NOVEL PET TRACERS FOR IMAGING OF ALZHEIMERS DISEASE

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NOVEL PET TRACERS FOR IMAGING OF ALZHEIMERS DISEASE

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2

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Alzheimer's disease & other dementias

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Research Abstract

? DESCRIPTION (provided by applicant): Several lines of investigations indicate that amyloid

formation precedes decades prior to beginning of neurodegeneration phase, and the presence of senile plaques (SPs) and neurofibrillary tangles (NFTs) in nondemented older adults could represent an earlier manifestation of AD prior to its clinical expression. To further embellish diagnostic nuclear medicine imaging resources, 18F-Avid-45,18F-Flutemetamol, and 18F-Florbetaben have recently gained FDA approval for A? imaging. Among these agents, 11C-PIB continues to be the most thoroughly investigated PET radiopharmaceutical for A? imaging. Recent reports indicate that 11C-PIB could not detect cerebral A? in a patient confirmed via clinical, cognitive, and cerebrospinal fluid biomarkers of AD, thus raising further concerns for sensitivity of PIB and other agents to detect AD variants characterized predominantly by diffuse A? plaques. Additionally, recent clinicopathological studies of PD patients have also indicated limitations of PIB imaging to differentiate PD patients with or without dementia, despite the presence of abundant A? in brains of those patients. To further supplement armamentarium of promising PET A? imaging agents, an easily accessible, efficient, highly specific 18F-PET agent and potentially capable of binding to both fibrillar and diffuse plaques, including the more dense sites on A? to enable high sensitivity for detection (at prodromal stages of the disease) would be highly desirable, and continues to be an unmet goal. To accomplish this objective, we have rationally designed a novel heterocyclic fluorescent molecule (18F-AI-187) from an entirely a new class of molecules that shows concentration dependent and saturable binding, with Kd values of 1.4±0.35nM and 2.9 ±1.35nM, to AD homogenates and preformed A?1-42 fibrils, respectively, the unlabeled fluorescent counterpart detects both fibrillar plaques and displays cerebral amyloid angiopathy (CAA) ex vivo in the hippocampus regions of brain sections in APPsw+/-/PS1 mice and also detects diffuse plaques, compact plaques, and vascular deposits (CAA) in human tissues. Further, the PET tracer 18F-AI-187 demonstrates an extremely high first pass extraction in brains (8.86 ± 0.32 %ID/g %ID/g; 2 min post tail-vein injection) of FVB mice, and followed by a washout (25% faster than 18F-Avid 45) in absence of targeted plaques. Compared with11C-PIB, 18F-Flutemetamol (metabolizes faster than 11C-PIB), and 18F-Avid45 that undergo facile metabolism in vivo, 18F-AI-187 remains non-metabolized in human serum. Therefore, the high first pass extraction into brains coupled with faster clearance from the blood pool and lack of metabolites offer critical characteristics that could enhance overall signal to background ratios and target specificity to assist image analysis. Preliminary multiphoton microscopy in live APPsw+/-/PS1 (15 months old) mice demonstrates that F-AI- 187 traverses blood brain barrier to instantaneously labels plaques in brain parenchyma and blood vessels (CAA), and plaques remain labeled for investigated time points. Preliminary, microPET/CT imaging shows higher brain uptake of the radiotracer (30 min post-tail-vein injection), and its retention in the cortex of transgenic mice compared with their age-matched Bl6 counterparts, consistent with the binding of the tracer to A? plaques. Finally and importantly, the agent is als highly specific for AD (displays no cross-reactivity with biomarkers of other neurodegenerative diseases); while also detecting diffuse and compact plaques in a PIB- A?+ AD case. Armed with this highly provocative data on our lead agent, now we propose to: 1) Perform complete pharmacokinetic analysis of 18F-AI-187 or the second generation of lead agents to determine their translational potential to serve as noninvasive A?-targeted probes in age-matched APPsw+/- transgenic mice (target specificity), WT counterparts (controls), and nonhuman primates (baseline SNR analysis) via evaluation of time-activity curves (TACs), using either microPET/CT or microPET/MR or PET/MR imaging, perform arterial metabolite analysis and dosimetry studies to identify highly specific imaging agents to advance translational leads into non-GMP-toxicology studies for eIND filing; 2) Perform focused SAR studies to develop second generation of novel heterocyclic molecules capable of detecting A? plaques in early stages of

AD prior to its clinical expression. 3) Perform complete biochemical characterization of second generation A?-targeted agents via multiple binding and competitive displacement assays for evaluation of targeted sites on A?, assess BBB permeability and ability to label plaques in parenchyma via biodistribution studies and 2-photon imaging, phosphorimaging studies in vitro, perform ex vivo binding studies of AD brain homogenates and human AD brain tissue sections, including specificity for A? compared with other biomarker proteins (tau, prion, TDP43,and ?-synclein) prevalent in other neurodegenerative diseases for determining target selectivity of second generation agents. Upon further biochemical validation, these novel molecular imaging agents could enable noninvasive PET interrogation of A? in patients at prodromal stages of AD, better guide stratification of AD patients from those of other neurodegenerative diseases, and assist analysis of the efficacy for new molecular-targeted disease-modifying therapies, thus overall assisting management of AD.

Lay Summary
PUBLIC HEALTH RELEVANCE: Several lines of investigations indicate that amyloid formation in Alzheimer’s disease (AD) precedes decades prior to beginning of the neurodegeneration phase. PET radiopharmaceuticals capable of detecting AD at prodromal stages can enable therapeutic interventions at earlier stages for better management of the disease. This project is focused upon a development of an ultrasensitive and a specific PET probe for noninvasive diagnosis of AD. The enclosed pilot data demonstrates extremely high penetration of a potent PET tracer in the brain, faster clearance from the blood pool as well as other non-targeted tissues in normal mice, and the agent labels plaques in brain parenchyma in live transgenic mice < 5 minutes post tail-vein injection. Preliminary microPET/CT imaging data also correlates with multiphoton imaging results in live transgenic mice. Finally, the agent is also specific for A compared with other neurodegenerative diseases. Successful execution of outlined objectives could enable deployment of an ultrasensitive PET tracer for imaging Aß, better guide stratification of AD patients from other neurodegenerative diseases, and assist in monitoring of effects of therapeutic drugs.

Further information available at:

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