EFFECT ON AMYLOID LOAD AFTER PERIPHERAL ADMINISTRATION OF A NEPRILYSIN FUSION PROTEIN TO TG2576 MOUSE

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Introduction: In order to investigate the possibility to inhibit formation and growth of amyloid plaques in the APP overexpressing Tg2576 mice, we used an Aβ degrading enzyme as therapeutic molecule.

Aim: To investigate effects on plasma and brain Aβ40 and 42 after peripheral neprilysin fusion protein (Fc-Nep) administration.

Methods: To confirm the biological activity of the Fc-Nep, Aβ degradation was performed in human and mouse plasma prior to the present in vivo study. Fc-Nep and vehicle were i.v. administered to 24-weeks old Tg2576 mice (20, 5 and 1 mg/kg) every second week for four months. Plasma PK profile was monitored throughout the study. Mice were terminated 72 hours after last dose and Aβ40 and 42 levels were analysed in plasma and brain (soluble and insoluble fraction). Aβ was extracted from brains with dietylamine and formic acid to obtain the soluble and insoluble brain Aβ fractions, respectively. Levels of Aβ40 and 42 were analyzed using commercially available ELISA kits.

Results: Fc-Nep exposure levels were as expected during the study. Aβ40 levels in soluble brain fraction of Fc-Nep treated mice (25 mg/kg) were significantly reduced compared to levels in vehicles. However, trends of a dose-response Aβ reduction were seen in both Aβ40 and 42 in both brain fractions. Plasma Aβ40 and 42 were significantly reduced at both 5 and 20 mg/kg doses.

Conclusions: Peripheral Fc-Nep administration result in a lowering of brain and plasma Aβ in Tg2576 mouse model.