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Neuroprotective and Neurorestorative effects of disease-modifying single-domain Antibody fragments 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 (A β) 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, A β subsequently can form oligomers, a molecular complex of monomer units. A β 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 A β plaque pathology with no improvements in cognition but indications of a slowing of cognitive decline.

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

PRIOADs were evaluated for their therapeutic efficacy in a pilot study using aged beagles with mild cognitive impairment. Following intraventricular infusion of PRIOAD for 3 months, there was a significant reduction of A β plaque burden in these animals. More importantly, 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

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 startup biotechnology companies in the UK and the US.

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