Development of EP2 receptor antagonists for suppression of Alzheimers neuropathology

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USA

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Development of EP2 receptor antagonists for suppression of Alzheimers neuropathology

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1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

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

Research Abstract

Lay Summary Alzheimer’s disease (AD), a neurodegenerative disorder, is a leading cause of dementia in elderly. AD leads to progressive loss of cognitive functions. Currently about 5.4 million Americans (1 in 8 persons 65 or older) are living with AD, and the number is expected to triple by the year 2050. Approximately $200 billion per year is spent on all aspects of caring for AD patients, yet there is no therapy on the horizon that clearly alters the disease progression and inevitable cognitive decline. The small molecule drugs that have been developed based on amyloid cascade hypothesis have not shown a clear clinical benefit so far. Thus it would be very important to focus on identification of novel drug targets and small molecules that work through novel mode of biological action for future AD therapy. COX-2 levels are increased at the early stage of AD, and its levels are correlated with levels of A?-peptides. Clinical studies suggest that COX-2 inhibitors may be useful as preventative for AD if they were given at asymptomatic stage of the disease, but they may offer little or no benefit to clinically diagnosed patients with cognitive deficits. However, chronic use of COX-2 drugs (examples, Vioxx and Bextra) resulted in adverse cardiovascular events, which is worrying for the AD patients who already are at increased risk for heart disease. Thus, future use of COX-2 drugs on patients will be limited. COX-2 catalyzes the first-step towards synthesis of five prostaglandins; PGD2, PGE2, PGF2, PGI2, and TxA2, which activate eleven prostanoid receptors, DP1, DP2, EP1, EP2, EP3, EP4, FP?, ?, IP and TP?, ? respectively. We hypothesize that targeting EP2, a specific prostanoid receptor downstream of COX-2, rather than a generic block of the entire COX-2 signaling is a superior therapeutic strategy for AD with an EP2 specific antagonist. In this study, we propose to develop an EP2 selective antagonist, to demonstrate a proof of concept whether EP2 antagonist suppresses inflammation, neurodegeneration and cognitive deficits in 5XFAD model of AD, and to establish a preliminary safety package for using EP2 drugs potentially on AD patients.

Lay Summary
Narrative Alzheimer’s disease (AD) is associated with substantial medical and societal burden, but, no therapy that clearly alters the disease progression is currently available. Gene knockout studies indicate that prostanoid receptor EP2 exacerbates AD pathology in rodents. Thus, we propose to develop an EP2 inhibitor with an overall goal to suppress neuropathology and cognitive deficits in rodent models of AD and human patients.

Further information available at:

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Investments > €500k

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United States of America

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