Orally-absorbed, small molecule microtubule-stabilizers for tauopathy treatment

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Contact information of lead PI
Country

USA

Title of project or programme

Orally-absorbed, small molecule microtubule-stabilizers for tauopathy treatment

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 2,138,384.40

Start date of award

15/06/2013

Total duration of award in years

4

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease Related Dementias (ADRD)... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Dementia... Frontotemporal Dementia (FTD)... Neurodegenerative... Neurosciences... Translational Research

Research Abstract

DESCRIPTION (provided by applicant): Protein misfolding and aggregation comprise the underlying common pathological mechanism of many neurodegenerative disorders. In the case of tauopathies, a group of neurodegenerative diseases which include Alzheimer's disease and frontotemporal dementias, the hyperphosphorylation and aggregation of the microtubule (MT)-associated protein tau is believed to have pathological consequences via toxic gain and/or loss of functions. Recent studies from our laboratories have demonstrated that treatment with low weekly doses of the brain-penetrant MT-stabilizing agent, epothilone D (epoD), resulted in improved axonal transport, reduced axonal dystrophy and decreased neuronal pathology in tau transgenic (Tg) mice. These results thus suggest that compensation for the loss of tau MT-stabilizing function may be a viable therapeutic strategy for the treatment of tauopathies. However, epoD and related congeners have potentially significant deficiencies as drug candidates. Furthermore, epoD is the only example of a brain-penetrant MT-stabilizing agent that has undergone in vivo efficacy studies in tau Tg animal models. As a result, the development and evaluation of additional CNS-active MT-stabilizing agents is clearly desirable so as to identify alternative and improved clinical candidates. The focus of the proposed research plan is to investigate a related series of triazolopyrimidine, phenylpyrimidine, pyridopyridazine, pyridotriazine, and pyridazine MT-stabilizing compounds. After synthesis, compounds will be evaluated for MT-stabilizing activities, ADME-PK properties, and potential safety liabilities (Aim 1). The most promising MT-stabilizers (d15) found to be brain-penetrant and orally bioavailable will progress to an assessment of pharmacodynamic effect and acute toxicity (Aim 2), followed by longer-term 1-month safety assessments (Aim 3) to identify preferred candidates (1-2) that will undergo efficacy studies in an established Tg mouse model of tauopathy (Aim 4).

Lay Summary

PUBLIC HEALTH RELEVANCE: Several lines of investigation suggest that brain-penetrant microtubule (MT)-stabilizing agents hold considerable promise as potential treatment for Alzheimer's disease and related tauopathies. However, to date, only a single brain-penetrant MT-stabilizing agent, epothilone D (epoD), has been tested in a transgenic mouse model of tauopathy. Furthermore, epoD and related congeners have potentially significant deficiencies as drug candidates, including an intravenous route of administration, P-glycoprotein interactions, and relatively complex and expensive syntheses. Thus, the focus of the proposed research plan is to investigate a related series of triazolopyrimidine, phenylpyrimidine, pyridopyridazine, pyridotriazine, and pyridazine MT- stabilizing agents to identify alternative and improved clinical candidate(s). Given their MT-stabilizing activity, favorable physical-chemical properties and synthetic accessibility, these compounds hold considerable promise as lead structures for the development of CNS-directed MT-stabilizing therapies.

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