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Single domain antibody fragments reverse cognitive function deficits and amyloid plaques in alzheimer's disease animal models

Mourad Tayebi

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 brillogenic 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. ere 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 mis-folded proteins implicated in neurodegenerative diseases. Immunotherapy studies have typically relied on the use of anti-Aβ antibodies targeting plaques in transgenic mouse models of AD, and subsequently translated to human clinical trials. However, the success rate of these translational studies has been limited. We have previously developed and characterized unique anti-Aβ single domain antibodies derived from camelids.

ese antibodies, 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 a nity to soluble oligomers derived from synthetic and native human Aβ but not their monomeric and brils counterparts; and (iii) not induce neurotoxic e ects and host immune responses in mice. PRIOADs were evaluated for their prophylactic and therapeutic e cacy in several AD animal models. Following a 2-weekly intraperitoneal administration of PRIOAD for 3 months, there was a signi cant reduction of Aβ plaque burden in these animals. More importantly, PRIOADs led to complete reversal of the cognitive de cits in these animals. e study was very encouraging and will be expanded to include larger number of animal cohorts prior to translation into human clinical trials.

Biography

Mourad Tayebi is a Professor of Biomedical Sciences and Director of Higher Degree Research at the School of Medicine, Western Sydney University. Mourad's research focuses on developing effective therapies and early diagnosis for Alzheimer's disease. Mourad's team developed novel therapeutics with the ability to transmigrate across the blood brain barrier and reverse cognitive deficits in animal models of Alzheimer's disease.

m.tayebi@westernsydney.edu.au

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