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Advancing disease-modifying therapies for Parkinson's disease: Current strategies and future directions

Kai-Min Wu,[1,2] Yizongheng Zhang,[1,2] Ting-Ting Wang,[3] Jia-Yi Wu,[1,2] Yu-Yuan Huang,[1,2] Peng Yuan,[2,4,5,*] and Jin-Tai Yu[1,2,6,*]

[1]Department of Neurology and National Center for Neurological Disorders, Huashan Hospital, Fudan University, Shanghai 200040, China

[2]State Key Laboratory of Brain Function and Disorders, MOE Frontiers Center for Brain Science, Shanghai Medical College, Fudan University, Shanghai 200032, China

[3]Department of Pharmacy, Huashan Hospital, Fudan University, Shanghai 200040, China

[4]Department of Rehabilitation Medicine, Huashan Hospital, Fudan University, Shanghai 200040, China

[5]MOE Innovative Center for New Drug Development of Immune Inflammatory Diseases, Institute for Translational Brain Research, Fudan University, Shanghai 200032, China

[6]Shanghai Academy of Natural Sciences (SANS), Fudan University, Shanghai 200032, China

*Correspondence: pyuan@fudan.edu.cn (P.Y.); jintai_yu@fudan.edu.cn (J.-T.Y.)

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Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder, characterized by the accumulation of α-synuclein (α-syn) aggregates and the loss of dopaminergic neurons in the midbrain. PD affects more than 10 million individuals worldwide, but no therapy has been proven to slow down its progression, posing a significant socioeconomic burden. Developing interventions to delay or halt disease progression remains a top priority for researchers. Recently, several disease-modifying approaches have been proposed for PD treatment, such as passive immunization, small-molecule inhibitors or gene editing therapy directly targeting α-syn aggregation, mitochondrial-targeted strategies, and cell replacement therapy. Our recent research has identified FAM171A2 as a novel neuronal receptor for pathological α-syn, offering a potentially viable target for disrupting α-syn transmission that is previously not known. Further development of these strategies could offer new hope for effective treatments of PD in the near future.

PATHOLOGICAL α-SYNUCLEIN TRANSMISSION DRIVES PD PATHOGENESIS

PD is a progressive neurodegenerative disease, characterized by a combination of motor symptoms (e.g., bradykinesia, rigidity, and tremor) and non-motor symptoms (such as cognitive impairment, depression and anxiety, autonomic dysfunction, hyposmia, and sleep disorders). Postmortem neuropathological examinations of PD patients have identified intraneuronal inclusions, called Lewy bodies, in dopaminergic neurons, which are predominantly composed of aggregated forms of α-syn.[1] Under physiological conditions, α-syn monomers are abundant in neuronal synaptic terminals, where they facilitate vesicle transport and neurotransmitter release. However, in pathological states, these naive unfolded proteins misfold and progressively aggregate into toxic oligomers, protofibrils, and mature fibrils. In addition to ultimately causing cell death, these pathological aggregates exhibit prion-like properties, capable of recruiting and converting naive α-syn into pathological species, thereby driving neurodegeneration.

Previous studies revealed that cell-to-cell transmission of pathological α-syn underlies PD pathogenesis. Experimental studies demonstrated that exogenously introduced pre-formed α-syn fibrils can trigger misfolding and aggregation of endogenous α-syn monomers in both cellular and *in vivo* models, supporting the prion-like propagation hypothesis. This concept aligns with Braak staging observed in human neuropathology, where Lewy body pathology progresses through a temporally and spatially predictable manner and correlates with clinical manifestation of different symptoms. Additionally, increasing evidence also suggests that α-syn pathology may originate from peripheral organs, such as gut and kidney.[2] Pathological α-syn from these peripheral sites can propagate to the brain and gradually spread to the midbrain. Intriguingly, the amount of α-syn pathology in substantia nigra showed significant correlation with the loss of local dopaminergic neurons in PD patients.[3] Notably, autopsies of PD patients who received human fetal midbrain neuron transplants revealed Lewy body pathology in grafted neurons,[4] providing additional direct evidence of α-syn transmission. Collectively, these findings underscore α-syn transmission as a key driver of neurodegeneration in PD.

CURRENT THERAPEUTIC STRATEGIES FOR PD AND THEIR LIMITATIONS

Currently available treatments for PD, including dopamine replacement therapy and deep brain stimulation, primarily alleviate symptoms but fail to halt disease progression. Substantial efforts have been made to develop disease-modifying therapies, including α-syn-targeting approaches (passive immunization, small-molecule inhibitors, gene editing therapies) and other therapies (mitochondrial-targeted strategies, anti-neuroinflammation approaches, and cell replacement therapy). However, most candidates have failed to demonstrate clinical benefits or yielded inconclusive results in trials, despite showing promising efficacy in preclinical studies.

Given the central role of α-syn aggregates in PD pathogenesis, strategies directly targeting α-syn have been a major focus (Figure 1). Passive immunotherapies against α-syn aggregates have shown efficacy in reducing pathological burden and functional deficits in preclinical PD models. However, most of them have not yielded success in clinical trials. The most promising endeavor, the PASADENA trial (NCT03100149) of a monoclonal antibody prasinezumab against fibrillar α-syn, missed the primary endpoint, but suggested potential benefits with additional analyses. The limited success of α-syn-targeted immunotherapy may be attributed to the following challenges. Firstly, human brain-derived α-syn aggregates exhibit high structural diversity, and it is uncertain which conformation(s) should be the most effective target for antibodies. Secondly, α-syn aggregates predominantly accumulate within neurons, but antibodies face limited intracellular penetrations. Thirdly, the process of antibody-mediated intracellular α-syn clearance remains poorly understood, raising questions about the mechanism of such immunotherapy. Fourthly, for antibodies targeting extracellular α-syn, as they transiently emerge before taken by another neuron, maintaining sustained therapeutic concentrations in the brain's extracellular space is pharmacologically challenging. Additionally, small-molecule therapeutics targeting α-syn oligomer formation (e.g., anle138b, UCB-0599) show promise in preclinical studies. However, due to the highly variable conformational dynamics of α-syn oligomers, the therapeutic efficacy of these compounds for PD still requires further validation in clinical trials. Recently, gene editing technology such as CRISPR has emerged as a precise and personalized editing tool capable of directly targeting causative genetic mutations, with encouraging results in preclinical PD studies. Nevertheless, key challenges, including its safety, effective delivery to the central nervous system, and minimizing off-target effects, should be addressed before clinical testing.

Beyond therapies targeting α-syn pathology directly, several complementary treatment strategies have emerged, including mitochondrial-targeted interventions, anti-neuroinflammatory approaches, and cell replacement therapies (Figure 1). Among these, mitochondrial-targeted strategies that enhance selective mitophagy, such as USP30 inhibitors and PINK1 activators, are now advancing to phase I clinical trials, marking a significant milestone in PD treatment development. In contrast, anti-neuroinflammatory approaches, despite strong preclinical promise, have failed to deliver positive clinical outcomes. Encouragingly, recent breakthroughs in cell replacement therapy offer new hope for PD modification. Two landmark studies published in *Nature* demonstrated remarkable progress: independent clinical trials exploring cell therapies derived from human induced pluripotent stem cells and human embryonic stem cells reported both safety and preliminary efficacy in PD patients.[5,6] While stem cells offer a disease-modifying strategy to treat PD, the invasive nature of

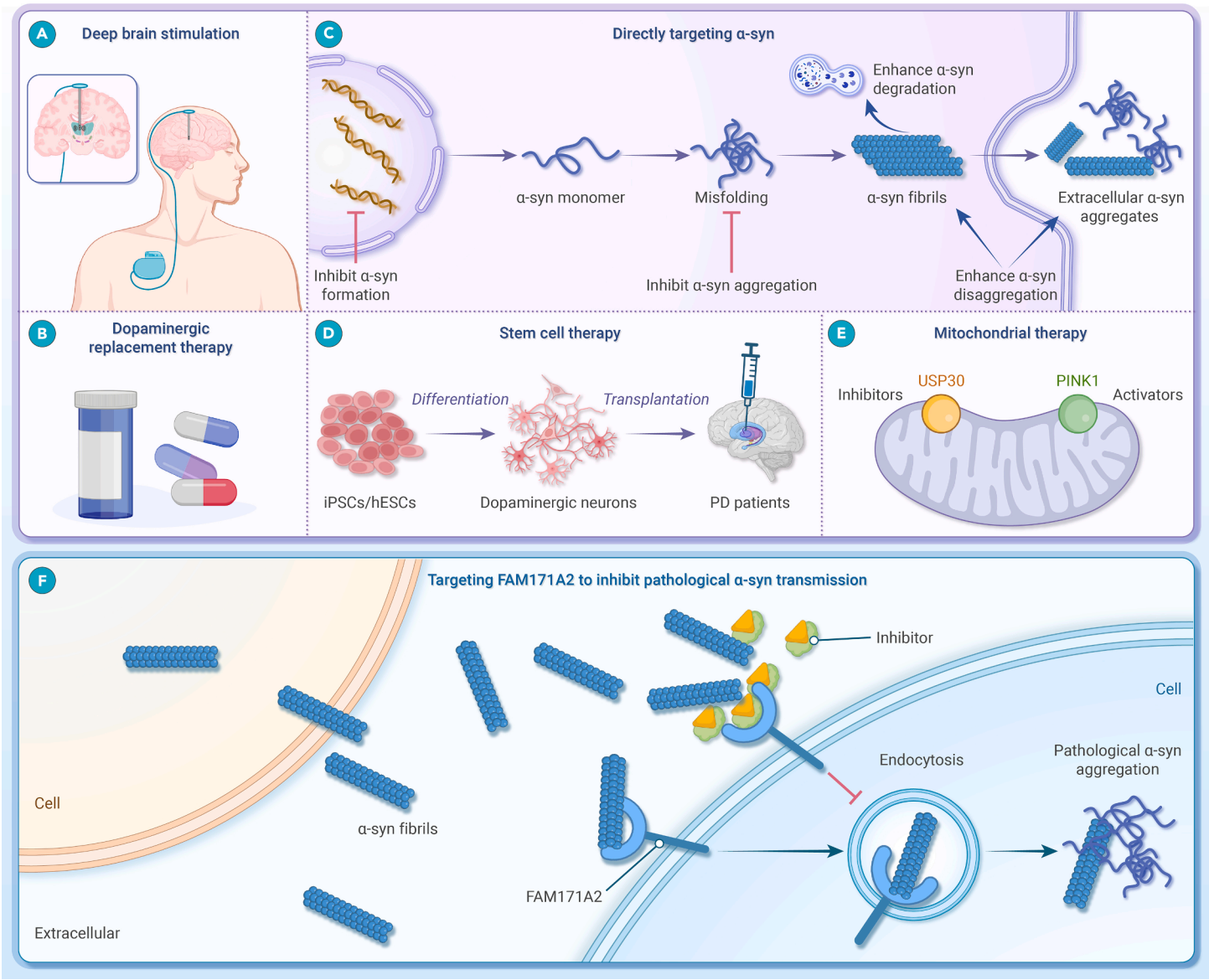

Figure 1. Current and future therapeutic strategies for PD (A) Deep brain stimulation and (B) dopamine replacement therapy constitute the cornerstone of clinical management for PD, primarily alleviating motor symptoms. For disease-modifying therapies, (C) directly targeting α-syn therapies by reducing its production, preventing aggregation, or enhancing degradation, including passive immunization, small-molecule inhibitors, gene editing therapies and lysosomal enhancer, have shown limited clinical success. (D) Stem cell replacement therapy and (E) mitochondrial based therapy have emerged as promising strategies. (F) Our recent research identifies FAM171A2 as a novel molecular target capable of blocking pathological α-syn transmission, offering a new avenue for disease-modifying interventions.

this treatment possesses safety concerns that may be overweighed only in end-stage patients.

BLOCKING α-SYN TRANSMISSION AS A NOVEL DISEASE-MODIFYING TREATMENT OF PD

Targeting the transmission of α-syn by inhibiting key regulators of this process represents another promising therapeutic strategy for preventing PD-related pathology. This approach offers dual advantages: it not only preserves physiological α-syn function, but also bypasses the challenge of directly targeting pathological diverse α-syn conformations. Therefore, elucidating the mechanisms underlying α-syn transmission is crucial. An important step in this process is the neuronal internalization of pathological α-syn aggregates. Previous studies have reported several candidate membrane proteins implicated in α-syn uptake,[7] including heparan sulfate proteoglycans, glycoprotein nonmetastatic melanoma protein B, low-density lipoprotein receptor-related protein 1, Fc gamma receptor IIB, lymphocyte-activation gene 3 (LAG3), and amyloid precursor-like protein 1/LAG3 complex. Recent advances have explored the inhibition of these receptors as potential treatment. Two anti-LAG3 antibodies, C9B7W and 410C9, reduced α-syn preformed fibril-induced pathology in cell culture models, while *in vivo* efficacy remains to be tested.[7] Importantly, we believe that, to qualify as a viable therapeutic target for PD, receptors should meet several key characteristics: (1) predominant neuronal expression, (2) selective recognition of pathological α-syn over physiological monomers, and (3) demonstrated *in vivo* regulation of α-syn propagation and neurotoxicity. However, none of the previously identified molecules fully satisfy these criteria.

Recently, our research found FAM171A2 as a novel neuronal receptor for pathological α-syn.[8] FAM171A2 is a single transmembrane protein with unknown function. We found that extracellular domain 1 of FAM171A2 has a high affinity to the C-terminal residues of α-syn fibrils, with a binding affinity 1,000-fold stronger than for monomeric α-syn. This binding promotes neuronal uptake of α-syn fibrils, as demonstrated in cultured neurons and mouse models of α-syn propagation. Importantly, neuron-selective FAM171A2 knockout in mice receiving injections of preformed α-syn fibrils reduced the spread of α-syn pathology across various brain regions, protected dopaminergic neuron from α-syn toxicity, and rescued motor deficits. FAM171A2 can be a viable target for PD patients, since we confirmed FAM171A2 expression in human midbrain neurons and its interaction with α-syn from postmortem brain tissues. The levels of FAM171A2 in cerebrospinal fluid correlated with α-syn aggregate contents in PD-affected brains, and variants that increase the expression of FAM171A2 are associated with elevated risks of developing PD in humans.

Unlike other preclinical therapies targeting α-syn pathology, such as antisense oligonucleotides that reduce α-syn production and lysosome-targeted strategies that enhance α-syn degradation, FAM171A2-targeted therapies specifically inhibit α-syn transmission while maintaining physiological α-syn monomer function.

To explore the potential druggability of FAM171A2, we leveraged the essential amino acid residues identified with nuclear magnetic resonance spectroscopy and AI-powered AlphaFold software to predict the binding interface between FAM171A2 and α-syn. This allowed us to performed an *in silico* screening of over 7,000 compounds, leading to the identification of the small-molecule bemcentinib, which can inhibit the interaction between FAM171A2 and α-syn fibrils (Figure 1). Bemcentinib is developed as a selective AXL receptor tyrosine kinase inhibitor that has demonstrated efficacy in inhibiting tumor metastasis in preclinical models of metastatic breast cancer and lung adenocarcinoma. Although the effectiveness of this drug against PD cannot be tested due to its poor blood-brain barrier permeability, we showed proof-of-principle evidence that intraventricular infusion of this drug can block neuronal uptake of α-syn fibrils in mice. Based on the promising lead compound bemcentinib, we propose a multidimensional medicinal chemistry optimization strategy, including structural modifications through hydrogen bond network reconstruction and bioisosteric replacement, molecular design innovations including scaffold hopping and privileged pharmacophore hybridization, as well as advanced delivery systems such as nanocarrier formulations and prodrug design. These multifaceted approaches are specifically designed to enhance the binding affinity, pharmacological efficacy, and blood-brain barrier penetration of bemcentinib-derived molecules.

PROSPECTS AND CHALLENGES

To date, no therapies have demonstrated unequivocal evidence of disease-modifying effects in PD, leaving the prevention or halting of progression a critical unmet need. We propose that blocking the interaction between FAM171A2 and α-syn fibrils could offer a novel disease-modifying treatment for PD. While our previous work provides ample support, this strategy still carries risks, particularly given the poorly characterized physiological functions of FAM171A2 and its unresolved safety profile as a druggable target. Therefore, systematic elucidation of its biological roles in humans is essential before advancing any FAM171A2-targeted therapies into clinical stages. Notably, while our focus has been on α-syn fibrils, diverse oligomeric and profibrillar α-syn species exist in PD brains. Thus, the efficacy of FAM171A2-targeted interventions against those species warrants systematic exploration. Given that α-syn aggregation underlies 95% of PD cases, FAM171A2-targeted therapies could benefit most patients. However, future clinical applications may still require patient stratification, potentially by disease stage or other biomarkers, to optimize precision medicine approaches and maximize therapeutic efficacy. Beyond PD, targeting FAM171A2 may hold broader therapeutic potential, as α-synucleinopathies encompass not only PD but also dementia with Lewy bodies (DLB) and multiple system atrophy (MSA). These disorders are characterized by distinct α-syn strains with cell-type-specific pathology. In MSA, pathological α-syn primarily accumulates in oligodendrocytes as glial cytoplasmic inclusions, whereas in DLB and PD, neuronal aggregates predominate. Investigating whether FAM171A2-mediated mechanisms exert consistent effects across these disorders could expand the utility of candidate PD therapies. Furthermore, our prior research identified *FAM171A2* as a risk gene for Alzheimer's disease and frontotemporal dementia,[9] suggesting its broader role in neurodegeneration and offering a promising avenue for cross-disease therapeutic development. Finally, as early diagnostic biomarkers for PD are increasingly crucial in drug development and clinical trial optimization, such as the development of α-syn PET and α-syn seed amplification assay,[10] their integration with disease-modifying therapies may redefine the current PD treatment paradigm.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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