All contributing authors are or were employees of Prevail Therapeutics
PR006, an AAV gene therapy vector expressing progranulin, improved FTD-GRN phenotypes \textit{in vitro} and \textit{in vivo}

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Overview

- Gene therapy approach
- Scientific rationale for the FTD-GRN program

Background

- PR006 is an AAV9-GRN vector
- *In vitro* efficacy data in an iPSC-derived neuron model
- *In vivo* efficacy and safety data in a *Grn* KO mouse model and in NHPs

PR006 Preclinical Efficacy and Safety

Clinical Development

- 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.
Frontotemporal dementia with $GRN$ 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

- **Healthy Individuals**: 0 mutations
- **Frontotemporal Dementia (Adult onset)**: 1 mutation (Heterozygous)
- **Neuronal Ceroid Lipofuscinosis (Childhood onset)**: 2 mutations (Homozygous)

Number of \textit{GRN} mutations $\rightarrow$ Decreasing progranulin $\rightarrow$ Increasing disease severity
## PR006 overview

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

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

### Lead Indication
- 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
FTD-GRN patient-derived neuronal cell model

- iPSC-derived neural progenitor cells (NPCs) from humans with GRN mutations expressed and secreted less progranulin than neural progenitor cells derived from healthy control subjects.

![Bar charts showing intracellular and secreted progranulin levels for FTD-GRN individuals and controls.](image)

- NPCs for all lines were successfully differentiated into neuronal cultures.

**FTD-GRN Neurons**
- FTD-GRN #1 ND50015 (M1L)
- FTD-GRN #2 ND50060 (R493X)

**Control Neurons**
- Control ND38555 (WT)

**Statistics**
- Determined using an unpaired t-test, *** = p < 0.001. Data are mean ± SEM (n=3).
**PR006 efficacy in human FTD-GRN neuronal cultures**

- **Progranulin expression**
  - PR006 transduction of neurons resulted in robust expression of progranulin protein secreted into the cell media

- **Cathepsin D maturation**
  - PR006 treatment of neurons improved the maturation of cathepsin D, a key lysosomal protease

- **Insoluble TDP-43 levels**
  - PR006 treatment of neurons decreased insoluble TDP-43, a hallmark of FTD-GRN pathology

**Statistics:** Determined using a t-test; *p<0.05, **p<0.01, ***p<0.001. Data is presented as mean ± SEM.

**Key terms:**
- iPSC: induced pluripotent stem cell;
- NPC: neural progenitor cell;
- CTSD: cathepsin D.
**PR006 dose-ranging efficacy and biodistribution in progranulin knockout mice**

- *Gm* KO mice exhibit a progressive phenotype, resulting in lysosomal defects and neuroinflammation
- Multi-dose adult *Gm* KO mouse mouse study to determine efficacious PR006 dose was conducted

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**ICV delivery:** PR006 or excipient

- Day 0
- 1 month
- 2 months
- 3 months

**Gm KO**

- Aged 4 months

**PR006 dose**

<table>
<thead>
<tr>
<th>PR006 dose</th>
<th>Total vg</th>
<th>vg / g brain</th>
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<tbody>
<tr>
<td>Low</td>
<td>$1.1 \times 10^9$</td>
<td>$2.7 \times 10^9$</td>
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<tr>
<td>Medium</td>
<td>$1.1 \times 10^{10}$</td>
<td>$2.7 \times 10^{10}$</td>
</tr>
<tr>
<td>High</td>
<td>$1.1 \times 10^{11}$</td>
<td>$2.7 \times 10^{11}$</td>
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</tbody>
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**Vector genomes (qPCR)**

- Protein expression (ELISA)
- Inflammatory markers
- Lipofuscinosis
- Gene expression (RNA seq)
- Histopathology (H&E)
PR006 increased progranulin in cerebral cortex of progranulin knockout mice

**Biodistribution**  
Dose dependent increase in vector genomes (GRN) detected in the cerebral cortex 3 months after ICV PR006 administration.

**Progranulin mRNA**  
PR006 dose-dependently increased expression of the GRN transgene in the cerebral cortex.

**Progranulin protein**  
PR006 increased progranulin protein levels in the cerebral cortex.

Means are presented +/- SEM (n=8-10 per group). Statistics determined by ANOVA followed by Dunnett’s multiple tests correction comparing each group to excipient-treated Grn KO mice; *** = p<0.001. Vector genome levels below 50 (dotted line) were considered not positive. Vg = vector genomes; LLOQ = lower limit of quantitation.
PR006 reduced lysosomal-related neuropathology in progranulin knockout mice

Mild to moderate lipofuscinosis, an indicator of lysosomal dysfunction, was observed in the hippocampus and thalamus of Grn knockout mice

PR006 dose-dependently reduced accumulation of lipofuscin throughout the brain

Ubiquitin accumulation was observed in the hippocampus and thalamus of Grn knockout mice

PR006 reduced ubiquitin accumulation in multiple brain regions

(L) Representative lipofuscin autofluorescence images from 18-month old Grn KO mice two months after receiving ICV excipient or PR006 (2.4 x 10^{11} vg/g brain).

(R) Means are presented +/- SEM (n=6-10 per group). Statistics determined by ANOVA followed by Dunnett’s multiple tests correction comparing each group to excipient-treated Grn KO mice; ** = p<0.01; *** = p<0.001. Vg = vector genomes.
PR006 reduced neuroinflammation in progranulin knockout mice

- *Gm* knockout mice exhibited increased neuroinflammation in the cerebral cortex as measured by gene expression of the proinflammatory cytokine TNFα (*Tnf*) and microglial marker CD68 (*Cd68*)
- PR006 treatment reduced gene expression of proinflammatory markers *Tnf* and *Cd68* in the cerebral cortex

Means are presented ± SEM (n=8-10 per group). Statistics determined by ANOVA followed by Dunnett’s multiple tests correction comparing each group to excipient-treated *Gm* KO mice; *** = p<0.001. Vg = vector genomes.
PR006 reduced neuroinflammation in progranulin knockout mice

- *Gm* knockout mice exhibited increased microgliosis in multiple brain regions as measured by IHC (protein expression) of the microglial marker Iba1.
- All three doses of ICV PR006 reduced microgliosis throughout the brain of *Gm* knockout mice.

Means are presented ± SEM (n=8-10 per group). Statistics determined by ANOVA followed by Dunnett’s multiple tests correction comparing each group to excipient-treated *Gm* KO mice; * = p<0.05; *** = p<0.001. Vg = vector genomes.
PR006 safety and progranulin expression in NHPs

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 (clinical and histopathological endpoints).

Third-party pathologist classified "extremely minor" degree of nerve fiber degeneration in spinal cord and glial cellularity in DRGs.

ICM PR006 treatment dose-dependently increased progranulin expression in the CSF.

NHPs received ICM administration of excipient, $6.5 \times 10^9$ vg/g brain PR006, or $6.5 \times 10^{10}$ vg/g brain PR006. 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

FTD-GRN Patients

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

PR006 (Open label, N=15)

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

- PR006 reversed lysosomal abnormalities and reduced TDP-43 pathology in FTD-GRN mutation carrier iPSC-derived neurons
- PR006 reduced lysosomal deficiencies and neuroinflammation in Grn KO mice
- PR006 administration via ICM injection was well-tolerated in NHPs, and there were no adverse observations
- Study startup activities ongoing for phase 1/2 clinical trial for FTD-GRN patients (PROCLAIM)
Thank You!

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