Volume 4, Issue 6, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

UNLOCKING THE REGENERATIVE POTENTIAL A COMPARATIVE STUDY OF INDUCED PLURIPOTENT STEM CELLS VS MESENCHYMAL STEM CELLS IN TREATING NEURODEGENERATIVE DISEASES

Uswah Zainab[*1], Aisha Akram [2], Sana Azam [3], Zainab Bibi [4], Naemal Usman [5], Syed Imran Zahid [6], Khalil Ur Rehman[7]

[*1,2,3,4,5,6,7]*Department of Biochemistry, Riphah International University Faisalabad Campus, Faisalabad, Punjab, 44000*

[*1]uswahzainab10@gmail.com

DOI: https://doi.org/10.5281/zenodo.20927245

Keywords

induced pluripotent stem cells, mesenchymal stem cells, neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, regenerative medicine, cell therapy, neuroprotection.

Article History

Received: 23 April2026
Accepted: 05 June 2026
Published: 21 June 2026

Corresponding Author: *
Uswah Zainab

Abstract

Millions of people suffer from these neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and Huntington's disease, and there is no known cure, therefore, new therapeutic strategies are needed. Stem cell-based regenerative medicine has become a promising approach and this review compares the two major stem cell types used for the treatment of these disorders: induced pluripotent stem cells (iPSCs) and mesenchymal stem cells (MSCs) comprehensively. Their various sources, differential activity, mode of action, pre-clinical data, clinical trial results, safety and translational issues are examined critically. Patient-specific autologous therapy, pluripotent differentiation potential to generate any neural cell type, unlimited expansion capacity for disease modeling and drug screening are the unique features of iPSCs. They do come with a number of drawbacks, however, such as teratoma formation due to the presence of leftover undifferentiated cells, genomic instability due to the reprogramming process, and the fact that their production cost is too great. Contrastingly, MSCs are easily accessible in various adult tissues, possess immune-privileged properties that allow for allogeneic transplantation without the need to immunosuppress, and release a large and diverse range of neurotrophic molecules, anti-inflammatory cytokines, and exosomes with neuroprotective functions, that pose no risk of teratoma development. They have limited inherent neural differentiation potential and significant differences in therapeutic efficacy between studies. When compared with MSCs, iPSCs have higher precision in disease modelling and have true cell replacement potential, but are at a significantly earlier stage in clinical translation, with less than 30 trials completed or ongoing. Most importantly, there is a lack of comparative studies of the direct head-to-head type. In conclusion, we believe that iPSCs and MSCs are optimally suited to different niches in the disease process: MSCs to paracrine-based neuroprotection and immunomodulation in early disease stages, and iPSCs to cell replacement strategies in later disease stages, although with potentially increased risk. The following directions for future development involve the manufacture of off-the-shelf iPSC-derived products, the engineering of MSC exosomes, the rational

Volume 4, Issue 6, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

combination approach, and stringent comparative trials for clinical decision making.

1. INTRODUCTION

The world is currently experiencing a global epidemic of neurodegenerative diseases; we estimate that currently there are about 55 million people living with dementia worldwide, of which 60-80% are cases of Alzheimer's disease, 10 million people are living with Parkinson's disease, and an estimated 200,000 people in the world suffer from amyotrophic lateral sclerosis. The numbers will double every 20 years because of population aging, and the current therapeutic strategies are simply not enough to solve this problem (Cecerska-Heryć et al., 2023). Current treatment for these terrible diseases is purely symptomatic, giving modest, short-lived cognitive benefits to Alzheimer's patients, transient motor improvement to Parkinson's patients, and a few months of longer life for amyotrophic lateral sclerosis patients with riluzole. This has created a critical need for more promising disease-modifying drugs that can slow or stop or even reverse the gradual neuronal decline that is characteristic of these diseases, and regenerative medicine is a paradigm that has emerged in this space.

Stem cells are the key to the promise of regenerative medicine for neurodegenerative diseases, and their unique properties include self-renewal, differentiation into specialized cell types, and potent paracrine signaling. Two main therapeutic strategies have been developed: one cell replacement approach involves transplantation of stem-cell-derived neural progenitors or mature neurons directly into the diseased brain; the other is a neuroprotective or immunomodulatory approach involving the delivery of cells that produce growth factors, anti-inflammatory molecules, and exosomes that promote the survival of existing endogenous neurons.(Fatima & Sinha). History of this field was set by first transplantation of fetal dopaminergic neurons from aborted fetuses in Parkinson's disease patients. These ground-breaking studies gave much needed proof-of-concept evidence that transplanted neurons were viable, integrated and clinically effective in some patients. Ethical issues around fetal tissue use, logistics of obtaining fetal tissue, quality variation, and the impracticality of scaling up fetal cell transplantation in a broad manner, however, ended up making fetal cell transplantation unfeasible. Since then, researchers have been searching for alternate sources of stem cells that would be more ethically and practically acceptable. In the different types of stem cells being studied, induced pluripotent stem cells and mesenchymal stem cells are the two most promising options for the treatment of neurodegenerative disorders, but they are very different in their properties, mechanisms and clinical pathways (Velikic et al., 2024). iPSC can be engineered to a pluripotent state by introducing defined transcription factors into somatic cells, such as the skin fibroblasts or peripheral blood mononuclear cells (PBMCs) and thereby allow for patient-specific autologous therapy, unlimited expansion in culture, and directed differentiation into any neural cell type (dopaminergic neurons for treatment of Parkinson's disease, motor neurons for amyotrophic lateral sclerosis, cholinergic neurons for Alzheimer's disease). By contrast, the therapeutic actions of mesenchymal stem cells are mainly mediated by secretion of neurotrophic factors, anti-inflammatory cytokines and exosomes, and they are also immune-privileged, lowly expressing major histocompatibility complex molecules, and can be easily isolated from bone marrow, adipose tissues and umbilical cord. Although there are a vast number of independent literatures that have been developed for each cell type, there has been no systematic side-by-side comparison of these two approaches. This gap is important to fill because there is a need for evidence-based information to guide research investments, to optimize clinical trials and to select cell types in specific disease scenarios. In the present review the organization is therefore made to provide such a comparative analysis. We will

Frontier in Medical & Health Research
ISSN: (e) 3007-1607 (p) 3007-1593

first explore the basic biology and derivation of iPSCs and MSCs, then provide detailed discussion on the mechanism of action of each cell type, take a disease by disease summary of preclinical evidence, discuss completed and ongoing clinical trials, discuss potential safety and ethical considerations, and lastly conduct a head-to-head comparative analysis. Finally, we discuss the future prospects and challenges of combination approaches, such as synergistic combinations that could eventually realize the full capacity of stem cell-based therapies in treating patients with neurodegenerative diseases.

2. Induced Pluripotent Stem Cells (iPSCs): Fundamentals

2.1. Derivation and Reprogramming

Takahashi and Yamanaka's discovery of induced pluripotent stem cells in 2006 changed the face of regenerative medicine, so much so that it was named the Nobel Prize in Physiology or Medicine in 2012. The key discovery was the identification of four transcription factors (Oct3/4, Sox2, Klf4 and c-Myc) that are enough to convert differentiated somatic cells back into a "pluripotent" state similar to that of embryonic stem cells(Mohite et al., 2024). These factors were initially reprogrammed using retroviral or lentiviral vector delivery and showed high reprogramming efficiency resulting from stable integration of the factors into the host genome. But there were legitimate concerns about the safety of the permanent genomic integration, namely insertional mutagenesis and the possibility of transgene reactivation, especially the oncogene c-Myc. For this reason, much effort has been focused on developing non-integrating methods for drug delivery which are clinically preferred(Frawley et al., 2024). The integration-free integration vectors have become one of the most widely used and they remain outside the chromosomes and are eventually lost when dividing cells are cultured. Sendai virus is an RNA virus that replicates in the cytoplasm and does not enter the nucleus or integrate into the host genome, and can be extremely efficient in reprogramming in various cell types and is easily cleared after several passages(Khedr et al., 2025). The synthetic mRNA reprogramming has no viral or DNA intermediates and is technically challenging and requires transfection every day. It has also been shown to be possible to directly transduce the recombinant reprogramming factors, but the efficiency is extremely low in that case. Either way, the reprogramming process can take 3–4 weeks to produce stable iPSC colonies that can be expanded and characterized, with a significant time commitment for each new cell line generated.

2.2. Characterization and Pluripotency Validation

After putative iPSC colonies have been formed, the cells need to be subjected to rigorous characterization to ensure that the cells are truly pluripotent and are appropriate for use in downstream applications. The first indication is the morphology, with bona fide iPSC colonies having a distinct flattened, compact, and tightly packed morphology with sharp borders and clearly distinguishable from the surrounding differentiated feeder cells or residual fibroblasts. Finally, expression of the canonical pluripotency markers, transcription factors Oct4 and Nanog, and cell surface antigens SSEA-4, Tra-1-60 and Tra-1-81 are examined by immunocytochemical and flow cytometric analyses(Mehrabadi, 2024). A good set of authentic iPSC lines should exhibit strong and consistent staining of these markers. The most definitive test for pluripotency is however the teratoma formation assay, which involves the injection of iPSCs into immunocompromised mice and spontaneous differentiation over a number of weeks. The teratomas formed are next removed, cut into, and analyzed histologically, looking for tissues derived from all three embryonic germ layers: endoderm (gut-like epithelium), mesoderm (cartilage, bone and muscle), and ectoderm (neural rosettes or epidermal structures)(Kamboj, Kumar, & Mitra, 2025). Although it is definitive, the teratoma assay is time consuming, expensive and ethically dubious, and alternative in vitro pluripotency assays that relate to teratoma formation are being

Frontier in Medical & Health Research
ISSN: (e) 3007-1607 (p) 3007-1593

sought(Ford et al., 2020). Lastly, the assessment of genomic stability is essential by karyotyping, usually by G-banding or newer methods such as single nucleotide polymorphism arrays or whole genome sequencing; the process of reprogramming can cause numerical abnormalities of the chromosomes, structural abnormalities of the chromosomes, or submicroscopic copy number abnormalities that can predispose to malignant transformation or reduce the ability to differentiate.

2.3. Neural Differentiation Protocols

To generate specific neural types by directed differentiation, the timing of pathways that mimic early development must be carefully controlled(NAZIR et al., 2024). The most commonly used protocol of neural induction involves dual SMAD inhibition, which involves the combination of two inhibitors: Noggin, a bone morphogenetic protein antagonist and SB431542, a transforming growth factor-beta inhibitor, both of which are added to differentiating iPSC cultures(Shen et al., 2025). This combination is effective in preventing differentiating cells from assuming other cell fates, and favours the development of neural rosettes, columnar epithelial structures resembling neural-tube-like progenitors(Carneiro-Pereira, Ferreira-Antunes, Campos, Salgado, & Sampaio-Marques, 2025). They are then isolated and expanded as neural progenitor cells, and can then be further differentiated as either neurons, astrocytes, or oligodendrocytes under the appropriate mitogenic and differentiation factors. The protocol includes floor plate induction with hedgehog agonist purmorphamine and fibroblast growth factor 8 as well as canonical WNT pathway activation, for generating dopaminergic neurons for Parkinson's disease cell therapy(W. Zhou et al., 2024). This pairing results in progenitors of the midbrain floor plate that give rise to tyrosine hydroxylase-positive, GIRK2-positive dopaminergic neurons that have electrophysiological characteristics of the substantia nigra pars compacta. Ca2+ neural progenitors with activation of sonic hedgehog signaling by sequential treatment with retinoic acid to caudalize neural progenitors and purmorphamine to activate sonic hedgehog signaling are efficient at producing HB9- and choline acetyltransferase-positive spinal motor neurons relevant to amyotrophic lateral sclerosis (ALS). Basal forebrain cholinergic identity is promoted using brain-derived neurotrophic factor, nerve growth factor and glial cell line-derived neurotrophic factor for the generation of cholinergic neurons relevant to Alzheimer's disease(Abdelrahman, 2024). The differentiation from pluripotent stem cells to a functional mature neuron takes 30 to 60 days depending on the lineage and maturity required.

2.4. Advantages of iPSCs

The use of induced pluripotent stem cells has a number of important benefits, which render them very attractive for basic science and therapeutic applications(Mahla). These differentiated cells can be transplanted back into the patient from whom they were derived, and in theory, this should mean no need for a recipient to be immunosuppressed, and no risk of immune rejection. This personalised approach is especially promising for chronic neurodegenerative diseases that require long-term survival of the graft(Gholamzad et al., 2023). Secondly, iPSCs can be cultured continuously without any end point, thus offering an essentially limitless supply of cells for transplant, disease modelling or drug screening purposes(Tatullo et al., 2024). Its ability to differentiate iPSCs into any type of neural cell that is of interest to study allows for the specific replacement of these lost populations in each disease, such as dopaminergic neurons in Parkinson's disease, motor neurons in amyotrophic lateral sclerosis, cholinergic neurons in Alzheimer's disease and striatal medium spiny neurons in Huntington's disease. In addition to therapeutic uses, iPSCs have transformed the field of disease modelling through the generation of living neurons from patients with known genetic mutations, recapitulating disease phenotypes in a dish and permitting mechanistic studies that previously were not possible(Kumar et al., 2026). In addition, these patient-derived neurons can be

Frontier in Medical & Health Research
ISSN: (e) 3007-1607 (p) 3007-1593

employed in high throughput drug screening to search for drugs that can restore disease-relevant phenotypes. Finally, the recent development of the CRISPR-Cas9 gene editing technology provides a means to correct disease-causing mutations in iPSCs obtained from patients with monogenic forms of neurodegenerative disease, which can then be used to generate isogenic control lines that contain only a single mutation at the disease locus, a valuable strategy for determining causality.

2.5. Limitations of iPSCs Although iPSCs are extremely promising, they have a number of significant drawbacks that hinder their clinical application(Noroozi & Pakzad, 2025). The most dreaded complication is teratoma which can develop from residual undifferentiated pluripotential cells left in the preparation of the transplant. Undifferentiated iPSCs, even if only a few, can form tumors known as teratomas, which are composed of disorganized tissues of multiple germ layers that can be harmful depending on the growth and location of the teratoma(Riza & Alzahrani, 2025). This risk cannot be completely eliminated by rigorous quality control performed by flow cytometry of pluripotency markers and terminal differentiation protocols. Another significant issue is genomic instability, where the reprogramming process itself may trigger changes of copy numbers, point mutations and epigenetic abnormalities(Ahmed, 2025). Worse yet, cultured iPSCs have been found to develop mutations in the tumour suppressor gene TP53, which give them a growth advantage and can lead to malignant transformation. The longer the cells are kept in culture, the more harmful mutations may occur. While donor cell-type specific methylation patterns can be epigenetically retained, this phenomenon may be cell line and reprogramming-dependent and will influence differentiation towards the original somatic lineage rather than towards desired neural fates(Yigitturk & Cavusoglu, 2025). The financial and logistical hurdles are huge, and existing estimates suggest that making an iPSC-based treatment for one patient would cost $50,000 to $100,000, with a three- to six-month turnaround from the biopsy to the cells being prepared for transplantation(Zeng, 2025). Last, significant differences have been found between iPSC lines from the same person and even between lines cultivated from the same reprogramming experiment (clones), making it critical to carefully characterize lines to ensure they are the best suited for the experiments and making standardization difficult.

3.1. Sources and Isolation

MSCs can be obtained from many different tissues, all with their unique advantages and disadvantages for therapeutic use in neurodegenerative diseases(Sethi et al., 2025). Bone marrow is the historical gold standard for isolation of MSCs, which are extracted from aspirates from the iliac crest and separated by density gradient centrifugation. This source is very well characterized, with decades of research supporting its biological properties, but the harvest process is extremely invasive and the harvest number and proliferative capacity of the MSCs decreases significantly with increasing donor age, which restricts the use for autologous application in elderly donors. Adipose tissue has proven to be an interesting alternative as it involves the extraction of MSCs from the stromal vascular fraction by collagenase digestion of liposuction aspirates(Belousova et al., 2024). The method provides an abundance of source tissue (minimally invasive liposuction), produces up to 500 times more MSCs per volume than bone marrow, and has a greater proliferative capacity for older donors, but is less monochromatic than the MSCs derived from bone marrow(Patel, Shukla, & Shukla, 2025).

Highly immature MSCs obtained from explant culture are derived from umbilical cord tissue including Wharton's jelly in which small fragments of umbilical tissue are directly cultured in a plastic dish, and cells migrate out onto the plastic surface(Gottipamula, Seetharam, & NK, 2026). The gain is significant: the collection is completely non-invasive, young cells with long telomeres, high capacity of expansion and excellent immunomodulatory properties. But, the MSCs found in umbilical cord are allogeneic and

Frontier in Medical & Health Research
ISSN: (e) 3007-1607 (p) 3007-1593

thus cannot be used autologously at a later age for the donor(Saliev & Singh, 2026). Dental pulp is an easily obtained and ethically unproblematic source, which is extracted from teeth and then subjected to enzymatic digestion with collagenase and dispase. The cells are particularly attractive to use for neurological applications because they are derived from the neural crest in early development and may have increased neurogenic potential including expression of neural crest markers including SOX10 which promote a Schwann cell-like phenotype(Y. Zhang, Wang, Kang, Lin, & Fan, 2023). The yield of a single tooth is however quite low and many teeth or expansion need to be used to achieve sufficient numbers of cells. The same type of enzymatic digestion is used to isolate additional perinatally-derived MSCs from amniotic fluid and placental tissues, which are also endowed with strong immunomodulatory abilities, but that are collected with ethical implications that should be addressed in clinical use, such as informed consent and the issue of who owns the tissue.

3.2. Characterization According to ISCT Minimal Criteria

The International Society for Cellular Therapy has drawn up a set of minimal criteria that must be met in order to define cells as MSCs, and that these criteria are met is essential for rigorous scientific investigation and to facilitate comparison between studies(Madhan, Mehta, Santoshkumar, Satishkarthik, & Aruljothi, 2025). First, MSCs must exhibit plastic adherence under standard tissue culture conditions, in that they attach well to plastic tissue culture surfaces and exhibit a fibroblast-like shape. This property is the most distinguishing characteristic of MSCs as compared to cells of the hematopoietic lineage that are kept in a liquid culture(Das et al., 2024). The second criterion is based on the expression of a defined set of surface markers determined by flow cytometry: MSCs must express CD73, CD90, and CD105 on more than 95% of the cells and they must be negative for the expression of hematopoietic markers such as CD11b, CD14, CD19, CD34, CD45, and HLA-DR, the major histocompatibility complex class II molecule, with negative expression defined as less than 2% positive cells(Choudhery, Arif, Mahmood, & Harris, 2026). The nature of this characteristic immunophenotype distinguishes MSCs from other cell types in tissue digests and establishes their non-hematopoietic nature. The third requirement is that the MSCs should have the ability to differentiate into osteoblasts, adipocytes and chondrocytes under specific inductive conditions. Osteogenic differentiation is confirmed by the deposition of mineralized extracellular matrix (stained with Alizarin Red), adipogenic differentiation is confirmed by accumulation of lipid-rich vacuoles (Oil Red O) and chondrogenic differentiation, usually performed in micromass or pellet culture, is confirmed by the production of sulfated proteoglycans (Alcian Blue) (Mayeen, Salma, Kasim, Mahmoud, & Haque, 2025). Although these criteria have been applied to define MSCs regardless of tissue source, they have been criticized for failing to take into account functional potency, and additional assays of immunomodulatory activity are increasingly recommended for cells to be used in therapy.

3.3. Neural Differentiation Potential – A Controversial Area

Perhaps the most controversial part of the stem cell story and the one most fiercely debated is the ability of MSCs to become functional neurons—where early promising claims met with current consensus diverged significantly(Kawatani et al., 2025). In the 2000s, a number of studies reported that treatment of MSCs with chemical cocktails containing beta-mercaptoethanol, dimethyl sulfoxide, butylated hydroxyanisole, or various growth factors could induce the expression of neural markers such as Nestin, beta-III tubulin, microtubule-associated protein 2 and glial fibrillary acidic protein(Nashwan et al., 2025). The changes in cell morphology, which usually involved the retraction of cytoplasm and elaboration of thin processes that resembled neurites, were generally assumed to represent

Frontier in Medical & Health Research
ISSN: (e) 3007-1607 (p) 3007-1593

transdifferentiation into neuronal cell types. In fact, intense further studies showed that many of these changes were actually related to the change in cellular stress or reorganization of the cytoskeleton, the framework that provides the structural support for the cell(Harun et al., 2025). Most importantly, the induced cells did not exhibit electrophysiological properties of mature neurons, such as generation and propagation of action potentials, voltage-gated sodium and potassium currents, or establishment of functional synapses. Lineage tracing studies and single-cell transcriptomic analyses all concur that MSCs are not very efficient at transdifferentiating into functional neurons(K. Yang et al., 2025). If anything, the neural markers that are expressed do so in a partial, transient expression, and are not enough to trigger the production of cells that can integrate into neural circuits or replace lost neurons. Some investigators have still reported generation of a progenitor-like neural cell type from MSCs under optimized culture conditions, but this result is controversial and the vast majority of evidence on the therapeutic effects of MSCs in neurodegenerative disease models suggest that they act mainly through paracrine mechanisms.

3.4. Advantages of MSCs

MSCs have a number of unique features that have made them the prime candidates for clinical use in neurodegenerative disorders. Due to their ease of availability from a variety of tissue sources, their quick expansion in culture with standard, Good Manufacturing Practice (GMP) compliant protocols, cells can be generated in large numbers in just 2-4 weeks, much faster than the time required for the production of iPS cells (3-6 months) (Zhong et al., 2024). MSCs have been defined as immune-privileged because they lack expression of major histocompatibility complex class II molecules and have a low level of expression of class I molecules, allowing allogeneic transplantation without the need of immunosuppressive drugs and without the need of HLA matching(Lai & Guo, 2024). This property allows the development of ready-to-use products to be given to any patient, significantly decreasing both the cost of the product and its logistical complexity, compared to autologous iPSC approaches. This teratoma-free situation is of major clinical translation benefit as hundreds of millions of MSCs can be used without fear of causing tumors because of their multipotent, not pluripotent, nature(Milczarek et al., 2023). The therapeutic effects of MSCs are mainly attributed to paracrine secretion of a cocktail of neurotrophic factors such as brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, and nerve growth factor, as well as to the potent immunomodulatory activity that involves inhibition of microglial activation, regulation of M1/M2 phenotype shift and augmentation of regulatory T cells. Further, there are extracellular vesicles called exosomes derived from mesosomes (MSCs) that are nano-sized vesicles containing messenger RNAs, microRNAs, and proteins that have been reported as recapitulating the neuroprotective effects of the parent cells(Zayed, Elwakeel, Ezzat, & Jeong, 2025). Because MSCs have an extensive clinical track record of over two hundred trials completed and ongoing, studies on a variety of neurological disorders, there are abundant safety and feasibility data to support further investigation.

3.5. Limitations of MSCs

Although MSCs are well tolerated and easily accessible for treatment, they have some important drawbacks limiting their potential in neurodegenerative diseases. The lack of neural differentiation that has been reported here above further restricts the scope of applicability for the replacement of lost neurons by MSCs, like in diseases like PD, where considerable dopaminergic neuronal damage has already taken place at the time of clinical diagnosis(Zeng, 2023a). These therapeutic effects are therefore indirect and reliant on the survival of endogenous residual neurons which may be limited in more severe disease states(Y.-P. Yang, Nicol, & Chiang, 2025). However, there is considerable variability in the potency of MSCs, as shown by various donors, tissue sources, isolation techniques, and culture conditions. Older donors' MSCs have limited

Frontier in Medical & Health Research
ISSN: (e) 3007-1607 (p) 3007-1593

proliferation, migration and secretory potential – a concern because the patients are aged. Likewise, long-term culture expansion results in cellular senescence, telomere shortening and a decrease in therapeutic potential(A. Zhang, Li, & Chen, 2024). Even within the same donor and source, there is Batch-to-Batch Heterogeneity, which makes standardization and regulatory approval difficult. Upon transplantation, MSCs have a limited survival in vivo, with most of them dying within days to weeks after their administration, regardless of the route of administration. The engraftment and differentiation into neural lineages are negligible and even their presence adequate to continue long-term paracrine effects is questionable(Jeyaraman et al., 2021). Last but not least, although it is rare, off-target differentiation into osteocytes, adipocytes and/or chondrocytes has been reported in ectopic transplant sites and worry has been raised about the potential of MSCs to promote tumour growth in patients with given malignancies owing to their immunomodulatory and pro-angiogenic properties(Su, Wang, Zhou, Liu, & Zhang, 2024). These restrictions highlight the need for appropriate patient selection, the use of potency assays to identify the best cell batches and the use of complementary and supplementary methods to increase the efficacy of the MSCs.

4. Mechanisms of Action in Neurodegenerative Diseases

4.1. iPSC-Based Mechanisms: The Cell Replacement Paradigm

The therapeutic mechanism of IPSC approaches for neurodegenerative diseases is based primarily on direct replacement of lost neurons, to restore the neural circuit and neurotransmitter function disrupted by progressive cell death(Lou, 2024). The differentiated neurons and iPSC-derived neural progenitors are terminally differentiated and, when grafted into the diseased brain, when conditions are optimal, they are integrated anatomically and functionally into the host neural network. Direct neuronal replacement is dependent upon the survival of the transplanted cells in the host environment, as well as their ability to send extensions (axons) to the correct target areas, receive inputs from host neurons, and connect with host efferent neurons to reestablish information flow through the disrupted pathways(Sun, Abelson, Babbar, & Damaser, 2019). Using animal models of Parkinson's disease, electrophysiology studies have shown that PD iPSC-derived dopaminergic neurons display spontaneous firing, are responsive to synaptic inputs, and release dopamine in a regulated manner, which strongly supports functional integration. The generation and release of neurotransmitters are important therapeutic endpoints, providing an endogenous replacement for the nigrostriatal projections that are lost in Parkinson's disease, and providing endogenous acetylcholine production and release for Alzheimer's disease therapeutic applications(J. Wang, Zhang, & Wang, 2024). In addition to these prototype applications, oligodendrocytes generated from iPSCs have been studied for use as remyelinating cells in other diseases, such as MS and ALS, where they can rewrap the axon and restore saltatory conduction to enable efficient neural transmission(Moretti, Lin, Peruzzotti-Jametti, Pluchino, & Mozafari, 2025). Further, the iPSC-derived astrocytes are not fully replacing lost neurons but rather provide trophic support by the secretion of glial cell line-derived neurotrophic factor and brain-derived neurotrophic factor, that support grafted and host neurons. The paradigm of cell replacement is conceptually elegant and is able to tackle the basic pathophysiological deficit in a neurodegenerative disease; however, it has enormous challenges to overcome, such as poor graft survival, inability to extend axons over disease-relevant distances, and the continued hostile disease environment in which both host and transplanted neurons still face threats.

4.2. MSC-Based Mechanisms: The Paracrine Paradigm

In contrast to the cell replacement strategy used in iPSCs, mesenchymal stem cells in neurodegenerative diseases typically have a therapeutic effect as a miniaturized biological factory that secretes a wide range of bioactive molecules rather than replacing lost

Frontier in Medical & Health Research
ISSN: (e) 3007-1607 (p) 3007-1593

neurons(Darban et al., 2024). The paracrine paradigm has been supported by a plethora of experimental studies that demonstrate that the neuroprotective and functional properties of intact cell transplantation can be readily reproduced simply by using MSC-conditioned medium or MSC-derived exosomes without cell integration(Peng, Zhang, Li, Yung, & Cheung, 2025). The fundamental difference in mechanism suggests how these two cell types should be used clinically, with MSCs being best suited to remodel and remodel the disease microenvironment with a focus on supporting the survival of existing, endogenous neurons rather than on reconstructing neural circuit function that has been already lost.

4.2.1. Neurotrophic Factor Secretion

Mesenchymal stem cells express a complex mixture of neurotrophic factors that have direct neurotrophic activity promoting the survival, growth, and function of neurons. These include glial cell line-derived neurotrophic factor, especially important for survival of dopaminergic neurons in Parkinson's disease; brain-derived neurotrophic factor, important for synaptic plasticity and cognitive function in Alzheimer's disease; Nerve growth factor, important for maintenance of cholinergic neurons in Alzheimer's disease; Neurotrophin-3, important for maintenance of proprioceptive sensory neurons in Alzheimer's disease; and ciliary neurotrophic factor, important for motor neuron survival in amyotrophic lateral sclerosis(Jia, Zhang, & Li, 2023). A group action of these trophic factors establishes a conducive microenvironment that may be able to decelerate or even stop the neurodegeneration process, without replacing the cells.

4.2.2. Immunomodulation

One of the strongest and best described mechanisms of action of MSCs in neurodegenerative diseases is their immunomodulatory properties, which are important because chronic neuroinflammation results from the activation of microglial cells and infiltration of peripheral immune cells, and is a significant component of disease pathogenesis(Rajalekshmi & Agrawal, 2025). MSCs can potently inhibit microglial activation by direct contact-dependent mechanisms and by secreting prostaglandin E2, transforming growth factor (TGF)-beta, and interleukin (IL)-10. They promote a change in the polarization of macrophages from the pro-inflammatory M1 phenotype producing damaging cytokines and ROS to anti-inflammatory M2 phenotype that facilitates tissue repair and resolution of inflammation(Mohammadi et al.). MSCs further enhance the number of regulatory T cells, which dampen hyperactive immune responses, and decrease the concentrations of pro-inflammatory cytokines such as interleukin-1 beta, interleukin-6, tumor necrosis factor alpha and interferon gamma. At the same time, they increase the levels of anti-inflammatory cytokines, including transforming growth factor-β and interleukin-10, thereby shifting the balance from neurotoxic to neuroprotective inflammation.

4.2.3. Exosome-Mediated Effects

Exosomes are small extracellular vesicles (40-150 nm) that have been identified as key mediators of the paracrine actions of MSCs. These exosomes contain complex cargo of microRNAs, mRNAs, proteins and lipids, which are transported to the target neurons and glia where they can modulate the expression and function of genes(Miceli, 2024). Exosomes have the following benefits over MSC transplantation: they can be delivered across the blood-brain barrier after systemic delivery, their composition is well defined and stable and can be characterized and standardized, and they do not trigger cellular engraftment or off-target differentiation.

4.2.4. Mitochondrial Transfer

A more recent discovery is that functional mitochondria are transferred from MSCs to injured neurons via the direct connection of Actin-containing membranous, structure called tunneling nanotubes(Y. Li et al., 2024). Oxidative stress and apoptotic cell death of vulnerable

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

neurons are prevented and bioenergetics is restored in cells by the healthy mitochondria provided by MSCs, as mitochondrial dysfunction is a common characteristic of most neurodegenerative diseases.

4.2.5. Additional Paracrine Actions

MSCs release vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF), which stimulate angiogenesis and enhance vascularization of damaged brain areas, leading to neuronal survival(Shi, Chen, Cai, Chen, & Tang, 2025). They also regulate the cellular recycling system (autophagy), which removes damaged organelles and protein aggregates, thereby facilitating removal of pathological proteins like amyloid-beta and alpha-synuclein. This paracrine network allows MSCs to act to alter the neurodegenerative environment without the need to replace any individual neuron, providing an alternative to cell replacement using iPSCs.

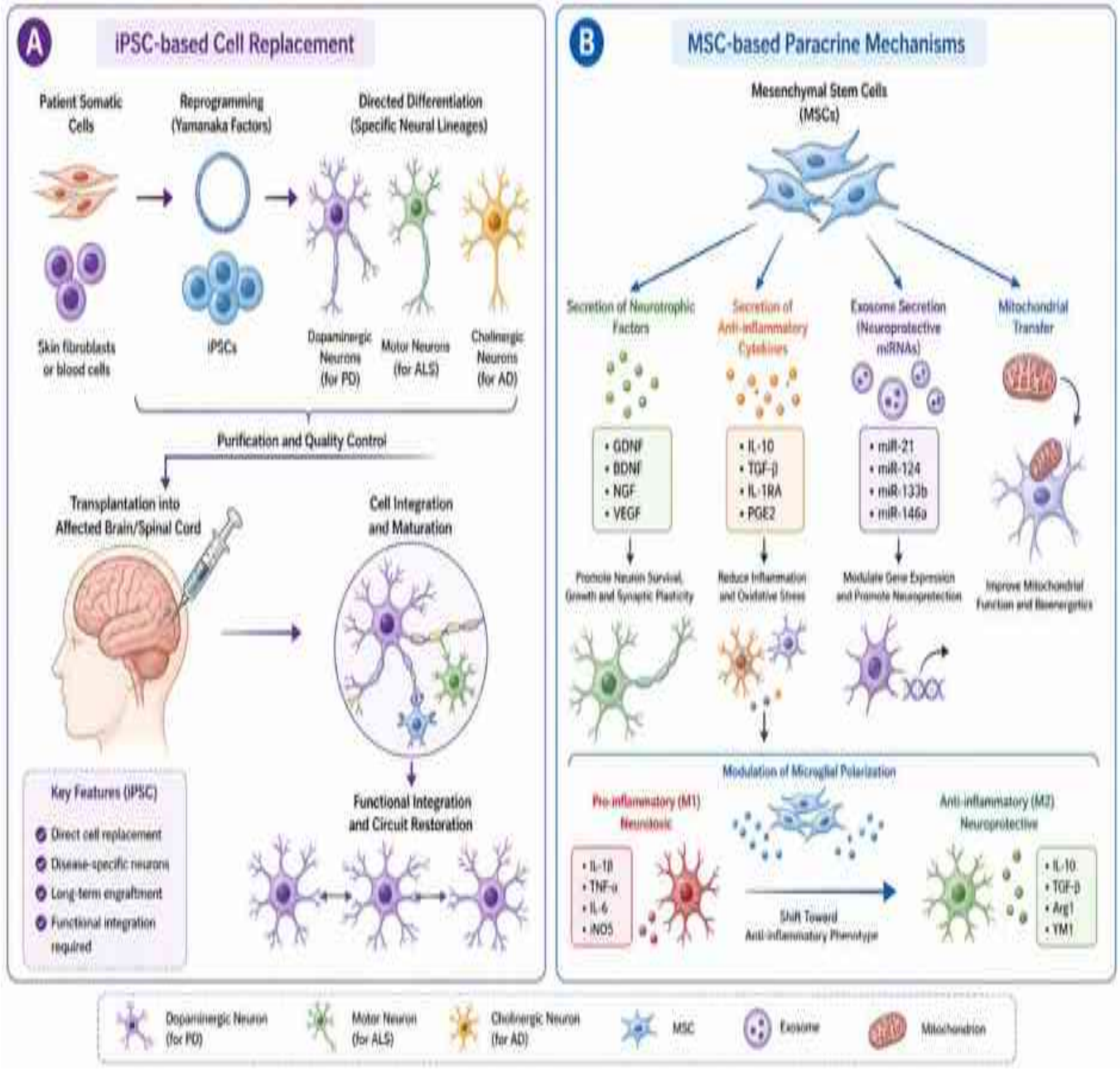
4.3: Comparative Table of Mechanisms

This schematic illustrates the fundamental mechanistic differences between the two stem cell approaches. iPSCs focus on direct cell replacement requiring functional integration into host neural circuits. MSCs operate indirectly through secretion of multiple factors that modify the host environment without replacing lost cells.

Volume 4, Issue 6, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593



Figre 1:

Schematic comparison of iPSC and MSC mechanisms of action in neurodegenerative diseases. (A) iPSC-based cell replacement: patient-derived iPSCs differentiate into disease-specific neurons (dopaminergic for Parkinson's disease, motor neurons for ALS, cholinergic for Alzheimer's disease) and are transplanted to replace lost neurons. (B) MSC-based paracrine mechanisms: MSCs secrete neurotrophic factors (GDNF, BDNF, NGF), anti-inflammatory cytokines (IL-10, TGF-β), and exosomes containing neuroprotective miRNAs, while also transferring mitochondria and shifting microglial polarization from pro-inflammatory M1 to anti-inflammatory M2 phenotype.

Volume 4, Issue 6, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Table 1 is showing a direct side-by-side comparison of key properties relevant to clinical translation for neurodegenerative diseases.

Table 1: Comparison of iPSC and MSC properties for neurodegenerative disease therapy

Property	iPSCs	MSCs
Pluripotency	Yes (pluripotent)	No (multipotent)
Differentiation to neurons	Highly efficient (>70%)	Poor (<5% or non-functional)
Teratoma risk	Yes (requires rigorous quality control)	None
Immune rejection (autologous)	None	None
Immune rejection (allogeneic)	Yes (requires HLA matching or editing)	Minimal (immune-privileged)
Manufacturing time	3-6 months	2-4 weeks
Cost per dose	Very high (50,000−50,000−100,000)	Moderate (5,000−5,000−20,000)
Scalability	High (unlimited)	Moderate (donor-dependent)
Genetic stability	Risk of mutations	Stable
Clinical trials (neuro)	~30	>200

5. Preclinical Evidence by Disease

5.1. Alzheimer's Disease

Induced pluripotent stem cells have been most significant in helping to study Alzheimer's disease to date, not for their therapeutic potential, but for their ability to model disease. iPSC-derived cortical or basal forebrain cholinergic neurons from patients with FAD, carrying mutations in the APP, PS1 or PS2 genes that result in the formation of the neurotoxic amyloid-beta 42 peptide, recapitulate FAD pathologies, such as elevated levels of the amyloid-beta 42 peptide, hyperphosphorylation of tau protein at epitopes bound by antibodies such as AT8 and PHF1(Shi

Frontier in Medical & Health Research
ISSN: (e) 3007-1607 (p) 3007-1593

et al., 2025). Such disease-in-a-dish studies have allowed mechanistic studies and drug screening which would not be possible with post-mortem human tissue. The replacement of cholinergic cell loss in Alzheimer's disease, however, has provided only partial benefits in terms of improved memory, as measured by the Morris water maze, graft survival, and functional integration with host circuits in rodent models of the disease. The long-term efficacy of cell replacement alone is compromised by the continued threat from the persistent disease microenvironment, which includes continued amyloid beta deposition and tau pathology, to both host and transplanted neurons(Jamali et al., 2024). There has been much more work conducted on MSCs in Alzheimer's disease preclinical models (APP/PS1 double transgenic mouse) and in mice that develop both amyloid and tau pathology (the 3xTg-AD). In several independent studies, transplantation of MSCs has been proven to cut the amount of amyloid-beta plaques in the brain by 30-50%, lower tau hyperphosphorylation and dramatically reduce microglial activation markers and the pro-inflammatory cytokines interleukin-1 beta and tumor necrosis factor-alpha(Zeng, 2023b). The positive effects are paralleled by higher levels of the proteins called brain-derived neurotrophic factor and nerve growth factor that help form memory in the hippocampus and cortex, regions of the brain essential to memory. Behavioral tests provide evidence of enhanced cognition in the Morris water maze, novel object recognition and contextual fear conditioning tasks. The route of administration significantly affects therapeutic efficacy; intravenous injection has very low brain penetration due to the trapping of MSCs in the pulmonary microvasculature, intracerebroventricular injection has the most uniform distribution throughout the brain parenchyma, and intranasal delivery of MSCs or secreted products directly to the CNS along the olfactory nerve pathway is a promising minimally invasive route(Brown et al., 2022). Interestingly, several studies have shown that administration of exosomes alone, derived from MSCs, can recapitulate many of the observed neuroprotective and cognitive effects of transplantation with whole cells in models of Alzheimer's disease, indicating that the therapeutic effects of MSCs in Alzheimer's disease models are mediated via the paracrine secretome rather than by direct cellular actions.

5.2. Parkinson's Disease

Perhaps the most advanced use of iPSC technology for any neurodegenerative disease has been in Parkinson's disease, where iPSCs have been used extensively in both disease modeling and cell replacement. Dopaminergic neurons derived from iPSCs of patients with LRRK2 mutations, alpha-synuclein mutations, and Parkin mutations faithfully reproduce the hallmark disease traits such as alpha-synuclein aggregation, mitochondrial dysfunction, and enhanced vulnerability to oxidative stress(Farabi et al., 2024). Midbrain floor plate-based differentiation protocols generate dopaminergic neurons that are authentic with attributes of the substantia nigra pars compacta, such as tyrosine hydroxylase, GIRK2 and aldehyde dehydrogenase 1 family member A1. These cells are successfully transplanted into the striatum of 6-hydroxydopamine-treated or MPTP-treated rodent models, and partially restore function, as measured by decreased amphetamine-induced rotation behavior by 50–70% and increased rotarod and cylinder performance(Cui et al., 2024). Most importantly, in non-human primates, grafted iPSC-derived dopaminergic neurons have been shown to survive for at least two years, to release dopamine, and to improve motor function, which are all key steps toward clinical translation. But, there have been several studies showing a variety of non-teratoma masses that grew over the grafted cells and displaced the normal brain tissue, underscoring the importance of quality control and the removal of any surviving proliferative cells. Mesenchymal stem cells (MSCs) have been tested in both 6-hydroxydopamine and MPTP rodent models of Parkinson's disease, and in transgenic mice overexpressing alpha-Syn(Han, Liu, Gong, Ma, & Sun, 2025). The predominant mechanism seems to be the protection of host dopaminergic neurons, as MSCs protect Tyrosine Hydroxylase

Frontier in Medical & Health Research
ISSN: (e) 3007-1607 (p) 3007-1593

(TH) positive neurons in the substantia nigra and their terminal processes in the striatum, not neuronal replacement. The extent of microglial activation is considerably decreased after MSC treatment, and there is an increase in the levels of dopamine in the striatum, albeit the restoration is partial and usually not to the extent of normalisation, but to 40-60% of that normal level(Marrelli, Paduano, & Tatullo, 2015). There are improvements in behaviour that have been observed consistently, but effects sizes have generally been smaller than those seen with transplantation of iPSC derived dopaminergic neurons. MSCs are also very safe to use, and are free of any reports of tumor formation or graft overgrowth. MSCs and gene therapy with GDNF have shown synergistic effects, in which the MSCs act as delivery vehicles for the trophic factor, and as modulators of the inflammatory microenvironment that may otherwise impair graft survival.

5.3. Amyotrophic Lateral Sclerosis

iPSCs have been remarkably useful to model ALS, with iPSC-derived motor neurons from patients with hexanucleotide repeat expansions in C9orf72, missense mutations in SOD1, or mutations in TDP-43 recapitulating axonal degeneration, protein aggregation, and electrophysiological abnormalities(Estarellas, Gomis, & Canals, 2025). But cell replacement approaches have been hindered by significant challenges; only ten percent of transplanted iPSC-derived spinal motor neurons are detectable at four weeks after transplantation in the SOD1-G93A rat model and there is only modest functional improvement. The very long axonal projections that must reach out from the spinal cord to contact muscles, stretching up to tens of centimeters in humans, represent a tremendous integration problem not addressed in preclinical models. Other strategies have been developed with iPSC-derived astrocytes (iAstrocytes), which have some potential to positively affect neuroinflammation and slightly extend survival, but which do not resolve the underlying issue of motor neuron loss(Estarellas et al., 2025). In the preclinical models of ALS, the properties of MSCs have been studied more in great extent, especially in the transgenic SOD1-G93A mice. MSCs when administered intrathecally or intravenously delay onset of disease for 7-14 days and extend survival by 10-20% over vehicle-treated controls. On histology, lower numbers of motor neurons in the spinal cord, lower numbers of microgliosis and astrogliosis, and higher numbers of glial cell line-derived neurotrophic factor and brain-derived neurotrophic factor are seen in the ventral horn(Verma, Tiwari, Shukla, Singh, & Veeranan, 2026). The positive preclinical findings led to the clinical advancement of an autologous MSC product called NurOwn by BrainStorm Therapeutics. The trial was negative overall, but post-hoc analyses indicated benefit in patients with less severe disease, highlighting the need for patient selection and the challenge of treating patients with more severe disease, where there is already significant motor neuron loss.

5.4. Huntington's Disease

A potential treatment for HD is replacement of medium spiny neurons derived from iPS cells, to restore the balance of neurotransmitters affected by the selective loss of these GABAergic projection neurons. Transplantation of animal models of Huntington's disease into the rodent striatum results in partial functional improvement, including improvement in motor coordination and cognition, yet the survival rate of grafts and integration within host circuits is still difficult(L. Zhang, 2025b). The effect of the secretion of brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor in these cells has also been evaluated, showing that these cells are neuroprotective, as well as demonstrating a reduction in huntingtin aggregate formation and improvement of motor function, though the effect size is small.

5.5. Multiple Sclerosis

Remyelination therapy using iPSC-derived oligodendrocytes has been studied in the context of MS. Transplanted cells can re-myelinate demyelinated axons in animal models, but the

Frontier in Medical & Health Research
ISSN: (e) 3007-1607 (p) 3007-1593

immune-mediated destruction continues, thereby reducing the efficacy of transplantation over the long term(Mondal, Talukdar, & Haque, 2025). There are, however, significant differences in the extent to which MSCs have been studied compared to oligodendrocytes, with the experimental autoimmune encephalomyelitis (EAE) model showing that MSCs decrease disease severity and suppress T-cell proliferation and stimulate the expansion of Tregs through immunomodulatory mechanisms, not necessarily by promoting remyelination.

Table 2 is showing the summarized key preclinical findings across major neurodegenerative diseases. Note the striking absence of direct head-to-head comparative studies a critical gap in the literature.

Table 2: Summary of preclinical studies comparing iPSC and MSC efficacy in neurodegenerative disease models

Disease	Model	iPSC Finding	MSC Finding	Head-to-head?	Winner
AD	APP/PS1 mice	Partial cognitive improvement with cholinergic neuron grafts	30-50% Aβ reduction, improved cognition	No	MSCs (more data)
PD	6-OHDA rat	Functional recovery with dopaminergic neuron grafts (70-80% rotation reduction)	Partial protection (30-40% improvement)	Rare	iPSCs (superior replacement)
ALS	SOD1-G93A mouse	Poor motor neuron graft survival (<10%)	Modest survival extension (10-20%)	No	MSCs (feasibility)
HD	R6/2 mouse	Striatal neuron grafts survive, modest benefit	Reduced aggregates, improved motor	No	Tie
MS	EAE mouse	Oligodendrocyte remyelination	Strong immunomodulation, reduced relapse	No	MSCs (safer, proven)

6. Clinical Trials – Completed and Ongoing

6.1. iPSC Clinical Trials in Neurodegenerative Diseases

In the clinical application of the induced pluripotent stem cell technology to neurodegenerative disorders, most trials have been at the phase I and phase I/II level and were conducted to examine the safety and feasibility of the therapy, with few focusing on efficacy(Velikova, Dekova, & Miteva, 2024). In 2018, pioneering neurosurgeon Jun Takahashi and his team at Kyoto University in Japan

Frontier in Medical & Health Research
ISSN: (e) 3007-1607 (p) 3007-1593

launched the first-in-human trial for iPSC-derived dopaminergic neurons for Parkinson's disease (PD), under ClinicalTrials.gov ID: NCT04802733. The trial uses a technique of generating iPSCs from the somatic cells of each patient and subsequently differentiating these cells into dopaminergic progenitor cells derived from the floor plate of the midbrain that are then stereotactically transplanted into the putamen. Interim results reported at 2 years post-transplantation have shown benefits of mild, clinically relevant motor function improvements, without any evidence of teratoma formation, off-target effects or graft overgrowth(L. Zhang, 2025a). One major drawback of this is the long manufacturing time from skin biopsy to transplant ready cells of three to six months during which patients can continue to progress. A phase I clinical trial involving iPSC derived astrocytes is underway at Cedars-Sinai Medical Center in Los Angeles for amyotrophic lateral sclerosis (ALS) (NCT04731168), for patients with C9orf72 associated disease. In the rationale for the use of astrocytes instead of motor neurons, it was recognised that dysfunction of these astrocytes plays a large role in motor neuron death, and that transplantation of healthy astrocytes could slow the progress of the disease by altering the glial environment(S. Li et al., 2025). The first iPSC trial was for age-related macular degeneration, which was also launched in Japan in 2014, with autologous iPSC-derived retinal pigment epithelium cell sheets being transplanted into patients with AMD with neovascular degeneration. This trial showed that the treatment was clinically safe for the several years that it was followed, but there was some visual improvement in a few patients, and a minor genetic anomaly was discovered in one of the patients that did not cause clinical damage but was a regulatory concern. Taken together, the current situation with iPSC trials for neurodegeneration is that the majority of trials are still in phase I/II and there are none in phase III to date. The major obstacles to faster progress are the very high cost of these drugs (when all regulatory, quality control and manufacturing costs are taken into account, one million dollars or more per patient batch); the absence of standardized Good Manufacturing Practice protocols that can be reliably transferred between institutions; and the high regulatory hurdles posed by concerns over teratoma risk, genomic instability, and off-target differentiation. The generation of allogeneic, off-the-shelf iPSC products from HLA-homozygous donors or genome-edited universal donor cells is a current research field which would significantly in turn cut the expenses and complexity of logistics.

6.2. MSC Clinical Trials in Neurodegenerative Diseases

In contrast to the number of clinical trials conducted with iPSCs which is still very small, mesenchymal stem cells have been assessed in more than two hundred clinical trials and the findings were extensive, supporting the design of larger trials to test efficacy across the whole spectrum of neurodegenerative diseases(Suzuki & Sakai, 2021). In the case of Parkinson's disease, over twenty clinical trials have been finished or are currently underway, including some of the larger trials that have been registered such as NCT01446614, NCT02611167, and NCT03356886. These trials have involved several routes of delivery of MSCs including intrastriatal injection directly into the putamen, intravenous infusion into the peripheral circulation, and intranasal administration via atomizing devices. Overall, the results show a very good safety profile with no reports of teratoma or malignancy related to MSCs and there is moderate to moderate improvement in the Unified Parkinson's Disease Rating Scale (UPDRS) scores, usually between 20 and 40 percent, over baseline but this can fade over time as the disease progresses(Che Shaffi, Hairuddin, Mansor, Syafiq, & Yahaya, 2024). The most extensively studied indication for MSC therapy is amyotrophic lateral sclerosis (ALS), with more than thirty clinical trials having been performed. The most advanced product in this area is NurOwn, an autologous MSC product that is differentiated towards a neurotrophic factor-secreting phenotype through culture in specially formulated media before injection, developed by

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

BrainStorm Therapeutics. Phase III trial NCT03280056 involved more than 200 patients and results demonstrated that the trial failed to meet the primary endpoint of a statistically significant benefit for the overall population in the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised. Pre-specified subgroup analyses showed a clinically relevant effect in patients with early disease and less severe disease, suggesting that the therapeutic window for MSC intervention in ALS may be limited to less severe disease and future trials should be enriched with less severe cases. It has not been approved by FDA or EMA and additional research is needed. In the case of MS, over 50 clinical trials have shown that MSCs are safe and well tolerated and have seen small reduction in relapse rates and improvements in the Expanded Disability Status Scale in some trials, including the large international study called MESEMS (NCT01854957). The effect sizes are still small, however, and none of the MSC products have been approved yet. Fifteen or more of the clinical trials have been completed for Alzheimer's disease, with most showing mild cognitive improvement on the Alzheimer's Disease Assessment Scale-Cognitive Subscale and the Mini-Mental State Examination; there is no evidence of any disease-modifying effects(J. Zhou et al., 2026). It should be noted that the FDA has approved two MSC products to date, one for non-neurological indications in children for the treatment of graft-versus-host disease after allogeneic stem cell transplant (ALST) and another for Crohn's disease, perianal fistulas (Alofisel). The pathway to regulation is still difficult and although the safety profile is encouraging, the efficacy in neurodegenerative disease still needs to be fully established.

6.3. Comparative Clinical Trial Landscape

This line graph illustrates the dramatic difference in clinical translation progress between the two cell types. MSCs have a 10-15 year head start and far more extensive clinical experience, while iPSCs are only recently advancing beyond early-phase safety trials.

Volume 4, Issue 6, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

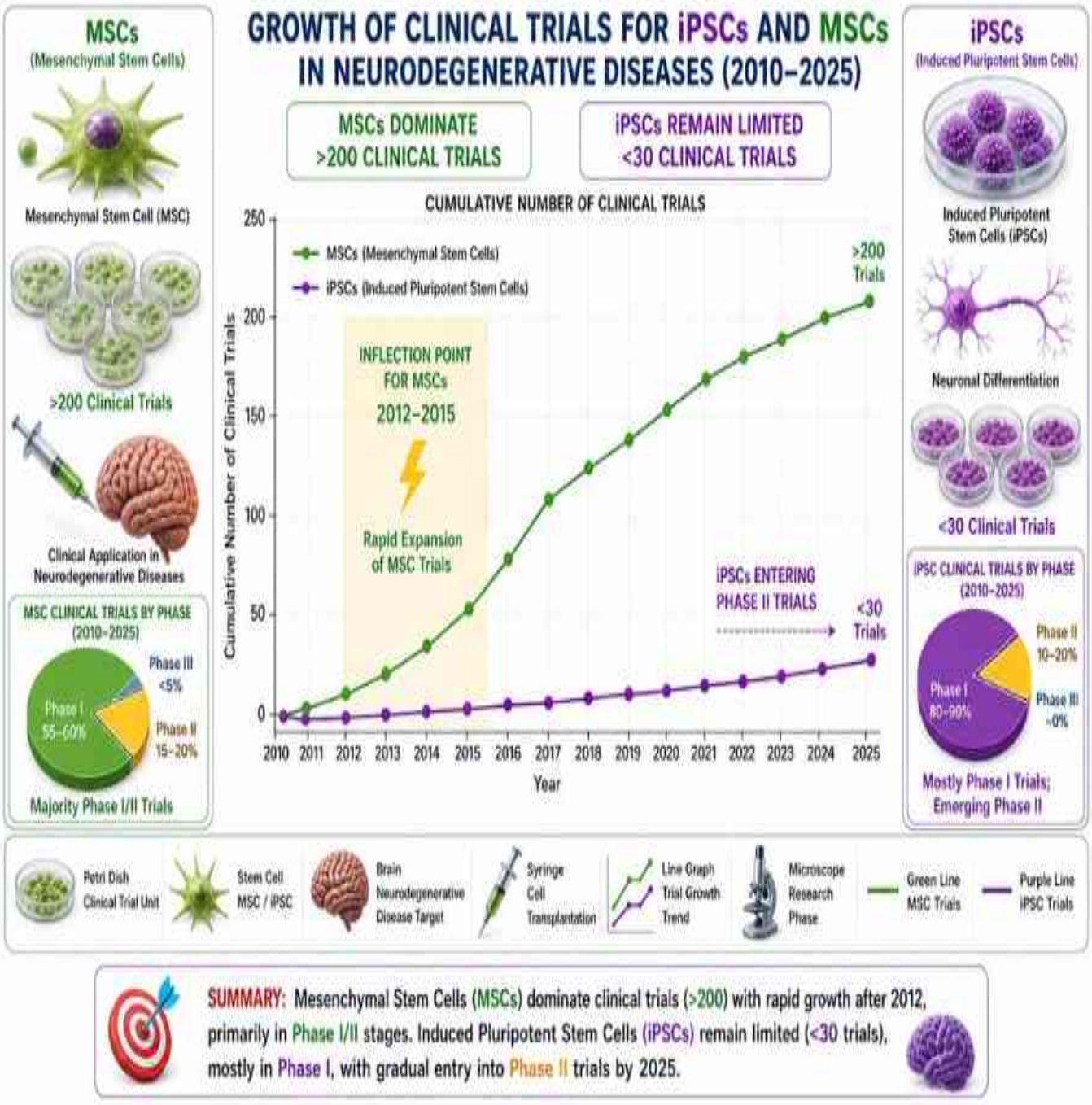


Figure 2: Growth of clinical trials for iPSCs and MSCs in neurodegenerative diseases (2010-2025).Cumulative trial count shows MSCs dominating with over 200 trials compared to fewer than 30 for iPSCs. Most MSC trials are phase I/II; iPSCs are mostly phase I. The inflection point for MSCs occurred in 2012-2015; iPSCs are only now entering phase II trials.

Frontier in Medical & Health Research
ISSN: (e) 3007-1607 (p) 3007-1593

The table 3 is showing the representative clinical trials demonstrating the relative maturity of MSC trials (phase II/III) compared to iPSC trials (phase I/II). Note that no iPSC product has advanced to phase III for neurodegeneration.

Table 3: Selected completed and ongoing clinical trials for iPSCs and MSCs in neurodegenerative diseases.

Disease	Cell Type	Sponsor	Phase	NCT Number	Status	Primary Outcome
PD	iPSC-derived dopaminergic neurons	Kyoto University	I/II	NCT04802733	Active, not recruiting	Safety (2 years)
PD	BM-MSC	Hadassah	II	NCT01446614	Completed	UPDRS improvement
PD	AD-MSC	Medipost	I/IIa	NCT02611167	Completed	Safety, motor function
ALS	iPSC-derived astrocytes	Cedars-Sinai	I	NCT04731168	Recruiting	Safety
ALS	MSC (NurOwn)	BrainStorm	III	NCT03280056	Completed	ALSFRS-R (missed primary)
AD	UC-MSC	Nature Cell	I/II	NCT03117738	Completed	Cognitive function (ADAS-cog)
MS	BM-MSC	MESEMS consortium	II	NCT01854957	Completed	Relapse rate

7. Safety and Ethical Considerations

7.1. iPSC Safety Concerns

While induced pluripotent stem cells are a promising clinical tool in the treatment of neurodegenerative diseases, there are several important safety issues that have hindered their widespread use. The greatest threat is that of teratoma formation from the presence of residual, undifferentiated pluripotent cells which do not follow the differentiation protocol and remain in the preparation for transplant(RASTOGI, 2026). A few undifferentiated iPSCs (e.g., a thousand

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

among millions of differentiated progeny) will form teratomas in immunocompromised hosts. Depending on their location and growth rate, these tumours may lead to a significant level of morbidity and consist of disorganized tissue from all three embryonic germ layers, including cartilage, muscle, epithelium and neural tissue. There are a number of risk mitigation strategies that have been created. To reduce the number of undifferentiated cells prior to transplantation, the cells can be sorted using flow cytometry to remove those that express surface pluripotency markers like SSEA-4, Tra-1-60 and Tra-1-81, but this will increase the cost of the procedure and decrease cell yield(C. Wang, Ge, Ge, Xu, & Jiang, 2025). Using genetic modification of cells, the genome of the iPSC can also be modified to contain suicide genes, such as the inducible caspase-9 gene that can be activated after the small molecule dimerizer is administered—this method would remove any cells that still have pluripotency, but would require genetic modification of the cells and has not yet been used in clinical trials. Rigorous terminal differentiation protocols together with comprehensive quality control testing, are most commonly used to guarantee no detectable pluripotent cells are present in the end product. Another critical safety issue for iPSC-based therapies is genomic instability. Copy number variations resulting from duplications and deletions of chromosomal segments and single nucleotide mutations across the genome can be induced by the reprogramming process(Chen & Li, 2025). The extended culture period needed to generate adequate cell populations for transplantation allows for the selection of cells containing mutations in oncogenes to be selected for. In cultured iPSCs the mutations of the TP53 tumour suppressor gene, which encodes p53, a protein that acts as a genome guardian, have been frequently observed, and these mutations provide a considerable growth advantage that could lead to malignant transformation. It is therefore critical that the iPSC lines are pre-screened prior to advancing to clinical use by either whole genome sequencing or high-density single nucleotide polymorphism (SNP) arrays. Differentiation from the desired cells types (off-target differentiation) may also occur in some cells within the graft despite the protocol used to induce them to differentiate into neural cells(Kumari, 2024). This may lead to neural differentiation protocols producing neural crest derivatives like Schwann cells, smooth muscle cells or melanocytes, which may affect the normal architecture of the tissue, or lead to functional problems. The safety considerations of allogeneic (from a healthy donor) use of iPSCs are added. In this situation suppression of the immune system is needed to prevent rejection of the transplanted cells because the donor cells are expressing foreign major histocompatibility complex molecules. Medications used to suppress the immune system have other side effects such as susceptibility to opportunistic infections, kidney damage and an enhanced risk of cancer(Al-kharboosh, Perera, Bechtle, Bu, & Quinones-Hinojosa, 2022). This is the reason that the development of HLA-homozygous iPSC banks has become a promising approach to overcome the challenge. In Japan, there is a bank of ten carefully selected HLA-homozygous lines which are thought to be sufficient to give a full HLA matching for about eighty percent of the Japanese population, which means that many patients can be transplanted without the need of immunosuppressive treatment. Similar banks are under development in other countries. iPSC therapy is expensive, which poses deep ethical questions. The current estimate of manufacturing cost per patient batch is between five hundred thousand to one million dollars, if regulatory compliance, quality control and Good Manufacturing Practice expenses are included(S. Yang et al., 2026). This price means that equitable access to medical innovation is also raised, as these treatments would only be accessible for patients in rich countries or those who have comprehensive insurance coverage, which could further contribute to existing health inequalities.

7.2. MSC Safety Concerns

Unlike the concerning safety profile of iPSCs, MSCs have an outstanding clinical safety record in

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

thousands of patients treated in clinical trials and commercial use. The risks of MSC therapy are very low. and generally manageable(Duda & Samiec, 2025). Thrombotic events, such as pulmonary embolism and myocardial infarction, have been observed after very high doses of MSCs (typically > two hundred million cells/IV infusion). The events are believed to be due to the relative large size of MSCs leading to occlusion of the microvessels, especially in patients with cardiovascular disease or hypercoagulable conditions. The risk can be reduced by reducing cell dose, slower infusion rates, and by screening patients for risk factors. The most frequent side effect of MSC therapy is transient fever which happens in about 10–20 percent of patients(Terzic & Nelson, 2013). This reaction is believed to be a consequence of the very rapid release of pro-inflammatory cytokines after infusion, and is usually transient and self-resolving, lasting just 24 to 48 hours unless specifically treated. In rare cases, ectopic tissue formation including ossification or cartilage formation where injection of the MSCs was performed in muscle or non-skeletal sites has been reported. But the frequency is extremely rare, and clinical signs of clinically important ectopic tissue are not reported in the central nervous system. Most importantly, MSCs do not pose any teratoma risk whatsoever since they are multipotent and not pluripotent and therefore cannot form the wide array of tissues necessary for teratoma formation(Terzic & Nelson, 2013). The MSCs have a very favourable allogeneic safety profile. To date, more than 10,000 patients have been infused with allogeneic MSCs in clinical trials and commercially, with no significant rejection events reported. The remarkable finding can be explained by the immune privileged status of MSCs, expressing only low levels of major histocompatibility complex class I molecules, and class II molecules under standard culture conditions. MSCs are also missing the co-stimulatory molecules (CD80 and CD86) that are necessary for naive T cell activation(Gordiienko, Shamshur, Novikova, Zlatskiy, & Zlatska). A worrisome literature, however, has come out indicating that MSCs could promote the growth of pre-existing tumors by their paracrine activities. Vascular endothelial growth factor, hepatocyte growth factor and transforming growth factor-beta are the same growth factors and immunomodulatory molecules that promote the survival of compromised neurons that can also promote tumour cell proliferation, angiogenesis and immune evasion. There is a theoretical concern of this which has to be approached with careful patient selection and exclusion of patients with active malignancies from MSC trials, and careful long term monitoring for emergence of occult malignancies(Mehdizadeh, Mamaghani, Hassanikia, Pilehvar, & Ertas, 2025). But when patients are carefully chosen and monitored, the safety of MSCs is still far greater than that of iPSCs, and that's why clinical trials using MSCs have progressed far more than trials using iPSCs.

Frontier in Medical & Health Research
ISSN: (e) 3007-1607 (p) 3007-1593

7.3. Ethical Comparison

Table 4 is showing that both cell types have favorable ethical profiles compared to embryonic stem cells, but iPSCs face greater safety-related ethical concerns (teratoma, genomic instability) and cost-related access issues.

Table 4: Ethical and safety comparison of iPSCs and MSCs

Ethical Issue	iPSCs	MSCs
Source tissue ethics	No fetal/embryo tissue (somatic cells) – minimal concern	Adult tissue, birth products – minimal concern
Teratoma risk	Yes – major safety barrier	No
Genomic instability	Yes – requires screening	Minimal
Immunosuppression needed	Autologous: no; Allogeneic: yes (HLA matching)	Allogeneic: no (immune-privileged)
Donor variability	Yes (line-specific)	Yes (age, source)
Regulatory approval pathway	Complex (new class)	Established (biologic)
Equitable access	Very expensive – potential two-tier medicine	Moderate cost – more accessible

8. Comparative Analysis – iPSCs vs MSCs Head-to-Head

8.1. Efficacy Comparison

It is important to understand that these two cells types (iPS cells and MSC) have different mechanisms of action when considering their use in treating neurodegenerative diseases, and direct comparisons of efficacy should be interpreted in the context of the particular therapeutic target. As for direct cell replacement, iPSCs are definitely better than MSCs(Hoang et al., 2025). Directed differentiation of the iPSCs into those specific neurons allows replacement of the corresponding neuronal population in each disease model, such as dopaminergic, motor, cholinergic, or striatal medium spiny neurons. They have been shown to extend axons over long distances, to form functional synapses with host neurons, and to restore neurotransmitter release in denervated target regions, in both rodents and non-human primates. By contrast, MSCs have no significant ability to differentiate into functional neurons under any protocol, and cannot replace lost populations of neurons(Drobiova et al., 2023). However, MSCs do an outstanding job when it comes to neuroprotection. They also secrete a large amount of neurotrophic factors, such as glial cell line-derived neurotrophic factor, brain-derived neurotrophic factor, nerve growth factor, and ciliary neurotrophic factor that foster the survival of surviving endogenous neurons and potentially slow the progression of the disease. The paracrine activity of MSCs is significantly stronger than that of iPSC-derived cells, especially astrocytes differentiated from iPSCs, and has been more extensively characterized. Compared to iPSCs,

Frontier in Medical & Health Research
ISSN: (e) 3007-1607 (p) 3007-1593

MSCs make for a much better immunomodulation. MSCs can directly modulate the function of immune cells via both contact-dependent and soluble mediator (such as prostaglandin E2, transforming growth factor-beta and interleukin-10) pathways(Waller, Neely, & Caron). They inhibit microglial activation, transform macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, enhance the numbers of regulatory T cells, and decrease the production of pro-inflammatory cytokines such as interleukin-1 beta, interleukin-6 and tumor necrosis factor-alpha. Theoretically, iPSCs can be differentiated to microglia-like cells which may have some immunomodulatory potential, but this process still has to be carried out at the preclinical level and has not yet been clinically translated(Matsuoka, Itohara, Hara, & Kobayashi, 2024). In terms of disease modification, both cell types have shown disease modifying properties in animal models; however, MSCs have significantly more clinical evidence of disease modification properties, because of more than two hundred clinical trials reporting functional outcomes, biomarker changes and survival. Overall, the effectivity comparisons suggest that iPSCs and MSCs have different optimal therapeutic applications, and that the two are not universally more effective than the other.

8.2. Safety Comparison

There is a huge difference between the safety profiles of iPSCs and MSCs, and this is likely to be a key determinant of the relative timelines for clinical translation. IPSCs have high endogenous risks that can be mitigated with time-consuming and expensive measures(Wu, Ahmad, Lin, Carbonneau, & Tran, 2023). Even with careful quality control, there is a risk that a few pluripotent cells might be missed and develop into a teratoma, the worst problem. Other risks such as copy number variations and mutations in oncogenes, such as TP53 and MYC, also exist and require thorough pre-screening of each cell line before clinical use. Each of these mitigation measures is costly and complicated, such as flow cytometry sorting, genomic sequencing, and careful in vitro and in vivo safety testing, but they can be managed to ensure product safety(Shim, 2025). As a comparison, the inherent risk of mesenchymal stem cells is very low. There is no teratoma risk, a basic safety benefit of their multipotent and not pluripotent nature. MSCs are not prone to genomic instability even following extended culture expansion and no MSC product has ever been linked to malignant transformation of the cells. The most frequently occurring adverse effects include mild fever and, in the high intravenous doses, infrequent thrombotic complications which can be easily controlled by patient monitoring and dosage modification. Ectopic tissue formation has been reported and is very rare and only in isolated case reports(Byun, 2026). The safety comparison suggests that there is a fundamental trade-off between the therapeutic ambition of iPSCs and the risk of their use, and the therapeutic profile of MSCs is safer, but less ambitious.

8.3. Practicality and Scalability

MSCs are also very useful from a practical and scalable point of view compared to iPSCs. An autologous iPSC approach is a treatment method that involves a customized manufacturing process, which takes 3-6 months from skin biopsy to the preparation of transplant-ready cells for each patient. The cost is very high, and today estimates run from five hundred thousand dollars to one million dollars per batch of patients(Kim, Lee, Kwon, Han, & Choi, 2026). Allogeneic iPSC banks based on HLA-homozygous donor lines have potential to provide off-the-shelf iPSC that could significantly lower the cost of the iPSC, however, the initial investment will be significant and each line will need to be well characterized and tested for safety before they can be released for clinical use. The manufacturing lead time also makes for delayed treatment for patients who need it – they have to wait months while the disease continues to run its course. MSCs, on the other hand, can readily be obtained as off-the-shelf allogeneic products. Thousands of patient doses can be made from a single donor MSC line,

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

cryopreserved and sent to clinical sites globally, where they can be rapidly used(Moreira, Kahlenberg, & Hornsby, 2017). The manufacturing process, from thaw to infusion, takes days, not months, and the expense of each dose is estimated to be five thousand to twenty thousand dollars, which is orders of magnitude cheaper than the cost of each dose of autologous iPSCs. This practicality benefit is what has enabled the enrolment of significantly more patients for the MSC trials than the iPSC trials and to progress much quicker.

8.4. Regulatory Status

MSC is far more well-regarded than induced pluripotent stem cells. MSC products have been approved by the European Medicines Agency (EMA) and the United States Food and Drug Administration (U.S. FDA) for non-neurological indications such as Prochymal for pediatric graft-versus-host disease, and Alofisel for perianal fistulas in Crohn's disease(Kruczek & Swaroop, 2020). These approvals set a precedent for approval processes for neurological indications and offer a regulatory path for future approvals in other therapeutic areas. However, no product has yet been approved for a particular indication in any country globally for iPSCs. All of the iPSC lines need to be extensively characterized prior to clinical application, which requires genome stability testing, pluripotency testing and teratoma risk assessment. The pathway is still new and complex, and there are no precedents to assist sponsors in regulating the pathway. process. Such regulatory uncertainty is a big hurdle for investing in iPSC-based therapies and will be a huge impediment in bringing such therapies to market for many years.

8.5. Complementary Roles – Not Either/Or

This decision tree proposes that the choice between iPSC and MSC therapy should be guided by disease stage and therapeutic goal. No single cell type is optimal for all patients or disease stages, suggesting complementary rather than competitive roles

Volume 4, Issue 6, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Figure 3: Proposed complementary clinical algorithm for selecting iPSC versus MSC therapy based on disease stage and goal. Early-stage disease with minimal cell loss – MSC-based neuroprotection and immunomodulation. Late-stage disease with substantial cell loss – iPSC-based cell replacement. Combination therapy (MSCs to prepare microenvironment, followed by iPSC grafts) may be optimal.

9. Challenges, Limitations, and Future Directions

9.1. Major Challenges Remaining

Although considerable efforts have been undertaken in the area of developing stem cell-based therapies for neurodegenerative disorders, there are still important and distinct challenges to overcome before such methods can be adopted in a clinical set-up. One of the most tough challenges for iPSCs is graft survival(Karima & Kim, 2024). Preliminary experiments have repeatedly shown that less than 10% of the iPSC-derived neurons survive at 6 months after injection and most of these cells die within the first few weeks after transplantation because they are mechanically damaged during the injection, are exposed to

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

oxidative stress, and are subject to inflammatory responses and withdrawal of trophic support. This poor survival rate requires the injection of many more cells than remain, adding to the production costs and the risk of adverse events from the actual injection process. Despite the fact that only a very small percentage of grafted cells survive, there is still very little successful integration of these cells into host neural circuits(Liu & Cheung, 2020). Electrophysiological experiments indicate that transplanted iPSC-derived neurons are able to generate action potentials, but they make significantly fewer contacts with host neurons, and they receive fewer afferent inputs than endogenous neurons do. The lack of complete synaptic integration could lead to expression of neurotransmitter molecules diffused beyond anatomically appropriate synapses, with corresponding non-physiological signalling and side-effects. In addition, the disease microenvironment continues to exist in the host brain, but not in the transplanted brain. Progressive deposition of amyloid-beta in AD keeps creating a toxic environment for both host and transplanted neurons, whereas progressive aggregation of alpha-synuclein has been observed from host to grafted cells in autopsied patients who received transplants of fetal dopaminergic cells decades prior to death in PD, and inflammatory and excitotoxic environment continues to threaten motor neuron survival in ALS(D. Li, Zou, & Zhao, 2025). This chronic disease will create an unfriendly environment for the iPSC grafts to grow, and may continue to harm them over time, necessitating repeat transplantation or the combination with other disease modifying therapies. Large-scale manufacturing of iPSC-based therapies is very challenging. The creation of each autologous iPSC line takes hundreds of thousands of dollars and more than three to six months to develop, and requires a somatic cell sample from a patient. Requirements for extensive quality control testing such as genomic stability screening, pluripotency validation, teratoma risk assessment and sterility testing increase additional time and cost. Despite the use of HLA-homozygous donor lines via allogeneic strategies, the process of large scale expansion under Good Manufacturing Practice (GMP) conditions is still technically challenging and expensive. The variability seen from one cell line to another in a patient and even between clones of the same reprogramming can cause problems with standardisation of iPSC products. This clonal variability is due to chance integration site, epigenetic changes and mutations that occur throughout culture and makes it virtually impossible to develop a true standardized off-the-shelf product. Neurological therapies based on iPSCs are yet to find regulatory approval anywhere in the world and their path is unclear. There have been legitimate concerns regarding the risk of teratoma formation and the safety of genetically manipulated cells raised by regulatory agencies, along with the question of genomic instability. Without an approved product, there is a high risk of poor return for investors as well as postponed clinical translation. Current estimates of the production cost of manufacturing autologous iPSC are over half a million dollars per dose, which would make these cells unaffordable for even the most generous health care systems, and would pose serious ethical issues about fairness in access(A. Y. L. Wang, Kao, Liu, & Loh, 2025). The challenges for MSCs are other and also extremely serious. Survival of MSCs after transplantation is not relevant to this construct as these cells do not survive in the brain after being transplanted. Several studies have shown that MSCs are not detected in circulation for days to weeks after their injection, intravenously, intracerebrally or intrathecally. It remains to be seen whether such short-term effects have a therapeutic value as well, as their paracrine effects may last after a while, but repeated administration of dosing may be required for sustained therapeutic benefit. The repetitive administration will add costs, multiple invasive procedures, and risk of adverse events like infection or immune sensitization. The microenvironment is not an inviolable barrier for MSCs, on the contrary the disease microenvironment is dynamically modified by MSCs by secreting trophic factors and immunological activities. The extent of the ability

Frontier in Medical & Health Research
ISSN: (e) 3007-1607 (p) 3007-1593

of MSCs to mediate the most aggressive stages of brain inflammation and protein aggregation is not clear, and as the disease progresses, the most severe stages may hinder even the most powerful MSC-mediated protection. Scaling manufacture of MSCs is more practical than iPSCs in which the allogeneic, off-the-shelf, products can be made from a single extensively characterized donor line and stored for global distribution. The manufacturing process takes only weeks, not months, and the cost of each dose is estimated at about twenty thousand dollars, which is ten times less than for autologous iPSCs. Despite the establishment of minimal criteria by the International Society for Cellular Therapy, however, standardization is still a great challenge. The secretory profile, immunomodulatory activity and production of neurotrophic factors of MSCs from various donors and tissues, as well as various passages of the same donor origin, differ significantly(Staniowski, Zawadzka-Knefel, & Skośkiewicz-Malinowska, 2021). There are very little assays that predict clinical efficacy (potencies) and batch-to-batch variability makes regulatory approval difficult. No MSC product has been approved for any neurodegenerative disease, although MSCs have been approved for other uses such as graft-versus-host disease and perianal fistulas in Crohn's disease. Allogeneic off-the-shelf MSC products have a more promising business model than iPSCs, and efficacy in the field of neurology is yet to be proven, while reimbursement is still unclear.

9.2. Emerging Strategies

The existing stem cell strategies have encouraged the emergence of several novel strategies that seek to improve safety, efficacy and scalability for clinical translation. The most promising progress is the development of the off-the-shelf induced pluripotent stem cells from HLA-homozygous donors. If donors are made homozygous at the major histocompatibility complex loci, a bank of ten to twenty carefully typed lines can theoretically give an exact match, i.e., a full HLA match, to eighty to ninety per cent of the population, making allogeneic transplantation without immunosuppression possible. The cost and manufacturing time is decreased to a remarkable extent compared to autologous iPSCs, since the same well-characterized cell line can be used to treat thousands of patients. Based on this, researchers have now succeeded in creating universal iPSC lines by knockout of the beta-2-microglobulin gene and the class II major histocompatibility complex transactivator gene, which removes the expression of both class I and class II HLA molecules, and makes them invisible to the host immune system(de Laorden, Rodilla, Arroyo-Hernández, & Iglesias, 2025). This universal donor cell type could then be given to any patient, irrespective of their HLA type, which is the ideal off the shelf product. An even more radical proposal to replace conventional cell transplantation is the use of iPSC-derived exosomes or isolated mitochondria in place of cells. These acellular strategies are free of the inherent limitations of genome instability, immune rejection and formation of teratoma, and may retain many of the therapeutic benefits. The nano-sized extracellular vesicles (exosomes, 40-150 nm in diameter) are thought to carry a large load of microRNAs, messenger RNAs, and proteins that can alter gene expression in recipient neurons and glial cells. As exosomes are able to enter the brain upon systemic administration, they represent an alternative to intracranial injection, which is less invasive. Likewise, the direct delivery of isolated functional mitochondria to injured neurons is being investigated as a potential approach to re-establishing the bioenergetic function of the cell in degenerative diseases associated with mitochondrial dysfunction(Guo, Dong, Liu, Liu, & Wang, 2026). Another advanced strategy to therapeutic efficacy is to engineer mesenchymal stem cells. The immunomodulatory and paracrine effects of MSCs together with the targeted delivery of strong neurotrophic factors can be achieved by genetically modifying MSCs to over-express glial cell line-derived neurotrophic factor (GC-gDNF) or brain-derived neurotrophic factor (BDNF). This 'hybrid therapy' can be called cell-mediated gene therapy and has yielded synergistic effects in pre-clinical

Frontier in Medical & Health Research
ISSN: (e) 3007-1607 (p) 3007-1593

models of Parkinson's disease and amyotrophic lateral sclerosis. Additionally, MSC-derived EVs can be loaded with exogenous therapeutic molecules, including small interfering RNAs and therapeutic molecules that are neuroprotective, to serve as drug delivery vehicles that utilize the natural targeting properties of MSC exosomes. An intellectually attractive but largely untested approach is combination therapy in which MSCs are first delivered to minimize neuroinflammation, which creates a more permissive microenvironment for neural grafts derived from iPSCs for delivery for neural replacement. It is thought that the inflamed and hostile brain microenvironment is responsible for a decreased survival rate of transplanted brain grafts and poor neuroplastic integration of implanted neurons and a preconditioning with MSCs could decrease the microglial activation in the brain, reduce oxidative stress, and increase levels of neurotrophic factors that would promote the survival and functional integration of the subsequent transplanted iPSC-derived neurons(Cai et al., 2020). The development of biomaterial scaffolds, such as hydrogels and nanofibers, that will improve graft survival and integration by providing mechanical support and releasing growth factors, as well as minimizing mechanical damage at the time of grafting, is also underway. So far the most futuristic is in vivo reprogramming in which endogenous glial cells (such as astrocytes or NG2+ progenitors) are directly transdifferentiated into functional neurons in the brain using viral vectors encoding neurogenic transcription factors. This approach does not require cell transplantation, avoiding all risks of ex vivo cell production and delivery to the graft. The ability to reprogram astrocytes in the striatum into neurons, with some efficiency, to extend axons to appropriate targets and enhance motor function has been shown in proof-of-concept studies in mouse models of Parkinson's disease and Huntington's disease, but the stability of the reprogrammed neurons over time is not known and their efficiency is still low.

9.3. Key Unanswered Questions

While great strides have been made, there are some important questions that remain to be answered before stem cell therapies can be systematically utilized for the treatment of neurodegenerative diseases. The best stage of disease for optimal success with either cell type is not yet known, and some studies suggest that the most vulnerable stage of disease is early, when there is still a large population of endogenous neurons left to protect, whereas cell replacement using iPSCs might only be used at a much later stage, once a significant amount of neurons have already been lost(Khodadoust et al., 2023). There is no definite dose-response relationship, and the minimal effective dose of MSCs has not yet been defined; clinical trials have employed from ten million, up to two hundred million cells per patient. Long term survival of iPSC-based grafts in the human brain is not known, since the longest follow-up for clinical trials is only 2-3 years. Whether the beneficial effects of MSC last beyond the disappearance of the transplanted cells remains unclear; however, recent evidence suggests that the beneficial effect of MSC may leave a biological memory that persists beyond the lifespan of the parent cells. There is no ability to predict individual patient response to stem cell therapy (genetic, biomarker, or imaging). Last, but by no means least, the potential for combination therapies using both MSCs and iPSCs to generate more than additive therapeutic effects has not been extensively explored in any preclinical model.

9.4. Roadmap for the Next Decade (2025 to 2035)

A realistic plan for the next decade is to picture a series of coordinated milestones. To minimize the variability between batches, long-term safety follow-up data should be published and ongoing phase II trials completed during the first 3 years; with particular focus on the standardization of MSC potency assays(Artamonov, Pyatakovich, & Minenko, 2024). By years 3–5, the first phase II trials of iPSC treatment in Parkinson's will be finished and iPSC banks will be created in several countries. From year 5 to 7, the field will start the

Volume 4, Issue 6, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

first head-to-head iPSC versus MSC clinical trial, which will probably be in moderately advanced Parkinson's disease, and will progress the development of MSC-engineered exosome products to be delivered intranasally. In years 7–10, the first regulatory approval of an MSC product for either Alzheimer's disease or amyotrophic lateral sclerosis (ALS) is feasible and the beginning of the first phase III iPSC trial is This timeline visualizes the expected progress of stem cell therapies over the next 10-15 years, possible. In more than 10 years, the use of personalized therapy, which combines MSC and iPSC, may be possible, and treatment may be defined by patient-specific biomarkers, ranging from stage of the disease, genetic profile and inflammatory status, in order to select the best cell type, dose, and route of administration for each patient.

highlighting the more advanced position of MSCs and the later, but accelerating, trajectory of iPSCs

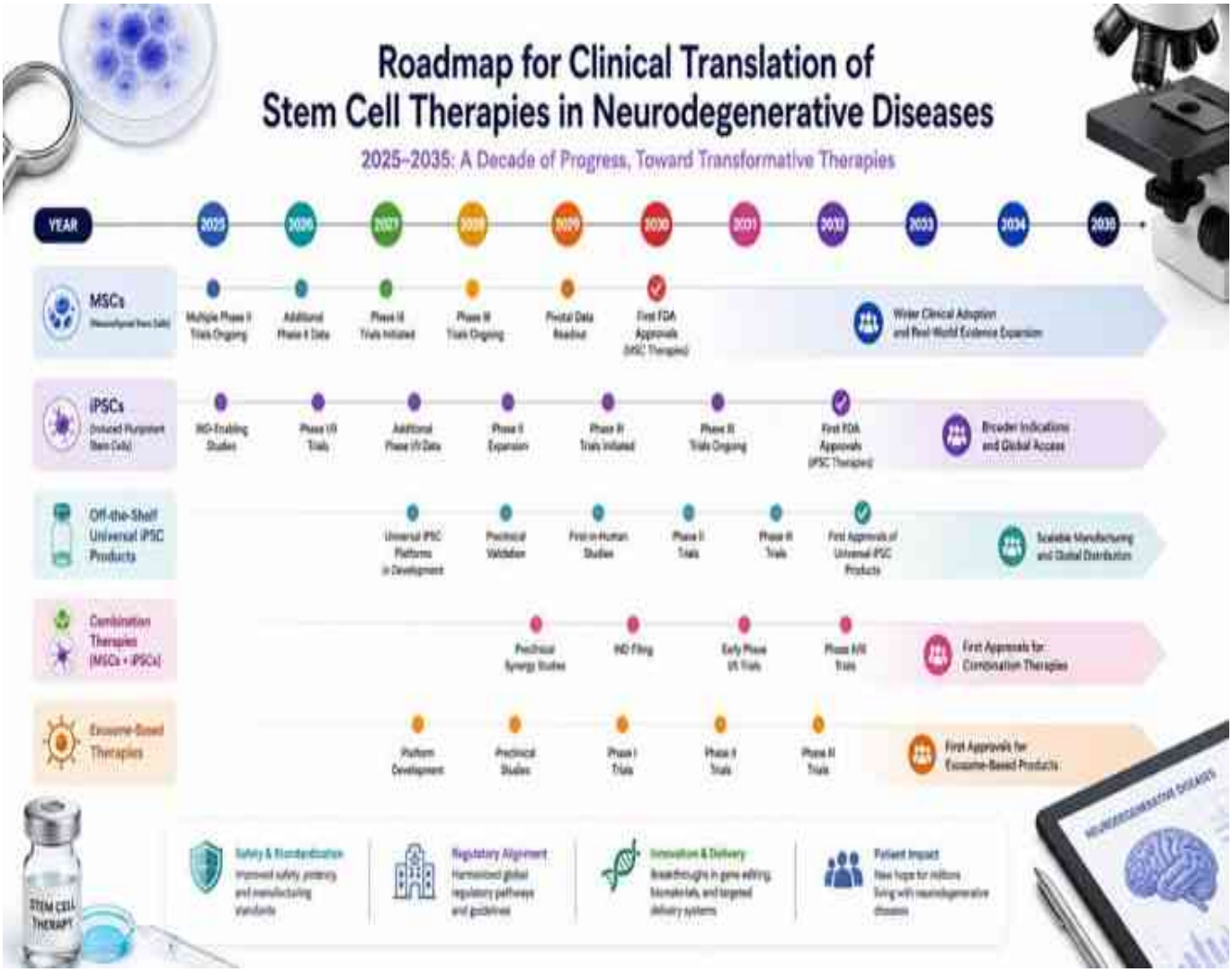


Figure 4: Roadmap for clinical translation of stem cell therapies in neurodegenerative diseases (2025-2035).* Projected milestones include completion of phase II/III MSC trials, advancement of iPSCs to phase III, emergence of off-the-shelf universal iPSC products, and first FDA approvals. Combination therapies and exosome-based products are expected to enter trials in the later part of this decade.

Frontier in Medical & Health Research
ISSN: (e) 3007-1607 (p) 3007-1593

This figure proposes a novel combination strategy where MSCs prepare the diseased microenvironment before iPSC grafting. No clinical trials have yet tested this approach, representing a major opportunity for future research.

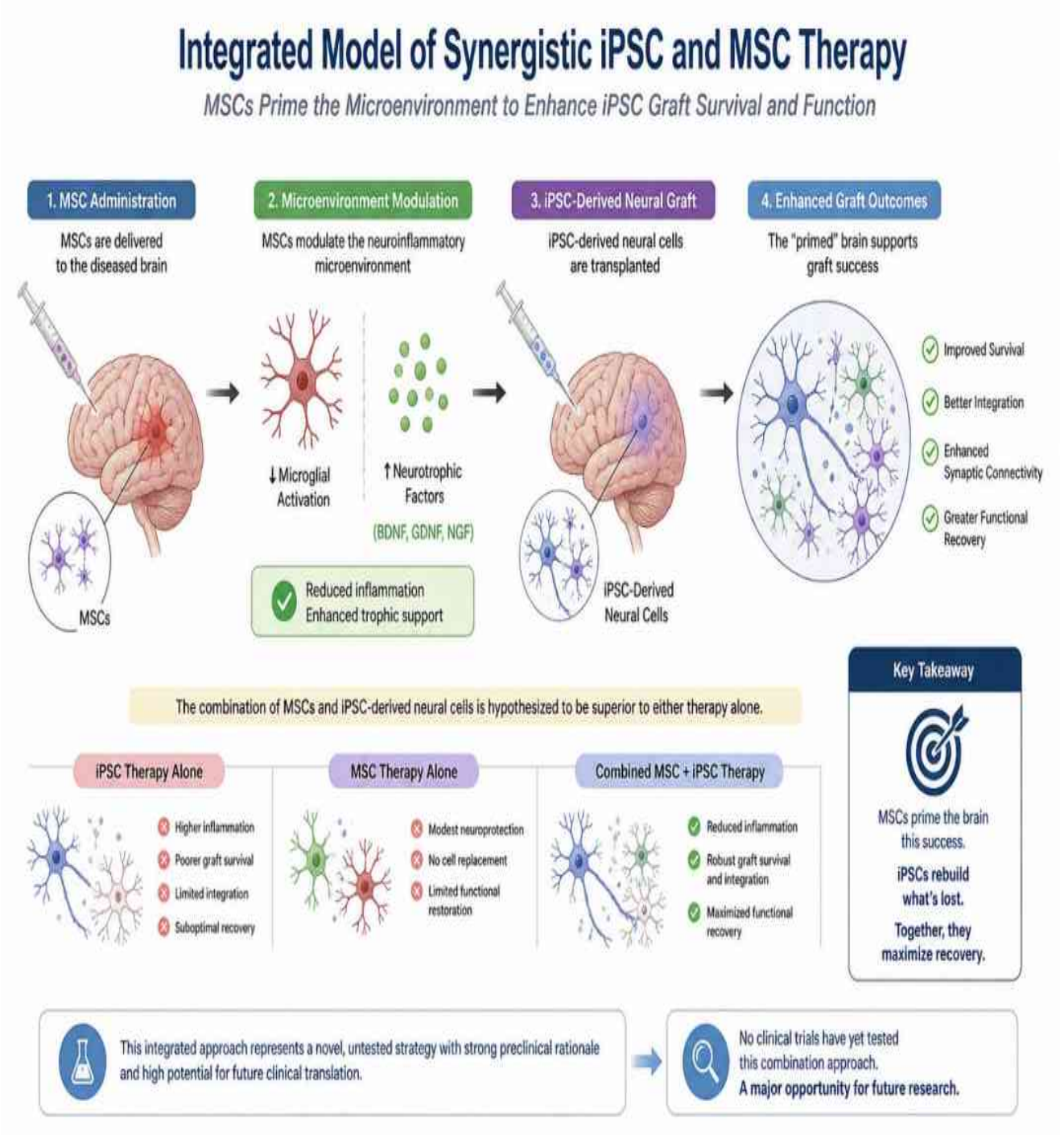


Figure 5:

Integrated model of synergistic iPSC and MSC therapy. In this proposed approach, MSCs are first administered to modulate the neuroinflammatory microenvironment (reduce microglial activation,

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

increase neurotrophic factors). This "primed" brain is then more receptive to iPSC-derived neural grafts, which have improved survival, integration, and functional benefit. The combination may be superior to either alone.

Conclusion:

iPS cells and MSCs are two therapeutic approaches that are both great but also have some fundamental differences in neurodegenerative diseases and they both fill complementary niches. These iPSCs are particularly versatile in their ability to replace cells, model patientspecific diseases, expand in number almost indefinitely, and precisely correct genetic errors, with the potential for true regeneration through direct replacement of lost neurons. MSCs have been found to be excellent at neuroprotection through paracrine factors such as growth factors and exosomes, immunomodulation, and safety with no teratoma risk, they are scalable as off-the-shelf therapeutics and are clinically ready with more than 200 trials in progress. Therefore, MSCs are more appropriate for early stage disease in which immunomodulation and neuroprotection may be used to preserve the remaining endogenous neurons, while iPSCs are better reserved for late stage disease where there is significant cell loss, and neuronal replacement is required. There are a number of important gaps that need to be filled in the field: the lack of head-to-head, direct comparisons of iPSCs with MSCs in the same disease models, essentially no combination therapy studies testing for synergies, lack of standardization in potency assays for MSCs in order to facilitate comparison across studies, and the need to bring down the cost of manufacturing and the regulatory process for iPSCs to enable their use. A future plan of sequential combination therapy could be considered, with MSCs first given to modify the microenvironment (via reducing inflammation and enhancing trophic support), and then iPSC-derived neural grafts later being introduced for cell replacement in a conditioned brain that is more permissive. Moving forward clinically, the timeline for regulatory approval is within five years for MSC products, and ten to fifteen years for the iPSC products, but this time will be necessary for completion of phase III; however, the value of knowing that they have the potential to generate real regeneration makes them worth investment. The unlocked regenerative potential is not a particular type of cell but rather represents a strategic toolkit and knowledge of when to use iPSCs, when to use MSCs, and when to combine them will shape the next generation of neuroregenerative medicine.

Funding

No funding

Conflict of interest

All authors have no conflict of interest.

REFRENCES

Abdelrahman, M. R. A. (2024). Unlocking regenerative potential: stem cell and tissue engineering innovations for permanent dental restoration. *Discover Medicine, 1*(1), 113.

Ahmed, F. A. M. (2025). Advances in regenerative medicine: Stem cell therapy and tissue engineering. *The Open European Journal for Research in Medical and Basic Sciences (OEJRMBS)*, 39-54.

Al-kharboosh, R., Perera, J. J., Bechtle, A., Bu, G., & Quinones-Hinojosa, A. (2022). Emerging point-of-care autologous cellular therapy using adipose-derived stromal vascular fraction for neurodegenerative diseases. *Clinical and Translational Medicine, 12*(12), e1093.

Artamonov, M. Y., Pyatakovich, F. A., & Minenko, I. A. (2024). Synergistic antioxidant effects of molecular hydrogen and cold atmospheric plasma in enhancing mesenchymal stem cell therapy. *Antioxidants, 13*(12), 1584.

Belousova, E., Salikhova, D., Maksimov, Y., Nebogatikov, V., Sudina, A., Goldshtein, D., & Ustyugov, A. (2024). Proposed mechanisms of cell therapy for Alzheimer's disease. *International journal of molecular sciences, 25*(22), 12378.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Brown, C., Agosta, P., McKee, C., Walker, K., Mazzella, M., Alamri, A., . . . Chaudhry, G. R. (2022). Human primitive mesenchymal stem cell-derived retinal progenitor cells improved neuroprotection, neurogenesis, and vision in rd12 mouse model of retinitis pigmentosa. *Stem cell research & therapy, 13*(1), 148.

Byun, J. (2026). The Promise and Challenges of Mesenchymal Stem Cell-Derived Extracellular Vesicles in Periodontal Disease. *Pathogens, 15*(4), 420.

Cai, J., Wu, J., Wang, J., Li, Y., Hu, X., Luo, S., & Xiang, D. (2020). Extracellular vesicles derived from different sources of mesenchymal stem cells: therapeutic effects and translational potential. *Cell & bioscience, 10*(1), 69.

Carneiro-Pereira, B., Ferreira-Antunes, F., Campos, J., Salgado, A. J., & Sampaio-Marques, B. (2025). Caloric restriction mimetics as priming agents of mesenchymal stem cells secretome to enhance regenerative responses to Parkinson's disease. *Molecules, 30*(11), 2260.

Cecerska-Heryć, E., Pękała, M., Serwin, N., Gliźniewicz, M., Grygorcewicz, B., Michalczyk, A., . . . Dołęgowska, B. (2023). The use of stem cells as a potential treatment method for selected neurodegenerative diseases. *Cellular and Molecular Neurobiology, 43*(6), 2643-2673.

Che Shaffi, S., Hairuddin, O. N., Mansor, S. F., Syafiq, T. M. F., & Yahaya, B. H. (2024). Unlocking the potential of extracellular vesicles as the next generation therapy: challenges and opportunities. *Tissue Engineering and Regenerative Medicine, 21*(4), 513-527.

Chen, H., & Li, Q. (2025). Recent advances in scalable exosome production: challenges and innovations. *Chinese Journal of Plastic and Reconstructive Surgery*.

Choudhery, M. S., Arif, T., Mahmood, R., & Harris, D. T. (2026). Stem cell derived exosomes: Emerging cell-free therapeutics for neurodegenerative disorders. *World Journal of Stem Cells, 18*(3).

Cui, M., Wu, W., Li, Q., Qi, G., Liu, X., Bai, J., . . . Sun, X. (2024). Unlocking the potential of human-induced pluripotent stem cells: cellular responses and secretome profiles in peptide hydrogel 3D culture. *Cells, 13*(2), 143.

Darban, Y. M., Askari, H., Ghasemi-Kasman, M., Yavarpour-Bali, H., Dehpanah, A., Gholizade, P., & Nosratiyan, N. (2024). The role of induced pluripotent stem cells in the treatment of stroke. *Current Neuropharmacology, 22*(14), 2368-2383.

Das, P., Pal, D., Roy, S., Chaudhuri, S., Kesh, S. S., Basak, P., & Nandi, S. K. (2024). Unveiling advanced strategies for therapeutic stem cell interventions in severe burn injuries: a comprehensive review. *International Journal of Surgery, 110*(10), 6382-6401.

de Laorden, E. H., Rodilla, B. L., Arroyo-Hernández, M., & Iglesias, M. (2025). Advances in human amniotic placenta membrane-derived mesenchymal stromal cells (hAMSCs) for regenerative medicine: Enhancing therapeutic potential with biomaterials and scaffolds. *Frontiers in Bioengineering and Biotechnology, 13*, 1590393.

Drobiova, H., Sindhu, S., Ahmad, R., Haddad, D., Al-Mulla, F., & Al Madhoun, A. (2023). Wharton's jelly mesenchymal stem cells: a concise review of their secretome and prospective clinical applications. *Frontiers in Cell and Developmental Biology, 11*, 1211217.

Duda, M., & Samiec, M. (2025). Can molecular attributes of mammalian granulosa cells and ovarian putative stem cells predestine them to be a promising tool for tissue engineering and regenerative medicine? *International journal of molecular sciences, 26*(21), 10667.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Estarellas, M., Gomis, C., & Canals, J. M. (2025). The Evolving Landscape of Stem Cell Therapies for Huntington's Disease. *Molecular Diagnosis & Therapy*, 1-27.

Farabi, B., Roster, K., Hirani, R., Tepper, K., Atak, M. F., & Safai, B. (2024). The efficacy of stem cells in wound healing: a systematic review. *International journal of molecular sciences, 25*(5), 3006.

Fatima, K. S., & Sinha, M. A Comparative Study of Unveiling Strategies of Stem Cell Therapy for Neurodegenerative Diseases.

Ford, E., Pearlman, J., Ruan, T., Manion, J., Waller, M., Neely, G. G., & Caron, L. (2020). Human pluripotent stem cells-based therapies for neurodegenerative diseases: current status and challenges. *Cells, 9*(11), 2517.

Frawley, L., Taylor, N. T., Sivills, O., McPhillamy, E., To, T. D., Wu, Y., . . . Wong, C. Y. (2024). Stem cell therapy for the treatment of amyotrophic lateral sclerosis: comparison of the efficacy of mesenchymal stem cells, neural stem cells, and induced pluripotent stem cells. *Biomedicines, 13*(1), 35.

Gholamzad, A., Sadeghi, H., Azizabadi Farahani, M., Faraji, A., Rostami, M., Khonche, S., . . . Hosseini, S. A. (2023). Neural stem cell therapies: promising treatments for neurodegenerative diseases. *Neurology Letters, 2*(2), 55-68.

Gordiienko, I., Shamshur, M., Novikova, S., Zlatskiy, I., & Zlatska, A. Regenerative potential and clinical application of mesenchymal stem cells-derived exosomes.

Gottipamula, S., Seetharam, R. N., & NK, V. (2026). Primed for Repair: Harnessing Hypoxia, Mechanobiology, and Gene Editing to Enhance MSC Potency and Clinical Translation. *Stem Cell Reviews and Reports*, 1-18.

Guo, Y., Dong, X., Liu, M., Liu, D., & Wang, J. (2026). Integrating 3D bioprinting and neural stem cell therapy for central nervous system repair: implications for regenerative neurosurgery. *Frontiers in Bioengineering and Biotechnology, 14*, 1763855.

Han, D., Liu, W., Gong, J., Ma, Y., & Sun, Z. (2025). Challenges and future perspectives in using mesenchymal stem cells for efficient bone fracture healing. *Frontiers in Bioengineering and Biotechnology, 13*, 1568914.

Harun, Z. Z., Azhar, A. A., Kim, Y.-J., Ibrahim, F. W., Ng, M.-H., Tan, J.-K., & Lokanathan, Y. (2025). Modulation of BDNF/TrkB Signalling Pathway in Alzheimer's Disease: Mechanistic Insights and the Role of Stem Cell Therapy. *Biomedicines, 13*(12), 2931.

Hoang, V. T., Nguyen, Q. T., Phan, T. T. K., Pham, T. H., Dinh, N. T. H., Anh, L. P. H., . . . Le, D. S. (2025). Tissue engineering and regenerative medicine: perspectives and challenges. *MedComm, 6*(5), e70192.

Jamali, F., Aldughmi, M., Atiani, S., Al-Radaideh, A., Dahbour, S., Alhattab, D., . . . Rahmeh, R. (2024). Human Umbilical Cord–Derived Mesenchymal Stem Cells in the Treatment of Multiple Sclerosis Patients: Phase I/II Dose-Finding Clinical Study. *Cell Transplantation, 33*, 09636897241233045.

Jeyaraman, M., Muthu, S., Gulati, A., Jeyaraman, N., GS, P., & Jain, R. (2021). Mesenchymal stem cell–derived exosomes: a potential therapeutic avenue in knee osteoarthritis. *Cartilage, 13*(1_suppl), 1572S-1585S.

Jia, Z., Zhang, S., & Li, W. (2023). Harnessing stem cell-derived extracellular vesicles for the regeneration of degenerative bone conditions. *International Journal of Nanomedicine*, 5561-5578.

Kamboj, N., Kumar, R., & Mitra, D. (2025). Immunomodulation in Autoimmune Disorders: Harnessing the Power of Stem Cell. *Stem Cell Therapeutics*, 409-462.

Karima, G., & Kim, H. D. (2024). Unlocking the regenerative key: Targeting stem cell factors for bone renewal. *Journal of Tissue Engineering, 15*, 20417314241287491.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Kawatani, K., Omana Suarez, G., Perkerson III, R. B., Parent, E. E., Nambara, T., Knight, J. A., . . . Alnobani, A. (2025). Human iPSC-derived MSCs induce neurotrophic effects and improve metabolic activity in acute neuronal injury models. *The Journal of Neuroscience, 45*(1), e0606242024.

Khedr, A. A., Abdelmaguid, A. M., Elshekh, A. H., El-Hanfy, S. A., Elmahdy, M. M., Hany, T., . . . Mohsen, M. (2025). Stem Cell Therapies for Neurodegenerative Diseases: Emerging Frontiers in Regenerative Medicine. *Frontiers in Scientific Research and Technology*.

Khodadoust, M. A., Boroumand, A., Sedaghat, A., Reihani, H., Farkhad, N. K., & Afshari, J. T. (2023). A closer look at Mesenchymal Stem cells (MSCs), their potential and function as game-changers of modern medicine. In *Recent Update on Mesenchymal Stem Cells*: IntechOpen.

Kim, A.-L., Lee, W. K., Kwon, S., Han, I., & Choi, B. H. (2026). Therapeutic Efficacy of Mesenchymal Stem Cells (MSCs) on Alzheimer's Disease: Review of Clinical Results. *Tissue Engineering and Regenerative Medicine*, 1-23.

Kruczek, K., & Swaroop, A. (2020). Pluripotent stem cell-derived retinal organoids for disease modeling and development of therapies. *Stem cells, 38*(10), 1206-1215.

Kumar, D., Gupta, S., Gupta, V., Tanwar, R., Rani, P., & Bansal, V. (2026). Stem Cells to Organoids: Pioneering the Future of Regenerative Therapies. *Stem Cell Reviews and Reports, 22*(1), 118-143.

Kumari, P. (2024). Stem Cells and Regenerative Medicine: Healing and Beyond. *ISBN: Book DOI: Price:695/-*, 37.

Lai, S., & Guo, Z. (2024). Stem cell therapies for chronic obstructive pulmonary disease: mesenchymal stem cells as a promising treatment option. *Stem cell research & therapy, 15*(1), 312.

Li, D., Zou, Y., & Zhao, Y. (2025). The interplay between mesenchymal stem cells and the immune microenvironment in rotator cuff tendon-to-bone healing: current progress and future directions. *Frontiers in Immunology, 16*, 1661340.

Li, S., Zhang, J., Sun, L., Yang, Z., Liu, X., Liu, J., & Liu, X. (2025). Mesenchymal stem cell-derived extracellular vesicles: current advances in preparation and therapeutic applications for neurological disorders. *Frontiers in Cell and Developmental Biology, 13*, 1626996.

Li, Y., Wang, Y., Zhang, Y., Zhu, Y., Dong, Y., Cheng, H., . . . Gao, J. (2024). Engineered mesenchymal stem cell-derived extracellular vesicles: kill tumors and protect organs. *Theranostics, 14*(16), 6202.

Liu, Z., & Cheung, H.-H. (2020). Stem cell-based therapies for Parkinson disease. *International journal of molecular sciences, 21*(21), 8060.

Lou, Y. (2024). Unlocking the code for stroke treatment and care. In (Vol. 16, pp. 11795735241280805): SAGE Publications Sage UK: London, England.

Madhan, S., Mehta, A., Santoshkumar, A., Satishkarthik, S., & Aruljothi, K. (2025). Stem Cell Interventions in the Treatment of Alzheimer's Disease. *Current Stem Cell Research & Therapy, 20*(4), 377-388.

Mahla, R. S. Neuronal Stem Cells and Regenerative Medicine: Harnessing the Potential for Neural Repair. In *Handbook of Regenerative Medicine* (pp. 233-245): CRC Press.

Marrelli, M., Paduano, F., & Tatullo, M. (2015). Human periapical cyst–mesenchymal stem cells differentiate into neuronal cells. *Journal of Dental Research, 94*(6), 843-852.

Matsuoka, T., Itohara, T., Hara, Y., & Kobayashi, N. (2024). Systematic Intravenous Administration of Autologous Mesenchymal Stem Cells Is Safe. *Journal of Clinical Medicine, 13*(23), 7460.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Mayeen, N. F., Salma, U., Kasim, N. H. A., Mahmoud, O., & Haque, N. (2025). Hurdles to overcome for mesenchymal stem cell translation from bench to bedside. *World Journal of Stem Cells, 17*(12), 114349.

Mehdizadeh, S., Mamaghani, M., Hassanikia, S., Pilehvar, Y., & Ertas, Y. N. (2025). Exosome-powered neuropharmaceutics: unlocking the blood-brain barrier for next-gen therapies. *Journal of Nanobiotechnology, 23*(1), 329.

Mehrabadi, S. (2024). Uncovering the Healing Power of Stem Cells: Harnessing Regenerative Therapies for Alzheimer's Disease. *Current Aging Science*.

Miceli, V. (2024). Use of priming strategies to advance the clinical application of mesenchymal stromal/stem cell-based therapy. *World Journal of Stem Cells, 16*(1), 7.

Milczarek, O., Swadźba, J., Swadźba, P., Starowicz-Filip, A., Krzyżewski, R. M., Kwiatkowski, S., & Majka, M. (2023). Comparative Analysis of the Results of Stroke Treatment With Multiple Administrations of Wharton's Jelly Mesenchymal Stem Cells–Derived HE-ATMP and Standard Conservative Treatment: Case Series Study. *Cell Transplantation, 32*, 09636897231195145.

Mohammadi, A. T., Amini, E. E., Ghanaat, M., Moradi, S., Mohagheghi, S. Z., Rouzbahani, A. K., . . . Hadilou, N. *Stem Cell Research And Textbook 2:(Dental-derived stem cells, Induced pluripotent stem cells, hematopoietic stem cells, Embryonic, and Cancer Stem cells)*: Nobel TM.

Mohite, P., Puri, A., Dave, R., Budar, A., Munde, S., Ghosh, S. B., . . . Dhara, B. (2024). Unlocking the therapeutic potential: odyssey of induced pluripotent stem cells in precision cell therapies. *International Journal of Surgery, 110*(10), 6432-6455.

Mondal, A., Talukdar, A., & Haque, R. (2025). Unlocking the Potential of Induced Pluripotent Stem Cells in Revolutionizing Cancer Therapy. *Current Stem Cell Research & Therapy, 20*(4), 360-376.

Moreira, A., Kahlenberg, S., & Hornsby, P. (2017). Therapeutic potential of mesenchymal stem cells for diabetes. *Journal of molecular endocrinology, 59*(3), R109-R120.

Moretti, E. H., Lin, A. L., Peruzzotti-Jametti, L., Pluchino, S., & Mozafari, S. (2025). Neural Stem Cell-Derived Extracellular Vesicles for Advanced Neural Repair. *Journal of Neurochemistry, 169*(8), e70170.

Nashwan, S., Ismail, M. A., Saleh, T., Al Hadidi, S., Alwohoush, E., Sarhan, M., . . . Ababneh, N. A. (2025). Comparative analysis of extracellular vesicles from induced and adipose-derived mesenchymal stem cells: Implications for regenerative medicine. *Plos one, 20*(6), e0325065.

NAZIR, M., KHASKHELI, H. K., HAMEED, A., ABBAS, T., RIAZ, D., REHMAN, S. U., & SAFDAR, M. (2024). Stem Cell Research: Unloking The Potential for Regenerative Therapies. *Current Studies in Health and Life Science*, 212.

Noroozi, H., & Pakzad, R. (2025). Unveiling the Healing Potential of Stem Cells: The Promising Role of Secretome Therapy in the Treatment of Pulmonary Degenerative Disorders-A Comprehensive Systematic Review. *Current Stem Cell Research & Therapy*.

Patel, J. C., Shukla, M., & Shukla, M. (2025). From bench to bedside: translating mesenchymal stem cell therapies through preclinical and clinical evidence. *Frontiers in Bioengineering and Biotechnology, 13*, 1639439.

Peng, J., Zhang, Z., Li, M., Yung, K. K. L., & Cheung, K.-h. (2025). From adipose to action: reprogramming stem cells for functional neural progenitors for neural regenerative therapy. *International journal of molecular sciences, 26*(14), 6599.

Rajalekshmi, R., & Agrawal, D. K. (2025). Synergistic potential of stem cells and microfluidics in regenerative medicine. *Molecular and Cellular Biochemistry, 480*(3), 1481-1493.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

RASTOGI, S. (2026). PRANSHUL SETHI[1]2, URVEE DAVE[3]. *Unravelling Neurodegenerative Diseases: Advances, Challenges, and Future Directions*, 383.

Riza, Y. M., & Alzahrani, F. A. (2025). Rewiring the Spine—Cutting-Edge Stem Cell Therapies for Spinal Cord Repair. *International journal of molecular sciences*, *26*(11), 5048.

Saliev, T., & Singh, P. B. (2026). STEM CELL REJUVENATION: MECHANISMS, MODALITIES, AND TRANSLATIONAL CHALLENGES IN REGENERATIVE ANTI-AGING MEDICINE. *Central Asian Journal of Medical Hypotheses and Ethics*, *7*(1), 34-43.

Sethi, P., Sen, A., Sonima, Madan, A., Waheed, S. M., & Bhunia, B. K. (2025). Unraveling the Mechanisms: Insights Into Stem Cell Behavior in Disease Microenvironments. *Stem Cell Therapeutics*, 1-37.

Shen, H., Chen, J., Liu, M., Zhao, M., Hu, D., Xie, F., . . . Qin, T. (2025). Research progress of extracellular vesicles derived from mesenchymal stem cells in the treatment of neurodegenerative diseases. *Frontiers in Immunology*, *16*, 1496304.

Shi, Z., Chen, S., Cai, W., Chen, W., & Tang, Y. (2025). Advances in photobiomodulation: Effects on mesenchymal stem cells and their paracrine factors. *Stem Cell Reviews and Reports*, *21*(7), 1918-1930.

Shim, Y.-M. (2025). *Modeling Neurodegenerative Diseases and Investigating Quiescent Adult Neurogenesis Using Neuropathologically Validated Human Brain Tissues*. 서울대학교 대학원,

Staniowski, T., Zawadzka-Knefel, A., & Skośkiewicz-Malinowska, K. (2021). Therapeutic potential of dental pulp stem cells according to different transplant types. *Molecules*, *26*(24), 7423.

Su, H., Wang, Z., Zhou, L., Liu, D., & Zhang, N. (2024). Regulation of the Nrf2/HO-1 axis by mesenchymal stem cells-derived extracellular vesicles: implications for disease treatment. *Frontiers in Cell and Developmental Biology*, *12*, 1397954.

Sun, D. Z., Abelson, B., Babbar, P., & Damaser, M. S. (2019). Harnessing the mesenchymal stem cell secretome for regenerative urology. *Nature Reviews Urology*, *16*(6), 363-375.

Suzuki, H., & Sakai, T. (2021). Current concepts of stem cell therapy for chronic spinal cord injury. *International journal of molecular sciences*, *22*(14), 7435.

Tatullo, M., Cocco, T., Ferretta, A., Caroppo, R., Marrelli, B., Spagnuolo, G., & Paduano, F. (2024). Unveiling the neurodegenerative alterations through oral stem cells. *Journal of Dental Research*, *103*(11), 1100-1108.

Terzic, A., & Nelson, T. J. (2013). *Regenerative medicine primer*. Paper presented at the Mayo Clinic Proceedings.

Velikic, G., Maric, D. M., Maric, D. L., Supic, G., Puletic, M., Dulic, O., & Vojvodic, D. (2024). Harnessing the stem cell niche in regenerative medicine: innovative avenue to combat neurodegenerative diseases. *International journal of molecular sciences*, *25*(2), 993.

Velikova, T., Dekova, T., & Miteva, D. G. (2024). Controversies regarding transplantation of mesenchymal stem cells. *World Journal of Transplantation*, *14*(2), 90554.

Verma, S., Tiwari, G. J., Shukla, S., Singh, S., & Veeranan, S. (2026). Stem Cells in Regenerative Medicine and Personalized Therapeutics. *Available at SSRN 6661640*.

Waller, M., Neely, G. G., & Caron, L. Human Pluripotent Stem Cells-Based Therapies for Neurodegenerative Diseases: Current Status and Challenges.

Wang, A. Y. L., Kao, H.-K., Liu, Y.-Y., & Loh, C. Y. Y. (2025). Engineered extracellular vesicles derived from pluripotent stem cells: a cell-free approach to regenerative medicine. *Burns & Trauma*, *13*, tkaf013.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Wang, C., Ge, F., Ge, F., Xu, Z., & Jiang, J. (2025). Harnessing stem cell therapeutics in LPS-induced animal models: mechanisms, efficacies, and future directions. *Stem cell research & therapy, 16*(1), 176.

Wang, J., Zhang, M., & Wang, H. (2024). Emerging landscape of mesenchymal stem cell senescence mechanisms and implications on therapeutic strategies. *ACS Pharmacology & Translational Science, 7*(8), 2306-2325.

Wu, K. Y., Ahmad, H., Lin, G., Carbonneau, M., & Tran, S. D. (2023). Mesenchymal stem cell-derived exosomes in ophthalmology: a comprehensive review. *Pharmaceutics, 15*(4), 1167.

Yang, K., Yuan, S., Wang, Y., Lin, A., Huo, F., Jin, Z., . . . Tian, W. (2025). Comparative analysis of dental-derived stem cells and alternative stem cell sources: properties and regenerative functions. *Frontiers in Bioengineering and Biotechnology, 13*, 1717849.

Yang, S., Li, K., Wang, N., Li, Z., Zhang, Z., Tuan, R. S., & Jiang, Y. (2026). Engineering Approaches to Modify Immunomodulatory Functions of Mesenchymal Stromal Cells (MSCs): Tissue Regeneration and Clinical Application. *Advanced Science*, e22601.

Yang, Y.-P., Nicol, C. J., & Chiang, M.-C. (2025). A review of the neuroprotective properties of exosomes derived from stem cells and exosome-coated nanoparticles for treating neurodegenerative diseases and stroke. *International journal of molecular sciences, 26*(8), 3915.

Yigitturk, G., & Cavusoglu, T. (2025). A Review of The Place of Adipose-Derived Stem Cells among Stem Cell Applications in Neurodegenerative Diseases. *Current Topics in Medicinal Chemistry*.

Zayed, M., Elwakeel, E., Ezzat, P., & Jeong, B.-H. (2025). Mesenchymal stem cell-derived exosomes as a potential therapeutic strategy for ferroptosis. *Stem cell research & therapy, 16*(1), 368.

Zeng, C.-W. (2023a). Advancing spinal cord injury treatment through stem cell therapy: a comprehensive review of cell types, challenges, and emerging technologies in regenerative medicine. *International journal of molecular sciences, 24*(18), 14349.

Zeng, C.-W. (2023b). Multipotent mesenchymal stem cell-based therapies for spinal cord injury: current progress and future prospects. *Biology, 12*(5), 653.

Zeng, C.-W. (2025). Stem cell-based approaches for spinal cord injury: the promise of iPSCs. *Biology, 14*(3), 314.

Zhang, A., Li, Q., & Chen, Z. (2024). Therapeutic efficacy and promise of human umbilical cord mesenchymal stem cell-derived extracellular vesicles in aging and age-related disorders. *International journal of molecular sciences, 26*(1), 225.

Zhang, L. (2025a). Mesenchymal Stem Cell Therapy and Its Clinical Application. *Mesenchymal Stem Cells-Biology, Therapeutics, and Beyond: Biology, Therapeutics, and Beyond*, 67.

Zhang, L. (2025b). Mesenchymal Stem Cell Therapy and Its Clinical Application Potential. In *Mesenchymal Stem Cells-Biology, Therapeutics, and Beyond*: IntechOpen.

Zhang, Y., Wang, L., Kang, H., Lin, C.-Y., & Fan, Y. (2023). Unlocking the therapeutic potential of irisin: harnessing its function in degenerative disorders and tissue regeneration. *International journal of molecular sciences, 24*(7), 6551.

Zhong, X.-L., Huang, Y., Du, Y., He, L.-Z., Chen, Y.-w., Cheng, Y., & Liu, H. (2024). Unlocking the therapeutic potential of exosomes derived from nasal olfactory mucosal mesenchymal stem cells: restoring synaptic plasticity, neurogenesis, and neuroinflammation in schizophrenia. *Schizophrenia Bulletin, 50*(3), 600-614.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Zhou, J., Pu, Y., Ren, X., Li, L., Chen, Z., Lo, E. H., & Li, W. (2026). Engineering small extracellular vesicles: unlocking the brain's secret passage for central nervous system therapies. *Journal of Cerebral Blood Flow & Metabolism*, *46*(2), 207-221.

Zhou, W., Wang, X., Dong, Y., Gao, P., Zhao, X., Wang, M., . . . Lu, Z. (2024). Stem cell-derived extracellular vesicles in the therapeutic intervention of Alzheimer's Disease, Parkinson's Disease, and stroke. *Theranostics*, *14*(8), 3358.