EFFECTIVE CLEARANCE OF SOLUBLE AMYLOID-B PROTOFIBRILS IN THE BRAIN OF TG-APP<sub>ARCSWE</sub> MICE AFTER TREATMENT WITH A CONFORMATION-SELECTIVE ANTIBODY WITHOUT INDUCING MICROBLEEDING

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Introduction: Soluble amyloid-β (Aβ) oligomers/protofibrils are suggested to play a central role in the pathogenesis of Alzheimer’s disease. The tg-APP<sub>ARCSWE</sub> mouse model expresses elevated levels of Aβ protofibrils in the brain, and is therefore a suitable model for investigating these Aβ assemblies in vivo.

Methods and results: The protofibril-selective monoclonal antibody mAb158 was given by weekly intraperitoneal injections to aged tg-APP<sub>ARCSWE</sub> mice, and clearance of soluble brain protofibrils was evaluated in brain TBS extract using a mAb158-based sandwich ELISA. The mAb158-based sandwich ELISA specifically detects Aβ protofibrils without interference from Aβ monomers, the amyloid precursor protein (APP), or low treatment antibody levels present in brain TBS extracts. Long-term treatment (4 months) of 12-14 months old tg-APP<sub>ARCSWE</sub> mice with mAb158 (0.3, 1 and 3 mg/kg) led to reduced levels of soluble Aβ protofibrils in brain in a dose-dependent manner (28%, 33% and 54%, respectively). Moreover, long-term treatment (3 months) of aged (18-24 months old) tg-APP<sub>ARCSWE</sub> mice with 12 mg/kg mAb158 led to reduced soluble Aβ protofibril levels (52%) in brain compared to placebo-treated mice. Congo red staining of brain sections from aged tg-APP<sub>ARCSWE</sub> mice suggested no significant reductions in cored Ab plaques or changes in cerebral amyloid angiopathy (CAA). Hemosiderin or hematoxylin and eosin staining of brain sections suggested no increase in microbleedings in aged mAb158-treated tg-APP<sub>ARCSWE</sub> mice compared to placebo-treated mice.

Conclusion: Treatment with mAb158 cleared the toxic Aβ protofibril from brain without affecting amyloid plaques or CAA and did not cause microbleeding in tg-APP<sub>ARCSWE</sub> mice.