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Lead Program in GBA-Parkinson's Disease

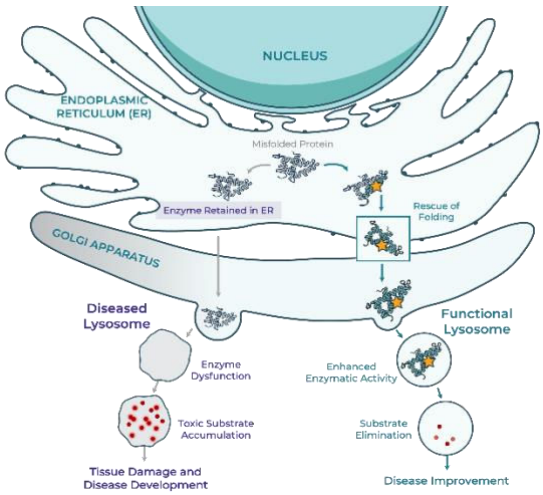
GBA-Parkinson's disease (GBA-PD) affects patients who harbor a mutation of the GBA gene, which is the most common genetic risk factor for PD.[1] This genetically defined subpopulation is estimated to represent up to 15%[2] of the more than 10 million PD patients globally[3]. GBA-PD patients experience an earlier onset of the disease, a faster progression of the disease, and a higher rate of cognitive decline associated with disease progression.[1]

GBA-PD is caused by heterozygous mutations in the GBA gene, which encodes the lysosomal enzyme beta-glucocerebrosidase (GCase). The primary role of GCase is to eliminate the substrate glucosylceramide (GlcCer) in the lysosome. However, mutations in the GBA gene cause the expression of misfolded GCase, which is then trapped in the endoplasmic reticulum and unable to traffic to the lysosome to clear substrate. In the absence of functional GCase, GlcCer and its deacylated lysolipid glucosylsphingosine (GlcSph) start to accumulate in the lysosome, causing toxicity in the cell. Notably, it also leads to the accumulation of α-synuclein, a neuronal protein that is the pathogenic hallmark of PD.[1]

Disease Modifying Mechanism of Action

Gain's GBA-PD program is targeting misfolded GCase at the very start of the disease cascade. The lead compound GT-02287 is a brain-penetrant small molecule that acts as a non-competitive pharmacological chaperone binding to GCase at an allosteric binding site. Both the allosteric site and compound are novel and were discovered using Gain's proprietary drug discovery platform SEE-Tx®.

As shown in the right side of the diagram, the postulated mechanism of action of GT-02287 is that it restores enzyme function by binding to misfolded GCase, stabilizing the enzyme such that it can traffic to the lysosome and eliminate toxic substrates, restore cell health and increase cell survival.



Extensive *In Vitro* and *In Vivo* Proof of Concept Data

Gain has generated an extensive package of *in vitro* and *in vivo* data demonstrating a beneficial effect at every step of the disease cascade. Specifically, administration of GT-02287 results in increased GCase enzyme levels and activity, increased trafficking to the lysosome, and depletion of toxic substrates GlcCer and GlcSph, as well as depletion of α-synuclein. The beneficial effect of restored GCase function is also seen in generally improved lysosomal function and reduction of inflammation. Most important, in relevant animal models, GT-02287 has been shown to increase the survival of dopaminergic neurons, increase dopamine levels, and improve locomotion deficits – demonstrating its potential to be a true disease modifying therapy. The program is currently in the GLP-toxicology phase, with expected readouts at the end of Q1 2023. A Phase 1 study in healthy volunteers is expected to be initiated in Q3 2023 in Australia.

Differentiation and Market Opportunity

Current PD therapies only treat the symptoms, but not the underlying pathology of the disease, and patients eventually experience a deterioration of those symptoms.[4] No other program has shown the ability to restore GCase function and improve every step of the disease cascade, making GT-02287 an attractive drug candidate with the potential to revolutionize the neurodegeneration space and provide treatment options for several diseases with extremely high unmet medical needs. The estimated peak sales potential of GT-02287 in GBA-PD alone is greater than $1.5B.[5]

In addition, the program has numerous indication expansion opportunities. Similar to GBA-PD patients, idiopathic PD patients also have reduced GCase activity and may benefit from treatment with GT-02287 as Gain's data has shown the same positive effect in wild type neuronal cells (i.e. cells without GBA gene mutations) as was shown in cells with GBA mutations. GT-02287 also has shown great promise preclinically in Gaucher disease (GD), which is caused by homozygous mutations of the GBA gene. The unmet medical need in GD is the neuronopathic form of GD that is not treatable by current enzyme replacement therapies (ERT) as they cannot penetrate the blood brain barrier. Further, toxic forms of α-synuclein are implicated in several neurodegenerative diseases, including Lewy body dementia and Alzheimer's. The well-established ability of GT-02287 to reduce toxic aggregation of α-synuclein could make it an attractive treatment option for these indications.

[1]Cells. 2019 Apr; 8(4): 364. [2]Eur J Neurol. 2022 Apr; 29(4): 1017–1024; [3]https://www.parkinson.org/understanding-parkinsons/statistics; [4]https://www.nhs.uk/conditions/parkinsons-disease/treatment;
[5]Company projection