Preclinical Alzheimers Disease Drug Development of Novel MAPK Inhibitors

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Country

USA

Title of project or programme

Preclinical Alzheimers Disease Drug Development of Novel MAPK Inhibitors

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 5,710,611.93

Start date of award

30/09/2012

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... Effectiveness Research... Neurodegenerative... Neurosciences... Translational Research

Research Abstract

DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is the sixth-leading cause of death in the United States, yet it is the only disease among the top 10 without a way to prevent, cure or slow its progression. AD kills more people than diabetes or breast cancer and prostate cancer combined. We hypothesize that AD is a progressive synaptic dysfunction disorder in which the glia-neuron axis is a key player and viable as a therapeutic development paradigm in the search for disease-modifying therapeutics. Appropriate communication and interactions between neurons and glia are key to brain homeostasis, and these dynamics are perturbed in disease. Targeting stressor-induced changes in both glia and neurons that contribute to pathology offers the potential to attenuate disease progression mechanisms present in a diverse array of CNS disorders. Regardless of whether the mechanism is a direct causative one or a contributor to disease susceptibility and onset, small molecule modulators of the process would be a major step in development of therapeutic regimes that add to the armamentarium for intervention. This proposal is focused on the stress-related protein kinase p38? MAPK, a key node in the signal transduction cascades of eukaryotic cells that amplify and transduce stress signals into physiological changes. The kinase is an established drug discovery target for diverse disorders, but only recently has become the focus of CNS drug discovery efforts. The increased pursuit of p38? MAPK as an AD target is due to a combination of landmarks, ranging from the demonstration of kinase activation in human CNS diseases, outcomes from animal model studies, and the demonstration of feasibility for generating CNS-penetrant inhibitors that can improve outcomes in animal models. We propose to use a validated drug discovery engine that successfully delivered novel CNS small molecule drug candidates that progressed to the same IND goal as this proposal and went through first-inhuman phase 1 studies with no adverse events. The specific aims for this project are: Aim 1. Optimize a second-generation inhibitor, MW01-10-181SRM, in order to improve non-GLP ADMET-related properties with retention of target activity, selectivity and in vivo function such that a single candidate can be prioritized for GLP IND-enabling evaluation. Aim 2. Perform GLP preclinical evaluation of a best-in-class candidate compound in order to generate an IND. Aim 3. Submit application for a new molecular entity IND to the FDA for phase 1 first-in-human clinical evaluation in future clinical development. Currently, there are no approved drugs that alter AD pathology progression, and no selective p38? MAPK inhibitor drugs in AD clinical trials (existing preclinical development efforts are focused on multi-kinase inhibitors). Therefore, the proposed development campaign will address scientific gaps in the field, and has the potential to yield novel small molecule candidates for first-in-human studies as deliverables.

Lay Summary

PUBLIC HEALTH RELEVANCE: The recent National Alzheimer’s Project Act (NAPA; Public Law 111-375) clearly defines the rapidly growing nature of the problem and requires a national plan in 2012. Campaigns initiated in 2013 will not reach a clear clinical outcome until 2020 or later, with reduction to standard clinical practice being post-2020 based on timeline precedents in drug development, clinical trial phases, and regulatory approval. The proposed campaign, if initiated within the coming year, falls well within this timeline and offers the potential for new molecular entity (NME) entry into the multi-drug arsenal needed to delay onset, slow progression, and treat existing AD across the long timeline of disease progression

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