Novel Strategies and Mechanisms to Target APOE and Alzheimers Disease

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USA

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Novel Strategies and Mechanisms to Target APOE and Alzheimers Disease

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3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

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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

Research Abstract

DESCRIPTION (provided by applicant): APOE genotype is by orders of magnitude the strongest genetic risk factor for late-onset Alzheimer's disease (AD). The ?4 allele increases risk of AD by ~ 3.7 fold and 2 copies ~ 12 fold; the ?2 allele decreases risk by ~ 50%. Evidence strongly suggests that a major reason underlying these effects is related to the ability of the apoE protein to interact with the amyloid-ß (Aß) peptide and in an isoform-dependent fashion influence Aß clearance and aggregation. ApoE may also influence brain function and dysfunction via additional mechanisms such as influencing synaptic/network activity and lipid metabolism. It is not yet clear how to target apoE biology to develop therapeutic strategies. Our preliminary data suggest the hypothesis that apoE4, when present in the brain interstitial fluid (ISF), reduces Aß clearance and enhances Aß oligomerization/fibrillization, as well as synaptic damage. Increasing apoE2, E3, and E4 via gene delivery methods decreases, is neutral, or increases Aß aggregation and its associated toxicity. Decreasing the amount of toxic apoE/Aß complexes might serve as a therapeutic approach. In fact, our preliminary data utilizing monoclonal antibodies to apoE shows strong effects of decreasing Aß pathology and improving brain network function possibly via microglial-mediated clearance of Aß aggregates. We hypothesize that 1) decreasing Aß aggregation and toxicity may be possible by increasing apoE2 levels in the ISF of the brain; 2) targeting apoE/Aß aggregates with anti-apoE antibodies may serve as a potential therapeutic approach; and 3) that apoE in the ISF and at the synapse may play important non-Aß related functions, which will be critical to understand in the context of any therapeutics based on an apoE mechanism. The specific aims are: 1) To determine whether altering apoE isoform level in specific compartments in the brain influences Aß pathology and associated Aß-dependent brain dysfunction in an isoform-specific and Aß-dependent manner. 2) To explore the effects of anti-apoE antibodies and their mechanism of action in human APP transgenic (Tg) mice expressing human apoE isoforms. 3) To explore potential effects of apoE isoforms on synaptic structure/network function in human apoE knockin mice, wild-type, and apoE knockout mice +/- Aß.

Lay Summary

PUBLIC HEALTH RELEVANCE: Alzheimer's disease is a major public health problem with no treatments that delay, slow, or prevent the disease. In this application, we are determining if we can target the major genetic risk factor for Alzheimer's disease, APOE, to enable new approaches to develop novel treatments.

Further information available at:

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Investments > €500k

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Alzheimer's disease & other dementias

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