Lead optimization of somatostatin-based therapeutic for Alzheimers Disease

https://neurodegenerationresearch.eu/survey/lead-optimization-of-somatostatin-based-therapeutic-for-alzheimers-disease/

Principal Investigators

WITT, KEN A

Institution

SOUTHERN ILLINOIS UNIV AT EDWARDSVILLE

Contact information of lead PI
Country

USA

Title of project or programme

Lead optimization of somatostatin-based therapeutic for Alzheimers Disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 2,431,797.25

Start date of award

15/06/2015

Total duration of award in years

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

Research Abstract

? DESCRIPTION (provided by applicant): The goal of this proposal is to advance an orally bioavailable first-in-class somatostatin receptor subtype-4 selective drug candidate with disease-modifying attributes for the treatment of Alzheimer’s disease (AD). The “”hit”” compound has been validated to enhance learning and memory in mouse models of AD and cognitive decline, with a reduction of beta-amyloid (Aß) oligomer levels within the brain. Our program has now advanced to lead optimization, which is accomplished through enhancement of “”drug-like”” properties of the lead series in tandem with well-defined advancement criteria, respective to modeling, in vitro screens and in vivo/ex vivo validation. This study will be accomplished via three specific aims. Based on outcomes within each aim, additional design adjustments and testing may be performed. Aim-1: Design and synthesis. Rational drug design strategies employing iterative in silico modeling, synthesis, and structure-activity relationship (SAR) studies will be conducted to enhance potency and selectivity, reduce potential toxicity, and enhance physiochemical properties for oral bioavailability. Synthetic methods will be further developed and applied to iterative and parallel medicinal chemistry where appropriate. Aim-2: In vitro screens. Using established in vitro methods, critical properties (i.e. solubility, receptor affinity and selectivity, activity, plasma binding, stability, permeability, and toxicity potential will be assessed in a sequential manner to delineate compound viability. Aim-3: In vivo/ex vivo assessments. Compounds meeting necessary criteria will be advanced to pharmacokinetic evaluations (i.v. and p.o.) for further delineation and identification of a primary lead. This lead will be tested via chronic p.o. administration in the 3xTg mouse model of AD at age-dependent intervals that coincide with critical periods of neuropathological development and learning/memory decline. Dosing range will be determined from pharmacokinetic data. Delineation of lead compound impact on learning and memory will be assessed via Morris water-maze, T-maze, and object recognition testing. Following final behavioral testing, cortical and hippocampal tissues will be evaluated to delineate changes in critical proteins/enzymes associated with AD pathology and proposed drug mechanism. This study will culminate in the advancement of a first-in-class AD drug candidate to the next stage of development. The aims of this study address priorities of National Institutes of Health, specific to drug discovery for nervous system disorders respective to drug-candidate lead optimization: FOA number: PAR-13-048.

Lay Summary

PUBLIC HEALTH RELEVANCE: Alzheimer’s disease (AD) is the most common neurodegenerative disorder in the elderly, affecting millions of people worldwide. Current medications have only modest clinical benefit and ultimately do not modify the course of the disease. The goal of this project is to advance a first-in-class orally bioavailable drug capable o mitigating AD pathology.

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

Database Tags:
N/A