Neuroprotective effect of GT-02287, a brain-penetrant structurally targeted allosteric regulator of glucocerebrosidase, leads to a significant reduction of plasma NfL levels and improvement in behavioural deficits in a mouse model of GBA1 Parkinson's disease

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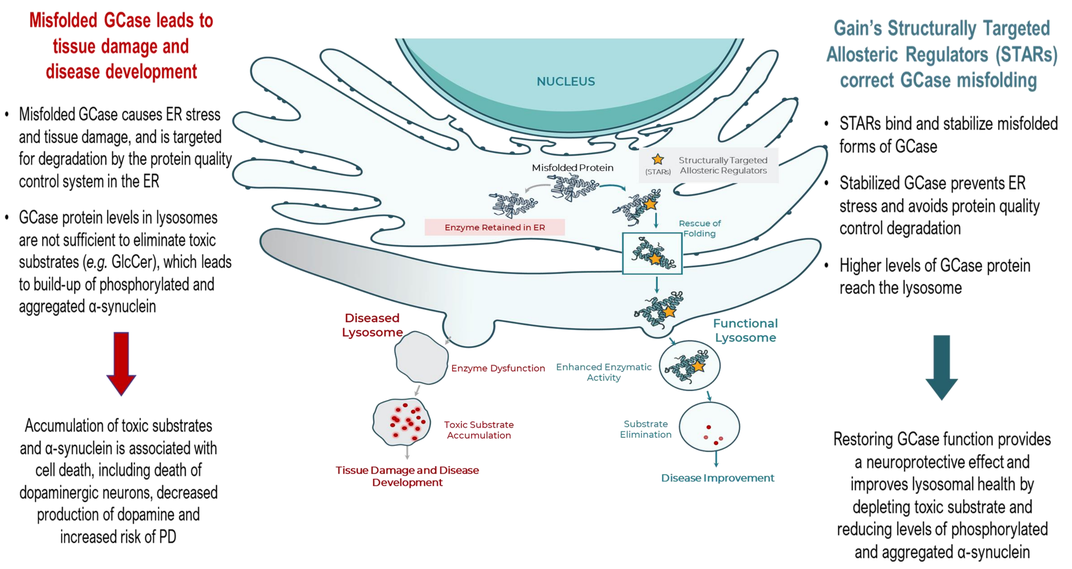
Objective

To investigate the effect of GT-02287 on relevant neuropathological biomarkers and motor function in a mouse GBA1-PD model.

Background

Mutations in the *GBA1* gene encoding lysosomal enzyme glucocerebrosidase (GCase) represent the most significant genetic risk factor for Parkinson's disease (PD). Misfolded and dysfunctional GCase expressed by mutated *GBA1* is linked to impaired lysosomal function and α-synuclein accumulation. Conduritol beta epoxide (CBE), a covalent inhibitor of GCase, can induce a partial deficit in GCase activity comparable to that associated with GBA1-PD. Gain Therapeutics applied its proprietary computational drug discovery platform, SEE-Tx®, to discover GT-02287, a small molecule allosteric GCase modulator. **GT-02287 stabilizes GCase, protects it from degradation, facilitates its trafficking to the lysosome and restores its function.**



Neurofilament light chain (NfL) is an emerging neurodegeneration biomarker that recently has been successfully used as a surrogate endpoint for accelerated approval in SOD1-ALS and exploratory endpoint in neuronopathic MPS II clinical trials.

Methods

Mice were treated with CBE (100 mg/kg, i.p.) and GT-02287 (30, 60, 90 or 120 mg/kg p.o.) q.d. for 14 days. Aggregated α-synuclein, tyrosine hydroxylase (TH) and neuronal nuclei (NeuN) were assessed by immunostaining and confocal microscopy, and Iba-1 expression levels by western blot. Striatal dopamine level was assessed by LC-MS/MS. Plasma NfL levels were assessed by ELISA. Motor deficits were assessed by the wire hang and beam walk tests.

Results

GT-02287 reduced aggregated α-synuclein, neuroinflammation, neuronal death and plasma NfL levels, as well as increasing striatal dopamine levels and motor function in CBE-injured mice.

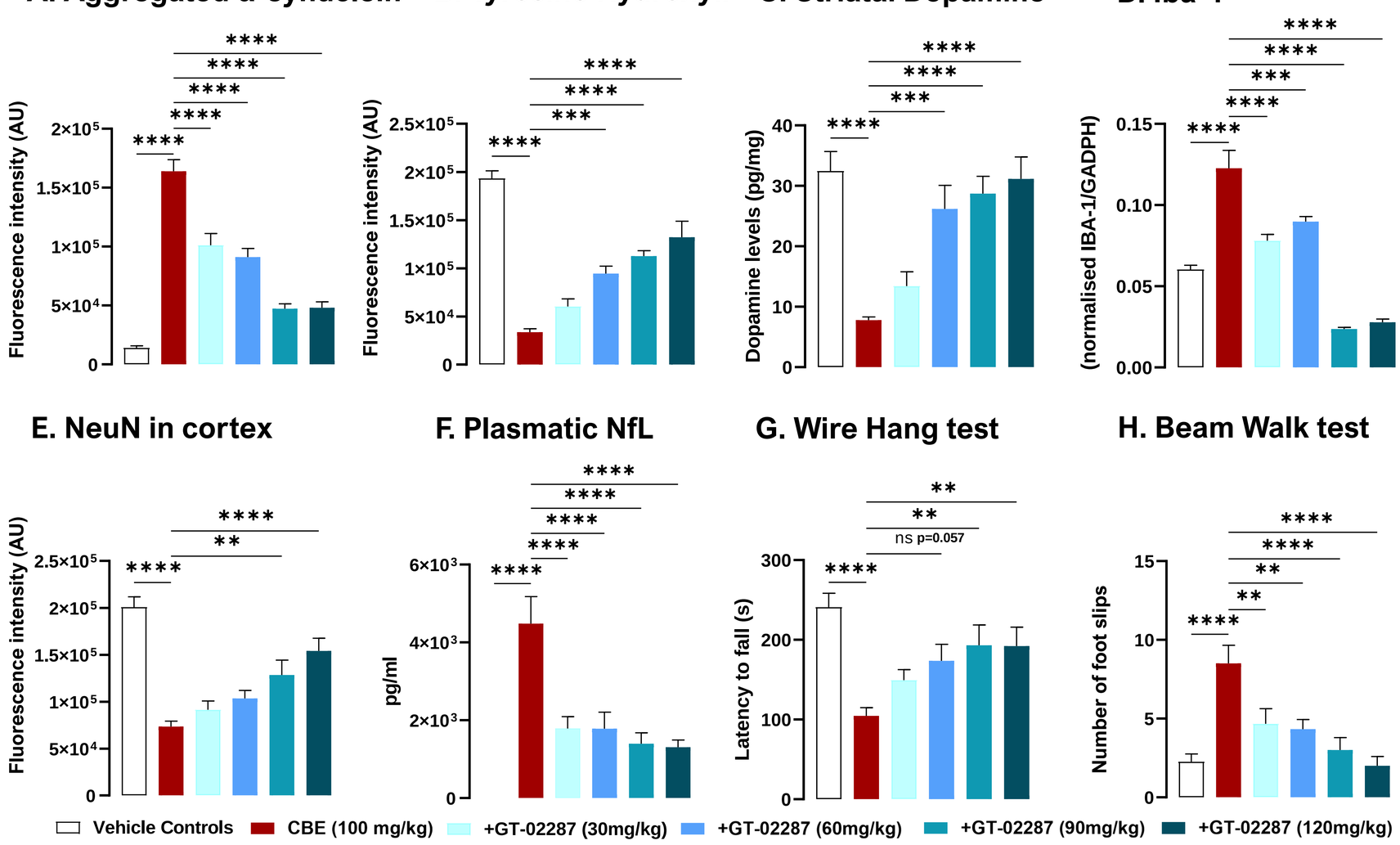


Fig.1 Aggregated α-synuclein (A) and tyrosine hydroxylase (TH) (B) levels in the substantia nigra; dopamine levels in the striatum (C); Iba-1 (D) and NeuN (E) in the cortex; neurofilament light chain (NfL) (F) levels in plasma, as well as neuromuscular strength (G) and motor coordination (H) in vehicle controls (white bars), CBE-injected mice (red bars) and CBE-injected mice orally treated with GT-02287 at 30 mg/kg Q.D. (light blue bars), 60 mg/kg Q.D. (medium blue bars), 90 mg/kg Q.D. (turquoise bars) and 120 mg/kg Q.D. (dark blue bars) for 14 days. Data is shown as mean ± S.E.M. (n=9-12), One-way ANOVA followed by Dunnett's Multiple Comparison Test. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001.

Conclusions

Augmentation of GCase function by GT-02287 protects against key pathophysiological hallmarks of PD and provides a neuroprotective effect reflected by a significant reduction in levels of plasma NfL, an emerging biomarker for neurodegeneration, as well as increasing motor function. GT-02287 emerges as a potential disease-modifying, orally bioavailable therapy for PD.