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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$Trx(A\beta15)_4$ 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 $Trx(A\beta15)_4$ 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, $Trx(A\beta15)_4$ preferentially elicits a humoral anti-inflammatory Th-2 type immune response.

We evaluated the effects of $Trx(A\beta15)_4$ 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 $Trx(A\beta15)_4$ 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 $Trx(A\beta15)_4$-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 $Trx(A\beta15)_4$-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.

1. Moretto N., Bolchi A., Rivetti C., Imbimbo B.P., Villetti V., Pietrini V., Polonelli L., Del Signore S., Smith K.M., Ferrante R.J., Ottonello S. (2007). J. Biol. Chem. Jan 31 (in press).