## **Supplementary Figure 1**



Supplementary Fig. 1: *In vitro* degradation of A $\beta$  variants in cerebrospinal fluid (CSF) CSF samples were obtained from the Neurology Clinic (University of Bonn) in accordance with the laws and the permission of the local ethical committee. Synthetic npA $\beta$  and pA $\beta$  peptides were dissolved in IDE assay buffer (**A** and **B**) or in human CSF (**C** and **D**) with purified IDE and incubated at 37°C. Sample aliquots of the react ion mixture were collected at indicated time intervals and analyzed by SDS-PAGE and silver staining. The degradation of both A $\beta$ variants is significantly reduced in CSF as compared to the IDE reaction buffer. Of note, phosphorylation of A $\beta$  also significantly reduced its degradation in the CSF (**C** and **D**). Values represent mean ± SD (n=3). \*\*\*, p<0.001 (*t test*)

## **Supplementary Figure 2**



Supplementary Fig. 2: Neprilysin dependent degradation of npA $\beta$  and pA $\beta$ . A-C) Synthetic npA $\beta$  and pA $\beta$  peptides were incubated with recombinant Neprilysin at 37 °C for various time intervals (0, 5, 15, 30 and 60 min). Sample aliquots of the reaction mixture collected at different time intervals were analyzed by SDS-PAGE and silver staining (**A and B**) or MALDI-TOF MS (**C**). Neprilysin show comparably low A $\beta$  degrading activity under the experimental condition (**A and B**). The peaks representing the cleavage products A $\beta$ 1-17, A $\beta$ 1-19, A $\beta$ 1-25 and A $\beta$ 1-29 are detected only in npA $\beta$  peptide after 30 min of incubation. Whereas no peaks were detectable with pA $\beta$  peptide (**C**). The corresponding mass of the cleavage products are mentioned in Table 1. Values represent means ± SD (n=4)