Macrocyclic Inhibitory Peptide with Potent Anti-amyloid Effect in Alzheimer's Animal Model

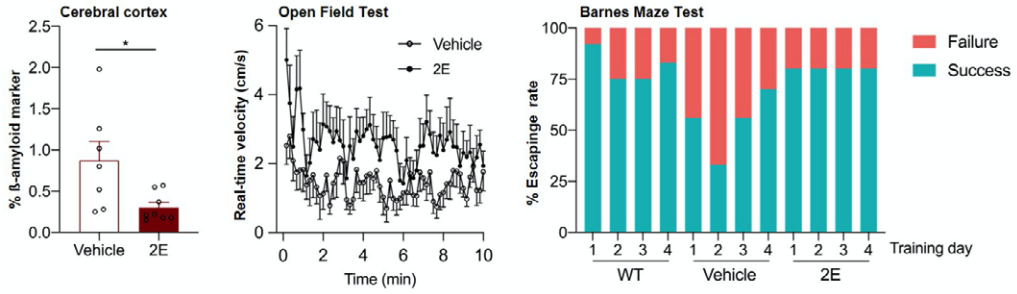
Reference No: B78094

CHALLENGE

Despite the established association between the pathogenesis of **Alzheimer's disease (AD)** and the presence of amyloid plaques of **β-amyloid peptide (Aβ)** in the brain, all anti-Aβ therapeutic strategies, mostly representing antibody-based approaches aiming at **blocking amyloid self-assembly** have so far failed. However, the development of anti-amyloid compounds is an important target of AD-related research. For this reason, there is an urgent need to develop **novel classes of amyloid inhibitors.**

INNOVATION

Here, we present synthetic medium sized **macrocyclic peptides, termed macrocyclic inhibitory peptides (MCIPs),** as a new class of highly potent **inhibitors** of **Aβ** amyloid self-assembly and related cytotoxic effects[1]. The **drug-like properties of our lead MCIP 2E** include their small size (<20 amino acids), high solubility, potent amyloid inhibitor function (nanomolar IC50) and **Aβ40(42)** binding affinity, target selectivity, good proteolytic stability in human plasma (in vitro) und BBB permeability (determined using in vitro models), and make them suitable drug candidates. For instance, one of the weak points of the antibodies is their extremely low BBB permeability.



***In vivo* data** from a murine Alzheimer's model shows decreased oligomer levels **(A)** and amyloid plaque load in the cerebral cortex. Behavioral tests demonstrate the candidate's effectiveness in partially **restoring locomotive impairments (B)** and **protecting from spatial learning** and **memory deterioration (C).** Unpublished data from Hao, Gökce, Bernhagen, Kapurniotu et. al., unpublished.

COMMERCIAL OPPORTUNITIES

Our lead macrocyclic peptide 2E was confirmed as a potent inhibitor of amyloidogenesis in several in vitro assays[1] and a mouse model of Alzheimer's disease (unpublished data):

- MW < 2000 Da
- **Cost-effective production** by routine solid phase peptide synthesis
- **High solubility**
- **High Aβ40(42) binding** affinity and amyloid inhibitor potency (nanomolar IC50)
- **Good proteolytic stability** in human plasma (in vitro)
- Effective crossing of **human blood brain barrier** (BBB) (in cell model)
- Promising data from **behavioral tests** with **no observed in vivo toxicity in mouse model**

DEVELOPMENT STATUS

Proof of concept of lead compound in 5xFAD mouse model of Alzheimer's disease.

REFERENCES:

1 doi: 10.1002/anie.201802979

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PCT filed 2019

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