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 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 to 50 to 100% of unaffected control level, signifying potential therapeutic efficacy. These small molecules bind to the target protein GCase, rescuing the mutant acid-β-glucosidase 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.

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. GD type 3 is the most common variant of the disease, with a later onset compared with type 2. GD type 2 is very rare, with an incidence of ~5% of all GD patients and infantile onset of central nervous system problems that are untreatable and typically fatal within 2 years.

Investigator Overview
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