<table>
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<tr>
<th>Company/Name</th>
<th>Honoraria/Expenses</th>
<th>Consulting/Advisory Board</th>
<th>Funded Research</th>
<th>Royalties/Patent</th>
<th>Stock Options</th>
<th>Ownership/Equity Position</th>
<th>Employee</th>
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<td>Prevail Therapeutics</td>
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PR001 gene therapy improved PD-GBA phenotypes in mouse models by increasing GCase activity

April 5, 2020
Asa Abeliovich, M.D., Ph.D.
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Overview

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

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

Next Steps
- Ongoing Phase 1/2 clinical trial design
Precision genetic medicine approach to neurodegenerative diseases

- 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
AAV9 is well-suited to deliver functional genes or gene knockdown to the CNS

- AAV9-based therapy has shown transformative efficacy and safety and is now approved for SMA
- The effectiveness of AAV9-based therapies is due to its ability to distribute broadly across the CNS
- AAV9 manufacturing process is well-characterized and scalable
- Prevail has licensed exclusive WW rights to AAV9 from REGENXBIO to deliver the genes in our lead programs
Human genetic studies of Parkinson’s have identified GBA1 mutations as clinically critical

- 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.

<table>
<thead>
<tr>
<th>Number of GBA1 Mutations</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>“Sporadic” Parkinson’s</td>
</tr>
<tr>
<td>1 mild / moderate mutation</td>
<td>PD-GBA with less severe phenotype</td>
</tr>
<tr>
<td>1 severe mutation</td>
<td>PD-GBA with more severe phenotype</td>
</tr>
<tr>
<td>2 mild / moderate mutations</td>
<td>Type 1 Gaucher disease</td>
</tr>
<tr>
<td>2 severe mutations</td>
<td>Neuronopathic Gaucher disease</td>
</tr>
</tbody>
</table>

At high risk of developing PD-GBA with more severe phenotype.
Evidence of effects of a GBA1 dose-dependent effect and mutation severity on the cognitive manifestations of PD

- Among patients with one mutant GBA1 allele, more severe mutations were associated with more rapid progression to dementia.
- Parkinson’s patients with two mutant GBA1 alleles present with more severe findings than patients with one mutant GBA1 allele or none.

Source: Liu et al., Annals of Neurology 2016; Thaler et al., Parkinsonism and Related Disorders 2017
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
- Inflammation
- Neurodegeneration
- α-Synuclein Aggregation

Parkinson’s Disease PATHOLOGY
PR001 mechanism of action in PD-GBA

Parkinson’s Disease
WITH GBA1 MUTATION

PR001 Treated

GBA1 GENE

PREVENTS ENZYMATIC DECAY OF GBA1

INCREASED GCase

INFLAMMATION REDUCED

FUNCTIONAL LYSOSOME

SECONDARY LIPIDS NORMALIZE

PRODUCT INCREASES

SUBSTRATE DECREASES (GLUCER, GLUSPH)

NEURODEGENERATION SLOWED OR STOPPED

PROTEIN AGGREGATION REDUCED
## PR001 overview

<table>
<thead>
<tr>
<th>PR001</th>
<th>Route of Administration</th>
<th>Lead Indications</th>
<th>Progress and Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>● AAV9 viral vector delivering the <strong>GBA1</strong> gene, which encodes glucocerebrosidase (GCase)</td>
<td>● Single intra-cisterna magna (ICM) injection</td>
<td>● Enrollment ongoing for Phase 1/2 PROPEL trial for PD-GBA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Parkinson’s disease with at least one <strong>GBA1</strong> mutation (PD-GBA)</td>
<td>● Site activation in process for Phase 1/2 PROVIDE trial for Type 2 Gaucher disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>○ Earlier disease onset, more rapid progression, and higher rate of dementia than sporadic PD</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>● Neuronopathic Gaucher disease (nGD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>○ Neurological form of Gaucher due to severe GCase deficiency</td>
<td></td>
</tr>
</tbody>
</table>
# PR001 preclinical studies

<table>
<thead>
<tr>
<th>Model</th>
<th>Study</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBE mice</td>
<td>Dose-ranging ICV PR001 efficacy studies</td>
<td>• PR001 transgene was delivered to and expressed in the CNS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PR001 transgene expression resulted in phenotypic correction</td>
</tr>
<tr>
<td></td>
<td>Long-term (6 month) ICV PR001 efficacy study</td>
<td>• GCase expression and resulting efficacy persisted</td>
</tr>
<tr>
<td>Gba1 knock-in mice expressing low levels of prosaposin (4L/PS-NA)</td>
<td>Dose-ranging ICV PR001 efficacy study</td>
<td>• PR001 demonstrated efficacy in genetic model</td>
</tr>
<tr>
<td></td>
<td>Maximal dose ICV PR001 efficacy study</td>
<td>• Efficacy achieved at max feasible dose</td>
</tr>
<tr>
<td>α-Synuclein transgenic (SNCA-A53T) mice treated with CBE</td>
<td>ICV PR001 efficacy study</td>
<td>• PR001 reduced α-Synuclein accumulation in mouse model</td>
</tr>
<tr>
<td>In vitro cell cultures</td>
<td>PR001 effect on α-Synuclein in HeLa cells</td>
<td>• PR001 reduced α-Synuclein accumulation in human cell line</td>
</tr>
<tr>
<td></td>
<td>PR001 effect on α-Synuclein in mouse hippocampal neurons</td>
<td>• PR001 reduced α-Synuclein accumulation in neurons</td>
</tr>
<tr>
<td>Healthy NHPs</td>
<td>Non-GLP NHP safety and biodistribution study of ICM PR001</td>
<td>• ICM delivery of PR001 resulted in exposure &amp; distribution comparable to efficacious exposures in ICV mouse studies</td>
</tr>
<tr>
<td></td>
<td>GLP NHP safety and biodistribution study of ICM PR001</td>
<td>• Determined PR001 dose expected to be safe and efficacious in humans</td>
</tr>
</tbody>
</table>

ICV, intracerebroventricular; ICM, intra-cisterna magna
**PR001 dose-ranging efficacy and biodistribution study in the CBE mouse model**

- Dose-ranging efficacy study with PR001 in CBE model
- Doses chosen based on CMC technical limitation and data from previous study
- Cisterna magna delivery route not feasible in mice; thus ICV delivery used

<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>
</tr>
<tr>
<td>Middle</td>
<td>$6.2 \times 10^9$</td>
<td>$4.2 \times 10^{10}$</td>
</tr>
<tr>
<td>High</td>
<td>$2.0 \times 10^{10}$</td>
<td>$1.3 \times 10^{11}$</td>
</tr>
</tbody>
</table>

ICV, intracerebroventricular
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
PR001 expression and efficacy persisted for at least 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 genetic mouse model

- Dose-ranging efficacy study with PR001 in genetic model 4L/PS-NA
- Doses chosen based on CMC technical and experimental limitation
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<0.01 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 genetic mouse model

- Single dose efficacy study with PR001 in genetic model 4L/PS-NA
- Dose chosen based on technical and experimental limitation

<table>
<thead>
<tr>
<th>PR001 dose</th>
<th>Total vg</th>
<th>vg/g brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>single</td>
<td>$1.5 \times 10^{10}$</td>
<td>$3.7 \times 10^{10}$</td>
</tr>
</tbody>
</table>
PR001 decreased α-Synuclein accumulation in the genetic mouse model

- Elevated insoluble α-Synuclein, and increased ratio of insoluble to soluble α-Synuclein, 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 efficacy study in α-Synuclein transgenic mice treated with CBE

α-Synuclein protein levels (Jess)

PR001 Delivery (ICV)

Day 0

2 weeks

3 weeks

PBS or 100 mg/kg CBE IP treatment

A53T

Aged 9-10 weeks (n=4-5/group)

<table>
<thead>
<tr>
<th>PR001 dose</th>
<th>Total vg</th>
<th>vg/g brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>single</td>
<td>$2.9 \times 10^{11}$</td>
<td>$7.4 \times 10^{11}$</td>
</tr>
</tbody>
</table>

ICV, intracerebroventricular
PR001 suppressed high molecular weight α-Synuclein accumulation in transgenic mice treated with CBE

- Quantitative Simple Western protein assay of hippocampus lysates from α-Synuclein transgenic mice treated with ICV vehicle control (vehicle), IP CBE with ICV vehicle, or IP CBE with ICV PR001
- PR001 suppressed accumulation of high molecular weight (HMW) α-Synuclein aggregates relative to monomer

Means are presented +/- SEM. N=3-5 per group. *: p<0.05 by ANOVA followed by Tukey’s HSD multiple tests correction. IP, intraperitoneal; ICV, intracerebroventricular
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 starting dose

NHP biodistribution with ICM delivery

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

NHP study: Control Dose = 0 vg/g brain weight; Low Dose = $6.2 \times 10^{10}$ vg/g brain weight PR001; High Dose = $2.3 \times 10^{11}$ vg/g brain weight PR001; N=3 per group

Dose dependent trend analysis using Williams’ Trend test across all brain regions and dose groups: p<0.05
No safety signals have been seen in PR001 animal studies

<table>
<thead>
<tr>
<th>PR001 study</th>
<th>ROA</th>
<th>Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBE mouse dose ranging study</td>
<td>ICV</td>
<td>No safety signals</td>
</tr>
<tr>
<td>Genetic mouse studies</td>
<td>ICV</td>
<td>No safety signals</td>
</tr>
<tr>
<td>Non-GLP NHP study</td>
<td>ICM</td>
<td>No safety signals</td>
</tr>
<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>
</tr>
</tbody>
</table>

- 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

**PD-GBA Patients**
- Single or biallelic GBA1 mutations
- Moderate to severe Parkinson’s disease
- Stable background PD medication

**PR001 Low Dose vs. Placebo (N=8, 6:2)**
- Single ICM injection
- 3 month biomarker readout
- 12 month clinical readout
- 5-year safety and clinical follow-up

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

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

- PR001 demonstrated efficacy 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 is underway
Thank You!

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Zarah Aziz