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MEETING ABSTRACT

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Aβ oligomer-eliminating D-enantiomeric peptides enhance cognition and impede neurodegeneration even by oral application

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Several lines of evidence suggest a central role of amyloid β peptide (Aβ) in the pathogenesis of Alzheimer's disease (AD). More than Aβ fibrils, small soluble and prion-like propagating Aβ oligomers are suspected to be the major toxic species responsible for disease development and progression. Therefore, eradication of these Aβ oligomers is our principal objective for therapy of AD. Previously, we have identified the fully D-enantiomeric peptide D3 by mirror-image phage display selection and showed that it was able to specifically eliminate Aβ oligomers and convert them into non-toxic species. D3 was able to reduce plaque load in transgenic AD mouse models and improved cognition even after oral application [1]. More recently, we developed derivatives of D3 with improved properties during a lead optimization strategy that focused primarily on the Aβ oligomer elimination efficiency.

We used our newly developed Aβ-QIAD (quantitative determination of interference with Aβ aggregate size distribution) to quantitatively measure Aβ oligomer elimination efficiency and thus target engagement [2]. Morris water maze and novel object recognition experiments in several transgenic mouse models were used to measure cognition enhancement of the compounds. Our most promising D3 derivative was able to enhance cognition and learning behavior even in 18-month-old transgenic AD mice with full-blown pathology even after oral application. SHIRPA and Rotarod assays were used to follow neurodegeneration in the TBA2.1 mouse model and its retardation by our compounds. Using HPLC and LC/MS, we investigated the stability of the compounds under various conditions. As expected from D-peptides, D3 and its derivatives showed superior pharmacokinetic properties, such as long half-lives and high oral bioavailability [3,4]. The presented compounds were able to eliminate Aβ oligomers as well as to enhance cognition and slow down neurodegeneration even after oral application.

D-enantiomeric peptides that specifically and efficiently eliminate Aβ oligomers are able to enhance cognition and impede neurodegeneration even when applied orally.

Keywords: amyloid β oligomers – D-enantiomeric peptides – oligomer elimination – therapy

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