PASSIVE IMMUNIZATION WITH ANTIBODY TARGETING N-TERMINAL TRUNCATED TAU REVERSES NEUROPATHOLOGY AND COGNITIVE DEFICITS IN TWO PRECLINICAL MOUSE MODELS OF AD.

**Aims** Clinical and neuropathological studies have shown that tau pathology better correlates with the severity of dementia than amyloid plaque burden, making the targeting of tau more clinically relevant than Aβ-directed therapies for the cure of Alzheimer’s disease (AD).

**Methods** We have explored whether passive immunization with the 12A12mAb (26-36aa of tau protein; DRKD(25)-QGGYTMHQDQE epitopes phosphorylation independent state) could improve the AD phenotype of two well-established mouse models, Tg2576 and 3xTg mice. 12A12 is a cleavage-specific monoclonal antibody (mAb) which selectively binds the pathologically-relevant neurotoxic 20-22kDa NH2-derived tau peptide (i.e. NH2htau) of tau protein without cross-reacting with its full-length physiological form(s).

**Results** We found out that intravenous (i.v.) administration of 12A12mAb into symptomatic (6-month-old) animals: (i) selectively engages and successfully neutralizes its target without cross-reacting with physiological full-length form of tau; (ii) reduces both pathological tau and APP/Aβ metabolisms involved in early disease-associated synaptic deterioration; (iii) improves episodic-like type of learning/memory skills in hippocampal-based NOR and OPR behavioural tasks; (iv) relieves the loss in hippocampal dendritic spine density in pyramidal CA1 neurons; (vi) rescues the AD-related electrophysiological deficits in induction of hippocampal LTP (Long Term Potentiation) at the CA3-CA1 synapses; (vii) mitigates the neuroinflammatory response (reactive gliosis).

**Conclusions** These findings point to the NH2htau fragment as a crucial candidate target for AD therapy and prospect the humanized counterpart of murine 12A12mAb (Patent PCT060934 “Antibody directed against a tau-derived neurotoxic peptide and uses thereof” filing date: 27.04.2018) as beneficial in contrasting the early Aβ-dependent and independent neuropathological and cognitive alterations in affected subjects.


**Keywords:** Tau cleavage, immunotherapy, Alzheimer's Disease (AD)

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