

**Title: Single domain antibody fragments reverse cognitive function deficits and restore memory in aged beagles**

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An active and promising area of research for Alzheimer’s disease (AD) is immunotherapy using antigens (active) or antibodies (passive) that target AD neuropathology. Senile plaques contain the beta-amyloid (Aβ) peptide that is derived from a longer precursor protein, amyloid precursor protein. Amyloid beta is produced as either a 40 or 42 amino acid peptide, the latter being more fibrillogenic and toxic than the shorter isoform. Initially produced as a soluble peptide, Aβ subsequently can form oligomers, a molecular complex of monomer units. Aβ oligomers are highly toxic to neurons and particularly damaging to synapses. There is strong evidence that oligomer accumulation may seed plaque aggregation and serves as an early molecular target for preventing AD. Interestingly, oligomers can be detected by antibodies based upon structure with less of a need to target the amino acid sequence of an individual protein making antibody development for oligomers a fascinating area to pursue. Antibodies developed against oligomers may be able to bind several misfolded proteins implicated in neurodegenerative diseases.

Immunotherapy studies have typically used transgenic mouse models of AD, and subsequently translated to human clinical trials. However, the success rate of these translational studies has been limited. In contrast, studies in another animal model, the aged canine, indicated that immunotherapy led to similar outcomes in AD clinical trials; reduced Aβ plaque pathology with no improvements in cognition but indications of a slowing of cognitive decline.

We have previously developped and chatacterized unique anti-Aβ single domain antibodies derived from camelids. These antibidies, we called PRIOAD, were able to (i) cross the in vitro and in vivo blood brain brain (BBB) in mice rats and in vitro human BBB model; (ii) bind with high affinity to soluble oligomers derived from synthetic and native human Aβ but not their monomeric and fibrils counterparts; and (iii) not induce neurotoxic effects and host mmune responses in mice.

PRIOADs were evaluated for their therapeutic efficacy in a pilot sutdy using aged beagles with mild cognitive imparement. Following intraventricular infusion of PRIOAD for 3 months, there was a significant reduction of Aβ plaque burden in these animals. More importanly, PRIOADs led to reversal of the cognitive deficits in beagles.

The study was very encouraging and will be expanded to include larger number of animal cohorts prior to translation into human clinical trials.

# Biography

Dr Tayebi is a Senior academic at the University of Melbourne and heads the protein misfolding disease group. Dr Tayebi has previously very successfully led to satrt up biotechnology companies in the UK and the US.

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