Targeting GBA1 for Parkinson’s disease research

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Background & Rationale

Mutations in the GBA1 gene, which encodes for lysosomal glucocerebrosidase (GCase), have been identified as causative for Gaucher disease (GD), a rare lysosomal storage disorder and represent the most common genetic risk factor for Parkinson’s disease (PD) (Sidorovsky et al., 2009). The proportion of PD patients that carry GBA1 mutations is estimated to be between 5% and 10%. The penetrance and lifetime risk of developing PD for GBA1 mutation carriers is estimated up to 20% at 70 years (Schipper 2015).

Decreased GCase activity has been reported in both PD patients with GBA1 mutations and without GBA1 mutations (Murphy et al., 2014). Emerging experimental evidence in cell-free systems, cells, animal models and patient samples suggests a correlation between this decreased activity and accumulation of alpha-synuclein (aSyn) (Fishbein et al., 2011; Gegg et al., 2012; Mazulli et al., 2011; Sardi et al., 2011).

These strong genetic and pathologic links make GCase an attractive target for PD drug development. As such, The Michael J. Fox Foundation (MJFF) has made robust investments to address key questions to effectively translate GCase therapeutically for PD patients. The current poster details MJFF activities which address critical gaps in our knowledge of role of GBA1 in PD and tackle key challenges facing GCase drug development.

MJFF is Making Robust Investments to Address Research & Therapeutic Challenges

Generating and characterizing preclinical models

Homozygous GBA D409V knock-in in Mouse [Available at the Jackson Laboratory Stock #10106]

Biochemical analysis.

How much of an increase (both amount and duration) of GCase activity is optimal for drug development?

Results from Amicus team

Results from Pfizer team

Biomarkers

Defining clinical outcomes measures and biomarkers in GBA1 cohorts

Parkinson's Progression Marker Initiative (PPMI) – Study Details

Funding diverse therapeutic programs targeting GCase

Summary

MJFF’s vision is to apply a holistic strategy to address research and therapeutic challenges to enable accelerated development of GBA1-targeting therapeutics and optimally informed clinical trials.

Homozygous GBA1 D409V knock-in mouse shows significant reductions in GCase activity and GCase probe signal, and significant increase in GcLiP levels in both brain and liver. Studies are underway for GBA1 D409V KI mouse cross-bred with aSyn transgenic mouse to determine if loss of GCase function affects aSyn induced pathology and related phenotypes.

Key Questions in Developing GCase Targeting Therapies

Genetics

- Is GBA1 mutation-associated PD phenotypically similar to idiopathic PD?
- Do human or mouse genetic studies provide insights into GCase activity needed for therapeutic efficacy?

Therapeutics

- What is the most optimal therapeutic modality for targeting GCase?
- How much of an increase (both amount and duration of increase) in GCase activity is needed to see efficacy?
- What cell culture models, animal models and endpoints are optimal for drug development?
- What is the potential utility of increasing GCase activity?

Biomarkers

- What are the target engagement and pharmacodynamic markers to inform clinical dose selection and to track drug efficacy?
- What are the most optimal, standardized and validated assays to measure GCase activity to measure ceramide pathway analytes?
- Could alpha-synuclein serve as a good biomarker in GCase targeting trials?

Clinical Cohorts

- What is the optimal patient population for Phase 1 and Phase 2/POC trials?
- How can we enrich for a population most likely to respond to GCase activation?
- Would GCase targeted therapies work in pan population or tailored patient populations?
- What clinical outcome measures should be used for Phase 2/POC trials?
- What should be the duration of the POc trial?