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MEETING ABSTRACT

A1.2

Treatment of Alzheimer's disease using small D-peptides

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For our research on a treatment for Alzheimer's disease we use transgenic mice that express two AD mutations, they develop the first amyloid β deposits at about five months of age, and the females develop cognitive deficits around 8 months of age (males at 10 months of age). We hypothesized that long-term treatments that interact with amyloid β(1–42) (Aβ42) would result in changes in amyloid deposition, and, likely, in the inflammatory reaction together resulting in improved cognition. In these studies we investigated the effects of small (12 aa), Aβ42-binding D-enantiomeric peptides on amyloid deposition, inflammation and cognition.

We use groups of AD Tg mice; the animals receive treatment for 1 month using Alzet minipumps, at the time point when cognition is declining (*i.e.*, at 7–9 months of age). At the end of the treatment period animals are tested for behavioral and cognitive changes. In the first studies we treated intracerebral, currently we use i.p. infusion as the method of choice.

Following behavioral analysis, the animals are sacrificed, the brain is cut in half, one half brain is cut in 35-µm sections, and these were stained with (1) amyloid β, (2) GFAP and CD11b. The density and size of labeling in the stained sections is quantified with densitometric analysis.

Four-week treatments with an Aβ42-binding peptide (*i.e.*, D3) significantly improved cognitive functioning, and significantly reduced deposition of amyloid β in Tg mouse models of AD, and inflammation was significantly decreased around the amyloid deposits in the D3-treated animals compared to the control mouse groups. However, it should be noted, that the first D-peptide, D1, negatively impacted both pathology and cognition. On the other hand, RD2, and combinations of our D-peptides (*e.g.*, D3-D3, RD2-D3), in general, did not change amyloid β pathology but did improve cognition significantly.

Taken together, this suggests that the properties of Aβ42-binding D-enantiomeric peptides influence the changes in amyloid β pathology. Fibril-binding peptides such as D1 have no positive effects on the development of the pathology and cognitive deficits of AD, while most Aβ oligomer-oriented peptides positively affect cognition, but not plaque pathology.

Keywords: Alzheimer's disease – amyloid β – oligomers – D-enantiomeric peptides

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