Small Molecule "Molecular Tweezers" that Inhibit Amyloid-β Fiber Formation

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SUMMARY

Researchers at UCLA have developed “molecular tweezers,” which can inhibit folding, assembly, and toxicity of amyloid-β that define Alzheimer’s disease (AD) pathology. In contrast to current therapies which only address symptoms, this therapy directly targets the disease mechanism of AD.

BACKGROUND

Alzheimer’s disease (AD) is an incurable neurodegenerative disease afflicting millions of Americans. Managed care of AD patients presents an enormous financial and social burden on society. Contributing to this burden is the dearth of effective treatments for AD. Current therapies target the symptoms rather than the cause of disease, which involves the deposition of the amyloid-beta (Aβ) and tau proteins into fibrous plaques or tangles in the brain. Aggregation of Aβ and tau proteins is neurotoxic, precipitates neuronal death and impairs cognitive signaling, all of which are characteristic of AD.

Therapeutic research efforts in AD continue to focus on the drivers of disease by targeting inhibition of Aβ production, enhancement of Aβ clearance, or disruption of Aβ assembly. Development of therapeutics had previously been hindered by our incomplete understanding of the disease. Recent studies, however, have greatly improved our understanding of the structure and the critical steps involved in the formation of the fibrous plaques. These findings are seeding the development of rationally designed therapies that target specific amino acids of Aβ fibers. Since they specifically target the disease mechanism, such approaches hold great promise for the treatment of AD.

INNOVATION

Researchers at UCLA have developed “Molecular Tweezers,” small molecules that inhibit the assembly of Aβ proteins. Using recent insights to the structure and assembly process of the Aβ protein, specific amino acids critical to fiber formation were identified and targeted in the design of the molecule. These “tweezers” inhibit the assembly and toxicity of Aβ in a non-neurotoxic manner. The invention represents a potential drug for the treatment of AD.

APPLICATIONS

- Therapeutic to inhibit progression of the Alzheimer’s Disease.
- The molecular tweezers and derivatives can be developed for other amyloid-related diseases including Parkinson’s disease, Creutzfeldt-Jakob disease and Gerstmann-Sträussler-Scheinker disease.

ADVANTAGES

- Inhibits the principle cause of AD instead of the symptoms.
- Disaggregates pre-existing Aβ40 and Aβ42 protein fibrils.
- The tweezer is non-toxic at concentrations up to 200 μM.

STATE OF DEVELOPMENT

The researchers have performed proof-of-concept studies demonstrating the ability of the molecular tweezers to inhibit assembly of Aβ in both in vitro assays and in vivo mouse models. Additional animal studies to further characterize efficacy and pharmacokinetics of the molecule and associated derivatives are underway. In addition, experiments to reveal the structure and mechanism of interaction have been initiated.

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OTHER INFORMATION

CATEGORIZED AS

- **Medical**
  - Disease: Central Nervous System
  - Therapeutics

RELATED CASES

2008-489-0

PATENT STATUS

Country	Type	Number	Dated	Case
Switzerland	Issued Patent	2403859	05/03/2017	2008-489
Germany	Issued Patent	2403859	05/03/2017	2008-489
France	Issued Patent	2403859	05/03/2017	2008-489
United Kingdom	Issued Patent	2403859	05/03/2017	2008-489
United States Of America	Issued Patent	8,791,092	07/29/2014	2008-489

RELATED MATERIALS

- A molecular tweezer for lysine and arginine. *J. Am. Chem. Soc.* (2005)
- Molecular tweezer and clip in aqueous solution: unexpected self-assembly, powerful host-guest complex formation, quantum chemical 1H NMR shift calculation. *J. Am. Chem. Soc.* (2006)
- Protection of primary neurons and mouse brain from Alzheimer's pathology by molecular tweezers. *Brain.* (2012)
- Researchers report potential new treatment to stop Alzheimer's disease. *UCLA Newsroom.* (2012)

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- Inhibition Of Lipofuscin Aggregation By Molecular Tweezers
- New Molecular Tweezers Against Neurological Disorders And Viral Infections
- Preventing Synuclein Accumulation as a Strategy for Improving Neuronal Survival and Regeneration after Spinal Cord Injury
- Treatment Of Lysosomal Storage Disorders

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