IND- and NDA-enabling toxicology studies for PTI-125, a novel small molecule for Alzheimers disease

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Contact information of lead PI
Country

USA

Title of project or programme

IND- and NDA-enabling toxicology studies for PTI-125, a novel small molecule for Alzheimers disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,582,568.81

Start date of award

01/08/2015

Total duration of award in years

2

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)... Biotechnology... Brain Disorders...

Dementia... Neurodegenerative... Neurosciences... Prevention... Translational Research

Research Abstract
? DESCRIPTION (provided by applicant): PTI-125 is a novel compound with a novel target, designed to treat and slow the progression of Alzheimer's disease (AD). PTI-125 works by binding extremely tightly to a particular site on filamin A (FLNA), a protein we recently demonstrated to be critical to beta amyloid's toxicity. Beta amyloid1-42 (Aß42) exerts its toxic effects by binding and hijacking the a7-nicotinic acetylcholine receptor (a7nAChR), disrupting its normal function and causing the signature tangles and plaques found in brains of AD patients. We recently showed that this toxic signaling by Aß42 requires the help of FLNA, which is recruited to interact with a7nAChR when Aß42 binds this receptor. Aß42's toxic signaling via a7nAChR also impairs the function of two other receptors key to cognition, memory and neuronal survival, the NMDA receptor and the insulin receptor. By disrupting the FLNA – a7nAChR association, PTI-125 prevents Aß42's toxic effects and restores normal function of these three receptors. PTI-125 also disrupts a similar association of FLNA with toll-like receptor-4 (TLR-4), a receptor responsible for releasing inflammatory cytokines; hence, PTI-125 has a second function of blocking the inflammation noted in AD brain. PTI-125 has passed the Ames and hERG tests (non-GLP) for mutagenicity and cardiac toxicity, respectively. It easily passes the blood brain barrier, has an estimated 75% oral bioavailability and has a reasonable half-life for a drug candidate. It was safe given orally for two months in mice. We know the effective concentrations in brain from brain slice culture experiments. PTI- 125 is ready to start the proposed IND-enabling studies to ensure safety prior to a clinical trial. In this proposal, our Phase I work will include the non-GLP dose selection studies, more formal PK/ADME work, genotoxicity studies and the GLP validation of previously developed analytical and bioanalytical methods. Barring unexpected toxicity in a dose range close to the anticipated therapeutic dose, we will proceed to the Phase II scope of work: GLP safety pharmacology and both 4-week and chronic GLP toxicology studies that would support a first-in-human study as well as clinical trials in AD and an NDA.

Lay Summary
PUBLIC HEALTH RELEVANCE: There is currently no approved therapeutic for Alzheimer's disease (AD) that can slow or halt the course of the disease. PTI-125 is a novel compound has been shown to alleviate multiple pathological features of AD in a mouse model of the disease as well as in postmortem brain tissue from AD patients, including receptor dysfunctions, inflammation, and the hallmark plaques and tangles. In this proposal, we will complete the 4-week and chronic GLP toxicology studies to ensure safety for a first-in-human clinical trial of PTI-125 and to support clinical trials in AD and an eventual new drug application (NDA).

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