Modulation of the Innate Immune Response by Fisetin Derivatives for the Treatment of AD

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Country

USA

Title of project or programme

Modulation of the Innate Immune Response by Fisetin Derivatives for the Treatment of AD

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,376,145.87

Start date of award

01/08/2013

Total duration of award in years

2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

fisetin, Alzheimer's Disease, Immune response, neuroinflammation, Flavonoids

Research Abstract

? DESCRIPTION (provided by applicant): There are currently no drugs or other therapeutic interventions that can reverse or halt the progression of Alzheimer’s disease (AD). Age is by far

the greatest risk factor for AD, and it is known from studies in both mice and humans that neuroinflammation is increased with old age and to an even greater extent in AD. Therefore, a drug that could reduce neuroinflammation and at the same time be neuroprotective would have an excellent chance in the clinic. To address this problem, we have devised a drug discovery program based upon a unique set of phenotypic screens for the toxicities to cortical neurons that occur with old age in combination with assays of anti-inflammatory activity. Our initial studies using this approach led to the identification of a molecule that modulates neuroinflammation in ways that are beneficial for altering AD progression. This is the flavonoid fisetin which our cell and animal studies have demonstrated inhibits multiple pro-inflammatory pathways. Fisetin, a rare natural flavonoid, was initially identified in the Maher laboratory as an orally active, novel neuroprotective and cognition-enhancing molecule. Fisetin protects nerve cells from multiple toxic insults and is therapeutically active in rigorous rodent models for memory, rabbit and mouse models for ischemic stroke, mouse and fly models of Huntington's disease and in transgenic AD mice. A series of much more potent fisetin derivatives, many of which maintain in vitro anti-inflammatory activity, was synthesized by SAR- driven iterative chemistry. Importantly, the derivatives do not suffer from the intellectual property challenges of the natural product fisetin and are covered under several pending patents held by the Salk Institute. From the 160 derivatives synthesized, we selected the best seven derivatives that maintain the biological activities of fisetin, including its anti-inflammatory activity, and furthe screened them in multiple assays relevant to neuroinflammation. In addition, pharmacokinetic studies were done to identify the derivatives with the best oral bioavailability and brain penetrance. Based on these studies, the best two derivatives were then tested in a stringent reversal paradigm in old symptomatic AD mice where CMS121 was found to be effective at reversing the AD phenotype. We now propose to advance CMS121 as a modulator of neuroinflammation and a clinical candidate for the treatment of AD. Specifically, we plan to (1) Test CMS121 in a novel model of old age- associated sporadic AD that accounts for 99% of the cases looking at both behavioral and biochemical changes with a focus on neuroinflammation; (2) Identify the biological target(s) of CMS121 and (3) Identify the key metabolites of CMS121 and conduct preliminary toxicology studies. The overall goal of the research described in this application is to obtain sufficient information about CMS121 to limit the risk of the expensive formal toxicology study needed for IND approval as well as provide the necessary information to increase the efficiency of these studies.

Lay Summary
PUBLIC HEALTH RELEVANCE: Currently there are no drugs that can prevent, slow or stop the progression of Alzheimer's disease. We propose to develop a novel compound that is both neuroprotective and able to harness the good aspects of the brain's immune system in order to prevent the loss of brain function in Alzheimer's disease. If successful, this approach could prove beneficial for the treatment not only of Alzheimer's disease but also a number of other age-related neurological disorders.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:

Alzheimer's disease & other dementias

Years:
2016

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