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Advances in the Application of Pluripotent Stem Cells in the Research and Treatment of Neurological Diseases

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Abstract. The development of induced pluripotent stem cell (iPSC) technology has opened new avenues for understanding and treating neurological disorders. iPSCs possess unlimited self-renewal and pluripotent differentiation capabilities, enabling their use in disease modeling, mechanism studies, and high-throughput drug screening. Compared with traditional treatments that mainly alleviate symptoms, iPSC-based approaches offer unique advantages in regenerative medicine by providing patient-specific cell sources for neuronal replacement, modulating immune responses, and promoting endogenous repair. Recent advances have demonstrated the application of iPSC-derived models in major neurological disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), and spinal cord injury (SCI). In AD research, iPSC-derived brain organoids have successfully reproduced key pathological hallmarks such as Aβ deposition and Tau hyperphosphorylation, serving as valuable platforms for drug discovery. For PD, iPSC-derived dopaminergic neurons and midbrain-like organoids have revealed critical pathogenic mechanisms and shown potential in transplantation therapy. In SCI, preclinical studies highlight the ability of iPSC-derived neural progenitors and engineered grafts to promote axonal regeneration and functional recovery. This review summarizes current progress, discusses challenges such as tumorigenicity and immune rejection, and explores future strategies to accelerate clinical translation.

Keywords: Induced pluripotent stem cells, Alzheimer's disease, Parkinson's disease, Spinal cord injury, Disease model

1. Introduction

Neurological diseases are a major cause of death and disability worldwide, and their global burden continues to rise, largely due to population aging, environmental changes, metabolic disorders, and lifestyle factors [1]. Despite decades of research, most treatments remain pharmacological and primarily provide symptomatic relief. Traditional drug therapy faces significant challenges: (1) heterogeneous etiologies hinder targeted intervention, often causing off-target effects [2]; (2) the blood-brain barrier limits drug delivery and individual variability affect outcomes [3]; and (3) long-term medication can lead to severe adverse effects [4]. Therefore, innovative and precise therapeutic strategies are urgently needed.

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In recent years, pluripotent stem cells (PSCs) have emerged as a promising platform for neurological disease research and treatment because of their self-renewal and multidirectional differentiation capabilities. Unlike totipotent stem cells, PSCs cannot form a complete organism but can be derived from somatic cells through induced pluripotent stem cell (iPSC) technology, avoiding ethical concerns and enabling controlled differentiation. These properties support wide applications in regenerative medicine, disease modeling, and drug discovery.

In the treatment of neurological diseases, PSC-based transplantation offers distinct advantages over conventional pharmacotherapy: (1) PSCs can be precisely directed to differentiate into specific neuronal or glial subtypes using gene-editing technologies, thereby minimizing side effects and enhancing therapeutic efficacy [5]; and (2) PSCs can be integrated with drug delivery systems to achieve more accurate, targeted interventions [6]. Furthermore, PSCs enable the establishment of physiologically relevant disease models, facilitate mechanistic studies, and support the preclinical safety assessment of novel therapeutics. At present, clinical trials investigating PSC-based interventions have been initiated for several neurological disorders, including Parkinson's disease, spinal cord injury, epilepsy, and amyotrophic lateral sclerosis.

This review summarizes recent advances in PSC applications for neurological disorders, emphasizing roles in regeneration, disease modeling, and personalized therapy, and explores future clinical translation.

1.1. Types and preparation of PSC

PSC possess self-renewal and multilineage differentiation capabilities, enabling the generation of specialized cell types for regenerative medicine and personalized therapy. Major PSC sources include embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), and expanded potential stem cells (EPSCs). Among these, iPSCs are particularly valued for their derivation from somatic cells, avoidance of ESC-related ethical issues, large-scale expansion potential, and suitability for autologous transplantation, reducing immune rejection [7, 8]. MSCs, as a non-embryonic stem cell source, have been extensively applied in neurological disease research and therapy due to their immunomodulatory and neuroprotective properties [9]. EPSCs, characterized by broader developmental potential and superior neural differentiation capacity, have emerged as a promising cell type for treating neural injuries and neurodegenerative disorders [10].

At present, approaches for reprogramming somatic cells into iPSCs include: (1) the ectopic expression of transcription factors-classically Oct3/4, Sox2, Klf4, and c-Myc (OSKM) [11]; (2) microRNA-mediated induction, such as the combined action of miRNA302/367 with HDAC2 modulation [12]; and (3) chemical reprogramming using small molecules such as VC6T and forskolin (FSK) [13].

Initially, iPSC generation relied on integrating reprogramming genes into the host genome via viral vectors, including retroviruses [11]. With technological advancements, non-viral delivery systems have increasingly become the preferred approach. For example, reprogramming factors can be introduced by direct RNA delivery through electroporation, by cationic carriers facilitating RNA transfection, or via cell-penetrating peptides (CPPs) enabling efficient intracellular protein delivery [14-16]. Compared with viral vectors, non-viral systems reduce the risk of insertional mutagenesis and host immune activation, thereby improving safety profiles [17]. Nonetheless, these approaches still face limitations such as relatively low delivery efficiency and prolonged reprogramming timelines [18].

Chemical reprogramming represents an attractive alternative, offering greater flexibility and precise temporal-spatial regulation of gene expression compared with transgene-based strategies.

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Small molecules, including vitamin C, CHIR99021, and FSK can modulate signaling pathways and epigenetic states to guide cell fate transitions with high controllability, thus enhancing clinical translation potential [13, 19, 20]. Given the ease of combination and adjustment, small-molecule cocktails hold particular promise for generating clinically relevant, lineage-specific cell types tailored for therapeutic applications.

1.2. Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by beta-amyloid (Aβ) deposition, neurofibrillary tangles (NFTs), and neuronal loss [21]. Current therapies, including acetylcholinesterase inhibitors, NMDA antagonists, and anti-Aβ antibodies, offer only symptomatic relief without altering disease progression [22].

The development of iPSCs technology has provided new possibilities for AD modeling and treatment. Over the past 15 years, iPSC-based models have evolved from simply recapitulating pathological hallmarks to enabling detailed exploration of disease mechanisms and therapeutic target identification. Early models generated from fibroblasts of early-onset familial AD patients carrying Presenilin 1 (PS1) and Presenilin 2 (PS2) mutations successfully reproduced disease-specific phenotypes and served as platforms for candidate drug validation [23]. Advances in 3D culture improved fidelity: neural stem cell cultures replicate Aβ plaques and tau pathology [24], and brain organoids exposed to human serum exhibit AD-like features [25]. Patient-derived organoids display Aβ aggregation and tau hyperphosphorylation, which β- and γ-secretase inhibitors can attenuate, supporting their value in preclinical studies [26].

iPSC models have revealed multiple AD-related pathways. Aberrant APP processing activates GSK-3β and promotes tau hyperphosphorylation [27]; APP V717I mutation elevates tau and Aβ species [28]; MAPT mutations accelerate neuronal maturation and excitability, driving tau accumulation [29]; and APP/PS1 mutations increase the Aβ42/Aβ40 ratio and reduce synaptic proteins, with homozygous APP variants producing severe phenotypes [30].

iPSC-derived neurons support high-throughput drug screening, enabling assays to identify compounds reducing Aβ toxicity [31]. Large-scale screens using patient-derived neurons have revealed synergistic drug combinations, including bromocriptine, sodium cromoglicate, and topiramate, which enhance anti-Aβ activity [32].

In terms of transplantation therapy, transplantation of iPSC-derived cells into 5XFAD transgenic AD mice has significantly improved cognitive performance, potentially via plaque reduction and differentiation of grafted cells into oligodendrocytes [33]. Table 1 provides a summary of recent advances in iPSC-derived models for Alzheimer's disease, highlighting their roles in disease modeling, mechanistic studies, and therapeutic development.

Overall, iPSC technology holds considerable promise for advancing AD research and therapy. Future directions include optimizing model stability, improving the fidelity of disease recapitulation, and integrating gene editing with high-throughput screening to accelerate the development of effective interventions.

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Table 1. iPSC-based models for Alzheimer's disease research

Disease Type	Stem Cell Type	Research Stage	Cell Source	Key Findings	Reference
Alzheimer's disease	iPSCs	In vitro	Human	Established an iPSC-based model recapitulating key AD pathological mechanisms, applied for candidate drug screening.	[8]
Alzheimer's disease	iPSCs	In vitro	Human	Reproduced Aβ aggregation and Tau hyperphosphorylation; confirmed that β- and γ-secretase inhibitors significantly reduced these pathologies, demonstrating potential for drug development.	[11]
Alzheimer's disease	iPSCs	In vitro	Human	MAPT gene mutations accelerate neuronal maturation and increase excitability, thereby promoting abnormal Tau accumulation.	[14]
Alzheimer's disease	iPSCs	In vitro	Human	APP and PS1 mutations increase the Aβ42/Aβ40 ratio and reduce synaptic protein levels; homozygous APP mutations cause more severe pathology.	[15]
Alzheimer's disease	iPSCs	In vitro	Human	Large-scale drug screening in patient-derived iPSC neurons identified a combination of bromocriptine, sodium cromoglicate, and topiramate with enhanced anti-Aβ effects.	[17]
Alzheimer's disease	iPSCs	In vivo	Mouse	Reprogrammed mouse fibroblasts into iPSCs and transplanted them into 5XFAD AD mouse brains, significantly improving cognitive deficits, likely via Aβ plaque reduction and differentiation into oligodendrocytes.	[18]

2.3 Parkinson's disease

Parkinson's disease (PD) is marked by dopaminergic neuron (DAn) loss in the substantia nigra and α-synuclein (α-syn) aggregation into Lewy bodies [34]. It manifests with motor symptoms—tremor, rigidity, bradykinesia, postural instability—and non-motor features such as constipation, sleep disturbances, and depression [35]. Current therapies, including dopamine replacement (levodopa, MAO-B inhibitors, dopamine agonists), deep brain stimulation, and rehabilitation, alleviate symptoms but do not halt progression or effectively address non-motor deficits [36–39].

iPSC technology models PD pathologies, supporting mechanistic studies and drug discovery. SNCA triplication-derived iPSCs reproduce α-syn accumulation, oxidative stress, and stressor sensitivity [40,41]. Gene editing enables isogenic controls for variant-specific analyses [42]. iPSC-derived DAn with LRRK2 p.G2019S mutations show elevated α-syn and stress-response gene expression [43]. Midbrain-like organoids (hMBOs) from SNCA triplication iPSCs exhibit age-dependent α-syn aggregation and progressive DAn loss [44].

iPSC models have revealed multiple pathogenic mechanisms of PD. For instance, The A53T SNCA mutation impairs mitochondrial function, increases reactive oxygen species (ROS) production, suppresses the MEF2C-PGC1α pathway, and triggers neuronal apoptosis [45]. Overexpression of α-syn can activate the IRE1α/XBP1-mediated unfolded protein response (UPR), elevating the pro-apoptotic factor CHOP [46]. Both SNCA triplication and A53T mutations are associated with α-syn oligomerization, cholesterol metabolism deficits, and endoplasmic reticulum stress [47]. Other PD-associated mutations, such as those in LRRK2, PINK1/Parkin, GBA, and VPS35-are linked to synaptic dysfunction, mitochondrial impairment, and defective protein degradation [48-52].

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iPSC-derived DAn transplantation has shown promising therapeutic potential in preclinical studies. In rodent models, the extent of neurite extension into the host striatum has been identified as a critical determinant of graft efficacy, with REST gene expression proposed as a biomarker for optimal transplantation timing [53]. Additionally, dopamine fiber density post-transplantation has emerged as a predictive marker for functional recovery, informing the design of ongoing and planned clinical trials [54]. Table 2 outlines key studies utilizing iPSC technology for Parkinson's disease.

Table 2. iPSC-based models for parkinson's disease research

Disease Type	Stem Cell Type	Research Stage	Cell Source	Key Findings	Reference
Parkinson's disease	iPSCs	In vitro (cell model)	Human	iPSC-derived dopaminergic neurons (DAn) from SNCA triplication patients reproduced α-synuclein accumulation, increased oxidative stress, and hypersensitivity to stressors.	[26]
Parkinson's disease	iPSCs	In vitro (cell model)	Human	DAn derived from iPSCs carrying the LRRK2 p.G2019S mutation exhibited elevated α-syn expression and upregulation of stress-response genes.	[28]
Parkinson's disease	iPSCs	In vitro (cell model)	Human	Both SNCA triplication and A53T mutation in DAn led to α-syn oligomerization, cholesterol metabolism defects, and endoplasmic reticulum stress.	[32]
Parkinson's disease	iPSCs	In vitro (mechanistic)	Human	Mutations in LRRK2, PINK1/Parkin, GBA, and VPS35 are closely associated with synaptic dysfunction, mitochondrial impairment, and abnormal protein degradation.	[33–37]
Parkinson's disease	iPSCs	In vivo (transplantation)	Human	The extent of neurite outgrowth into the host striatum was a key factor influencing transplantation outcomes; REST gene expression could serve as an indicator for optimal transplantation timing.	[38]
Parkinson's disease	iPSCs	In vivo (transplantation)	Human	Dopaminergic fiber density was identified as an important predictor of transplantation efficacy, facilitating the development of related clinical trial plans.	[39]

2.4 Spinal cord injury

Spinal cord injury (SCI) is a debilitating central nervous system disorder caused severe sensory, motor, and autonomic deficits, with high disability and socioeconomic burden [55]. Current treatments-pharmacological therapy, decompression surgery, and rehabilitation—mainly alleviate symptoms without restoring full function.

iPSC-based strategies show promise for SCI repair. iPSC-derived neural progenitors (NPCs), neural stem cells (NSCs), and oligodendrocyte progenitors (OPCs) promote remyelination, axonal regeneration, and synaptic reconstruction [56,57]. Preclinical studies report region-specific NPCs enhance motor recovery in mice, while cannabinoid receptor activation improves OPC myelination efficiency [56].

In rat models, transplanted iPSC-derived NPCs differentiate in vivo into neurons and astrocytes, establishing functional synaptic networks [58]. Combined with rehabilitation, grafted NSCs boost synaptic activity, secrete neurotrophic factors, and improve motor recovery [59]. Synergistic effects have also been observed with combinatorial transplantation strategies for example, co-delivery of brain-derived neurotrophic factor (BDNF) overexpressing mesenchymal stem cells and iPSC-

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derived motor neuron precursors (iMNPs) significantly promotes axonal regeneration and functional recovery in chronic SCI models [60].

In terms of neural circuit reconstruction, iPSC-derived pyramidal neuron precursors (PNPs) can form synaptic connections with host neurons post-transplantation while exerting anti-inflammatory effects that improve the local immune milieu [61]. Furthermore, composite constructs, such as TrkC-modified NSCs with aligned collagen scaffolds, further improve motor function and matrix remodeling [62].

Table 3 summarizes iPSC-based SCI interventions and combinatorial strategies. Future directions include integrating iPSC transplantation with biomaterials, gene editing, and exosome engineering to accelerate clinical translation.

Table 3. iPSC-based strategies for spinal cord injury treatment

Disease Type	Stem Cell Type	Research Stage	Cell Source	Key Findings	Reference
Spinal cord injury	iPSCs	In vivo (animal model)	Human	iPSC-derived neural progenitor cells (NPCs) with spinal cord region specificity significantly promoted motor function recovery in moderate SCI models. iPSC-derived OPCs showed enhanced myelination efficiency after CB1R and CB2R activation.	[41]
Spinal cord injury	iPSCs	In vivo (animal model)	Human	Transplantation of iPSC-derived NPCs promoted in vivo differentiation into neurons and astrocytes and facilitated the formation of functional synaptic networks.	[43]
Spinal cord injury	iPSCs	In vivo (animal model)	Human	When combined with rehabilitation training, transplanted NS/PCs enhanced synaptic activity, secreted neurotrophic factors, improved cell survival and differentiation, and promoted motor function recovery.	[44]
Spinal cord injury	iPSCs	In vivo (animal model)	Human	Co-transplantation of brain-derived neurotrophic factor (BDNF)-overexpressing engineered mesenchymal stem cells with iPSC-derived motor neuron progenitors (iMNPs) demonstrated synergistic effects on axonal regeneration and motor function improvement in chronic SCI models.	[45]
Spinal cord injury	iPSCs	In vivo (animal model)	Human	iPSC-derived pyramidal neuron progenitors (PNPs) formed synaptic connections with host neurons after transplantation and exhibited anti-inflammatory properties, improving the local immune microenvironment.	[46]
Spinal cord injury	iPSCs	In vivo (animal model)	Human	A composite tissue engineered by combining TrkC-modified NSCs with linearly aligned collagen scaffolds effectively improved motor function, promoted synapse formation, and facilitated extracellular matrix remodeling in SCI rats.	[47]

3. Conclusion

At present, Conventional treatment modalities for neurological diseases-pharmacotherapy, surgery, and rehabilitation are hindered by intrinsic limitations. Pharmacological approaches often suffer from low delivery efficiency, poor target specificity, and systemic side effects; surgical interventions are applicable to a narrow patient subset and carry procedural risks; rehabilitation primarily serves as an adjunctive measure, with variable efficacy across individuals.

The advent of iPSC technology has created unprecedented opportunities for both research and therapy in neurological disorders. iPSCs can replace lost or damaged neurons, modulate immune responses, promote endogenous repair, and provide neurotrophic support to injured neural circuits [63]. However, several challenges still impede clinical translation, including optimization of cell

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sourcing and differentiation protocols, refinement of delivery systems, and mitigation of safety concerns such as tumorigenicity and immune rejection.

Currently, most findings are derived from preclinical animal models, and there remains a paucity of validation from large-scale, multi-center clinical trials. Given the multifactorial pathogenesis of neurological diseases, single-modality therapies are unlikely to achieve optimal outcomes. Multimodal strategies-combining iPSC transplantation with gene editing, neuroprotective pharmacotherapy, rehabilitation, advanced biomaterials, 3D bioprinting, or optogenetic modulation-offer a promising path toward synergistic, multi-targeted interventions.

In the future, the integration of iPSC-based approaches with emerging technologies such as single-cell omics, organoid modeling, and advanced neuroimaging will enable the development of personalized and precision therapies. As iPSC technologies continue to mature, they are poised to play a pivotal role in bridging basic research and clinical application, ultimately transforming the therapeutic landscape for neurological diseases.

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