Buck Institute Technology Summary

APP-selective BACE Inhibitors (ASBIs) for use in Alzheimer's Disease

Buck Institute Case No. BI-397.

Summary

Buck has synthesized and developed a family of **APP-selective BACE Inhibitors (ASBIs)** that have shown:

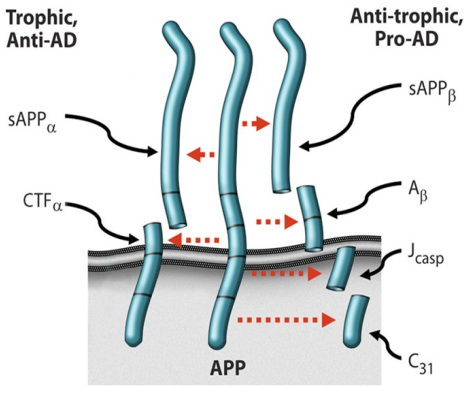
- Efficacy *in vivo*
- Selectivity for APP as shown by other BACE targets such as Neuregulin-1
- Blood brain barrier permeability

Background

Alzheimer's disease (AD) is a progressive neurodegenerative disease affecting one in eight Americans. It is the fifth leading cause of death for those ages 65 and older and the incidence is increasing in frequency with increasing population and life expectancy.

Although amyloid deposition in senile plaques is a hallmark of AD, it is synaptic loss and neuronal death that represent the functional basis of cognitive impairment. Neurodegeneration has been linked to amyloid precursor protein (APP) cleavage into four smaller cytotoxic peptides (Fig.1). Alternatively, APP can be cleaved into two smaller peptides; a trophic pathway resulting in neuroprotection, neurite growth, and synaptic maintenance (anti-AD). Shifting the directionality of this cleavage could favor synaptic maintenance and prevent the progression of AD.

Fig. 1



The first and rate-limiting step in the pro-amyloidogenic pathway (AD direction) cleavage of APP is through B-site APP cleavage enzyme-1 (BACE1). BACE1 cleavage of APP results in the release of sAPPβ into the extracelluar space. The remaining C-terminal fragment (CTF) undergoes further cleavage by γ-secretase, leading to the release of Aβ and C31/Jcasp via the APP intracellular C-terminal domain (AICD). Although BACE1 is a compelling target for AD treatment, multiple studies have demonstrated that inhibition of this enzyme leads to significant off-target pathology. Therefore, the optimal BACE inhibitor would be one that would bind to APP rather than BACE, leading to APP-specific BACE inhibition (ASBI).

The Technology

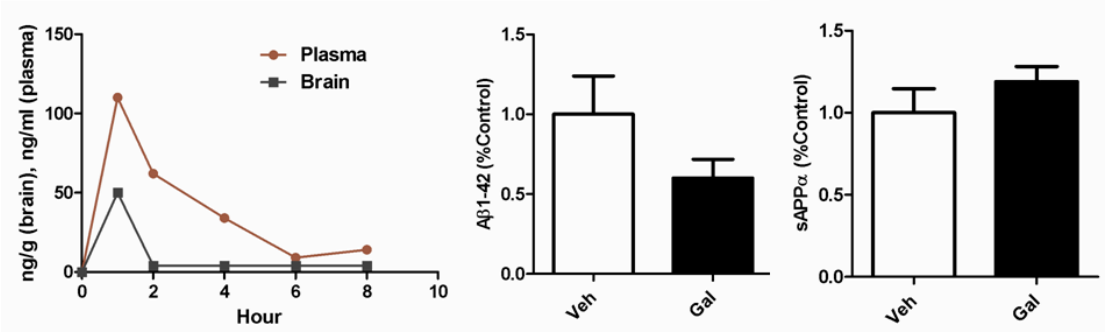
While there is a large drug discovery effort focused on development of direct BACE inhibitors, none so far have advanced significantly in clinical testing. The Bredesen laboratory at the Buck Institute has identified a chemical family of ASBI drugs and prodrugs. These inhibit APP pro-AD cleavage while also reducing off-target BACE1 inhibition effects.

Studies in the Bredesen Laboratory have demonstrated that their ASBI drug was able to lower sAPPα levels without changing APP levels in the SHSY-5Y neuroblastoma cell line. Subcutaneous administration of an ASBI drug to an AD mouse model showed that the drug could be detected in the brain (Fig 2A) and effectively decreased Aβ42 levels (Fig 2B).

Fig.2

A. ASBI drug crosses the BBB (10mg/kg, sub-Q)

B. ASBI drug decreases Aβ1-42 and increases sAPPα in combined hippocampus/cortex



These results in AD transgenic mice indicate that the ASBI drug was able to switch APP processing from the pro-AD pathway to the anti-AD, pro-trophic pathway. Furthermore, through medicinal chemistry the Bredesen laboratory has developed a prodrug, with the objective of further increasing ASBI drug brain levels. This prodrug is currently being tested. Additional ASBIs that are novel compounds are under development and look promising in mouse models.

Opportunity

Alzheimer's disease is an increasingly common and exceedingly costly neurodegenerative disease with no currently known effective treatment. The Buck Institute controls intellectual property for use of these ASBI drugs and prodrugs as therapeutics for AD and related neurodegenerative indications. The Buck seeks developmental partners who can collaborate and further develop these agents.

The Buck Institute is the only free-standing institute dedicated to aging and age-related research in the United States. We actively partner with industry to develop therapeutics, diagnostics or tools that make a difference. For more information on this or another technology or opportunity, please contact:

Carlotta Duncan, Ph.D
Business Development & Licensing Officer
Phone - 415-209-2000 x6728; cduncan@buckinstitute.org