(30): e2401843.

[143] Abbas A, Huang X, Ullah A, et al. Enhanced spinal cord repair using bioengineered induced pluripotent stem cell-derived exosomes loaded with miRNA. Mol Med, 2024, 30(1): 168.

[144] Sawamoto N, Doi D, Nakanishi E, et al. Phase I/II trial of iPS-cell-derived dopaminergic cells for Parkinson's disease. Nature, 2025, 641(8064): 971-977.

[145] Ilic D, Liovic M. Industry updates from the field of stem cell research and regenerative medicine in May 2024. Regen Med, 2024, 19(9-10): 445-454.

[146] Ragni E, Parolini O, Silini AR. Editorial: MSC-Derived Extracellular Vesicles and Secreted Factors as "Cell-Free" Therapeutic Alternatives in Regenerative Medicine. Front Bioeng Biotechnol, 2022, 10: 842128.

[147] Schweitzer JS, Song B, Herrington TM, et al. Personalized iPSC-Derived Dopamine Progenitor Cells for Parkinson's Disease. N Engl J Med, 2020, 382(20): 1926-1932.

[148] Takahashi J. iPS cell-based therapy for Parkinson's disease: A Kyoto trial. Regen Ther, 2020, 13: 18-22.

[149] Raja WK, Mungenast AE, Lin YT, et al. Self-Organizing 3D Human Neural Tissue Derived from Induced Pluripotent Stem Cells Recapitulate Alzheimer's Disease Phenotypes. PLoS One, 2016, 11(9): e0161969.

[150] Mertens J, Reid D, Lau S, et al. Aging in a Dish: iPSC-Derived and Directly Induced Neurons for Studying Brain Aging and Age-Related Neurodegenerative Diseases. Annu Rev Genet, 2018, 52: 271-293.

[151] Genchi A, Brambilla E, Sangalli F, et al. Neural stem cell transplantation in patients with progressive multiple sclerosis: an open-label, phase 1 study. Nat Med, 2023, 29(1): 75-85.

[152] Nawar AA, Farid AM, Wally R, et al. Efficacy and safety of stem cell transplantation for multiple sclerosis: a systematic review and meta-analysis of randomized controlled trials. Sci Rep, 2024, 14(1): 12545.

[153] Li Z, Dong X, Tian M, et al. Stem cell-based therapies for ischemic stroke: a systematic review and meta-analysis of clinical trials. Stem Cell Res Ther, 2020, 11(1): 252.

[154] Cudkowicz ME, Lindborg SR, Goyal NA, et al. A randomized placebo-controlled phase 3 study of mesenchymal stem cells induced to secrete high levels of neurotrophic factors in amyotrophic lateral sclerosis. Muscle Nerve, 2022, 65(3): 291-302.

[155] Jiang S, Bao X, Zhong C, et al. Mapping the global clinical landscape of stem cell therapies for neurological diseases from 1998 to 2023: an analysis based on the Trialtrove database. Stem Cell Res Ther, 2025, 16(1): 41.

[156] Zhu W, Li M, Zou J, et al. Induction of local immunosuppression in allogeneic cell transplantation by cell-type-specific expression of PD-L1 and CTLA4Ig. Stem Cell Reports, 2023, 18(12): 2344-2355.

[157] Ramos-Zúñiga R, González-Pérez O, Macías-Ornelas A, et al. Ethical implications in the use of embryonic and adult neural stem cells. Stem Cells Int, 2012, 2012: 470949.

[158] Leeper TJ, Hobolt SB, Tilley J. Measuring subgroup preferences in conjoint experiments. Political Analysis, 2020, 28(2): 207-221.