Fyn Inhibition by AZD0530 for Alzheimers Disease

https://neurodegenerationresearch.eu/survey/fyn-inhibition-by-azd0530-for-alzheimers-disease/

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Country

USA

Title of project or programme

Fyn Inhibition by AZD0530 for Alzheimers Disease

Source of funding information

NIH (NIA)

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18/06/2013

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3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Alzheimer's Disease, fluorodeoxyglucose positron emission tomography, Cerebrospinal Fluid, tau Proteins, src-Family Kinases

Research Abstract

DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is a neurodegenerative condition with a massive health burden, but no therapeutic option to slow or halt progression. It

is estimated that up to 14 million Americans will suffer from AD by 2050, which, apart from the human cost, could have a catastrophic effect on our health care system and the broader economy. This application aims to assess the potential therapeutic benefit of AZD0530 (Saracatinib) for AD. AZD0530 is a selective inhibitor of Src family kinases, and has been developed primarily for the treatment of cancer. However, our data show that Fyn kinase, a member of the Src family kinases, also plays a fundamental role in the pathogenesis of AD. Multiple studies implicate Fyn kinase in the synaptic pathophysiology of AD, with links to both Aß and Tau pathology. For transgenic AD mice, genetic removal of Fyn kinase alleviates, and overexpression of Fyn exacerbates, the impairment of synaptic density and spatial memory. The A beta peptide is thought to trigger AD. Our work, confirmed and extended by others, showed that Cellular Prion Protein (PrPC) acts as a toxic Aß oligomer receptor. Downstream signaling from the A beta-PrPC complex is of major interest, as it might provide for a selective therapeutic target in AD. Recently, engagement of PrPC by A beta was found to activate Fyn kinase, initiating a detrimental signaling cascade with synaptic dysfunction. These data provide a direct mechanistic link between A beta and Fyn kinase in AD. In addition, Fyn kinase interacts directly with Tau, and the synaptic function of Fyn requires dendritic Tau. We hypothesize that blocking Fyn kinase is an effective therapeutic strategy in AD. AZD0530 safely inhibits Src family kinases, including Fyn, with high potency in humans. This application will validate the predicted benefit of AZD0530 in a mouse model of AD while measuring pharmacodynamic parameters, and initiate clinical trials. A Phase 1b trial will determine cerebrospinal fluid drug levels in AZD0530-treated human AD subjects and confirm safety and tolerability. Achievement of milestones for the preclinical and clinical Phase 1 studies will support the initiation of a Phase 2a proof-of concept clinical trial. A total of 159 patients will be studied in a 12-month, double-blind randomized placebo-controlled trial of AZD0530 in mild Alzheimer’s disease. The primary outcome measures will include the slowing of a decline in regional brain glucose metabolism as measured by 18F-FDG PET imaging (a validated surrogate marker for clinical progression in AD), as well as assessments of safety and tolerability. Secondary outcomes will include standard clinical efficacy measures, rate of change in MRI volumes, and CSF total Tau and phospho-Tau. The goal of this project is to provide evidence in support of a multi-center Phase 3 trial of AZD0530 in AD.

Lay Summary

PUBLIC HEALTH RELEVANCE (provided by applicant): Alzheimer’s disease is a devastating neurodegenerative disorder, for which there is currently no effective treatment to slow or halt progression. Beta amyloid peptide accumulates in the brains of those with Alzheimer’s, and is thought to play a major role in triggering the dementia. We recently characterized a molecular pathway by which ss-amyloid damages neurons, and showed that the protein termed Fyn kinase is crucial. Our data suggest that blocking Fyn will have a significant therapeutic benefit for Alzheimer’s. Astra Zeneca has developed a blocker of Fyn and related kinases (AZD0530) for the treatment of cancer. Chronic AZD0530 administration is well tolerated in humans, and we propose to test its potential as a novel Alzheimer’s disease modifying therapy.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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