Development of a PET Tracer Selective for Cerebral Amyloid Angiopathy

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Country

USA

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Development of a PET Tracer Selective for Cerebral Amyloid Angiopathy

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NIH (NIA)

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1

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... Cerebrovascular... Dementia... Diagnostic Radiology... Neurodegenerative... Neurosciences... Rare Diseases... Vascular Cognitive Impairment/Dementia

Research Abstract
? DESCRIPTION (provided by applicant): Positron emission tomography (PET) imaging of hallmark amyloid pathology can facilitate clinical diagnosis of Alzheimer's disease (AD). Our research group at the University of Pittsburgh pioneered development of amyloid-binding PET radioligands by careful preclinical characterization of the Thioflavin-T analog Pittsburgh Compound-B (PiB). Though PiB and longer-lived F-18-labeled A?-selective analogs have transformed the field by allowing in vivo detection and monitoring of fibrillar amyloid-? (A?) deposits, this technique cannot distinguish between A? deposits in brain parenchymal plaques and in blood vessels with cerebral amyloid angiopathy (CAA), which can co-occur in AD brains. Detecting CAA selectively has important implications for AD treatment management and efficacy, because CAA increases the risk of cerebral microhemorrhages which are a side effect of many experimental and promising AD therapies. The objective of this proposal is to develop a novel method to selectively image A?-containing CAA in cerebral blood vessels, for use in future clinical trials. Our preliminary studies identified several promising candidate compounds from a panel of analogues of the amyloid-binding dye Congo red (CR). We intend to modify these compounds, aiming to optimize their selectivity for CAA, and to test the most promising compounds in the transgenic APP/PS mouse model which recapitulates AD-defining amyloid plaque pathology as well as CAA. Guided by the lead compounds from our pilot studies, we will synthesize a wide range of novel CR analogues with moderate lipophilicity, and determine their binding affinities to fibrillar A? using in vitro binding assays (Aim 1). We are experienced with he chemistry and pharmacology of CR dyes, and have a long, successful history of synthesizing and testing hundreds during the development of PiB and during our preliminary studies of CAA-selective compound candidates. The second major goal of our proposal is to inject these compounds in living APP/PS mice, to assess compound selectivity for CAA vs. parenchymal plaques in ex-vivo histological analyses (Aim 2). In parallel, we will use in-vivo multiphoton microscopy to evaluate further our lead compounds' selectivity for CAA and characterize their brain kinetics in living APP/PS mice (Aim 3). Best candidate CAA-selective compounds will be subsequently radiolabeled and injected in APP/PS mice at nanomolar concentration, as in human PET studies, followed by ex-vivo autoradiography analyses to quantify positive autoradiography signal in CAA vs. parenchymal plaques (Aim 4). Successful completion of these studies will provide novel CAA-selective compounds which can be radiolabeled for use in future PET imaging studies in living people, as a valuable tool to aid in diagnosis and selection of subjects for clinical trials, and to evaluate effects of therapies.

Lay Summary
PUBLIC HEALTH RELEVANCE: We propose to design, produce, and characterize novel compounds for labeling toxic deposits of amyloid-beta peptide in brain blood vessels, for use in future imaging studies in living patients. We will use a mouse model with amyloid-beta deposits in the brain, similar to those in humans with Alzheimer's disease, to test each compound's selectivity for deposits in blood vessels versus deposits in amyloid-beta plaques.

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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