Genetic Causes of PD: A Pathway to Disease Modification

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Highlights:

- Parkinson Disease is genetically diverse and a number of different genes have been linked to its pathogenesis.
- No disease modifying therapy for Parkinson disease have been discovered so far, but in recent years many genetically targeted therapies have been proposed.
- The most promising targeted therapies under investigation involve *GBA1*, *LRRK2* and *SNCA.*

Abstract

The underline neuropathology of Parkinson disease is pleiomorphic and its genetic background diverse. Possibly because of this heterogeneity, no effective disease modifying therapy is available. In this paper we give an overview of the genetics of Parkinson disease and explain how this is relevant for the development of new therapies.

Keywords: Parkinson disease, genetics, LRRK2, GBA1, SNCA, disease modifying, therapy

1. Introduction

Parkinson disease (PD) is the second most common neurodegenerative disease and its prevalence has doubled between 1990 and 2016; in 2016 it was estimated there were over 6 million people with PD that year(Ray Dorsey et al., 2018). Despite significant progress in our understanding of the pathogenesis of the disease, much is still unknown and to date no disease modifying therapy exists. In recent years, the search for a 'cure' for PD has focused on targeting the therapeutic approach on the underlying genetics of PD. In this review, we give an overview of how different genes play a role in the development of PD and how this is relevant for developing future treatments.

2. The genetic causes of Parkinson disease

In the 1980s, PD was viewed as a "non-genetic" disease, driven by environmental factors. This concept was supported by the low concordance in twin siblings of PD cases(Eldridge and Ince, 1984; Ward et al., 1983) and by evidence of some toxins and infectious causes of parkinsonism. In 1997, a mutation was identified in the alpha-synuclein gene (*SNCA*) as the first cause of familial PD (Polymeropoulos et al., 1997). Subsequently, mutations in several different genes were described as causes of familial cases of PD including *LRRK2* the most common cause of familial PD described to date(Paisán-Ruíz et al., 2004; Zimprich et al., 2004). Finally, candidate gene and genome wide association studies have identified more genes linked to sporadic forms of PD, e.g. *GBA1*(Sidransky et al., 2009).

PD can be classified as familial or sporadic, according to the presence or absence of a clear family history, approximately 5-10% of PD is considered familial. About 3-5% of familial PD cases show clear Mendelian inheritance and have a known monogenic cause (Kumar et al., 2011).

Genes involved in familial monogenic forms of PD have previously been assigned a PARK number, in order of discovery. It is important to remember that the list of PARK genes includes some genes for which evidence is not convincing and is not comprehensive, like in the case of PARK4, initially thought to be a different locus and only later recognised as the previously assigned PARK1 (*SNCA*). Monogenic forms of PD can be further classified according to their mendelian pattern: *LRRK2* is the most common autosomal dominant PD and accounts for around 10% of all autosomal dominant PD cases(Hernandez et al., 2016), while PRKN accounts alone for almost half of recessive, early onset PD cases(Blauwendraat et al., 2019; Hernandez et al., 2016). Overall, monogenic causes of PD are rare, even the most common, LRRK2 mutations account for <1% of PD. In sporadic PD, the majority of sporadic PD cases carry genetic variants that increase the risk of PD. These variants can be viewed either as risk factors or as genetic causes of PD with incomplete penetrance and carriers develop the disease only in the presence of additional "hits", both genetic and environmental. Among these risk factors, *LRRK2*, *GBA1*, *SNCA and MAPT* are most common and the ones that are consistently picked up by GWAS studies(Chang et al., 2017). The most relevant and best understood genes associated with the pathogenesis of PD are listed in table 1.

3. One disease, many pathologies

PD is defined clinically by the presence of parkinsonism (i.e. resting tremor, bradykinesia, postural instability and muscular rigidity) and by the response to treatment with levodopa(Heinzel et al., 2019). The pathological hallmark of PD is the presence of Lewy bodies and Lewy neurites with neurodegeneration in the substantia nigra pars compacta. However, the underlying neuropathology is pleomorphic. For example, some of the genetic forms of parkinsonism e.g. parkin-related do not exhibit Lewy bodies(Johansen et al., 2018).

The heterogenicity of the genes associated with PD also suggests different cellular pathways are involved. *PRKN*, *PINK1* and *DJ-1* share a common pathway, related to mitochondrial function and mitophagy. On the other hand, *GBA1* is a lysosomal enzyme and *LRRK2* also seems to be linked to lysosomal function. Finally, *SNCA* is directly responsible for altering the expression of alpha-synuclein (A-SYN), the main component of LB. Yet another pathogenic pathway is suggested by the identification of MAPT as a risk gene for sporadic PD(Satake et al., 2009).

This suggests that there are several different causes of the PD phenotype, although some with different pathology and involving different pathways. Understanding the mechanisms by which specific gene mutations result in PD neurodegeneration will enable us to stratify patients, potentially with disease modifying therapies specific to the pathway(s) involved in their disease.

Gene name	Familial/monogenic PD (Dominant/recessive pattern)	Relevant risk factor for sporadic PD	Function	Age of onset
SNCA/PARK1-4	yes (Dominant)	yes	Unknown	Age of onset dependent on copy-number,
PRKN/PARK2	yes (Recessive)	no	Mitochondrial	Early
UCHL1/PARK5	yes (Dominant)	no	Ubiquitin-proteasome	Late
PINK1/PARK6	yes (Recessive)	no	Mitochondrial	Early
DJ-1/PARK7	yes (Recessive)	no	Mitochondrial	Early
LRRK2/PARK8	yes (Dominant)	yes	Unknown/lysososomal	Late
ATP13A2/PARK9	yes (Recessive)	no	Lysosomal	Early
GIGYF2/PARK11	yes (Dominant)	no	Possibly IGF-1 signaling	Late
HTRA2	yes (Dominant)	no	Mitochondrial	Late
PLA2G6/PARK14	yes (Recessive)	no	Membrane homeostasis	Early
FBXO7/PARK15	yes (Recessive)	no	Ubiquitin-proteasome/Mitochondrial function	Early
VPS35/PARK17	yes (Dominant)	no	Vesicular trafficking	Late
DNAJC6/PARK19	yes (Recessive)	no	Synaptic endocytosis	Early
SYNJ1/PARK20	yes (Recessive)	no	Synaptic endocytosis	Early
DNAJC13/PARK21	yes (Dominant)	no	Intracellular vescicular formation	Early
CHCHD2/PARK22	yes (Dominant)	no	Mitochondrial	Late
VPS13C/PARK23	yes (Recessive)	yes	Unknown/Mitochondrial	Early
POLG	yes (Dominant)	no	Mitochondrial	Early
LRP10	yes (Dominant)	no	Unknown	Late
TMEM230	yes (Dominant)	no	Unknown/vesicular trafficking	late
EIF4G1	yes (Dominant)	no	protein synthesis	late
MAPT	no	yes	Stabilise axonal microtubules	Late
GBA1	no	yes	Lysosomal	Late
KAT8	no	yes	Autophagy	Late
BST1	no	yes	Immune response	Late
MCCC1	no	yes	Mitochondrial	Late
SCARB2	no	yes	Lysosomal	Late
TMEM175	no	yes	Lysosomal	Late

Table 1: genes involved in PD pathogenesis.

4. A candidate gene for targeted therapy

In the past decade, efforts were made to translate the knowledge of the genetics of PD into disease modification.
In this section we discuss what we consider qualify a gene as a good candidate for targeted therapy.

- High prevalence in PD
  While PD is a common disease, each gene associated with the disease is present only in a small portion of patients. LRRK2 p.G2019S, possibly the most common mutation associated with sporadic PD, accounts for around 1% of cases(Healy et al., 2008). If a targeted therapy for PD would be employable only in PD patients carrying a specific mutation, ideally those mutations should be frequent in the PD population.
- Good knowledge of pathogenic mechanism
  Understanding the pathway that leads from mutations in some genes to PD pathogenesis is crucial in order to develop therapies to reverse these effects.
- Biomarkers
  Clinical trials require measurable outcomes to assess efficacy of therapies. To this end, reliable and specific biomarkers are invaluable.
- Relevance of targeted therapy for idiopathic PD
  The ongoing clinical trials targeting a specific gene in PD only recruit participants carrying mutations in that gene. However, some of these therapies might be effectively employed in all PD patients. It is the case, for example, with potential therapies for *GBA1* mutation carriers. As discussed later in this paper, while *GBA1* mutations can increase the risk of developing PD, it is also true that *GBA1 activity* is perturbed in PD patients without *GBA1* mutations(Mazzulli et al., 2011) and it can be postulated that targeting *GBA1 could have a beneficial effect in these patients*.

The genes involved in the pathogenesis of PD that best meet these criteria are *SNCA*, *GBA1* and *LRRK2*. Indeed, compounds targeting these genes have made it into clinical trials. They are discussed in sections 5, 6 and 7 and listed in table 2. A graphical representation of the main mechanisms of action of these compounds is provided in figure 1.

targeted gene	compound name	name of study	Sponsor	phase	completion year	reference
SNCA	NPT200-11		Neuropore Therapies and UCB Pharma	1	2016	CLINICALTRIALS.GOV ID: NCT02606682
	PD03A	AFF011	Affiris AG	1	2016	CLINICALTRIALS.GOV ID: NCT02267434
	PD01A	AFF008AA	Affiris AG	1	2017	CLINICALTRIALS.GOV ID: NCT02618941
	BIIB054	SPARK	Biogen	2	2022	CLINICALTRIALS.GOV ID: NCT03318523
	PRX002	PASADENA	Hoffmann-La Roche	2	2021	CLINICALTRIALS.GOV ID: NCT03100149
	Nilotinib	PD Nilotinib	Georgetown University	2	2020	CLINICALTRIALS.GOV ID: NCT02954978
	Nilotinib	NILO-PD	Northwestern University	2	2020	CLINICALTRIALS.GOV ID: NCT03205488
	K0706	PROSEEK	Sun Pharma Advanced Research Company Limited	2	2021	CLINICALTRIALS.GOV ID: NCT03655236
GBA1	GZ/SAR402671	MOVES-PD	Genzyme	2	2023	CLINICALTRIALS.GOV ID: NCT02906020
	Ambroxol	AiM-PD	University College, London	2	2018	CLINICALTRIALS.GOV ID: NCT02941822
	Ambroxol		Lawson Health Research Institute	2	2021	CLINICALTRIALS.GOV ID: NCT02914366
	LTI-291		Lysosomal Therapeutics Inc.	2	2018	Nederlands Trial Register: NTR6960
LRRK2	DNL201		Denali Therapeutics Inc.	1	2019	CLINICALTRIALS.GOV ID: NCT03710707
	DNL151		Denali Therapeutics Inc.	1	2020	CLINICALTRIALS.GOV ID: NCT04056689

Table 2: List of clinical trials of disease modifying targeted therapies for PD.

Fig.1: Mechanism of action of genetically targeted PD investigational compounds.

5. SNCA

5.1 SNCA as a therapeutic target

Multiple lines of evidence have implicated the presynaptic neuronal protein, α-synuclein (A-SYN), as a therapeutic target in PD. The discovery of the first PD-causing mutation in 1997, an autosomal dominant A53T mutation in the *SNCA* gene, encoding A-SYN, led to a revolution in genetic research in PD (Polymeropoulos et al., 1997). *SNCA* duplication and triplication cases were subsequently reported (Chartier-Harlin et al.; Singleton et al., 2003), with a dose effect observed as the age of disease onset is

proportional to A-SYN gene dosage (Fuchs et al., 2007). The notion of a pathogenic role for A-SYN in PD was further supported by immunohistochemistry studies which revealed aggregated A-SYN as the most significant constituent of Lewy bodies (Baba et al., 1998; Spillantini et al., 1997) and Lewy neurites (Takeda et al., 1998). This pathological form of A-SYN is subject to post-translational modification such as nitration, ubiquitylation, truncation and phosphorylation (Anderson et al., 2006; Fujiwara et al., 2002; Giasson et al., 2000; Tofaris et al., 2003). Experimental model systems also revealed cell-to-cell transmission between interconnected brain regions as key to the pathological spread of A-SYN, in addition to the induction of PD-like motor deficits in wild-type mice following a single intrastriatal injection of fibrillar A-SYN (Luk et al., 2012). Taken together, such evidence highlights the importance of A-SYN not only as a marker of PD but also as an important factor in its pathogenesis (Brundin and Melki, 2017; Sardi et al., 2018). Thus, subsequent research has sought potential therapies attempting to decrease the level of A-SYN or its ability to propagate by targeting key steps in its molecular pathogenesis.

5.2 Reduction of α-Synuclein Production

One active area of research that has not yet reached clinical phase trial, is aimed at targeting the synthesis of A-SYN prior to its aggregation. RNA interference (RNAi) technologies, which neutralise mRNA molecules, have been used to investigate this. Studies revealed that infusions of short hairpin and small interfering RNA into the striatum and hippocampus of murine and primate models, reduced A-SYN production, even 3 weeks post-infusion (Lewis et al., 2008; McCormack et al., 2010; Sapru et al., 2006), and attenuated progressive motor deficits seen in rotenone-exposed rats (Zharikov et al., 2015). Of note, although these animals demonstrated no signs of toxicity and even *SNCA* ko mice have no marked deficit, other studies have reported significant degeneration of the nigrostriatal system with a more marked suppression of A-SYN production (Collier et al., 2016; Gorbatyuk et al., 2010; Kanaan and Manfredsson, 2012). This suggests that caution must be applied when targeting its production and a safe threshold of suppression must be established.

Another emerging therapeutic approach is to reduce transcription of the A-SYN gene with β2-adrenergic receptor (β2AR) agonists, compounds that regulate the transcription of A-SYN through Histone 3 lysine 27 acetylation (Gronich et al., 2018; Mittal et al., 2017). The impact of administering β2AR agonists in adjunct to levodopa to PD patients has been evaluated in several small open label studies which have reported increased daily time in on phase, reduced latency to treatment response and improved parkinsonism symptoms with this combination therapy (Alexander et al., 1994; Hishida et al., 1992; Uc et al., 2003). However, it is important to note that the utility of β2AR agonists as an adjunct therapy to levodopa has not yet been assessed in large, randomised controlled trials (Magistrelli and Comi, 2019). An additional promising line of research is aimed at reducing the production of A-SYN by using antisense oligonucleotide (ASO) therapy. Given the recent successes of ASOs in the treatment of spinal muscular

atrophy (Mercuri et al., 2018) and Huntington disease (Wild and Tabrizi, 2017), researchers have begun to assess the potential use of ASO therapy in PD with studies on rodent models, revealing reduced deposition and spread of A-SYN (Cole et al., 2016).

5.3 Inhibiting α-Synuclein Aggregation

The misfolding or aggregation of A-SYN and formation of LB results in neurotoxicity. It follows that preventing this could be a neuroprotective therapy for PD. Intrabodies, small antibody fragments which bind to intracellular A-SYN and prevent oligomerization and can be delivered as proteins or genes, are generating significant scientific interest.

Viral vector-based delivery of the intrabodies NbSyn87 and VH14*PEST resulted in reduced aggregated α-synuclein and nigrostriatal degeneration, as well as, the restoration of striatal dopamine and motor function in rodents overexpressing α-synuclein (Chatterjee et al., 2018). Still in the early stages of exploration for PD targets, intrabodies are yet to reach PD clinical trials with questions such as how to obtain a clinically effective CSF concentration still unanswered.

Two therapies designed to inhibit A-SYN aggregation are currently in early clinical trials. The first, developed by Neuropore Therapies and UCB Pharma, is the small molecule NPT200-11. Studies have revealed improved A-SYN pathology, neuroinflammation and motor function in PD animal models following NPT200-11 administration (Price et al., 2018). A small phase 1 study was also completed in 2016 where NPT200-11 was well-tolerated in healthy volunteers (ClinicalTrials.gov identifier: NCT02606682), and a further phase 1b study is being planned (McFarthing and Simuni, 2019). Moreover, a biologic compound NPT088 with high affinity for misfolded proteins (Krishnan et al., 2017; Levenson et al., 2016), originally developed by Proclara Biosciences as a therapy for Alzheimer's Disease, has been shown to bind to aggregated A-SYN, decrease the accumulation of proteinase K-resistant protein and restore levels of tyrosine hydroxylase, required for neurotransmitter synthesis, in PD mouse models (Krishnan et al., 2014).

5.4 Increasing α-Synuclein Clearance

An alternative strategy, currently in clinical trials, is to enhance the clearance of A-SYN. Therapeutic approaches currently in the clinic include the use of immunotherapies and activation of autophagy pathways.

5.4.1 Immunotherapies

Immunotherapy to increase degradation of extracellular A-SYN is in the initial stages of clinical development. Recent discoveries suggesting that extracellular A-SYN is key for aggregate transmission between cells have highlighted the potential of this therapeutic approach in halting PD pathogenesis (Desplats et al., 2009; Lee, 2008; Volpicelli-Daley et al., 2011). Clinical programs utilise two forms of anti-A-

SYN immunotherapy: passive immunisation, i.e. antibodies specific to A-SYN, and active immunisation, i.e. injections of modified A-SYN that stimulate the endogenous production of antibodies.

The search for passive immunisation therapy for PD has resulted in four active human clinical trials (Lundbeck, Biogen, Roche, Astra Zeneca). The most advanced of these use the humanised IgG1 monoclonal antibodies BIIB-054 and Prasinezumab RO7046015/PRX002 (Zella et al., 2019). In ascending-dose Phase 1 studies, both were well-tolerated and exhibited a greater binding affinity for aggregated A-SYN compared to monomeric(Brys et al., 2019; Jankovic et al., 2018). Recently, both antibodies have entered Phase 2 studies where approximately 300 early PD patients have been recruited. The SPARK trial aims to evaluate safety and pharmacokinetic/pharmacodynamic profile of BIIB-054 (ClinicalTrials.gov Identifier: NCT03318523), as opposed to a change in total MDS-UPDRS scores with PRX002 in the PASADENA trial (ClinicalTrials.gov Identifier: NCT03100149). In addition, one active immunotherapy vaccine has successfully completed Phase 1 trials (AFFITOPE PD01A/PD03A, AFFiRiS, Austria). In patients with early-stage PD, good levels of immunogenicity were reported alongside no serious adverse events (ClinicalTrials.gov Identifiers: NCT02267434; NCT02618941). These studies were neither designed nor powered to assess clinical efficacy (McFarthing and Simuni, 2019).

It is notable that further active and passive immunisation approaches are in development; AbbVie launched a Phase I trial of ABBV-0805 and United Neuroscience's UB312 project is due to enter Phase 1 trials in 2019 (McFarthing and Simuni, 2019). However, immunotherapy as means to increase A-SYN degradation has some difficulties: inducing off-target responses; need for frequent administration; lack of immune response (specific to active therapy) and whether the limited penetration of antibodies into the central nervous system (CNS) is sufficient to result in significant clearance of A-SYN (Lindström et al., 2014). However, the finding that the antibody aducanumab reduced brain amyloid-beta plaques in patients with Alzheimer's Disease supports the notion that a clinically effective CNS antibody concentration can be obtained (Sevigny et al., 2016).

5.4.2 Autophagy-enhancing agents

Autophagy is one of the main routes for the degradation of intracellular A-SYN aggregates (Webb et al., 2003; Xilouri et al., 2016) and the potential of autophagy-enhancing agents as a neuroprotective therapy for PD is under current investigation. Rapamycin acts via the mammalian target of rapamycin (mTOR), known to regulate macroautophagy. Studies have shown that rapamycin reduced A-SYN aggregation and associated neurodegeneration in PC12 cells expressing wild-type or mutant A-SYN (Webb et al., 2003), and in A-SYN-overexpressing rats (Decressac et al., 2013) and mice (Crews et al., 2010). Similarly, lithium is another autophagy enhancer and its neuroprotective effects have been repeatedly reported in both *in vitro* and *in vivo* models (Forlenza et al., 2014). However, both rapamycin and lithium lack specificity, interfering

with various cellular pathways, and cause side-effects, making them unsuitable for use as a prolonged high-dosage therapy.

Recent studies have also indicated that the mitochondrial pyruvate carrier (MPC) inhibitor, MSDC-0160, acts to block the mTOR pathway (Ghosh et al., 2016). MSDC-0160 administration protects dopaminergic neurones against 1-methyl-4-phenylpyridinium (MPP+) insult in cell and animal models, attenuating disease progression in two mouse models of PD(Ghosh et al., 2016). mTOR inhibition and its subsequent enhancement of autophagy is believed to be the mechanism by which MSDC-0160 halts neurodegeneration (Ghosh et al., 2016). In addition, further support for the neuroprotective effect of MPC inhibition originates from the finding that MPC inhibitor UK-5099 prevents damage to cortical neurones following excitotoxic injury by regulating glutamate release (Divakaruni et al., 2017; Vacanti et al., 2014). Taken together, investigations of MSDC-0160 suggest that MPC inhibition could be used as a therapeutic approach to reduce α-synuclein aggregation, but it is important to note that a demonstration that this can be achieved in mammalian disease models is required first.

Interestingly, anti-cancer drugs have emerged as a promising approach to enhance autophagic clearance. Nilotinib, used as second-line treatment for chronic myelogenous leukaemia, acts as an inhibitor of Abelson murine leukemia viral oncogene homolog 1 (c-Abl) and is under investigation as a PD therapy. Increased c-Abl activity has been reported in brain tissues of PD patients and can lead to an increase in A-SYN phosphorylation and aggregation (Brahmachari et al., 2016; Lindholm et al., 2016). An increase in c-Abl levels has also been shown to reduce the function of Parkin, a key mediator of mitophagy (Lonskaya et al., 2014). Nilotinib administration prevented dopaminergic neuron loss (Karuppagounder et al., 2014) and normalised striatal motor behaviour in MPTP-treated mice (Tanabe et al., 2014), through to increase in A-SYN deposition into lysosomes where it is degraded (Hebron et al., 2013). Further, a small open-label safety trial evaluated the effects of nilotinib in 12 patients with advanced PD and dementia with Lewy bodies, where a beneficial effect on motor/non-motor symptoms and changes in surrogate disease markers such as A-SYN levels and dopamine metabolism were reported (Pagan et al., 2016). Despite significant caveats with this study which included a lack of a placebo group and non-homogenous cohort of participants (resulting in intra and inter-group baseline differences) (Wyse et al., 2016), these findings prompted further investigations. Specifically, larger, randomised, placebo-controlled, double blind Phase IIa trials are ongoing to determine the tolerability and safety of nilotinib administration, as well as evaluate whether sufficient CNS penetration is possible at non-toxic drug concentrations (ClinicalTrials.gov Identifiers: NCT02954978 and NCT03205488) (Pagan et al., 2019). Another c-Abl compound, K0706, is currently being tested in the PROSEEK study, a phase 2 randomised trial (ClinicalTrials.gov Identifier: NCT03655236). Aim of the PROSEEK study is to assess safety and efficacy of K0706 in early PD patients.

5.5 Specific challenges with *SNCA* targeted therapy

Despite being a promising pathway to disease modification in PD, key obstacles and unanswered questions hinder the development of neuroprotective therapies targeting A-SYN. Main challenges are an incomplete understanding of the complexity of the pathogenesis of this disease in addition to a lack of measurable end-points and preclinical models.

First, although the involvement of A-SYN toxicity is well-established in the pathogenesis of PD, its exact contribution relative to other key molecular events (e.g. inflammation, impairment of autophagy, lysosomal/mitochondrial dysfunction, oxidative stress) has been the source of frequent debate (Burré et al., 2018; Dehay et al., 2015; Oueslati, 2016). In particular, it remains unclear whether A-SYN aggregation initiates cellular dysfunction or vice versa. Therapies targeting A-SYN will have limited efficacy in ameliorating PD symptoms if A-SYN aggregation is not the primary cause of disease.

Second, conflicting reports regarding the pathogenic conformation of A-SYN have complicated efforts to develop a therapy targeting this protein. A-SYN, long described as a natively unfolded ~14 kDa monomer (Burré et al., 2013; Theillet et al., 2016; Weinreb et al., 1996), can take up various conformations physiologically including: dimers; trimers; tetramers and higher-molecular-weight soluble oligomers which can subsequently, become insoluble fibrils with a 1000-fold increase in toxicity compared to oligomers (Pieri et al., 2012). Moreover, tetrameric A-SYN seems to be more resistant to aggregation (Bartels et al., 2011; Tsika et al., 2010), and distinctive aggregation properties are associated with different α-synuclein strains (Mamais et al., 2013). Thus, a more comprehensive understanding of the pathogenic properties of different α-synuclein conformations in PD is key when establishing which form emerging therapies should target (Melki, 2015; Peng et al., 2018).

Third, the role of post-translational modifications of A-SYN is not fully understood. Although hyperphosphorylation of serine residue 129 of A-SYN in LB is a specific pathological hallmark of PD (Anderson et al., 2006; Saito et al., 2003), its relevance to initiating and exacerbating disease has been questioned on the finding that it only accounts for 5% of all A-SYN (Kellie et al., 2014) and experimental studies modifying the phosphorylation of A-SYN have generated conflicting results (Chen and Feany, 2005; Lee et al., 2011; Oueslati et al., 2013; Sato et al., 2011). Moreover, A-SYN can undergo truncation at the C-terminus by calpains (Dufty et al., 2007). It is notable that calpain inhibitors reduce A-SYN deposition in transgenic mouse models (Diepenbroek et al., 2014; Hassen et al., 2018), although the converse, i.e. an enhancement of A-SYN pathology, is not observed with increased calpain activity (Diepenbroek et al., 2014). Additional work is thus required to determine the relevance of Ser129 phosphorylation and truncated α-synuclein in PD pathogenesis in order to establish the validity of therapies targeting these modifications.

Lastly, animal models are only partially successful in replicating the A-SYN pathology of PD. Transgenic mouse models under current investigation only express 30-50% of dopaminergic neuronal loss (Janezic et al., 2013; Thiruchelvam et al., 2004; Wakamatsu et al., 2008). Alternatives, such as viral vector-mediated

overexpression models, demonstrate greater nigrostriatal degeneration however, are also more labour intensive and subject to greater variability (Dehay and Fernagut, 2016).

In addition, the field would benefit from the development of imaging techniques to map the extent of A-SYN pathology in patients and by the development of a biofluid-based biomarker, neither of which are currently available (Sardi et al., 2018).

6. GBA1

6.1 GBA1 as a therapeutic target

There are over 300 *GBA1* mutations known to be pathogenic for the lysosomal storage disorder Gaucher Disease (GD)(Hruska et al., 2008). GD is an autosomal recessive disease and heterozygous *GBA1* mutations carriers allele do not develop the disease. This view has changed in recent years with the recognition that *GBA1* mutations, both monoallelic and biallelic, are also risk factors for PD, and the estimated odds ratio for any *GBA1* mutation in PD patients versus controls is 5.43 according to a big multicentric study(Sidransky et al., 2009). Moreover, GBA1 mutations are highly prevalent in sporadic PD cases, with the two most common mutations being present in 3-7% of patients(Lesage et al., 2011; Neumann et al., 2009; Sidransky et al., 2009)..

The mechanisms that links *GBA1* and PD have not been fully elucidated yet and potentially include a number of different cellular mechanisms, possibly mutation specific. Glucocerebrosidase (GCase), the product of expression *GBA1,* is a lysosomal enzyme. Its main substrate is glucosylceramide (GC), that is hydrolysed into glucose and ceramide. The systemic manifestations of GD are mainly caused by the accumulation of GC, especially in macrophages. While less clearly supported by experimental evidence(Matthew E Gegg et al., 2015), substrate accumulation seems to play a role also in the pathology of neuronopathic GD and of *GBA1*-PD(Kim et al., 2018; Rocha et al., 2015; Suzuki et al., 2015). In particular, human dopaminergic induced pluripotent stem cells (iPSCs) with *GBA1* mutations show accumulation of A-SYN and GC(Schöndorf et al., 2014a), that can be reverted by treatment with an inhibitor of the enzyme GC-synthase(Kim et al., 2018). Also rats treated with the GCase inhibitor conduritol B epoxide show increased levels of A-SYN(Manning-Boğ et al., 2009).

A second proposed mechanism is related to the misfolding of mutant GCase. Usually, GCase travels from the endoplasmic reticulum (ER) to the Golgi and on to the lysosomes, but some *GBA1* mutations might interfere with this process. The mutant GCase would then cause saturation of the ubiquitin-proteasome and ER associated protein degradation systems, leading to the inability of the cell to degrade other proteins, like A-SYN.(Bendikov-Bar and Horowitz, 2012; Fernandes et al., 2016; Schöndorf et al., 2014b). Other possible mechanisms that could link GBA1 mutations and PD are mitochondrial disfunction and inhibition of autophagy(Gegg and Schapira, 2018; Toffoli et al., 2020).

Very interestingly, it seems that there is a bidirectional feedback between GCase and A-SYN and that A-SYN accumulation can lead to decrease GCase deficiency(Gegg et al., 2012; Mazzulli et al., 2011). This finding suggests that targeting GCase might have an effect on A-SYN pathology even in PD patients that do not carry *GBA1* mutations.

6.2 Translational studies

The systemic manifestations of GD can be treated by administering GCase through periodic infusions. However, enzyme replacement therapy (ERT) is unable to cross the blood brain barrier and is thus not useful in treating the neuronopathic manifestations of GD, nor can it be employed to treat *GBA1*-related PD. Alternative strategies have been implemented to treat *GBA1*-PD, the most promising being substrate reduction therapy and small molecule chaperones.

6.2.1 Substrate reduction therapy

Substrate reduction therapy (SRT) is a viable alternative to ERT for the treatment of GD(Pastores and Hughes, 1993). SRT acts by inhibiting the enzyme GC-synthase, thus reducing the accumulation of GC when GCase activity is low. Given its ability to cross the blood brain barrier (BBB), SRT might be effective in alleviating the *GBA1*-PD pathology.

GZ667161 is a GC-synthase inhibitor able to improve lifespan and reduce brain pathology in a mouse model of neuronopathic GD after peritoneal administration(Cabrera-Salazar et al., 2012).

In a mouse model homozygous for the *GBA1* mutation p.D409V, oral treatment with GZ667161 reduced the accumulation of GC and of Lewy Bodies (LB) and improved cognitive outcomes (Sardi et al., 2017).

Interestingly, GZ667161 was able to produce similar results in a mouse model of synucleinopathy, carrying mutant *SNCA* but wild type *GBA1* genes(Sardi et al., 2017). On the basis of these findings, in 2016 Sanofi-Genzyme launched a phase 2 double-blinded clinical trial with venglustat (GZ/SAR402671), an analogue of GZ667161, in GBA1-PD patients (ClinicalTrials.gov identifier: NCT02906020). The trial is expected to close in 2021-2023.

Of note, some concern regards tolerability of SRT, as it can consistently cause side effects, in particular diarrhea(Stirnemann et al., 2017).

6.2.2 Chaperoning GCase to the lysosome

A different strategy for the therapy of *GBA1*-PD is to facilitate the transport of mutant GCase to the lysosomes, increasing its activity and reducing the level of unfolded proteins in the ER/cytoplasm. This has been achieved in experimental settings through the use of small molecule chaperones (SMCs). SMCs are classified as inhibitory and non-inhibitory. Inhibitory SMCs bind the active site of GCase and inhibit the enzyme until it reaches the lysosomes, where the low pH dissociates the chaperone from the GCasem and

reverses the inhibition. Non-inhibitory SMCs bind to a different site and do not have inhibitory activity. The first inhibitory SMCs described, NN-DNJ, was able to increase GCase activity *in vitro* in fibroblasts with a *GBA1* mutation(Sawkar et al., 2002). NN-DNJ is part of a class of compounds called iminosugars and after the promising results with NN-DNJ, other iminosugars were tested (Mena-Barragán et al., 2016; Steet et al., 2006). One of them, isofagomine was studied in a phase 1 clinical trial, but failed to show significant improvements in GD patients(Shayman and Larsen, 2014). As a class, iminosugars have a strong inhibitory activity toward GCase that makes it difficult to find a therapeutic window. Other non-iminosugar inhibitory SMCs have been identified in the following years(Zheng et al., 2007) and recently a new molecule, ambroxol, has gained a lot of attention. Ambroxol was able to increase GCase activity in GD fibroblasts *in vitro*(Maegawa et al., 2009) and reduced A-SYN accumulation in a mouse model of PD(Migdalska-Richards and Schapira, 2016). This lead to the initiation of 2 clinical trials on ambroxol in PD patients. The first one is an phase IIA prospective, single-center, open label clinical trial to evaluate the safety, tolerability and pharmacodynamic effects of ambroxol in 20 PD patients with or without *GBA1* mutations. It started in 2016, recently completed the data collection phase and is currently in press(ClinicalTrials.gov identifiers: NCT02941822). The second one is a randomized, placebo-controlled trial in 75 patients with PD dementia, started in 2015 and expected to terminate in 2021 (ClinicalTrials.gov identifiers: NCT02914366).
Of the non-inhibitory SMCs, the compounds NCGC00188758 and NCGC607 showed the ability to lower A-SYN accumulation and downstream pathology in dopaminergic neurons derived from patients with *GBA1*-PD(Aflaki et al., 2016; Mazzulli et al., 2016). Lysosomal Therapeutics Inc. is running a clinical trial on LTI-291, a non-inhibitory SMCs (Netherlands Trial Register: NTR6960). The trial is a phase 2 randomized, placebo-controlled, double-blind study and recruitment was completed in 2018.

6.2.3 Gene therapy

Gene therapy consists of using viral vectors to insert wild type *GBA1* alleles into the genome of *GBA1* mutation carriers. If successful, gene therapy would be able to restore normal GCase activity, curing GD and possibly nullifying the increased risk of PD in *GBA1* mutation carriers. Promising results have been achieved with gene therapy in animal models of GD. Using a spleen focus–forming virus and a self-inactivating lentiviral vector, two different groups were able to transfect a normal *GBA1* gene in bone marrow cells of a mouse model of GD. After reinfusing the transfected cells into the animals, the animals corrected the GD phenotype(Dahl et al., 2015; Enquist et al., 2006).
In 2019, a gene therapy for spinal muscular atrophy using the adeno-associated virus AAV-9 vector was approved by the FDA(Dangouloff and Servais, 2019). This prompted Prevail Therapeutics to announce that they are starting a phase 1-2 clinical trial with a *GBA1* gene therapy program, PR001, using the same AAV-9 as a vector.

6.3 Specific challenges with GBA1 targeted therapy

The main obstacle in developing a *GBA1* targeted therapy for PD is that the underlying pathogenesis has not been fully clarified yet. Whether A-SYN accumulation in dopaminergic neurons of patients with *GBA1* mutations is caused by accumulation of substrates of GCase, by saturation of the ubiquitin-proteasome pathway or by alternative mechanisms is still a matter of debate.

First, while substrate accumulation plays a clear role in the systemic manifestations of GD, it is uncertain whether it is also a factor in the neurological manifestations of *GBA1*-PD. Indeed, while many studies suggest that SRT is effective in animal models of *GBA1*-PD, several studies did not observe accumulation of GC in the brain of PD patients with or without *GBA1* mutations(Boutin et al., 2016; Clark et al., 2015; Matthew E. Gegg et al., 2015) and only one study showed increased levels of glucosylsphingosine, a secondary substrate of GCase, in the hippocampus of PD patients without *GBA1* mutations(Rocha et al., 2015). If substrate accumulation does not take place in the brain of *GBA1*-PD patients or in that of idiopathic PD patients, then SRT is less likely to have an impact on the pathology.

A second limitation regards the multitude of *GBA1* mutations linked to PD. Indeed, these mutations affect GCase activity and its conformation in different ways(Gan-Or et al., 2015; Smith et al., 2017), and there are some mutations that are pathogenic for PD but do not cause GD, like p.E326K(Siebert et al., 2014). These differences imply that targeted therapies that are effective on some mutations might not be effective on others. For example, p.E326K produces a very modest decrease in GCase activity(Malini et al., 2014) and thus substrate reduction therapy might have less effect on this mutation.

Finally, even though gene therapy inserts a wild-type GBA1 gene in the genome of mutation carriers, the mutant GCase protein is still translated and it is possible that this misfolded GCase can still cause A-SYN pathology. Indeed, the majority of patients with *GBA1*-PD are heterozygous for *GBA1* mutations, suggesting a gain-of-function mechanism.

7. LRRK2

7.1 LRRK2 as a therapeutic target

LRRK2 mutations are the most frequent genetic variants in familial PD. The p.G2019S mutation, the most common *LRRK2* mutation, is found in approximately 1% of sporadic PD cases and 4% of familial PD cases according to a multicenter study conducted in 2008(Healy et al., 2008). In Ashkenazi Jewish and North African populations the frequency is significantly higher, respectively 14.3%-18.8%(Orr-Urtreger et al., 2007; Ozelius et al., 2006) and 39.3%(Hulihan et al., 2008). More than 100 *LRRK2* mutations have been described(Rubio et al., 2012), but only 6 of them have been associated to PD by linkage: p.R1441C, p.R1441G, p.R1441H, p.Y1699C, p.I2020T and p.G2019S, with the latter being by far the most common(Healy et al., 2008; Lorenzo-Betancor et al., 2012). These mutations show a relatively high

penetrance and were described in familial forms of PD. The penetrance of the p.G2019S mutation is estimated to be 42.5-74% by the age of 80 in non-Ashkenazi Jewish(Healy et al., 2008; Lee et al., 2017) and 25% in the Ashkenazi Jewish population(Marder et al., 2015). Several other variants have been described as risk factors for sporadic PD by association studies. These variants are common in the general population, but increase the risk of developing PD by various degrees(Ross et al., 2011; Wu et al., 2012).

The LRRK2 protein has both GTPase and kinase activity and mutations that are pathogenic for PD seem to act by increasing the protein's kinase activity both *in vitro*(West et al., 2005) and *in vivo*(Sheng et al., 2012). The pathological mechanism of *LRRK2* mutations has been investigated in iPSC and animal models. From cellular models, it emerged that p.G2019S can lead to disorganization of the nuclear membrane, mitochondrial dysfunction and intracellular calcium homeostasis(Cooper et al., 2012; Howlett et al., 2017; Liu et al., 2012; Schwab and Ebert, 2015). In all cases, correction of the genotype or inhibition of *LRRK2* kinase activity reversed the pathology. One cellular model also investigated the pathogenic mutation p.R1441C, with similar findings(Cooper et al., 2012). Additional evidence from animal models shows that the p.G2019S mutation induces dopamine neurons pathology(Xiong et al., 2018) that can be reversed by administration of *LRRK2* kinase inhibitors(Lee et al., 2010). Moreover, *LRRK2* inhibitors have proved effective in contrasting induced alpha-synuclein pathology in *LRRK2* mutated or, interestingly, wild-type mice(Bae et al., 2018; Lavalley et al., 2016; Qin et al., 2017).

Numerous studies have shown an alteration of *LRRK2* function in PD pathology associated with other PD causing mutations. The vacuolar protein sorting associated protein 35 (*VPS35*), causing autosomal dominant forms of PD(Vilariño-Güell et al., 2011), has been associated to *LRRK2* and, very interestingly, *VPS35* mutants show increased phosphorylation of Rab10, substrate of LRRK2(Mir et al., 2018). Similarly, *LRRK2* has been linked to *PINK*/*PRKN* pathology in iPSCs and pharmacological inhibition of *LRRK2 in vitro* was able to partially recover *PINK*/*PRKN* related impaired mitophagy(Bonello et al., 2019). Even more important, *LRRK2* kinase activity is increased in sporadic PD cases without *LRRK2* mutations(Di Maio et al., 2018) and some mild evidence suggests that treatment with *LRRK2* kinase inhibitors might attenuate A-SYN pathology in cell and animal models of PD without *LRRK2* mutations(Andersen et al., 2018a; Smith et al., 2016).

Taken together, these data suggest that kinase inhibition of *LRRK2* might be beneficial in A-SYN pathology in *LRRK2* mutated individuals and possibly also in *LRRK2* wild type PD individuals.

7.2 Inhibition of *LRRK2* kinase activity

To reverse *LRRK2*-related PD pathology, efforts have concentrated on reducing *LRRK2* kinase activity. The earliest compounds were non-selective kinase inhibitors, unable to cross the BBB and with low potency(Anand et al., 2009; Covy and Giasson, 2009; Nichols et al., 2009). Nonetheless, they led to the development of a new generation of selective compounds, more active in inhibiting *LRRK2* kinase activity

and with fewer off-target effects, even though they were still not reaching good concentrations in the brain(Deng et al., 2011; Ramsden et al., 2011; Yao et al., 2013). HG10-102-01 was the first compound capable of crossing the BBB and showed *LRRK2* inhibition in the brain of mice following intra-peritoneal delivery(Choi et al., 2012). This was a major advancement in the field and allowed the design of a second generation of selective *LRRK2* inhibitors. Following HG10-102-01, other BBB penetrant small molecule inhibitors were developed, like GNE-7915 GNE-0877, GNE-9605, JH-II-127, TAE684 and PF-06447475. Together with a higher efficacy, these compounds came with oral availability, although the pharmacokinetic properties were still not suitable for clinical trials(Estrada et al., 2014, 2012; Hatcher et al., 2015; Henderson et al., 2015; Zhang et al., 2012). This preclinical research culminated in the development of 2 compounds with exceptional potency and selectivity in inhibiting *LRRK2* kinase activity, optimal brain penetration and pharmacokinetics and a good safety profile: MLi-2 and PFE-360(Andersen et al., 2018b; Fell et al., 2015; Scott et al., 2017).

MLi-2 was able to reduce *LRRK2* kinase activity in the brain of mice by 90% after 1 hour of administration and proved highly selective when tested against over 300 kinases. Moreover, it didn't cause any adverse effect after reaching brain and plasma concentrations 100 times higher than the IC_{50}. Of note, MLi-2 was not able to reverse PD pathology in a mouse model of mitochondrial dysfunction related to PD(Fell et al., 2015). PFE-360 gave similar results in rats, with almost complete peripheral inhibition of *LRRK2* kinase activity after 1h of oral exposure(Andersen et al., 2018b).

On the basis of these findings, Denali therapeutics began testing two promising compounds in humans. DNL201 was already tested in a phase 1a trial on 122 healthy subjects and now entered phase 1b in PD patients with and without *LRRK2* mutations to assess safety, pharmacodynamics and pharmacokinetics. Closing date for this trial was September 2019 (ClinicalTrials.gov Identifier: NCT03710707). A similar compound, DNL151 also entered phase 1b trial with the same design, with estimated completion date in February 2020 (ClinicalTrials.gov Identifier: NCT04056689).

7.3 Specific challenges with LRRK2 therapy

Despite the promising results achieved so far and the expectations for the ongoing clinical trials, *LRRK2* targeted therapy faces several challenges.

First, toxicity is a potential concern. To assess the effect of loss of *LRRK2* kinase activity, *LRRK2* deficient animal models were studied, with the discovery of abnormalities in the kidneys and lungs(Herzig et al., 2011). In particular, *LRRK2* knock-out (KO) mice displayed lysosomal changes in kidney proximal tubule cells and accumulation of lamellar bodies in type 2 pneumocytes(Herzig et al., 2011). In a second mouse model carrying a *LRRK2* kinase inhibitory mutation, the same alterations were observed in the kidneys but not in the lungs(Herzig et al., 2011). In KO mice kidneys showed macroscopic changes in weigh, color and size(Tong et al., 2012). These lungs and kidney alterations were also observed in *LRRK2* KO rats and were

linked to serum and urine abnormalities(Baptista et al., 2013; Ness et al., 2013). Additionally, KO rats alterations in liver and spleen were reported, but not reproduced in different experiments(Baptista et al., 2013; Ness et al., 2013). The same alterations in lungs and kidneys were observed in mice treated with *LRRK2* kinase inhibitors MLi-2 and PFE-360, confirming that their cause is likely to be a reduction in *LRRK2* kinase activity(Andersen et al., 2018b; Fell et al., 2015). A potential effect of *LRRK2* inhibition on immune response has also been postulated (Zhao and Dzamko, 2019). Of note, all the adverse effects observed in animals after pharmacological inhibition of *LRRK2* were reversible and did not affect lifespan.

A second limitation in the development of *LRRK2* targeted therapies is the lack of specific biomarkers. The most widely used measure of LRRK2 kinase activity *in vivo* is by quantifying phosphorylation levels of two serine residues in the *LRRK2* protein, Ser910 and Ser935(Dzamko et al., 2010). Indeed, a number of *LRRK2* kinase inhibitors showed the ability to reduce phosphorylation of Ser910 and Ser935(Andersen et al., 2018b; Fell et al., 2015). However, this approach presents some limitations. First, incubating *LRRK2 in vitro* after treatment with kinase inhibitors and then washout of the drugs demonstrates unphosphorylated Ser910 and Ser935. This suggests that Ser910 and Ser935 are not the product of autophosphorylation and as such are not a direct measurement of *LRRK2* enzymatic activity (Dzamko et al., 2010). Second, some *LRRK2* mutations, like R1441C, a mutation that is supposed to increase kinase activity(West et al., 2005), shows lower levels of phosphorylation of Ser910 and Ser935(Dzamko et al., 2010). If we accept the theory that PD causing pathogenic mutations in *LRRK2* act by increasing kinase activity, it seems counterintuitive that mutations like R1441C decrease phosphorylation. It is possible that these mutations produce structural abnormalities in the *LRRK2* protein that make it less prone to phosphorylation by other enzymes(Dzamko et al., 2010). Even if this is the case, measuring Ser910 and Ser935 phosphorylation seems unsuitable to assess *LRRK2* activity in the presence of these mutations.

An alternative method is measuring phosphorylation of *LRRK2* kinase substrate Rab10(Steger et al., 2016; Thirstrup et al., 2017). However, phosphorylation of Rab10 was not increased in neutrophils of p.G2019S mutation carriers, suggesting it might not be a reliable indicator of *LRRK2* activity either(Fan et al., 2018). This might be explained by the presence of addtional limiting factors for the phosphorylation of Rab10 by *LRRK2*(Liu et al., 2018). In summary, we are still missing a reliable marker of *LRRK2* activity and the best approach for the moment seems to be measuring phosphorylation of Ser910 and Ser935 together with phosphorylation of Rab10(Zhao and Dzamko, 2019).

8. Conclusions

Research on a genetically targeted therapy for PD is moving rapidly and provides promising results for the development of disease modification. However, a better understanding of the underlying pathogenesis of PD and the development of specific biomarkers is required in order to support the development of these new drugs.

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