Review

Brain Organoids in Parkinson's Disease Drug Development: Human-Specific Models for Translational Discovery

Alise Zagare and Jens Schwamborn *

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Review

Brain Organoids in Parkinson's Disease Drug Development: Human-Specific Models for Translational Discovery

Alise Zagare [1,2] and Jens Schwamborn [1,2,*]

[1] Developmental and Cellular Biology, Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg, 2, place de l'Université, L-4365 Esch-sur-Alzette, Luxembourg

[2] OrganoTherapeutics SARL, 29 Rue Henri Koch. 4354 Esch-sur-Alzette, Luxembourg

* Correspondence: jens.schwamborn@uni.lu

Abstract

Organoids are three-dimensional, stem-cell–derived cultures that mimic the structure and function of human tissues, providing improved physiological relevance over traditional 2D cell cultures and animal models. Their ability to replicate patient-specific biology makes them valuable for drug discovery, toxicity testing, and personalized medicine, enabling the prediction of individual responses to therapies. In the context of Parkinson's disease (PD), midbrain organoids recapitulate key neurodegenerative phenotypes, including dopaminergic neuron loss, α-synuclein aggregation, metabolic dysfunction, and neuroinflammation, and have been successfully used to test various therapeutic strategies. Because PD is highly heterogeneous and current treatments remain largely symptomatic, there is an urgent need for improved preclinical models to overcome translational failures. Organoids offer a powerful solution to accelerate the development of effective disease-modifying treatments.

Keywords: brain organoids; midbrain organoids; personalized medicine; precision medicine; Parkinson's disease; neurodegeneration; disease modeling; human iPSC; NAMs; 3D cell culture; drug discovery; translational neuroscience

1. Introduction

Today's increasingly aging population has an unmet need to tackle age-associated diseases. Among these, neurodegenerative diseases, such as Parkinson's disease (PD), are a rapidly growing global health burden with cases projected to rise substantially over the coming decades and associated healthcare costs increasing accordingly (Su et al., 2025). Despite decades of research on PD, therapeutic progress has been limited, and many drug candidates that show promise in animal models fail in clinical trials (Le et al., 2014; Marshall et al., 2023). From 1999 until 2019, in 357 clinical trials, 152 compounds were studied and tested, with an overall success rate of 14.9% (Boucherie et al., 2021). More recent data from the 2024 report 107 drug candidates in 136 active Phase 1–3 clinical trials, with most still in Phase II and only 12% reaching Phase III (McFarthing et al., 2024). The drugs that succeed are widely used for symptom management, such as levodopa and dopamine agonists. They often provide substantial motor improvement, especially in the early years of treatment, however, they do not halt or reverse neurodegeneration, highlighting the ongoing need for disease-modifying therapies (Sako et al., 2023).

It is well known that animal systems do not fully replicate human brain physiology, genetic diversity, or disease progression (Antony et al., 2011; Burns et al., 2015; La Manno et al., 2016; Potashkin et al., 2010; Saiga et al., 2025). Whereas human iPSC–derived brain organoids offer a more physiologically relevant platform by recapitulating key aspects of human neural architecture, cell–cell interactions, and patient-specific genetic backgrounds (Hou & Kuo, 2022; Wang et al., 2026;

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Zagare et al., 2022a). Organoids demonstrate clear neurodegeneration phenotypes and allow investigation of early disease molecular mechanisms due to their embryonic-like developmental state, while more mature cultures reveal advanced phenotypes, such as protein aggregation (Frattini et al., 2025; Muwanigwa et al., 2024; Rosety et al., 2023; Smits et al., 2019a). Moreover, it has been shown that organoids robustly recapitulate PD phenotypes across independent organoid generation rounds or batches, providing evidence of their reproducibility (Zuccoli et al., 2025). These characteristics make brain organoids appealing not only for target validation but also for therapeutics development and neurotoxicity studies. This is improving the predictive value of preclinical testing and facilitating identification of more effective therapeutic candidates for neurodegenerative disorders compared with traditional animal or 2D cellular models (Boussaad et al., 2020; Hongen et al., 2024; Hu et al., 2025; Jarazo et al., 2022; Kim et al., 2023; Schwartz et al., 2015; Zagare et al., 2025; Zhang et al., 2024).

Notably, there have been recent efforts to phase out animal testing. In 2022 FDA Modernization Act 2.0, removed the formal mandatory requirement for animal testing prior to clinical trials, encouraging the inclusion of human-relevant *in vitro* data in preclinical studies. Following that, on April 10, 2025, a strategic plan was announced to replace animal testing in the development of monoclonal antibodies and biologic therapies, including vaccines, cell and gene therapies and therapeutic proteins, with New Approach Methodologies (NAMs). NAMs include human-derived models, such as human organoids, organ-on-chip systems, and computational models, designed to assess human drug safety and efficacy more reliably than animal models (X. Song et al., 2026; van der Zalm et al., 2022). Organoids are already widely used for drug screening and toxicology testing across multiple organs, offering more human-predictive models for safety and efficacy assessment. Over the past decade, organoid research has expanded rapidly, with publications growing from fewer than 20 per year before 2012 to over 1,000 annually by 2022, indicating a sharp increase that has continued in recent years (Wan et al., 2024). Moreover, some drugs have already entered clinical trials based primarily on preclinical data from human-derived models such as organoids or organ-on-a-chip systems (Parvatam et al., 2025). Nevertheless, such cases still remain rare and are assessed individually rather than representing a standard preclinical procedure. Considering the human brain's particularities and differences from animal models, organoids should be strongly considered as a preclinical tool in drug development, also for neurodegenerative diseases.

In this review, we summarize available studies demonstrating drug effects, focusing on PD phenotype amelioration in human-specific organoids. We emphasize the translational value of these human-specific organoids as part of NAMs for evaluating drug efficacy and mechanism. Importantly, PD is a highly heterogeneous disease, and current therapies are largely symptomatic with limited efficacy across patient populations. Organoids offer a unique opportunity to address this heterogeneity by enabling patient-specific drug screening, testing multiple therapeutic strategies on individualized models, and identifying interventions that are most likely to be effective for a given genetic or cellular background. By combining mechanistic insights with personalized efficacy testing, organoids provide a powerful platform to guide the development of targeted and precision therapies for PD.

2. Brain Organoids for PD Research: Generation and Features

Brain organoids are three-dimensional stem cell-derived *in vitro* cultures capable of self-organizing driven by region-specific cell fate commitment. They are able to recapitulate key aspects of human brain development *in vitro* and neuronal functionality in terms of electrophysiology and neurotransmitter release (Lancaster & Knoblich, 2014; Monzel et al., 2017; Park et al., 2023; Smits et al., 2019a). Also, transcriptomic and epigenetic signatures recapitulate the early development of the human brain (Luo et al., 2016; Zagare et al., 2022b). For PD research, focus is on cell patterning toward a ventral midbrain fate to generate dopaminergic neurons of the substantia nigra, the primary neuronal population affected in PD. This process generally involves stepwise differentiation of human pluripotent stem cells (hPSCs), including induced pluripotent stem cells (iPSCs) and

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embryonic stem cells (ESCs), toward a neural lineage. Neural induction is first achieved by directing hPSC toward a neuroectodermal fate through inhibition of BMP and TGFβ signaling pathways. Subsequent ventral midbrain patterning is induced by activation of canonical WNT and Sonic Hedgehog (SHH) signaling, promoting the specification of floor plate progenitors. In many protocols, these patterning steps occur within three-dimensional aggregates derived from hPSCs, formed as embryoid bodies (Fiorenzano et al., 2021; Jo et al., 2016). Alternatively, neuroectodermal progenitors can first be generated as an intermediate population (Monzel et al., 2017; Reinhardt et al., 2013; Smits et al., 2019a). Subsequent midbrain organoid generation from these prepatterned progenitors is robust and allows observation of reproducible disease-relevant phenotypes (Monzel et al., 2017; Zuccoli et al., 2025).

Over time, midbrain-specific organoids develop cellular and molecular characteristics of the human midbrain, including the presence of tyrosine hydroxylase (TH)-positive dopaminergic neurons, astrocytes, and oligodendrocytes, and exhibit spontaneous neuronal activity (Jo et al., 2016; Monzel et al., 2017). Notably, longer cultures of midbrain organoids demonstrate the presence of neuromelanin, a hallmark of human substantia nigra dopaminergic neurons, providing evidence of their maturation and nigrostriatal identity (Frattini et al., 2025; Monzel et al., 2017). Importantly, organoids generated from patient iPSCs provide a personalized platform for disease investigation and drug screening on patients genetic background. In addition, organoids harboring PD-associated mutations in genes such as *GBA1, SNCA, LRRK2, RHOT1,* and *PINK1* recapitulate key pathological hallmarks of the disease, which include α-synuclein aggregation, mitochondrial dysfunction, oxidative stress, and progressive dopaminergic neuron vulnerability (Chemla et al., 2025; Kurniawan et al., 2025; Muwanigwa et al., 2024; Rosety et al., 2023; Smits et al., 2019b; Zagare et al., 2025). Recent advances have enabled the incorporation of microglia and vascular-like structures into organoids, further improving physiological relevance and enabling the investigation of neuroinflammatory pathways as well as the role of vasculature functionality in PD progression (Sabate-Soler et al., 2022; Zimmermann et al., 2025).

3. Organoid Models of Parkinson's Disease and Applications in Drug Discovery

a. Rescue of Dopaminergic Neuron Loss

Human midbrain organoids have been successfully used to recapitulate PD–associated cellular phenotypes, such as dopaminergic neuron loss, neuroinflammation, altered metabolism and accumulation of pathological α-synuclein forming aggregate-like structures (Frattini et al., 2025; Jarazo et al., 2022; Kurniawan et al., 2025; Rosety et al., 2023; Zagare et al., 2025). Several studies also demonstrate rescue of the observed phenotypes and provide a platform to evaluate potential therapeutic interventions (Table 1). For example, Boussaad et al. showed that the c.192G>C pathogenic variant in *PARK7* (DJ-1) induced aberrant exon 3 skipping, resulting in reduced levels of correctly spliced full-length mRNA and decreased DJ-1 protein expression (Boussaad et al., 2020). Reduced DJ-1 levels in PD models have been shown to increase oxidative stress, impair mitochondrial function, and enhance vulnerability of dopaminergic neurons (Lv et al., 2025; Martinat et al., 2004). Similarly, Boussaad and colleagues observed significantly reduced levels of TH^+ dopaminergic neurons in midbrain organoids generated from CRISPR/Cas9-engineered neuronal progenitors harboring a pathogenic variant in *PARK7* gene. They showed that this selective TH^+ dopaminergic neuron loss can be reversed in a dose-dependent manner by combining treatment with 1 mM phenylbutyrate (PB) and the splicing modulator RECTAS. Both molecules were selected from literature-based evidence as potential rescue strategies with a synergetic effect. Overall, the study demonstrates that correcting RNA mis-splicing and its downstream consequences can ameliorate disease-associated phenotypes in patient-based midbrain models of PD. Another study by Jarazo et al. showed that patient-derived midbrain organoids with *PINK1* mutations demonstrated an altered proteomics profile, suggesting dysregulation of metabolism, autophagy, inflammation, cell cycle and cell survival pathways. After midbrain organoid treatment with 2-hydroxypropyl-β-cyclodextrin, a

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known modulator of autophagy by increasing nuclear translocation of transcription factor EB (*TFEB)* - a master regulator of lysosomal biogenesis and autophagy (W. Song et al., 2014) - the proteomics profile was ameliorated, and midbrain organoids showed restored levels of TH^+ dopaminergic neurons (Jarazo et al., 2022).

Using a toxin-induced model to recapitulate dopaminergic degeneration, Mendes-Pinheiro et al. observed reduced TH^+ dopaminergic neuron levels and increased fragmentation after organoid treatment with 6-OHDA. This study showed that this PD model is responsive to bone-marrow-derived mesenchymal stem cell (MSC) secretome treatment, and considering its potential neuroprotective and neuroregulatory effects, rescued TH+ dopaminergic neuron levels as well as reduced their fragmentation (Mendes-Pinheiro et al., 2023).

While the above studies primarily assessed dopaminergic neuron survival, other work focused on functional restoration of dopaminergic signaling, assessing also dopaminergic neuron functionality. An et al. demonstrated a sensitive electrochemical sensing platform for detecting the response of brain organoids. They observed functional deficits in dopamine release in PD patient midbrain organoids, which were restored by levodopa, confirming dopaminergic pathway responsiveness and their developed platform utility (An et al., 2024). Similarly, addressing dopaminergic dysfunction in a genetic context, Zagare et al. demonstrated impaired dopamine release, decreased dopaminergic neuron numbers, and altered lipidomic profile in *GBA1*-N409S variant carriers (GBA-PD) (Zagare et al., 2025). In addition, this study shows the application of organoids in studying comorbidities by investigating type 2 diabetes associated insulin resistance role in PD development. They showed that increased insulin sensitivity restores cellular viability in GBA-PD midbrain organoids. In addition, treatment with the anti-diabetic drug pioglitazone not only improved dopaminergic neuron survival but also enhanced dopamine secretion. Further, they identified *FOXO1* as a downstream effector of impaired insulin signaling in GBA-PD, and demonstrated that targeted ASO-mediated downregulation of FOXO1 protein significantly increased dopaminergic neuron numbers, dopamine release, as well as cellular viability.

b. Microglia-Mediated Neuroinflammation

Advanced organoid models incorporating patient-derived microglia enable the study of neuroinflammatory mechanisms in PD and their impact on neuronal survival. Kurniawan et al. observed that *LRRK2*-G2019S affected microglia were proinflammatory, secreting elevated levels of TNFα and exhibited metabolic changes to sustain their activity (Kurniawan et al., 2025). Further, this study showed that midbrain organoids experienced selective TH+ dopaminergic neuron loss upon TNFα treatment as well as when co-cultured with microglia harboring *LRRK2*-G2019S pathogenic variant, reflecting key features of neuroinflammation in PD (Kurniawan et al., 2025). Treatment with the metabolic modulator, oxamic acid, aimed at inhibiting glycolysis as the main metabolic player fueling microglia inflammatory activation, restored levels of dopaminergic neurons in midbrain organoids co-cultured with *LRRK2*-G2019S microglia. Overall, this study demonstrates that advanced midbrain organoid models incorporating microglia provide a robust platform to investigate microglial roles in PD and enable the modulation of their functionality and metabolism within a physiologically relevant context, rather than in traditional 2D culture systems.

c. Targeting α-Synuclein Pathology

In addition to neuronal loss and inflammation, α-synuclein aggregation represents another central pathological hallmark of PD. Also, α-synuclein aggregation has been successfully modeled and targeted in organoid systems. Kim et al. used optogenetic induction of α-synuclein aggregation in human iPSC-derived midbrain organoids, resulting in pathological α-synuclein accumulation and PD-like cellular phenotypes (Kim et al., 2023). This was reversed by the molecule BAG956 through enhanced autophagic clearance of α-synuclein aggregates.

Zhang et al. challenged organoids with α-synuclein preformed fibrils, resulting in pathological α-synuclein aggregation and apoptosis (Zhang et al., 2024). They used the antiviral drug tilorone to

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inhibit α-synuclein uptake and propagation, reducing aggregation and stabilizing neuroinflammation and metabolic signature. Tilorone was a promising candidate because of its lysosomotropic and immune-modulating properties, which can inhibit α-synuclein endocytosis and aggregate propagation (Fischer et al., 1996).

Finally, targeting lysosomal dysfunction in *GBA1*-associated PD, Frattini et al. reported that patient-derived *GBA1*-L444P organoids endogenously accumulated α-synuclein and displayed characteristic *GBA1* mutation features, such as reduced glucocerebrosidase (GCase) enzyme activity, endoplasmic reticulum retention of mutant GCase and increased levels of its substrate – glucosylceramide. Mutant GCase is prone to misfolding and is retained in the ER, compromising chaperone-mediated autophagy and lysosomal function, resulting in impaired α-synuclein clearance and promoting its accumulation. They used ambroxol, a GCase enhancer currently in clinical trials for PD, which was able to increase the protein amount and enzymatic activity of the GCase, resulting in a reduction of α-synuclein aggregate numbers. Additionally, they found that GZ667161, a glucosylceramide synthase inhibitor, effectively reduced GlcCer levels and also decreased α-synuclein aggregate levels in *GBA1*-L444P mutant midbrain organoids.

Collectively, these studies show that human midbrain organoids can reproduce PD-related molecular and cellular phenotypes—including α-synuclein aggregation, dopaminergic neuron vulnerability, lysosomal dysfunction, and neuroinflammation—and serve as a versatile platform for testing interventions that rescue these disease-relevant phenotypes (Table 1). Together, these data support the application of midbrain organoids as a robust preclinical platform for therapeutic compound screening.

Table 1. Summary of therapeutic interventions tested in organoid models for PD phenotype amelioration.

Reference	Organoid Model	PD model	Molecule / Intervention	Target / Mechanism	Effect / Outcome
Kurniawan *et al.*, 2025	Midbrain organoids	Healthy midbrain organoid +*LRRK2*-G2019S microglia	Oxamic acid	Inhibition of lactate dehydrogenase, aiming to reduce glycolysis and mTOR-dependent metabolic reprogramming	Decreased microglial inflammation, reducing levels of TNF-α; improved dopaminergic neuron survival
Frattini *et al.*, 2025	Patient-derived midbrain organoids	*GBA1*-L444P	Ambroxol	GCase enhancer	Restored GCase protein levels and increased its enzymatic activity; reduced levels of misfolded GCase restored dopaminergic neuron levels; reduced Lewy body-like fibrillary α-synuclein deposition
Frattini *et al.*, 2025	Patient-derived midbrain organoids	*GBA1*-L444P	GZ667161	Glucosylceramide synthase inhibitor	Reduced glucosylceramide levels; reduced levels of misfolded GCase; reduced Lewy body-like fibrillary α-synuclein deposition
Zagare *et al.*, 2025	Patient-derived midbrain organoids	*GBA1*-N370S	FOXO1-ASOs	Blocking of FOXO1 protein translation	Improved dopamine release; increased dopaminergic neuron levels and cellular viability
Zagare *et al.*, 2025	Patient-derived midbrain organoids	*GBA1*-N370S	Pioglitazone	Modulation of metabolic/insulin signaling	Improved dopamine release; increased dopaminergic neuron levels
Zhang *et al.*, 2024	Midbrain organoids	α-synuclein preformed-fibril treatment	Tilorone	Inhibition of α-synuclein uptake/propagation	Reduced a-synuclein fibril internalization; ; reduced apoptosis, and stabilization of inflammation profile
An *et al.*, 2024	Patient-derived midbrain organoids	*PRKN* (1 bp del; ex3–4 del); *LRRK2*-G2019S	Levodopa	Dopaminergic pathway activation	Increased dopamine release; demonstrated functional organoid response

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Kim *et al.*, 2023	Midbrain organoids	Optogenetic induction of α-synuclein aggregation	BAG956	Autophagic clearance enhancement of α-synuclein aggregates	Reduced pathological α-synuclein levels; increased survival of dopaminergic neurons
Mendes-Pinheiro *et al.*, 2023	Midbrain organoids	6-OHDA treatment	MSC secretome	Neurotrophic / neuroprotective effects	Rescued dopaminergic neuron loss; reduced their fragmentation/ neurodegeneration
Jarazo *et al.*, 2022	Patient-derived midbrain organoids	*PINK1*- p.Q456X; *PINK1*-p.I368N	2-Hydroxypropyl-β-Cyclodextrin (2-HP-β-CD)	Autophagy modulation	Normalized PD-associated proteomics signature; restored dopaminergic neuron levels
Boussaad *et al.*, 2020	Midbrain organoids	*PARK7*-p.E64D	Splicing modulator RECTAS + Phenylbutyrate	Corrects splicing defect in DJ-1	Rescued dopaminergic neuron loss

4. Discussion and Future Perspectives

In this review, we shed light on evidence that organoids are capable of recapitulating complex features of the human brain, and therefore complex diseases such as PD. Recent studies using human-derived brain organoids, particularly midbrain-specific models, have demonstrated significant potential for preclinical drug testing in PD. These organoids successfully recapitulate midbrain-specific dopaminergic neuron populations and key PD hallmarks, loss of nigrostriatal dopaminergic neurons, α-synuclein aggregation, neuroinflammation and other PD-associated phenotypes, allowing researchers to evaluate the efficacy of candidate therapeutics in a human-relevant system. Here, we highlighted investigations that have reported rescue of PD-associated phenotypes following treatment with selected compounds, highlighting the ability of organoid platforms to model drug responses and mechanism-of-action *in vitro*.

While not diminishing the value of 2D cultures and animal models, organoids offer several opportunities, including reduced ethical concerns, recapitulation of human biology, and physiological relevance, making them a relevant platform for human drug screening. Enabling patient-specific disease modeling, mechanistic studies, and assessment of therapeutics efficacy and safety, organoids provide a robust platform for therapeutics development as well as the development of personalized treatments for PD.

The rapid advancement of human-derived organoid models is reshaping preclinical drug development. Despite this progress, regulatory frameworks for integrating these models as complementary or even primary tools for testing drug safety and efficacy remain underdeveloped. Successful incorporation of organoid-derived data into regulatory submissions will require standardized protocols, clear validation criteria, and agreement on relevant endpoints for disease modeling. Ensuring reproducibility and data harmonization across laboratories will be essential to build regulatory confidence.

In PD drug development, midbrain-specific organoids could play a central role in evaluating dopaminergic neuron survival, α-synuclein pathology, and neuroinflammatory responses, ultimately guiding the design of safer and more effective therapeutics.

These findings underscore the value of organoids and other NAMs as predictive preclinical models that bridge the gap between conventional animal studies and clinical outcomes. By enabling human-specific assessments of drug safety and efficacy, these models can accelerate the identification and optimization of therapeutics, inform patient-specific treatment strategies, and support regulatory adoption of human-relevant testing approaches. Collectively, current organoid-based studies illustrate a promising shift toward accurate, efficient, and translationally relevant preclinical research for PD and potentially other neurodegenerative disorders.

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Conflicts of Interest: J.S. is a co-inventor on a patent covering the generation of midbrain organoids (WO2017060884A1). Furthermore, J.S. is a co-founder and shareholder of the company OrganoTherapeutics which makes use of midbrain organoid technology. A.Z. is a lead scientist in OrganoTherapeutics.

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