THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

BETA-GLUCOCEREBROSIDASE (GBA1/GCASE)

The most common genetic form of Parkinson's disease (PD) is caused by heterozygous mutations in the *GBA1* gene which encodes the lysosomal enzyme GCase, leading to decreased activity and accumulation of the substrates glucosylsphingosine (GlcSph) and glucosylceramide (GlcCer). Patients with *GBA1* mutations present as clinically and pathologically similar to idiopathic PD, but with increased cognitive impairment. There are a number of models available that use gene mutations or other means to reduce GCase activity. Below you will find a list of those that are commonly used. Please note, this list is by no means comprehensive. A good review of models can be found here.

CBE MODEL

- Description: Conduritol- β -epoxide (CBE) is a potent, selective, and irreversible competitive inhibitor of GCase. This model involves systemic administration of CBE to reduce GCase activity and study resulting changes within the brain. Chronic treatment (28 days) with a 50mg/kg dose results in reduction of GCase activity similar to what is seen in PD patients (~50%) with neuroinflammation. No alpha-synuclein pathology is observed at this dose. Chronic treatment with a 100mg/kg results in ~90% reduction of GCase activity, accumulation of GlcCer and GlcSph, alpha-synuclein aggregation, neuroinflammation, and cortical neuron loss. Degeneration of the nigrostriatal system and motor deficits are not observed.
- Recommended Use: This model is recommended when the primary objective is to decrease GCase activity and a rapid, inducible model is preferred. It is not recommended if one wants to consider effects of *GBA1* mutations outside of GCase activity reduction or model nigrostriatal degeneration.
- Helpful Resources:
  - 50mg/kg Model – Rocha et al. (2015). *Antioxid Redox Signal,* 23(6): 550-564.
  - 100mg/kg Model – Mus et al. (2019). *Neurobiol Dis,* 124: 289-296.

GBA1 D409V KI MOUSE

- Description: The D409V mutation is not a PD-linked mutation but was chosen for use in a rodent model because it results in substantial reduction of GCase activity. In this model, a D409V point mutation in the mouse *Gba1* gene leads to dramatic reduction in GCase activity and accumulation of GlcSph (but not GlcCer) substrates. There are two different *GBA1* D409V KI mouse lines in the field. The nigrostriatal system remains intact in both lines and motor deficits are not observed. Differences exist in GCase express and extent of hippocampal pathology:
  - Grabowski Line - In the homozygous line GCase activity is reduced 75% with GlcSph increase ~4-fold in brain. Mice display more robust aSyn pathology and inflammation in the hippocampus with cognitive impairments.
  - MJFF Line - In this homozygous line, brain GCase activity is reduced 90% and brain GlcSph increases ~12-fold. Some report hippocampal pathology including increased aSyn, inflammation, and cognitive impairments.
- Recommended Use: This model is recommended for researchers who are interested in a model with constitutive, substantial GCase activity reduction. It is a useful model for studying the hippocampal/memory-associated changes resulting from decreased GCase activity. It is not suited for studies into nigrostriatal pathology.
- Helpful Resources:
  - Commercial Availability
    - The Grabowski line is not commercially available. The MJFF line is available at JAX (JAX #019106).
  - Characterization of the Grabowski line: Sardi et al. (2011). *PNAS,* 108(29): 12101-12106.
  - MJFF-funded characterization of the MJFF line: Polinski et al. (2021). *PloS One,* 16(6): e0252325.
  - Hippocampal evaluation of the MJFF line: Clarke et al. (2019). *Neurochem Int,* 129: 104502.

ICON KEY

Protein Expression Level			Protein/Gene Species		Mutation	Pathology				
Endogenous Expression	Over-expression	Knockout	Human	Rodent	Mutant	Nigrostriatal Degeneration	α-Synuclein Pathology	Inflammation	Motor Impairments	Cognitive Impairments

GBA1 L444P KI MOUSE

- Description: This model has a heterozygous L444P point mutation in the mouse *Gba1* gene to model the more aggressive *GBA1* mutation in Parkinson's disease patients. The line displays ~30% loss of GCase activity in brain, GlcSph accumulation in brain, neuroinflammation, and alpha-synuclein pathology. No nigrostriatal degeneration is observed, brain GlcCer levels are not elevated, and there are no deficits in olfaction, cognition, or motor behavior.
- Recommended Use: This model is recommended for researchers interested in using a model with a more aggressive patient-related point mutation in GBA under physiological expression conditions. It is suited for biological studies into the relationship between GBA, synuclein, and/or inflammation.
- Helpful Resources:
  - Commercial Availability - A line from the Ginns lab is available at JAX (#024574). A line from the Proia lab is available at the MMRRC (ID 117) but has off target effects on metaxin and is only available to non-profits.
  - Alternative Options - A line also exists that overexpresses the human *GBA1* gene with an L444P mutation on a mouse *Gba1* knockout background. This line is available at JAX (JAX #024574) and is suitable for studies using pharmacological chaperones specific for human GCase.

LESS COMMON MODELS

- *GBA1* N370S Mouse: This model either has an N370S mutation in mouse *Gba1* or expresses human *GBA1* with the N370S mutation. This model may be selected as the N370S mutation is the most common mutation in PD patients. This model is not commonly used because reduction in GCase activity is modest and other phenotypes are absent.
  - If you are interested in a GBA1 N370S mouse model, a line exists that overexpresses the human *GBA1* gene with an N370S mutation on a mouse *Gba1* knockout background. This line is available at JAX (JAX #032791).
- *Gba1* Knockout Mouse: Knockout of the mouse *Gba1* gene could also be a strategy for reducing GCase activity. However, this is generally not pursued as it is preferable to retain expression of the GCase protein in models as is seen in humans. Furthermore, homozygous knockout of the *Gba1* gene is lethal.
  - A line with conditional knockout in the nigra was developed to enable homozygous deletion of the gene. The line displays a 40% reduction in GCase activity, GlcCer accumulation, and microglial activation but no aSyn pathology, nigrostriatal degeneration, or motor deficits. This model is described in Soria et al (2017).

GBA-ASYN COMBINATION MODELS

- No GBA transgenic/knockin model displays nigrostriatal degeneration or synuclein pathology in the substantia nigra as is seen in Parkinson's disease patients. To generate such a model, groups have attempted the following (titles provide hyperlink to example publication):
  - CBE+MPTP – Increase in aSyn expression and striatal degeneration.
  - MJFF GBA D409V KI Mouse + aSyn PFFs – pS129 aSyn pathology, striatal neurochemistry deficits, and loss of nigral dopamine neurons at 6 months post-injection, not exacerbated by D409V mutation.
  - MJFF GBA D409V KI x mThy1 hSNCA Mouse – Increased pS129 aSyn and grip strength deficits at 12 months. Nigral dopamine neurons intact. Line is available at JAX (JAX #029124).
  - Proia GBA L444P KI Mouse + MPTP – Striatal neurochemistry deficits, loss of nigral neurons, inflammation, increased aSyn expression, mitochondrial dysfunction, and motor deficits.
  - Proia GBA L444P KI Mouse + aSyn PFFs – Nigral pS129 aSyn pathology and loss of nigral dopamine neurons at 10 months post-injection, not exacerbated by L444P mutation. No motor deficits observed.
  - Proia GBA L444P KI Mouse + AAV Hu WT aSyn – AAV aSyn in aged mice resulted in pS129 aSyn pathology (similar extent between genotypes). Loss of nigral neurons occurred and was exacerbated by L444P mutation.
  - Proia GBA L444P KI x Human A53T aSyn on Mouse *SNCA* KO – Increased aSyn pathology (in hippocampus), motor deficits, and GI dysfunction at 14 months. Line is at MMRRC (ID 037633-JAX) for non-profit groups only.

ICON KEY

Protein Expression Level			Protein/Gene Species		Mutation	Pathology				
Endogenous Expression	Over-expression	Knockout	Human	Rodent	Mutant	Nigrostriatal Degeneration	α-Synuclein Pathology	Inflammation	Motor Impairments	Cognitive Impairments