Neuropharmacology 171 (2020) 108085

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

New hopes for disease modification in Parkinson's Disease

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ARTICLE INFO

Keywords:
Disease modifying
Neuroprotection
Parkinson's disease
Risk screening
Prevention

ABSTRACT

To date, despite numerous clinical trials, no intervention has been demonstrated to modify the progression of Parkinson's disease (PD). However, over the past decades encouraging progress has been made towards a better understanding of molecular pathways relevant for the neurodegenerative process in PD. This is also based on new insights into the genetic architecture of the disease, revealing multiple novel targets for potentially disease-modifying interventions. Important achievements have also been made in the field of risk markers and combinations thereof, in the form of risk algorithms, will hopefully soon provide the possibility to identify affected individuals at yet pre-diagnostic or prodromal stages of the illness. Such phases of the disease would provide an ideal window for neuroprotection trials. Taken together, these developments offer hope that a breakthrough towards modifying the course of PD might be reached. In this article we summarize various approaches currently pursued in this quest.

This article is part of the special issue entitled 'The Quest for Disease-Modifying Therapies for Neurodegenerative Disorders'.

1. Introduction

Parkinson's Disease (PD) is the second most common neurodegenerative disorder affecting about 6 million people worldwide with an estimated rise to twice that number over the next generation (GBD, 2016 Parkinson's Disease Collaborators, 2018). Its pathological hallmarks include cell loss in the pars compacta of the substantia nigra (SNc) with the formation of Lewy bodies and Lewy neurites consisting of neuronal and axonal aggregates of misfolded α-synuclein, resulting in dopaminergic denervation of the corpus striatum (caudate nucleus and putamen) (Dickson et al., 2009). Striatal dopamine depletion underlies the cardinal PD motor features of bradykinesia, rigidity and a characteristic 5 Hz resting tremor. Neurodegeneration and α-synuclein pathology, however, involve multiple additional areas of the brainstem and cortex as well as the peripheral autonomic nervous system giving rise to a plethora of non-motor symptoms including cognitive dysfunction, apathy and depression, orthostatic hypotension, constipation, urogenital dysfunction, smell loss, sleep-wake disorders and pain (Schapira et al., 2017).

Pharmacological dopamine substitution with L-Dopa, dopamine agonists and enzyme blockers of MAO-B and COMT is remarkably effective in controlling the motor symptoms of PD and deep brain stimulation (DBS) can reverse long-term complications of L-Dopa treatment like dyskinesias and motor response oscillations (Espay and Lang, 2017; Poewe et al., 2017). In addition, multiple symptomatic therapies are able to alleviate many of the non-motor problems of PD (Seppi et al., 2019). Physical and exercise-based therapies complement the therapeutic armentarium, which overall offers prevention of serious disability and maintained quality of life for most patients over many years.

Despite of all refinements of symptomatic PD therapy over the past decades, however, none of the available treatments has yet been shown to slow or prevent disease progression. In the long term a majority of PD patients will eventually experience marked impairment of motor and non-motor function and reach key disability milestones like postural instability with recurrent falls, severe dysarthria and dysphagia, symptomatic orthostatic hypotension and urinary retention or incontinence as well as cognitive decline with dementia and hallucinosis (Coelho and Ferreira, 2012; Poewe et al., 2017; Poewe and Mahlknecht, 2009). Treatment options for all of these late stage complications are very limited and agents that could prevent their occurrence through slowing of disease progression are a major unmet need in the management of PD.

Recently, significant progress has occurred in two areas that are equally relevant for current research towards developing disease-modifying therapies for PD: first, a large number of markers for PD risk as well very early stages of the disease has been identified and incorporated into diagnostic algorithms for prodromal PD. These have been tested in a variety of datasets, including population-based samples, with promising results. In addition, new insights into the genetic architecture of PD have led to a refined understanding of the molecular pathways involved in the cellular pathogenesis revealing multiple novel

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https://doi.org/10.1016/j.neuropharm.2020.108085
Received 29 January 2020; Accepted 31 March 2020
Available online 13 April 2020

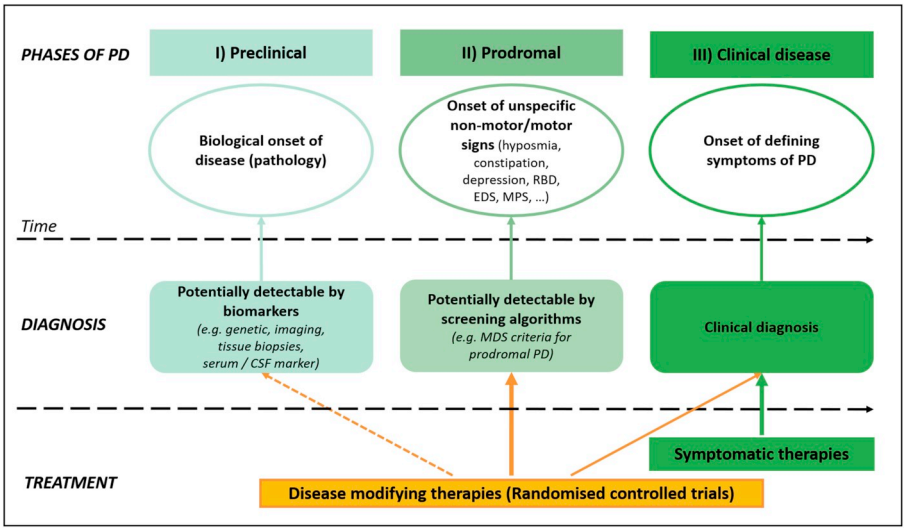

Fig. 1. Conceptual phases of Parkinson's disease. Abbreviations: CSF = cerebrospinal fluid; EDS = excessive daytime somnolence; MDS = movement disorders society; MPS = mild parkinsonian signs; PD = Parkinson's disease; RBD = REM-sleep behavior disorder.

targets for potentially disease-modifying interventions. Taken together, these developments offer new hope that a breakthrough in the quest for disease modification in PD might be reached in the new decade.

2. Early diagnosis and prodromal PD

The diagnosis of PD continues to be based on the presence of cardinal motor features (Postuma et al., 2015), which only appear as soon as the pathological process has significantly advanced to a neuronal loss in the SN of 40–60% and to a striatal dopamine depletion of 60–70% (Fearnley and Lees, 1991; Greffard et al., 2006). Lewy body pathology will have reached and damaged other peripheral and central nervous structures (Braak et al., 2002; Del Tredici and Braak, 2012), leading to a variable picture of prodromal signs (Boeve, 2013) that may appear many years before defining motor symptoms (Fig. 1). In fact, multiple population-based or other cohort studies have shown that hyposmia, constipation, depression, and idiopathic REM Sleep Behavior Disorder (RBD) significantly increase risk for incident PD in otherwise healthy individuals (Abbott et al., 2001; Ishihara and Brayne, 2006; Mahlknecht et al., 2020; Postuma et al., 2019; Ross et al., 2008). The same is true for subtle motor disturbances, insufficient for a formal diagnosis of parkinsonism, that precede the full motor syndrome of PD and have also been associated with substantially increased PD risk in elderly populations (Darweesh et al., 2017; Mahlknecht et al., 2020; Postuma et al., 2012).

Biomarkers for PD risk or the earliest stages of disease are an intensely researched area. There is now evidence from imaging studies that certain markers are capable of indicating increased PD risk in the population as well as in risk-cohorts (e.g. hyposmic individuals, patients with iRBD, and asymptomatic gene mutation carriers). Midbrain hyperechogenicity in the area of the SN on transcranial sonography is a very strong risk marker with relative risks of 17–21 over 3–5 years in the general elderly population (Berg et al., 2013, 2011). Similarly, reduced striatal dopaminergic uptake on SPECT scans has recently been associated with a 17.5-fold increased risk for PD among hyposmic individuals (Jennings et al., 2017). In addition to these established imaging markers, various features on advanced magnetic resonance imaging (MRI) such as loss of dorsolateral nigral hyperintensity in the region of nigrosome 1 (swallow-tail sign) on iron-sensitive sequences hold potential as biomarkers for prodromal PD (Mahlknecht et al., 2017; Heim et al., 2017).

Genetic signatures of PD and PD risk have been derived from genome-wide association studies (GWAS). Although the effects of single genetic susceptibility factors seem to be small with odds ratios for each locus ranging from 0.7 to 1.8, combined risk profile analysis can show substantial cumulative risk in a comparison of the highest and lowest quintiles of genetic risk with odds ratio of around 3 to 4, explaining 16–36% of the heritable risk of PD (Nalls et al., 2011, 2014, 2019). With recent advances genetic profiling and derived genetic risk scores have become more easily accessible and may additionally be combined with clinical and imaging biomarkers to accurately predict PD risk (Heinzel et al., 2019; Nalls et al., 2015). Mutations in glucocerebrosidase (GBA) gene stand out as variants indicating highly increased risk of about 5-fold (Sidransky et al., 2009) with high penetrance (Anheim et al., 2012). Discovery of these and other mutations have not only lead to a better understanding and definition of the presymptomatic and prodromal phases of PD, but also revealed novel targets for potentially disease-modifying interventions (see section 3.5 and Toffoli et al., 2020 for review).

Although associated with substantial risk for PD none of the markers currently identified can by itself predict onset of disease (Mahlknecht et al., 2015). Screening algorithms that can reliably detect prodromal cases have therefore become an important research goal. To this end, in 2015 a task force of the International Parkinson's disease and Movement Disorder Society (MDS) has proposed research diagnostic criteria for prodromal PD (Berg et al., 2015). In this data-driven, probabilistic approach, the effect size of a large number of risk and prodromal markers was derived from at least two prospective cohort studies or meta-analysis per marker. Post-test probability for prodromal PD is calculated including age-specific disease prevalence as pretest probability based on the assumption of a 10-year prodromal period as well as positive or negative likelihood ratios (LR + or LR-) of different risk and prodromal markers using a Bayesian naïve classifier methodology. Probable prodromal PD was operationally defined by a post-test probability of ≥80% (Berg et al., 2015). In 2019 a first update of the MDS research criteria was presented, integrating new evidence for risk and prodromal markers published since 2015 (Heinzel et al., 2019). This included an adaptation of likelihood ratios as well as integration of new markers. While prospective evaluations of the criteria (and their update) are awaited, evidence from retrospective applications of the criteria to existing longitudinal population-based cohorts seem promising (Mahlknecht et al., 2018; Pilotto et al., 2017). Interestingly, a high predictive accuracy of the MDS criteria for conversion into PD or dementia with Lewy bodies over 4 years has also been detected in a recent cohort study in 121 patients with idiopathic RBD (PPV 81%) (Fereshtehnejad et al., 2017) and a cohort of LRRK2 mutation carriers

(PPV 47–67%) (Mirelman et al., 2018).

Other global approaches to estimate PD risk using a set of various risk markers have been published since. The PREDICT PD approach combines simple risk markers derived from a comprehensive meta-analysis of early non-motor features and risk factors that can be assessed remotely (Noyce et al., 2017). It was initially implemented in an online-based cohort study, showing an association with established PD risk markers as disease-state surrogates in a cross-sectional analysis and, more importantly, with incident PD during follow-up over 3 years with a hazard ratio of 4.4 (Noyce et al., 2017). A validation attempt in the population-based Rotterdam study showed a weaker association of the risk score with incident PD with a hazard ratio of 1.3 that did not significantly improve classification and discrimination beyond age and sex (Darweesh et al., 2016). Another simple "reduced" risk score was recently developed and applied to two large American cohorts in 69,968 women of the Nurses' Health Study (NHS) and 45,830 men in the Health Professionals Follow-up Study (HPFS) (Kim et al., 2018). The (protective) factors included were total caffeine intake, smoking, physical activity, and negative family history of PD for the NHS, and additionally total flavonoid intake and dietary urate index for the HPFS. Individuals in the highest quintile compared with the lowest quintile of reduced risk scores had significantly lower hazard ratios for incident PD of 0.33 in the NHS and 0.18 in the HPFS (Kim et al., 2018).

While the MDS prodromal PD criteria are designed to diagnose "probable prodromal PD" for research purposes, these two scores may be more useful as a simple first screening steps that could partially also be used online, filtering subjects suitable for further in person evaluations. Subjects with an elevated risk may then consecutively be invited for further assessment steps of increasing specificity, aiming to identify those who will finally go on to develop disease. These may include genetic testing, polysomnography, transcranial sonography, and/or DaT-Scan, which are more costly and time-consuming, and may therefore only be used in more defined group of subjects.

As research in this field advances, new markers may be included in the MDS criteria or other risk estimation instruments. This emphasizes a major strength of a combined risk score, as new evidence can be integrated easily and may improve diagnostic accuracy. It is hoped that with prospective validation and further refinement of these algorithms identifying individuals with increased PD risk and prodromal disease can reliably be achieved and inclusion of such individuals into disease modification trials will soon be possible (Fig. 1).

3. Novel targets for disease modification

In the past 30 years a large number of controlled trials of putative neuroprotective or disease modifying agents have been conducted in PD - sparked off by the famous DATATOP trial in 1989, which failed to show slowing of disease progression by the MAO-B inhibitor selegiline (deprenyl) due to confounding symptomatic effects of this agent (Parkinson Study Group, 1993). Multiple therapeutic targets with good evidence for their potential validity in PD pathogenesis from in vitro and in vivo experiments were subsequently explored but none of these trials succeeded to show disease-modifying efficacy in patients (Foltynie and Langston, 2018; Lang and Espay, 2018). Recent advances in genetics of PD have greatly enhanced understanding of molecular pathways involved in the cellular pathogenesis of PD and have revealed multiple novel targets for disease modifying approaches. At the same time, epidemiological research and insights gained from experimental disease models have added further candidate approaches (see Fig. 2). A non-exhaustive list of targets, drugs and their stage in development is presented in the table.

3.1. Calcium homeostasis

A number of epidemiological studies has shown a reduced risk for PD users of L-type calcium channel blockers to treat hypertension (Becker et al., 2008; Pasternak et al., 2012). Consistent with such observations it has been shown that dopaminergic neurons of the SNc as well as other neuronal populations affected by PD pathology like the locus coeruleus, raphe nuclei or the dorsal vagal motor nucleus have spontaneous pacemaking properties dependent on L-type Cav1.3 Calcium channels, which promote entry of calcium into the cell (Chan et al., 2007). Enhanced calcium entry into SNc neurons has been associated with increased oxidative stress, mitochondrial damage and cell death. Blockade of L-type channels by the dihydropyridine channel blocker isradipine was shown to be neuroprotective in animal models of parkinsonism (Ilijic et al., 2011; Sulzer and Surmeier, 2013).

Isradipine, marketed to treat hypertension in the US, has the highest affinity for Cav1.3/Cav 1.2 channels of all available agents and has good CNS penetration. Its safety and tolerability was tested in a dose finding phase 2 trial in subjects with early PD with satisfactory tolerability of doses up to 10 mg/d (Parkinson Study Group, 2013). In order to assess efficacy of isradipine as a disease-modifying agent in PD a placebo-controlled phase 3 trial was recently completed and published in abstract form. It had randomized 336 patients with early untreated PD to receive either two daily doses of 5 mg of isradipine or matching placebo and the primary outcome was the change versus baseline of the MDS-UPDRS total score after 36 months. Unfortunately, there was no difference between treatment arms of this or any of the secondary outcomes as published in abstract form (Simuni and Parkinson Study Group, 2019). Lack of selectivity of isradipine for Cav1.3 channels as well as dosing issues may have contributed to the negative results, which therefore do not ultimately refute a potential role of dysregulated calcium homeostasis in the cellular pathology of PD.

3.2. Targeting iron overload

Iron overload in the Substantia Nigra (SN) has been noted as a consistent feature in post-mortem studies of PD brains since the 1980's (Dexter et al., 1987). In vivo demonstration of increased nigral iron content in PD became possible through advanced MRI techniques such as R2* relaxometry, susceptibility weighted imaging or more recently quantitative susceptibility mapping (QSM) (Guan et al., 2017; Langkammer et al., 2016) and loss of dorsolateral nigral hyperintensity on iron-sensitive MRI has recentyl been proposed as a simple marker for neurodenerative forms of parkinsonism including PD (Mahlknecht et al., 2017). Iron overload can potentially contribute to nigral cell loss through several mechanisms including increased mitochondrial oxidative stress, a role of iron in programmed cell death (ferroptosis) and effects on the accumulation and aggregation of α-synuclein (Masaldan et al., 2019). Two small placebo controlled trials in PD subjects have provided some evidence for beneficial effects of iron chelation with deferiprone on disease progression. One used a delayed start design in patients in early disease stages and found that motor function as assessed by the Unified PD Rating Scale (UPDRS) at 12 months was superior in subjects of the early start group as compared to patients started with a delay of 6 months (Devos et al., 2014). A smaller parallel-group double-blind placebo-controlled trial of deferiprone in 22 patients with early PD under stable symptomatic therapy showed only a trend for improvement of UPDRS motor scores in the active treated group after 6 months, but reductions in iron content of the dentate and caudate nucleus on T2* MR imaging (Martin-Bastida et al., 2017). A much larger placebo-controlled trial of iron chelation with deferiprone (FAIRPARK-II; NCT02655315) has recently completed recruitment of 270 patients with early untreated PD and will assess effects on disease progression using the MDS-UPDRS change over 12 months as the primary outcome, but will also evaluate imaging measures of brain iron (Devos et al., 2020).

3.3. Insulin signaling

There is a robust body of evidence from experimental studies that

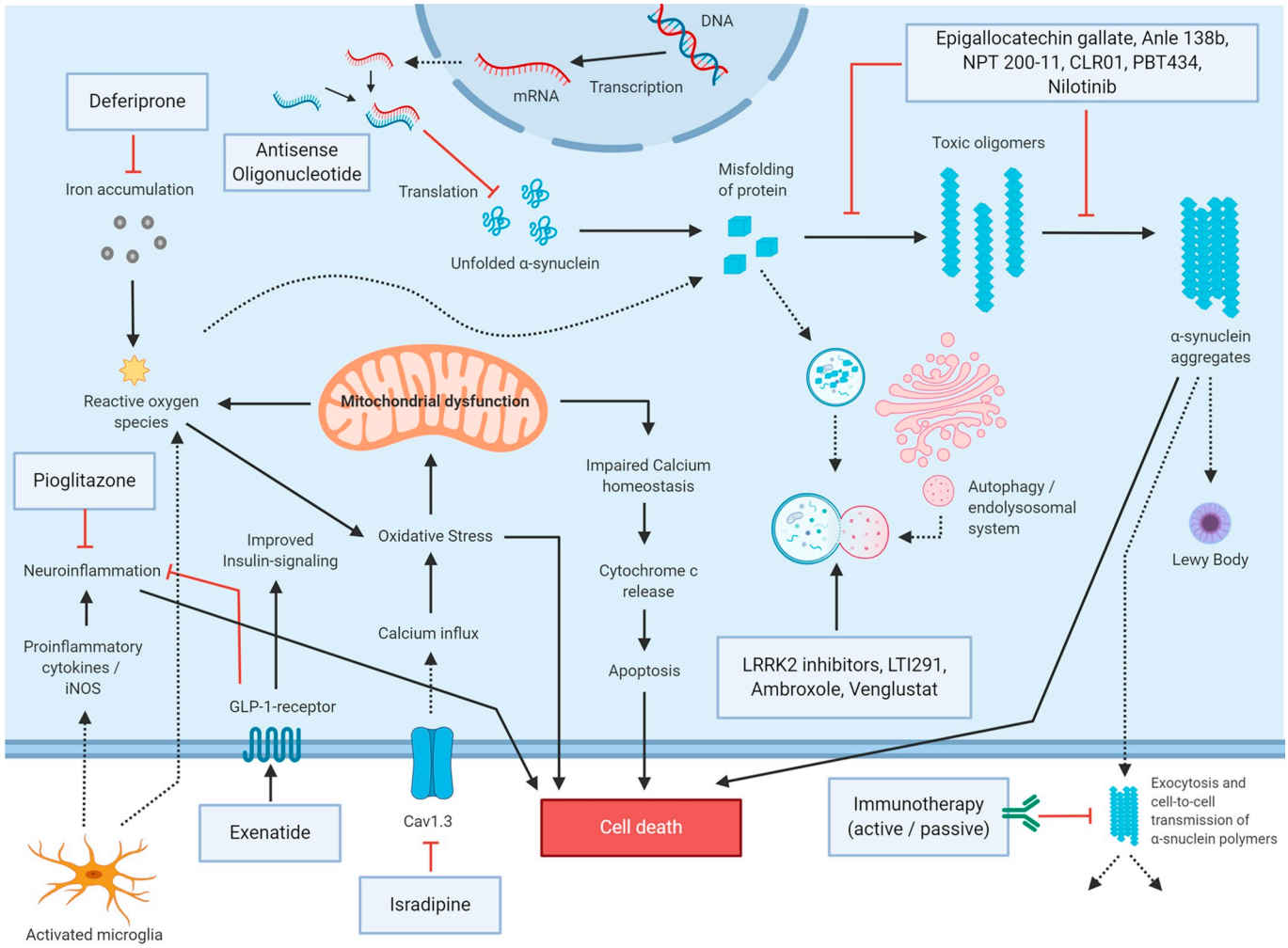

Fig. 2. Mechanisms shown to be involved in the pathophysiological cascade of PD and potential treatment targets. See text for details. Abbreviations: $Ca_v1.3$ = Calcium channel, voltage-dependent; DNA = Deoxyribonucleic acid; GLP-1 = Glucagon-like peptide-1; iNOS = Nitric oxide synthases; LRRK2 = Leucine-rich repeat kinase 2; mRNA = Messenger ribonucleic acid.

peripheral insulin resistance promotes PD specific brain pathology and dopaminergic degeneration and epidemiological research strongly suggest and increased PD risk in individuals with type 2 diabetes (Athauda and Foltynie, 2016). In fact, the recent update of the MDS prodromal PD criteria has included Type 2 Diabetes into the algorithm with a likelihood ratio of 1.5 (Heinzel et al., 2019). These findings have opened up the insulin-signaling pathway as a novel target for disease modification. One major advantage of this new avenue is that already licensed drugs for the treatment of type 2 diabetes with known safety profiles can be tested in PD neuroprotection trials without undergoing first drug development steps. Among the most promising class of substances are glucagon-like peptide-1 (GLP-1) agonists as described in detail in a related article in this issue of the journal (Mejido et al., 2020). They activate GLP-1 receptors to promote glucose-level-dependent insulin secretion, inhibit glucagon secretion, and slow gastric emptying. Their neuroprotective properties have been demonstrated in many PD animal models and may relate to an improved brain insulin signaling and might also act through a positive effect on neuroinflammation (Athauda and Foltynie, 2016). Exenatide, a GLP-1 agonists, has recently been tested in a double blind, phase II, RCT (Athauda et al., 2017). Sixty patients with moderate PD were randomly assigned (1:1) to receive 2 mg exenatide or placebo subcutaneously once weekly over 48 weeks followed by a 12-week washout period. At the end of the study patients in the treatment group had lower off medication MDS-UPDRS III scores compared with the placebo group (−3·5 points), suggesting a possible disease modifying effect of treatment. However, none of the secondary endpoints were positive. Further phase II/III trials with exenatide and other similar substances are underway (clinicaltrials.gov; NCT04154072, NCT02953665, NCT03439943, NCT03659682) and will determine whether antidiabetic drugs may be capable of modifying the natural history of PD.

3.4. Synuclein proteostasis

A solid body of evidence supports a central role of pathological species of the synaptic protein α-synuclein in PD pathogenesis. The starting point was the discovery of a missense mutation in the α-synuclein gene as the cause of dominantly inherited PD in a large kindred in Southern Italy (Polymeropoulos et al., 1997) followed by the demonstration of α-synuclein as a major component of Lewy bodies and Lewy neurites in sporadic PD (Spillantini et al., 1997). Since then it has been shown that an increase in the α-synuclein wild-type gene dose through duplication or triplication is sufficient to cause PD and that sequence variations in regulatory region of this gene are associated with PD risk (for review see Domingo and Klein, 2018). Misfolding of α-synuclein with the formation of polymers and defective clearance through the endolysosomal system have been shown to result in Lewy body type aggregates (Dehay et al., 2015; Xilouri et al., 2016). The

Table 1
Candidate drugs for disease-modification in PD (non-exhaustive list).

Target	Drug	Mechanism	Stage of development	Outcome [REF]/registration number
Calcium homeostasis	Isradipine	L-type calcium channel blocker	Phase III	Negative (Simuni and Parkinson Study Group, 2019)
Reducing iron overload	Deferiprone	Iron chelation	Phase II	Ongoing (FAIRPARK-II); NCT02655315)
Insulin signaling	Exenatide	GLP-1 agonist	Phase II	Primary endpoint positive, secondary endpoints negative (Athauda et al., 2017)
	NLY01	GLP-1 agonist	Phase II	Ongoing; NCT04154072
	Liraglutid	GLP-1 agonist	Phase II	Ongoing; NCT02953665
	Lixisenatide	GLP-1 agonist	Phase II	Ongoing; NCT03439943
	Semaglutide	GLP-1 agonist	Phase II	Ongoing; NCT03659682
α-Synuclein proteostasis	Antisense oligonucleotides (ASO) Small interfering RNAs (siRNAs)	Reducing α-synuclein production	Preclinical	Nakamori et al., (2019)
	anle138b	Inhibition of α-synuclein aggregation	Phase I	Ongoing; NCT04208152
	NPT200-11	Inhibition of α-synuclein aggregation	Phase I	Ongoing; NCT02606682
	PBT434	Iron chelation; Inhibition of α-synuclein aggregation	Phase I	Ongoing; ACTRN12618000541202
	nilotinib	Inhibition of α-synuclein aggregation	Phase II	Safety established, alterations in exploratory biomarkers demonstrated (Pagan et al., 2019)
	PRX002/RG7935 (Prasinezumab)	Anti-α-synuclein antibody	Phase 2	Ongoing; NCT03100149
	BIIB054 (Cinpanemab)	Anti-α-synuclein antibody	Phase II	Ongoing; NCT03318523
	Lu AF82422	Anti-α-synuclein antibody	Phase I	Ongoing; NCT03611569
	MEDI1341	Anti-α-synuclein antibody	Phase I	Ongoing; NCT03272165
	ABBV-0805	Anti-α-synuclein antibody	Phase I	Ongoing; NCT04127695
	PD01A	Active α-synuclein immunization	Phase I Phase II planned	Ongoing; NCT02618941, NCT02216188
Endolysosomal function	DNL 201	LRRK2 inhibitor	Phase Ib	Favorable safety, biomarker evidence for target engagement in PD subjects; NCT03710707
	DNL 151	LRRK2 inhibitor	Phase I	Favorable safety, biomarker evidence for target engagement in HV; NCT04056689
Genotype specific therapies	ambroxole	Modulator of GCase activity	Phase I (published)Phase II	CSF penetration and biochemical effects demonstrated (Mullin et al., 2020) Ongoing; NCT02914366
	LTI-291	Modulator of GCase activity	Phase II	Ongoing; EudraCT2017-004086-27
	Venglustat	glucosylceramide synthase inhibitor	Phase II	Ongoing; NCT02906020
Neuroinflammation	Pioglitazone	Antidiabetic drug; PPAR γ agonist	Phase II	Negative (NINDS Exploratory Trials in Parkinson Disease (NET-PD) FS-ZONE Investigators, 2015)
	Inzomelid	NLRP3 inflammasome inhibitor	Phase I	NCT04015076

Abbreviations: GCase = β-Glucocerebrosidase; HV = healthy volunteers; LRRK2 = Leucine-rich repeat kinase 2; PD = Parkinson's disease; PPAR γ = peroxisome proliferator-activated receptor.

detection of Lewy bodies in grafted embryonic neurons in the brains of PD patients that had received these transplants many years before death (Kordower et al., 2008; Li et al., 2008) first raised the possibility of cell-to-cell transmission of oligomeric species of α-synuclein and subsequent research has fostered the concept of prion-like propagation of misfolded α-synuclein as a key mechanism driving disease progression in PD (Brundin and Melki, 2017; Luk et al., 2012). Taken together, these discoveries have paved the way for multiple novel therapeutic approaches targeting different aspects of α-synuclein proteostasis (see Fig. 2).

3.4.1. Reducing α-synuclein production

Considering that increased production of α-synuclein is sufficient to initiate disease in familial PD caused by duplication or triplication of the α-synuclein gene it seems plausible to use gene interference approaches with small interfering RNAs (siRNAs) or antisense oligonucleotides (ASO's) to reduce synthesis of the protein. These approaches have recently led to encouraging results in Huntington's disease, where a phase 2 trial showed dose dependent lowering of mutant Huntingtin protein in the CSF as well as some signals for clinical efficacy and a large phase 3 trial is currently ongoing (Tabrizi et al., 2019). For PD α-synuclein lowering is still in pre-clinical stages of development (Nakamori et al., 2019), but the first anti-synuclein ASO phase 1 trial in multiple system atrophy (MSA) is expected to start in the first half of 2020 (NCT04165486).

3.4.2. Small molecule chaperons and inhibitors of α-synuclein aggregation

Based on the concept that misfolding and oligomer formation is a critical step in the initiation of α-synuclein pathology in PD small molecules that can target specific regions of the α-synuclein molecule and interfere with its propensity to become phosphorylated and misfold and polymerize are actively explores as disease-modifying agents. The polyphenole *epigallocatechin gallate* has been shown to reduce the formation of α-synuclein oligomers and neurotoxicity in cell culture and animal models and was recently tested for disease-modification in a phase 2 randomised placebo-controlled trial in patients with MSA (Levin et al., 2019). This trial failed to detect significant differences from placebo in changes of the Unified MSA Rating Scale (UMSARS) after one year and high doses above 1200 mg were associated with hepatotoxicity. *Anle138b* is another small molecule which has been shown to inhibit the formation of α-synuclein aggregation in in vitro and in vivo models (Wagner et al., 2013) and studies in transgenic MSA and PD mouse models have provided some evidence for beneficial behavioral effects (Heras-Garvin et al., 2019; Wegrzynowicz et al., 2019). The drug has entered clinical development with a currently running Phase I trial (NCT04208152).

Other small molecule inhibitors of α-synuclein polymerization in pre-clinical development include *NPT 200-11*, which interacts with regions in the protein that are critical for misfolding and oligomer formation (Price et al., 2018) and the molecular tweezer *CLR01*, which was shown to inhibit the assembly of α-synuclein into β-sheet rich fibrils and caused disintegration of pre-formed fibrils in vitro (Prabhudesai et al., 2012) and in an mouse model of MSA (Herrera-Vaquero et al., 2019).

PBT434 is a conservative iron chelator and novel small molecule inhibitor of iron-mediated protein aggregation. It has been shown to reduce α-synuclein assemblies, probably involving the iron response element in α-synuclein mRNA, and to prevent α-synuclein accumulation and neuronal loss in a transgenic model of MSA (Finkelstein et al., 2019).

The kinase inhibitor *nilotinib*, an approved drug for the treatment of chronic myeloic leukemia, has been shown to reduce phosphorylation and promote degradation of misfolded α-synuclein through inhibition of c-Abl and to protect against cell death in PD models (Pagan et al., 2016). An phase II RCT has established safety and demonstrated alterations in exploratory biomarkers in PD patients (Pagan et al., 2019).

3.4.3. Immunotherapy

Prion-like propagation with cell-to-cell transmission of misfolded polymeric α-synuclein species is believed to play a critical role in the progression of pathology in PD (see Brundin and Melki, 2017 for review). Immunotherapeutic approaches targeting α-synuclein follow the rationale of reducing the build up and cell-to-cell propagation of pathogenic oligomeric assemblies. Experimental studies have shown that monoclonal α-synuclein specific antibodies can promote the degradation of α-synuclein aggregates and protect dopaminergic neurons (Benner et al., 2004; Masliah et al., 2005), prevent cell-to-cell transmission (Bae et al., 2012; Games et al., 2014) and reduce behavioural deficits in animal models (Masliah et al., 2011). Several humanised or fully human monoclonal α-synuclein specific antibodies are in different stages of clinical development (see Table 1).

Two of these (Prasenezumab and Cinpanemab) have by now shown good safety and tolerability as well as evidence for target engagement with lowering of α-synuclein plasma levels and CSF penetration in multiple ascending dose studies in PD patients (Brys et al., 2019; Jankovic et al., 2018). Both are currently tested in two large phase 2 disease-modification trials involving around 300 early PD patients each (NCT03100149, NCT03318523). Both have similar designs with 52 weeks of 4-weekly double blind i.v. infusions with different antibody doses or placebo followed by a second year of dose-blinded treatment with active drug in all subjects. The Prasenezumab trial is expected to provide results of the 52-week analysis in 2020.

Whereas these 'passive' approaches involve monthly, hospital-based, intravenous infusions of monoclonal antibodies, active immunotherapy uses immunization to induce highly specific, self-produced antibody responses that are long-lasting and can be maintained via booster injections over extended intervals.

PD01A is a novel therapeutic vaccine developed using the AFFITOPE® technology. AFFITOPEs are short peptides, which mimic an epitope of the target protein – in the case of PD01A an epitope in the native c-terminal region of human α-synuclein. This peptide is coupled to a carrier protein and absorbed to aluminium hydroxide as an immune-adjuvant. PD01A was designed to induce antibodies with selectivity for aggregated α-synuclein, which could be shown to decrease in the brains of PD mouse models following immunization along with behavioral improvements (Mandler et al., 2014). A small open-label study in 24 PD patients followed for 52 weeks after 4 priming vaccinations and then for a further 76 weeks after two booster injections suggested satisfactory safety and tolerability and a dose-dependent boostable immune response to the immunizing peptide and cross-reactivity of induced antibodies with the α-synuclein target epitope (Volc et al., 2020). A phase 2 efficacy trial of PD01A in early PD has recently been announced (AFFIRIS press release: https://affiris.com/investors/; last accessed 01/29/2020).

3.5. Endolysosomal function and genotype-specific therapies

Dysfunctional clearance of misfolded and oligomeric species is believed to play an important role in the intracellular accumulation and aggregation of α-synuclein assemblies (Bellomo et al., 2020; Jackson and Hewitt, 2016). Consistent with this genetic mutations impacting the autophagic-lysosomal pathway have been identified either as causes of or risk factors for PD (Chang et al., 2017). The most important example of the former are LRRK2 mutations causing autosomal dominant PD through a mechanism involving increased kinase activity, which may impair autophagy and lysosomal function and thus contribute to the build up of pathological α-synuclein species (Orenstein et al., 2013). Inhibitors of *LRRK2* are therefore pursued as potential disease modifying therapies in PD and Denali Therapeutics has started clinical trials of LRRK2 kinase inhibitors. DNL 201 and DNL 151 are CNS penetrant small molecules currently in early clinical development (NCT03710707, NCT04056689). A phase 1b trial of DNL201 in PD subjects and a phase 1 study of DNL151 in healthy volunteers recently

reported favorable safety data and biomarker evidence for target engagement (Denali press release: https://denalitherapeutics.com/investors/press-releases; last accessed 01/29/2020). Whether this will remain a genotype-specific therapeutic approach benefiting only those carrying the mutation or whether kinase inhibitors might modify progression in all PD subjects by reducing phosphorylation and thus propensity for aggregation of α-synuclein remains to be tested (Tolosa et al., 2020).

Mutations in *GBA*, the gene encoding glucocerebrosidase (Gcase) are the single most important genetic risk factor for PD and are present in 5–15% of patients of Caucasian descent and around 25% of Ashkenazi Jewish patients (Sidransky et al., 2009; Zhang et al., 2018). Gcase is a lysosomal enzyme degrading glucosylceramide and its deficiency in homozygote mutation carriers causes Gaucher disease characterized by multiorgan lysosomal accumulation of glucocerebrosides. Heterozygotes do not develop disease but have a 5–6 fold increased risk to develop PD (Sidransky et al., 2009) and intriguingly significant reductions of brain GCase activity have been observed in both GBA-mutation positive and negative and PD subjects (Gegg et al., 2012). Experimentally, inhibition of GCase leads to α-syn accumulation (Yang et al., 2017), while increasing Gcase activity reduces α-syn accumulation (Migdalska-Richards et al., 2016; Sardi et al., 2018). Targeting Gcase activity as a disease modifying strategy in PD has advanced along several approaches (see Fig. 3).

Based on findings of reduced Gcase activity in the parkinsonian brain drugs capable of enhancing this activity appear obvious candidates for potential disease modification. *Ambroxole*, which has been in clinical use as a cough medicine for decades, was shown to be able to modulate GCase activity. It acts as a pH-dependent chaperone with inhibitory activity at neutral pH. It binds to the active site of the enzyme, inhibiting activity and facilitating transport into the lysosome where under acidic conditions the enzyme elutes and becomes activated. Indeed, ambroxole increased GCase activity and reduced α-synuclein levels both in cellular and in in vivo models (McNeill et al., 2014; Migdalska -Richards et al., Ann Neurol, 2016). A recent open-label trial investigated safety of high-dose therapy with oral ambroxole in 18 subjects with PD (9 with and 9 without GBA mutations) and tested CSF penetration and biochemical effects (Mullin et al., 2020). Doses of up to 1.26 g per day over 6 months (a level about tenfold of the recommended marketed dose) were found to be safe and well tolerated. Oral administration led to an increase in CSF levels of ambroxole and CSF GCase activity decreased by 19%, while CSF α-synuclein levels and CSF levels of GCase protein increased. These biochemical are consistent with the postulated mechanism of action of ambroxole and thus prove target engagement. A larger placebo-controlled phase II trial of ambroxole in PD is now ongoing (NCT02914366).

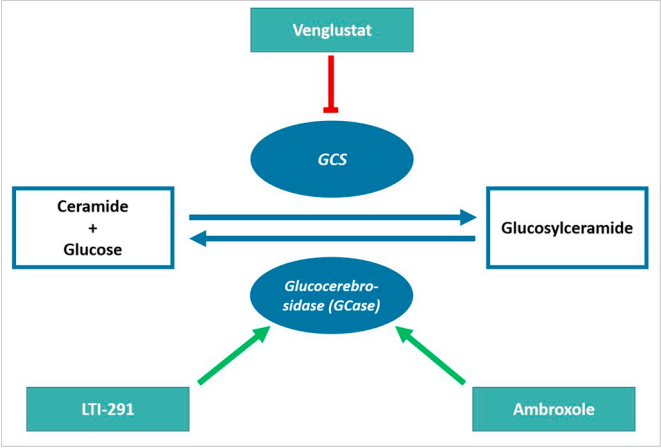

Fig. 3. Targeting GCase activity for disease-modification in PD. Substrate reduction via glucosylceramide synthase (GCS) inhibition or small molecule enhancers of GCase activity.

LTI-291 is another small-molecule with modulatory effects on GCase activity via binding to the active site of the enzyme, which is currently tested in an early phase small trial in PD subjects with GBA patients (EudraCT2017-004086-27).

Inhibiting the build-up of Glucosylceramides through substrate reduction for GCase via inhibition of glucosylceramide synthase (see Fig. 3) is the rationale behind the established use of GCS inhibitors like Miglustat or Eliglustat in Gaucher disease. Venglustat is a CSF-penetrant GCS inhibitor which was shown to reduce α-synuclein aggregation in an overexpressing transgenic mouse model (Sardi et al., 2017). A large phase 2 placebo-controlled trial of venglustat in PD subjects with GBA mutations has recently completed recruitment and will assess effects on the progression of UPDRS motor scores and a variety of secondary outcomes over one year and further 2 years of follow-up (NCT02906020). This trial had a 36 weeks dose-finding first part, the results of which were recently presented in abstract form and showed dose dependent lowering of Glucosylceramide in plasma and CSF (Fischer et al., 2019).

More details on the role of genetic causes of PD in the pathway to disease modification can be found in a related article in this issue of the journal (Toffoli et al., 2020).

3.6. Neuroinflammation

A large body of evidence from post-mortem, imaging and biofluid studies suggests that neuroinflammation plays a prominent role in PD pathogenesis (Moehle and West, 2015; Ransohoff, 2016). Activated microglia are present in the *S. nigra* and other areas of the PD brain and can contribute to neuronal damage and cell death via release of pro-inflammatory cytokines and induction of nitric oxide synthase (iNOS) and reactive oxygen species (Janda et al., 2018; Lee et al., 2019). Several of the currently known risk genes for PD encode proteins expressed in immune cells and α-synuclein aggregation induces immune responses and conversely neuroinflammation can promote α-synuclein misfolding (Gao et al., 2008; Hirsch and Hunot, 2009). Several approaches targeting neuroinflammation have been tested in preclinical PD models including agonists of the peroxisome proliferator-activated receptor γ (PPAR γ) like the antidiabetic drugs pioglitazone or rosiglitazone which exhibited protective effects in PD animal models (Carta and Pisanu, 2013; Lee et al., 2019). A large phase 2 futility trial of pioglitazone in patients with early PD, however, failed to provide evidence for disease-modification, but the authors recommended to re-test the drug in a larger trial (NINDS Exploratory Trials in Parkinson Disease (NET-PD) FS-ZONE Investigators, 2015). Microglial activation is associated with the assembly of the NLRP3 inflammasome, which acts as a key driver of neuroinflammatory responses with activation of caspase-1 and release of interleukin 1-β (Heneka et al., 2018). The NLRP 3 inflammasome has recently been shown to play an important role in the pathogenesis of tauopathies (Ising et al., 2019) and the small molecule NLRP3 inhibitor MCC950 was shown to reduce α-synuclein aggregation loss of dopaminergic neurons in a PD mouse model (Gordon et al., 2018) highlighting the NLRP3 inflammasome as a potential target for disease-modification in PD. Inzomelid is an oral and brain-penetrant NLRP3 inflammasome inhibitor that has entered phase I clinical development as potential disease-modifying treatment for PD (NCT04015076).

4. Conclusions

PD stands out among the neurodegenerative diseases by the availability of multiple highly efficacious symptomatic therapies, which in their different combinations offer a prospect of extended periods of satisfactory symptom control for a majority of patients. However, to date there is no intervention that could slow or prevent the inevitable progression of PD that leads to severe disability from a plethora of

motor and non-motor problems in late stage disease. Current hopes for a breakthrough in the quest for effective disease modification in PD have gained momentum from recent advances in defining at-risk populations as well as the earliest prodromal stages of the disease. For the first time there is now a realistic possibility that population-based screening programs for PD risk and prodromal disease might become feasible. This has increased the urgency to find therapies that could slow progression or ultimately prevent or delay disease onset and could thus be offered to those at risk or in their earliest stage of disease. Driven by an accelerated discovery process of the genetic underpinnings of PD insights into the molecular pathways responsible for the progression of pathology have expanded to an impressive extent. Multiple novel targets for disease modification have emerged from this and several have reached advanced stages of clinical development. James Parkinson's hope, expressed in his monograph of 1817, that *'…. some remedial process may ere long be discovered by which at least the progress of the disease may be stopped'* may finally meet its fulfillment in the coming decade.

Funding

There was no specific funding for the preparation of this article. KM is supported by a research grant from the Tiroler Wissenschaftsförderung (grant number: UNI-0404/2245).

Financial disclosures for the past 12 months

W.P. reports consultancy and lecture fees in relation to clinical drug programs for PD from AbbVie, Allergan, AstraZeneca, BIAL, Boehringer-lngelheim, Boston Scientific, Britannia, Cynapsus, Grünenthal, Intec, Ipsen, Lundbeck, Medtronic, Merz Pharmaceuticals, Novartis, Neuroderm, Orion Pharma, Prexton, Teva, UCB, and Zambon and royalties from Thieme, Wiley Blackwell, Oxford University Press, and Cambridge University Press outside of the submitted work.

K.S. reports personal fees from Teva, UCB, Lundbeck, AOP Orphan Pharmaceuticals AG, Roche, Grünenthal, and Abbvie; honoraria from the International Parkinson and Movement Disorders Society; research grants from the FWF Austrian Science Fund, Michael J. Fox Foundation, and International Parkinson and Movement Disorder Society outside the submitted work.

K.M. and P.M. have nothing to report.

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