Novel models with greater translational value have been recognized as being necessary for evaluating Alzheimer’s disease (AD) therapeutics. Here we describe several features of the aged dog that supports its value as a model of AD progression, and as a tool for rapid or longitudinal screening of novel AD therapeutics. The aging dog models aspects of both the pathophysiology and cognitive decline observed in Alzheimer’s disease’s progression. The current study assessed the effects of age and acute BACE inhibition on CSF amyloid in dogs.

**PAT pathophysiology**

Aged dogs exhibit both early amyloid-β and tau pathologies

Canine amyloid-β (Aβ) protein precursor shows approximately 96% homology to the human sequence and the protein is processed into Aβ isoforms that are analogous in pattern and identical in sequence to that seen in humans (Fig. 1).

Endogenous Aβ is naturally deposited into plaques of the diffuse subtype in aged dogs, which are vulnerable to post translational modification and are fibrillar in the ultrastructural level - cerebral amyloid angiopathy (CAA) is also found in aged dogs. The pattern of Aβ deposition parallels that seen in humans and occurs over a 3- to 4-year window permitting the examination of interventions that may slow or halt deposition (Fig. 2).

**COGNITION**

Aged dogs show domain specific and progressive cognitive decline

Aged dogs show cognitive impairment that is correlated with pathology and is domain specific, such as on measures of selective attention (Fig. 6).

**CSF biomarkers**

CSF Aβ42 decreases in Beagles consistent with that seen in conversion to AD (Fig. 7).

Intraneuronal hyperphosphorylated tau is also detected in aged dogs that is similar in some respects to the neurofibrillary tangle pathology seen in AD (Fig. 4).

**CONCLUSIONS**

1) The aged dog is a unique natural model of AD progression.
2) Aβ pathology in aged dogs shows similar deposition, identical protein isoforms and oligomeric forms as those seen in humans.
3) Additional pathology includes the development of tau-like pathology, increases in oxidative stress, neuronal loss, decreased neurogenesis, reduced neuronal health, cholinergic deficits and brain atrophy.
4) The pattern and progression of cognitive decline in translational neuropsychological tests are consistent with that seen in AD conversion.
5) Similar to subjects that convert from MCI to AD, Aβ42 in the CSF decreases and phospho-tau increases with advancing age in dogs.
6) Here we replicated the findings that CSF Aβ42 decreases with increasing age in dogs. Previous work has linked this decrease in CSF to deposition of amyloid plaques.
7) We also demonstrated that a BACE inhibitor acutely lowers CSF Aβ42, and that this is least robust in aged dogs, likely due to the relatively lower levels of CSF Aβ42 in this age group.
8) Collectively, this supports the use of aging dogs for examining disease modifying AD therapeutics. AD relevant biomarkers such as CSF Aβ42 and tau levels can be used to select target subject groups representing various stages of AD progression, which can then be examined longitudinally for establishing preclinical efficacy.

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