GABA-A alpha-5 agonists for the treatment of amnestic Mild Cognitive Impairment

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Country

USA

Title of project or programme

GABA-A alpha-5 agonists for the treatment of amnestic Mild Cognitive Impairment

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 2,109,471.56

Start date of award

15/01/2012

Total duration of award in years

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... Translational Research

Research Abstract

DESCRIPTION (provided by applicant): The overall objective of this U01 application is to develop an orally active, optimized lead compound for the treatment of amnestic mild cognitive impairment (aMCI). The proposed therapy is based on the observation that memory loss in aMCI, a borderline condition between normal aging and Alzheimer's Disease (AD), is associated with excess activity in the CA3/dentate gyrus (DG) region of the hippocampus. Reducing excess activity, or normalizing it, is expected to improve memory in these patients. Preclinical studies in an animal model of this condition, in which hippocampal CAS neurons are hyperactive in aged rats with memory loss, demonstrates that selective GABAA ?5 receptor agonists are effective therapeutic agents to improve memory. We have identified several different chemical series that are selective for GABAA ?5 receptors. Compounds within these series were originally developed by large pharmaceutical companies to optimize inverse agonist activity with the objective of improving cognition. This approach was not efficacious in the clinic; indeed the science supporting our proposed work would predict that such an approach would fail. Still these chemical series have drug like properties that provide a starting point for optimization of selective ?5 receptor agonists. Under the specific aims we will use established in vitro assays in a medicinal chemistry program to optimize selectivity and agonist efficacy for GABAA ?5 subunit containing receptors and conduct early ADME and toxicology work to determine suitability for administration to animals. In vivo studies will then be performed in an animal model of memory loss in aging that mirrors many features observed in aged humans, particularly aMCI. Companion studies to determine in vivo receptor occupancy using multiple tracers with liquid chromatography coupled to tandem mass spectral detection (LC/MS/MS) will also be conducted to validate engagement of target GABAA ?5 receptors, as well as selectivity for that receptor subtype, at doses that are behaviorally efficacious. In the final phase of the project we will complete all materials, including pharmacokinetics and toxicology, good manufacturing practice (GMP) synthesis and formulation for lead GABAA ?5 receptor agonist filing with the FDA.

Lay Summary

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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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