LONG-TERM TREATMENT WITH A NEW ANTI-Oligomeric β-amyloid VACCINE MARKEDLY REDUCES BRAIN β-amyloid LOAD IN A TRANSGENIC MOUSE MODEL OF ALZHEIMER’S DISEASE

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Trx(Aβ15)4 is a new recombinant immunoconjugate antigen obtained by tandem multimerization of the 15-aminoacid N-terminal fragment of the β-amyloid peptide (Aβ) within the active site loop of bacterial thioredoxin. Administration of Trx(Aβ15)4 to BALB/c mice generates antibodies that selectively attack fibrillar and oligomeric Aβ, but not the physiological monomeric species of Aβ (1). When formulated with alum as immunoadjuvant, Trx(Aβ15)4 preferentially elicits a humoral anti-inflammatory Th-2 type immune response.

We evaluated the effects of Trx(Aβ15)4 on brain β-amyloid pathology in mice (Tg2576) transgenic for human amyloid precursor protein carrying a double mutation (K670N/M617L) linked to familial Alzheimer’s disease (AD). Thirteen 9-month-old Tg2576 mice received Trx(Aβ15)4 subcutaneously (100 nmoles/injection) with complete Freund’s adjuvant at Day 1 and additional injections with incomplete Freund’s at Week 2 and every 4 weeks thereafter for a total of 18 weeks. A control group of 13 age-matched Tg2576 mice was injected with vehicle only. The percent of brain area with Aβ plaques (Aβ-amyloid load) and the number of plaques in hippocampus and cerebral cortex were measured by immunohistochemistry using commercial anti-Aβ antibodies (6E10, Signet Laboratories). Images were obtained with a digital microscope colour camera (Nikon DS) and analysed with a dedicated software (NIS-Elements, Nikon).

At Week 12, there was a robust immune response in serum of Trx(Aβ15)4-treated animals with an anti-Aβ42 antibody titer exceeding 10 μg/mL in all animals. At the end of treatment (Week 18), β-amyloid load in Trx(Aβ15)4-treated animals was reduced, compared to vehicle-treated animals, by 93.0 ± 5.7% in hippocampus (p < 0.01) and by 66.0 ± 4.9% in cerebral cortex (p < 0.05). This dramatic decrease of the β-amyloid load was accompanied by a marked reduction in the number of plaques in both hippocampus (-90.4 ± 6.1%, p < 0.01) and cortex (-80.6 ± 3.7%, p < 0.01). Measurements of soluble oligomeric Aβ are underway.

This proof-of-concept study confirms the promising therapeutic potential of Trx(Aβ15)4 for the treatment of AD.