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CLINICAL, PROGNOSTIC AND BIOCHEMICAL MARKERS OF EARLY MANIFESTATIONS OF PARKINSON'S DISEASE AND METHODS OF THEIR CORRECTION

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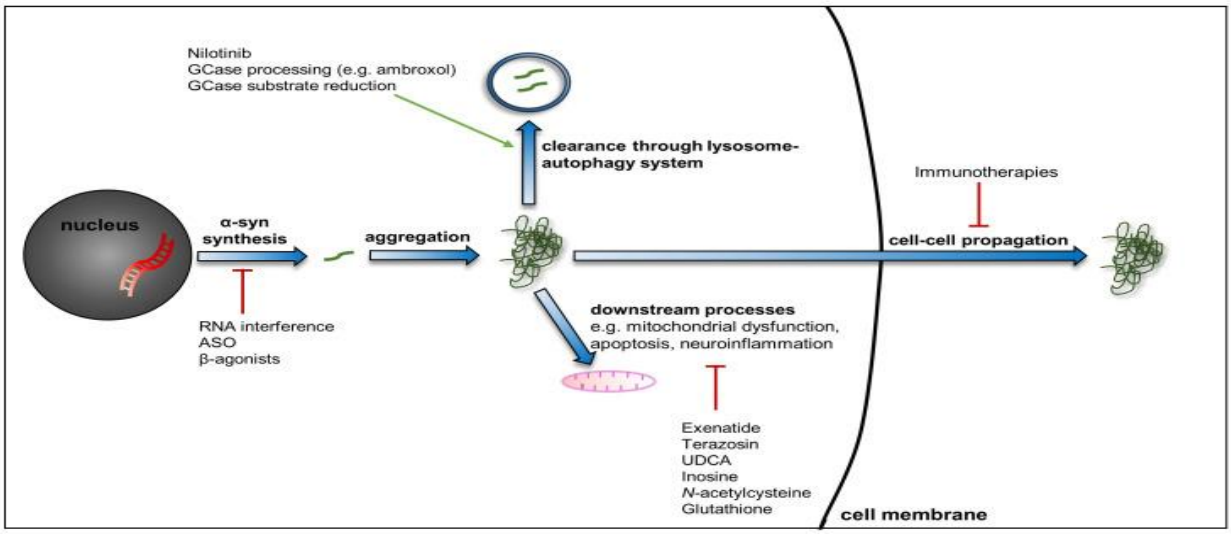
ABSTRACT

Parkinson's disease (PD) is a common neurodegenerative disease typified by a movement disorder consisting of bradykinesia, rest tremor, rigidity, and postural instability. Treatment options for PD are limited, with most of the current approaches based on restoration of dopaminergic tone in the striatum. However, these do not alter disease course and do not treat the non-dopamine-dependent features of PD such as freezing of gait, cognitive impairment, and other non-motor features of the disorder, which often have the greatest impact on quality of life. As understanding of PD pathogenesis grows, novel therapeutic avenues are emerging. These include treatments that aim to control the symptoms of PD without the problematic side effects seen with currently available treatments and those that are aimed towards slowing pathology, reducing neuronal loss, and attenuating disease course. In this latter regard, there has been much interest in drug repurposing (the use of established drugs for a new indication), with many drugs being reported to affect PD-relevant intracellular processes. This approach offers an expedited route to the clinic, given that pharmacokinetic and safety data are potentially already available. In terms of better symptomatic therapies that are also regenerative, gene therapies and cell-based treatments are beginning to enter clinical trials, and developments in other neurosurgical strategies such as more nuanced deep brain stimulation approaches mean that the landscape of PD treatment is likely to evolve considerably over the coming years. In this review, we provide an overview of the novel therapeutic approaches that are close to, or are already in, clinical trials.

Key words: α-synuclein, deep brain stimulation, drug repurposing, immunotherapies, gene therapies, neural grafting, Parkinson's disease.

INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disease characterised by a movement disorder consisting of bradykinesia, rest tremor, and rigidity, along with postural instability, a range of other more-subtle motor features, and many non-motor features. Many of the core motor features result from the loss of a specific population of neurons: the dopaminergic neurons of the substantia nigra pars compacta, which project axons to the striatum. As such, most of the current pharmacological treatment approaches for PD aim to restore dopaminergic tone in the striatum [1, 15]. Whilst often effective at improving motor function, current treatments are associated with significant side effects due to delivery of dopamine to extra-striatal regions, variability in their absorption and transit across the blood–brain barrier, and the non-physiological continuous release of dopamine and its effects on the dopamine receptors within the basal ganglia. Patients frequently develop cognitive problems, levodopa-induced dyskinesias, and on-off fluctuations, which we have estimated to occur in 46%, 56%, and 100% of cases, respectively, at 10 years from diagnosis based on data from our ongoing community-based incident study in PD. All of these factors coupled with some of the neuropsychiatric features of PD have a significant impact on quality of life in advancing PD. Many features of PD (such as cognitive impairment and autonomic dysfunction) have a mainly non-dopaminergic basis, resulting from neurodegeneration at other sites in the central nervous system as well as the enteric and autonomic nervous systems [2, 4, 10]. It is often these features that have the most detrimental impact on the quality of life of patients with PD, yet treatment options remain limited for these elements of disease. Levodopa, the precursor of dopamine, was first developed for the treatment of PD in the 1960s and continues to be the most-effective therapeutic agent for PD in 2020. Other dopaminergic drugs have since been used, including inhibitors of dopamine metabolism as well as dopamine receptor agonists, but these are generally less well tolerated and less effective. Thus, there is an urgent need for better therapies, including disease-modifying treatments [3, 4 ,11]. However, the requirement for relevant pre-clinical disease models for testing such agents and the lack of robust biomarkers for diagnosing PD and the identification of prodromal disease, which would allow for treatment before significant neuronal loss had occurred, pose barriers to drug discovery [5, 6, 9, 12].It is on this background that a number of new developments are emerging that may transform the management of PD over the coming years, and we will now discuss those that are in, or soon to be in, clinical trials (Figure 1).



The pathological hallmark of PD is the presence of abnormal aggregates of α-synuclein The role of α-synuclein in PD is not clear, but it is presumed to play a central pathogenic role, as demonstrated by the fact that mutations or duplications/triplications of the gene (*SNCA*) cause rare familial forms of PD , coupled with many independent studies showing the detrimental effects of manipulating α-synuclein in cell and animal models Potential pathogenic mechanisms of α-synuclein include dysfunction of vesicular transport, perturbations in the lysosome–autophagy system, mitochondrial dysfunction, and oxidative stress, for example [6, 7, 13] . It has also been proposed that pathological forms of α-synuclein can act in a prion-like fashion, allowing pathology to spread from cell to cell, and the "strains" underlying this are now being identified. This in turn means the disease follows a pattern of pathology that results from the sequential involvement of a number of anatomical structures [8, 14]. All of this suggests that therapies designed to reduce levels of α-synuclein or the propagation of toxic "strains" may limit PD progression. One experimental approach to restricting the propagation of α-synuclein is to use antibodies to target and degrade extracellular α-synuclein and thus prevent it from "infecting" neighbouring cells. Passive and active immunisation techniques against α-synuclein have been shown to convey neuroprotective effects in animal models, with the results of early clinical trials in humans starting to emerge. Other approaches to reducing α-synuclein levels include anti-sense oligonucleotide and ribonucleic acid (RNA) interference techniques to reduce its synthesis, though these remain in pre-clinical stages and are thus not discussed in detail here. A humanised monoclonal antibody targeting the C-terminus of aggregated α-synuclein (prasinezumab or PRX002, Prothena) has been shown to reduce free serum α-synuclein by approximately 97% and to be well tolerated in phase I clinical trials, with a phase II trial currently underway. Another antibody, BIIB054 (Biogen), targeting the N-terminal portion

of α-synuclein reduces the propagation of α-synuclein pathology and improves the motor phenotype in a PD model involving injection of α-synuclein pre-formed fibrils into mice. This antibody has also been found to be well tolerated in humans and is under investigation in a phase II clinical trial [13]. The company AFFiRiS are approaching this problem in a different way by investigating a range of treatments consisting of α-synuclein fragments or α-synuclein-mimicking epitopes designed to induce an active immune response against α-synuclein, with phase I trials completed. These products have been administered subcutaneously in early trials and seem to be well tolerated. One of these, AFFITOPE PD01A, conveyed a dose-dependent immune response to the peptide itself and to α-synuclein and is now being taken forward to phase II trials [23]

The use of immunotherapies to limit the propagation of PD pathology is an interesting avenue for further exploration, but important questions remain, not least the extent to which PD in the clinic is driven by protein spread. In addition, the ability of these antibodies to cross the blood–brain barrier and influence α-synuclein homeostasis in the brain is potentially an obstacle for their use in the clinic. [25] Furthermore, neuroprotective effects of such immunotherapies appear in part to be due to intracellular effects, and their ability to enter cells may influence their efficacy. Engineered fragments (intrabodies and nanobodies) may allow for greater central nervous system penetration and entry to the cell, but these are yet to enter clinical trials . Another concern is the potential consequences of suppressing the physiological function of α-synuclein, an abundant protein whose function is incompletely understood. Suppression of α-synuclein levels in some models has been shown to be detrimental , and evaluation of the long-term safety of this approach will be important. It is for this reason that some groups have sought to reduce α-synuclein through drug therapies, including the repurposing of β-agonists (see below). One class that is under consideration, but yet to enter clinical trials, is the β-adrenergic receptor agonists, given recent epidemiological and *in vitro* work demonstrating an association with reduced α-synuclein levels and risk of PD, thought to be mediated through modulation of *SNCA* transcription . Given that such agents are widely used in the treatment of reversible airway obstruction, and have been for many years, moving this to the clinic should be relatively straightforward. [21] Of those that have gone to clinical trials, the glucagon-like peptide-1 (GLP-1) analogue exenatide, which is used for the treatment of type two diabetes mellitus, has advanced the most. This agent has been trialled in PD patients after a similar compound (exendin-4) was found to convey neuroprotective effects in cell and animal models of nigral degeneration . Several mechanisms have been proposed to mediate this effect through GLP-1

receptor activation, including inhibition of apoptosis, reduced microglial activation and neuroinflammation, reduced oxidative stress, and promotion of neurogenesis . In an initial open-label trial, exenatide was found to be safe in PD patients (though some experienced problems with weight loss), and there was an associated improvement in cognitive and motor function, which persisted after cessation of treatment This was followed by a double-blind randomised placebo-controlled trial, which reported that once-weekly exenatide was associated with a reduction in Unified Parkinson's Disease Rating Scale (UPDRS) motor scores in comparison to the placebo group . [23] A multicentre phase III trial is currently in set-up, in which participants will receive weekly exenatide or placebo. A pegylated form of exenatide (NLY01), which harbours enhanced pharmacokinetic properties, has also recently been taken to a phase I trial in healthy volunteers, with results awaited. Another repurposed drug that has been trialled for PD is nilotinib. This is an ABL tyrosine kinase inhibitor used in the treatment of chronic myelogenous leukaemia. ABL activity inhibits the activity of Parkin, which is important in the initiation of mitophagy, and nilotinib is proposed to enhance autophagy activity, potentially reducing the accumulation of α-synuclein aggregates . An initial phase I trial reported that the drug was well tolerated and safe, with preliminary reports of benefits on motor and cognitive function . However, there was no placebo group in this study, and some of the clinical effects observed may have been due to baseline differences between the groups and withdrawal of monoamine oxidase inhibitors in a number of subjects . Nevertheless, nilotinib has now progressed to randomised placebo-controlled trials and , and it appears to reduce the ratio of pathogenic oligomeric α-synuclein to total α-synuclein in the cerebrospinal fluid (CSF) . However, a recent press release for the NILO-PD trial showed that, while safe and tolerable, nilotinib did not offer any clinical benefit.Terazosin, an α_1-adrenergic antagonist used in benign prostatic hypertrophy, has recently emerged as a putative treatment for PD. Terazosin has been found to activate phosphoglycerate kinase-1 and the chaperone protein HSP90, which is involved in multiple intracellular stress responses [15]. It has been shown to have neuroprotective effects in neurotoxin models of nigrostriatal degeneration in invertebrates and rodents, including after delayed administration. Additionally, terazosin reduced α-synuclein levels in transgenic mice and in neurons derived from patients with *LRRK2* mutation-associated PD . Furthermore, a retrospective epidemiological study found that people taking terazosin have a reduced relative risk of PD . However, terazosin reduces blood pressure and can cause orthostatic hypotension, which is a problem in many patients with advancing PD and may limit its applicability in this disease[28].

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