Nomethiazoles harnessing GABA and NO mimetic activity for Alzheimers therapy

https://www.neurodegenerationresearch.eu/survey/nomethiazoles-harnessing-gaba-and-no-mimetic-activity-for-alzheimers-therapy/

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Country

USA

Title of project or programme

Nomethiazoles harnessing GABA and NO mimetic activity for Alzheimers therapy

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NIH (NIA)

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30/09/2016

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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)... Biotechnology... Brain Disorders... Dementia... Neurodegenerative... Neurosciences... Translational Research... Women's Health for IC Use

Research Abstract

? DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) occurs in one out of eight Americans of age 65 and affects 43% of the elderly over 85. Current FDA-approved drugs provide short-term symptomatic relief of AD. There is a pressing need to discover new disease-modifying medications. AD is multifactorial in origin and progression. A drug attenuating several underlying factors is a preferred therapy for AD. Nomethiazoles are a class of small molecules that address synaptic dysfunction through NO/cGMP signaling and harness the neuroprotective and GABA-mimetic activities of a methylthiazole (MZ) pharmacophore. Activation of the NO/cGMP/CREB signaling pathway, essential for learning and memory, is known to be attenuated in AD brains; whereas, the MZ pharmacophore provides neuroprotection against neuronal loss and has anti-inflammatory actions in the brain. Preliminary data show that nomethiazoles reverse cognitive deficits, slow Aß accumulation, and provide a positive biomarker profile in AD transgenic mouse models. We have: positive data on the prototype nomethiazole in four different AD mouse models; a U01-funded drug discovery project that yielded 4 candidate 2nd generation nomethiazoles; and STTR Phase 1 data indicating improved pharmacokinetic properties of 2 of these candidates. The objective of this Phase 2 proposal is to de-risk and select one drug candidate for future full IND-enabling studies. In Aims 1 and 2, two advanced mouse models of AD will be used to select the preferred nomethiazole and to provide a unique spectrum of preclinical animal efficacy data: 1) E4FAD a transgenic mouse model of familial AD, incorporating human apoE4, the major genetic risk factor for AD, which increases risk 20-fold and is biased against women; and 2) an accelerated oxidative stress model of age-related AD that manifests age-dependent hallmark AD biomarkers, neuronal loss, and cognitive decline. In Aim 1, rescue and reversal of cognitive decline will be studied in these models. In Aim 2, quantitative biomarkers will be measured of target engagement, attenuation of AD hallmark pathology and inflammation, and rescue of synaptic and neuronal function. In Aim 3, drug scale-up, selected rodent pharmacokinetics, toxicology, and safety pharmacology will be studied to de-risk full IND studies. Completion of Aims 1&2 and Aim 3 will provide persuasive evidence of prospective efficacy and safety, respectively.

Lay Summary

PUBLIC HEALTH RELEVANCE: Alzheimer’s disease (AD) occurs in one out of eight Americans of age 65 and affects 43% of the elderly over 85. Current FDA-approved drugs provide short-term symptomatic relief of AD. The proposed research will lead to development of new disease-modifying medications.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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