Hydrophobically Interspaced, Charged Peptides for the Treatment and Prevention of Dementia

An Innovative and efficacious therapeutic strategy to prevent and/or treat AD and other dementias.

Technology

Development and progression of AD depends on the pathological interaction of the apoE protein with the Aβ peptide to produce the conformational changes that lead to intra and extra-cellular fibrillary amyloid deposition. The inventors have analyzed the sequences of Aβ and apoE and have detected important regions, never recognized before, within apoE that stabilize its pathological pro-fibrillogenic conformational function and where Aβ is potentially bound. The key to this apoE pathological function lies in these stretches of the protein presenting pairs of charged amino acids, encompassed and interspaced by different pairs of hydrophobic amino acids; a perfect combination for tight binding of different parts of the molecule assuring conformational function and binding to substrates (i.e., Aβ). The inventors have designed peptides where the interspaced hydrophobic amino acids are complementary to the oppositely charged amino acids within apoE; with special care on the minimum workable size of the peptides and the specific bulk of the amino acids side chains, which are also complementary to the appropriate regions. Most peptides also have a motif able to bind Aβ at the critical 21-24 region. Binding of these peptides to apoE destabilizes its structure and prevents the direct pathological interaction of the apoE on Aβ in multiple ways, while at the same time preventing Aβ-Aβ pro-fibrillar interaction; thereby disrupting the pathology and progression of AD. Experiments in AD mouse models crossed to different human apoE backgrounds found that treatment with the peptides inoculated peripherally, was associated with penetration of the Blood Brain Barrier (BBB) and clear cognitive benefits in several behavioral tests (Figure 1). Importantly, these therapeutic peptides have shown no evidence of any toxicity.

Background

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease in the USA. Dementia-related diseases predominately affect people aged 65 years and older. One in three seniors dies with AD or other form of dementia. It is estimated that AD will cost the US ~$345 billion in 2023 and increase to ~$1 trillion by 2050, as the aging population increases. The cause of AD involves the accumulation of fibrillar Amyloid beta (Aβ) in plaques in the extracellular space in the brain and in cerebral blood vessels. The apolipoprotein E4 (apoE4) genotype is known to be the major genetic risk factor for developing AD. ApoE co-localizes with Aβ in plaques and interacts with Aβ as a "pathological chaperone". The inventors have developed short synthetic homologue peptides, each with multiple actions preventing the apoE 'chaperone' pathological conformation, acting as competitive inhibitors of Aβ binding to ApoE or apoE to Aβ, as well as preventing Aβ fibrillogenesis directly even at critical Aβ concentrations. Even though the currently available therapies deliver modest cognition benefits, they fail to prevent the

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progression of the disease and are symptomatic. The current therapy with peptides developed by the inventors affects the pathology of AD directly and inhibits the progression of the disease.

Applications

- Treatment of neurodegenerative conditions including AD and other related dementias
- Therapeutic inhibitor could also serve as an early-prevention therapy for patients identified as having a high risk of developing AD

Advantages

- Simple short peptide sequences for easy scalable production (all peptides between 10 and 15 amino acids)
- Unique anti-fibrillogenic dual action inhibiting apoE action on Aβ and Aβ-Aβ interaction
- Proven efficacy with L- or D- (longer half-life) amino acids
- Clear cognitive benefits were shown in AD animal models carrying different Human apoE backgrounds (See Figure 1)
- Versatile peripheral administration methods with BBB penetration to treat/prevent AD
- No toxicity observed in vivo in AD animal models

Intellectual Property

Provisional patent application pending