BACE1 as a Therapeutic Target for Alzheimers Disease

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Country

USA

Title of project or programme

BACE1 as a Therapeutic Target for Alzheimers Disease

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NIH (NIA)

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€ 1,444,149.54

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01/09/2003

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14

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... Genetics... Neurodegenerative... Neurosciences... Translational Research

Research Abstract
DESCRIPTION (provided by applicant): BACE1 is the rate-limiting enzyme for Abeta generation

in Alzheimer’s disease (AD) and is a prime drug target. BACE1 inhibitor drugs have recently entered into clinical trials. However, the safety and efficacy of these agents are unknown. BACE1 deficient (BACE1-/-) mice exhibit neurological phenotypes, suggesting BACE1 inhibitors may incur mechanism-based toxicities. However, BACE1-/- phenotypes may reflect consequences of BACE1 deficiency during development, in which case BACE1 inhibitors may be free of side effects. Even more uncertain is the stage of AD at which BACE1 inhibition would be most efficacious. This R01 will address three questions that are critical for the development of safe, effective BACE1 inhibitors for AD: 1) Is BACE1 required in the adult, or dispensable after development? 2) Does developmental compensation occur in BACE1-/- mice, preventing BACE1 null phenotypes that would otherwise appear in the adult? 3) At what stage of AD will BACE1 inhibitor drugs be most effective: before (prevention) or after (treatment) symptom onset? To address these questions, we have generated conditional BACE1 knockout (BACE1fl/fl) mice. In Aim 1, we will determine whether BACE1 gene inactivation in the adult causes neurological phenotypes that are observed in BACE1-/- mice. BACE1fl/fl mice will be bred with CamKII¿-iCre mice to inactivate BACE1 in excitatory neurons of the adult forebrain. In Aim 2, we will determine whether BACE1 gene inactivation in the adult produces novel BACE1 null phenotypes in the nervous system and periphery. BACE1fl/fl mice will be bred with R26-cre-ERT2 mice to inactivate BACE1 globally following administration of tamoxifen. In Aim 3, we will determine whether BACE1 gene inactivation in the adult will reduce amyloid burden after the start of plaque deposition. BACE1fl/fl; R26-cre-ERT2 mice will be bred with APPswe/PS1deltaE9 amyloid plaque model mice to inactivate BACE1 globally following administration of tamoxifen. For all Aims, mice will be aged and analyzed for behavior, electrophysiology, histology, and biochemistry. In addition, Aim 3 mice will be analyzed for amyloid plaque load and Abeta levels. Together, these Aims will determine the overall utility of BACE1 inhibition as an AD therapeutic strategy in terms of its potential side effect profile and efficacy.

Lay Summary
PUBLIC HEALTH RELEVANCE: Alzheimer’s disease (AD) is an intractable neurodegenerative disorder with no disease-modifying therapy. BACE1 inhibitors are currently in clinical trials for AD, but the safety and efficacy of these agents are unknown. This application will determine the overall utility of BACE1 inhibition as a therapeutic strategy in terms of its potential side effect profile and efficacy for AD.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

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