

Mesenchymal Stem Cells in Neurodegenerative Disorders: A Review of Current Evidence and Therapeutic Perspectives

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ABSTRACT

Disorders of the central nervous system (CNS), including Alzheimer's disease, Parkinson's disease, multiple sclerosis, cerebral palsy, stroke, and spinal cord injury, are associated with neuronal damage, neuronal loss, inflammation, and impaired neurological function and remain major challenges in medicine. Despite advances in pharmacological, surgical, and rehabilitative interventions, many of these disorders lack definitive or fully effective treatments. In recent years, stem cell-based therapies have received considerable attention as potential approaches for neural repair and functional recovery. Mesenchymal stem cells (MSCs) have attracted particular interest because of their distinctive biological properties, including their capacity for differentiation, secretion of neurotrophic factors, immunomodulatory and anti-inflammatory effects, and migration toward injured tissues. Compared with other stem cell types, including neural stem cells, embryonic stem cells, and induced pluripotent stem cells, MSCs offer several potential advantages, such as relatively easy accessibility, availability from multiple sources, including bone marrow, adipose tissue, and umbilical cord blood, and fewer ethical concerns. This narrative review examines published studies on the application of MSCs in neurological disorders, with particular emphasis on their biological characteristics, potential mechanisms of action, cellular sources, and advantages compared with other stem cell types. The available evidence regarding the use of MSCs in neurodegenerative diseases and other CNS disorders, including Alzheimer's disease, Parkinson's disease, multiple sclerosis, stroke, and spinal cord injury, is also reviewed and discussed. Overall, available evidence suggests that MSCs may support neural function and repair through neurotrophic, anti-inflammatory, immunomodulatory, and regenerative mechanisms. However, despite encouraging findings from preclinical studies and some clinical investigations, current clinical evidence remains limited and heterogeneous. Differences in cell source, cell preparation and administration, dosage, treatment timing, and long-term outcomes may influence therapeutic effects. Therefore, well-designed and adequately powered clinical studies are needed to establish the efficacy and safety of MSC-based therapies and to determine their potential advantages over other cell-based approaches.

Keywords: Mesenchymal stem cells; Neural stem cells; Neurodegenerative disorders; Central nervous system

INTRODUCTION

Disorders of the central nervous system (CNS) represent a group of injuries for which no definitive or fully effective treatment currently exists. Nevertheless, recent advances in cellular biology and

tissue engineering have substantially reshaped therapeutic strategies for nervous system injuries¹. This review critically examines current treatment approaches by analyzing available studies and highlighting the characteristics of mesenchymal

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stem cells (MSCs) utilized in managing neurodegenerative diseases, with particular emphasis on conditions such as Alzheimer's disease, multiple sclerosis (MS), Parkinson's disease, and cerebral palsy. CNS lesions are often associated with widespread neural damage, including extensive tissue loss, neuronal death, and disruption of nerve fibers. These injuries may arise from stroke, hemorrhage, edema, or inflammatory processes, and they frequently result in impairments in voluntary and limb movements or, in severe cases, can be fatal². Research has also shown that neurodegenerative diseases are closely associated with severe inflammation³. Following an initial brain injury, activation of certain mechanisms triggers the release of various supportive and neurotrophic factors. However, the impact of these factors on neuronal proliferation and the survival of stem cells requires further investigation⁴. Neurogenesis in the adult brain is regulated by a variety of molecular and cellular mechanisms. Changes in neurotransmitter levels have been proposed as influential factors in adult brain neurogenesis, providing insight into the organization of stem and progenitor cells. In degenerative brain diseases, an imbalance of neurotransmitters affects the rate of neuronal death. Many of the agents employed to investigate these processes are drugs routinely prescribed for neurological disorders, including degenerative conditions such as epilepsy and stroke⁵. Over the years, researchers have proposed a range of strategies to address CNS damage, encompassing pharmacological interventions, surgical procedures, physiotherapy, and cell-based therapies⁶. Among these, the replacement of lost or damaged cells through stem cell therapy has emerged as one of the most promising approaches for CNS repair⁷. Several types of stem cells have been studied for their regenerative potential in the CNS, including neural stem cells, intrinsic neural progenitors, olfactory ensheathing cells, and bone marrow-derived stromal cells⁸.

Within the framework of stem cell therapy, neurological disorders can be categorized into three primary groups. The first group comprises diseases marked by the selective loss of cells in specific brain regions, such as Parkinson's disease, Alzheimer's

disease, and multiple sclerosis. The second group includes conditions in which neurons are destroyed as a result of acute injuries, including stroke, traumatic brain injury, and spinal cord injury. The third group consists of disorders in which neurons lose function without undergoing structural destruction, as observed in epilepsy⁹. In recent decades, accumulating evidence has underscored the pivotal role of MSCs in the treatment of various neurological disorders—a topic that will be explored in detail in this review.

This narrative review aims to provide a comprehensive overview of the role of stem cell-based approaches in neurological disorders, with a particular focus on mesenchymal stem cells (MSCs) and their potential advantages over other stem cell types. The review discusses the biological characteristics and therapeutic mechanisms of MSCs, including their differentiation potential, neurotrophic effects, anti-inflammatory properties, and immunomodulatory functions. It further examines the application of MSCs and other stem cell-based approaches across a broad range of neurological conditions, including Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, autism spectrum disorder, cerebellar ataxia, epilepsy, peripheral nerve injury, spinal cord injury, stroke, and brain tumors. Particular emphasis is placed on the potential advantages, limitations, and challenges associated with MSC-based therapies, as well as strategies for optimizing their therapeutic effects. By integrating findings from published studies, this review aims to provide a balanced perspective on the current evidence, potential clinical applications, and remaining challenges of MSC-based therapy in neurological disorders and to identify priorities for future research.

MATERIALS AND METHODS

As this manuscript is a narrative review, relevant literature was identified primarily through searches of PubMed, Google Scholar, and Web of Science. The search focused on studies related to mesenchymal stem cells, neural stem cells, stem cell-based therapies, and their applications in neurological and neurodegenerative disorders. Relevant keywords

and combinations of terms, including mesenchymal stem cells, neural stem cells, neurodegenerative disorders, central nervous system, and the names of specific neurological diseases, were used to identify relevant publications. Relevant and high-quality original research articles and review articles were considered, with particular emphasis on studies addressing the biological properties, therapeutic mechanisms, potential applications, advantages, limitations, and future perspectives of MSC-based therapies in neurological disorders.

Stem cells

Stem cells are undifferentiated, primitive cells, a subset of which—known as pluripotent stem cells—possess the remarkable ability to develop into virtually any cell type in the body. These cells can self-renew through division and, when exposed to specific physiological cues or laboratory conditions, can differentiate into specialized cells such as cardiomyocytes, hepatocytes, keratinocytes, and others. Through repeated proliferation, a single stem cell has the potential to generate millions of progeny, which can continue to multiply over extended periods as long as they remain in an undifferentiated state¹⁰. The first systematic research into stem cells dates back to the 1960s, laying the foundation for decades of subsequent exploration into their regenerative potential¹¹. In 1981, scientists successfully isolated mouse stem cells and cultured them in the laboratory. By 1988, they were able to culture human embryonic stem cells in a way that maintained their properties after repeated passages. These cells proliferate *in vivo* for long periods and form teratomas when injected into immunodeficient mice. Stem cells can give rise to various cell types when provided with the necessary and sufficient stimuli. Stem cells are present in various tissues, where they have the capacity to proliferate, establish tissue-specific cell lineages, and repair damaged tissues. These cells are also found in the adult human nervous system¹² and can differentiate into neurons under the influence of extracellular signals¹³. Stem cells possess three key characteristics: the ability to divide and renew themselves for long periods, a lack of specialization towards a specific tissue, and the potential to

differentiate into specialized cells¹¹. Stem cells are classified into two main types based on their origin and differentiation potential: embryonic stem cells (ESCs) and adult stem cells (ASCs). Embryonic stem cells have the ability to develop into any cell type derived from the three primary germ layers of the body and are considered totipotent at the early blastocyst stage. These cells are obtained from the inner cell mass of the embryo and cultured *in vitro* before potential implantation into the uterus. In contrast, adult stem cells can differentiate into a more limited range of cell types, which is why they are often described as pluripotent. Major sources of adult stem cells include bone marrow, umbilical cord blood, and adipose tissue. In adult mammals, adipose tissue contains stem cells that are functionally similar to those in bone marrow and can differentiate into neurons, glial cells, and functional endothelial cells. Umbilical cord blood also harbors stem cells capable of differentiating into multiple blood and neural lineages, making it a readily accessible and cost-effective source¹⁴. Embryonic stem cells are derived from a living embryo, which is why their extraction is prohibited in many countries, as destroying an embryo with the potential to develop into a human is considered ethically unacceptable. In contrast, adult stem cells are obtained from fully developed individuals, and since their collection does not endanger the donor's life, they are largely free from the same ethical constraints. Broadly, stem cells are categorized into two main groups: embryonic and adult. Embryonic stem cells are isolated from embryos at early developmental stages, typically the blastocyst stage, and at this point they can be either pluripotent or totipotent. Totipotent cells possess the ability to differentiate into all cell types of the body, encompassing derivatives of the ectoderm, mesoderm, and endoderm. While these cells have demonstrated remarkable success in research by generating diverse cell types, their clinical use remains highly limited due to a pronounced tendency to form tumors and undergo malignant transformation¹⁰. Pluripotent embryonic stem cells exhibit a remarkable capacity for proliferation and self-renewal, which is advantageous because it allows multiple cell grafts to be generated from a

single laboratory sample. However, this very characteristic also elevates the risk of tumor formation. Moreover, since the derivation of these cells necessitates the destruction of a human embryo at the blastocyst stage, regulations regarding their use vary across countries. For instance, embryonic stem cell research is strictly prohibited in Germany¹⁵. These differing perspectives are often rooted in religious beliefs. For example, some religions, such as Orthodox Christianity, regard an embryo at the blastocyst stage as a fully formed human being, rendering embryonic stem cell research ethically unacceptable. In contrast, within Islamic thought, an embryo is considered a complete human only after the soul has been breathed into it, resulting in a more permissive stance toward embryonic stem cell research.

Induced pluripotent stem cells (iPSCs) are artificially generated in the laboratory and share many characteristics with embryonic stem cells. By reprogramming the gene expression profile of a differentiated cell, it can be reverted to an undifferentiated, pluripotent state. In 2006, Japanese scientist Shinya Yamanaka successfully reprogrammed skin fibroblasts into pluripotent cells by simultaneously upregulating four transcription factors: OCT4, c-MYC, KLF4, and SOX2. Because iPSCs are derived from somatic cells, they circumvent the ethical concerns associated with human embryos and have a wide range of research applications. One particularly important application is disease modeling, which has greatly advanced our understanding of disease mechanisms, especially in the context of neurological disorders. Despite their considerable potential, iPSCs face several limitations in clinical applications, primarily related to safety concerns during their production. Their pluripotent nature carries an inherent risk of tumor formation, and the viral vectors commonly employed to reprogram gene expression may further elevate the risk of malignancy. In addition, the genetic manipulation process induces extensive epigenetic modifications, which can unpredictably alter cellular behavior and properties, posing additional challenges for therapeutic use.

Adult stem cells, in contrast, are multipotent, meaning they can differentiate into only a limited

range of cell types. Because they are derived directly from the tissues of an organism, they are often referred to as tissue-specific stem cells. These cells are present in very small numbers across various body tissues and play a vital role in maintaining tissue homeostasis and repairing damaged tissues by generating multiple cell types within a given tissue. Examples of tissue-derived stem cells include hematopoietic stem cells, epidermal stem cells, and neural stem cells. Due to their restricted differentiation potential, adult stem cells have become increasingly important in clinical applications, and numerous ongoing clinical trials are evaluating their safety and efficacy in disease treatment and tissue regeneration. Stem cells, in general, hold immense promise for regenerative medicine, positioning stem cell research as one of the fastest-growing and most dynamic areas of biomedical science. Nevertheless, the successful therapeutic application of stem cells requires a comprehensive understanding of their biology as well as the underlying mechanisms of the diseases being targeted. Figure 1 shows a comparison of stem cell sources used in the treatment of neurological diseases.

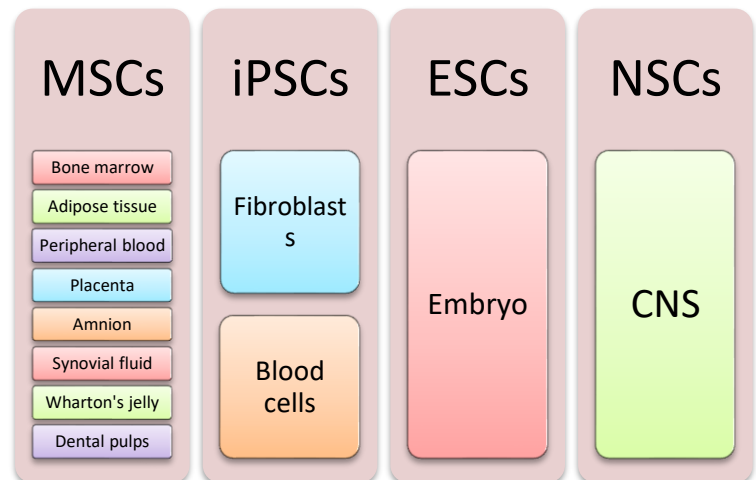


Figure 1. Comparison of different stem cell sources used for the treatment of neurological diseases.

Mesenchymal Stem Cells

In the late 1960s, Friedenstein and colleagues first discovered MSCs as multipotent stem cells¹⁶. MSCs are non-hematopoietic cells capable of differentiating into various lineages, including

mesoderm (adipocytes, osteocytes, and chondrocytes), ectoderm (neurocytes), and endodermal lineages (hepatocytes). Initially, MSCs were considered stromal cells rather than stem cells¹⁷.

Several researchers attempted to rename MSCs as drug-signaling cells due to their ability to secrete metabolic molecules at sites of disease, injury, and inflammation. Subsequently, some studies suggested that MSCs can release prostaglandin E2 (PGE2), which plays a major role in their self-renewal ability, immunomodulation, and the initiation of a cascade of events indicating their stemness. Therefore, the term MSCs remains justified¹⁸. MSCs have been isolated from various tissues and organs, including bone marrow, adipose tissue, Wharton's jelly, peripheral blood, umbilical cord, placenta, amniotic fluid, and dental pulp. MSCs express a wide range of surface markers and cytokine profiles depending on their source of isolation¹⁹. However, the common hallmark markers of MSCs are CD73, CD105, and CD90, while they lack expression of CD45, CD34, CD14 or CD11b, CD79 α or CD19, and HLA-DR. Over the past decades, MSCs have demonstrated diverse biological roles, including multilineage differentiation, immunomodulation, angiogenesis, anti-apoptotic and anti-fibrotic activity, chemotherapeutic uptake, and tissue repair promotion²⁰. MSCs have several properties that make them a suitable source for cell therapy, such as high proliferative potential, ease of isolation from various sources, and rapid large-scale expansion for clinical use. Unlike iPSCs, MSCs pose fewer ethical concerns, carry a lower risk of teratoma formation, and can migrate into tissues damaged by chemotherapy, making them valuable for therapeutic applications. MSCs have several properties that make them a suitable source for cell therapy, such as high proliferative potential, ease of isolation from various sources, and rapid large-scale expansion for clinical use. Unlike iPSCs, MSCs pose fewer ethical concerns, carry a lower risk of teratoma formation, and can migrate into tissues damaged by chemotherapy, making them valuable for therapeutic applications. Furthermore, MSCs are capable of secreting a wide range of bioactive molecules, including proteins, chemokines, growth

factors, microRNAs (miRNAs), and cytokines, underscoring their broad therapeutic potential²¹. Figure 2 shows neurological disorders that have been treated with MSCs.



Figure 2. Overview of neurological disorders that have been treated with mesenchymal stem cells

Neural Stem Cells

Neural stem cells with self-renewal capacity are found in specific regions of the adult mammalian brain. Under appropriate culture conditions and in response to various growth factors, these cells can differentiate into distinct neuronal, glial, and oligodendrocyte phenotypes. They offer several advantages over embryonic stem cells, including reduced risk of immune rejection and the absence of significant genetic or epigenetic abnormalities. However, transplanting human stem cells into mouse models poses challenges due to immune-mediated rejection and practical limitations. To overcome this, researchers developed a brain injury model in immunodeficient mice and transplanted human neural stem cells into the damaged regions. The results demonstrated that prolonged administration of these cells after brain injury (for two months or longer) significantly improved cognitive function in the mice. Furthermore, 9–25% of the transplanted cells survived for at least five months post-transplantation, differentiating into mature neurons, astrocytes, and oligodendrocytes. This study highlights the potential of human neural stem cell transplantation as an effective strategy for repairing neuronal damage²². As a complementary

approach, researchers have explored the potential of growth-promoting genes to enhance neural stem cell function. Phillips and colleagues demonstrated that introducing nerve growth factor (NGF) genes into neural stem cells via a viral vector, followed by transplantation into brain-injured mice, significantly increased the survival of pyramidal neurons in the hippocampus and improved cognitive, learning, and motor functions in these animals²³. Currently, neural stem cells are typically administered to animal models through stereotaxic surgery or direct injection into the lateral ventricles, strategies that enhance their survival within the nervous system. The timing of transplantation also plays a critical role in therapeutic efficacy. Comparative studies indicate that administering neural stem cells 2–7 days after traumatic brain injury (TBI) results in better functional outcomes than injections given after two weeks, whereas administration one month post-TBI does not significantly improve performance²⁴. Despite their promising potential, the clinical translation of neural stem cells remains limited due to difficulties in large-scale culture and production. Nevertheless, recent reports highlight successful cases of neural stem cell therapy for nervous system damage²⁵. Additionally, several studies have

explored the ability of MSCs to differentiate into neural stem cells. One of the major obstacles in detecting and studying stem cells is the lack of specific markers or distinct morphological features to distinguish and identify these cells from one another. Therefore, their functional characteristics in a laboratory environment are used for identification. In 1992, Reynolds and Weiss developed a method for generating neurospheres using a serum-free culture medium, demonstrating the presence of neural stem cells in the brains of adult mice and mouse embryos²⁶. Differentiated cells of the central nervous system are unable to grow and survive under such conditions and are eventually destroyed, whereas neural stem cells, even at low densities, enter the proliferation phase and form multipotent colonies, or neurospheres. By isolating and culturing cells containing neurospheres, additional secondary neurospheres can be generated. If these cells are placed in a differentiation culture medium, they develop into the primary cell types of the central nervous system. Thus, Reynolds and Weiss showed that these isolated cells exhibit the fundamental characteristics of stem cells. Generally, two methods are used to differentiate neural stem cells: (1) differentiation into neurospheres at low density, which is used to demonstrate the multipotent nature of neurospheres, and (2) differentiation into isolated single cells at high density, which is used to determine the percentage of cell types generated. In the study by Sagha et al., the differentiation of neural stem cells into mature nervous system cells was achieved by culturing neurosphere-derived cells in a differentiation medium. Immunocytochemistry and specific markers were used to identify these cells. Due to the lack of definitive markers for neural stem cell identification, *in vitro* neurosphere formation method remains a reliable approach for isolating and studying both embryonic and adult neural stem cells²⁷.

Alzheimer's Disease

Alzheimer's disease is the most common severe neurodegenerative disease, causing the loss of structural and functional properties of neurons. It is reported to be the fifth leading cause of death

among people over 65 years of age, with more than five million cases in the United States each year (Alzheimer's Association, 2017). The World Health Organization estimates that the worldwide prevalence of Alzheimer's disease will increase fourfold by 2050²⁸. Alzheimer's is a progressive disease that begins gradually and becomes more severe over time, often spanning several years. This disease affects various brain functions. The first symptom of Alzheimer's is usually minor memory problems. As the disease progresses, memory problems become more severe, and subsequent symptoms appear, such as confusion, disorientation, getting lost in familiar places, impaired decision-making, planning difficulties, speech and language disorders, and more.

In Alzheimer's disease, spherical protein structures (amyloid bodies) form outside neurons in some areas of the brain, and filamentous protein structures appear in the cell bodies of neurons²⁹. Amyloid beta consists of 36-43 amino acid peptides and is the main component of amyloid plaques in the brains of Alzheimer's patients. This protein is expressed in cells of the nervous system and plays a role in cell-cell adhesion, extracellular matrix contact, and the cytoskeleton. Senile plaques are composed of protein filaments called amyloid bodies and other proteins, including apolipoprotein E, synuclein, and alpha-1-antichymotrypsin. The formation of these plaques seems to be a major factor in the development of Alzheimer's. These plaques interrupt communication between nerve cells, eventually causing these cells to die and brain tissue to deteriorate³⁰.

Some important brain chemicals are reduced in patients with Alzheimer's. These chemical messengers help transmit signals around the brain. When these substances are reduced, signals are not transmitted properly. There is still no cure for Alzheimer's disease, but medications can slow the progression of the disease and reduce the severity of memory impairment and behavioral problems. After years of clinical testing of existing hypotheses and drug treatments, Alzheimer's disease remains untreatable and is one of the greatest obstacles to modern medicine. There is now a significant global

demand for the development of new and effective treatments³¹.

New stem cell therapy techniques that control neurogenesis in Alzheimer's disease patients have opened new perspectives for treatment development. Research into Alzheimer's disease treatment is focused on transplanting progenitor stem cells from target tissue to replace damaged tissue cells or reduce the destructive effect of the disease on brain tissue³². MSCs have been widely used in cell therapy due to their easy availability, rapid in vitro cell culture, lack of ethical restrictions compared to embryonic stem cells, and their potential for use in autologous transplants, which avoids transplant rejection or side effects associated with immunosuppression³³. In brain disorders, drug delivery requires crossing the blood-brain barrier, and MSCs can cross this barrier to reach the site of injury. Given their accessibility compared to embryonic stem cells, MSCs may be a promising source for stem cell therapy. However, they have the disadvantage of generating only a limited number of cell lineages and having a limited survival rate and short half-life after transplantation, which varies depending on the donor cell population and the location from which the cells are isolated and cultured³⁴.

Beta-amyloid (AB) plays a major role in Alzheimer's disease, and neuroinflammatory processes mediated by microglial cells and astrocytes, resulting from AB plaques, contribute to the pathogenesis of Alzheimer's disease. In one study, human placental amniotic membrane-derived MSCs were investigated for their potent immunomodulatory and paracrine effects in a transgenic mouse model. AMSCs increased local concentrations of the neurotransmitters acetylcholine, brain-derived neurotrophic factor (BDNF), and nerve growth factor (NGF). AMSCs showed evidence of improved spatial learning six weeks after intravenous injection in mice³⁵. However, these findings are based on a preclinical animal model, and differences in disease pathology, treatment timing, cell source, and administration route should be considered when interpreting their potential clinical relevance. Paracrine effects of MSCs, including the production of growth factors, anti-inflammatory cytokines, and

anti-apoptotic regulation, promote neuronal regeneration and myelination. MSCs are likely to exert phagocytic effects on abnormal AB plaques and have anti-inflammatory effects in the brains of Alzheimer's patients via microglia, which helps prevent neuronal death and enhances neuronal differentiation. However, the specific time point at which MSCs need to act remains unclear because conditions in the brain of Alzheimer's patients vary depending on the stage of the disease³⁶.

To date, there is little evidence for the functional or synaptic maturation of neurons derived from MSCs in the body. In one study, nine patients with symptoms of Alzheimer's disease were selected and divided into two groups. Stem cells were obtained from human umbilical cords, with one group receiving a low dose (3×10^6 cells) and the other a high dose (6×10^6 cells) injected into the hippocampus. No changes in disease symptoms or pathology were observed during 24 months of follow-up. Therefore, the effects of MSCs, which have often been reported in animal models of Alzheimer's disease, are not well understood in humans to date³⁵. This difference between preclinical findings and limited clinical evidence highlights the need for larger, well-controlled clinical trials and standardized treatment protocols before the therapeutic efficacy of MSCs in Alzheimer's disease can be established.

Parkinson's Disease

A degenerative neurological disease is caused by the destruction of dopaminergic neurons in the substantia nigra of the brain. The disease is associated with decreased dopamine production due to the destruction of neuro-pigmented cells in the substantia nigra in the basal ganglia of the brain. Nerve fibers or pathways run from the substantia nigra to the striatum, where neurotransmitters play a key role in controlling complex body movements. The loss of dopamine stores in this brain region leads to an increase in excitatory neurotransmitters relative to inhibitory neurotransmitters, resulting in an imbalance that affects voluntary movements³⁷. Dopamine acts through interactions with its receptors. Dopamine receptors are divided into two main groups: the D1 family (D1 and D5) and the D2

family (D2, D4, D3). Type 3 dopamine receptors are abundantly expressed during development in neuroepithelial regions and are involved in neurogenesis. D2 receptors are located in the sensorimotor part of the striatum³⁸. This disease usually occurs in older individuals after the age of 60 and is the second most common neurodegenerative disease after Alzheimer's disease, with 1 in 100 people over the age of 60 affected. However, it can also occur in younger individuals, accounting for 5 to 10 percent of patients³⁹. Four common symptoms of Parkinson's disease are tremors at rest (tremors in the hands and feet while at rest), slowness of movement, stiffness in the hands and feet or body, and poor balance. When two or more of these symptoms are present in a patient, especially when they occur more on one side than the other, a diagnosis of Parkinson's disease is made⁴⁰. In the early stages of the disease, the tremor is mild and usually occurs on one side of the body and does not require treatment. However, as the disease progresses, the individual, who initially hides their trembling hand in their pocket or purse or constantly holds something to control the tremor, is no longer able to hide the severe tremors, especially when trying to concentrate. Various environmental and genetic factors contribute to the spread of this disease. One of the reasons for the development of mitochondrial defects, defective autophagy (self-eating), and the accumulation of damaged proteins in the cell is the damage to dopaminergic cells and a decrease in dopamine, leading to movement disorders in the patient⁴¹. Drugs such as Levodopa, Amantadine, Biperiden, and Selegiline are prescribed for the treatment of Parkinson's disease and improve the patient's daily activities. However, long-term administration of levodopa and other dopamine receptor agonists can result in side effects, such as motor fluctuations, dyskinesia, and neurological complications⁴². Cell therapy and gene therapy are of interest for the treatment of neurodegenerative diseases. In recent years, the treatment of Parkinson's disease using stem cells has received much attention⁴³. MSCs are immunologically less potent than other adult stem cells due to the lack of MHCII. These cells are also easily extracted and have the ability to be

autologously transplanted into the patient. MSCs have a high ability to differentiate into neural and dopaminergic stem cells in vitro and after transplantation. Cell therapy in Parkinson's disease with these cells is based on three strategies: a) secretion of neurotrophic factors, b) cell replacement, and c) anti-inflammatory effects. Postmortem studies in Parkinson's models exposed to the drug MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) have shown that microglia are activated in the cell and their number increases^{44,45}. A study has shown that MSCs have the ability to reduce inflammation by reducing microglial activity and increasing anti-inflammatory factors such as TGF- β , IL-6, and IL-10⁴⁵. Inflammatory factors may provide signals for MSCs to migrate to sites of tissue damage. In one study, these cells were observed to secrete six neurotrophic factors, including GDNF, BDNF, NGF, IGF-1, NT-3, and BFGF⁴⁶. Growth factors released by MSCs may prevent the progression of neuronal degeneration and may even promote the growth of new neurons in the Parkinson's disease brain⁴⁷. In previous research, treatment of Parkinson's disease model mice using bone marrow-derived MSCs showed increased levels of DA neurons and Brain-derived neurotrophic factor (BDNF), as well as reduced levels of TGF- β 1 (Transforming Growth Factor Beta 1) and MCP-1 (Monocyte Chemoattractant Protein-1), which are factors controlling the body's inflammatory responses. Intravenous injection of bone marrow-derived MSCs was performed as a direct injection into the striatum, where the cells have the ability to migrate to the damaged area and treat it. However, previous experiments showed that the effectiveness of direct infusion was more pronounced than intravenous injection, and behavioral tests were more efficient. In a study of Parkinsonian rats labeled with 5-Bromo-2'-deoxyuridine, MSCs were transplanted into the substantia nigra at the site of hydroxydopamine (6-OHDA) injection into their brains. Behavioral changes in rats were examined before and 4 and 8 weeks after mesenchymal stem cell transplantation. Tyrosine hydroxylase (TH) expression in the substantia nigra and striatum, as well as the survival and differentiation of MSCs, were assessed by immunohistochemistry and immunofluorescence.

The abnormal behavior of Parkinsonian rats was significantly improved after MSC administration, and the number of hydroxylase-positive cells in the substantia nigra and the optical density of hydroxylase-positive fibers in the striatum were significantly increased. The transplanted MSCs were able to survive and migrate in the brain, differentiating into nestin-expressing cells and GFAP-specific cells⁴⁸.

Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter in the mammalian central nervous system that plays an important role in the positioning of neural progenitors and the maturation of neuronal pathways during postnatal development. GABA is secreted as a neurotransmitter by neuronal and glial cells and acts as an excitatory and modulatory effector of the nervous system. Neurons that secrete GABA are termed GABAergic neurons⁴⁹. Gharibani et al. showed that BMSCs differentiate into GABAergic neuron-like cells in the presence of β -Mercaptoethanol and retinoic acid and then by induction in the presence of potassium chloride. As a result, BMSCs differentiate into GABAergic neuron-like cells upon stimulation with retinoic acid and keratin. A notable point is the decrease in the yield and number of stem cells present in the bone marrow of elderly patients, which makes the treatment of the disease using these types of cells difficult⁴⁹. One of the problems with stem cell therapy is the large number of stem cells required. Large numbers of adipose-derived MSCs can be obtained through non-invasive liposuction surgery⁵⁰. To date, there have been no reports of adverse reactions such as tumorigenesis, chromosomal abnormalities, or immune rejection. Adipose-derived mesenchymal stem cell (hAD-MSC) transplantation significantly increased tyrosine hydroxylase (TH) expression compared to patients treated with the drug cerebrolysin, which is used to treat Parkinson's disease. ADSCs can ameliorate ROS (reactive oxygen species) induced by 6-hydroxydopamine in mouse mesencephalic neurons⁵¹. Jouy et al. used a combination of gene therapy and adipose-derived mesenchymal stem cell transplantation to treat rhesus monkeys with hemiplegic Parkinson's disease. Histological analyses

showed that the transplanted neurons survived and adapted to the host environment, and increased dopamine levels were observed in the affected brain area. The combination of these two treatments resulted in significant improvements in the motor and behavioral symptoms of the treated monkeys⁵². Although combination strategies may enhance the therapeutic effects of MSCs, they also introduce additional variables that complicate the assessment of MSC-specific efficacy and safety. Furthermore, evidence from animal models cannot be directly extrapolated to humans because of differences in disease progression, immune responses, cell survival, and treatment delivery. Human adipose stromal cells (ASCs) have multiple differentiation potentials and can differentiate into neuronal-like cells in a neurogenic induction environment, exhibiting morphological changes and expression of neuronal markers such as class III β -tubulin⁵³. In a recent study, the effects of intravenous transplantation of adipose-derived stem cells (ADSCs) on hippocampal neurogenesis following 6-hydroxydopamine (6-OHDA) lesions were investigated. Parkinsonian models were established by bilateral injection of 6-OHDA into the substantia nigra of male Wistar rats. Positron emission tomography (PET) imaging revealed elevated dopamine levels in the striatum following ADSC transplantation, and immunohistochemical analysis using anti-tyrosine hydroxylase (TH) antibodies confirmed the recovery of dopaminergic neurons in the substantia nigra. The results demonstrated that ADSC transplantation via the caudal vein provided neuroprotection in the hippocampus and effectively prevented 6-OHDA-induced neuronal death⁵⁴.

Endometrium-derived MSCs (EDMSCs) are an attractive and novel source of adult stem cells that are readily available and exhibit significant differentiation capacity⁵⁵. Recent studies have shown that stem cells in the endometrium have a higher differentiation potential than other MSCs and can be used to regenerate other organs. In women, using these cells for themselves eliminates concerns about transplant rejection. Endometrial tissue is obtained by hysterectomy, curettage, and Pap smear⁵⁶. Treatment of Parkinson's disease in monkeys with EDSCs resulted in significant

improvement, with homovanillic acid levels decreasing by 70% compared to the untreated group. After the injection of undifferentiated EDSCs into the mouse striatum and genetic analysis of the brain, human cells were observed in the injection area and homologous cells in the substantia nigra, indicating their migration to the affected area. In contrast, when transplanted with differentiated EDSCs, no concentration of these cells was observed in the substantia nigra. Previous studies have shown the ability of EDSCs to express CD90, CD146, and PDGF-RB and to differentiate into dopamine-secreting neuron-like cells^{57,58}. Differentiated cells form dendritic-like and axon-like fibers that mimic synaptic organization and structure. In addition, these cells express neuronal cell markers such as nestin and tyrosine hydroxylase, the rate-limiting enzyme for dopamine synthesis. Transplantation of undifferentiated EDSCs into MPTP-treated rats showed that the transplanted cells could enter the striatum, then migrate to the substantia nigra, and differentiate spontaneously *in vivo*, leading to increased dopamine concentrations. The endometrium is, therefore, an important source of stem cells with remarkable regenerative and differentiation potential. After intracerebral injection, EDSCs can be recruited to the striatum, migrate to the injured area, differentiate into TH-positive cells, and protect endogenous dopaminergic neurons, thereby increasing dopamine concentrations⁵⁸. The lack of this type of cell in men for use in treating their own disease and preventing transplant rejection is one of the challenges and limitations in using this type of cell.

Huntington's Disease

Huntington's disease (HD) is a neurodegenerative disorder of the central nervous system caused by an inherited CAG three-nucleotide repeat expansion in exon 1 of the huntingtin (HTT) gene, which encodes the huntingtin protein⁵⁹. Pathological changes are characterized by generalized brain shrinkage and marked degeneration of the striatum (caudate nucleus and putamen) (60). Although the prevalence of HD is only 10–4 per 100,000, it severely affects the quality of life of patients in various ways, including movement, cognition, mental status, and other

functional disabilities. Movement disorders typically include chorea (involuntary jerking or writhing movements) and loss of coordination. Psychiatric symptoms, such as depression, psychosis, and obsessive-compulsive disorder, are common in HD⁶¹. Death usually occurs approximately 20 years after the onset of symptoms⁵⁹.

Current treatments for HD aim at relieving symptoms, as there is no disease-modifying therapy. Therapeutic efforts based on pathogenic mechanisms have been investigated, including gene silencing, anti-apoptotic/caspase inhibition, transglutaminase inhibition, antioxidant stress, autophagy regulation, and exercise. Unfortunately, none of these have met the criteria for clinical translation. For example, silencing mutant HTT expression is an attractive approach; however, allele specificity and off-target effects have not been fully resolved. Treatment of mouse models with antioxidants has been beneficial, whereas trials of creatine in symptomatic patients have been disappointing⁶². These findings highlight the difficulty of translating promising preclinical strategies into clinically effective treatments, emphasizing the need for approaches that demonstrate both sustained efficacy and acceptable safety in human studies.

Liang et al. comprehensively collected a wide range of outcome measures and conducted the first meta-analysis on the therapeutic effects of MSCs for HD. Their study shows that MSC treatment has beneficial effects on brain morphology, motor coordination, muscle strength, neuromuscular electromyography activity, cortical-related motor function, striatal-related motor function, and male-specific body weight gain in rodent models of HD. Three clinical trials of MSC therapy for HD (NCT04219241, NCT03252535, NCT02728115) have been registered on ClinicalTrials.gov. However, none have reported results yet⁶². Studies have shown that MSC transplantation can increase survival rates and extend lifespan in rodents with Huntington's disease^{63,64}, although side effects and other safety concerns have not yet been fully evaluated. Therefore, despite encouraging preclinical results, the absence of reported clinical outcomes and the limited long-term safety data remain important

barriers to clinical translation. Future studies should prioritize standardized cell preparation, optimal dosing and delivery routes, and long-term assessment of efficacy and safety.

Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune disease that destroys the myelin sheath in the central nervous system, the cause of which is still unknown. These lesions can disrupt the ability of parts of the nervous system responsible for communicating with the rest of the body, leading to many physical signs and symptoms, such as loss of balance, fatigue, blurred vision, and numbness in the legs or arms. Numerous epidemiological and genetic studies emphasize the role of both genetic and environmental factors in the development of MS. The disease affects people of all ages but is most common in those between the ages of 20 and 40 years. MS is more prevalent in women than in men and is also more common in parts of the world such as Northern Europe, the United States, and Canada. Individuals with a family history of multiple sclerosis (MS) are at a higher risk of developing the disease compared to the general population⁶⁵. Currently, a combination of pharmacological and physical therapies is employed to alleviate symptoms or, in some cases, slow disease progression. Corticosteroids, such as methylprednisolone and prednisolone, are commonly used to reduce symptom severity, although a definitive cure for MS remains elusive⁶⁶. Recently, stem cell-based strategies have emerged as a promising approach for MS treatment. Both embryonic and adult-derived stem cells have demonstrated potential in promoting myelin repair. Stem cell therapy for MS can involve multiple mechanisms, including cell replacement, regulation of neurotrophic factors, modulation of inflammatory cytokines, and adjustment of apoptotic pathways. To study these interventions in preclinical settings, the experimental autoimmune encephalomyelitis (EAE) model is widely used. EAE serves as an established animal model to investigate the inflammatory and behavioral characteristics of MS. It is induced either by direct exposure to antigens or through the transfer of myelin-specific T cells, leading to T cell

activation against myelin antigens and subsequent demyelination⁶⁷. Although EAE provides valuable information about the immunological mechanisms of MS and the potential effects of stem cell therapies, it does not fully reproduce the complex and heterogeneous pathology of human MS. Therefore, positive findings obtained in EAE models should be interpreted cautiously when considering their clinical applicability.

Studies have demonstrated that human bone marrow-derived MSCs can significantly influence the progression of multiple sclerosis following transplantation. Notably, MSC treatment exerts beneficial effects on neuronal populations in EAE model animals by promoting oligodendrocyte proliferation, inhibiting excessive astrocyte growth, and modulating the host immune response. In one study, several MS patients were treated with bone marrow stem cells, and 16 out of 20 patients (80%) recovered. Bone marrow-derived stem cells (BMSCs) appear to localize to damaged areas and reduce inflammation through paracrine effects⁶⁸. BMSCs have the ability to secrete many autocrine or paracrine factors that prevent apoptosis⁶⁹. Neurotrophic and neural factors from these cells increase the viability and proliferation of neuroglial cells. Previous studies have shown that transplantation of differentiated BMSCs produces better therapeutic outcomes than transplantation of undifferentiated BMSCs. In animal models, BMSCs reduce immune attacks on the myelin sheath by suppressing T-lymphocyte proliferation, reducing inflammation, inducing the growth and proliferation of oligodendrocytes, and promoting tissue regeneration⁷⁰. Despite these encouraging findings, differences in cell preparation, differentiation protocols, treatment doses, administration routes, and patient characteristics make comparisons across studies difficult. In addition, the reported clinical recovery in small patient cohorts should be interpreted cautiously because the absence of larger controlled trials limits conclusions regarding the efficacy of MSC therapy.

Studies have demonstrated that in vitro induction of human adipose-derived MSCs (hAdMSCs) leads to the production and secretion of neurotrophic factors. Due to their dual capacity to modulate

immune responses and stimulate neurogenesis, these cells hold significant potential for the treatment of neurodegenerative diseases. Adipose-derived stem cells (ADSCs) secrete a variety of neurotrophic factors (NTFs), including brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and glial cell line-derived neurotrophic factor (GDNF). In addition, ADSCs possess several advantageous properties, such as the absence of HLA-class II antigen expression, the ability to migrate via $\alpha 4\beta 1$ integrin expression, and pronounced antioxidant and anti-apoptotic capabilities⁷¹. Recent studies have shown that intravenous administration of human ADSCs can modulate the course of the EAE model, particularly during peak disease severity, by regulating interleukin-17 levels. Furthermore, murine ADSCs have been reported to suppress T-cell proliferation through the activity of nitric oxide synthase (NOS) and cyclooxygenase-2 (COX-2). These findings indicate that ADSCs, owing to their broad therapeutic properties, can replace degenerated neurons, create a supportive microenvironment for surviving neurons, and promote tissue regeneration. Collectively, these characteristics make ADSCs a promising cell source for the treatment of multiple sclerosis⁷².

Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a heterogeneous group of neurodevelopmental conditions with onset in the first three years of life. It is characterized by repetitive behaviors, a restricted range of activities, and impaired social communication⁷³. The number of reported cases of ASD has increased in recent decades. The World Health Organization estimates that one in 270 people has ASD, with a prevalence four times higher in males than in females⁸⁹. The prevalence of ASD in Europe is approximately 1%, with a total of three million patients currently living with the condition. In the United States, a 30% increase in the prevalence of ASD in children was observed from 2012 to 2014 alone. It is currently estimated that ASD affects more than two million people, with approximately one in 68 American children having ASD^{74,75}.

In its most severe form, ASD is considered a chronic and debilitating disorder that compromises the full

potential of the affected individual. In the United States, the lifetime cost of supporting an individual with ASD is estimated to be between \$1.4 million and \$2.4 million, depending on the degree and severity of involvement. Beyond the financial aspect, ASD is a condition that severely undermines social integration and places a significant emotional burden on the families of those affected⁷⁶.

Currently, there are no effective pharmacological treatments to address the core symptoms of ASD, such as communication impairment, social maladjustment, or lack of empathy (Thompson Foundation for Autism, 2012)⁷⁷. Treatment options include non-specific medications, as well as behavioral, occupational, and speech therapy, along with specialized educational and vocational support. Currently available treatments, such as psychotropic medications, are prescribed to improve irritability, seizures, mood disorders, or hyperactivity syndrome, but they are not disease-modifying compounds in themselves⁷⁸.

Although the exact cause of ASD is unknown, recent studies have shown that genetic and environmental factors play a role in the development of the disorder. Environmental factors associated with an increased risk of ASD include prematurity, birth complications, maternal teratogen exposure, environmental toxins, and advanced parental age. In addition, inflammation and immune disorders are strongly implicated in ASD⁷⁹.

The precise mechanism of action of MSCs in ASD is a subject of ongoing research, but there are several potential mechanisms through which MSCs may exert therapeutic effects, including cellular immunomodulation, molecularly mediated neuroprotection, and restoration of functional neural circuits⁸⁰. Since persistent immune dysregulation may contribute to the pathophysiology of subgroups of patients with ASD, suppression of the cellular immune response with MSCs could have potential therapeutic benefits. MSCs may also provide neuroprotection through anti-inflammatory mechanisms by inhibiting neuronal apoptosis, microglial activation, astrocyte proliferation, and oxidative stress molecules⁸¹. Koh et al. (2015) showed that umbilical cord blood (UCB)-derived MSCs enhance neuronal survival through the

secretion of neurotrophic factors. In several other models, MSCs have the ability to reduce the number and activation of microglial cells, which play an important role in the development of ASD⁸². It is unclear whether this phenomenon is caused by a direct effect of MSCs or is mediated through the activation of cytokines (i.e., TGF- β , IL-6). Finally, MSCs may also contribute to synaptogenesis and the regeneration of functional neural pathways by providing bioactive factors that stimulate the function of intrinsic neural progenitor cells. Various molecular targets, including tissue plasminogen activator (tPA), synaptophysin, brain-derived neurotrophic factor (BDNF), and neurotransmitter receptors, are implicated. Koh demonstrated through a series of in vitro experiments using co-culture, patch clamp, inhibition, and biochemical techniques that human UC-derived MSCs can induce synapse formation and enhance synaptic function, and that thrombospondin proteins, both produced by UC-derived MSCs, are essential for their synaptic effects⁸³.

Cerebellar Ataxia

Cerebellar ataxia (CA) is a heterogeneous neurological disorder characterized by impairments in balance and coordination due to cerebellar dysfunction. Individuals with CA often present with a range of clinical features, including dysarthria and nystagmus, reflecting the variable involvement of cerebellar circuits. Currently, no definitive therapy exists for CA; pharmacological interventions primarily aim to alleviate symptoms rather than address the underlying pathological mechanisms. Among the various forms of CA, spinocerebellar ataxia (SCA) is particularly notable for its autosomal dominant inheritance pattern. Treatment of SCA is further complicated by the presence of multiple mutation types, as highlighted in prior studies⁸⁴. SCA encompasses several subtypes, generally classified according to the specific genetic mutations involved, with polyglutamine expansion repeat ataxias being the most prevalent. These mutations drive progressive neuronal degeneration, especially affecting Purkinje cells within the cerebellum, ultimately impairing motor coordination.

Given the limited efficacy of conventional treatments, research has increasingly focused on novel therapeutic strategies such as stem cell-based approaches. MSCs, in particular, have been investigated extensively in preclinical models of SCA. Experimental evidence demonstrates that MSCs can migrate to the cerebellum in mouse models and secrete neurotrophic factors that support Purkinje cell survival⁸⁵. However, most of this evidence is derived from preclinical studies, and it remains uncertain whether the neuroprotective effects observed in animal models can be consistently reproduced in humans. Therefore, although MSCs show potential to mitigate neuronal loss and promote cerebellar repair, further studies are required to establish their clinical applicability. These findings underscore the potential of MSC therapy not only to mitigate neuronal loss but also to promote cerebellar repair mechanisms, offering a promising avenue for future clinical applications in SCA patients.

Tsai and colleagues conducted a detailed investigation into the therapeutic potential of human MSCs derived from umbilical cord Wharton's jelly in a transgenic mouse model of SCA1. By directly injecting these MSCs into the cerebellum, they observed that the cells remained localized for several months without differentiating into unintended cell types. Importantly, the MSCs secreted a spectrum of trophic factors and cytokines—including neutrophil-activating protein-2 (NAP-2), angiopoietin-2, brain-derived neurotrophic factor (BDNF), CXCL-16, and platelet-derived growth factor-AA—which collectively contributed to neuroprotection. These paracrine effects mitigated cerebellar atrophy and preserved Purkinje cell integrity, demonstrating a potent mechanism by which MSC therapy could counteract neurodegeneration in SCA1⁸⁶.

Correia and colleagues evaluated the therapeutic potential of human MSCs (hMSCs) and their secreted factors in the CMVMJD135 mouse model of SCA3/Machado-Joseph Disease. Their study examined the effects of both direct MSC transplantation and injection of MSC-conditioned medium (secretome) into multiple central nervous system regions, including the cerebellum, striatum/substantia nigra, and spinal cord, with

behavioral assays used to assess motor and phenotypic outcomes. Interestingly, direct injection of hMSCs into the cerebellum produced minimal improvement, whereas spinal cord injections led to slight behavioral enhancements. In contrast, administration of MSC secretions demonstrated region-specific benefits: injection into the cerebellum resulted in more pronounced therapeutic effects compared with injections into the striatum/substantia nigra or spinal cord. Remarkably, despite initially presenting with more severe deficits, mice receiving MSC secretions exhibited greater overall improvements than those treated with MSCs themselves. The study also highlights that repeated MSC administrations may provide more durable therapeutic benefits than a single injection, and that targeting multiple CNS regions could be more advantageous than focusing on a single site. Collectively, these findings support the preclinical efficacy of MSCs and their secretions, offering valuable insights for optimizing future therapeutic strategies in SCA⁸⁷.

Epilepsy

Epilepsy is a chronic neurological disorder defined by the occurrence of recurrent, unprovoked seizures, which arise from abnormal electrical activity within the brain. The clinical manifestations of epilepsy are highly variable, depending on both the type of seizure and the brain regions involved. Focal (or partial) seizures often present with localized symptoms, such as sensory disturbances—including tingling sensations, altered perception of taste or smell—or involuntary movements affecting specific parts of the body. In contrast, generalized seizures typically involve widespread neuronal networks, leading to loss of consciousness, sudden falls, and uncontrolled, extensive motor activity. While the precise etiology of epilepsy remains unknown in many cases, several risk factors have been identified. Severe head injuries can precipitate seizure activity, as can structural brain diseases such as tumors, strokes, or central nervous system infections. Additionally, genetic predispositions contribute to certain forms of epilepsy, highlighting the complex interplay between inherited and environmental factors in disease development^{88,89}.

Management of epilepsy typically begins with the administration of antiepileptic drugs aimed at controlling seizure activity. When pharmacological treatments prove insufficient, alternative interventions—including surgical procedures, vagus nerve stimulation, or specialized dietary regimens—may be considered. In a notable case study, Liu and colleagues⁹⁰ treated a 26-year-old patient with a 17-year history of refractory epilepsy using autologous MSCs derived from the patient's own olfactory mucosa. Following *in vitro* expansion, the MSCs were delivered intrathecally. Over an eight-year follow-up period, the patient exhibited substantial improvements in seizure type, frequency, severity, and duration, along with enhanced cognitive function. Neuroimaging also revealed a reduction in brain atrophy, highlighting the potential for long-term structural and functional recovery. In preclinical studies, Hegazy et al.⁹¹ explored the synergistic effects of combining the antiepileptic drug levetiracetam (LEV) with MSC therapy in a mouse model of acute epilepsy. Their results demonstrated that the combined treatment more effectively mitigated behavioral and biochemical abnormalities and attenuated pathological changes in brain tissue during the acute phase, compared with either intervention alone. Although these findings suggest a potential synergistic effect between MSCs and conventional antiepileptic therapy, the study was conducted in an acute animal model, which may not adequately represent the complex and chronic nature of drug-resistant epilepsy in humans. In addition, the optimal cell dose, delivery route, treatment timing, and long-term safety of combined MSC and antiepileptic therapy remain to be established. These findings suggest that MSCs, particularly when used alongside conventional antiepileptic medications, may offer a promising strategy for enhancing therapeutic outcomes in epilepsy.

Stem Cell-Based Peripheral Nerve Injury

Peripheral nerve injuries (PNIs) account for approximately 2.8% of all traumatic injuries and often result in substantial functional impairment and disability. The repair of peripheral nerves is a highly orchestrated process involving intricate cellular and

molecular changes in both neurons and Schwann cells⁹².

Following severe injury, when axonal connections with neuronal cell bodies are disrupted, the distal segment of the affected nerve undergoes Wallerian degeneration—a carefully regulated process that eliminates damaged axonal material and prepares the nerve environment for regeneration⁹³. During this degeneration phase, Schwann cells within the distal nerve segment dedifferentiate into a non-myelinating phenotype, proliferate, and phagocytose cellular debris and myelin remnants. Circulating macrophages are also recruited to the injury site, contributing to clearance. Subsequently, Schwann cells align along their basement membrane to form tubular structures known as B ngner’s canals, which serve as guiding pathways for regenerating axons to reach their appropriate target organs⁹⁴.

Beyond providing structural guidance, Schwann cells secrete critical growth factors—including nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF)—produce extracellular matrix molecules such as laminin and fibronectin, regulate local immune responses, and remyelinate newly regenerated axons, all of which are essential for functional recovery⁹⁵. These multifaceted roles have led to numerous investigations exploring Schwann cell-based therapies for PNIs⁹⁶. However, challenges in isolating and expanding autologous Schwann cells in sufficient numbers within a clinically relevant timeframe have limited their practical application. Consequently, stem cells have emerged as a promising alternative due to their accessibility, proliferative capacity, and regenerative potential⁹⁷. Recent studies suggest that stem cells can enhance peripheral nerve repair through multiple mechanisms: differentiating into Schwann-like cells to remyelinate axons, secreting neurotrophic factors, producing extracellular matrix components, and modulating immune responses at the injury site⁹⁵.

Several studies have demonstrated the positive effects of neural stem cell transplantation on the healing process of peripheral nerve injuries. Implanting neural stem cells in collagen scaffolds and transplanting them into the injured sciatic nerve

resulted in the differentiation of these cells into Schwann-like cells that survived for more than two months⁹⁸. Neural stem cells can differentiate into motor neurons in culture or after transplantation into injured peripheral nerves in animals, expressing choline acetyltransferase (a marker of motor neurons). These cholinergic axons extend myelinated branches toward target muscles, such as the gastrocnemius muscle, where they inhibit atrophy and improve electromyographic and motor parameters⁹⁹. However, the use of neural stem cells carries disadvantages, including difficulties in cell extraction and the risk of tumorigenesis.

Wharton’s jelly MSCs present a lower tumorigenic risk and can be used in both undifferentiated stem form or as differentiated cells in culture. When placed in an appropriate differentiation medium, these cells can differentiate into neuron- and glial cell-like phenotypes. Wharton’s jelly MSCs have demonstrated positive effects in promoting nerve repair in animal models of peripheral nerve injury. Researchers have also differentiated these cells into Schwann-like cells in culture, which can produce neurotrophic factors and stimulate axonal sprouting¹⁰⁰.

Amniotic fluid MSCs are another type of stem cells that, while exhibiting characteristics of both MSCs and neural stem cells, have shown the ability to differentiate into neural cells and secrete neurotrophic factors. For instance, transplantation of these cells into the crushed sciatic nerve of rats has enhanced axonal repair, myelination, and improved motor functions. However, the viability of these cells in host tissues is limited, prompting researchers to explore ways to increase their survival after transplantation by modulating inflammatory responses and inhibiting programmed cell death through growth factor and anti-inflammatory treatments or genetic modifications¹⁰¹.

Several studies have been conducted to understand the mechanisms by which MSCs influence peripheral nerve repair. These mechanisms may operate through paracrine secretion, growth factors, immune modulation, Schwann cell differentiation, cell-cell interactions, or a combination of these factors¹⁰².

There is strong evidence that bone marrow MSCs promote peripheral nerve repair through the secretion of neurotrophic factors¹¹⁹. Protein content analysis of bone marrow MSC culture media has revealed the presence of neurotrophic factors such as GDNF, BDNF, CNTF, NGF, and bFGF. The proximity of these culture media to cultured neurons promotes neuronal outgrowth and enhances neuronal viability. Conversely, the addition of a neutralizing antibody to NGF inhibits its stimulatory effects, further supporting this finding¹⁰³.

Bone marrow MSCs can also directly influence peripheral nerve repair by stimulating the growth and proliferation of Schwann cells¹¹⁹. Some researchers have even used gene transfer to express growth factors at physiological levels in these cells. However, clinical application of this method remains challenging due to the risk of tumorigenesis¹⁰⁴.

Paracrine effects are not the only mechanism by which bone marrow MSCs promote peripheral nerve repair. An important feature of these cells is their high plasticity, allowing them to undergo phenotypic changes in response to environmental conditions. These cells can differentiate into Schwann cell-like cells in culture and in vivo. Transplantation of these Schwann-like cells into injured peripheral nerves in rats induces myelination and enhances the repair process⁹⁵.

A small percentage of MSCs transplanted into injured peripheral nerves differentiate into Schwann cell-like cells under the influence of growth factors and cytokines released from the injured tissues. Furthermore, bone marrow MSCs can be differentiated into Schwann-like cells using special differentiation media, which are capable of myelinating and supporting regenerating axons¹⁰².

In addition to these characteristics, bone marrow MSCs can modulate the immune system and reduce tissue inflammation through cell interactions and the release of soluble factors. These cells inhibit the proliferation and activation of T lymphocytes by preventing monocyte differentiation into dendritic cells and suppressing inflammatory signaling. They can also inhibit myelin-sensitive lymphocytes that contribute to neurodegenerative diseases⁹⁵.

Damaged neurons secrete nitric oxide, which stimulates Schwann cells to produce erythropoietin

(a neuroprotective factor). There is evidence suggesting that MSCs also produce nitric oxide and secrete erythropoietin, which may contribute to their protective effects on the peripheral nervous system. Overall, bone marrow MSCs show promising potential for peripheral nerve repair due to these unique properties¹⁰⁵.

Spinal Cord Injury Treatment

Spinal cord injuries are characterized by long-term functional deficits following the loss of the main neurons of the central nervous system and the subsequent disruption of the signaling system to the motor organs. Various factors contribute to the lack of production and proliferation of spinal cord axons, with the most common causes being a decrease in the growth potential of neurons in the nervous system. This is caused by inhibitory signals originating from damaged myelin, as well as lesions in glial cells resulting from inflammatory responses¹⁰⁶. Patients with spinal cord injury often experience symptoms such as loss of movement and sensation and an inability to perform voluntary movements. Current treatments, including rehabilitation and physiotherapy, are still ineffective in treating the disease, and many approaches are needed to improve symptoms. In recent years, stem cell use has become one of the most promising methods, opening new avenues for the treatment of this disease¹⁰⁷. Stem cells have garnered significant attention due to their ability to replace neurons, remyelinate axons, protect glial cells, induce angiogenesis, reduce inflammation, and promote neuroplasticity through the production of neural progenitor cells¹⁰⁸.

In the use of adult stem cells, there is a possibility that the stem cells may integrate with the existing stem cells in the spinal cord and perform their functions, though this theory is still under investigation. Newsome et al. rejected this theory, considering this phenomenon to be unique to liver cells. As a result, the hypothesis of using adult stem cells and their integration with host cells as a therapeutic framework has not yet been widely accepted. Additionally, the potential risks of using these cells, such as uncontrolled changes in cell behavior, lack of function, and improper

differentiation, are issues that must be addressed¹⁰⁹. These limitations highlight that the therapeutic benefits of MSCs may not necessarily depend on long-term engraftment or neuronal replacement, but may instead be mediated primarily through transient paracrine and immunomodulatory effects. MSCs derived from the patient's bone marrow are considered a suitable option to accelerate clinical trials. These cells can be prepared autologously, facilitating faster access to therapeutic interventions¹²⁸. Various basic and clinical studies have confirmed the ability of these cells to generate neurons and axons, proliferate astrocytes, reform myelin sheaths, induce sweating, and even improve function¹¹⁰.

According to various animal studies, the optimal window for injecting MSCs is approximately 7 to 21 days after the lesion is created¹¹¹. Labeling methods that allow for non-invasive tracking of cells, such as magnetic resonance imaging, facilitate targeted cell-based therapies¹¹². These methods are typically used to monitor and track cells. Studies conducted in 2004 and 2005 showed that human bone marrow-derived MSCs, labeled in vitro with iron oxide nanoparticles, were able to migrate to the lesion site and were detectable via nuclear magnetic resonance. This capability has enabled the investigation of cell homing to specific sites and the ability to track them¹¹³. Bone marrow-derived MSCs can be administered in various ways, including local injection, intravenous injection, or spinal injection. Consequently, autologous cells extracted from the patient can be used throughout the treatment period. The results of animal studies in established models may be generalized to humans, and it is noteworthy that the standard time for cell injection is typically 3 to 4 weeks after lesion formation¹¹⁴.

Sykova et al. (2006) concluded that injecting cells near the lesion site, or even into the cerebrospinal fluid, resulted in better outcomes in disease models. The main reason for the observed improvement is likely the reduction in tissue loss around the lesion site due to the secondary injury process, as well as the loss of glial cells in the lesion area. This helps minimize damage and promote subsequent repair¹¹⁰. Another ability of MSCs is the production of pro-inflammatory cytokines in the spinal cord area,

including interleukin-1, tumor necrosis factor, and interleukin-6, which suppress immune responses resulting from the lesion due to their anti-inflammatory properties¹¹⁵.

Several successful clinical trials are underway to explore the use of MSCs as therapeutic agents. For example, in a clinical trial conducted by Park et al. in Korea in 2012, MSCs from the patient's own bone marrow were used for cell therapy of spinal cord injury. In this study, the cells were injected directly into the injury site, and the results reported improved motor function in 6 out of 10 patients. Follow-up treatment and magnetic resonance imaging after 6 months showed improved motor symptoms, better daily activity, and a reduction in the extent of the lesion in the spinal cord of 3 out of 6 patients¹¹⁶. Although these findings are encouraging, the small sample size and limited follow-up period prevent definitive conclusions regarding efficacy and long-term safety. Larger, controlled clinical trials with standardized cell products, dosing regimens, and outcome measures are therefore needed before MSC-based therapy can be considered an established treatment for spinal cord injury.

Stroke

Acute stroke is the third leading cause of death and the leading cause of disability in various countries worldwide. It is typically caused by the rupture of cerebral microvessels, leading to neuronal death and loss of nerve cells. This phenomenon triggers a series of events, including severe inflammatory responses in the body. Strokes are generally classified into two categories: hemorrhagic and ischemic. Ischemic strokes account for 80% of all cases¹¹⁷. Following the acute phase of the disease, various medical treatments, including anticoagulants and tissue plasminogen activators, are recommended for long-term patient care. However, most patients experience persistent motor impairments and physical disabilities, highlighting the urgent need for therapeutic strategies to repair neurological damage. The primary lesion in stroke patients mainly affects two types of cells: endothelial cells and nerve cells. As a result, these patients' brains are more receptive to cell transplantation than those with

other neurological diseases. Therefore, cell therapy has emerged as a promising alternative intervention¹¹⁸.

Several types of cells are being considered for cell therapy in stroke treatment, including embryonic stem cells, MSCs derived from bone marrow and adipose tissue, induced pluripotent stem cells, neural stem/progenitor cells capable of generating neurons and glial cells, hematopoietic/endothelial progenitor cells, and hematopoietic cells isolated from bone marrow. Bone marrow MSCs have shown potential for repairing and regenerating lost neural tissue by enhancing sensory function and increasing neuronal synapses. Additionally, their anti-inflammatory properties help reduce tissue damage by lowering tissue plasminogen levels in the lesion area^{117,119}. Nevertheless, the extent to which these effects result from direct neuronal replacement versus paracrine, immunomodulatory, and angiogenic mechanisms remains unclear. This distinction is important for optimizing cell type, dose, and administration route in future clinical applications.

Savitz et al. investigated the effects of bone marrow MSCs in a rat model. In this study, the cells were first labeled with green fluorescent protein (GFP) using a retroviral vector and then injected. Sixty days after injection into the sciatic nerve of the rats, the effectiveness of the treatment was evaluated. The results demonstrated axonal regeneration, Schwann cell proliferation, and cell migration to the lesion site¹²⁰.

Huang et al. examined the production of neurotrophic factors by transplanted cells in a rat model. The cells were injected via the tail vein 48 hours after stroke, and neurological function was assessed 14 days post-injection. The results indicated a significant improvement in motor function in the treatment group, along with a notable reduction in programmed cell death within the ischemic area¹²¹.

Ghazavi et al. investigated, for the first time, the therapeutic effects of MSCs derived directly from adipose tissue in a rat model of ischemic stroke. These cells were genetically engineered to enhance the expression of the fibroblast growth factor-1 (FGF-1) gene. After inducing a stroke, the engineered

stem cells were intravenously injected into the diseased model. The presence of the cells in the lesion area was examined two hours post-injection, while physiological and behavioral improvements in the mice were evaluated 24 hours after cell therapy. The results demonstrated that engineered stem cells could enhance the biological properties of stem cells, promoting tissue repair¹²².

Additionally, a study published by the same research team in 2017 revealed that fibroblast growth factor-1 enhances the angiogenic properties of stem cells, further supporting their potential in stroke treatment¹²³.

Brain Tumors

Brain tumors are broadly classified into primary and secondary types. Primary tumors arise from the cells of the brain itself, whereas secondary tumors, or metastatic brain tumors, originate from malignant cells that have spread to the brain from other parts of the body¹²⁴. Among primary brain cancers, glioblastoma multiforme represents one of the most aggressive and lethal forms of adult malignancy. Despite considerable advances in neurosurgery, chemotherapy, and radiotherapy, these tumors remain notoriously difficult to treat effectively. A major challenge in managing brain cancers is their capacity to infiltrate healthy brain tissue distant from the main tumor mass. This invasive behavior contributes to high rates of local recurrence, often occurring near the surgical resection site even after aggressive multimodal therapy¹²⁵.

The presence of the blood-brain barrier significantly limits the efficacy of many therapeutic approaches, contributing to the poor prognosis and short survival times observed in patients with brain cancer. This challenge underscores the urgent need for the development of novel diagnostic and therapeutic strategies that are highly effective, rapid, and precise. Currently, the standard treatment for glioblastoma involves a multimodal approach, including surgical resection of the tumor, chemotherapy with Temozolomide, and radiotherapy¹²⁶.

Cell therapy and the use of stem cells have gained significant attention in glioblastoma treatment. Stem cells, due to their inherent tendency to cross the

blood-brain barrier and home to lesion sites, are used as carriers for therapeutic agents. These cells can be administered through various routes, including intravenous, carotid, and even peritoneal injection. Among different types of stem cells, mesenchymal and neural stem cells have been studied the most^{127,128}.

Stem cell-based strategies for treating brain cancers are diverse and include approaches such as engineered stem cells, drug-carrying cells, cells delivering antitumor proteins, cells carrying oncolytic viruses, and stem cell-derived exosomes. Dickson et al., engineered stem cells were used for the targeted delivery of interferon-beta (IFN- β) in a mouse model of neuroblastoma. The stem cells were injected intravenously, and the gene transfer was performed using adenoviruses. The study demonstrated successful gene transfer to the tumor area¹²⁹.

Modified or engineered stem cells are commonly utilized to release apoptotic proteins, anti-proliferative proteins, and immune-stimulating molecules. One such protein is TRAIL, which binds to DR4/5 cell death receptors widely expressed on the surface of cancer cells, leading to increased apoptosis or caspase-mediated cell death. In a study involving both mesenchymal and neural stem cells, TRAIL gene transfer via lentiviruses showed antitumor effects in mouse models of aggressive glioblastoma. Recent studies have further emphasized the efficacy of TRAIL-engineered stem cells against glioblastoma, although additional research is needed to confirm these findings^{130,131}.

Bagci-Onder et al. investigated a secondary brain cancer model derived from metastatic breast cancer. In this study, MSCs engineered with the TRAIL gene were used for treatment. The TRAIL protein induced increased cell death in metastatic cancers. The results highlighted the effectiveness of the treatment in the studied mouse model¹³².

Another promising approach in stem cell-based therapy for brain tumors involves the genetic manipulation of stem cells to express anti-proliferative proteins. These stem cells exert antitumor effects through the secretion of cytokines such as interferon-beta. Nakamizo et al., human MSCs derived from bone marrow were used to

assess their anti-proliferative properties in a mouse model of glioma. The MSCs secreted interferon-beta and were injected into the cerebral arteries of the mice. The results confirmed the tropism of stem cells toward the glioma site and demonstrated improved survival rates in treated mice compared to the control group¹³³.

Another application of cell therapy is the release of immune-regulatory molecules, such as interleukins (IL), which modulate immune responses. Various studies have demonstrated that neural stem cells engineered with interleukin-12 (IL-12) can reduce tumor size in both mouse and rat glioblastoma models. Similarly, in a study utilizing human MSCs secreting IL-12 and IL-18 in a mouse model of glioblastoma, interleukin-releasing stem cells activated natural killer cells and tumor-specific T lymphocytes, leading to reduced tumor proliferation and increased survival. Another example of stem cell-assisted immunotherapy involved the injection of MSCs along with interferon-gamma-producing cells in a rat glioblastoma model. This study revealed a 54% reduction in tumor growth due to the synergistic effect of IFN- γ with cell therapy, whereas stem cells alone did not inhibit tumor growth, and immunotherapy alone resulted in only a 21% immunogenic response. The observed synergy may be attributed to the increased expression of MHC class I and II following MSC and IFN- γ injection. Increased IFN- γ levels also suppress prostaglandin and interleukin-10 secretion, both of which play immunosuppressive roles^{134,135}.

Some studies have explored the use of stem cells secreting tumor-killing toxins, such as *Pseudomonas* exotoxin (PE). PE inhibits protein synthesis by inactivating elongation factor-2 (EF-2). However, this approach remains controversial due to potential systemic toxicity and adverse effects on healthy tissues. Additionally, the short therapeutic window of this strategy poses a challenge¹³⁶.

Stuckey et al., MSCs engineered with EF-2 were used. These stem cells secreted PE under the influence of EF-2. The toxin directly affected interleukin-13 receptor expression and increased endothelial growth factor receptor (EGFR) expression in a glioblastoma model. The release of IL-13-PE from stem cells enhanced survival rates and facilitated the

elimination of residual tumor cells post-surgery. This method demonstrated superior efficacy compared to the administration of IL-13-PE alone¹³⁷.

Another application of engineered stem cells is the expression of transforming enzymes within their structure. Using this strategy, prodrugs are converted into active drugs through enzymatic reactions for glioblastoma treatment. Currently, the three main prodrugs used in this context are cytosine deaminase (CD), 5-fluorocytosine (5-FC), and herpes simplex virus thymidine kinase (HSV-TK)^{138,139}. In various studies, mesenchymal and neural stem cells modified with the 5-FC/CD system have been employed in mouse models of glioblastoma and medulloblastoma. The results demonstrated tumor growth inhibition and improved survival rates. Another study investigated human MSCs expressing both cytosine deaminase and thymidine kinase. The combined use of these genes resulted in greater efficacy and enhanced antitumor properties in the animal model¹⁴⁰.

Stem cells can also serve as carriers for oncolytic viruses, which selectively infect and kill tumor cells while sparing healthy tissue. Despite its advantages, this approach faces limitations due to the immune system's clearance of the virus, which reduces therapeutic efficacy. Martínez et al., hyaluronic acid-coated MSCs were used to deliver an oncolytic virus in a mouse glioblastoma model. Hyaluronic acid, a key component of the extracellular matrix, facilitated efficient virus delivery to the lesion site. As hyaluronic acid degraded, the virus was gradually released, prolonging its antitumor effect¹⁴¹.

The final cell-based cancer therapy strategy involves extracellular vesicles. These vesicles, released by various cells, can carry miRNA, mRNA, proteins, and lipids. Numerous studies have highlighted the ability of stem cell-derived vesicles to deliver therapeutic agents in a paracrine manner. These vesicles can transport specific miRNAs, such as miRNA-124 and miRNA-145, both of which have demonstrated antitumor effects in mouse glioblastoma models^{142,143}. Pacioni et al., MSC-derived exosomes containing paclitaxel were evaluated. The exosomes exhibited a natural tendency to migrate to the lesion site, where they released the drug. The study confirmed the therapeutic effects of these vesicles in

vitro and later validated their efficacy in an animal glioblastoma model. Importantly, no adverse effects on healthy tissue surrounding the tumor were observed¹⁴⁴. Overall, the available evidence indicates that stem cells and their derived products, including exosomes, have considerable potential for tumor targeting and therapeutic delivery. However, most of the evidence remains at the preclinical stage, and standardization of production, determination of appropriate dosing, control of distribution and therapeutic stability, and demonstration of safety and efficacy in clinical studies remain major challenges. Therefore, well-designed and long-term clinical studies are essential to determine the true therapeutic value of these approaches for brain tumors. The proposed mechanisms, preclinical and clinical evidence, and major limitations of mesenchymal stem cell-based therapies across neurological disorders are summarized in Table 1.

Strategies for Optimizing the Effect of Stem Cell Therapy

Routes of Administration and Injection Site

Determining the appropriate route for stem cell engraftment plays a crucial role in the effectiveness of treatment. Intravenous injection, intrathecal injection, and direct intramedullary injection are common methods for engrafting stem cells into the body¹⁴⁵. Based on available studies in animal models, intrathecal injection is more effective than intravenous injection. However, the adhesion of these cells to the subarachnoid layer prevents them from reaching the injury site. To achieve successful treatment, a large number of cells must be injected to ensure that some reach the injury site in the brain¹⁴⁶. However, in the chronic stages of spinal cord injury (SCI), these cells lack homing capabilities. Thus, direct injection into the injured area of the spinal cord—despite the potential risks of cerebrospinal fluid leakage, internal bleeding, or other injuries—may be a more effective method of delivering cells to the damaged site. In intramedullary injection, selecting the injection site is crucial. The proximal region above the lesion is more suitable for stem cell survival¹⁴⁷. However, injecting an inappropriate volume of cells can be harmful, as excessive pressure on surrounding

healthy tissue may cause damage. Consequently, their use is limited. It is important to note that if sufficient stem cells can be injected into the cavity of the damaged area, multiple injections are more effective than a single injection¹⁴⁸.

The Right Time for a Stem Cell Transplant

The first three days after a nervous system injury are referred to as the acute phase. The chronic phase extends beyond twelve months after the injury. The period between these two phases is known as the subacute phase. Spontaneous recovery of the nervous system occurs rapidly during the first three months after injury, then slows over the following twelve months, while the extent of damage remains constant.

Immediately after injury, during the acute phase, secondary events such as the release of oxygen free radicals, excitatory neurotransmitters, and inflammatory molecules create a lethal environment for transplanted cells. Additionally, a hypoxic state, resulting from reduced blood supply to the damaged

tissue (perfusion deficiency), makes this phase unsuitable for cell therapy. However, some researchers have proposed alternative timing for stem cell injections to enhance the treatment of nervous system damage¹⁴⁹.

In the chronic phase, glial scarring acts as a physical barrier to axonal regrowth, and axonal growth is significantly reduced compared to the acute and subacute phases. Studies based on animal models have shown diminished neuronal growth and decreased levels of growth-promoting proteins in this phase, making the survival of transplanted stem cells particularly challenging.

In contrast, during the subacute phase, the inflammatory response decreases, and glial plaques have not yet formed. As a result, cell injections during this phase have shown better survival rates compared to the chronic phase. Therefore, the subacute phase is considered the optimal window for stem cell therapy¹⁴⁸.

Table 1: Therapeutic potential of mesenchymal stem cells in neurological disorders: proposed mechanisms, preclinical and clinical evidence, and major limitations

Neurological disorder	Potential therapeutic effects of MSC-based therapy	Main proposed mechanisms	Major preclinical findings	Current clinical evidence	Major limitations
Alzheimer's disease	Potential neuroprotective and immunomodulatory effects	Paracrine signaling, secretion of neurotrophic factors, attenuation of neuroinflammation, and modulation of microglial activity	Improved cognitive performance and reduced neuroinflammation and neuronal injury in experimental models	Very limited early clinical evidence; clinical efficacy has not been established	Small and heterogeneous clinical studies, variability in MSC products, and uncertainty regarding optimal dose and route
Parkinson's disease	Potential neuroprotective effects and support of dopaminergic neuronal function	Immunomodulation, secretion of neurotrophic factors, and paracrine signaling	Improved motor outcomes and increased survival of dopaminergic neurons in preclinical models	Early-phase clinical studies have primarily evaluated safety and feasibility; therapeutic efficacy remains unproven	Small sample sizes, limited controlled evidence, and insufficient long-term follow-up
Huntington's disease	Potential neuroprotective and immunomodulatory effects	Paracrine signaling and modulation of neuroinflammatory responses	Reduced neuronal injury and improved behavioral outcomes in experimental models	Extremely limited human clinical evidence; efficacy remains unestablished	Lack of adequately powered clinical trials and uncertainty regarding optimal cell source, dose, and route
Multiple sclerosis	Potential immunomodulatory and neuroprotective effects	Regulation of immune responses, attenuation of inflammation, and secretion of trophic and reparative factors	Reduced neuroinflammation and demyelination and improved neurological outcomes in experimental models	Clinical studies support feasibility and short-term safety, but efficacy results remain inconsistent and definitive benefit has not been established	MSC heterogeneity, variable treatment protocols, limited sample sizes, and inconsistent clinical outcomes

Neurological disorder	Potential therapeutic effects of MSC-based therapy	Main proposed mechanisms	Major preclinical findings	Current clinical evidence	Major limitations
Autism spectrum disorder	Potential immunomodulatory and paracrine effects	Modulation of immune responses and paracrine signaling	Some experimental studies report improvements in behavioral and neurological phenotypes	Early-phase clinical evidence is limited and preliminary; efficacy has not been established in adequately controlled trials	Small study populations, clinical heterogeneity, open-label designs, and insufficient long-term efficacy and safety data
Spinal cord injury	Potential neuroprotective, anti-inflammatory, and tissue-reparative effects	Anti-inflammatory signaling, neurotrophic support, angiogenesis, and paracrine signaling	Improved motor recovery and reduced tissue damage in animal models	Early clinical studies support feasibility and short-term safety, with preliminary signals of functional improvement; efficacy remains uncertain	Uncertainty regarding optimal timing, dose, MSC source, route of administration, and rehabilitation protocols
Stroke	Potential neuroprotective and restorative effects	Anti-inflammatory signaling, angiogenesis, paracrine signaling, and modulation of neuroplasticity	Improved neurological recovery and reduced tissue injury in animal models	Clinical studies and meta-analyses suggest potential functional benefit, but findings remain heterogeneous and definitive efficacy has not been established	Variability in cell products, treatment timing, dose, route, patient selection, and outcome measures
Brain tumors	Potential use as cellular vehicles for targeted delivery of therapeutic agents	Tumor tropism and delivery of therapeutic molecules to tumor sites	MSC migration toward tumor tissue and experimental use as carriers for therapeutic agents	Clinical evidence is very limited; application remains largely experimental	Uncertainty regarding effects on tumor microenvironment and tumor progression, together with safety and targeting concerns
Peripheral nerve injury	Potential enhancement of axonal regeneration and functional recovery	Neurotrophic factor secretion, paracrine signaling, and support of Schwann-cell activity	Enhanced axonal regeneration and functional recovery in experimental models	Limited human clinical evidence; clinical efficacy remains insufficiently established	Limited clinical studies, methodological heterogeneity, and lack of standardized treatment protocols

Use of Complement Factors

The use of complementary factors is considered essential for the survival of stem cells. For example, a combination of trophic factors, including epidermal growth factor (EGF), fibroblast growth factor type 2 (FGF2), and platelet-derived growth factor (PDGF), enhances the survival of transplanted cells. Additionally, the use of macrophage granulocyte colony-stimulating factor, chondroitinase, and gene editing to promote the secretion of supportive molecules can also be effective (148).

Multiple Injections and Single Injections

Park and his group demonstrated motor improvement in 60% of patients using multiple injections of BM-MSC, whereas single injections of BM-MSC did not yield promising results, with motor

improvement occurring in only two of sixteen patients. Therefore, multiple injections are more effective than single injections ¹¹⁶.

Conclusion and Future Research

MSCs have been proposed as a promising therapeutic option for neurological disorders due to their unique properties, including their ability to differentiate into various cell types, anti-inflammatory effects, and immune-modulating capabilities. Research has shown that these cells can be effective in treating diseases such as Alzheimer's, Parkinson's, stroke, and spinal cord injury through mechanisms such as releasing growth factors, reducing inflammation, and improving neuronal survival. However, despite these promising findings, the clinical evidence remains variable, and

differences in study design, cell sources, doses, administration routes, and patient characteristics make it difficult to draw definitive conclusions regarding their therapeutic efficacy.

However, challenges remain, including standardizing culture and propagation methods, optimizing delivery routes, and ensuring the safety and long-term efficacy of these cells. Manufacturing and quality-control challenges, variability in cell preparation, potential safety concerns, and uncertainties regarding long-term outcomes remain important barriers to clinical translation. Therefore, well-designed randomized controlled clinical trials with standardized protocols and adequate long-term follow-up are needed to establish the safety and efficacy of MSC-based therapies. In the future, advancements in genetic engineering, bio-nanoparticles, and smart drug delivery systems could enhance the effectiveness of MSCs in treating neurological disorders.

Progress in clinical trials and the establishment of standardized protocols for their use will pave the way for broader and more practical applications in regenerative medicine and neurological disease treatment. Future research should therefore focus not only on optimizing MSC production and delivery but also on defining standardized manufacturing procedures, appropriate patient selection, optimal dosing and administration strategies, and long-term safety and efficacy outcomes. Therefore, future research should focus on optimizing production processes and deepening the understanding of these cells' functional mechanisms to fully harness their potential in patient treatment.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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