Preclinical assessment of an ABCA1 agonist as a novel therapeutic for AD

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Country

USA

Title of project or programme

Preclinical assessment of an ABCA1 agonist as a novel therapeutic for AD

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

403279.8165

Start date of award

01/08/2015

Total duration of award in years

2

Keywords

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

Research Abstract

DESCRIPTION (provided by applicant): APOE4 is the greatest genetic risk factor for sporadic Alzheimer’s disease (AD), increasing risk up to 15-fold compared to APOE3. As APOE4 carriers can respond anomalously in clinical trials, sometimes negatively, there is a critical lack of

therapeutics targeting mechanistic pathways of APOE4-induced AD risk. Genetic evidence supports the role of amyloid-ß peptide (Aß), particularly Aß42, as a causative agent in AD, with soluble oligomeric aggregates (oAß) recognized as the likely proximal neurotoxins. As congruent lines of evidence indicate that apolipoprotein E (apoE) isoform-specific modulation of soluble Aß levels may impart APOE4-induced AD risk, our therapeutic goal is to develop apoE-based approaches to reduce oAß levels. Enabled by the development of the novel ELISAs and the new EFAD mouse model (overexpressing Aß42 and expressing human APOE), we have dissected potential pathways underlying the correlation between apoE4 and increased levels of soluble Aß. Our data demonstrate that compared to apoE3, lipoprotein- association/lipidation of apoE4 is reduced, resulting in lower levels of apoE4/Aß complex and higher levels of soluble oAß, compromising synaptic viability. ABCA1 is a promising therapeutic target for testing this hypothesis because ABCA1 is a major transporter of lipid to apoE-containing lipoproteins in the CNS. Using EFAD mice, we recently demonstrated that 1-week treatment with RXR agonists increased ABCA1 levels, apoE4 lipidation, and soluble apoE4/Aß complex levels, while lowering soluble Aß levels and increasing synaptic protein levels. However, in brain regions with low Aß pathology at time of treatment (both E3FAD and E4FAD mice), no beneficial effects were observed and levels of soluble Aß were actually increased. While these data provide target validation for ABCA1, the detrimental off-target effects, attributed to severe hepatomegaly, limit RXR agonist utility in long-term treatment protocols. Artery Therapeutics developed novel ABCA1 agonists, including CogPep B, for the treatment of peripheral cardiovascular disease. CogPep B demonstrates high potency for increasing the activity and levels of ABCA1 in vitro, has a high maximal tolerated dose in vivo and is brain penetrant with concentrations 2-6-fold above the in vitro KM at a dose lower than that proposed herein. In addition, preliminary data demonstrate that CogPeP B increases synaptic protein levels and improves memory in APOE4-targeted replacement (TR) mice compared to APOE3-TR. For the first time, this proposal will assess the CNS effects of CogPep B in treatment (Aim 1) and prevention (Aim 2) protocols in male and female EFAD mice. To meet the ambitious goal set by the Department of Health to prevent or effectively treat of AD by 2025 requires novel therapeutic candidates to target mechanism(s) of APOE4-induced AD risk. This R21 tests such a therapeutic through the preclinical repurposing of CogPep B in the AD-relevant EFAD mice. From a drug discovery standpoint, the repurposing of CogPep B will facilitate successful translation to clinical trials, n alternative safer than current nuclear receptor agonists.

Further information available at:

Types:
Investments < €500k

Member States:
United States of America

Diseases:
N/A

Years:
2016

Database Categories:
N/A

Database Tags:

N/A