Development of a Small Molecule that Blocks Alpha Synuclein Transmission in Neurodegenerative Disorders

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BACKGROUND

There is a strong correlation with aging and the onset of developing a neurodegenerative disease such as Alzheimer's or Parkinson's disease, amyotrophic lateral sclerosis, frontotemporal dementia (FTD) and Creutzfeldt-Jacob disease, Dementia with Lewy Bodies (DLB), Multiple system atrophy (MSA) and others. A universal commonality among these diseases is the presence of misfolded aggregated proteins in the brain or with cells of the brain. Very strong evidence supports a role of spreading of misfolded proteins from cell to cell and across the brain in disease progression. Moreover, these aggregated proteins can take different forms and be used help diagnosis the specific neurodegenerative disease.

Parkinson's disease (PD) is characterized by loss of striatal dopaminergic signaling and the presence of alpha-synuclein-containing Lewy bodies and neurites. Research has shown the importance of alpha-synuclein (α-Syn) from examining people with PD at autopsy and the pathology associated with the disease which contains misfolded and aggregated α-Syn. Moreover, a mutation in the gene encoding α-Syn (SNCA) or simple overexpression of wild-type α-Syn will lead to PD. The misfolding and spread of α-Syn are central to disease initiation and progression. The presence of misfoided α-Syn is also seen in other synucleinopathy diseases including Alzheimer's disease (AD) and Dementia with Lewy Bodies (DLB), the two most prevalent progressive dementia diseases and MSA.

One of the most common forms of symptomatic treatment for early stages of PD is the use of monoamine oxidase B inhibitors and in later stages the use of dopamine receptor agonists (DRAs) and /or levodopa. The treatment must find a good balance between clinical benefits and risks. Ultimately, these treatments fail to show improvement over the course of 2-5+ years, therefore, new alternative treatments are needed especially those attacking the underlying course of the disease. Small molecule binding to native states of globular proteins has been successfully to block misfolding and aggregation most notably in the case of targeting transthyretin to treat systemic amyloidosis. By contrast, targeting of intrinsically disordered proteins such as native monomeric α-synuclein (α-Syn) with small molecules has been challenging due to their inherent structural heterogeneity and the absence of persistent structural elements.

TECHNOLOGY DESCRIPTION

Researchers at UC San Diego have developed a novel strategy to treat PD by using small molecules interacting with native α-Syn that could protect and stabilize specific conformations present in the ensemble, which in turn could provide protective action. A compound has been identified that displayed protective activity in preventing the transmission of α-Syn from cell to cell thus supporting the notion that small molecules can target an intrinsically disordered protein such as α-Syn. This compound does not directly affect the process of α-Syn misfolding or aggregation and thus offers a novel mode-of-action beyond previously described aggregation blockers.

APPLICATIONS

One compound blocks the cell-to-cell propagation of α-Syn and thus has potential to block the spread and pathogenesis of α-Syn in synucleinopathies such as PD, AD, DLB, and MSA. Thus, the compound has potential uses as a therapeutic in the above synucleinopathies.

STATE OF DEVELOPMENT

The compound has been synthesized and tested *in vitro* in neuronal cultures.

INTELLECTUAL PROPERTY INFO

This technology is patent pending and available for licensing and/or research sponsorship.

PATENT STATUS

Patent Pending

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OTHER INFORMATION

KEYWORDS

Alpha Synuclein, a-Syn, Parkinson's disease, Alzheimer's disease, Dementia with Lewy Bodies, protein aggregation, small molecule, neurodegeneration, synucleinopathies

CATEGORIZED AS

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

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