PRECLINICAL DEVELOPMENT OF THE NOVEL GCASE ALLOSTERIC MODULATOR GT-04686 IN A GBA1 PARKINSON'S DISEASE MODEL

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Background

Reduced glucocerebrosidase (GCase) activity is thought to contribute to the pathogenesis of both GBA1 associated and sporadic Parkinson's disease (PD), highlighting GCase activity enhancement as a promising therapeutic approach. Utilizing its Magellan™ virtual screening platform, Gain Therapeutics developed rexaceract, a small-molecule Structurally Targeted Allosteric Regulator (STAR) of GCase, currently in clinical development as a potential disease modifying therapy for PD.

Expanding on this platform, Gain has identified a structurally distinct chemical series, leading to the novel GCase modulator GT-04686. This promising compound has been characterized in previously established *in vitro* PD models as well as in the *in vivo* model presented here.

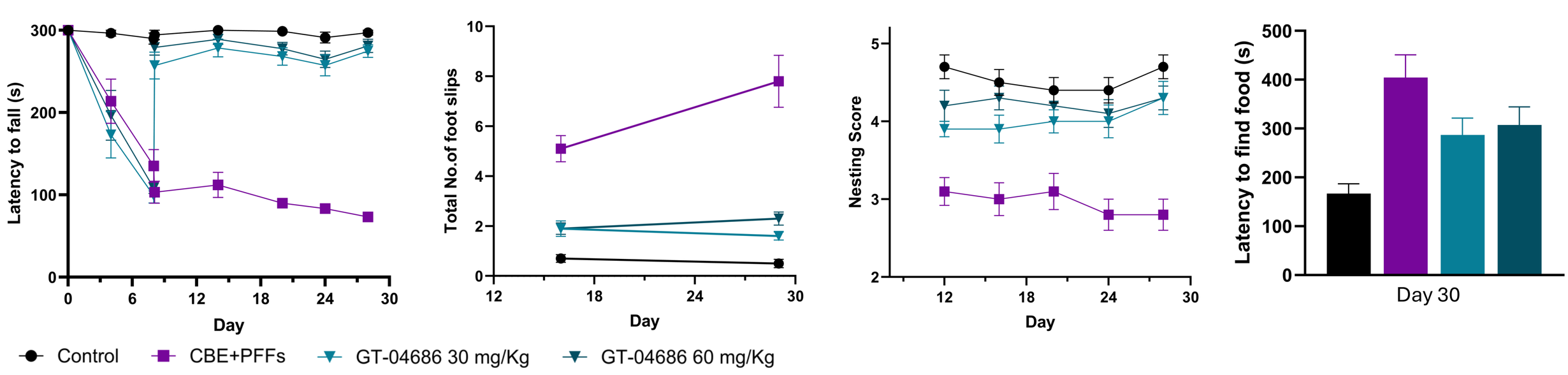
Methods

To model GBA1-PD, C57BL/6 mice received a single intrastriatal injection of α-synuclein preformed fibrils (PFFs) on day 1, combined with a chronic low-dose intraperitoneal administration of conduritol β-epoxide (CBE), a covalent GCase inhibitor, at 50 mg/kg every other day from day 1. In a delayed treatment paradigm, beginning on day 8, GT-04686 (30 or 60 mg/kg) was administered orally once daily until day 30. Motor and non-motor functions were evaluated on days 28-29, and brain biomarkers were analyzed at sacrifice on day 30. Motor and non-motor functions were evaluated on days 28-29, and brain biomarkers were analyzed at sacrifice on day 30.

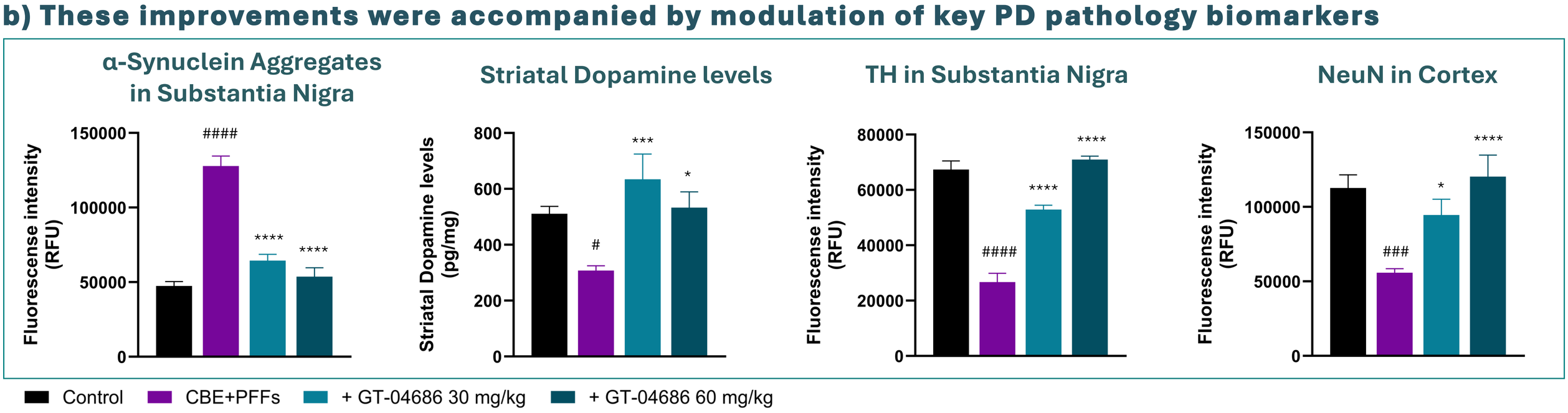
Results

- Delayed oral administration of GT-04686 (30 and 60 mg/kg, from day 8) restored wire hang latency to near-control levels and reduced foot slips vs. untreated CBE+PFFs mice. GT-04686 also improved nesting scores toward control levels and ameliorated the olfactory deficit.
- Effects were accompanied by fewer α-synuclein aggregates in the substantia nigra and by restoration of striatal dopamine, tyrosine hydroxylase (TH) in the substantia nigra and cortical NeuN toward control levels, suggesting neuroprotection.

a) GT-04686 improved motor function and complex behaviors in the GBA1-PD model



b) These improvements were accompanied by modulation of key PD pathology biomarkers



***In vivo* effect of GT-04686 in a CBE/PFFs mouse model**. Data is shown as mean ± SEM, n = 10.
Significant difference as compared to sham control * Significant difference as compared to CBE+PFFs vehicle control. One-way ANOVA followed by Dunnett's multiple comparison test. #/* $P < 0.05$; ###/*** $P < 0.001$; ####/**** $P < 0.0001$.

Conclusions

The orally bioavailable and brain-penetrant compound GT-04686 restored both motor and complex behavioral function and positively modulated biomarkers of neurodegeneration in the GBA1-PD model. These results support positioning for IND-enabling studies in PD and potentially other GCase-deficient pathologies. GT-04686 is the second Magellan™-derived compound seeking clinical entry, underscoring the potential of AI-driven drug discovery.

Acknowledgements

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