05y. Drug Development & Clinical Trials: other

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D-PEPTIDES DEVELOPED TO BE THERAPEUTICALLY ACTIVE AGAINST BETA-AMYLOID OLIGOMERS SHOW PROMISING PHARMACOKINETIC PROPERTIES

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Objectives: To date, no treatment exists to cure Alzheimer's disease (AD). Aggregation of beta-amyloid (Abeta) plays an important role in the pathology of AD. Currently, Abeta oligomers are thought to be the most toxic species. D3, a D-enantiomeric peptide (D-peptide), was developed that specifically eliminates Abeta oligomers in vitro and has been shown to improve cognition and reduce plaque load and inflammation in transgenic Alzheimer's mice. D-peptides have several advantages over L-peptides since they are less immunogenic and more protease-resistant. Therefore, they are thought to remain longer in the body providing more time to be therapeutically active. Here, we show pharmacokinetic studies of some derivatives of D3 in mice and estimate their plasma protein binding.

Methods: Radioactively labelled peptide was administered via several administration routes and organs were harvested at different time points post injection. The amount of radioactive D-peptide in the organ homogenate was measured by liquid scintillation counting. Furthermore, binding to plasma proteins as well as brain membranes was determined, also using radioactively labelled peptide as indicator.

Results: Results show that all D-peptides indeed reach the brain where they may exhibit their therapeutic activity. Furthermore, the peptides show small elimination constants and long half-lives of more than a day in plasma as well as a high bioavailability after i.p., s.c. or p.o. administration.

Conclusions: Promising pharmacokinetic properties confirm that D-peptides may be very potent AD-therapeutic agents on their way to clinical studies.