Exploring Parkinson’s Disease Inhibitor Efficacy on a Non-dopaminergic Target

https://neurodegenerationresearch.eu/survey/exploring-parkinsons-disease-inhibitor-efficacy-on-a-non-dopaminergic-target/

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Country

Luxembourg

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Exploring Parkinson's Disease Inhibitor Efficacy on a Non-dopaminergic Target

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2

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Research Abstract

Parkinson’s disease (PD) is one of the most frequent neurodegenerative diseases, and since aging is a major risk factor for PD, the disorder represents a growing social and financial burden for modern societies with high longevity. Although existing drug therapies, focusing on restoring dopamine levels in the brain reduced due to neurodegeneration, can alleviate some of the main symptoms, a gradual loss of efficacy and several adverse effects limit their utility.Non-dopaminergic protein drug targets are therefore being investigated to develop alternative and causative treatments for PD. Among recently proposed candidate targets, the protein RGS4 is of particular interest for multiple reasons: 1.) RGS4 double-knockout mice have been shown to

be significantly less impaired in the 6-OHDA model of PD; 2.) RGS (Regulator of G-protein signaling) proteins tend to have a unique tissue distribution, specificity and function; 3.) The molecular structures for RGS4 and first inhibitors are available; 4.) Known inhibitors have either low binding affinity or limited bioavailability (according to in-silico predictions by the PI), providing an opportunity for developing new high-affinity, selective and bioavailable inhibitors to pave the way for a novel therapeutic approach.The main project goal is therefore to apply and further develop a self-devised virtual screening pipeline to identify and prioritize new RGS4 inhibitors and experimentally validate selected compounds in vitro and in vivo. For this purpose, the principal investigator has implemented a software tool that efficiently scores the structural similarity of candidate compounds with known inhibitors in a manner that – in contrast to most conventional pre-filtering approaches – takes into account the molecules' full structural flexibility. This software will be optimized for efficiency during the project and combined with open source tools for docking, pharmacophore modelling and in silico prediction of ADMETox properties to rank commercially available small molecule compounds as potential bioavailable inhibitors for RGS4. A final selection of compounds will then be verified experimentally using a dedicated ligand binding assay and subsequent tests in a 6-OHDA mouse model for PD. Apart from the possibility of obtaining a patentable, bioavailable inhibitor for RGS4 that passes the blood-brain barrier, the project would provide a fast software for flexible ligand similarity search and a detailed pharmacophore description of the RGS4 binding interface for publication.In summary, the project will provide a preclinical proof-of-concept evaluation and efficacy testing for an alternative non-dopaminergic treatment of PD, combining academic research with pharmaceutical screening practices and computational biology with experimental validation.

Further information available at:

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