Identification And Development Of Dual nSMase2-AChE Inhibitors For Neurodegenerative Disorders

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SUMMARY

UCLA researchers in the Department of Neurology, and the Department of Chemistry & Biochemistry have developed small molecule inhibitors of both the neutral sphingomyelinase 2 (nSMase2) and acetylcholinesterase (AChE) as novel therapeutics for neurodegenerative disorders caused by protein aggregation.

BACKGROUND

Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) are increasingly being realized to share common molecular mechanisms for disease pathogenesis – protein aggregation and inclusion body formation. These protein aggregates generally consist of misfolded proteins which act as a source for proteopathic seeds that can be packaged in vesicles to accelerate the growth of the aggregates and propagate the neuronal spread of the misfolded proteins.. Deposition of disease-specific proteins in specific brain regions results in neuropathological lesions.

Misfolded protein aggregates are often found in extracellular vesicles (EVs) purified from blood and cerebrospinal fluid of patients with neurodegenerative diseases. EVs, particularly small EVs such as exosomes, are speculated to be involved in the amyloid proteopathic seeding process. Neutral sphingomyelinase 2 (nSMase2) is an enzyme involved in ceramide-mediated exosome production, and inhibition of nSMase2 has shown beneficial effects in animal models of primary tauopathy, AD, and Lewy body dementia.

INNOVATION

Researchers at UCLA have identified several small molecule inhibitors against both nSMase2 and acetylcholinesterase (AChE), which are important drug targets for neurodegenerative diseases. Inhibition of nSMase2 activity represents a promising strategy to control exosome-mediated proteopathic seed propagation, and inhibition of AChE helps to compensate for the loss of cholinergic neurons and slow down cognitive deterioration.

APPLICATIONS

- Therapeutics for neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis

ADVANTAGES

- Inhibition of both nSMase2 and AChE
- Great propensity to be brain permeable

STATE OF DEVELOPMENT

Completed *in vitro* cell-based nSMase2 and AChE dose response assays. Currently in the process of conducting secondary and tertiary functional screens and *in vivo* testing in AD and PD models.

RELATED MATERIALS

- Duong, A.T.H., Simmons, B.J., Alam, M.P., Campagna, J., Garg, N.K. and John, V., 2019. Synthesis of fused indolines by interrupted Fischer indolization in a microfluidic reactor. Tetrahedron letters, 60(3), pp.322-326.

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OTHER INFORMATION

KEYWORDS

Small molecule inhibitor, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, protein aggregation, protein misfolding, neutral sphingomyelinase 2, acetylcholinesterase

CATEGORIZED AS

- **Medical**
  - Disease: Central Nervous System
  - New Chemical Entities, Drug Leads
  - Therapeutics

RELATED CASES

2019-279-0

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Published Application	2023-011394	04/13/2023	2019-279
European Patent Office	Published Application	EP4087847	11/16/2022	2019-279

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- New 3D-Exoquant Method For The Analysis Of Surface Molecules And Quantification Of Tissue-Specific Exosomes In Biological Fluids
- Allosteric BACE Inhibitors For Treatment Of Alzheimer's Disease

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