ApoE4-targeted therapeutics that normalize SirT1

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Country

USA

Title of project or programme

ApoE4-targeted therapeutics that normalize SirT1

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NIH (NIA)

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15/08/2015

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2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Dementia... Neurodegenerative... Neurosciences... Prevention... Translational Research

Research Abstract

? DESCRIPTION (provided by applicant): Our studies link for the first time the major risk factor

for Alzheimer's disease – ApoE4 – with major longevity determinants, the Sirtuins; and identify the first candidate therapeutics that target this new link. Alzheimer's disease (AD) currently afflicts more than 5.4 million people in the US at an estimated cost to society of greater than $200 billion per year. The currently approved drugs for AD provide only short-term symptomatic relief but do not alter disease progression. The dominant risk factor for Alzheimer's disease (AD) is the epsilon-4 (e4) allele of apolipoprotein E (ApoE4), which is present in about two-thirds of AD patients. The ApoE4 allele (chromosomal locus 19q13) confers increased risk for sporadic and late-onset AD (LOAD). Despite over a decade of knowledge that the ApoE4 allele is somehow contributory to the disease process, the precise molecular mechanisms underlying ApoE4-associated AD risk remain unclear. Our studies shed light on a novel mechanism for ApoE4-mediated toxicity and revealed a key mediator – SirT1 – that is differentially affected by ApoE4 vs. ApoE3. Interestingly, while both ApoE3 and ApoE4 bind to APP, only ApoE4 associates with nanomolar affinity (Kd ~80nM), and only ApoE4 significantly: (a) reduces the ratio of sAPPa to Aß; (b) reduces SirT1 expression, resulting in a marked reduction of SirT1 levels and in the ratio of neuroprotective SirT1 to neurotoxic SirT2; (c) triggers tau and APP phosphorylation; and (d) induces programmed cell death. In our initial screen of a clinical library we have identified a promising hit (A03) that is a repurposing candidate, is highly brain permeable, and reverses the reduction of SirT1 levels. As part of this proposal we plan to complete the preclinical testing of A03 and develop new chemical entity (NCE) analogs of A03 for further development. In addition, through screening and ""hit-to-lead"" optimization we plan to discover new lead candidates for further testing. The eventual goal of the proposal is to provide 1-2 candidates for non-GLP toxicity testing. Our data support the hypothesis that neuronal connectivity – influenced by the ratios of critical mediators including sAPPa:Aß, SirT2:SirT1, APP:p-APP, and tau:p-tau – is programmatically altered by ApoE4. The collaboration with the Clinical Core and the Gylys lab is important in this project, as it would provide preliminary analysis of plasma and CSF samples from ApoE genotyped patients for levels of SirT1. Such data would be extremely useful for future development of ApoE4-targeted drug candidates to clinical testing and SirT1 as a potential plasma biomarker in MCI/AD. In addition, comparing SirT1 with other biomarkers in plasma/CSF that are affected by the sirtuin/NFkB signaling is planned and would help further elucidate the role of ApoE4 in AD. The overall primary objective of this project is to identify potent, orally active, brain permeable SirT1-enhancing lead candidates that are suitable for further preclinical IND development as the first ApoE4- targeted SirT1 therapeutics for AD and to development the tools necessary to ascertain target engagement and efficacy.

Lay Summary

PUBLIC HEALTH RELEVANCE: Our studies link for the first time the major risk factor for Alzheimer's disease (AD) – ApoE4 – with major longevity determinants, the Sirtuins; specifically SirT1 is significantly decreased in the presence of ApoE4, and we have through screening identified the first candidate therapeutic that targets this new link and reverses the SirT1 decrease. Currently there are no drugs that specifically target ApoE4 neurotoxicity leading to AD; between 65-80% of all AD patients have at least one ApoE4 allele and thus effective ApoE4 specific drugs would have widespread use in mild cognitive impairment (MCI) and AD. The overall objective of this project is to identify potent, orally active, brain permeable SirT1-enhancing lead candidates that are suitable for further preclinical IND development as the first ApoE4-targeted therapeutics for AD.

Further information available at:

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