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Prevail Therapeutics overview

- Potential disease-modifying targets identified based on human genetics
- Targeting genetically defined patient populations
- Gene delivery with AAV9 vector has a track record of efficacy and safety

- Phase 1/2 PROPEL trial for Parkinson’s with GBA1 mutations (PD-GBA) underway; PD-GBA affects >90K Americans
- Potential for rapid proof-of-concept for PR001 in neuronopathic Gaucher disease; PROVIDE trial planned to initiate enrollment in 2H 2020

- PR006 IND active for frontotemporal dementia with GRN mutations (FTD-GRN)
- Phase 1/2 PROCLAIM trial on track to initiate enrollment in 2H 2020

- Expertise in developing therapies for neurodegenerative diseases
- Additional genetically-validated targets in Parkinson’s, Alzheimer’s, ALS, FTD
- Leaders in gene therapy manufacturing and process development
Rapid execution in developing gene therapies for patients with urgent unmet needs

2017

- **AUGUST 2017:** Seed financing and REGENXBIO license
- **OCTOBER 2017:** Lab space secured in NYC

2018

- **MARCH 2018:** $75M Series A
- **MAY 2018:** REGENXBIO second agreement

2019

- **MARCH 2019:** $50M Series B
- **MAY 2019:** PR001 PD-GBA IND active
- **DECEMBER 2019:** PR001 nGD IND active

2020

- **JUNE 2019:** $125M IPO
- **MARCH 2020:** PR006 FTD-GRN IND active
Management and Board of Directors

Experienced Management Team

- Asa Abeliovich, MD, PhD
  CEO and Founder
- Yong Dai, PhD
  Chief Technology Officer
- Franz Hefti, PhD
  Chief Development Officer
- Brett Kaplan, MD
  Chief Financial Officer
- Emily Minkow
  Chief Business Officer
- Jeff Sevigny, MD
  Chief Medical Officer
- Kira Schwartz, JD
  General Counsel

Board of Directors

- Francois Nader, MD
  Non-Executive Chairman

- Asa Abeliovich, MD, PhD
  CEO and Founder

- Tim Adams
  Independent

- Carl Gordon, PhD, CFA
  OrbiMed

- Ran Nussbaum
  Pontifax

- Morgan Sheng, MBBS, Ph.D., FRS
  Independent

- Peter Thompson, MD
  OrbiMed
Unique pipeline of potentially disease-modifying AAV9 gene therapies for neurodegenerative diseases

<table>
<thead>
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<th>Indication</th>
<th>Approach</th>
<th>Stage of Development</th>
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<td>Discovery</td>
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<td>PR001</td>
<td>PD-GBA</td>
<td><strong>GBA1 Gene Transfer</strong></td>
<td>propel</td>
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<td></td>
<td>Type 2 GD</td>
<td><strong>GBA1 Gene Transfer</strong></td>
<td>provide</td>
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<tr>
<td>PR006</td>
<td>FTD-GRN</td>
<td><strong>GRN Gene Transfer</strong></td>
<td>proclaim</td>
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<tr>
<td>PR004</td>
<td>Synucleinopathies</td>
<td><strong>GBA1 Gene Transfer + α-Synuclein Knockdown</strong></td>
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**FTD granted by FDA for PR001 for the treatment of PD-GBA**

**ODD & RPDD granted by FDA for PR001 for the treatment of GD & nGD, respectively**

**ODD & FTD granted by FDA for PR006 for the treatment of FTD & FTD-GRN, respectively**

*Prevail owns worldwide commercial rights to all product candidates in the pipeline*
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
## 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
- Phase 1/2 PROPEL trial for PD-GBA underway
- Study startup activities ongoing for Phase 1/2 PROVIDE trial for Type 2 Gaucher disease
Parkinson’s disease progression

- With disease progression motor symptoms worsen and cognitive & behavioral symptoms emerge
- Benefit of existing symptomatic therapies diminishes as disease progresses
- No disease-modifying therapy available

Source: Kalia and Lang, Lancet 2015; 386: 896
RBD: REM behavioral sleep disorder; EDS: excessive daytime sleepiness; MCI: mild cognitive impairment
Neuronopathic Gaucher disease overview

- Type 2 Gaucher disease presents in infancy and involves rapidly progressive neurodegeneration leading to death in infancy or early childhood.
- Type 3 Gaucher disease presents in childhood or adulthood and also involves neurologic symptoms.
- Type 2 and Type 3 GD are together referred to as neuronopathic Gaucher disease (nGD).
- There are no FDA approved therapies for nGD.
  - ERT approved for Type 1 GD does not cross the blood-brain barrier.

Source: Sidransky, Molecular Genetics and Metabolism (2004)
ERT= enzyme replacement therapy
PD-GBA and neuronopathic GD are a continuum of pathology with the same underlying genetic mechanism

Number and severity of GBA1 mutations $\rightarrow$ Decreasing enzyme activity $\rightarrow$ Increasing disease severity

- **0 mutations**
  - “Sporadic” Parkinson's

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

- **1 severe mutation**
  - PD-GBA with more severe phenotype

- **2 mild / moderate mutations**
  - Type 1 Gaucher disease

- **2 severe mutations**
  - Type 2 & 3 Gaucher disease (neuronopathic)

At elevated risk of PD-GBA with more severe phenotype
PR001 mechanism of action in PD-GBA

Parkinson’s Disease WITH GBA1 MUTATION

INCREASED GCASE

SUBSTRATE DECREASES (GLUCER, GLUSPH)
PRODUCT INCREASES
SECONDARY LIPIDS NORMALIZE
FUNCTIONAL LYSOSOME

NEURODEGENERATION SLOWED OR STOPPED
INFLAMMATION REDUCED
PROTEIN AGGREGATION REDUCED

PR001 Treated

GBA1 GENE

PR001
PR001 efficacy in CBE mouse model

Activity and substrate reduction (CBE dose-ranging efficacy study)

- **GCase Activity**
  - PR001 low dose = 1.3x10^{10} vg/g brain
  - PR001 mid dose = 4.2x10^{10} vg/g brain
  - PR001 high dose = 1.3x10^{11} vg/g brain

- **GluCer**
  - Vehicle
  - CBE
  - PR001 low dose
  - PR001 medium dose
  - PR001 high dose

- **Astroglisis (glial scarring)**
  - Percentage of animals with astroglial scarring

Activity and substrate reduction (CBE 6-month efficacy study)

- **GCase Activity**
  - Vehicle
  - CBE
  - PR001 low dose
  - PR001 high dose

- **GluCer**
  - Vehicle
  - CBE
  - PR001 low dose
  - PR001 high dose

Efficacy (CBE dose-ranging efficacy study)

- **Rotarod**
  - Vehicle
  - CBE
  - PR001 low dose
  - PR001 medium dose
  - PR001 high dose

Means are presented +/- SEM. *: p<0.05; **: p<0.01; ***: p<0.001. By one-way ANOVA and 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. Activity, substrate and astroglisis (glial scarring) measured in the cortex PR001 low dose = 1.3x10^{10} vg/g brain, PR001 mid dose = 4.2x10^{10} vg/g brain, PR001 high dose = 1.3x10^{11} vg/g brain.
PR001 efficacy in genetic mouse model

- 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
P-value: *p<0.05, ***p<0.001 by one-way analysis of variance followed by Tukey HSD
#: p<0.05 for effect of PR001 injected dose by multiple linear regression for genotype and dose across all animals
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:
  - 6x safety margin to PD-GBA starting dose
  - 5x safety margin to nGD 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

NHP study: Control Dose = 0 vg/g brain weight; Low Dose = 6.2x10^10 vg/g brain weight PR001; High Dose = 2.3x10^11 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
PR001 PD-GBA Phase 1/2 trial
*Open label, ascending dose*

**PR001 PD-GBA Patients**
- Single or biallelic *GBA1* mutations
- Moderate to severe Parkinson’s disease
- Stable background PD medication

**Study Design**
- **Single ICM injection**
- **2 month biomarker readout**
- **12 month clinical readout**
- **5-year safety and clinical follow-up**

**Groups**
- **PR001 Low Dose (N=6)**
- **PR001 High Dose (N=6)**

**Endpoints**
- Safety and tolerability
- Key biomarkers: GCase, GluCer, GluSph (CSF and blood)
- Additional biomarkers: α-Synuclein, NfL, DAT SPECT, MRI
- Efficacy: MDS-UPDRS, cognition, ADLs
PROPEL PD-GBA Phase 1/2 trial: early patient data
As of August 2020

Background

- Two PD-GBA patients enrolled in PROPEL trial prior to protocol change to open-label design: one administered PR001; one received sham procedure
- Patient who received PR001 (1.4x10^{14} vg) also diagnosed with Gaucher disease (GBA1 mutations in both chromosomal copies)

Biomarkers

- CSF GCase enzyme activity increased from undetectable at baseline to normal level at ~Month 3

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Day 0</th>
<th>~Month 3</th>
<th>Normal range (adult)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCase activity in CSF (μmol/L/d)</td>
<td>Undetectable</td>
<td>3.0</td>
<td>1.1 - 8.1</td>
</tr>
</tbody>
</table>

Clinical Safety and Efficacy

- PR001 ICM administration well-tolerated
- Patient did not complete protocol-specified immunosuppression regimen due to steroid intolerance
- Three months following PR001 administration, patient experienced SAEs presumed to be AAV9-immune mediated
- Patient’s condition responded to additional immunosuppressive treatment; SAEs have markedly resolved
- PROPEL protocol amended to include modified immunosuppression regimen
Goal of PR001 treatment is to deliver the *GBA1* gene to restore GCase activity in PD-GBA patients

- Human genetics suggest increasing GCase activity by 20-30% of healthy levels expected to be clinically meaningful
- Mouse model data show linear correlation between GCase activity and behavioral performance

Source: Liu et al., Annals of Neurology 2016; Thaler et al., Parkinsonism and Related Disorders 2017
PR001 Type 2 Gaucher disease Phase 1/2 trial
Open label

Type 2 Gaucher Patients
- Infants 0-24 months old
- Biallelic GBA1 mutations
- Neurological signs & symptoms consistent with Type 2 Gaucher disease
- Stable SoC background medications

Single ICM injection
2 month biomarker readout
12 month clinical readout
5-year safety and clinical follow-up

PR001 (Open label, N=15)

Safety and tolerability
- Key biomarkers: GCase, GluCer, GluSph (CSF and blood)
- Time to clinical event (e.g., tracheostomy, PEG placement, death)
- Efficacy: behavior, cognition, gross motor, function, QoL

ICM: intra-cisterna magna; QoL: quality of life; SoC: standard of care; PEG: percutaneous endoscopic gastrostomy
Type 2 Gaucher compassionate use: early patient data
As of August 2020

Background

- Type 2 Gaucher disease patient dosed with PR001 (1.3x10^{14} vg) in Jan 2020 following compassionate use request
- Patient was ~22 months old at dosing

Biomarkers

- CSF GCase enzyme activity increased from undetectable at baseline to normal level at Month 4

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Month 1</th>
<th>Month 4</th>
<th>Normal range (adult)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCase activity in CSF (μmol/L/d)</td>
<td>Undetectable</td>
<td>1.0</td>
<td>4.7</td>
<td>1.1 - 8.1</td>
</tr>
</tbody>
</table>

Clinical Safety and Efficacy

- PR001 ICM administration well-tolerated; no AEs reported
- Patient clinically stable; no apparent worsening of the patient’s neurological symptoms since PR001 administration
- Follow-up clinical assessments are planned
## PR001 market opportunity

### Disease Overview

**PD-GBA**
- PD patients with at least one *GBA1* mutation
- Earlier onset, faster progression, and higher prevalence of dementia

**Neuronopathic GD**
- Type 2 Gaucher: Severe progressive neurologic disease; mortality by age 2
- Type 3 Gaucher: Juvenile or adult onset with multiple neurological manifestations

### Treatment & Unmet Need

**PD-GBA**
- No therapies to slow or stop disease progression
- Benefit of symptomatic therapies diminishes as disease progresses

**Neuronopathic GD**
- No effective therapies for the neurologic manifestations of Gaucher
- ERTs used for peripheral manifestations; do not enter the brain

### Market Size

**PD-GBA**
- Parkinson’s prevalence 7M worldwide, 1M in US
- 7-10% of PD patients worldwide have *GBA1* mutation

**Neuronopathic GD**
- >1,000 patients in the major markets
- 6% of Gaucher cases in the US but higher prevalence in other regions

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**Source:**
## PR006 overview

### PR006
- AAV9 viral vector delivering the *GRN* gene, which encodes progranulin

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

### Lead Indications
- Frontotemporal dementia with *GRN* mutation (FTD-GRN)
  - Rapidly progressive dementia impacting behavior and language
  - Leads to death within 3-10 years

### Progress and Status
- FTD-GRN IND active and study startup activities ongoing for Phase 1/2 PROCLAIM trial
Frontotemporal dementia with \textit{GRN} mutation is caused by progranulin deficiency

- FTD pathology includes neurodegeneration and inflammation
- Progranulin is a secreted factor that is enriched in lysosomes
- Progranulin deficiency leads to lysosomal dysfunction

Number of \textit{GRN} mutations causes varying degrees of progranulin deficiency resulting in spectrum of disease.

Number of \textit{GRN} mutations $\rightarrow$ Decreasing progranulin $\rightarrow$ Increasing disease severity

- 0 mutations
  - Healthy Individuals
- 1 mutation (Heterozygous)
  - Frontotemporal Dementia (Adult onset)
- 2 mutations (Homozygous)
  - Neuronal Ceroid Lipofuscinosis (Childhood onset)
PR006 efficacy in aged *Grn* knockout mouse model

- Vector genomes were observed to be present in the cerebral cortex 2 months after ICV PR006 administration.

14-16-month-old mice were dosed with 2.4x10^11 vg/g brain ICV PR006, and after 2 months, mice were sacrificed and vector genomes and progranulin protein levels were quantified. Statistics determined using Kruskall-Wallis; * = p < 0.05, ** = p < 0.01. Data is presented as mean ± SEM (n=5/excipient group and n=7/PR006 group). Vector genome levels below 50 (dotted line) were considered not positive. Vg = vector genomes; WT= wildtype.

- PR006 treatment increased CSF expression of progranulin protein in progranulin knockout mice.

- PR006 treatment increased cerebrocortical expression of progranulin protein in progranulin knockout mice to near normal levels.
### PR006 efficacy in adult *Grn* knockout mouse model

<table>
<thead>
<tr>
<th>Progranulin expression</th>
<th>Lipofuscinosis</th>
<th>Neuroinflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progranulin mRNA</strong></td>
<td><strong>Lipofuscin accumulation</strong></td>
<td><strong>Neuroinflammation (Tnf mRNA)</strong></td>
</tr>
<tr>
<td>(cerebral cortex)</td>
<td>(hippocampus)</td>
<td>(cerebral cortex)</td>
</tr>
<tr>
<td>PR006 dose-dependently increased expression of the <em>GRN</em> transgene</td>
<td>PR006 dose-dependently reduced accumulation of lipofuscin, an indicator of lysosomal dysfunction, throughout the brain</td>
<td>PR006 treatment reduced gene expression of proinflammatory cytokine TNFα (<em>Tnf</em>)</td>
</tr>
</tbody>
</table>

Means are presented +/- SEM. N=8-10 per group. **p<0.01, ***p<0.001 by ANOVA followed by Dunnett's multiple tests correction comparing each group to excipient-treated *Grn* KO mice. PR006 low dose = 2.7x10^9 vg/g brain, PR006 mid dose = 2.7x10^10 vg/g brain, PR006 high dose = 2.7x10^11 vg/g brain.
PR006 safety and progranulin expression in NHPs

Results

- ICM PR006 administration resulted in widespread transduction in the CNS and periphery, and elevated progranulin protein levels in the CSF
- No adverse PR006-related findings in GLP NHP tox study with 2.4x safety margin to clinical starting dose
- ICM PR006 treatment dose-dependently increased progranulin expression in the CSF

NHPs received ICM administration of excipient, PR006 low dose = 6.5x10⁹ vg/g brain or PR006 high dose = 6.5x10¹⁰ vg/g brain

Bars represent mean ± SEM. P-value: *p<0.05, by one-way dose dependence response analysis using William’s trend test. ICM = intra-cisterna magna
PR006 FTD-GRN Phase 1/2 trial
*Open label, ascending dose*

**FTD-GRN Patients**
- 30-80 years old
- Single pathogenic *GRN* mutation
- Symptomatic disease stage
- Stable background medications

**Safety and tolerability**
- Key biomarkers: progranulin, NfL, volumetric MRI
- Efficacy: CDR plus NACC FTLD; measures of behavior, cognition, language, function, QoL

**PR006 FTD-GRN Phase 1/2 trial**
- **PR006 Low Dose (N=5)**
- **PR006 Mid Dose (N=5)**
- **PR006 High Dose (N=5)**
### PR006 market opportunity

| **Disease Overview** | - Progressive and devastating early-onset form of dementia  
|| - Leads to death within 3-10 years |
| **Treatment & Unmet Need** | - No therapies approved for FTD  
|| - No therapies have shown disease modification |
| **Market Size** | - FTD prevalence ~50,000 in US; ~80-110,000 in EU  
|| - 5-10% of FTD patients have a *GRN* mutation |

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**FTD-GRN**

CMC strategy and capabilities

Established internal process development capabilities; working with CDMOs to supply clinical trials with drug product

**Phase 1/2 Material**
- Robust adherent HEK293 process to maximize speed to the clinic
- Partnership with established CDMO

**Phase 3 and Commercial Material**
- Baculovirus platform to establish high-yield scalable process
- Process development and scale up completed; demonstrated promising yield and potency
- Partnered with Lonza to develop and manufacture drug supply for late-stage clinical trials and commercial production using baculovirus platform
- GMP manufacturing and comparability studies underway
Prevail Therapeutics summary

- Developing potentially disease-modifying gene therapies for neurodegenerative disorders
- PR001 Phase 1/2 trial for PD-GBA underway
- PR001 Phase 1/2 trial for GD2 to initiate enrollment in 2020
- PR006 Phase 1/2 trial for FTD-GRN to initiate enrollment in 2020
- Pipeline of gene therapy programs for neurodegenerative diseases using a precision genetic medicine approach