

A NOVEL NEUROPROTECTIVE THERAPY FOR ALZHEIMER'S DISEASE

<https://neurodegenerationresearch.eu/survey/a-novel-neuroprotective-therapy-for-alzheimer%c2%92s-disease/>

Principal Investigators

ABRAHAM, MENACHEM

Institution

KLOGENE THERAPEUTICS, INC.

Contact information of lead PI

Country

USA

Title of project or programme

A NOVEL NEUROPROTECTIVE THERAPY FOR ALZHEIMER'S DISEASE

Source of funding information

NIH (NIA)

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01/06/2016

Total duration of award in years

1

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)... Behavioral and Social Science... Biotechnology... Brain Disorders... Dementia... Genetics... Neurodegenerative... Neurosciences... Translational Research

Research Abstract

? DESCRIPTION (provided by applicant): Alzheimer's disease (AD) is one of the most significant public health problems of the 21st century with the number of patients in the US estimated to grow from 5 million to 15 million by 2050, and an annual cost of care projected to reach \$1.1 trillion. Current treatments for AD have limited effect for a short duration, and only serve to alleviate symptoms and do not treat the underlying causes of disease. There is a pressing need to develop better therapies to relieve the cognitive impairments of the disease and delay/eliminate the need for the institutionalization of AD patients. The goal of the proposed studies is to test novel neuroprotective compounds that increase the expression of the Klotho gene and demonstrate significant cognitive improvement in animal models of AD. Loss of Klotho accelerates the development of aging-like phenotypes, including cognitive deficits, while its overexpression in mice prolongs lifespan and improves cognition. We have reported that the levels of Klotho in the brain decrease with age across species. We have further shown that: 1) pretreatment with Klotho is able to rescue primary hippocampal neurons from amyloid- β (A β) and glutamate toxicity; 2) Klotho induces oligodendrocyte differentiation and remyelination; and 3) elevating levels of Klotho enhances cognitive functions in mice, and synaptic and cognitive impairments can be prevented in the presence of A β in a transgenic mouse model that simulates key aspects of AD. These results suggested that boosting Klotho protein levels in the brain would protect it from A β and other toxic insults and prevent cognitive deterioration. As demonstration of the feasibility of this approach, a high throughput screen was conducted for small molecules that elevated Klotho expression and a series of compounds was identified that are able to penetrate the BBB and stimulate the production of Klotho within the brain. These compounds are non-polar and fulfill Lipinski's rule of 5. These drugs aim to prevent and reverse the pathogenic effects of elevated A β levels in the brain. In this Direct to Phase II proposal, Klogene Therapeutics will evaluate our top three compounds in order to determine which one would be most suitable for cognitive tests in an AD mouse model. We propose to characterize these compounds using in vitro ADMET assays, PK, and in vivo testing to determine the pharmacodynamic effect in the brain. We will choose a lead candidate and scale up compound production to perform cognitive testing in an AD mouse model. The expectation is that AD mice treated with the compound would have significant cognitive improvement. In parallel, we will identify backup compounds with potentially improved characteristics. At the successful conclusion of this Phase II SBIR, we will be poised to move forward into IND-enabling studies to support human clinical trials. The proposed studies will help bring a novel therapy to patients to treat the underlying mechanisms of AD.

Lay Summary

PUBLIC HEALTH RELEVANCE: Our aging population faces near epidemic proportions of cognitive loss from Alzheimer's disease (AD), multi- infarct dementia, fronto-temporal dementia and ""normal"" cognitive loss associated with aging; 5.3 Million people suffer from AD in the US alone, resulting in over \$200 billion in annual cost. Amyloid clearing strategies have been pursued for many years by the biotech industry but so far have not resulted in a drug. There is an urgent need to identify novel and effective therapeutic approaches. Klogene Therapeutics' neuroprotective strategy, which is based on boosting the levels of the Klotho protein in the brain, is such an approach.

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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