Novel bivalent multifunctional ligands towards Alzheimers disease

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Country

USA

Title of project or programme

Novel bivalent multifunctional ligands towards Alzheimers disease

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NIH (NIA)

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01/08/2012

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5

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... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is a devastating neurodegenerative disorder and the leading cause of dementia. Emerging evidence has recognized small, soluble oligomers of amyloid-?-peptide (A?Os) as the major toxic species for cognition impairment in AD. Furthermore, evidence has been accumulating that oxidative stress, biometal dyshomeostasis, and neuroinflammation may also contribute to the pathology of AD. Numerous small molecules targeting each of these risk factors have been developed and tested in preclinical and clinical trials, however, none of them has been approved by FDA as AD-modifying agents. This may suggest that one of the alternative and promising strategies is to use multifunctional ligands to tackle these risk factors simultaneously. Furthermore, evidence has increasingly underscored the important roles of cell membrane/lipid rafts (CM/LR) in the pathology of AD and CM/LR have been implicated to associate with all the identified risk factors in AD. This indicates that this relationship can be exploited therapeutically to develop strategic distinct multifunctional agents by incorporating this factor into molecular design. The overall goa of this proposal is to validate and develop more potent bivalent multifunctional A? oligomerization inhibitors (BMAOIs) that contain a multifunctional A?O-inhibitor with intrinsic antioxidant/metal chelating functions and a CM/LR anchor moiety as lead compounds for further preclinical studies. The central hypothesis of this application is that these BMAOIs will anchor the multifunctional A?O-inhibitor moiety inside, or in the vicinity of, CM/LR where A? oligomerization, Ab/biometal interactions, and oxidative stress occur to increase its local concentration and accessibility, thus enhancing its efficiency. Preliminary studies in our laboratory have reached the proof-of- concept of the BMAOIs strategy and resulted in the identification of two promising lead compounds for further optimization. Three specific aims are proposed to achieve our objective in this application. In aim 1, a series of BMAOIs will be designed and synthesized based on the newly identified lead compounds to modify and optimize the spacer domain, CM/LR anchor domain and A?O-inhibitor domain. In aim 2, the designed BMAOIs will be evaluated in various in vitro assays including inhibition of A?O formation in association with protective activity in human neuroblastoma MC65 cells as well as neuroprotective effects on differentiated SH-SY5Y and mouse primary neurons. The co-localization of BMAOIs with CM/LR will also be investigated in MC65 cells and mouse primary neurons. In addition, antioxidant and metal complexation properties of selected BMAOIs will be tested. In aim 3, potent BMAOIs that passed the selection criteria of aim 2 will be evaluated for their effects on cognition and A? pathology in transgenic TgCRND8 mice. The proposed research is innovative because we seek a new class of BMAOIs targeting A?Os, oxidative stress, A?/biometal interactions and CM/LR as novel pharmacological tools and potential AD-modifying agents. The outcome of this study would be a novel, validated, BMAOIs strategy available and ultimately benefit pharmacotherapy for AD.

Lay Summary

Alzheimer’s disease (AD) is a devastating neurodegenerative disorder and the leading cause of dementia that places enormous social, economic and medical burdens to our society. The research proposed in this application will validate and provide novel bivalent multifunctional A? oligomerization inhibitors as a strategically distinct intervention for AD patients, therefore it is relevant to public health.

Further information available at:

Types:

Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

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2016

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