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Neurodegenerative Diseases

Restoring acid-β-glucosidase activity by non-inhibitory small molecule chaperones

Brief Description of Technology

Restore GCase activity in the brain for Gaucher and Parkinson's

TECHNOLOGY ID

2017-0701

BUSINESS OPPORTUNITY

Exclusive License or Sponsored Research

TECHNOLOGY TYPE

Small Molecule

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Technology Overview

Gaucher disease (GD) is an inherited disorder where the body does not make enough glucocerebrosidase (GCase), an enzyme that breaks down fatty chemicals in the body. GD phenotypes and up to 10% of Parkinson's Disease cases are caused by mutations in the GBA1 gene coding GCase. Reduced GCase activity appears to be a common feature; carriers with 50% GCase activity do not develop clinical symptoms. Current GCase replacement therapy is only effective for visceral organs and not accessible to the brain.

Pharmacological small molecule chaperones enhanced GCase activity, signifying potential therapeutic efficacy. These small molecules bind to the target protein GCase, rescuing the mutant GCase activity by stabilizing the protein and lysosomal localization. Enhancing lysosomal GCase will increase GCase catalytic activity, improve substrate (glycolipids) catabolism, and prevent alpha-Syn aggregation. Our focused library design approach has generated novel small molecule hits which are able to enhance Gcase activity. These hits have CNS penetrable molecular properties and desirable in-vitro ADME properties to be orally bioavailable.

Applications

- Neuronopathic Gaucher disease (GD Type 2 and 3)
- Parkinson's disease

Advantages

- Non-competitive interaction with GCase and allosteric activation
- Lead compound has high blood brain barrier permeability and some central nervous system-drug like properties.

Market Overview

Annual incidence of GD is ~1/60,000. Neuronopathic GD (Type 2 and Type 3) accounts for 10% of total patients and there are no approved treatments to manage CNS involvement. About 5-10 % Parkinson's Disease (PD) population carry GBA1 mutations which could be treatable by the drugs which restores GCase activity.

Investigator Overview

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