university of groningen

Unravelling Parkinson's disease: could Mitochondria and α-Synuclein hold the key to a Cure?

Essay BMS

MSc Biomedical Sciences

Gerardo Nigro, s6084583, g.nigro@student.rug.nl

Supervisors: Prof Ulrich L.M. Eisel, Prof Amalia M. Dolga

2024/2025

Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disease affecting millions of people worldwide, characterized by loss of dopamine neurons. The presence of α-synuclein protein aggregates and mitochondrial dysfunction play a key role in disease progression, creating a vicious cycle that drives neurodegeneration. This essay focuses on current knowledge of mitochondrial and α-synuclein mechanisms in PD, evaluating the most promising therapies. It discusses treatments aimed at restoring mitochondrial health (like gene therapies, mitophagy enhancers, and mitochondrial biogenesis stimulators) and approaches targeting α-synuclein aggregation (like immunotherapies and molecular agents), separately. Then, the great potential of combined therapies that address both mitochondrial dysfunction and α-synuclein, such as iCP-parkin (improved-Cell Permeable Parkin), is highlighted. This holds the promise of modifying the progression of PD, with the hope of giving patients a better life.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, defined by four motor symptoms: tremor at rest, bradykinesia, rigidity, and postural instability. As shown in Figure 1, it is also characterised by a variety of non-motor symptoms, including cognitive impairment, depression, mood disturbances, and sleep disorders (Vázquez-Vélez & Zoghbi, 2021).

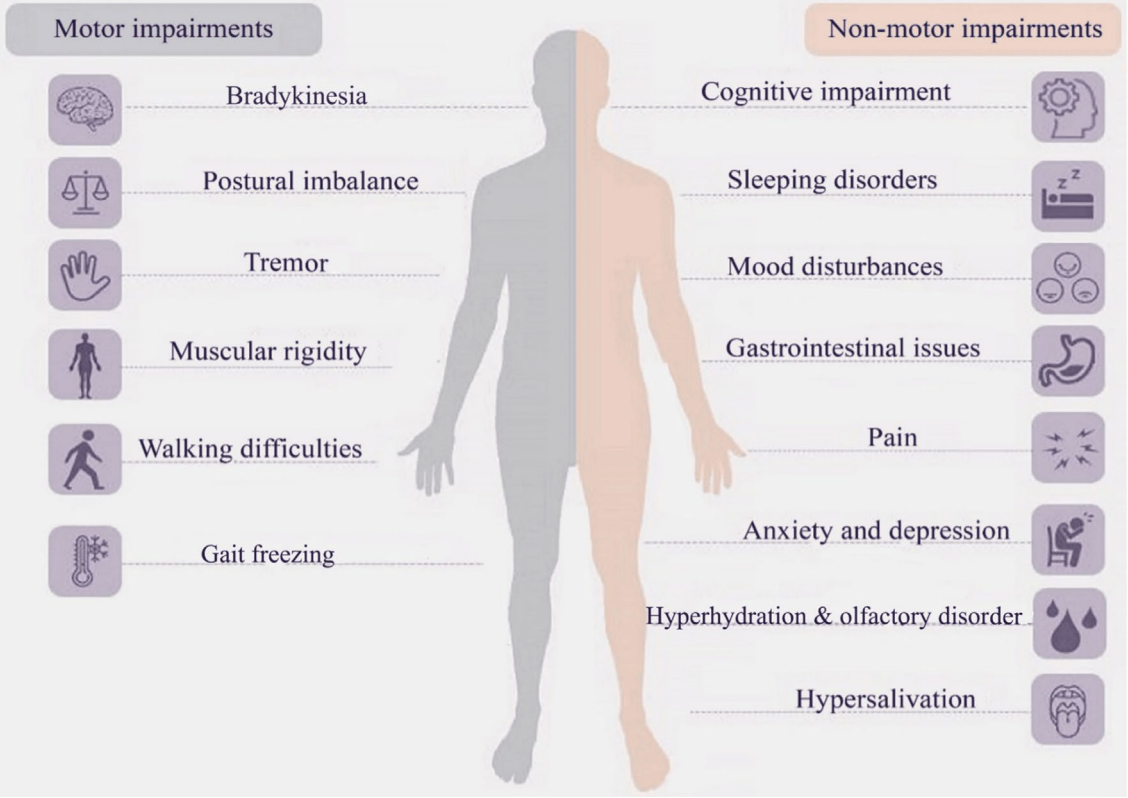

Figure 1: Impairments of Parkinson's disease. The impairments are divided into motor impairments (difficulty with movement and physical coordination) and non-motor impairments (difficulties not directly related to the movement) (Alotaibi et al., 2024).

The first hallmark of PD is the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc), resulting in a decrease in dopamine release in the striatum, which alters the circuits by which the basal ganglia control movement. (Vázquez-Vélez & Zoghbi, 2021)

The second major indicator of PD is the presence of Lewy bodies (LBs) and Lewy neurites. The difference lies in their location and shape: Lewy bodies are spherical, dense aggregates found inside the soma, whereas Lewy neurites are filamentous inclusions located within

axons and dendrites (Kanazawa et al., 2008). They are aggregates of α-synuclein found both inside and outside the SNc. PD may be classified as a synucleinopathy, sharing overlapping symptoms with dementia with Lewy bodies. (Kanazawa et al., 2008; Vázquez-Vélez & Zoghbi, 2021).

Parkinson's disease is a complex condition rather than a single, linear illness; it falls into three main categories, each with its own causes and characteristics. Acknowledging these categories helps doctors and researchers better understand the disease and tailor treatments.

The most common type is idiopathic Parkinson's disease, named due to the lack of knowledge regarding its exact cause. There is no single specific genetic mutation or environmental factor. Instead, it appears to be a combination of multiple small genetic risks and environmental factors that work together over time. This form typically progresses more slowly than the others (Bloem et al., 2021; Kalia & Lang, 2015).

Genetic (or familial) Parkinson's disease accounts for about 10 to 15% of cases. This form occurs due to inherited mutations in certain genes, such as SNCA and LRRK2 (dominant) or PINK1 and Parkin (recessive). These genetic forms, which will be discussed later, have usually helped scientists learn a lot about how PD develops at the molecular level (Klein & Westenberger, 2012; Lesage & Brice, 2009).

Secondary Parkinsonism differs from the latter because it results from other causes, such as side effects from certain medications, exposure to toxins, infections, or other brain diseases. This category is important because it often requires different treatment and typically has a distinct outlook compared to the other types (Jankovic, 2008).

1.1 Epidemiology

Over the last few decades, the number of people living with PD worldwide has more than doubled, exceeding six million. According to the 2015 Global Burden of Disease study, PD has grown faster than any other neurological condition. While an aging population accounts for some of this increase, the rise in age-adjusted prevalence, disability-adjusted life years (DALYs), and mortality indicates that other factors are also involved ((GBD, 2018).

The improvement of case identification, driven by more sensitive diagnostic criteria, better data collection, and increased clinical awareness, undoubtedly leads to higher reported

rates. However, this alone does not fully explain the rise, especially in wealthier nations where surveillance methods have largely stayed the same (Dorsey, 2018).

As people live longer overall, they spend more years with PD, regardless of whether new diagnosis rates have changed. Pooled analyses show that the average disease duration has increased by roughly 2.5 years every ten years. Rapid industrial growth and exposure to toxins like pesticides, solvents, and heavy metals may also be contributing to this trend. Another possible factor is the worldwide decline in smoking prevalence. Smokers seem to develop PD less often, possibly because of nicotine's neuroprotective effects (Quik et al., 2012). Indeed, research has shown a significant enhancement of subventricular zone (SVZ) precursor cell proliferation, perhaps due to a nicotine-induced increase in fibroblast growth factor 2 (FGF-2) mRNA in the SVZ (Mudò et al., 2007).

Parkinson's disease prevalence climbs drastically with age, although the oldest age groups may be undercounted because of misdiagnosis or institutionalisation. Despite more sophisticated modelling, reliable data are still scarce in low-income regions. In fact, mortality records tend to understate PD deaths, while surveys can miss cases if participation is low (Galea & Tracy, 2007).

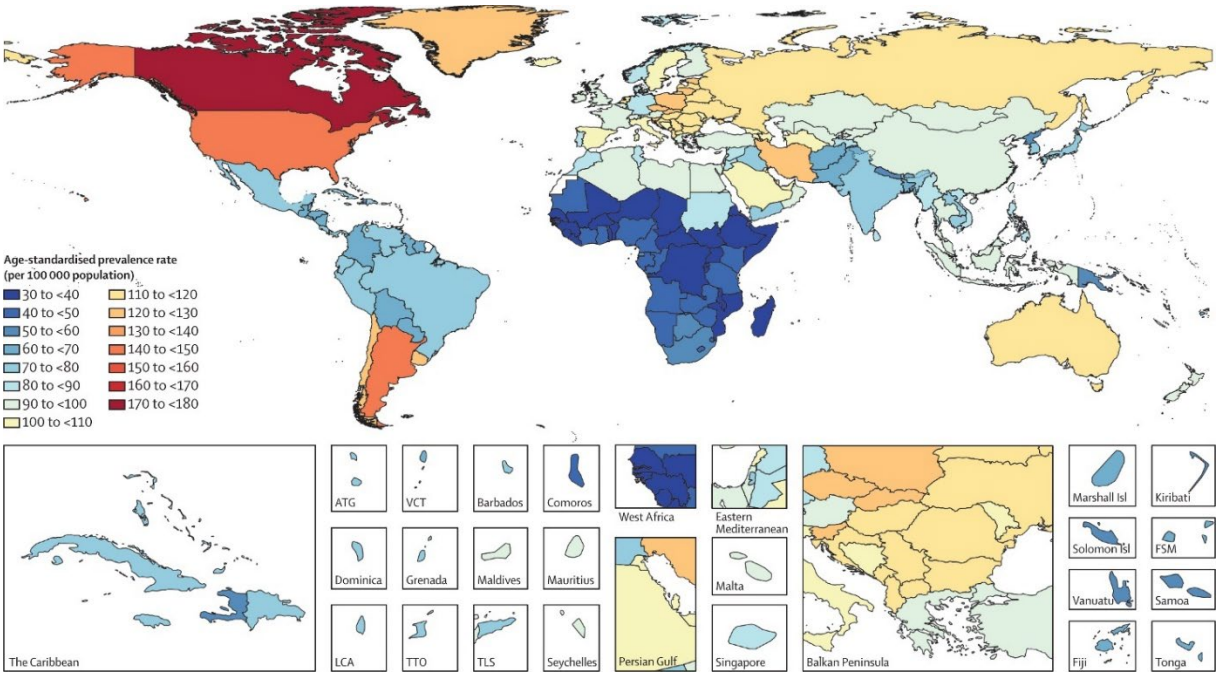

Figure 2: Age-standardized prevalence of Parkinson's disease per 100.000 people by location. It represents the prevalence of Parkinson's disease for both sexes, ranging from 30 to 180. The lowest prevalence is shown in Africa, South America (except for Argentina, Chile, and Uruguay), and South Asia. On the other side, the highest prevalence is shown in North America, where it reaches its peak in Canada (Dorsey, 2018).

To better understand the purpose of this essay, it is worth discussing the role of mitochondrial dysfunction and α-synuclein aggregation in PD. The next chapters will focus on their involvement in the disease and promising therapeutic strategies. In the end, with all the knowledge acquired and clinical trials pointed out, this essay will answer one crucial question: how effective is targeting mitochondrial function and α-synuclein aggregation to reverse neurodegeneration in Parkinson's disease?

1. Interaction between mitochondrial Dysfunction and α-Synuclein aggregates

Research increasingly highlights a feedback loop between mitochondrial dysfunction and α-synuclein aggregation in PD. Aggregated α-synuclein binds more strongly than monomers to mitochondrial membranes, disrupting their ability to produce ATP (adenosine triphosphate). This leads to decreased respiration and increased production of reactive oxygen species (ROS) in neurons. Moreover, the rise in ROS damages mitochondria and encourages further α-synuclein misfolding, reinforcing the cycle (Figure 3) (Wang et al., 2019). A review published in 2023 emphasized that mitochondria are a key target of α-synuclein toxicity (Sohrabi et al., 2023). This vicious cycle is a central mechanism behind neurodegeneration in PD. Given this, it is crucial to thoroughly examine mitochondrial dysfunction and its role in neural death and α-synuclein aggregation.

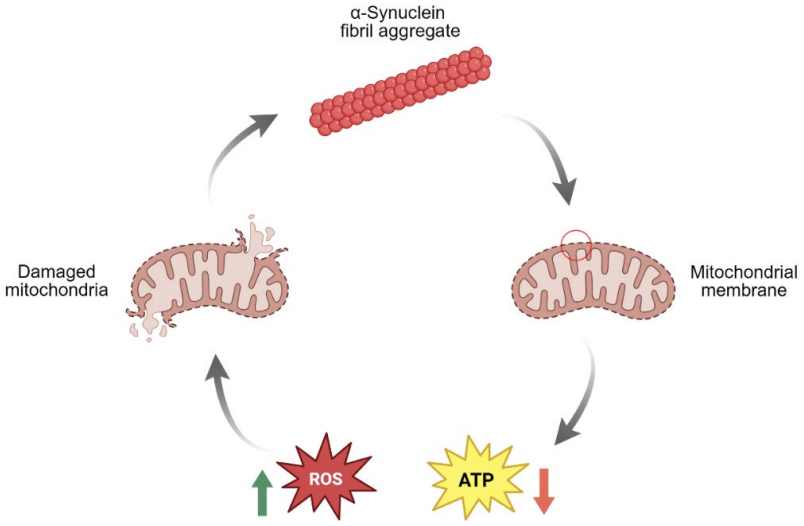

Figure 3: Vicious cycle between mitochondrial dysfunction and α-synuclein aggregation in Parkinson's disease. The vicious cycle starts with α-synuclein aggregates binding mitochondrial membrane, resulting in incapability of producing ATP and an increase in ROS. The outcome is the presence of damaged mitochondria that trigger more α-synuclein aggregation.

1.1 Mitochondria

Defects in mitochondrial respiration are increasingly recognized as central to the pathogenesis of Parkinson's disease, due to their impact on energy production, calcium homeostasis, and the cellular stress response.

Mitochondria are organelles found as clusters in the cytosol. Their main function is to generate energy in the form of adenosine 5' triphosphate (ATP), and they are also involved in the metabolism of lipids and amino acids, crucial for maintaining cellular membrane integrity and signalling pathways. They store intermediate products of pyruvate oxidation and the Krebs cycle and play a role in scavenging free radicals and in controlling apoptosis (Bose & Beal, 2016). As for their genetic material, mitochondria carry 10-100 or more copies of a small circular DNA (mtDNA). Recent studies have shown that mitochondria undergo constant morphological changes through continuous cycles of fusion and fission, resulting in mitochondria with different morphologies. The balance between fusion and fission determines most functions of mitochondria, controls their bioenergetic function, mitochondrial turnover, and protects mtDNA (Franco-Iborra et al., 2016).

The researchers began to associate mitochondrial dysfunction with PD when MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine) was identified as a neurotoxin. In 1983, Langston and colleagues reported a group of patients who developed rapid-onset Parkinsonism after exposure to a contaminated synthetic heroin analogue containing MPTP. MPTP selectively targets mitochondria by inhibiting Complex I of the electron transport chain (ETC). MPTP, after crossing the blood-brain barrier, is taken up by neurons, is converted into MPP+, and blocks Complex I. This results in energy failure and an increase in oxidative stress in dopaminergic neurons of the SNc (Langston et al., 1983).

Other toxins, such as rotenone, pyridaben, trichloroethylene, and fenpyroximate, also contribute to Complex I inhibition. Disruptions in the activity of the electron transport chain (ETC) caused by these toxins lead to reduced mitochondrial movement, increased mitochondrial permeability transition, elevated levels of reactive oxygen species (ROS), and heightened activity of nitric oxide synthase in the mitochondria. Importantly, Complex I deficiency has been observed in the substantia nigra, skeletal muscles, and platelets of PD patients (Bose & Beal, 2016).

1.1.1 Gene mutations causing mitochondrial dysfunction

Mutations in specific genes cause mitochondrial dysfunction and are known to play a role in familial forms of PD. Examples include Parkin, DJ-1, UCHL-1, LRRK2, PTEN-induced kinase1 (PINK1), NURR1, vacuolar protein sorting 35 (VPS35), HtrA2 (serine protease). When mutated, these genes can directly or indirectly promote mitochondrial dysfunction (Bose & Beal, 2016).

Parkin, encoded by the PARK2 gene, is an E3 ubiquitin ligase involved in the ubiquitination of substrate proteins to control crucial cellular processes, such as protein catabolism, immune response, and apoptosis. In PD, loss of Parkin function due to genetic mutation or post-translational inactivation leads to the inability of mitochondria to remove damaged proteins. Autosomal recessive mutations in the PARK2 gene are linked to the early-onset PD, whereas heterozygous mutations in PARK2 are linked to more common sporadic PD cases (Safreena et al., 2024).

PINK1 (PARK6) is a mitochondrial kinase that detects damaged mitochondria and recruits Parkin to initiate mitophagy, defined as the selective degradation of damaged or dysfunctional mitochondria by autophagy, helping maintain cellular health and energy balance (MacVicar, 2013). Mutations in this gene lead to reduced mitochondrial respiration and ATP production, as well as increased α-synuclein aggregation in cell culture models of PD (Liu et al., 2009). Moreover, mice that lack PINK1 are more susceptible to the toxic effects of oxidative stress and increased mitochondrial dysfunction (Bose & Beal, 2016).

Peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α) is a key regulator of mitochondrial biogenesis. In postmortem PD brains, researchers have observed a decrease in PGC-1α in both the substantia nigra and white blood cells (Bose & Beal, 2016). As for the latter, a study carried out by Yang *et al.* in 2019 found that PD patients exhibited higher DNA methylation levels in the PGC-1α promoter region in peripheral blood leukocytes compared to healthy controls. This hypermethylation was inversely correlated with PGC-1α mRNA expression, suggesting that epigenetic silencing of PGC-1α contributes to its reduced expression in these cells (Yang et al., 2020).

TOMM40 is a mitochondrial translocase located between the putative transmembrane domain and the mitochondrial-targeting sequence. To localize PINK1 in the mitochondria and be phosphorylated, PINK1 needs TOMM40. Therefore, dysfunction of PINK1 causes defects in its localization as well as impaired mitophagy (Bose & Beal, 2016).

DJ-1, whose mutations are known to cause a rare, early-onset form of autosomal recessive Parkinson's disease, is a mitochondrial peroxiredoxin-like peroxidase that has a role in scavenging mitochondrial ROS. Animal models, like DJ-1-deficient flies and mice, have shown that the absence of this gene increases sensitivity to oxidative stress, while its overexpression appears to offer a protective effect against such damage. In both humans with DJ-1 mutations and knockout mice, mitochondria exhibit impaired respiratory function, decreased membrane potential, elevated levels of reactive oxygen species (ROS), and noticeable changes in mitochondrial shape. In 2010, Perier *et al.* conducted an experiment using transgenic mice that overexpressed a mitochondrially targeted form of DJ-1. They established that these mice were protected against MPTP-induced ROS production and dopaminergic cell death, supporting the role of mitochondrial ROS in neurodegeneration in PD (Perier et al., 2010).

On the other hand, LRRK2 (PARK8) mutations are associated with a more common, late-onset, autosomal dominant form of the disease. Dopaminergic neurons in *Caenorhabditis Elegans* expressing the G2019S LRRK2 mutation showed increased vulnerability to mitochondrial toxins, and this genetic variant has also been linked to enhanced mitochondrial fission involving dynamin-like proteins (Bose & Beal, 2016; Wang et al., 2012). Moreover, mitochondrial abnormalities have been observed in the striatum of aged homozygous LRR2 G2019S knock-in mice, suggesting a link between LRRK2 and mitochondrial dysfunction in PD (Yue et al., 2015). Indeed, there is increased damage to mtDNA in neuronal cells derived from induced pluripotent stem cells (iPSCs) obtained from patients carrying the homozygous or heterozygous G2019S and heterozygous R1441C mutations in the LRRK2 gene (Sanders et al., 2014). To support this LRRK2 involvement, a new study published in 2025 showed that blocking the overactivation of LRRK2 using the inhibitor MLi-2 can reverse early signs of PD in mice. Treatments restored the cell structures, improved neuron communication, and promoted recovery in dopamine pathways (Jaimon et al., 2025).

High temperature requirement A2 (HTRA2) is involved in caspase-dependent apoptosis. In a study published in 2005, Strauss *et al.* screened patients with PD for mutations in HTRA2. The results highlighted a heterozygous mutation (G399S) and a polymorphism (A141S) associated with PD. In both cases, there was an atypical increase in the protease activity of HTRA2, leading to greater mitochondrial dysfunction caused by enlarged mitochondria and disorganized cristae than in the A141S risk allele polymorphism. Overexpression of HTRA2 caused by the G399S mutation causes cells to become more susceptible to stress-induced

death (Strauss et al., 2005). It is worth pointing out that in another study published three years later by Simón-Sánchez and Singleton, no association between G399S or A141S has been found (Simón-Sánchez & Singleton, 2008).

Exome sequencing of individuals carrying mutations in the VPS13C gene revealed that loss-of-function mutations in VPS13C are linked to a distinct form of early-onset PD, marked by early cognitive decline and rapid progression and pathological features resembling those seen in diffuse Lewy body disease. VPS13C, a lipid-transport protein and a sensor of lysosome stress or damage, partially localizes to the outer mitochondrial membrane. Silencing this gene leads to several mitochondrial abnormalities, including reduced membrane potential, mitochondrial fragmentation, increased respiration, and heightened PINK1/Parkin-dependent mitophagy. These results suggest that VPS13C loss-of-function contributes to the development of autosomal recessive early-onset Parkinsonism through disruption of mitochondrial homeostasis (Lesage et al., 2016).

1.2 α-synuclein

The other key player both in this essay and in PD is α-synuclein, a 14 kDa protein primarily expressed in neurons, where it is enriched at the presynaptic terminal, regulating trafficking and the release of neurotransmitters. It can be found either as a disordered monomer or in an α-helical, multimeric conformation. As summarized in Figure 4, by recruiting additional monomers, α-synuclein can form protofilaments and amyloid fibrils and convert to β-sheets. The aggregation of these fibrils will result in the formation of Lewy bodies and Lewy neurites, the hallmarks of PD. Both α-synuclein fibrils and oligomers contribute to cellular toxicity at different levels (Spillantini et al., 1998; Spillantini et al., 1997).

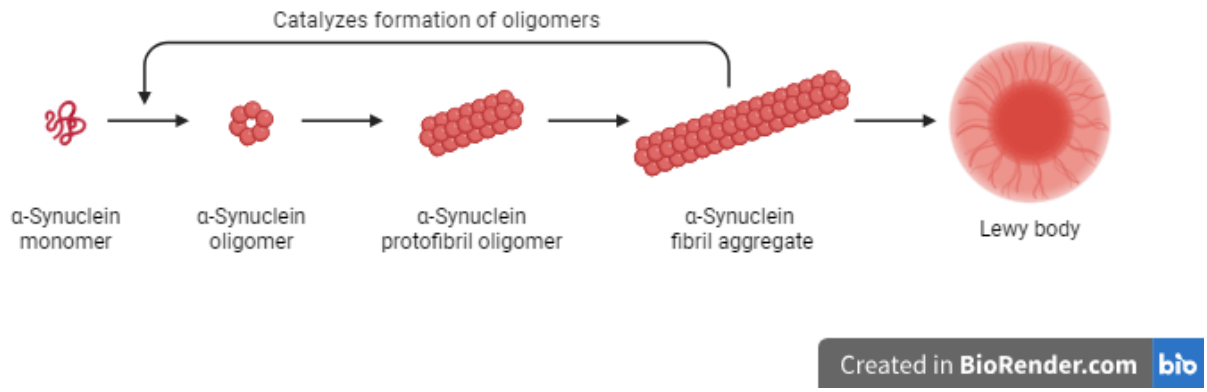

Figure 4: Process of α-synuclein aggregation. It begins with a single α-synuclein that binds other monomers resulting in a α-synuclein protofibril oligomer. With the binding of other oligomers, the first α-synuclein fibril aggregate is formed. Many α-synuclein aggregates lead to a Lewy body.

Injecting short fragments of α-synuclein fibrils into the striatum leads to a significant reduction of dopamine neurons in the SNc, a decrease in dopamine transporter-positive terminals in the striatum, triggers the formation of α-synuclein inclusions in brain regions such as the SNc, cortex, and amygdala, and leads to motor impairments. These findings highlight the role of fibril fragments capable of seeding in driving PD-like symptoms. This is particularly important for immunotherapy treatments that target fibrillar forms of α-synuclein or its monomeric forms (Abeliovich et al., 2000; Gorbatyuk et al., 2010; Zharikov et al., 2015).

Moreover, different structural forms of α-synuclein fibrils (Figure 5) appear to cause distinct disease features, supporting the idea that various “strains” of α-synuclein may underlie different synucleinopathies. For instance, fibrils formed under certain conditions can adopt a ribbon-like shape. In animal models, conventional fibrils cause significant loss of dopamine neurons and motor impairments. On the other hand, ribbon-like fibrils tend to promote α-synuclein accumulation in oligodendrocytes, a defining feature of Multiple System Atrophy (MSA), another disorder linked to α-synuclein pathology. Notably, α-synuclein fibrils are capable of cross-seeding tau inclusions like those found in Alzheimer’s disease. Therefore, distinct structural conformations of α-synuclein could lead to mixed pathologies by cross-seeding tau (Hijaz & Volpicelli-Daley, 2020; Woerman et al., 2018; Yamasaki et al., 2019).

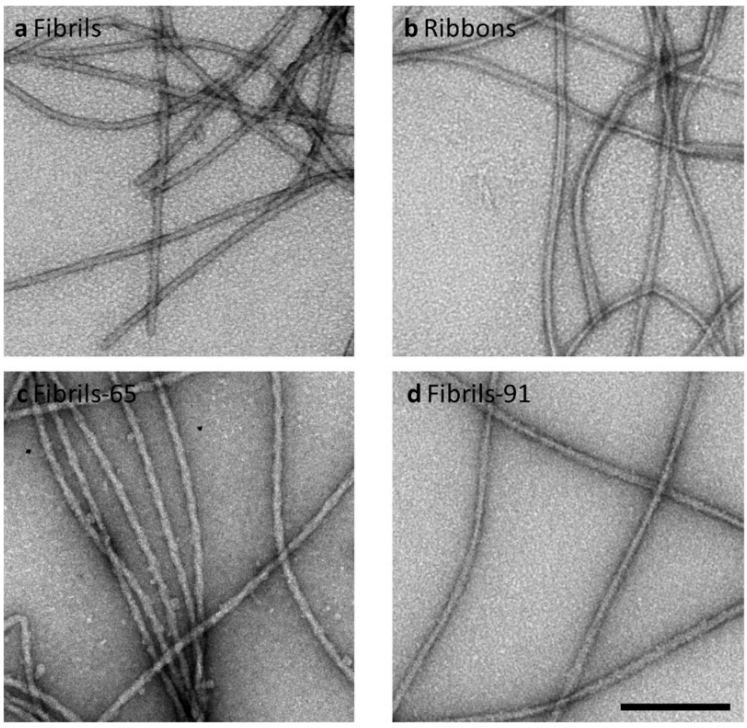

Figure 5: TEM images of the α-synuclein fibrillar polymorphs. Electron micrographs of α-synuclein a) fibrils, b) ribbons, c) fibrils-65, d) fibrils 91 (Makky et al., 2016).

For α-synuclein fibrils to form inclusions and spread across brain regions, they must first attach to the surface of neurons and enter the cell. Research has shown that specific cell-surface proteins are involved in the internalization of these fibrils. Indeed, a proteomics screen showed that the α3-subunit of the Na^+/K^+ ATPase binds specifically to fibrils, but not to monomers or oligomers, highlighting its potential role in their uptake (Shrivastava et al., 2015). Interestingly, fibrillar α-synuclein, but not its monomeric form, binds selectively to receptors like LAG3, APLP1 (amyloid-β precursor-like protein 1), and neurexin1β. LAG3, an immune checkpoint receptor on activated T cells and NK cells, is also expressed in neurons and microglia, where it contributes to the uptake of α-synuclein fibrils. Removing LAG3 can significantly reduce both the spread of these fibrils between neurons and their harmful effects. Similarly, neurexin1β, a protein concentrated at presynaptic terminals, has been found to assist in the internalization of acetylated fibrillar α-synuclein (Birol et al., 2019).

Moreover, the uptake of fibrils relies on heparan sulfate proteoglycans (HSPGs). For this reason, it has been suggested that even targeting HSPGs could prevent the spread of pathologic α-synuclein (Holmes et al., 2013; Shrivastava et al., 2015).

Therefore, fibrils engage with multiple binding partners, indicating a wide-ranging and possibly overlapping entry mechanism. In α-synucleinopathies, certain neuron types, such

as dopaminergic, noradrenergic, cholinergic, and glutamatergic cells, accumulate abundant Lewy inclusions, whereas most GABAergic neurons remain largely unaffected (Spillantini et al., 1998). This differential susceptibility appears to be partially linked to the local concentration of α-synuclein: neurons enriched in α-synuclein at their presynaptic terminals tend to form fibrils more easily. This is consistent with studies showing that higher α-synuclein concentrations accelerate aggregate formation. Nonetheless, the type of neurotransmitter alone cannot account for this difference. Indeed, dopaminergic neurons in the SNc show much greater vulnerability than those in the adjacent ventral tegmental area (VTA), despite a lack of thorough quantification of VTA neuron loss (Blesa & Przedborski, 2014; Giguère et al., 2018).

Some neuron types may be more prone to α-synuclein buildup simply because they express lower levels of key degradation helpers. For instance, glutamatergic neurons have less of BAG3, a protein related to autophagy. Experiments highlight that reducing BAG3 leads to more tau clumps, whereas increasing BAG3 promotes their clearance, and it likely plays a similar role for α-synuclein. Interestingly, a group of PD patients carrying the G51D α-synuclein mutation also develops aggregates not just in neurons but in oligodendrocytes (Kiely et al., 2013).

When neurons take up synthetic α-synuclein fibrils, they start to clump into deposits that look just like those in Parkinson’s patients. This model allows scientists to study how these clumps form, see how they harm neurons, and test ways to stop the process. Under normal conditions, α-synuclein remains in a flexible, unstructured form or assembles into helix-shaped clusters on cell membranes. Identifying the factors that trigger its conversion to rigid β-sheet structures and, eventually, full fibrils is essential for unravelling the disease’s progression (Killinger & Kordower, 2019).

Genetic studies have linked the amount of α-synuclein to disease risk. Nearly all individuals with a duplication or triplication of the SNCA gene ultimately develop PD. Even subtle changes in its genetic sequence increase disease risk (Soldner et al., 2016).

Under normal conditions, α-synuclein’s N-terminal region folds into an amphipathic helix that docks onto membranes and assembles into protective multimers. Mutations in this region that involve A30P or G51D weaken membrane binding, flooding the cytosol with monomers and boosting amyloid formation (Ysselstein et al., 2015). The central NAC domain is the core of aggregation: when it detaches from the membrane and enters the cytosol, it binds to other monomers, initiating the formation of protofibrils and fibrils (Waxman et al., 2009).

Lipids are also involved. Indeed, anionic lipids in synaptic vesicles favour α-synuclein binding, whereas oxidized lipids or short fatty acids (e.g., oleic acid) enhance exposure of the NAC domain (Lv et al., 2019).

Exosomes can carry α-synuclein between neurons. There's growing evidence that exosomal α-synuclein plays a role in triggering new clumps in distant brain areas, potentially fuelling the gradual spread and neuron damage seen in PD (Danzer et al., 2012; Ngolab et al., 2017).

For decades, we've known that damaging mitochondria drives α-synuclein clumping. Chronic MPTP exposure leads to α-synuclein aggregates. By increasing oxidative stress, Complex I inhibition chemically modifies α-synuclein, through nitration and oxidation, making it more likely to assemble (Betarbet et al., 2000; Paxinou et al., 2001; Sherer et al., 2002).

In the following sections, the evidence and the limitations of mitochondria-focused therapies will be explored, from bioenergetic boosters and mitophagy enhancers to α-synuclein fibril disruptors that also preserve mitochondrial health.

1.3 Neuroinflammation

Neuroinflammation has emerged as a central feature for PD onset and development, interfacing with mitochondrial dysfunction, α-synuclein aggregates, and genetic risk factors (Xue et al., 2024). A meta-analysis found that PD patients exhibit higher levels of IL-6 and TNF-α compared to controls, highlighting systemic inflammation and central immune activation (Qu et al., 2023).

At the cellular level, misfolded α-synuclein binds microglial toll-like receptors (TLR2 and TLR4), triggering assembly of the NLRP3 inflammasome and maturation of IL-1β and IL-18, which sustain dopaminergic neuron injury. Also, genetic studies have detected variants of specific loci (BST1 and HLA-DR) that modulate antigen presentation and adaptive responses in PD, leading to the conclusion that both innate and adaptive immunity contribute to disease progression. Impaired mitochondrial clearance, which may be due to the PINK1/Parkin pathway dysfunction, releases mtDNA and ROS that further activate microglial inflammasomes, creating a loop between mitochondrial stress and innate immunity (Xue et al., 2024).

Astrocytes are also involved in this process by releasing cytokines and chemokines and, under chronic inflammatory conditions, may facilitate blood-brain barrier permeability and infiltration of peripheral T-cells and monocytes, amplifying the neuroinflammation (Zhao et al., 2024). Cytokine release, inflammasome activation, glial signalling, and oxidative stress enhance α-synuclein aggregation and promote progressive dopaminergic neurodegeneration in PD (Dias et al., 2013).

2. Therapies

Many therapies have been developed for PD, both for early and advanced stages, including treatments aimed at various pathological mechanisms. However, considering that a specific question requires a clear answer, this chapter will focus on therapies targeting only mitochondria and α-synuclein.

2.1 Therapies targeting mitochondria

Mitochondrial dysfunction in PD often involves problems with the ETC and increased oxidative stress. Since these two issues are linked, many treatments aim to address both.

Several compounds that target mitochondria have been studied for their potential to improve motor symptoms and mitochondrial function in PD patients, especially those promoting mitochondrial biogenesis.

Exenatide is a GLP-1 receptor agonist currently used for type 2 diabetes mellitus, but pre-clinical studies also showed its ability to pass the blood-brain barrier, stimulating mitochondrial biogenesis and exerting neuroprotection through GLP-1 receptors. In a single-blind trial, exenatide was well-tolerated by PD patients, and the treated group showed an improvement in the MDS-UPDRS (Movement Disorders Society Unified Parkinson's Disease Rating Scale) after 1 year of treatment. This suggests that exenatide may also have an acute effect on motor symptoms. These results were followed by a double-blind, randomised, placebo-controlled trial, including participants with moderate-severity PD. Unfortunately, researchers found no advantage in the use of exenatide compared with placebo on any measures of Parkinson's disease severity. They also stated that further investigations are needed to explain the reasons for this discordance (Vijiaratnam et al., 2025).

2.1.1 Enhancing mitophagy

Mitochondrial health depends not only on creating new mitochondria but also on removing damaged ones, a process called mitophagy. In PD, issues with mitophagy are significant, especially since mutations in the genes Parkin and PINK1, which regulate mitophagy, are linked to early-onset PD. Therefore, scientists have been exploring ways to enhance mitophagy as a treatment. For instance, kinetin was tested to activate PINK1, but unfortunately, it showed no benefit in animal models (Orr et al., 2017). Conversely, celastrol showed promise by protecting brain cells through activating mitophagy in cell and mouse studies, inhibiting dopaminergic neural loss (Lin et al., 2019).

2.1.2 Mitochondrial biogenesis

Besides making new mitochondria and the process of mitophagy, mitochondrial biogenesis is also crucial. Research suggests that in PD, especially when Parkin is deficient, making new mitochondria might be a bigger issue than clearing old ones. This defect is linked to lower levels of PGC-1α, a key regulator of mitochondrial production. Targeting molecules involved in this pathway, like AMPK, SIRT1, and PPAR, offers a promising route for therapy. Various compounds have been tested to stimulate mitochondrial biogenesis. Ferulic acid, a natural plant compound, helped improve mitochondrial health in animal studies. A novel approach involves RNS60, a saline solution with oxygen nanobubbles, which can boost mitochondrial production in brain cells. Baicalein, a natural flavone of *Scutellaria baicalensis Georgi*, was able to enhance mitochondrial production in a PD rat model (Zhang et al., 2017).

2.1.3 Gene therapy

Over the last years, researchers have been exploring several innovative therapies to target mitochondria. One promising avenue involves gene therapy, which involves the delivery of functional copies of genes to replace or support damaged ones.

Two genes frequently implicated in hereditary forms of PD are PINK1 and Parkin. Mutations in either gene disrupt the cell's ability to manage damaged mitochondria. Experiments in animal models have shown that reintroducing healthy versions of these genes can reverse many of the disease's cellular effects. For example, increasing Parkin expression in mice protected neurons from mitochondrial damage and reduced motor symptoms. Similar results

were seen when PINK1 was reintroduced in fly models, where it improved mitochondrial structure and restored normal cellular function (Prasuhn et al., 2020). Notably, it has been found that Parkin can sometimes make up for the loss of PINK1, and when combined with DJ-1, the protective effects are even stronger. These findings support the idea that replacing or boosting these genes may help slow or even reverse the disease process in some patients (Haque et al., 2012).

Moreover, researchers are experimenting with mtDNA-complexed TFAM ((mitochondrial transcription factor A) or recombinant TFAM, a protein critical for maintaining mitochondrial DNA. Delivering TFAM directly to cells or using it to stabilize mitochondrial DNA has shown encouraging results in restoring mitochondrial bioenergetics of impaired neurons (Prasuhn et al., 2020).

Finally, a critical area of focus is mitochondrial dynamics and trafficking. Neurons, especially those producing dopamine affected in PD, rely heavily on the proper movement and distribution of mitochondria to meet energy requests throughout their axons. When this process occurs, it can lead to widespread cellular dysfunction. Drugs like Mdivi-1 (Mitochondrial Division Inhibitor 1) have shown the ability to reduce neurodegeneration, α-synuclein aggregation, mitochondrial dysfunction, and oxidative stress in α-synuclein rat models (Bido et al., 2017).

Altogether, these approaches represent a shift toward treating the root causes of mitochondrial dysfunction in Parkinson’s disease, rather than just managing symptoms.

Novel mitochondrial therapies

Emerging experimental treatments to target mitochondrial dysfunction in PD have also been explored, although most remain at an early clinical stage. Mitochondrial transplantation involves introducing healthy mitochondria into damaged neurons to restore bioenergetic function, although its applications are limited to models. Stem cell therapies focus on replacing lost dopaminergic neurons or modulating inflammation, but clinical translation is limited due to ethical and safety concerns. Inhibition of soluble epoxide hydrolase (sEH), an enzyme linked to inflammation and oxidative stress, has shown protective effects on mitochondria in animal studies. Photobiomodulation, the use of red to near-infrared light, seems to enhance mitochondrial activity and improve motor symptoms in human trials (Prasuhn et al., 2020).

2.2 Therapies targeting α-synuclein

As previously stated, α-synuclein aggregates are one of the drivers of PD pathogenesis. The focus of this chapter will be the therapies targeting α-synuclein, discussing promising therapies.

2.2.1 Graphene Quantum Dots (GQDs)

Researchers have shown that graphene quantum dots (GQDs) can bind α-synuclein through electrostatic and hydrophobic interactions, leading to the disruption of its β-sheet fibrils and preventing further aggregation. In primary neuronal cultures, GQDs not only reduced cytotoxicity caused by α-synuclein but also restored synaptic transmission and mitochondrial membrane potential. In addition to this, GQDs decreased Lewy body inclusions. Notably, GQDs cross the blood-brain barrier in vivo to exert these effects, improving motor outcomes. (Kim et al., 2018).

Based on these results, a hybrid nanocomposite named MABM-GQD has been synthesized. It maintains the anti-aggregation and brain-penetration properties of GQDs while enhancing the capacity of drug loading. Spectroscopic analyses, imaging techniques, and molecular dynamics confirmed that MABM-GQDs cleaved α-synuclein fibrils by destabilizing their structure. Also, MABM-GQDs preserved neuronal membrane integrity, reduced oxidative stress, and improved cell viability in vitro. In murine models, MRI proved that MABM-GQDs led to reduced α-synuclein pathology, attenuated neuroinflammation, protection of dopamine neurons, and increased cerebral blood flow (Kaliyaperumal et al., 2023).

Therefore, while GQDs were developed to target α-synuclein aggregation, they were also able to restore mitochondrial and synaptic function being a secondary benefit resulting from reduced α-synuclein toxicity.

2.2.2 TFE3

Overexpression of TFE3 (transcription factor E3) demonstrates strong neuroprotective effects in an AAV-α-synuclein (AAV: adeno-associated virus) mouse model of Parkinson’s disease. In this model, co-injection of AAV vectors expressing human α-synuclein and TFE3 into the SNc significantly prevented dopaminergic neuron loss compared to α-synuclein alone and preserved both neuronal terminals and motor function. Behavioural tests

confirmed that TFE3 mitigated α-synuclein-induced motor deficits. Ultimately, TFE3 restored autophagy by increasing key lysosomal and autophagic markers (Lamp1, p62, and LC3), clearing out substrate accumulation. TFE3 also regulated mitochondrial quality control. It transcriptionally upregulated Parkin, boosting mitophagy and promoting the clearance of dysfunctional mitochondria, as seen by reduced accumulation of mitochondrial markers like Tom20 and VDAC1. Additionally, TFE3 stimulated mitochondrial biogenesis by increasing PGC-1α and TFAM expression, reversing the mitochondrial deficits caused by α-synuclein overexpression. Altogether, these findings highlight TFE3's role in modulating autophagy, limiting α-synuclein aggregation and spread, and maintaining mitochondrial integrity. This suggests TFE3 as a promising target for therapeutic intervention in PD (He et al., 2025).

2.2.3 Immunotherapies

Immunotherapies aim to target extracellular α-synuclein to slow disease progression by enhancing its clearance (Alfaidi et al., 2024). Passive and active immunizations are both under study. Passive immunization involves the administration of monoclonal antibodies against α-synuclein, providing immediate but temporary antibody presence and requiring repeated dosing (Rodger et al., 2023). On the other hand, active immunization (like UB-312) stimulates the patient's immune system to produce antibodies via vaccination, potentially offering longer protection and immune memory but with the risk of autoimmune reactions (Knecht et al., 2022).

Both strategies are under evaluation, but peptide-based active immunotherapies are preferred to passive ones due to their cost of treatment, route of administration (intramuscular), requiring fewer doses, and induction of polyclonal antibodies, reducing off-target effects and immune reactions. Also, they can be used before the onset of symptoms. However, due to its location in cerebrospinal fluid (CSF) and interstitial fluid (ISF) of the brain parenchyma, α-synuclein limits the effects of immunotherapy (Nimmo et al., 2022).

UB-312

UB-312, a peptide vaccine designed by Vaxxinity, targets pathological α-synuclein oligomers and fibrils while avoiding harmful pro-inflammatory T-cell responses (Nimmo et al., 2022).

The findings highlighted the prevention of motor decline, significantly reducing α-synuclein oligomers (but not monomers) in the hippocampus, striatum, and cortex of mice. This resulted in the prevention of muscle strength and coordination decline. It also affected microglial activity in many brain regions, though not in the substantia nigra. There was no increase in T-cell infiltration, and no effect of immunization on glial cell activation was shown (Nimmo et al., 2022). Subsequently, a human trial was conducted to assess UB-312's safety and tolerance, demonstrating good results (Yu et al., 2022). These findings demonstrated the benefits of treating early PD with UB-312, preventing the progression of both motor and non-motor symptoms (Nimmo et al., 2022). However, a further study revealed the known challenge of translating biomarker changes into clinical benefits, and it is still uncertain whether the antibodies generated after immunization can penetrate cells to target pathological intracellular α-synuclein. Therefore, the researchers suggest optimizing doses and assessment methods to improve outcomes (Alfaidi et al., 2024).

2.3 Therapies targeting both mitochondria and α-synuclein

After discussing the therapies that focus solely on either mitochondrial dysfunction or α-synuclein aggregates, the last chapter is dedicated to combined therapies. Earlier in this essay, I discussed the vicious cycle that involves mitochondrial dysfunction and α-synuclein aggregates in PD. Therapies that target both aspects may have the potential to enhance the disease-modifying effects and put an end to this cycle of neurodegeneration in a more efficient way than strategies focusing only on a single pathway.

2.3.1 iCP-PARKIN

One of the most promising therapies has been described in a study published in 2020 by Chung *et al.*, in which the authors established the benefits of iCP-Parkin (improved-Cell Permeable Parkin) (Chung et al., 2020).

As stated earlier, Parkin acts as an E3 ubiquitin ligase downstream of PINK1 and DJ-1 in response to mitochondrial damage during mitophagy. Therefore, Parkin can be used for an effective PD therapy. After identifying crucial factors that facilitate the transport of Parkin across the blood-brain barrier and deliver it to deep brain tissues efficiently, an advanced macromolecule transduction domain (aMTD) sequence and a solubilization domain (SD)

were attached to the protein, obtaining iCP-Parkin. The protein suppressed neuronal toxicity in cultured cells and animals with damaged mitochondria and aggregated α-synuclein, as confirmed by immunostaining and Western blot. Moreover, iCP-Parkin increased the levels of key mitochondrial proteins involved in energy production, mitochondrial dynamics, and biogenesis. Also, changes in proapoptotic and antiapoptotic biomarkers were detected. Regarding oligomeric and filamentous forms of α-synuclein, their levels decrease by 93% and 80%, respectively, even though the mechanisms are still unknown. Two theories have been proposed: iCP-Parkin may influence the level of protein turnover, thereby affecting Lewy body formation; alternatively, iCP-Parkin may inhibit the pathways responsible for producing pathological forms of α-synuclein. Overall, these results suggest that motor deficits caused by PD may be reversible and that iCP-Parkin has great therapeutic potential as a PD-modifying agent, perhaps overcoming the limitations of drugs like L-DOPA (Chung et al., 2020).

3. Discussion

Parkinson's disease remains a challenging condition to treat, partly because processes like mitochondrial dysfunction and α-synuclein aggregation are involved (Wang et al., 2019). Research is increasingly shifting from managing symptoms to addressing the causes, offering hope for disease-modifying therapies. Many compounds aimed at improving mitochondrial function have been tested. For instance, exenatide was able to promote mitochondrial biogenesis and improve motor symptoms, showing encouraging results in early trials. However, larger studies highlighted the difficulty of translating preclinical success into clinical outcomes (Vijiaratnam et al., 2025). Research has shown that mitophagy, the process of removing damaged mitochondria, is another promising therapeutic target. This is due to its involvement in the early-onset PD, particularly when mutations in genes such as Parkin and PINK1 occur (Orr et al., 2017). The use of compounds like celastrol has demonstrated neuroprotective effects in preclinical models (Lin et al., 2019). The same goes when mitochondrial biogenesis is stimulated, such as when PGC-1α is targeted. Also, treatments that include ferulic acid, baicalein, or RNS60 have improved mitochondrial health in animal studies (Zhang et al., 2017). Gene therapy offers a cutting-edge approach by restoring the function of genes like Parkin and PINK1. Indeed, reintroducing these genes can reverse mitochondrial defects and improve motor function. Translating these results into

effective human treatments will require overcoming challenges, including the delivery across the blood-brain barrier (Haque et al., 2012).

Researchers have shown that graphene quantum dots (GQDs) reduced cytotoxicity caused by α-synuclein and restored synaptic transmission and mitochondrial membrane potential, decreasing Lewy body inclusions. This occurred thanks to their ability to cross the blood-brain barrier, improving motor outcomes (Kim et al., 2018).

Overexpression of TFE3 demonstrates strong neuroprotective effects in AAV-α-synuclein mouse models affected by PD, significantly preventing dopaminergic neuron loss compared to α-synuclein alone. It also preserved both neuronal terminals and motor functions, restored important autophagic markers, boosted mitophagy, and stimulated mitochondrial biogenesis (He et al., 2025).

The involvement of the immune system in PD adds even more complexity. In fact, mutations in LRRK2 influence immune responses and mitochondrial stress, increasing neuroinflammation. For this reason, the peptide vaccine UB-312 has been developed. It has shown the ability to reduce toxic α-synuclein oligomers and slow motor decline in animal models and early human trials. Nevertheless, it is also highlighted how antibodies have difficulty in penetrating cells to target α-synuclein effectively (Alfaidi et al., 2024; Nimmo et al., 2022; Yu et al., 2022). Given the interplay between mitochondrial dysfunction and α-synuclein aggregates, therapies targeting both may be the most effective. For instance, iCP-Parkin improves mitochondrial function and significantly reduces toxic α-synuclein fibrils, leading to better motor outcomes (Chung et al., 2020).

The mentioned therapies are still experimental, and PD heterogeneity complicates the development of effective treatments. Challenges involve the drug delivery to the brain, the reduction of side effects, and the development of biomarkers that can more precisely measure the disease progression and the treatment efficacy. Further research and clinical trials will be crucial in translating these promising approaches into treatment options.

4. Conclusions

Parkinson’s disease remains a complex and multifactorial neurodegenerative disorder, for which there is still no definitive cure, with mitochondrial dysfunction and α-synuclein aggregates playing a key role in neuronal degeneration. Even though traditional therapies

mainly focus on symptomatic relief, new treatments targeting mitochondria and α-synuclein offer promising scenarios for disease modification. Exenatide and gene therapies to restore Parkin and PINK1 function, demonstrate the potential to counter mitochondrial dysfunction (Haque et al., 2012; Vijiaratnam et al., 2025). At the same time, innovative immunotherapies like UB-312 and molecular agents like graphene quantum dots (GQDs) and TFE3 highlight the ability to modulate α-synuclein aggregation and propagation (He et al., 2025; Kaliyaperumal et al., 2023; Kim et al., 2018). It is also remarkable approaches like iCP-Parkin that link mitochondria restoration and the clearance of α-synuclein pathological forms, driving new therapies toward targeting both features (Chung et al., 2020). Nevertheless, the translation of preclinical successes to clinical efficacy remains a complex issue to solve, emphasizing the need for improved patient stratification, optimized dosing, and new biomarkers that reflect disease progression and treatment response in humans. In conclusion, these new therapies bring real hope for neuroprotection and neurorestoration, and a better understanding of the mitochondrial and α-synuclein relationship, combined with innovative treatments, holds the promise for altering the course of Parkinson's disease and making patients' lives better.

Disclaimer: ChatGPT was used with the sole purpose of rephrasing some sentences.

References

Abeliovich, A., Schmitz, Y., Fariñas, I., Choi-Lundberg, D., Ho, W. H., Castillo, P. E.,…Rosenthal, A. (2000). Mice lacking alpha-synuclein display functional deficits in the nigrostriatal dopamine system. *Neuron*, *25*(1), 239-252. https://doi.org/10.1016/s0896-6273(00)80886-7

Alfaidi, M., Barker, R. A., & Kuan, W. L. (2024). An update on immune-based alpha-synuclein trials in Parkinson's disease. *J Neurol*, *272*(1), 21. https://doi.org/10.1007/s00415-024-12770-x

Alotaibi, S., Alfayez, L., & Alkhudhair, M. (2024). Parkinson's Disease: Current Treatment Modalities and Emerging Therapies. *Cureus*, *16*(12), e75647. https://doi.org/10.7759/cureus.75647

Betarbet, R., Sherer, T. B., MacKenzie, G., Garcia-Osuna, M., Panov, A. V., & Greenamyre, J. T. (2000). Chronic systemic pesticide exposure reproduces features of Parkinson's disease. *Nat Neurosci*, *3*(12), 1301-1306. https://doi.org/10.1038/81834

Bido, S., Soria, F. N., Fan, R. Z., Bezard, E., & Tieu, K. (2017). Mitochondrial division inhibitor-1 is neuroprotective in the A53T-α-synuclein rat model of Parkinson's disease. *Sci Rep*, *7*(1), 7495. https://doi.org/10.1038/s41598-017-07181-0

Birol, M., Wojcik, S. P., Miranker, A. D., & Rhoades, E. (2019). Identification of N-linked glycans as specific mediators of neuronal uptake of acetylated α-Synuclein. *PLoS Biol*, *17*(6), e3000318. https://doi.org/10.1371/journal.pbio.3000318

Blesa, J., & Przedborski, S. (2014). Parkinson's disease: animal models and dopaminergic cell vulnerability. *Front Neuroanat*, *8*, 155. https://doi.org/10.3389/fnana.2014.00155

Bloem, B. R., Okun, M. S., & Klein, C. (2021). Parkinson's disease. *Lancet*, *397*(10291), 2284-2303. https://doi.org/10.1016/s0140-6736(21)00218-x

Bose, A., & Beal, M. F. (2016). Mitochondrial dysfunction in Parkinson's disease. *J Neurochem*, *139 Suppl 1*, 216-231. https://doi.org/10.1111/jnc.13731

Chung, E., Choi, Y., Park, J., Nah, W., Jung, Y., Lee, J.,…Jo, D. (2020). Intracellular delivery of Parkin rescues neurons from accumulation of damaged mitochondria and pathological α-synuclein. *Sci Adv*, *6*(18), eaba1193. https://doi.org/10.1126/sciadv.aba1193

Danzer, K. M., Kranich, L. R., Ruf, W. P., Cagsal-Getkin, O., Winslow, A. R., Zhu, L.,…McLean, P. J. (2012). Exosomal cell-to-cell transmission of alpha synuclein oligomers. *Mol Neurodegener*, *7*, 42. https://doi.org/10.1186/1750-1326-7-42

Dias, V., Junn, E., & Mouradian, M. M. (2013). The role of oxidative stress in Parkinson's disease. *J Parkinsons Dis*, *3*(4), 461-491. https://doi.org/10.3233/jpd-130230

Dorsey, E. (2018). Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*, *17*(11), 939-953. https://doi.org/10.1016/s1474-4422(18)30295-3

Franco-Iborra, S., Vila, M., & Perier, C. (2016). The Parkinson Disease Mitochondrial Hypothesis: Where Are We at? *Neuroscientist*, *22*(3), 266-277. https://doi.org/10.1177/1073858415574600

Galea, S., & Tracy, M. (2007). Participation rates in epidemiologic studies. *Ann Epidemiol*, *17*(9), 643-653. https://doi.org/10.1016/j.annepidem.2007.03.013

GBD. (2018). Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*, *17*(11), 939-953. https://doi.org/10.1016/s1474-4422(18)30295-3

Giguère, N., Burke Nanni, S., & Trudeau, L. E. (2018). On Cell Loss and Selective Vulnerability of Neuronal Populations in Parkinson's Disease. *Front Neurol*, *9*, 455. https://doi.org/10.3389/fneur.2018.00455
Gorbatyuk, O. S., Li, S., Nash, K., Gorbatyuk, M., Lewin, A. S., Sullivan, L. F.,…Muzyczka, N. (2010). In vivo RNAi-mediated alpha-synuclein silencing induces nigrostriatal degeneration. *Mol Ther*, *18*(8), 1450-1457. https://doi.org/10.1038/mt.2010.115
Haque, M. E., Mount, M. P., Safarpour, F., Abdel-Messih, E., Callaghan, S., Mazerolle, C.,…Park, D. S. (2012). Inactivation of Pink1 gene in vivo sensitizes dopamine-producing neurons to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and can be rescued by autosomal recessive Parkinson disease genes, Parkin or DJ-1. *J Biol Chem*, *287*(27), 23162-23170. https://doi.org/10.1074/jbc.M112.346437
He, X., Chen, M., Fan, Y., Wu, B., & Dong, Z. (2025). TFE3-mediated neuroprotection: Clearance of aggregated α-synuclein and accumulated mitochondria in the AAV-α-synuclein model of Parkinson's disease. *Genes Dis*, *12*(2), 101429. https://doi.org/10.1016/j.gendis.2024.101429
Hijaz, B. A., & Volpicelli-Daley, L. A. (2020). Initiation and propagation of α-synuclein aggregation in the nervous system. *Mol Neurodegener*, *15*(1), 19. https://doi.org/10.1186/s13024-020-00368-6
Holmes, B. B., DeVos, S. L., Kfoury, N., Li, M., Jacks, R., Yanamandra, K.,…Diamond, M. I. (2013). Heparan sulfate proteoglycans mediate internalization and propagation of specific proteopathic seeds. *Proc Natl Acad Sci U S A*, *110*(33), E3138-3147. https://doi.org/10.1073/pnas.1301440110
Jaimon, E., Lin, Y. E., Tonelli, F., Antico, O., Alessi, D. R., & Pfeffer, S. R. (2025). Restoration of striatal neuroprotective pathways by kinase inhibitor treatment of Parkinson's disease-linked LRRK2-mutant mice. *Sci Signal*, *18*(893), eads5761. https://doi.org/10.1126/scisignal.ads5761
Jankovic, J. (2008). Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry*, *79*(4), 368-376. https://doi.org/10.1136/jnnp.2007.131045
Kalia, L. V., & Lang, A. E. (2015). Parkinson's disease. *Lancet*, *386*(9996), 896-912. https://doi.org/10.1016/s0140-6736(14)61393-3
Kaliyaperumal, P., Renganathan, S., Arumugam, K., & Aremu, B. R. (2023). Engineered graphene quantum dot nanocomposite triggers α-synuclein defibrillation: Therapeutics against Parkinson's disease. *Nanomedicine*, *47*, 102608. https://doi.org/10.1016/j.nano.2022.102608
Kanazawa, T., Uchihara, T., Takahashi, A., Nakamura, A., Orimo, S., & Mizusawa, H. (2008). Three-layered structure shared between Lewy bodies and lewy neurites-three-dimensional reconstruction of triple-labeled sections. *Brain Pathol*, *18*(3), 415-422. https://doi.org/10.1111/j.1750-3639.2008.00140.x
Kiely, A. P., Asi, Y. T., Kara, E., Limousin, P., Ling, H., Lewis, P.,…Holton, J. L. (2013). α-Synucleinopathy associated with G51D SNCA mutation: a link between Parkinson's disease and multiple system atrophy? *Acta Neuropathol*, *125*(5), 753-769. https://doi.org/10.1007/s00401-013-1096-7
Killinger, B. A., & Kordower, J. H. (2019). Spreading of alpha-synuclein - relevant or epiphenomenon? *J Neurochem*, *150*(5), 605-611. https://doi.org/10.1111/jnc.14779
Kim, D., Yoo, J. M., Hwang, H., Lee, J., Lee, S. H., Yun, S. P.,…Ko, H. S. (2018). Graphene quantum dots prevent α-synucleinopathy in Parkinson's disease. *Nat Nanotechnol*, *13*(9), 812-818. https://doi.org/10.1038/s41565-018-0179-y
Klein, C., & Westenberger, A. (2012). Genetics of Parkinson's disease. *Cold Spring Harb Perspect Med*, *2*(1), a008888. https://doi.org/10.1101/cshperspect.a008888
Knecht, L., Folke, J., Dodel, R., Ross, J. A., & Albus, A. (2022). Alpha-synuclein Immunization Strategies for Synucleinopathies in Clinical Studies: A Biological

Perspective. *Neurotherapeutics*, *19*(5), 1489-1502. https://doi.org/10.1007/s13311-022-01288-7
Langston, J. W., Ballard, P., Tetrud, J. W., & Irwin, I. (1983). Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. *Science*, *219*(4587), 979-980. https://doi.org/10.1126/science.6823561
Lesage, S., & Brice, A. (2009). Parkinson's disease: from monogenic forms to genetic susceptibility factors. *Hum Mol Genet*, *18*(R1), R48-59. https://doi.org/10.1093/hmg/ddp012
Lesage, S., Drouet, V., Majounie, E., Deramecourt, V., Jacoupy, M., Nicolas, A.,…Brice, A. (2016). Loss of VPS13C Function in Autosomal-Recessive Parkinsonism Causes Mitochondrial Dysfunction and Increases PINK1/Parkin-Dependent Mitophagy. *Am J Hum Genet*, *98*(3), 500-513. https://doi.org/10.1016/j.ajhg.2016.01.014
Lin, M. W., Lin, C. C., Chen, Y. H., Yang, H. B., & Hung, S. Y. (2019). Celastrol Inhibits Dopaminergic Neuronal Death of Parkinson's Disease through Activating Mitophagy. *Antioxidants (Basel)*, *9*(1). https://doi.org/10.3390/antiox9010037
Liu, G., Zhang, C., Yin, J., Li, X., Cheng, F., Li, Y.,…Yu, S. (2009). alpha-Synuclein is differentially expressed in mitochondria from different rat brain regions and dose-dependently down-regulates complex I activity. *Neurosci Lett*, *454*(3), 187-192. https://doi.org/10.1016/j.neulet.2009.02.056
Lv, Z., Hashemi, M., Banerjee, S., Zagorski, K., Rochet, J. C., & Lyubchenko, Y. L. (2019). Assembly of α-synuclein aggregates on phospholipid bilayers. *Biochim Biophys Acta Proteins Proteom*, *1867*(9), 802-812. https://doi.org/10.1016/j.bbapap.2019.06.006
MacVicar, T. (2013). Mitophagy. *Essays Biochem*, *55*, 93-104. https://doi.org/10.1042/bse0550093
Mudò, G., Belluardo, N., Mauro, A., & Fuxe, K. (2007). Acute intermittent nicotine treatment induces fibroblast growth factor-2 in the subventricular zone of the adult rat brain and enhances neuronal precursor cell proliferation. *Neuroscience*, *145*(2), 470-483. https://doi.org/10.1016/j.neuroscience.2006.12.012
Ngolab, J., Trinh, I., Rockenstein, E., Mante, M., Florio, J., Trejo, M.,…Rissman, R. A. (2017). Brain-derived exosomes from dementia with Lewy bodies propagate α-synuclein pathology. *Acta Neuropathol Commun*, *5*(1), 46. https://doi.org/10.1186/s40478-017-0445-5
Nimmo, J. T., Smith, H., Wang, C. Y., Teeling, J. L., Nicoll, J. A. R., Verma, A.,…Carare, R. O. (2022). Immunisation with UB-312 in the Thy1SNCA mouse prevents motor performance deficits and oligomeric α-synuclein accumulation in the brain and gut. *Acta Neuropathol*, *143*(1), 55-73. https://doi.org/10.1007/s00401-021-02381-5
Orr, A. L., Rutaganira, F. U., de Roulet, D., Huang, E. J., Hertz, N. T., Shokat, K. M., & Nakamura, K. (2017). Long-term oral kinetin does not protect against α-synuclein-induced neurodegeneration in rodent models of Parkinson's disease. *Neurochem Int*, *109*, 106-116. https://doi.org/10.1016/j.neuint.2017.04.006
Paxinou, E., Chen, Q., Weisse, M., Giasson, B. I., Norris, E. H., Rueter, S. M.,…Ischiropoulos, H. (2001). Induction of alpha-synuclein aggregation by intracellular nitrative insult. *J Neurosci*, *21*(20), 8053-8061. https://doi.org/10.1523/jneurosci.21-20-08053.2001
Perier, C., Bové, J., Dehay, B., Jackson-Lewis, V., Rabinovitch, P. S., Przedborski, S., & Vila, M. (2010). Apoptosis-inducing factor deficiency sensitizes dopaminergic neurons to parkinsonian neurotoxins. *Ann Neurol*, *68*(2), 184-192. https://doi.org/10.1002/ana.22034

Prasuhn, J., Davis, R. L., & Kumar, K. R. (2020). Targeting Mitochondrial Impairment in Parkinson's Disease: Challenges and Opportunities. *Front Cell Dev Biol*, *8*, 615461. https://doi.org/10.3389/fcell.2020.615461

Qu, Y., Li, J., Qin, Q., Wang, D., Zhao, J., An, K.,…Xue, Z. (2023). A systematic review and meta-analysis of inflammatory biomarkers in Parkinson's disease. *NPJ Parkinsons Dis*, *9*(1), 18. https://doi.org/10.1038/s41531-023-00449-5

Rodger, A. T., M, A. L., & Carter, W. G. (2023). Are Therapies That Target α-Synuclein Effective at Halting Parkinson's Disease Progression? A Systematic Review. *Int J Mol Sci*, *24*(13). https://doi.org/10.3390/ijms241311022

Safreena, N., Nair, I. C., & Chandra, G. (2024). Therapeutic potential of Parkin and its regulation in Parkinson's disease. *Biochem Pharmacol*, *230*(Pt 3), 116600. https://doi.org/10.1016/j.bcp.2024.116600

Sanders, L. H., McCoy, J., Hu, X., Mastroberardino, P. G., Dickinson, B. C., Chang, C. J.,…Greenamyre, J. T. (2014). Mitochondrial DNA damage: molecular marker of vulnerable nigral neurons in Parkinson's disease. *Neurobiol Dis*, *70*, 214-223. https://doi.org/10.1016/j.nbd.2014.06.014

Sherer, T. B., Betarbet, R., Stout, A. K., Lund, S., Baptista, M., Panov, A. V.,…Greenamyre, J. T. (2002). An in vitro model of Parkinson's disease: linking mitochondrial impairment to altered alpha-synuclein metabolism and oxidative damage. *J Neurosci*, *22*(16), 7006-7015. https://doi.org/10.1523/jneurosci.22-16-07006.2002

Shrivastava, A. N., Redeker, V., Fritz, N., Pieri, L., Almeida, L. G., Spolidoro, M.,…Triller, A. (2015). α-synuclein assemblies sequester neuronal α3-Na+/K+-ATPase and impair Na+ gradient. *Embo j*, *34*(19), 2408-2423. https://doi.org/10.15252/embj.201591397

Simón-Sánchez, J., & Singleton, A. B. (2008). Sequencing analysis of OMI/HTRA2 shows previously reported pathogenic mutations in neurologically normal controls. *Hum Mol Genet*, *17*(13), 1988-1993. https://doi.org/10.1093/hmg/ddn096

Sohrabi, T., Mirzaei-Behbahani, B., Zadali, R., Pirhaghi, M., Morozova-Roche, L. A., & Meratan, A. A. (2023). Common Mechanisms Underlying α-Synuclein-Induced Mitochondrial Dysfunction in Parkinson's Disease. *J Mol Biol*, *435*(12), 167992. https://doi.org/10.1016/j.jmb.2023.167992

Soldner, F., Stelzer, Y., Shivalila, C. S., Abraham, B. J., Latourelle, J. C., Barrasa, M. I.,…Jaenisch, R. (2016). Parkinson-associated risk variant in distal enhancer of α-synuclein modulates target gene expression. *Nature*, *533*(7601), 95-99. https://doi.org/10.1038/nature17939

Spillantini, M. G., Crowther, R. A., Jakes, R., Hasegawa, M., & Goedert, M. (1998). alpha-Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with lewy bodies. *Proc Natl Acad Sci U S A*, *95*(11), 6469-6473. https://doi.org/10.1073/pnas.95.11.6469

Spillantini, M. G., Schmidt, M. L., Lee, V. M., Trojanowski, J. Q., Jakes, R., & Goedert, M. (1997). Alpha-synuclein in Lewy bodies. *Nature*, *388*(6645), 839-840. https://doi.org/10.1038/42166

Strauss, K. M., Martins, L. M., Plun-Favreau, H., Marx, F. P., Kautzmann, S., Berg, D.,…Krüger, R. (2005). Loss of function mutations in the gene encoding Omi/HtrA2 in Parkinson's disease. *Hum Mol Genet*, *14*(15), 2099-2111. https://doi.org/10.1093/hmg/ddi215

Vijiaratnam, N., Girges, C., Auld, G., McComish, R., King, A., Skene, S. S.,…Foltynie, T. (2025). Exenatide once a week versus placebo as a potential disease-modifying treatment for people with Parkinson's disease in the UK: a phase 3, multicentre, double-blind, parallel-group, randomised, placebo-controlled trial. *Lancet*, *405*(10479), 627-636. https://doi.org/10.1016/s0140-6736(24)02808-3

Vázquez-Vélez, G. E., & Zoghbi, H. Y. (2021). Parkinson's Disease Genetics and Pathophysiology. *Annu Rev Neurosci*, *44*, 87-108. https://doi.org/10.1146/annurev-neuro-100720-034518

Wang, X., Becker, K., Levine, N., Zhang, M., Lieberman, A. P., Moore, D. J., & Ma, J. (2019). Pathogenic alpha-synuclein aggregates preferentially bind to mitochondria and affect cellular respiration. *Acta Neuropathol Commun*, *7*(1), 41. https://doi.org/10.1186/s40478-019-0696-4

Wang, X., Yan, M. H., Fujioka, H., Liu, J., Wilson-Delfosse, A., Chen, S. G.,…Zhu, X. (2012). LRRK2 regulates mitochondrial dynamics and function through direct interaction with DLP1. *Hum Mol Genet*, *21*(9), 1931-1944. https://doi.org/10.1093/hmg/dds003

Waxman, E. A., Mazzulli, J. R., & Giasson, B. I. (2009). Characterization of hydrophobic residue requirements for alpha-synuclein fibrillization. *Biochemistry*, *48*(40), 9427-9436. https://doi.org/10.1021/bi900539p

Woerman, A. L., Kazmi, S. A., Patel, S., Freyman, Y., Oehler, A., Aoyagi, A.,…Prusiner, S. B. (2018). MSA prions exhibit remarkable stability and resistance to inactivation. *Acta Neuropathol*, *135*(1), 49-63. https://doi.org/10.1007/s00401-017-1762-2

Xue, J., Tao, K., Wang, W., & Wang, X. (2024). What Can Inflammation Tell Us about Therapeutic Strategies for Parkinson's Disease? *Int J Mol Sci*, *25*(3). https://doi.org/10.3390/ijms25031641

Yamasaki, T. R., Holmes, B. B., Furman, J. L., Dhavale, D. D., Su, B. W., Song, E. S.,…Diamond, M. I. (2019). Parkinson's disease and multiple system atrophy have distinct α-synuclein seed characteristics. *J Biol Chem*, *294*(3), 1045-1058. https://doi.org/10.1074/jbc.RA118.004471

Yang, X., Xu, S., Qian, Y., He, X., Chen, S., & Xiao, Q. (2020). Hypermethylation of the Gene Coding for PGC-1α in Peripheral Blood Leukocytes of Patients With Parkinson's Disease. *Front Neurosci*, *14*, 97. https://doi.org/10.3389/fnins.2020.00097

Ysselstein, D., Joshi, M., Mishra, V., Griggs, A. M., Asiago, J. M., McCabe, G. P.,…Rochet, J. C. (2015). Effects of impaired membrane interactions on α-synuclein aggregation and neurotoxicity. *Neurobiol Dis*, *79*, 150-163. https://doi.org/10.1016/j.nbd.2015.04.007

Yu, H. J., Thijssen, E., van Brummelen, E., van der Plas, J. L., Radanovic, I., Moerland, M.,…Dodart, J. C. (2022). A Randomized First-in-Human Study With UB-312, a UBITh® α-Synuclein Peptide Vaccine. *Mov Disord*, *37*(7), 1416-1424. https://doi.org/10.1002/mds.29016

Yue, M., Hinkle, K. M., Davies, P., Trushina, E., Fiesel, F. C., Christenson, T. A.,…Melrose, H. L. (2015). Progressive dopaminergic alterations and mitochondrial abnormalities in LRRK2 G2019S knock-in mice. *Neurobiol Dis*, *78*, 172-195. https://doi.org/10.1016/j.nbd.2015.02.031

Zhang, X., Du, L., Zhang, W., Yang, Y., Zhou, Q., & Du, G. (2017). Therapeutic effects of baicalein on rotenone-induced Parkinson's disease through protecting mitochondrial function and biogenesis. *Sci Rep*, *7*(1), 9968. https://doi.org/10.1038/s41598-017-07442-y

Zhao, Y., Huang, Y., Cao, Y., & Yang, J. (2024). Astrocyte-Mediated Neuroinflammation in Neurological Conditions. *Biomolecules*, *14*(10). https://doi.org/10.3390/biom14101204

Zharikov, A. D., Cannon, J. R., Tapias, V., Bai, Q., Horowitz, M. P., Shah, V.,…Burton, E. A. (2015). shRNA targeting α-synuclein prevents neurodegeneration in a Parkinson's disease model. *J Clin Invest*, *125*(7), 2721-2735. https://doi.org/10.1172/jci64502