The Open Neurology Journal
DOI: 10.2174/011874205X512493261103041510, 2026, 20, e1874205X512493
ISSN: 1874-205X
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REVIEW ARTICLE OPEN ACCESS

Molecular Heterogeneity of α-synuclein Pathology and Its Implications for Cell Therapy in Parkinson's Disease

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Abstract:
Parkinson's Disease (PD) is one of the major progressive neurodegenerative disorders and is predicted to become a growing global health burden in the near future owing to the aging population. The marked loss of dopaminergic neurons and the deposition of Lewy bodies in the brain are hallmarks of PD, leading to motor dysfunction and reduced quality of life. Several molecular and cellular mechanisms have been identified as underlying the pathogenesis of PD, highlighting the molecular heterogeneity. Moreover, numerous non-motor and motor symptoms emerge at different stages of PD progression. Although there is currently no cure for PD, levodopa and other medications are widely used to alleviate PD symptoms. However, prolonged use of these medications can lead to several complications and reduced effectiveness. Consequently, there is an urgent need for novel therapies for PD. Cell therapy is an emerging approach that is gaining attention as a potential treatment for PD. This review specifically aims to summarize the molecular heterogeneity of α-synuclein (α-syn) pathology, the cellular mechanisms underlying PD pathology, PD symptoms, and the potential of cell therapy as a treatment for PD. Moreover, key findings from recently published studies on cell therapy for PD are discussed, including therapeutic outcomes, challenges, limitations, and future directions. Overall, this review provides insights into the heterogeneity of α-syn pathology and other possible molecular mechanisms in PD, and discusses the potential of cell therapy for future clinical applications in PD management.

Keywords: Alpha-synuclein pathology, Cell therapy, Emerging treatment, Molecular heterogeneity, Neurodegeneration, Parkinson's disease.

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Cite as: Kodippili S, Mapa M. Molecular Heterogeneity of α-synuclein Pathology and Its Implications for Cell Therapy in Parkinson's Disease. Open Neurol J, 2026; 20: e1874205X512493.
http://dx.doi.org/10.2174/011874205X512493261103041510

Received: May 23, 2026
Revised: September 10, 2026
Accepted: September 11, 2026
Published: November 24, 2026

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1. INTRODUCTION

Parkinson's Disease (PD) is a progressive Neurodegenerative Disorder (ND) that is characterized by two major pathological hallmarks, including the loss of dopaminergic neurons (DaNs) in the substantia nigra and the accumulation of Lewy bodies, which are mainly composed of misfolded alpha-synuclein (α-syn) [1]. Moreover, PD is the fastest-growing ND [2], imposing a substantial burden on the global healthcare sector, society, and the economy [3]. The prevalence of PD increases to approximately 3% among people aged over 65 years and 5% among those over 85 years of age, illustrating the substantial impact of aging on PD prevalence [4]. As PD is one of the major contributors to global disability [5], increasing attention has been directed toward its potential growth trends. Recent findings have revealed that the incidence, prevalence, and years lived with disability of PD are increasing in most countries and regions, aligning with the aging tendency of the

population [5-7]. Notably, a higher PD prevalence is observed in countries with a greater sociodemographic index and human development index [7]. In addition, the number of people living with PD is projected to reach 25.2 million by 2050, which would be a 112% increase compared to 2021 [2].

PD is highly heterogeneous in terms of age of onset, rate of progression, and clinical manifestations [8, 9]. Although the exact biological mechanism underlying this variability in clinical phenotypes has not yet been fully elucidated, molecular heterogeneity, especially the heterogeneity of α-syn aggregates, may substantially contribute to heterogeneity in clinical phenotype and prognosis [8, 10]. Moreover, PD is considered a multifactorial disease, with both endogenous and exogenous factors contributing to its pathogenesis [11]. Aging is the main risk factor for PD [12]. Other risk factors include environmental and genetic factors, epigenetic modifications, lifestyle, diet, comorbidities, and drugs [13]. For instance, exposure to pesticides [14] and dairy milk consumption [15, 16] have been associated with an increased risk of PD, whereas ibuprofen and other non-aspirin Nonsteroidal Anti-Inflammatory Medications (NSAIDs) have been associated with a reduced risk of PD [17].

Low dopamine (DA) levels resulting from the loss of DaNs in the substantia nigra of individuals with PD are the primary cause of motor disturbances such as resting tremor, bradykinesia, rigidity, and postural reflex disturbances [18]. These motor dysfunctions markedly affect PD patients' regular work and ultimately reduce their quality of life. Notably, these motor impairments often appear only after the disease has been developing silently for years [19]. Thus, PD can be classified into three different stages based on symptom onset: preclinical, prodromal, and clinical stages. Neurodegeneration begins without clinical signs during the preclinical stage [20]. Subsequently, non-motor symptoms of PD, including idiopathic rapid eye movement sleep behavior disorder, constipation, anxiety, hyposmia, and depression, are commonly observed during the prodromal stage as a result of continuous neurodegeneration (Fig. **1**). The first motor symptoms appear during the clinical stage due to the loss of approximately 40-60% of DaNs [20]. Consequently, patients enter the early stage of PD, as shown in Fig. (**1**). During the mid-stage of PD, 3,4-dihydroxy-L-phenylalanine (L-dopa)-induced complications are typical [20].

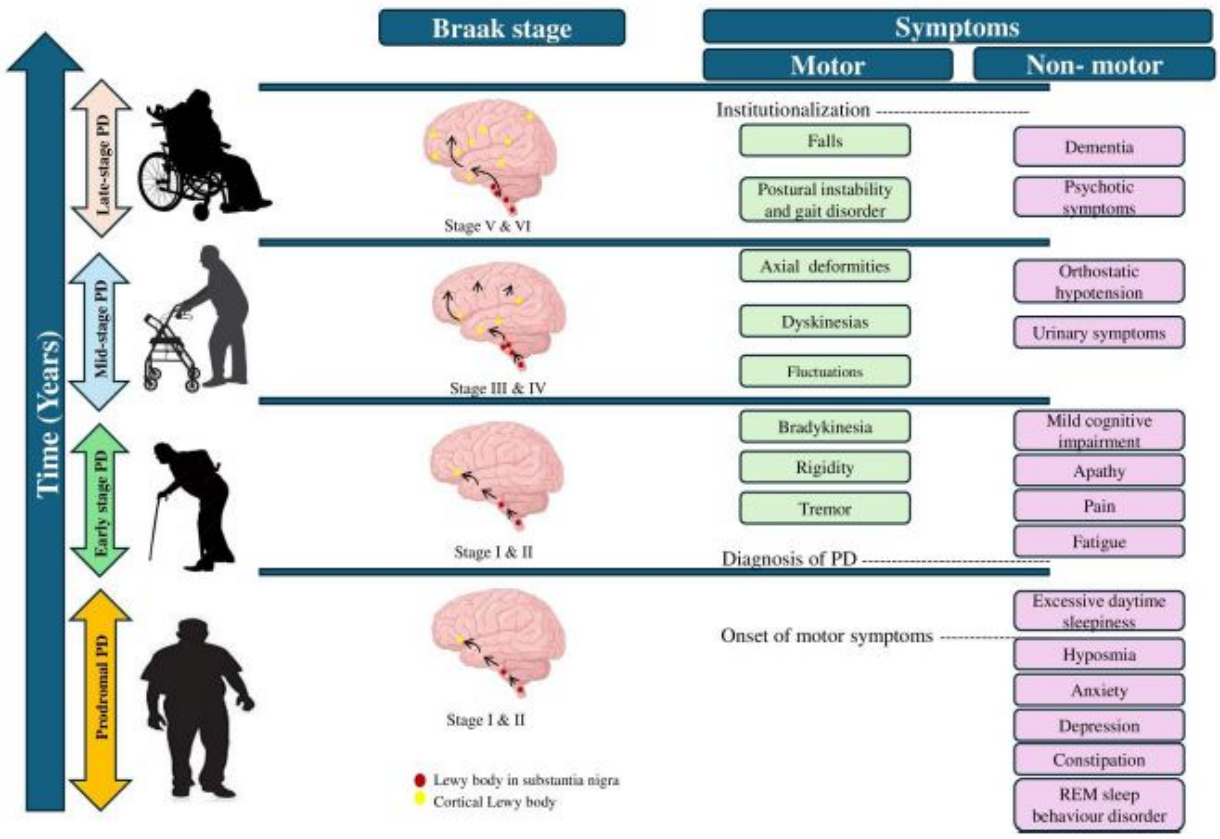

Fig. (1). The proposed progression stages of PD, based on the appearance of clinical symptoms and the Braak staging system. Clinical symptoms and Lewy body propagation are highly heterogeneous among patients. The Braak staging system does not account for all PD cases.

The Braak staging system of PD describes the appearance of pathological Lewy bodies in the brainstem and olfactory bulb in the early stages and their gradual spread into the cortex as the disease progresses [20, 21] (Fig. **1**). However, Braak staging is one of several models that describe the distribution of α-syn inclusions across different stages of PD and does not explain all cases of PD. Furthermore, the α-syn origin and connectome (SOC) model explains the variation in the origin sites of pathological α-syn aggregates among individuals with PD, resulting in two main α-syn propagation routes, namely, brain-first and body-first [22]. The brain-first model proposes that α-syn aggregation, accumulation, and pathology begin unilaterally (mainly in the olfactory bulb or amygdala) and then spread. In contrast, the body-first model proposes that pathological α-syn aggregates originate in the peripheral nervous system (mostly the enteric nervous system) and then spread to the central nervous system [22]. This SOC model further suggests that the clinical heterogeneity of PD may reflect the molecular heterogeneity of α-syn aggregates in terms of structure, conformation, and function, depending on the site of origin and route of propagation.

2. LITERATURE REVIEW METHODOLOGY

This narrative review aimed to summarize and critically evaluate the evidence on the molecular heterogeneity of α-syn pathology and its implications for cell therapy in PD. A literature search was conducted using the PubMed database from February to September 2026. Search terms included variations and combinations of terms such as "alpha-synuclein (α-synuclein) pathology", "Parkinson's disease (PD)", "molecular heterogeneity", "cell therapy", "stem cell therapy". Boolean operators (AND, OR) were used to combine these search terms. In addition, the reference lists of relevant articles were manually screened to identify additional sources that were not recognized by the primary search. No strict date restriction was applied to the search, as the aim was to gather both fundamental literature (on the pathology of PD, the cellular and molecular mechanisms of PD, and early cell therapy approaches) and the most recent evidence on the molecular heterogeneity of α-syn pathology and its implications for cell therapy studies in PD management. The full texts of relevant articles were assessed in detail, and grey literature was excluded. Articles that met the inclusion criteria were peer-reviewed and published in English.

3. MOLECULAR AND CELLULAR MECHANISMS OF PD

Notably, NDs, including PD, are no longer considered isolated diseases because of their multifaceted symptoms, varied patterns of disease progression, and treatment responses [23]. Overlaps in genetic and molecular mechanisms have been reported among NDs [24, 25]. For instance, a genetic correlation among amyotrophic lateral sclerosis (ALS), Lewy body dementia (LBD), and PD has been identified at the transmembrane protein 175 (TMEM175) locus [24]. Moreover, aging, oxidative stress, defective proteostasis, calcium ion-induced excitotoxicity, and neuroinflammation have been identified as convergent mechanisms shared among Alzheimer's disease (AD), PD, and ALS [25].

In PD, several molecular and cellular mechanisms, including misfolded protein aggregation, genetic and epigenetic modifications, impairment of protein degradation pathways, mitochondrial dysfunction, oxidative stress, neuroinflammation, and oral and gut dysbiosis, have been linked to both sporadic and familial PD [26]. Furthermore, PD pathology involves several interconnected molecular pathways rather than a single pathway, as illustrated in Fig. (**2**). Therefore, it is imperative to understand these fundamental mechanisms and the molecular heterogeneity of PD in order to develop the most effective, safe, and disease-modifying therapeutic interventions.

3.1. Genetic and Epigenetic Modifications

Genetic factors play a crucial role in the pathogenesis of PD. Although most PD cases are sporadic and idiopathic, about 10-15% of cases are familial or inherited forms that follow Mendelian inheritance, with both autosomal recessive and autosomal dominant modes [27]. Mutations in the α-syn (SNCA) and leucine-rich repeat kinase 2 (LRRK2) genes are known to cause the autosomal dominant form of PD, while mutations in the Parkin (PARK2), PINK1 (PARK6), DJ-1 (PARK7), and ATP13A2 (PARK9) genes are associated with autosomal recessive PD [28]. Collectively, these six genes have been strongly linked to monogenic PD. Moreover, they are involved in different biological pathways, and mutations in these genes contribute to the pathogenesis of PD.

In addition, epigenetic mechanisms, such as DNA methylation, post-translational modifications of histones, microRNAs and long non-coding RNAs, have been linked to PD pathology. For instance, S-adenosyl homocysteine, a byproduct of the S-adenosylmethionine methylation reaction, is rapidly metabolized into homocysteine, which is recognized as a potential risk factor for PD [29]. Moreover, microRNAs are directly associated with biological pathways that are involved in PD pathology [30].

3.2. Aggregation of Misfolded Proteins

The SNCA gene encodes the native form of the cytoplasmic protein α-syn. The key role of α-syn is to regulate neurotransmitter release at presynaptic terminals by stimulating the soluble N-ethylmaleimide-sensitive factor attachment protein receptor-complex assembly [31]. However, under pathological conditions, the biological, functional, and structural properties of α-syn can differ substantially from those of the native protein.

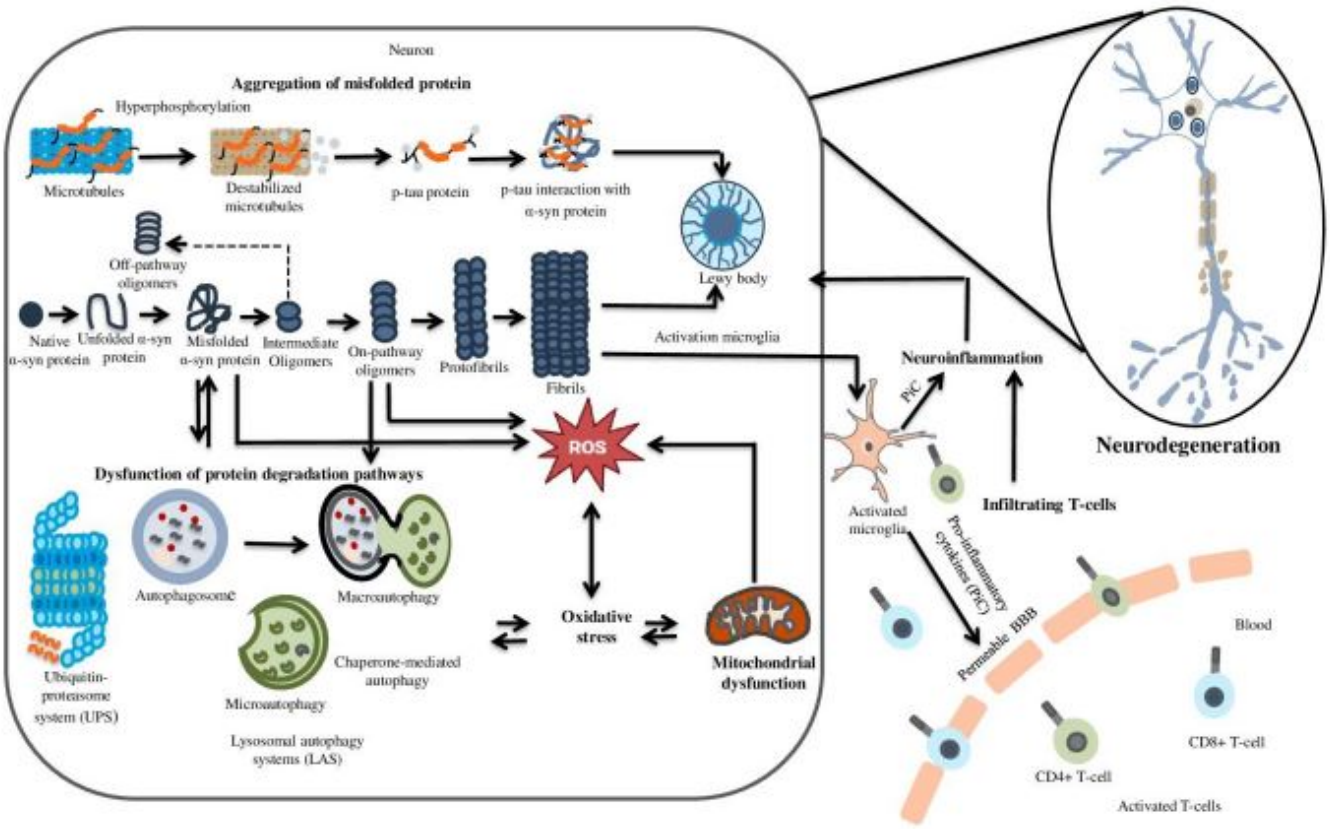

Fig. (2). Major molecular pathways and their interactions in PD pathology, highlighting the molecular heterogeneity in the development and progression of PD.

Table 1. Heterogeneity of α-syn conformers and their clinical relevance.

α-syn Aggregate Conformer	Predominant Cell Type	Clinical Syndrome	Progression Rate	Detectability by SAA	References
Lewy fold	Neurons	Parkinson's disease, PD dementia and Dementia with Lewy bodies	Gradual progression	High detectability has been reported, with a sensitivity of 97.8% and a specificity of 100% in a specific study cohort and assay setting.	[8, 36, 47]
Multiple system atrophy-derived α-syn filaments (Types I and II)	Oligodendrocytes	Multiple system atrophy	Faster progression than PD	Successful amplification with preserved structural and biological characteristics has been reported in a specific assay setting.	[37, 48, 49]
JOS fold	Neurons	Juvenile-onset synucleinopathy	Rapid progression	Not yet reported	[38]

3.2.1. Structural and Conformational Heterogeneity of α-syn Aggregates

The heterogeneity of α-syn can be considered along at least two complementary axes: structural (morphological) heterogeneity, which describes the physical organization of the aggregates, and functional heterogeneity, which describes differences in seeding, propagation, toxicity, and cellular interactions. These dimensions require different analytical approaches and may have distinct diagnostic and therapeutic implications.

The process of α-syn misfolding and aggregation involves multiple steps and ultimately results in a spectrum of various α-syn species and multiple conformational states, including monomers, oligomers, protofibrils, and fibrils [18]. Oligomers are prefibrillar α-syn species that show considerable structural heterogeneity in molecular weight and morphology [32]. Off-fibrillar-pathway oligomers contribute to the formation of amorphous, non-fibrillar assemblies. In contrast, on-fibrillar-pathway oligomers act as precursors and lead to α-syn fibril formation. Fibrils of α-syn are well-ordered

cross-β-sheet structures that exhibit heterogeneity in length, width, morphology, and protofilament organization. Some of these fibrils can be incorporated into inclusions, such as Lewy bodies, Lewy neurites, or glial cytoplasmic inclusions. Moreover, some α-syn fibrils are involved in the spread of pathology between neurons [33, 34]. Notably, the polymorphic nature of α-syn fibrils gives rise to distinct structural and conformational heterogeneity, ultimately resulting in differences in α-syn conformers across synucleinopathies [33, 35]. For example, only one dominant α-syn filament type, made of a single protofilament and called the "Lewy fold", is found in the brains of patients with PD, PD dementia (PDD), and dementia with Lewy bodies (DLB) [36], whereas two distinct types of α-syn filaments are found in the brain-derived inclusions of patients with Multiple System Atrophy (MSA) [37]. Furthermore, each of these MSA filament types consists of two different asymmetric protofilaments (PF-IA, PF-IB, PF-IIA, PF-IIB) with an extended N-terminal arm and a compact C-terminal body [37]. Additionally, mutations in SNCA contribute to the formation of a distinct α-syn fibril conformer and cause Juvenile-Onset Synucleinopathy (JOS) [38] Table **1**. Importantly, this structural heterogeneity can now be investigated using structural and imaging approaches, including cryo-electron microscopy for near-atomic fibril structure [36, 37], conventional electron microscopy or atomic force microscopy for fibril morphology or dimensions [39], and super-resolution or single-molecule imaging for aggregate-size distributions and spatial heterogeneity [40]. Moreover, biochemical fractionation, size-exclusion chromatography, and native separation methods can further help to resolve aggregate-size distributions [41]. This structural characterization of α-syn aggregates supports molecular classification of pathology, identification of disease-associated aggregate populations, comparison of brain-derived and experimental aggregates, and assessment of whether particular antibodies or therapeutic strategies preferentially target specific aggregate structures.

The functional heterogeneity of α-syn describes differences in biological activity. Different α-syn assemblies may differ in seeding efficiency and amplification kinetics, cellular uptake and propagation, membrane disruption, neuronal toxicity, impairment of proteostasis, inflammatory activation, cell-type tropism, and host-to-graft transmission [8]. For instance, MSA-derived α-syn filaments exhibited approximately 1000-fold higher seeding potency than Lewy body-derived α-syn, which may explain the rapid clinical progression of MSA [42]. Moreover, the same study also highlighted that the intracellular environment plays a key role in determining the identity of the α-syn strain, rather than the strain's identity determining which cell type is affected. In addition, one study showed that brain homogenates from MSA patients transmitted α-syn pathology efficiently to transgenic mice expressing α-syn, whereas PD-derived brain homogenates failed to induce such pathology [43]. These results support a possible explanation for the more aggressive progression of MSA compared with PD. The study also highlighted that the differences in seeding activity, propagation, and biological behaviors of pathological α-syn contribute to pathological and clinical heterogeneity across synucleinopathies [43]. The functional heterogeneity of α-syn conformers can now be evaluated using various functional assays, including Seed Amplification Assays (SAA) such as real-time quaking-induced conversion (RT-QuIC) or related amplification assays for seeding competence and kinetics, cell-based seeding or biosensor assays, neuronal uptake and propagation assays, toxicity and membrane-damage assays, animal transmission studies, and assays measuring microglial or inflammatory responses. For example, SAA/RT-QuIC can accurately differentiate between PD and MSA conformers in cerebrospinal fluid based on proteoform-specific aggregation kinetics [44]. The study showed that α-syn seeds of MSA exhibited faster propagation and greater aggregation kinetics than those of PD [44]. In addition, single-molecule seed amplification assays (smSAA) have also revealed the functional heterogeneity of α-syn aggregates. Furthermore, data from the Parkinson's Progression Markers Initiative (PPMI) showed variation in SAA positivity among subgroups of PD, with lower positivity in LRRK2 carriers [45] and higher positivity in patients with hyposmia [46]. Therefore, these findings suggest that PD is not a single molecular entity. Importantly, this functional heterogeneity may be particularly useful for patient stratification, prediction of disease progression, evaluation of graft vulnerability, and selection or monitoring of therapies targeting propagation or seeding activity.

Moreover, pathological α-syn can propagate *via* brain-first or body-first routes, according to the SOC model described in the Introduction. The heterogeneity of α-syn aggregates contributes to the clinical variability observed in patients with PD. Clinical subtypes have been identified based on disease presentation, medication responsiveness, and progression, namely mild-motor predominant, intermediate, and diffuse-malignant [50]. The mild-motor predominant subtype is associated with mild motor symptoms, a good response to DA medication, and slow progression, whereas the intermediate subtype is characterized by moderate motor and non-motor symptoms and moderate progression. In contrast, the diffuse-malignant subtype shows rapid disease progression, resistance to DA medication, and severe motor symptoms [50].

Importantly, emerging evidence shows that α-syn pathology alone does not define PD [51, 52]. Co-pathologies, such as phosphorylated tau (p-tau), amyloid-β (Aβ), and TAR DNA-binding protein 43 (TDP-43), which are also associated with AD, ALS, frontotemporal dementia, and other neurodegenerative diseases, significantly contribute to PD pathology and the heterogeneity of the disease [51-55]. For example, severe Lewy body pathology with AD neuropathological changes was found in a cohort of autopsy-confirmed PD patients, highlighting the potential impact of cross-seeding between

α-syn and Aβ on the rapid progression of PD [52]. Moreover, an elevated cerebrospinal fluid p-tau/total tau ratio was identified as a predictor of a higher risk of motor complications among patients with PD [54]. In addition, p-tau is known to interact with α-syn in Lewy bodies (Fig. **2**), consequently leading to rapid loss of DaNs in the brain [56]. The coexistence of tau aggregates and α-syn aggregates has been found to affect disease progression, protein misfolding, and molecular interactions in individuals with PD [57]. Furthermore, mutations in the TARDBP gene, which encodes the TDP-43 protein, have been identified as one of the genetic contributors to the clinical heterogeneity of PD [55]. A recent study also revealed that these co-pathologies (α-syn, p-tau, and Aβ) exacerbate proteinopathy and synergistically enhance neuroinflammation and neurodegeneration [58]. Overall, these co-pathologies and their associated cross-seeding interactions with α-syn (α-syn/p-tau and α-syn/Aβ*)* may substantially contribute to PD heterogeneity [59]. Therefore, co-pathologies should also be taken into account during therapeutic intervention, rather than treating PD entirely as a synucleinopathy.

Biological classification frameworks that rely primarily on biological markers rather than clinical symptoms have been introduced, including the Synucleinopathy-Neurodegeneration-Genetics (SynNeurGe) and the Neuronal α-synuclein Disease Integrated Staging System (NSD-ISS). These frameworks aim to improve diagnosis, patient stratification, precision medicine, and disease staging by addressing the molecular heterogeneity of PD [60]. SynNeurGe provides a comprehensive framework that integrates α-syn pathology, genetics, and neurodegeneration with clinical features. In contrast, NSD-ISS provides a staging system based on biological markers and clinical impairment, enabling the monitoring of PD progression. However, limitations, including biomarker availability and validation, restrict the clinical use of these frameworks [60].

3.3. Impairment of Protein Degradation Pathways

The Ubiquitin-Proteasome System (UPS) and lysosomal autophagy system play crucial roles in balancing protein synthesis and degradation [61]. Notably, these protein degradation pathways are important for refolding or degrading misfolded proteins, including α-syn, which has a strong impact on PD. Thus, impairment of either of these proteostasis systems can increase α-syn levels in nigral DaNs and intensify neurotoxicity [62]. Moreover, α-syn oligomers have been found to inhibit UPS [63] and macroautophagy [64] (Fig. **2**). Aggregated α-syn can also impair the chaperone-mediated autophagy system [65]. In addition, mutations in PD-associated genes (PARK2, UCHL1) also significantly contribute to the impairment of protein degradation mechanisms [66].

3.4. Mitochondrial Dysfunction

Mitochondrial dysfunction is well established as a key feature of PD pathology. The activity of electron transport chain complex I in DaNs has been found to be impaired in PD patients as a result of oxidative damage, α-syn aggregation [67], assembly defects, exposure to environmental toxins, and genetic mutations in mitochondrial DNA and nuclear DNA-encoded subunits [68]. Consequently, these changes lead to increased free radical production and dysregulated mitophagy [67]. Moreover, mutations in SNCA, Parkin, PINK1, DJ-1, and LRRK2 alter the function of mitochondria. The transcription coactivator peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) plays an important role in regulating mitochondrial biogenesis. However, hypermethylation of the gene encoding PGC-1α reduces its expression in individuals with PD [69] and consequently disturbs mitochondrial adenosine triphosphate production [70]. In addition, downregulation of PGC-1α amplifies the α-syn oligomerization, thereby increasing neurotoxicity [71]. Furthermore, alteration of the mitochondrial fission and fusion mechanisms is a critical feature of impaired mitophagy-driven mitochondrial dysfunction. For example, mutations in genes encoding for the proteins dynamin-related protein 1, mitochondrial fusion proteins 1 and 2, and optic atrophy 1, which are involved in mitochondrial fission and fusion, contribute to electron transport chain impairment and degeneration of DaNs [72, 73].

3.5. Oxidative Stress

Oxidative stress is recognized as a common mechanism of cellular dysfunction that arises from an imbalance between Reactive Oxygen Species (ROS) and antioxidant defenses at the cellular level (Fig. **2**). DA auto-oxidation has been suggested to generate free radicals and reactive quinones that increase methamphetamine-induced toxicity, oxidative stress, and modification of PD-related proteins [74, 75]. Moreover, an *in vitro* experiment has suggested that DA derived from L-dopa can itself trigger oxidative stress in serotonin neurons and consequently generate excess cytotoxic ROS [76]. However, the results of the ELLDOPA study did not demonstrate clinically significant L-dopa-induced PD progression [77]. In addition, oxidative phosphorylation in mitochondria is the major process that produces ROS in cells [78] and a deficiency in complex I of the respiratory chain is believed to be the primary source of ROS in PD [75]. Complex I inhibitors, such as rotenone and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), have also been shown to induce oxidative damage in cells [79, 80]. Furthermore, various genetic mutations linked to mitochondrial dysfunction lead to oxidative stress in DaNs [81].

3.6. Neuroinflammation

PD has increasingly been proposed as a multi-organ syndrome rather than a disease restricted to the dopaminergic midbrain, because it may affect multiple axonal pathways in the central and peripheral nervous systems [82-84]. This concept highlights the potential contribution of systemic immune responses in PD, alongside local immune responses driven by activated microglia. However, this framework remains debated.

As a major resident immune cell type, microglia

contribute to clearing foreign substances in the brain *via* phagocytosis and cytotoxicity mechanisms [85]. Although ramified microglia (with a small cell body and long branches) contribute to maintaining an immunologically stable environment, under pathological conditions such as the presence of aggregated α-syn, oxidative stress, neurotoxins, and ion imbalances, these microglia transform into a fully activated phagocytic form known as activated microglia (with thickened and retracted branches) [85]. However, overactivated microglia induce neuroinflammation, produce pro-inflammatory cytokines such as interleukin-6 (IL-6), IL-1, IL-17A, and Tumor Necrosis Factor-alpha (TNF-α) [86], and express inflammasomes such as the nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing 3. Ultimately, these neuroinflammatory reactions accelerate the loss of DaNs and reduce the integrity of the Blood-Brain Barrier (BBB) [87]. For example, α-syn fibrils, TNF-α, and prostaglandin E_2, which are associated with PD, cause microglial activation and consequently induce marked neurotoxicity by releasing glutamate and retaining iron [88]. Moreover, peripheral inflammatory mechanisms lead to increased BBB permeability by altering the expression of proteins such as claudin-5 and occludin within BBB junctions [89]. Because of the increased permeability of the BBB, activated T-cells (cytotoxic T-lymphocytes – CD8+ and T-helper cells–CD4+) infiltrate the inflamed brain region and trigger the production of neurotoxic factors (Fig. **2**) [90, 91].

3.7. Oral and Gut Dysbiosis

Oral and gut dysbiosis is an alteration in the diversity and balance of the oral and gut microbiota, caused by external and internal factors under diseased conditions [92]. The oral-gut-brain axis is a bidirectional communication pathway that comprises the oral-gut axis (functional interaction of microbiota *via* the bloodstream and the digestive tract), the gut-brain axis (interaction mediated by neural, immune, and endocrine pathways), and the oral-brain axis (mediated by the trigeminal nerve) [93]. This oral-gut-brain axis plays a substantial role in PD progression by mediating oral and gut dysbiosis. For example, a preclinical animal study demonstrated that oral administration of the periodontal pathogen, *Porphyromonas gingivalis* (oral gavage of 10^9 colony-forming units) induced gut dysbiosis, enhanced T-lymphocyte and myeloid-cell responses in the peripheral and central nervous systems, and impaired glymphatic function, which triggered neuroinflammation and ultimately led to cognitive decline [94]. Moreover, oral pathogens, including *Veillonella parvula* and *Streptococcus* mutans, have also been found to cause motor dysfunction, microglial activation, and T-helper cell infiltration in the brains of animal models [95]. In addition, oral species, such as *Lactobacillus, Tannerella forsythia, and Prevotella intermedia,* have been identified as potential pathogens in the soft tissues of PD patients. *Streptococcus pneumoniae, Mycoplasma orale, and Streptococcus constellatus* are endogenous opportunistic pathogens that show increased abundance [96]. Furthermore, the abundance of *Lachnospiraceae* and *Prevotellaceae* is decreased, while that of *Verrucomicrobiaceae* and *Lactobacillaceae* is increased during gut dysbiosis in patients with PD [97]. Moreover, changes in the gut microbiome community have also been shown to promote misfolding and aggregation of α-syn in the intestine [98]. The levels of bacterial short-chain fatty acids decrease, whereas lipopolysaccharide levels increase, in PD as a result of gut dysbiosis [99]. Consequently, this leads to increased gut leakiness, production of pro-inflammatory cytokines, increased α-syn deposition in the gastrointestinal tract, and activation of mucosal immune cells, eventually resulting in systemic inflammation [97, 100]. In addition, preclinical evidence has demonstrated gut-to-brain propagation of α-syn through the vagus nerve. Intestinal organoid and transgenic mouse models showed that α-syn originating in intestinal epithelial cells was transferred through the vagal pathway and detected in the dorsal motor nucleus and the vagus nerve [101], highlighting the role of the gut-brain axis in PD.

4. OVERVIEW OF CURRENT PD TREATMENT APPROACHES

Currently, there are no effective disease-modifying treatments for PD that can slow, delay, or reverse its progression. Symptomatic therapies are widely used to manage motor symptoms of PD. L-dopa is considered the gold standard for PD treatment [102]. L-dopa is most often administered in combination with decarboxylase inhibitors such as benserazide and carbidopa to improve its bioavailability and half-life [103]. In addition, DA agonists (apomorphine, pramipexole, ropinirole, and rotigotine) are used to enhance dopaminergic activity. Catechol-O-methyltransferase inhibitors (entacapone, tolcapone, and opicapone) and monoamine oxidase B (MAO-B) inhibitors (selegiline, rasagiline, and safinamide) are used to reduce the metabolism of endogenous DA [104-106]. However, prolonged use of these medications leads to motor complications, such as dyskinesias, and off-target effects, such as hallucinations and impulse control disorders [107]. Moreover, these medications are not very effective for patients with late-stage PD. Deep Brain Stimulation (DBS), which stimulates a target brain region with electrical signals *via* an implanted electrode, is a surgical therapy for PD [108]. However, DBS remains an underutilized therapy for PD because of the potential risks of neurosurgical procedures and other adverse effects [109]. In addition, a novel non-invasive method called magnetic resonance–guided focused ultrasound has been approved by the Food and Drug Administration (FDA) to treat dyskinesia, rigidity, bradykinesia, and tremor-dominant PD [110]. However, this method has limitations such as dependence on scalp properties, potential adverse effects, lack of adjustability, and unilaterality [110]. In addition, transcranial ultrasound stimulation is another non-invasive neuromodulation method that is still in the optimization stage, with limited research to date [111]. Recent efforts have also focused on the continuous delivery of

dopaminergic drugs to achieve a more linear dopaminergic tone. Levodopa-carbidopa intestinal gel (LCIG) and levodopa-entacapone-carbidopa intestinal gel (LECIG) are advancements in PD treatment that help individualize the dose of levodopa while maintaining a sustained DA level in the brain [112-114]. Nevertheless, the use of LCIG and LECIG therapies is limited by their high cost, surgical complications, and the undesirability of attached infusion pumps. Overall, these current treatments neither halt PD progression nor effectively alleviate symptoms in patients with advanced PD [115]. Therefore, global research attention is increasingly focused on developing novel anti-Parkinson's therapies that are more effective and safer to overcome the drawbacks of existing treatment approaches.

5. CELL THERAPY AS AN EMERGING THERAPEUTIC APPROACH FOR PD

Cell therapy is a key approach in regenerative medicine that treats or prevents diseases through the administration of cells that have been specifically selected, manipulated, or engineered outside the body [88]. Due to the capability of selected cells to replace lost or damaged DaNs in the brain, researchers have increasingly investigated the potential of cell-based therapy to restore DA levels, reduce neuroinflammation, and produce neurotrophic factors in the brains of patients with PD, ultimately mitigating the limitations of existing PD treatments.

However, the therapeutic success of cell therapy for PD can only be achieved by considering PD as a heterogeneous disease. Notably, different α-syn conformers may interact differently with transplanted neurons or therapeutic antibodies. Moreover, the functional heterogeneity of α-syn, especially its seeding potency and propagation, may determine how rapidly host pathology is transmitted to a graft and consequently may influence graft function, survival, and vulnerability. Therefore, the structural and functional heterogeneity of α-syn should be carefully considered during cell therapy. Although cell therapy has not yet been approved by the FDA for PD, numerous studies have been conducted over several decades to achieve robust and promising outcomes. However, the outcomes of these studies may largely depend on the cell source, cell dose, immunosuppression, endpoints, and follow-up period Table **2**.

Tissue transplantation is one of the key areas of cell replacement therapy. Notably, human fetal ventral mesencephalic tissue (hfVM) is considered the gold standard for cell therapy because of its high content of dopaminergic neuroblasts [116]. Although earlier open-label studies of hfVM transplantation demonstrated promising results in PD [117, 118], the outcomes of double-blind, placebo-controlled trials were different. These trials did not support fetal transplantation as a potential therapy because of the lack of a treatment effect and the emergence of "off"-medication dyskinesia. Furthermore, those double-blind studies highlighted the need for careful consideration of standardized cell dosage, the PD stage of the graft recipient, immunosuppression, and surgical techniques in future research [119, 120]. TransEuro was a recent, open-label, multicenter trial designed to evaluate the sequential bilateral grafting of hfVM in patients with moderate-stage PD, while reducing the variability seen in previous hfVM transplantation trials [121]. The results showed no clear difference in the change from baseline in the Unified Parkinson's Disease Rating Scale (UPDRS) Part III score between the treatment and control groups during the follow-up period (Table **2**). A surgical site-specific difference in the UPDRS-III score was found in the TransEuro trial, which may be attributed to the use of different grafting devices (the original and newly modified Rehncrona–Legradi (R–L) device), differences among neurosurgeons across sites, the PD stage of patients, and differences in graft cellular composition. However, [^{18}F]fluorodopa positron emission tomography imaging showed an improvement in mean dopamine uptake in seven patients 18 months after grafting, but only one patient reached near-normal levels. Moreover, the trial had limitations, including tissue availability, differences in surgical procedures and devices, and patient heterogeneity Table **2**.

Notably, graft durability is one of the crucial factors in cell therapy. Studies with long-term follow-up have demonstrated graft durability and survival after transplantation of hfVM [116, 122, 123]. For example, a patient with PD who received a graft derived from embryonic ventral mesencephalon showed considerable motor improvement and restoration of DA levels 24 years after transplantation, despite approximately 11-12% of the grafted neurons carrying α-syn-positive inclusions [122]. Furthermore, this study suggested the seeding ability of α-syn over decades and the spread of host pathology to the graft [122], reflecting the vulnerability of grafts to pathology over time. However, if the seeding potency of α-syn is strain-dependent, the vulnerability of the graft may also depend on the α-syn strain. Therefore, patients with MSA-derived α-syn strains may be poor candidates for cell therapies that have been validated in Lewy-body diseases, including PD.

Stem cell therapies are considered potent treatments for PD because stem cells can self-renew *via* unlimited replication and differentiate into a variety of cell types [124]. The potential of stem cells to differentiate into DaNs has led to their use in neural grafting. Several types of stem cells, including Embryonic Stem Cells (ESCs), Epiblast Stem Cells (EpiSCs), Human Adipose-Derived Stem Cells (hASCs), Human Umbilical Cord Mesenchymal Stem Cells (hUC-MSCs), and Induced Pluripotent Stem Cells (iPSCs), have shown therapeutic potential for PD in preclinical and clinical studies [125-130].

ESCs are derived from the inner cell mass of the blastocyst, which is an early stage of embryonic development. The potential of Human Embryonic Stem Cell (hESC)-derived DaNs for PD treatment has been evaluated in numerous research studies. In an open-label

phase I clinical trial, dopaminergic neuron progenitor cell product (bemdaneprocel) derived from hESCs was grafted bilaterally into the putamen of patients with PD (Table **2**). This study demonstrated that grafting hESC-derived DaNs was safe and tolerable, with no evidence of serious adverse events or tumor formation directly related to the transplantation [126], thereby achieving the primary outcome of the study. In addition, improvements in motor symptoms and graft survival were also reported. However, limitations, including the small sample size, open-label study design, placebo effects, variability of PD symptoms, and the short follow-up period, may have influenced these outcomes of the study (Table **2**). Therefore, the safety and tolerability of cell therapy should be validated in long-term follow-up studies with a larger sample size to better understand host-to-graft pathology. In addition, preclinical studies have supported the survival of hESC-derived immature midbrain DaNs in Non-Human Primates (NHPs). López-Ornelas *et al.* [131] studied the transplantation of hESC-derived immature midbrain DaNs into parkinsonian monkeys treated with MPTP. This study showed that hESC-derived DaNs can generate action potentials, express dopaminergic markers, and release DA *in vitro*, highlighting the potential for graft survival (Table **2**). Nevertheless, the generalizability of these short-term follow-up results to humans with PD may be limited by the small sample size and the variation in disease presentation at the molecular and clinical levels among patients.

Table 2. Recent preclinical and clinical trials of cell therapy approach against PD.

Trial/Study	Model/Species	Sample Size (n)	Cell Source and Derivation	Dose	Immunosuppression	Follow-Up	Primary Outcomes	Key Limitations	References
TransEuro trial (NCT01898390)	Human (Moderate PD individuals)	Grafted:11 Control:16	Human fetal mesencephalic tissues	3 fetuses/hemisphere	Yes	3 years	• No overall clinical effect	• Lack of tissue availability • Site-to-site variation • Differences in transplantation devices • Heterogeneity in procedures and patient characteristics; open-label study design	[121]
Phase I trial (NCT04802733)	Human (PD individuals)	Grafted:12 (Low dose:5, high dose:7)	Dopaminergic progenitor cells derived from human embryonic stem cells	Low dose: 0.9 million cells/hemisphere High dose: 2.7 million cells/hemisphere	Yes	Primary end point: 1 year Secondary and exploratory end points: 2 years Long-term monitoring: 5 years	• Safety and tolerability at one year post-transplantation	• Small sample size • Open-label study design • Placebo effects • Variability in PD symptoms • Short follow-up period	[126]
Preclinical study	Parkinsonian monkey model	2	Human embryonic stem cells derived immature midbrain DaNs	8×10^6 cells/ hemisphere	Yes	10 months	• Integration and survival of graft • Improved motor behaviors with dopamine release	• Small sample size • Limited generalizability of results to human PD; short follow-up period	[131]
Preclinical study	Hemiparkinsonian rat model	Grafted:7 Sham:8	DaNs derived from engineered mouse embryonic stem cells engineered to produce GDNF	5×10^5 viable cells	Yes	14 weeks	• Graft survival and enhanced midbrain differentiation	• Limited generalizability of results to human PD • No significant motor recovery compared with control	[125]
Preclinical study	Mouse 6-hydroxydopamine (6-OHDA) lesion model pre-treated with L-DOPA	>6/group	Mature midbrain dopaminergic precursors derived from mouse Epiblast Stem Cells (EpiSCs) and primary fetal mouse ventral mesencephalon tissue	3×10^5 cells	No	16 weeks	• No significant difference in functional ability	• L-Dopa and amphetamine-induced abnormal involuntary movements • Limitation in generalizability of results to human PD • Small sample size • Short follow-up period	[127]
Preclinical study	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD mouse model	Grafted:9 MPTP (vehicle): 9 Control: 9	Human adipose-derived stem cells	1×10^6 cells	No	13 weeks	• Survival of DaNs in nigrostriatal pathway • Restoration of neurotrophic factors	• Limited generalizability of results to human PD • Small sample size • Mechanism of action unclear	[137]
Preclinical study	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)- induced PD mouse model	Control group:15 Cell only group:15 PD model group:15 Treatment group:15	Human umbilical cord mesenchymal stem cells	1×10^6 cells	No	6 days	• Neuroprotective effect *via* the gut-brain axis	• Limited generalizability of results to human PD • Small sample size	[128]

Trial/Study	Model/Species	Sample Size (n)	Cell Source and Derivation	Dose	Immunosuppression	Follow-Up	Primary Outcomes	Key Limitations	References
Phase I/II trial (jRCT2090220384)	Human (PD individuals)	7	Dopaminergic progenitors derived from induced pluripotent stem cells	Low dose group: 2.1-2.6 × 10^6 cells/hemisphere High dose group: 5.3-5.5 × 10^6 cells/ hemisphere	Yes	24 months	• Safety and potential clinical benefits	• Lack of postmortem histological analysis • Unclear patient eligibility criteria • Placebo effect • Open-label study design • Single-center trial • Small sample size	[129]
Preclinical study	Parkinsonian monkey model	Autologous:5 Allogeneic: 5	Dopaminergic neurons derived from rhesus monkey induced pluripotent stem cells (RhiPSCs)	Autologous:1-22 million cells; allogeneic:5.5-6 million cells	No	24 months	• Recovery of motor and depressive symptoms with autologous grafting, but not allogeneic grafting	• Small sample size	[130]

Gene modification can play an important role in cell therapy approaches by enhancing graft survival and reducing α-syn pathology. Moreover, neurotrophic factors, including Glial Cell Line-Derived Neurotrophic Factor (GDNF) and brain-derived neurotrophic factor (BDNF), are important for neuroplasticity and the survival of neurons [132]. A study revealed that mouse ESCs transduced with a lentivirus carrying the human GDNF gene differentiated into DaNs and showed enhanced survival of grafted cells and midbrain differentiation after grafting into parkinsonian rats, due to the GDNF expression [125]. In addition, host-to-graft propagation of α-syn pathology is one of the key issues that should be addressed in cell therapy to enhance the therapeutic benefits [133]. Advances in gene-editing tools, such as the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) and CRISPR-associated protein 9 nickase (CRISPR/Cas9n) systems, provide a promising solution for gene modification in this context. For instance, deletion of the endogenous SNCA gene in hESCs using CRISPR/Cas9n resulted in resistance to the formation of α-syn aggregates [134]. However, the origin of ESCs is an important consideration in cell line selection because of the risk of prion contamination, such as that associated with bovine spongiform encephalopathy and variant Creutzfeldt–Jakob disease [135].

Several other stem cells and their paracrine factors [136] have been evaluated for use in stem cell therapy for PD. Transplantation of mature midbrain dopaminergic precursors derived from mouse EpiSCs and primary fetal mouse VM tissue into the striatum of 6-hydroxydopamine (6-OHDA)-lesioned mice pre-treated with L-DOPA was examined by Precious *et al.* [127] to evaluate the function of DaNs derived from EpiSCs against the gold standard, primary fetal VM, in an allograft system. The results showed that tyrosine hydroxylase immune-positive cells and graft volume were not different between the two groups after 16 weeks of transplantation, and both groups showed 80% graft survival. The rotarod test was the only measure to show a significant difference in functional improvement between the two cell sources. The other measures showed no significant difference. Moreover, the rate and severity of drug-induced abnormal movements were similar in both groups, with no significant difference (Table **2**). However, variation in host-to-graft propagation of α-syn pathology and graft vulnerability between these cell sources is important to evaluate over a long-term follow-up period, due to the potential for α-syn accumulation in the graft over time [122]. Park and Chang *et al.* [137] also studied MPTP-induced PD models using repeated intravenous transplantations of hASCs, as described in Table **2**. Interestingly, this study showed the restoration of neurotrophic factors such as BDNF and GDNF in the striatum, along with increased survival of DaNs Table **2**.

The role of the gut-brain axis is crucial in cell therapy. A study evaluated the neuroprotective effects of hUC-MSCs on PD mouse models after intranasal administration. The results revealed motor improvement, a higher number of tyrosine hydroxylase-positive cells (93.08 cells), and an increased DA level (1.56 ng/mg) in the substantia nigra after cell administration [128]. Notably, this study further demonstrated that intranasal administration of hUC-MSCs modulated the gut microbial composition and preserved the goblet cells in the colon, thereby lowering gut inflammation [128], suggesting that the gut-brain axis is a mechanism for neuroprotection. This finding highlights the role of the gut-brain axis in the treatment of PD and the need for cell therapy not only to restore the DaNs in the brain, but also to maintain gut health.

Induced pluripotent stem cells (iPSCs) are pluripotent-state cells that are obtained through cellular reprogramming [138]. Moreover, the properties of iPSCs compared with other cell sources, such as genetic manipulation ability, allogeneic and autologous source availability, immunological compatibility, and the absence of ethical issues, have specifically gained attention for developing cell-based therapy [139]. iPSCs are transplanted through autologous or allogeneic grafting. Autologous grafting of iPSCs has shown potential for personalized treatment and may minimize the risk of graft rejection. However, because the cells are derived from PD patients themselves, they may transmit the inherent genetic liability to the graft [140]. When iPSCs are derived from a PD individual who carries mutations in genes such as SNCA, GBA1, and LRRK2, the resulting iPSCs may retain the underlying genetic characteristics associated with PD pathology. Consequently, this may increase the vulnerability of the graft to PD. However, the genetic-engineering solutions currently exist, as previously described [134]. Moreover, heterogeneity of cell batches

due to genetic variation among individuals, the need for reprogramming, batch-wise protocol optimization and standardization, high cost, and time requirements further limit autologous grafting [141]. Meanwhile, off-the-shelf availability, cost-effectiveness, and established standardization protocols highlight the advantages of allogeneic grafting, even though there is a risk of graft rejection [141]. Research studies have demonstrated both therapeutic improvements and associated limitations of autologous and allogeneic iPSCs grafting Table **2**.

Dopaminergic progenitors produced from iPSCs (established using peripheral blood cells) were bilaterally transplanted into seven PD patients in an open-label, phase-I/II, single-centre trial (jRCT2090220384), as described in Table **2**. The results showed that the treatment was safe, with no serious adverse events, such as hospitalization or death. Interestingly, there was a gradual increase in graft size over 24 months, without tumor formation. Notably, dopamine levels showed increases of 7% and 63.5% in the low- and high-dose brain hemispheres, respectively, in treated patients, according to [^{18}F]fluorodopa positron emission tomography imaging results. Although motor function improved with and without medication after cell therapy, the combined Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) parts I + II + III OFF score showed only mild improvement. Moreover, this study had limitations including a placebo effect that could have influenced the results [129] (Table **2**). Tao *et al.* [130] studied the effectiveness of autologous transplantation of iPSCs compared with allogeneic transplantation in PD monkey models without immunosuppression. In this study, primary dermal fibroblasts were isolated from rhesus monkeys and reprogrammed into rhesus monkey iPSCs (RhiPSCs). Transplantation of DaNs derived from RhiPSCs was evaluated for its effects on motor function and depressive behavior in PD monkeys. The results demonstrated recovery of motor and depressive signs with autologous grafting, but not with allogeneic grafting [130]. Moreover, DA activity, tyrosine hydroxylase-positive neurons, and fibers were higher with autologous grafting than with allogeneic grafting, highlighting greater DA neuron survival. Nevertheless, inflammatory and immune responses ($CD3^+$, $CD45^+$, $CD68^+$, GFAP+) were higher around allogeneic grafts than around autologous grafts. These resulting differences in immune responses were primarily driven by immune rejection of the allogeneic grafts, which occurred due to the absence of immunosuppression.

Overall, all of the above preclinical and clinical trials provide a comprehensive understanding of addressing the heterogeneity of PD pathology through cell therapy, rather than focusing only on DA restoration through the replacement of DaNs.

6. FUTURE DIRECTIONS

Molecular heterogeneity of PD, especially the structural and conformational heterogeneity of α-syn, is widely recognized as a key determinant of disease progression, phenotypes, and therapeutic responses. The α-syn conformer-dependent biological characteristics contribute to the variation in pathology and symptoms among PD patients. Therefore, molecular stratification by SAA will be important for patient selection before the enrollment of patients in clinical trials, rather than relying on clinical stratification. It may provide a homogeneous group of PD individuals with similar molecular and phenotypic characteristics, contributing to more reliable experimental outcomes. Moreover, most cell therapy research has primarily aimed to improve the motor symptoms of PD as a symptomatic treatment, with little concern for non-motor symptoms. Future cell therapy-related research is needed to address this limitation. Furthermore, the identification of non-invasive biomarkers will help overcome the limitations of animal models of PD, such as their failure to replicate the true pathophysiology [142]. In addition, it is imperative to design cell therapy with cost-effectiveness, scalability, and market acceptance in order to ensure commercial viability and accessibility for future clinical applications. However, cell therapy is still at the experimental stage and has not been approved for clinical applications. Therefore, considerable attention to preclinical and clinical trials is required not only to enhance the treatment efficacy but also to ensure long-term safety measures. The combination of cell therapy with disease-modifying therapies for PD treatment may produce a synergistic effect compared with individual therapies. Therefore, investigating the combination of cell therapy with other potential disease-modifying therapies will be crucial in the future.

CONCLUSION

Heterogeneity of α-syn aggregates is one of the major molecular mechanisms that primarily determines the rate of disease progression, clinical phenotypes, and pathology in PD, depending on the α-syn conformer and its functional properties. In addition, other molecular mechanisms are also important for understanding PD pathology. Cell therapy is a promising therapeutic approach for PD. DaNs derived from different cell sources are potentially effective in replacing lost DaNs in the brain and restoring DA levels, providing therapeutic benefits at the experimental level. However, the outcomes have shown differences between experiments, due to the variation in cell sources, experimental design, PD patients, sample sizes, and follow-up periods. Moreover, cell therapy should address the heterogeneity of PD pathology, rather than limiting its focus to DaNs replacement. Therefore, molecular stratification of PD will be important for the development of cell therapy as a personalized treatment approach.

AUTHORS' CONTRIBUTIONS

S.P.K., M.S.T.M: Writing - Original draft; M.S.T.M., S.P.K: Writing - Review and editing; M.S.T.M: Supervision; M.S.T.M, S.P.K: Conceptualization; M.S.T.M: Funding acquisition.

LIST OF ABBREVIATIONS

PD	=	Parkinson's disease
ND	=	Neurodegenerative disorder
DaNs	=	Dopaminergic neurons
α-syn	=	Alpha-synuclein
NSAIDs	=	Nonsteroidal anti-inflammatory drugs
DA	=	Dopamine
L-Dopa	=	3,4-Dihydroxy-L-phenylalanine
SOC	=	α-Synuclein Origin and Connectome
AD	=	Alzheimer's disease
ALS	=	Amyotrophic lateral sclerosis
LBD	=	Lewy body dementia
TMEM175	=	Transmembrane protein 175
SNCA	=	Alpha-synuclein gene
LRRK2	=	Leucine-rich repeat kinase 2
PDD	=	Parkinson's disease dementia
DLB	=	Dementia with Lewy bodies
MSA	=	Multiple system atrophy
JOS	=	Juvenile-onset synucleinopathy
SAA	=	Seed amplification assay(s)
RT-QuIC	=	Real-time quaking-induced conversion
SmSAA	=	Single-molecule seed amplification assay(s)
PPMI	=	Parkinson's Progression Markers Initiative
p-tau	=	Hyperphosphorylated tau
Aβ	=	Amyloid-beta
TDP-43	=	TAR DNA-binding protein 43
NSD-ISS	=	Neuronal α-Synuclein Disease Integrated Staging System
SynNeurGe	=	Synucleinopathy-Neurodegeneration-Genetics
UPS	=	Ubiquitin-proteasome system
PGC-1α	=	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
ROS	=	Reactive oxygen species
MPTP	=	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
IL	=	Interleukin
TNF-α	=	Tumor necrosis factor-alpha
BBB	=	Blood-brain barrier
MAO-B	=	Monoamine oxidase B
DBS	=	Deep brain stimulation
FDA	=	Food and Drug Administration
LCIG	=	Levodopa-carbidopa intestinal gel
LECIG	=	Levodopa-entacapone-carbidopa intestinal gel
hfVM	=	Human fetal mesencephalic tissue
UPDRS	=	Unified Parkinson's Disease Rating Scale
ESCs	=	Embryonic stem cells
EpiSCs	=	Epiblast stem cells
hASCs	=	Human adipose-derived stem cells
hUC-MSCs	=	Human umbilical cord mesenchymal stem cells
iPSCs	=	Induced pluripotent stem cells
hESCs	=	Human embryonic stem cells
MDS-UPDRS	=	Movement Disorder Society-Unified Parkinson's Disease Rating Scale
NHPs	=	Non-human primates
CRISPR	=	Clustered Regularly Interspaced Short Palindromic Repeats
CRISPR/Cas9n	=	CRISPR-associated protein 9 nickase
GDNF	=	Glial cell line-derived neurotrophic factor
6-OHDA	=	6-Hydroxydopamine
BDNF	=	Brain-derived neurotrophic factor
RhiPSCs	=	Rhesus monkey induced pluripotent stem cells

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

Financial support was received from the Research Council, University of Sri Jayewardenepura, Sri Lanka through Grant Number RC/URG/FOT/2024/61.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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