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Perspective

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A personalised and comprehensive approach is required to suppress or replenish SNCA for Parkinson's disease

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Based on the prevailing α-synuclein "gain-of-function" hypothesis, reducing α-synuclein levels and removing its aggregates is a current focus of disease-modifying therapies for Parkinson's disease. Emerging evidence of α-synuclein "loss-of-function" suggests that it may be necessary to replenish monomeric α-synuclein levels. We propose a personalized and comprehensive approach for different Parkinson's subgroups based on whether α-synuclein is likely to contribute to disease pathogenesis through a "gain-of-function", "loss-of-function", or both mechanisms.

Alpha-synuclein (α-Syn), encoded by the *SNCA* gene, has been linked to Parkinson's disease (PD) since 1997 when the first pathogenic missense mutation (A53T) was identified. Since then, many other *SNCA* mutations, including gene duplication and triplication in some familial cases have confirmed the determinant role of this gene in PD[1–3]. Over two decades of efforts have been elucidating the physiological functions of α-Syn in synaptic vesicle exocytosis, endocytosis, dopamine release, and innate immune defence[4–6]; however, the underlying mechanisms of how α-Syn mutants cause the disease are yet to be fully uncovered. Predominantly known as a "natively unfolded and intrinsically disordered" monomer, physiological α-Syn is enriched in the presynaptic nerve terminals and participates in synaptic neurotransmission. This protein is highly dynamic and can adapt to several conformational changes of which the functional consequences are modulated by several factors including its variant β-Syn that has been shown to act as either an anti-aggregation agent against α-Syn or an amyloidogenic protein[7].

In addition, α-Syn co-exists in an equilibrium of monomers and multimers, including tetramers[8] (Fig. 1), which adopt an α-helical membrane-bound structure and facilitate its functions in synaptic neurotransmission and in exocytosis and vesicle turnover[9]. Compared to aggregation-prone monomeric forms, α-Syn tetramers exhibit little or no amyloid-like aggregation potential[10]. Familial PD-causing mutations have been shown to destabilise α-Syn tetramers and decrease the ratio between tetramer and monomer, which is thought to initiate PD pathogenesis[11,12]. In addition, *SNCA* missense mutations were found to cause misfolding of the protein and generate "toxic" α-Syn species. Thus, prevailing research focus has been on the "gain-of-function" and the toxicity of the pathological α-Syn species. However, emerging evidence indicates that the loss of physiological functions of the α-Syn protein, which is sequestered into α-Syn aggregates may contribute to PD pathogenesis. In this paper, we will discuss evidence supporting both α-Syn "gain-of-function" and "loss-of-function" hypotheses and provide our perspective on developing personalized and comprehensive therapeutic approaches targeting α-Syn.

α-Syn "gain-of-function" hypothesis

A "gain-of-function" hypothesis is supported by the findings in both familial and sporadic cases of the hallmark Lewy body pathology, which largely comprises α-Syn aggregates with a plethora of non-proteinaceous components including lipids, nucleic acids, and degraded cellular structures[13]. As the main Lewy body component, α-Syn aggregates are considered to be initiated by the misfolding and accumulation of phosphorylated α-Syn, which was found to be enhanced by *SNCA* missense mutations[14], as shown in Fig. 1. While genetic overexpression of the wild-type α-Syn as a result of *SNCA* gene multiplications, expansions of the Rep-1 polymorphism in the promoter region, genetic variants in the 3′-untranslated region[15,16], or intronic polymorphisms of the gene[17] was believed to disrupt the synthesis-clearance balance[18], resulting in accumulation of the protein and formation of abnormal oligomeric and fibrillar α-Syn species that have been assumed to have a toxic dose effect[19].

However, the regulation of *SNCA* expression by these polymorphisms may be different in brain regions or even in different neuronal subpopulations[15]. As seen in Table 1, the complex correlations between *SNCA* expression and *SNCA* genotypes may require further investigations in larger cohorts to clarify its underlying disease mechanisms. In an observational study of over 1,000 PD patients, Rep-1 genotypes that were

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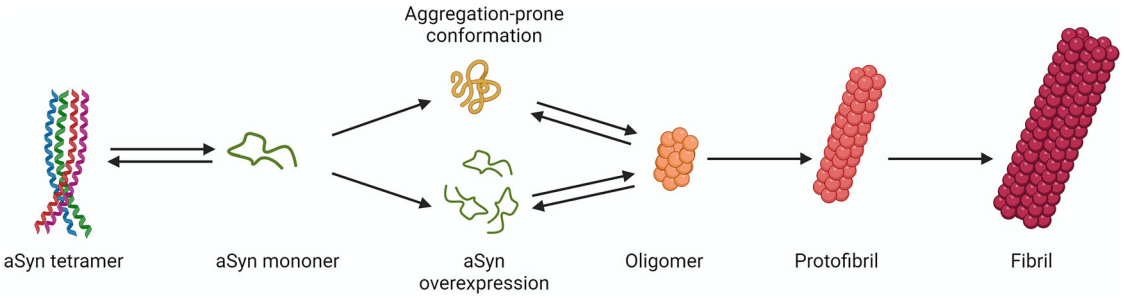

Fig. 1 | Monomeric alpha-synuclein (α-Syn) is an intrinsically disordered protein that constantly undergoes transformation into different conformations. Missense mutations that make α-Syn aggregation-prone, or *SNCA* duplication or triplication, or polymorphisms that increase the expression of monomeric α-Syn facilitate the formation of toxic soluble oligomers which elongate into protofibrils and fibrils. Image modified from Richard Smith et.al. European Journal of Neurology 2023[101].

initially identified as increasing risk of PD via an increased *SNCA* expression were in fact found to associate with better motor and cognitive outcomes than genotypes associated with lower *SNCA* expression[20]. In addition, the lack of PD clinical symptoms or prodromal features was unexpectedly found in some aged individuals (over 61 yrs of age) with a *SNCA* duplication[21], which generally leads to disease onset at a mean age of 46.9 or 34.5 in cohorts carrying heterozygous or homozygous *SNCA* duplications[22].

α-Syn conformers, including soluble α-Syn oligomers and insoluble fibrils have been considered to be "toxic" through damaging mitochondria, disrupting axonal transport, compromising microtubular function, and triggering lysosomal leakage; and have been shown to propagate disease pathology and neurodegeneration in PD animal models[23]. The accumulation of presynaptic α-Syn oligomers has been visualized in patient brains with dementia with Lewy bodies, another synucleinopathy, and has been hypothesized to cause synaptic dysfunctions[24]. However, it should be emphasised that, as in the case of the proposed role of "toxic oligomers" of amyloid-β in Alzheimer's disease, the concept of α-Syn oligomer toxicity in PD has not yet been fully supported by human studies or conclusively proven in experimental animal models at a physiological level of the *SNCA* gene or the α-Syn protein. Nor has evidence of toxicity been found with any types of dopamine-induced α-Syn oligomers in differentiated SH-SY5Y cells or in isolated rat synaptosomes[25]. Intriguingly, within the conformationally heterogenous α-Syn pool, a subtype of fibril-rich and pS129-positive α-Syn aggregates was recently found to be neuroprotective by detoxifying a lipid-rich class of highly dynamic α-Syn inclusions[26]. The findings from rapid and scalable iPSC inclusionopathy models may shed light on the molecular subtypes and functional consequences of α-Syn aggregates, however further investigations are needed in more intricate disease modelling systems.

Nevertheless, the "gain-of-function" hypothesis has been leading the majority of therapeutic developments to reduce the levels of α-Syn or remove α-Syn aggregates. Some of those approaches have demonstrated both the ability to clear established Lewy body pathology and to prevent dopaminergic neuron dysfunctions[27]. However, suppressing α-Syn has recently been challenged, following negative results of the first two Phase 2 clinical trials of monoclonal antibodies targeting the N and C termini of α-Syn[28,29]. Possible pitfalls, including improper study design or execution, failure to enrol the most suitable patients, incorrect drug dosage, or insufficient understanding of disease mechanisms have been discussed as possible factors leading to failed clinical trials[30]. These initial unsuccessful outcomes should not, however, necessarily impact the further development of anti-Syn therapies; but may instead serve to prompt a redefinition of the concept of a α-Syn "gain-of-function" hypothesis so as to develop effective therapeutic strategies. In fact, in a more recent publication by Pagano et. al., results of the clinical trial of Prasinezumab, a monoclonal antibody targeting aggregated α-Syn, demonstrated some level of symptomatic benefits in a subgroup of PD patients with a more rapidly progressive disease phenotype[31]. It will be interesting to further investigate the underlying factors that lead to a faster disease progression and a more favourable response to lowering α-Syn aggregates.

Gain-of-function caused by genetic mutations refers to new or enhanced activity, or increased expression of a protein resulting from genetic variants. Thus, the term "gain-of-function" may be appropriate when applied to *SNCA* multiplications or genetic variants in the 5′ or 3′ UTR or intronic regions, where gene dosage is increased or transcription is enhanced and there is demonstrable overexpression of normal α-Syn protein[32] as shown in some cases in Table 1. However, known *SNCA* missense mutations, including A53T, A30P, E46K, and A53E have minimal effects on the transcription or translation of *SNCA*. Rather, these point mutations tend to alter the protein structure and its biochemical properties, making it more susceptible to aggregation and leading to the generation of "toxic" α-Syn species. Therefore, *SNCA* point mutations may contribute to PD in a "toxic gain-of-function" manner, or in combination with a "loss of function" resulting from depletion of the physiological form of the protein. This may also occur as a result of haploinsufficiency as found in familial PD cases carrying the A53T and A30P *SNCA* mutations[33,34].

Emerging evidence pointing to α-Syn "loss-of-function"

Emerging lines of evidence including the poor correlation between Lewy body pathology (including Braak staging) and disease severity and duration[35,36] have questioned the "gain-of-function" hypothesis and have drawn attention to the possibility that α-Syn "loss-of-function" could contribute to PD pathogenesis[37]. Notwithstanding a few post-mortem studies that have reported an increased expression of α-Syn protein or mRNA in small numbers of PD brains[38–40], many more investigations have demonstrated significantly reduced levels of α-Syn[41–47] in sporadic PD brains. Although insoluble α-Syn species accumulate over the course of the disease; reduced levels of soluble α-Syn have been found in PD-vulnerable brain regions[23], which subsequently results in a reduction of its levels in the cerebrospinal fluid (CSF) and in venous blood as has been shown in a series of investigations in both sporadic[48–52] and *SNCA* duplication patients[53]. The latter finding is intriguing as an increased gene dosage would normally be thought to correlate with more protein production. This controversial finding may be attributed to the challenges in measuring the steady state level of soluble α-Syn because of its variable half-life, ranging from a few hours to over 2 weeks[54] as reported using different experimental approaches, and the half-life being significantly reduced under an overexpression condition[55].

Nevertheless, as argued in a recent review, overexpression of the protein may lead to supersaturation, lowering the nucleation barrier for the soluble-to-insoluble phase transformation of soluble monomeric α-Syn to Lewy pathology, reducing the levels of soluble α-Syn in the brain and CSF[56]. Therefore, genetic overexpression does not necessarily cause a "gain-of-function" and may actually be compatible with a "loss-of-function". It has recently been argued that depletion of the functional monomeric or tetrameric forms of α-Syn could essentially play a more important role than the Lewy body pathology in the neurodegenerative process[57,58]. Similar findings

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Table 1 | Correlations between *SNCA* genotypes and expression of *SNCA* mRNA and α-Syn protein in familial and sporadic PD

	SNCA genotypes	Differential expression		Tissue types	References
		SNCA mRNA	α-Syn protein		
Familial PD	Triplication	PD > Ctrl	PD > Ctrl, protein extracted by Tris-buffered saline	Substantia nigra	Farrer, et al. 2004[71]
	Duplication	n.d.	PD < Ctrl, monomeric α-Syn extracted by Tris-HCL	Frontal cortex	Ikeuchi, et al. 2008[72]
	G209A/A53T	G209A allele absent or significantly reduced in PD	n.d.	PBMC	Markopoulou, et al. 1999[34]
		G209A allele reduced in PD	n.d.	PBMC	Kobayashi, et al. 2003[73]
	G88C/A30P	PD < Ctrl	PD < Ctrl, HPLC	PBMC	
		n.d.	No difference in monomeric α-Syn extracted by Tris-HCL between PD and Ctrl.	Frontal cortex	Seidel et al. 2010[74]
Sporadic PD	NACP-Rep1	259/259 < 261/261, 259/263, 259/261, 263/263	n.d.	Temporal cortex, substantia nigra	Linnertz et al. 2009[16]
		n.d.	259/259 < 261/261, 259/263, 259/261, 263/263, monomeric α-Syn extracted by Tris-HCL. No difference between PD and Ctrl	PBMC	Fuchs, et al. 2007[15]
	SNP rs356219	CT > TT, CC; No difference between PD and controls	n.d.	Substantia nigra	
		TT > CT, CC; No difference between PD and controls	n.d.	Cerebellum	
		TT > CT, CC;	n.d.	Temporal cortex	Linnertz et al. 2009[16]
		TT, CT > CC	n.d.	substantia nigra	
		TT < GA, GG[#]	n.d.	Frontal cortex	McCarthy et al. 2011[75]
		n.d.	TT > CT, CC; PD < Ctrl, protein extracted by a proprietary nondenaturing lytic buffer	Cerebellum	Westerlund, et al. 2008[43]
	SNP rs356204	n.d.	AA > GG, AG; PD < Ctrl, protein extracted by a proprietary nondenaturing lytic buffer	Cerebellum	
	SNP rs2737209	n.d.	GG > AG, AA; PD < Ctrl, protein extracted by a proprietary nondenaturing lytic buffer	Cerebellum	
	SNP rs36515	AA > GA, GG	n.d.	Temporal cortex, substantia nigra	Linnertz et al. 2009[16]
		AA < GA, GG[#]	n.d.	Frontal cortex	McCarthy et al. 2011[75]
	SNP rs2736990	AA < GA, GG[#]	n.d.	Frontal cortex	

PD Parkinson's disease, *Ctrl* healthy controls, *n.d.* no data, *HPLC* high-performance liquid chromatography, *PBMC* peripheral blood mononuclear cells; #: SNCA112 transcript.

have also been reported in prion disease and polyglutamine disorders where normal cellular functions are compromised because of the sequestration of physiological proteins into non-functional aggregates[59].

The pathologic accumulation of α-Syn is not associated with any significant increase in expression of the protein which instead generally results in depressed expression levels while the disease progresses[60]. This is supported by recent post-mortem RNAscope data demonstrating that *SNCA* transcription that is preserved in early disease stages in the substantia nigra neurons is gradually reduced during Lewy body formation and disease progression[61], which is in line with previous investigations[47,62]. In addition to these findings in human brain tissues[63], decreased levels of endogenous soluble somatic and nuclear α-Syn were also detected after the intracerebral introduction of pre-formed α-Syn fibrils (PFFs), which in mouse models act as a seed for the accumulation and aggregation of wild-type α-Syn. Minimum levels of synaptic and soluble α-Syn are found after the administration of α-Syn PFFs, indicating that physiologically functional α-Syn is sequestered and diminished during the aggregation process[8,64]. Although α-Syn fibrils, or possibly the intermediate α-Syn oligomers could result in the progressive loss of dopaminergic neurons observed in these a-Syn PFF models, the diminished levels of endogenous functional α-Syn could also play a contributory role due to the loss of its physiological activities including but not limited to protecting dopaminergic neurons from damage induced by noxious cellular stimuli[65].

However, these experimental observations need to be interpreted with caution, as in some rodent and non-human primate α-Syn PFF models, *SNCA* knockdown with antisense oligonucleotides was found to prevent dopaminergic cell dysfunction[27] or reduce the regional spread of phosphorated α-Syn (pS129) pathologies[66]. Evaluations of motor functions in these *SNCA*-lowered mice will, however, be required to confirm any therapeutic effects following the reduction of pS129 α-Syn, a surrogate marker of pathology, which can also be physiologically triggered by neuronal activities[67]. Thus, caution is needed in interpreting changes in the levels of pS129 or α-Syn aggregates, which are generally labelled by pS129, without distinguishing its physiological and pathological forms. Interestingly, a naturally occurring high abundance of pS129 has been reported in some brain regions[68] and an up to threefold variation in pS129 levels can occur as a result of neuronal activities to positively regulate synaptic transmission[69]. Furthermore, one subtype of pS129-postive α-Syn aggregate was recently found to be neuroprotective in iPSC models[26].

Other intriguing experimental data has shown a significant loss of nigral dopaminergic neurons in adult rats following α-Syn suppression by the injection of siRNAs and the extent of neuronal loss was correlated with the degree of α-Syn depletion in a dose-dependent manner[70]. In addition, a region-specific, tier-related degeneration of nigral dopaminergic neurons and striatal innervation was demonstrated in non-human primates treated with short hairpin RNAs (shRNA) targeting *SNCA*[37,71]. Although these studies involved relatively small numbers of animals and presented limited data, their results may have suggested that adequate levels of functional α-Syn are required for neuronal survival; and it is noteworthy that neurodegeneration was rescued by replenishing normal α-Syn in one of those studies[70]. Similar outcomes were demonstrated in adult rats receiving shRNA targeting *SNCA*, where α-Syn knockdown resulted in a 50% loss of nigrostriatal neurons in the substantia nigra pars compacta, a loss of nigrostriatal terminals, and a depletion of dopamine within the striatum[72]. However, the use of AAV vectors, and the loss of the antimicrobial (anti-viral) activity of α-Syn and of effects on innate immune responses because of its depletion, were possible confounding factors in those studies and could have contributed to the neuronal loss[73–75]. Indeed, the depletion of functional α-Syn was shown to initiate a neuronal-mediated inflammatory cascade, involving both innate and adaptive immunity, which resulted in the death of affected neurons in PD models[72,76].

In a recent population-scale analysis of rare *SNCA* variants, one participant with a *SNCA* whole gene deletion demonstrated PD prodromal features at the age of 54[21]. While the other five *SNCA* deletion cases were symptom-free at an average age of 51, whether they would develop the disease warrants follow-up investigations[21]. Although aging is a key risk factor for developing PD, it is noteworthy that studies in both humans and monkeys have shown that cytosolic levels of α-Syn in nigral dopamine neurons do not fall, but actually increase with aging[77], possibly representing a compensatory mechanism against aging-related neuronal death. Whether neurodegeneration is initiated by manipulating *SNCA* levels may depend on the levels of functional α-Syn as discussed elsewhere[8]. Although the minimum level of α-Syn required to maintain its physiological synaptic functions is still undetermined, it has been suggested that neurodegeneration may start to occur when α-Syn levels fall below a threshold of ~30%[8], with recent evidence showing that no neurodegeneration or motor dysfunctions were noted after ~68% α-Syn knockdown[66].

Therefore, restoring the levels of soluble and physiologically functional α-Syn might be beneficial in those having less than 30% of physiological α-Syn protein; meanwhile, considerations could be given to first validating the efficacy of such an approach in experimental disease models. However, as proposed elsewhere, most animal models while useful to evaluate molecular mechanism, drug toxicity, and safety, could be unreliable or misleading to test such a disease hypothesis or to validate therapeutic efficacy of certain compounds, as witnessed by the poor correlation between animal model based-success and clinical trial-success[78]. Moreover, possible detrimental effects of supplementing an excess of monomeric α-Syn without knowing what the baseline levels are in individual PD patients also need to be considered and could conceivably increase α-Syn aggregation and fibril formation. It has been shown that at high concentrations monomeric α-Syn undergoes a liquid-to-gel phase transition, which can act as a reservoir of trapped α-Syn oligomers and fibrils[79].

Personalized and comprehensive strategies

Based on the current state of knowledge and the complexity of PD at a genetic and molecular level[80], a biological classification based on the presence or absence of pathological α-Syn, as well as *SNCA* genotypes, and biochemical phenotypes[81] will be essential for PD diagnostics and precision drug development. Further to the application of a biological definition of α-Syn in PD disease staging[82], we believe a biological or biochemical definition of α-Syn at a personalised level will be the key to the discovery of novel therapies targeting underlying pathogenesis in a precision medicine manner[83]. Therefore, it is likely, as outlined below that distinct but comprehensive approaches will be needed for different subgroups of patients carrying distinct *SNCA* mutations or disease-modifying alleles, or with different *SNCA* biochemical phenotypes (Table 1).

1. Although such cases are rare, proof-of-principle verification of the efficacy of α-Syn suppression strategies could begin in patients with *SNCA* gene multiplications with increased α-Syn levels[41], in whom reducing levels of endogenous α-Syn would intuitively make sense. However, the level of soluble α-Syn in CSF, or ideally in the brain may need to be checked for each individual patient before α-Syn is reduced by any means. As previously indicated, an increased gene copy number does not necessarily increase its protein expression and low CSF levels of α-Syn have been reported in *SNCA* duplication patients[53]. It follows that the finding of a low level of α-Syn in the CSF would be considered as an indication for α-Syn replacement rather than α-Syn suppression therapy.
2. Similarly, PD patients with disease-modifying *SNCA* polymorphisms, including expanded Rep-1 alleles, genetic variants in the 3′-untranslated region, and intronic polymorphisms, would be the second patient subset in which anti-α-Syn treatment might be considered, provided that evidence of increased α-Syn expression is demonstrated.
3. On the other hand, as decreased levels of soluble α-Syn has been demonstrated in post-mortem studies in familial PD with the *SNCA* A53T and A30P mutations[84], it may be beneficial to restore levels of monomeric α-Syn in such cases. There is a scarcity of studies exploring the levels of soluble α-Syn in patients carrying other *SNCA* missense mutations including A30G, E46K, H50Q, G51D, A53E, and A53V. However, since these mutations were found to contribute to α-Syn

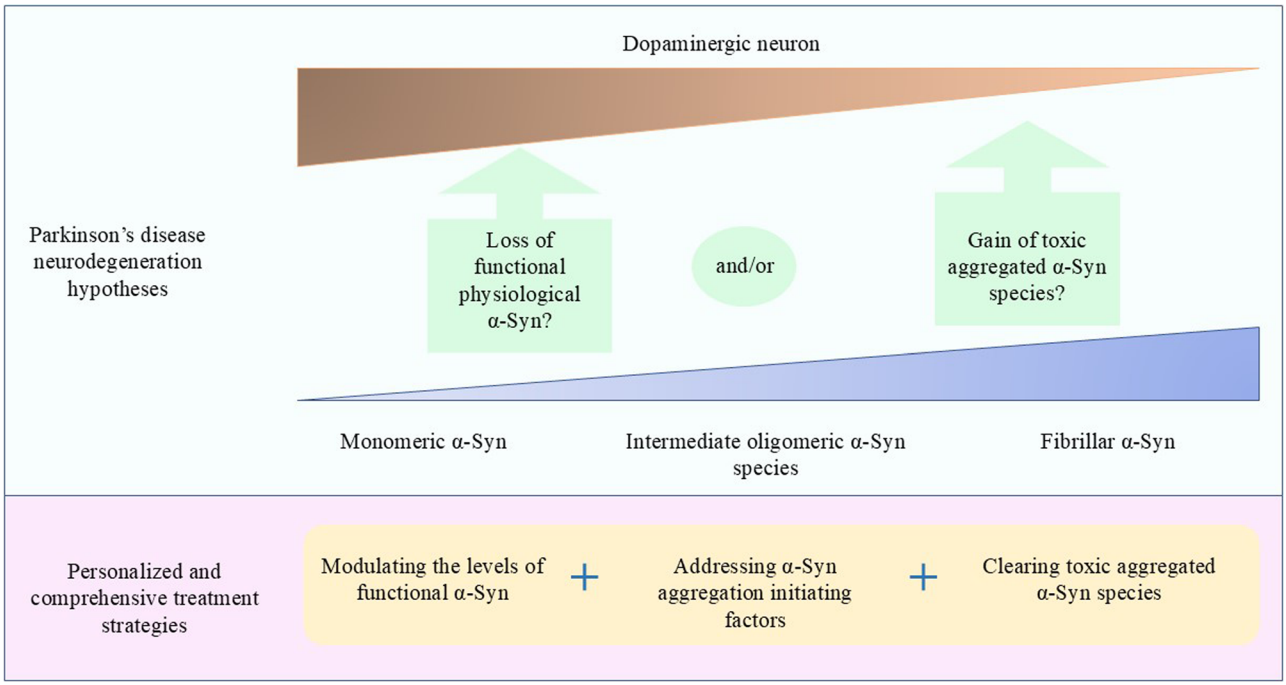

Fig. 2 | Personalized and comprehensive approaches targeting α-Syn for the development of effective disease-modifying treatments. The questions over whether α-Syn "loss-of-function" or "gain-of-function" or a combination of both contributes to PD still need to be resolved. It is proposed that a comprehensive approach including fine-tuning monomeric α-Syn levels by either reducing or increasing its level, addressing the underlying mechanisms involved in α-Syn accumulation and aggregation, and removing toxic α-Syn is likely to be required.

pathology by altering α-Syn phosphorylation or interfering with specific steps during α-Syn aggregation, it may still be likely that soluble α-Syn is depleted and that further reducing α-Syn levels could exacerbate neurodegeneration.

Because of the rarity of such cases and of *SNCA* gene multiplications, these strategies would have to be trialled at a later stage through the orphan drug approaches rather than the conventional randomised clinical trials, once decisions have been made as to the appropriate therapeutics and at what stage of the disease to administer them. It is likely that such proof-of-principle assessment of therapeutic approaches in these forms of genetic PD would be more likely to succeed if performed in an early disease stage or even in the prodromal stage in cases with high-penetrance mutations.

4. For the majority of patients with other monogenic forms of PD who are associated with α-Syn pathology and with idiopathic PD, further systematic and comprehensive investigations are required to elucidate the dominant underlying molecular mechanisms and whether levels of functional α-Syn are depleted or raised in relation to an established normal range, before deciding whether α-Syn suppression or replacement is more appropriate. Bearing in mind that any constituent in the human body should be within a certain range and α-Syn may have dual and opposing roles in the disease[15].

Future perspectives

Parkinson's disease is a complicated disorder driven by multiple processes rather than by a single protein, even in those rare cases with a *SNCA* mutation. Therefore, comprehensive therapeutic strategies are likely to be required in parallel with a personalized approach to either suppress or replenish α-Syn to a certain level required to implement its critical functions. The removal of α-Syn fibrils could potentially restore the levels of functional α-Syn by reducing the seeding of monomers; however, it might possibly result in the production of "toxic" intermediate pre-fibril α-Syn oligomers, which are thought to exist in equilibrium with monomeric α-Syn and to undergo slow conversion to fibrils[19]. Crucially, the initiating factors mediating conformational changes in endogenous α-Syn, or more importantly for wild-type monomeric α-Syn to oligomerize and to form fibrils, or factors involved in phase transition of soluble proteins into insoluble amyloids[85] need to be better and fully understood.

In light of the complexity and heterogeneity of PD, our perception is therefore that the ideal disease-modifying strategy should comprise a combination of personalized approaches. These (Fig. 2) include maintaining physiological α-Syn levels, removing toxic α-Syn conformers, clearing α-Syn seeding fibrils, and addressing α-Syn aggregation initiating factors, which are likely to include post-translational modifications in α-Syn and as yet unknown modifications in the cellular milieu. Additionally, potential therapeutic targets should also include the endolysosomal pathway, mitochondrial function, neuroinflammation, and glucose and lipid metabolism, all of which may contribute to PD pathogenesis individually or synergistically, with or without α-Syn.

Alternatively, disease-modifying strategies could focus on stabilising α-Syn tetramer by using small molecules or modulating the levels of PD related genes, including *LRRK2* and *GBA1* which has been shown to increase the α-Syn tetramer : monomer ratio, improve lysosomal integrity, and attenuate motor and cognitive functions in PD mouse models[86,87]. However, further investigations are required to elucidate the mechanisms of how these PD-linked genes participate in α-Syn dysregulation. The reduction of GCase protein and the loss of GCase enzyme activity caused by *GBA1* mutations are believed to cause α-Syn to aggregate and subsequently form Lewy body pathology; however, the "gain-of-function" hypothesis due to enzyme misfolding is also considered as an important contributor to the disease. Postmortem studies have shown the presence of Lewy body pathology in patients carrying *GBA1* variants, however the degree of the pathology varies[88]. Diverse pathological findings have also been found in LRRK2-PD. For example, the typical a-Syn pathology was found in some G2019S cases, the most common *LRRK2* mutation; while the absence of Lewy pathology has been related to other mutations including R1441H, R1441G, and I2020T[89–91]. In addition, the classic synucleinopathy was less frequently found in autosomal recessive PD cases especially those carrying

PARK2 mutations[92,93], which, however, may be due to the paucity of human data or caused by distinct disease mechanisms[94].

Nevertheless, huge gaps must be filled before viable therapies will reach patients. These include but are not limited to the identification of dominant toxic α-Syn species, mechanisms of α-Syn aggregation and oligomerization, precise animal models to provide proof-of-concept, and reliable biomarkers for use in well-designed clinical trials in patient cohorts that have undergone careful clinical and biochemical phenotyping and genotypic evaluations. Furthermore, the development of accurate and sensitive techniques to monitor levels of physiologically functional α-Syn will be essential to determine which *SNCA* patients are suitable for either *SNCA* suppression or replacement therapy and will be a key monitor in clinical trials.

The α-Syn seed amplification assay (SAA) has been developed to detect α-Syn seeds in CSF or blood samples and has shown huge potential in diagnosing PD and differentiating PD from other synucleinopathies[95,96]. Although negative results were reported in certain PD subpopulations including normosmic PD or LRRK2-PD[96,97], which was proposed to have distinct disease patho-mechanisms, SAA would be a promising tool to monitor treatment strategies that reduce α-Syn seeding aggregates. Other methods, including single-molecular ELISA[98], nanopore detection system combined with molecular carriers[99], and molecular magnetic resonance imaging (MRI) technology[100] have also shown some promise in detecting oligomeric α-Syn in different sample types. The development of such tools to accurately quantify the levels of monomeric α-Syn would be critical to test the disease hypotheses and to select the right patient groups for the future clinical trials.

Getting the right treatment for PD is challenging; however, we are optimistic that continued investigations of therapeutic approaches targeting α-Syn and adopting a personalised, yet comprehensive approach will ultimately lead to an improved quality of life for people with PD.

Data availability

Not applicable.

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Author contributions

D.L. played the major role in the conceptualising, writing and revision of the manuscript; W.Y. contributed to the conceptual content and critical review of the manuscript; S.C. contributed to the conceptual content and critical review of the manuscript; S.W. contributed to the critical review of the manuscript; F.M. played a significant role in the conceptualisation, critical review and revision of the manuscript. All the authors have read and approved the manuscript.

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