All contributing authors were or are employees of Prevail Therapeutics
PR001 gene therapy increased GCase activity and ameliorated GBA1-associated disease phenotypes

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Patty Sheehan, Ph.D.
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Overview

Background
- Gene therapy approach
- Scientific rationale for the PD-GBA program

PR001 Preclinical Efficacy and Safety
- PR001 is an AAV9-GBA1 vector
- *In vivo* efficacy in mouse models
- *In vivo* safety data in NHPs and mouse models

Clinical Development
- Ongoing Phase 1/2 clinical trial design
Human genetic studies have identified genes that cause or increase risk of neurodegenerative diseases
Many of these genes are involved in lysosomal function
Gene therapy can enable delivery of a functional gene to the CNS
We plan to develop our therapies for genetically-defined patient populations with corresponding mutations
Many PD causative and risk genes are directly involved in lysosomal function and trafficking.

GBA1 mutations (present in 7-10% of PD patients) increase the risk of developing PD and impact the severity, age of onset, rate of progression of disease, and likelihood of dementia.

Source: Abeliovich and Gitler, Nature 2016; Bras, Guerreiro, Hardy, Cell 2015
PD-GBA and neuronopathic GD are a continuum of pathology with the same underlying genetic mechanism.

Number and severity of GBA1 mutations ➔ Decreasing enzyme activity ➔ Increasing disease severity

- **0 mutations**
  - “Sporadic” Parkinson’s
  - PD-GBA with less severe phenotype

- **1 mild / moderate mutation**
  - PD-GBA with more severe phenotype

- **1 severe mutation**
  - Type 1 Gaucher disease
  - At elevated risk of PD-GBA with more severe phenotype

- **2 mild / moderate mutations**
  - Type 2 & 3 Gaucher disease (neuronopathic)
PD-GBA: mechanism of disease

Parkinson’s Disease
WITH GBA1 MUTATION

INSUFFICIENT GCASE ACTIVITY

SUBSTRATE INCREASES (GLUCER, GLUSPH)

PRODUCT DECREASES (CERAMIDE)

SECONDARY LIPID CHANGES

DYSFUNCTIONAL LYSOSOME

NEURODEGENERATION

INFLAMMATION

α-SYNUCLEIN AGGREGATION

Parkinson’s Disease
PATHOLOGY

Parkinson’s Disease
WITH GBA1 MUTATION

INSUFFICIENT GCASE ACTIVITY

SUBSTRATE INCREASES (GLUCER, GLUSPH)

PRODUCT DECREASES (CERAMIDE)

SECONDARY LIPID CHANGES

DYSFUNCTIONAL LYSOSOME

NEURODEGENERATION

INFLAMMATION

α-SYNUCLEIN AGGREGATION
PR001 overview

**PR001**
- AAV9 viral vector delivering the *GBA1* gene, which encodes glucocerebrosidase (GCase)

**Route of Administration**
- Single intra-cisterna magna (ICM) injection

**Lead Indications**
- Parkinson’s disease with at least one *GBA1* mutation (PD-GBA)
  - Earlier disease onset, more rapid progression, and higher rate of dementia than sporadic PD
- Neuronopathic Gaucher disease (nGD)
  - Neurological form of Gaucher due to severe GCase deficiency

**Progress and Status**
- Patient dosing initiated for Phase 1/2 PROPEL trial for PD-GBA
- Study startup activities ongoing for Phase 1/2 PROVIDE trial for Type 2 Gaucher disease
PR001 dose-ranging efficacy and biodistribution study in the CBE mouse model

- CBE is a pharmacological inhibitor of GCase
- Dose-ranging efficacy study with PR001 in CBE model
- Intra-cisterna magna delivery route not feasible in mice; thus ICV delivery used

ICV PR001 Delivery
(low, middle, high dose)

<table>
<thead>
<tr>
<th>PR001 dose</th>
<th>Total vg</th>
<th>vg/g brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>$2.0 \times 10^9$</td>
<td>$1.3 \times 10^{10}$</td>
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<tr>
<td>Middle</td>
<td>$6.2 \times 10^9$</td>
<td>$4.2 \times 10^{10}$</td>
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<tr>
<td>High</td>
<td>$2.0 \times 10^{10}$</td>
<td>$1.3 \times 10^{11}$</td>
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PR001 increased GCase activity and decreased glycolipid accumulation in the cerebral cortex of the CBE model

- Vector genomes were observed to be present in the cerebral cortex 5 weeks after ICV PR001 administration
- CBE treatment reduced GCase enzyme activity and increased glycolipid accumulation in the brain
- PR001 increased GCase enzyme activity and suppressed glycolipid accumulation in the brain

Means are presented +/- SEM. N=6-10 per group. *: p<0.05; **: p<0.01; ***: p<0.001 by ANOVA followed by Tukey's HSD multiple tests correction. Vector genome levels below $10^2$ (dotted line) considered not significant. GluSph, glucosylsphingosine
PR001 decreased neuropathology and increased behavioral performance in the CBE model

Gliosis:
- CBE induced reactive astrogliosis (evidenced by glial scarring) and microgliosis (evidenced by Iba1 immunoreactivity)
- PR001 significantly reduced reactive astrogliosis and microgliosis in a dose-dependent manner

Behavior:
- CBE reduced motor performance in a rotarod test
- PR001 significantly suppressed motor performance deficit

Means are presented +/- SEM. N=6-10 per group.
*: p<0.05; **: p<0.01; ***: p<0.001. by one-way ANOVA and Sidak’s post hoc test for multiple comparisons for Iba1 immunoreactivity or Fischer’s exact test for glial scarring.
For rotarod, nominal p values were calculated by linear regression in the CBE-treated groups, with gender corrected for as a covariate.
**PR001 long-term efficacy study in the CBE model**

CBE was given IP daily for approximately 6 months to establish a long-term model in order to evaluate persistence of transgene expression and efficacy.

<table>
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<tr>
<th>PR001 dose</th>
<th>Total vg</th>
<th>vg/g brain</th>
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</thead>
<tbody>
<tr>
<td>single</td>
<td>$2.0 \times 10^{10}$</td>
<td>$1.3 \times 10^{11}$</td>
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</table>

ICV, intracerebroventricular; IP, intraperitoneal
PR001 expression and efficacy persisted for 6 months post-treatment

- PR001 increased GCase activity and suppressed glycolipid substrate accumulation at 6 months post-treatment

Means are presented +/- SEM. N=10-11 per group. (*): p<0.2; *: p<0.05; ***: p<0.001 by ANOVA followed by Tukey’s HSD multiple tests correction.
PR001 dose-ranging efficacy study in the 4L/PS-NA mouse model

- 4L/PS-NA mice are homozygous for the V394L Gba1GD mutation and express a low level of prosaposin protein
PR001 increased GCase activity, decreased glycolipid accumulation, and increased motor performance

- PR001 increased GCase enzyme activity (cortex)
- 4L/PS-NA mice exhibited glycolipid accumulation
- PR001 suppressed lipid accumulation (cerebellum)
- 4L/PS-NA mice exhibited motor behavior dysfunction
- PR001 improved motor function in a beam walk test

Each bar represents the mean ± SEM. N=7-10 per group. P-value: *p<0.05, ***p<0.001 by one-way analysis of variance followed by Tukey HSD. †: p<0.1 for effect of PR001 injected dose by multiple linear regression for genotype and dose across all animals.
PR001 single-dose efficacy study in the 4L/PS-NA mouse model

- Single dose efficacy study with PR001 in genetic model 4L/PS-NA
PR001 decreased α-Synuclein accumulation in the 4L/PS-NA mouse model

- Elevated insoluble α-Synuclein, and increased ratio of insoluble to soluble α-Synuclein, observed in 4L/PS-NA mouse cortex
- PR001 reduced insoluble α-Synuclein and decreased the ratio of insoluble to soluble α-Synuclein protein in cortex

Each bar represents the mean ± SEM. N=3-5 per group. (*): p=0.09 and 0.19 in A and B respectively, by ANOVA followed by Tukey’s HSD multiple tests correction.
PR001 safety and GCase expression in NHPs

Safety

- No PR001-related safety events or adverse findings were observed in three NHP studies.
- Highest dose tested in NHPs provides:
  - 9x safety margin to PD-GBA clinical starting dose.

NHP GCase expression following ICM delivery

- Broad distribution of PR001 vector to all brain areas.
- Significant elevation of GCase protein levels in brain tissue.

Dose dependent trend analysis using Williams’ Trend test across all brain regions and dose groups: p<0.05; n=3 per group.

Excipient: $6.2 \times 10^{10}$ vg/g brain

PR001: $2.3 \times 10^{11}$ vg/g brain
No safety signals have been seen in PR001 animal studies

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<thead>
<tr>
<th>PR001 study</th>
<th>ROA</th>
<th>Histopathology</th>
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<tr>
<td>CBE mouse dose ranging study</td>
<td>ICV</td>
<td>No safety signals</td>
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<tr>
<td>Genetic mouse studies</td>
<td>ICV</td>
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<tr>
<td>Non-GLP NHP study</td>
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<tr>
<td>GLP NHP tox study</td>
<td>ICM</td>
<td>No safety signals</td>
</tr>
<tr>
<td>High-dose non-GLP NHP study</td>
<td>ICM</td>
<td>No safety signals</td>
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- All doses observed to be well-tolerated to date (NOAEL not reached)
- No PR001-related adverse clinical labs, including liver panel tests such as ALT/AST
- No PR001-related pathology or inflammation in the dorsal root ganglia (DRG)
PR001 PD-GBA Phase 1/2 trial
Randomized, double-blind, sham procedure-controlled

- Single or biallelic GBA1 mutations
- Moderate to severe Parkinson's disease
- Stable background PD medication

- Safety and tolerability
- Key biomarkers: GCase, GluCer, GluSph (CSF and blood)
- Additional biomarkers: α-Synuclein, NfL, DAT SPECT, MRI
- Efficacy: MDS-UPDRS, cognition, ADLs

PR001 Low Dose vs. Placebo (N=8, 6:2)
PR001 High Dose vs. Placebo (N=8, 6:2)

ICM: intra-cisterna magna; MDS-UPDRS: Movement Disorders Society Unified Parkinson's disease Rating Scale; ADLs: Activities of Daily Living; NfL: neurofilament light; DAT: Dopamine transporter; SPECT: single photon emission computed tomography
Conclusions

- PR001 has shown positive results in multiple PD-GBA mouse models
  - PR001 reversed glycolipid accumulation, decreased neuroinflammation, improved behavioral abnormalities, and reduced α-Synuclein burden

- PR001 administration via ICM injection was well-tolerated in NHPs

- A Phase 1/2 clinical trial in PD-GBA patients is underway

- An additional clinical trial in Type 2 Gaucher patients is planned to initiate this year
Thank You!

Asa Abeliiovich
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Jennifer Daily
Jason Politi
Yong Dai
Franz Hefti

Tim Fenn
Sid Kamalakaran
Swetha Garimalla
Zarah Aziz