Targeting ASYN in Parkinson's Disease Treatment: Identification of Effective Inhibitors of Alpha-Synuclein Aggregation Through in Silico Methods

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ABSTRACT

Background: Parkinson's disease is the second most common neurodegenerative disease worldwide. In 2016, it affected 6.1 million individuals globally, an increase from 2.5 million in 1990, with an age-standardized prevalence increase of 21.7% during this period (Dorsey *et al*., 2018) (Marsden, 1994). The disease also caused 3.2 million disability-adjusted life years (DALYs) and 211,296 deaths in 2016. Parkinson's disease is caused mainly by the depletion of dopaminergic neurons in the substantia nigra pars compacta (Price *et al*., 2023) (Grewal *et al*., 2024). A key feature of the pathophysiology of the disease is the accumulation of aggregates of misfolded alpha-synuclein protein. The structure formed as a result of said aggregation is referred to as a Lewy body (Hebron *et al*., 2013).

Under normal physiological conditions, alpha-synuclein is present in the form of a single, unaggregated, monomeric molecule. While two forms of alpha-synuclein exist; namely, propagating and non-propagating forms, whereby propagating forms of the protein are capable of clumping together to form larger structures (Lewy bodies), and non-propagating forms of the protein are unable to do so – these are found in a stable equilibrium, and the presence of propagating alpha-synuclein variants in equilibrium does not contribute to the initiation of Parkinson's disease pathogenesis (Mahul-Mellier *et al*., 2014) (Migdalska-Richards *et al*., 2016).

On the other hand, during the development of Parkinson's disease, the balance between the propagating and non-propagating forms of alpha-synuclein is disrupted, resulting in the accumulation of misfolded multimeric clumps. This accumulation within neuronal cells is one of the hallmarks of Parkinson's disease, and is therefore a common therapeutic target for the disorder (O'Hara *et al*., 2018) (Giladi *et al*., 2023).

Novel therapeutic approaches targeting misfolded alpha-synuclein aim to target the multimeric forms of the protein, while allowing the monomeric forms to remain undisrupted. An example of such an approach is the administration of Anle138b, which is a newly discovered inhibitor of the multimerization of alpha-synuclein.

An alternative strategy involves inducing autophagy targeting the accumulation of alpha-synuclein aggregates. Nilotinib, a c-Abl tyrosine kinase inhibitor, follows this technique, reducing alpha-synuclein toxicity in the substantia nigra and thus improving motor function. Another drug adapting a similar method of intervention is K0706, also known as vodobatinib, which is another c-Abl tyrosine kinase inhibitor (Giladi *et al*., 2023).

A third common technique is enhancing the degradation of glycosphingolipids via enhancing glucocerebrosidase activity, which is an enzyme that breaks down glucosylceramide, a glycosphingolipid, into glucose and ceramide. There is an inverse relationship between glucocerebrosidase and alpha-synuclein, indicating that an increased glucocerebrosidase (GCase) activity could reduce alpha-synuclein toxicity. Drugs that follow this pathway include Ambroxol and LTI-291 among several others, all of which are glucocerebrosidase-activating molecules. A similar approach is to inhibit the biosynthesis of glucosylceramide, which can be achieved using drugs such as Venglustat. PR001, also known as

LY3884961, is a gene therapy that uses Adeno-Associated Virus serotype 9 (AAV9) as a vector to deliver a functional Glucosylceramidase Beta 1 (GBA) gene to the brain, increasing glucocerebrosidase activity (Abeliovich *et al*., 2021). However, the first in-human study exploring drug safety of this molecule is ongoing and likely to end in June of 2027.

Objective: The aim of this study is to identify the most promising candidates that can target, bind to the active site, and inhibit alpha-synuclein (ASYN) protein aggregation.

Methodology: This is an in-silico study, constituted by virtual high-throughput screening of ligands that act as inhibitors of multimerization of the misfolded alpha-synuclein protein variant in Parkinson's disease, using bioinformatic tools and databanks such as National Center for Biotechnology Information (NCBI), PubChem, Basic Local Alignment Search Tool (BLAST), Molecular docking, Molecular Dynamics (MD) simulations. The screening is followed by identifying the most suitable hit molecule (ligand/lead/drug) and its subsequent molecular docking, Molecular Dynamics (MD) simulation and ligand toxicity analysis to test its efficacy against the targ*et al*pha-synuclein (ASYN) in-silico.

Result: The results expected from this study, including the successful identification, optimization, and in-silico testing of such a ligand, provide a basis for developing new therapies aimed at blocking the formation of Lewy bodies by inhibiting the aggregation of misfolded alpha-synuclein molecules.

Conclusion: The findings from the study could potentially be implemented in an in-vivo model of Parkinson's disease to test its efficiency in a physiologically relevant environment, as well as subsequent testing in clinical trials to test the safety and tolerance of the drug.

Keywords: Alpha-Synuclein Protein, Molecular Docking, Neurodegenerative Disease, Parkinson's Disease, SNCA Gene.

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