Screening for enhancers of sAPPalpha

https://neurodegenerationresearch.eu/survey/screening-for-enhancers-of-sappalpha/

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USA

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Research Abstract

? DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) currently afflicts more than 5.4 million people in the US at an estimated cost greater than $200 billion per year. Currently approved drugs offer only short-term symptomatic relief but do not alter disease progression. The neuritic plaques that are a hallmark of AD brain result from increased generation and/or decreased clearance of the amyloid beta peptide (A?) which originates from amyloid precursor protein (APP). APP may be processed by two pathways. In one, it undergoes sequential ?-

secretase and ?-secretase cleavages to generate soluble amyloid precursor protein beta (sAPP?) and A?; in the other, it is cleaved by an ?-secretase to generate soluble amyloid precursor protein alpha (sAPP?), a pro-cognitive peptide that may prevent AD. This project proposes to advance our previous studies that successfully identified the sAPP?-enhancer tropisetron (F03) with the goal of identifying new sAPP?-enhancers as new chemical entities (NCEs) constituting a novel class of therapeutics for AD. Our strong foundation of preliminary data indicates a high probability that the specific aims of this project can be achieved. We have had early success utilizing our iterative, hierarchical chemical-genetics screening approach in the identification of F03 – a drug used for post- operative nausea and vomiting – from a small clinical compound library. F03 was shown to consistently but modestly increase sAPP? in vitro and in vivo in a mouse model of AD, and to significantly improve memory in the AD model after four weeks of oral treatment. F03 is now in clinical trials for mild cognitive impairment (MCI) due to AD as a repurposed drug. Here, we propose utilizing our high-throughput screening (HTS) assay, iterative screening flowscheme, and the large UCLA compound library to identify compounds with sAPP?-enhancing effects greater than F03. In the primary HTS screen, “”hits”” that increase sAPP? will be identified. In the secondary screen, hits are validated using a second in vitro model. Prioritized hits will then be further validated by ex vivo organotypic cultue of AD model brain and brain penetrance determined by parallel artificial membrane permeability analysis (PAMPA) and in vivo pharmacokinetic (PK) analysis. Finally, we will determine the mechanisms by which hits induce sAPP? enhancement using the CEREP Bioprint profile, drug affinity responsive target stability (DARTS), in silico target ID using the similarity ensemble approach, and by a new gel-enhanced target identification approach (GET). While other new approaches to identify therapeutics for AD and MCI are under development, their clinical outcomes remain uncertain. By identifying compounds with sAPP? enhancing effects greater than F03, we may find promising NCEs for further clinical development. Perhaps most importantly, our mechanistic studies of such enhancers may further elucidate the role of sAPP? in the etiology of AD, providing new direction for therapeutic development.

Further information available at:

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