Non-clinical and early clinical development of PBFT02, an AAV gene therapy for FTD with *GRN* mutations (FTD-*GRN*)

SE Browne, YG Ni, KJ Quadrini, T Voss, MS Forman, J Chavez, N Miller, C Hinderer, JM Wilson

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Disclosures

- Sue Browne, Ph.D, Yan Yi, Ph.D and Juan Chavez, MD, Ph.D are employees of Passage Bio, Inc. (the “Company”) and have certain equity interests in the Company
- James Wilson, MD, Ph.D is a paid advisor to the Company and has certain equity interests in the Company.
- James Wilson, MD, Ph.D and Christian Hinderer are inventors on patents that have been licensed to the Company and for which they may receive payments.

FTD-*GRN*: A Devastating Adult Disease

Frontotemporal Degeneration, FTD

- Rapidly progressive, fatal, neurodegenerative disease affecting the frontal and temporal lobes of the brain
- Common cause of early-onset dementia
  - Onset typically between ages of 40 and 65 years

FTD-*GRN*

- 5 to 10% of FTD is caused by mutations in the ***granulin*** **(*GRN*)** gene
  - Haploinsufficiency reduces brain **progranulin** to 30-50% of normal
- Prevalence in EU + US is ~18,000
- **No approved disease-modifying therapy**

Loss of inhibition

Apathy

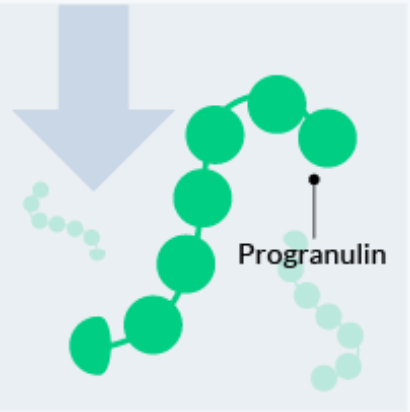
Social withdrawal

Hyperorality (mouthing of objects)

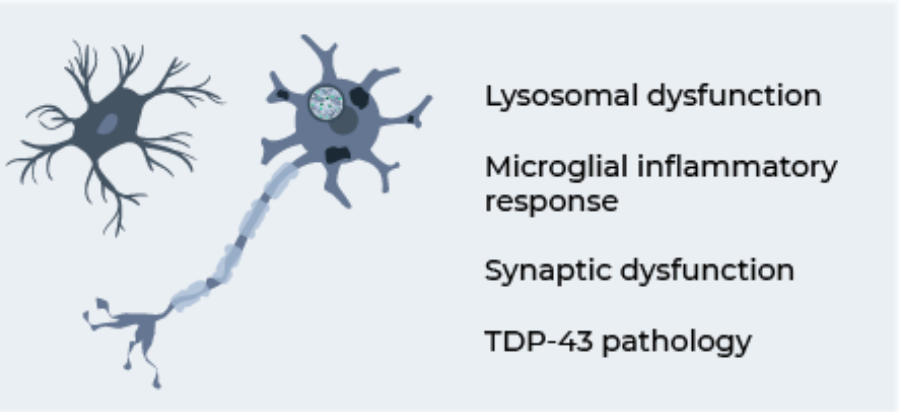
Ritualistic compulsive behaviors

Progranulin (PGRN) Deficiency is the Defining Characteristic of FTD-*GRN*, Leading to Neurodegeneration

Progranulin is critical to maintaining CNS cell homeostasis



Decrease in PGRN levels



Neuronal dysfunction, pathological changes, and inflammation

Vulnerability of neurons in affected regions

Neurodegeneration

Our approach: **AAV gene therapy to deliver functional PGRN to the brain**

Rhinn H et al. *Trends Pharm Sci*. 2022, 43:641-652.

PBFT02 Development Pathway

- Transgene cassette design
- Dose ranging in granulin-deficient mice
- Vector selection in NHPs
- Clinical lead biodistribution, safety, toxicology in NHPs

Penn University of Pennsylvania | GENE THERAPY PROGRAM

Discovery → Pre-clinical → IND

- Ph 1/2 clinical study in FTD-*GRN*

PassageBio

Phase 1/2 → Pivotal → Filing/Comm

upliFT-D

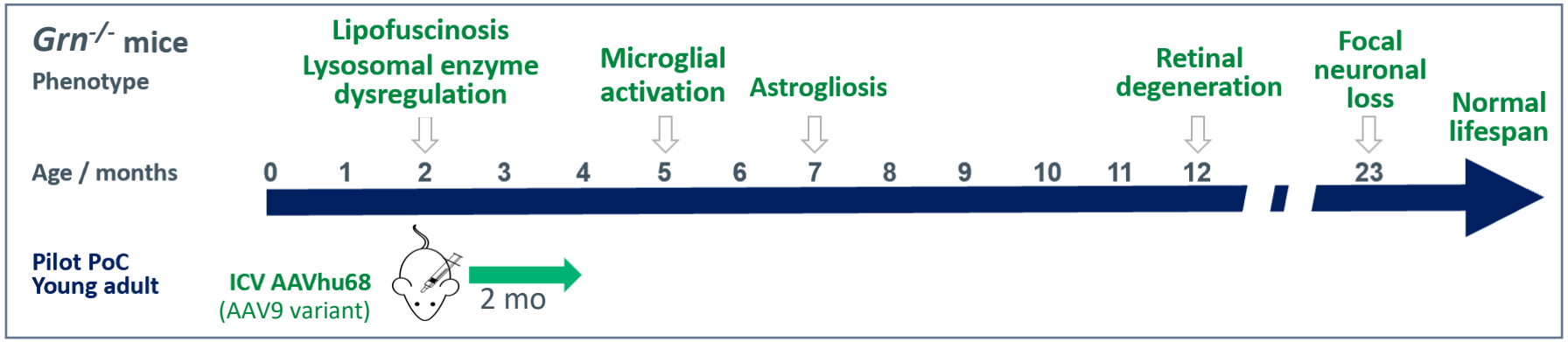
Abbreviations: NHP, non-human primate

h*GRN* Transgene Cassette Optimized

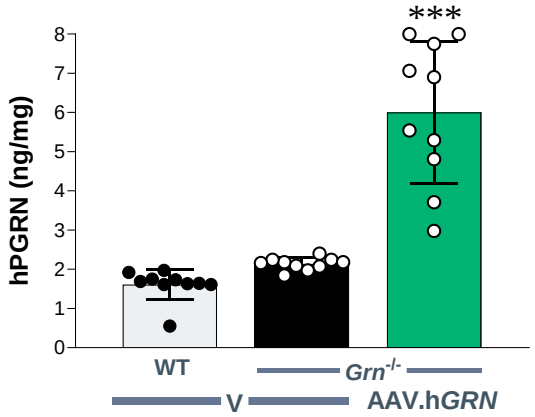
- Codon-optimized sequence of the human *GRN* gene under the control of the ubiquitous CB7 promoter
- Designed to deliver functional *GRN* genes encoding PGRN to brain and spinal cord
- Ability to transduce multiple CNS cell types

Proof of Concept: h*GRN* Transgene Delivery Improved Lysosomal Function in PGRN-Deficient Mice

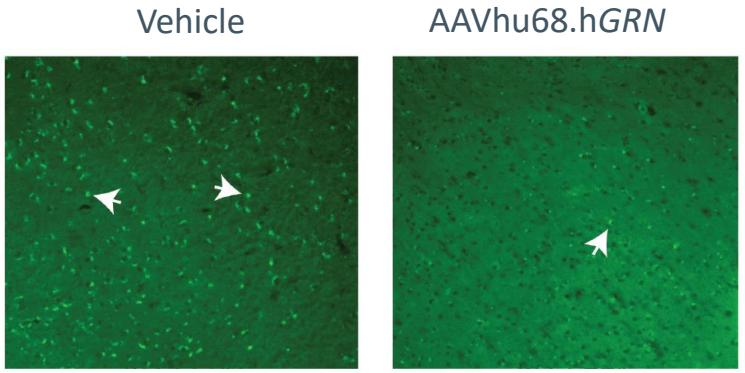
Efficacy in *Grn* knockout mice after tool AAVhu68.h*GRN* vector ICV administration to CSF



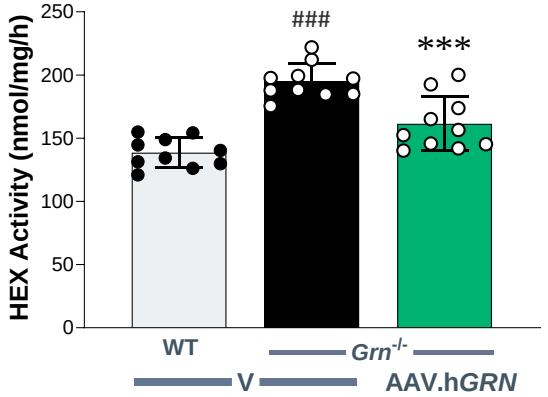
hPGRN Expressed in Brain of *Grn*$^{-/-}$ mice



Reduced Lipofuscin Fluorescence in Thalamus



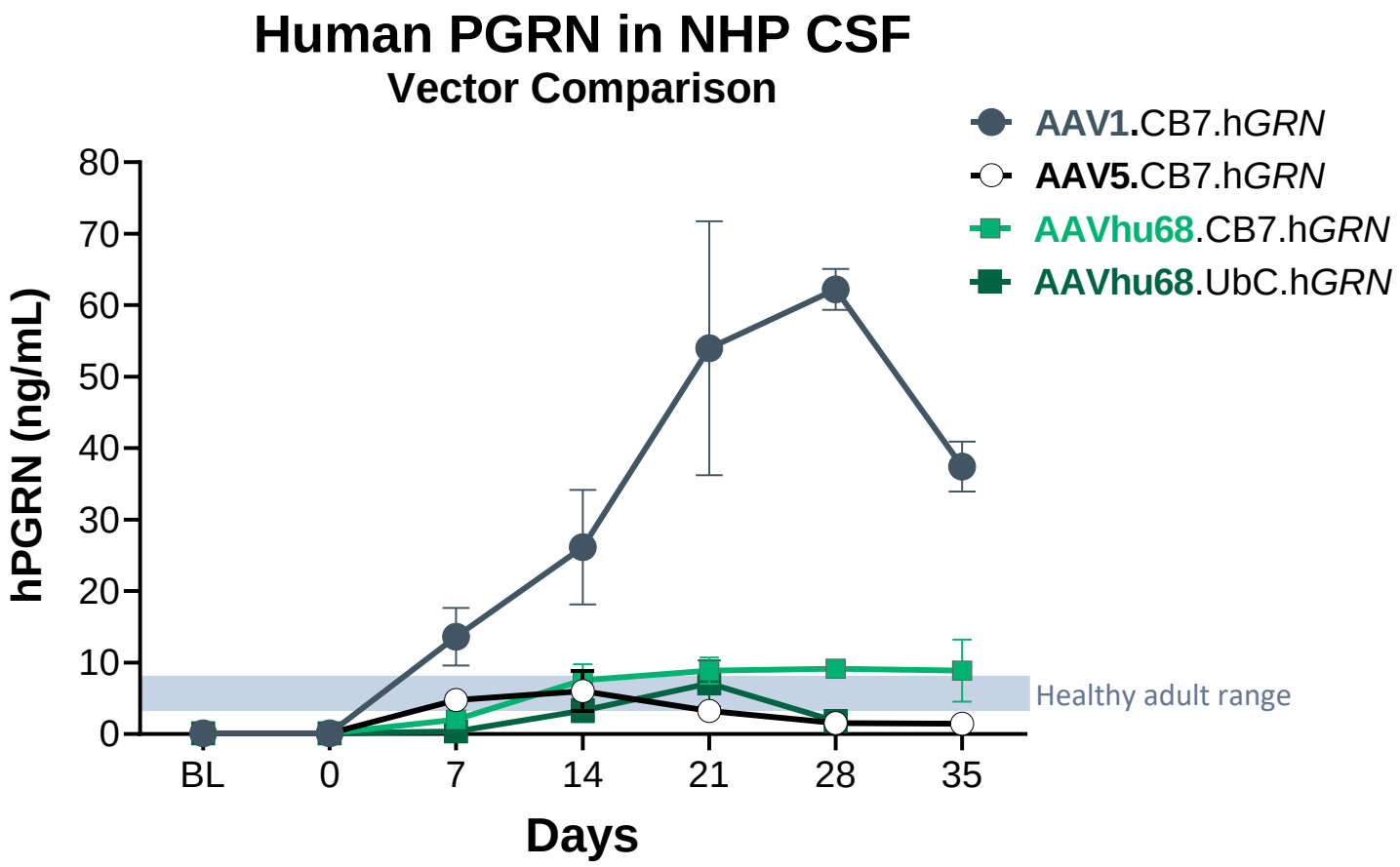
Reduced Brain Hexosaminidase Activity



Tissue collected 60 days post-ICV administration. N = 10/gp ### $p < 0.005$ vs WT + V control; *** $p < 0.005$ vs GRN-/-+ V , one-way ANOVA + Tukey's multiple comparisons test

Abbreviations: CSF, cerebrospinal fluid; *GRN/Grn,* granulin gene; ICV, Intra-cerebroventricular; PBS, phosphate-buffered saline; V, Vehicle. *Reference:* Hinderer et al., *Annals Clin Trans Neurology.* 2020.

AAV1 Selected as Vector Serotype after a Capsid Comparison Study in NHPs



- Superior hPGRN levels in CSF after **AAV1** compared to **AAV5** and **AAVhu68** (AAV9 variant)
  - Clinical delivery route, ICM
- **AAV1.*hGRN*** selected as clinical candidate, **PBFT02**

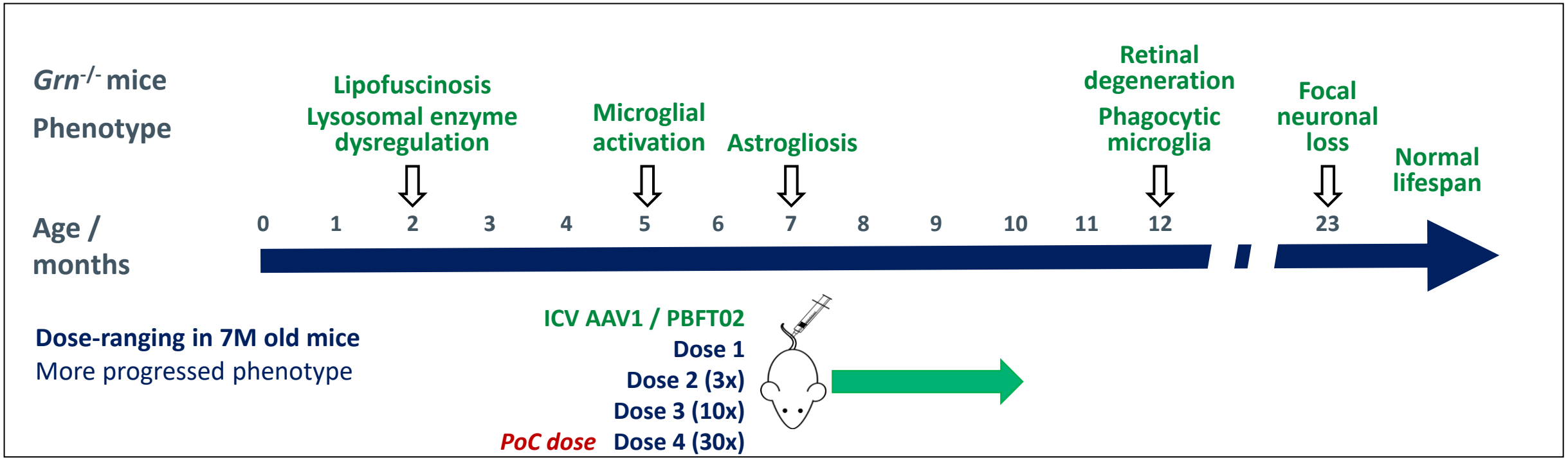
PBFT02 taken into IND-enabling studies

- Dose escalation in mice
- Safety, tolerability, and biodistribution in NHPs

Rhesus macaques (n=2/group) ICM-delivered AAV.hPGRN (3.3 x 10^{11} GC/g brain), day 0
Size and duration of elevation muted by immune response to human PGRN.
Shading: Healthy adult human sample range, n = 61 (Passage Bio data)

Abbreviations: CSF, cerebrospinal fluid; ICM, intra-cisterna magna; hGRN, human granulin gene; NHP, non-human primate; PGRN, progranulin. *Reference:* Hinderer et al., *Annals Clin Trans Neurology.* 2020

PBFT02 Dose Selection: Efficacy in *Grn*$^{-/-}$ Mice



- Assayed four PBFT02 doses
  - Starting from 1/30 lower than dose used in prior mouse proof of concept (PoC) study

Abbreviations; *GRN,* granulin gene; ICV, Intra-cerebroventricular; M, month.

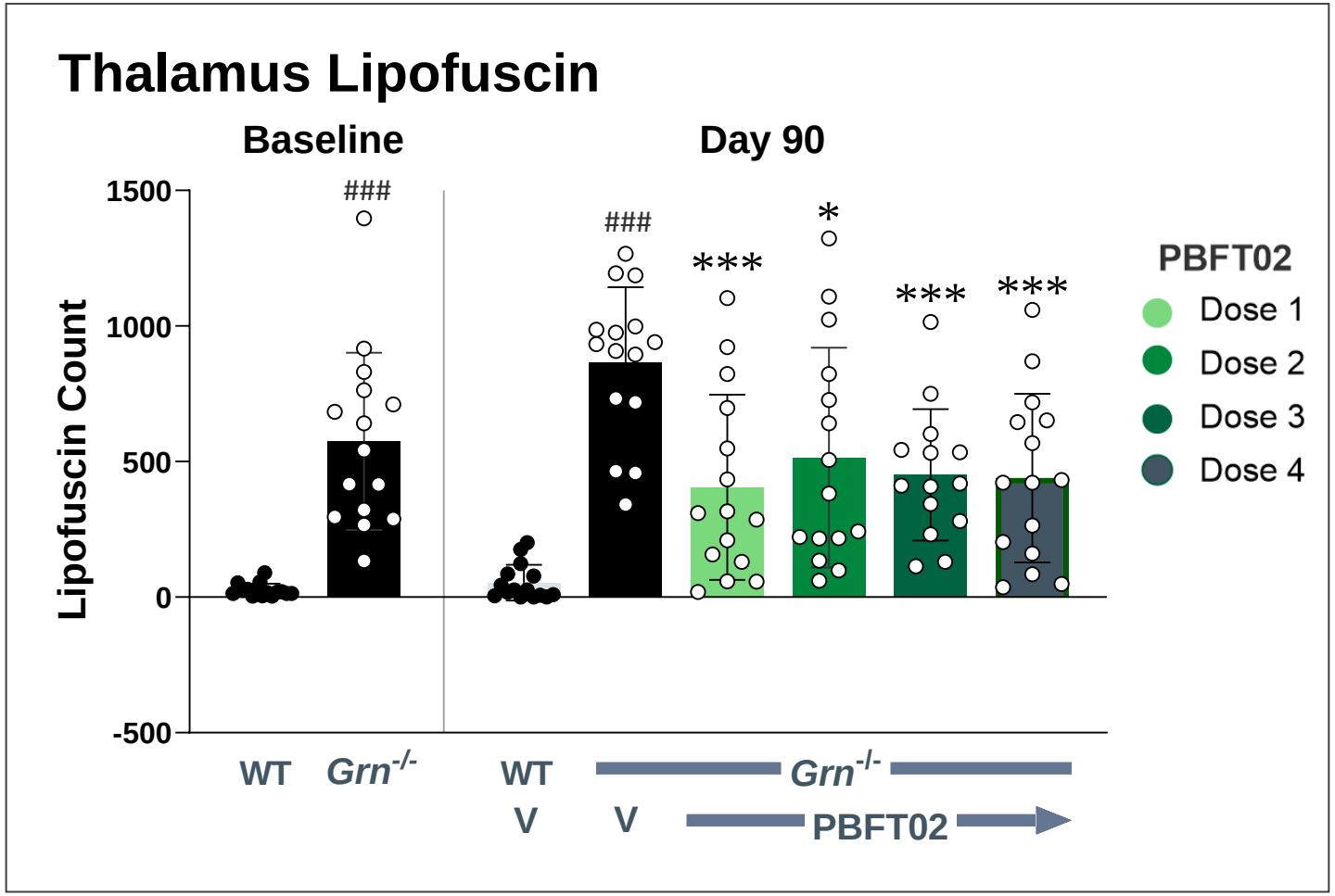
Reference: Hinderer et al., *Annals Clin Trans Neurology.* 2020

PBFT02 Improved Lysosomal Function in the Brain

Dose ranging in *Grn*$^{-/-}$ mice after intra-CSF delivery

Lipofuscin deposition in brain was reduced by ICV PBFT02

- Partially reversed existing pathology
- Also effective in cortical and sub-cortical regions after ICV administration

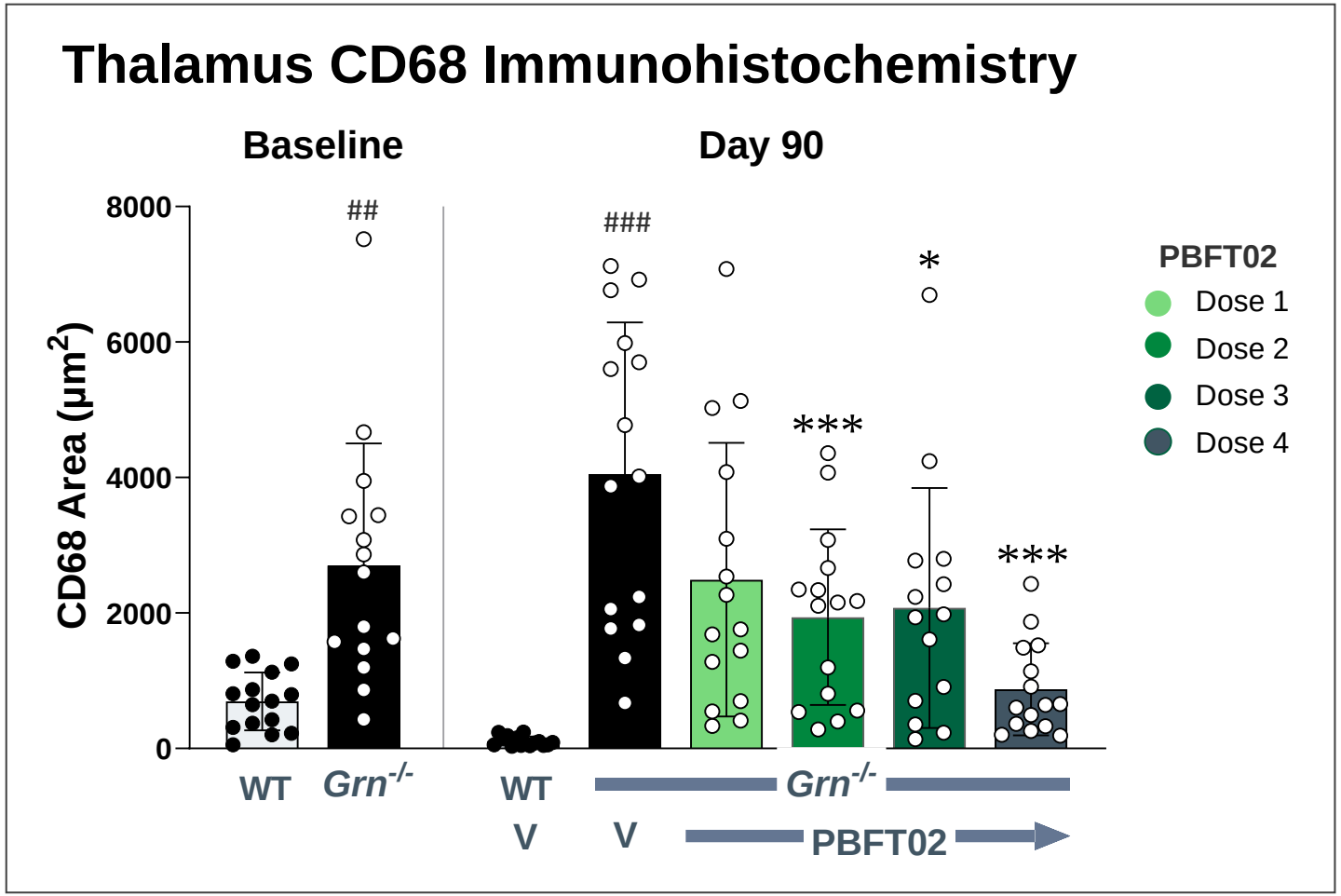


10 *Grn*$^{-/-}$ and WT mice (n=14-15/gp) ICV-administered PBFT02 or vehicle (V). Baseline controls are untreated mice on Day 1. Bars: mean +/- SEM.

$^{###}p < 0.005$ vs WT control; $^{*}p < 0.05$, $^{***}p < 0.005$ vs *Grn*-/- + V , one-way ANOVA then Tukey's multiple comparisons test. *Abbreviations*; *Grn*, granulin gene; ICV, Intra-cerebroventricular; V, vehicle; WT, wildtype

Neuroinflammation Reduced in the Brain after PBFT02

Dose ranging in *Grn*$^{-/-}$ mice after intra-CSF delivery

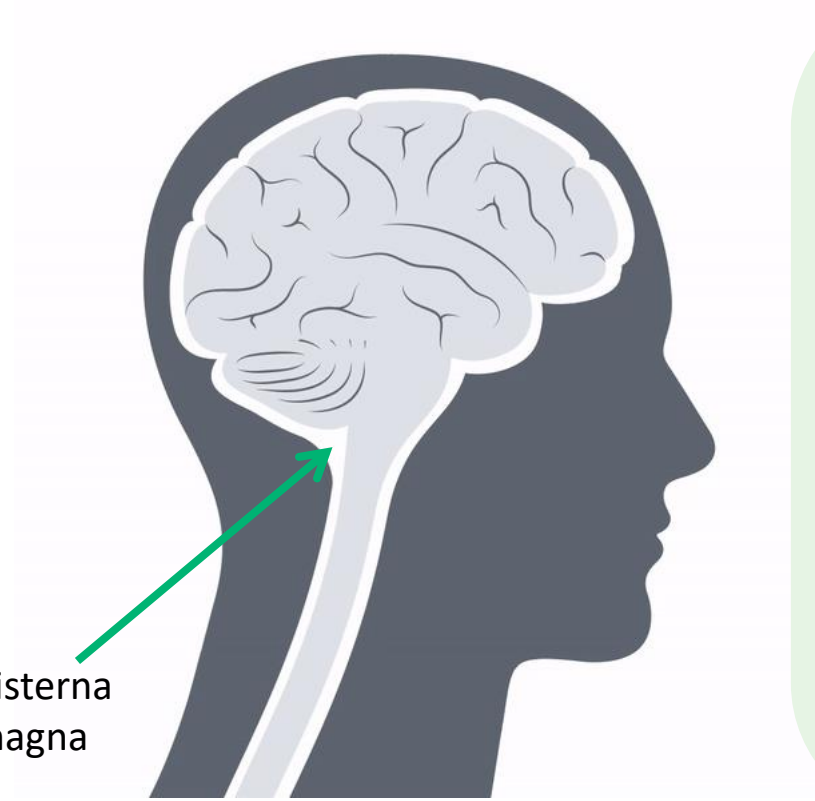


Activated microglia reduced in both cortical and sub-cortical brain regions after ICV PBFT02

- From combined mouse data, Dose 1 established as minimum effective dose
- Dose 2, 3 and 4 equivalents taken forward into NHP studies

11 *Grn*$^{-/-}$ and WT mice (n=14-15/gp) ICV-administered PBFT02 or vehicle (V). Baseline controls are untreated mice on Day 1. Bars: mean +/- SEM.
$p < 0.01$; ### $p < 0.005$ vs WT; * $p < 0.05$, *** $p < 0.005$ vs *Grn*$^{-/-}$ + V , one-way ANOVA then Tukey's multiple comparisons test. *Abbreviations; GRN,* granulin gene; ICV, Intra-cerebroventricular; V, vehicle; WT, wildtype

Intra-Cisterna Magna (ICM) Administration of PBFT02 Enables PGRN Delivery Throughout CNS



- Directly delivers vector into the CSF via a single infusion, to reach CNS, PNS, and peripheral tissues[1]
  - Allows for broad CNS biodistribution
  - Lower doses compared to IV systemic delivery
  - Reduced impact of neutralizing antibodies
- Brief, < 1 h, non-surgical, CT-guided procedure
  - Infusion catheter **does not** enter brain tissue
- **Expressed PGRN directly impacts transduced cells**
- **Secreted PGRN cross-corrects proximal cells**

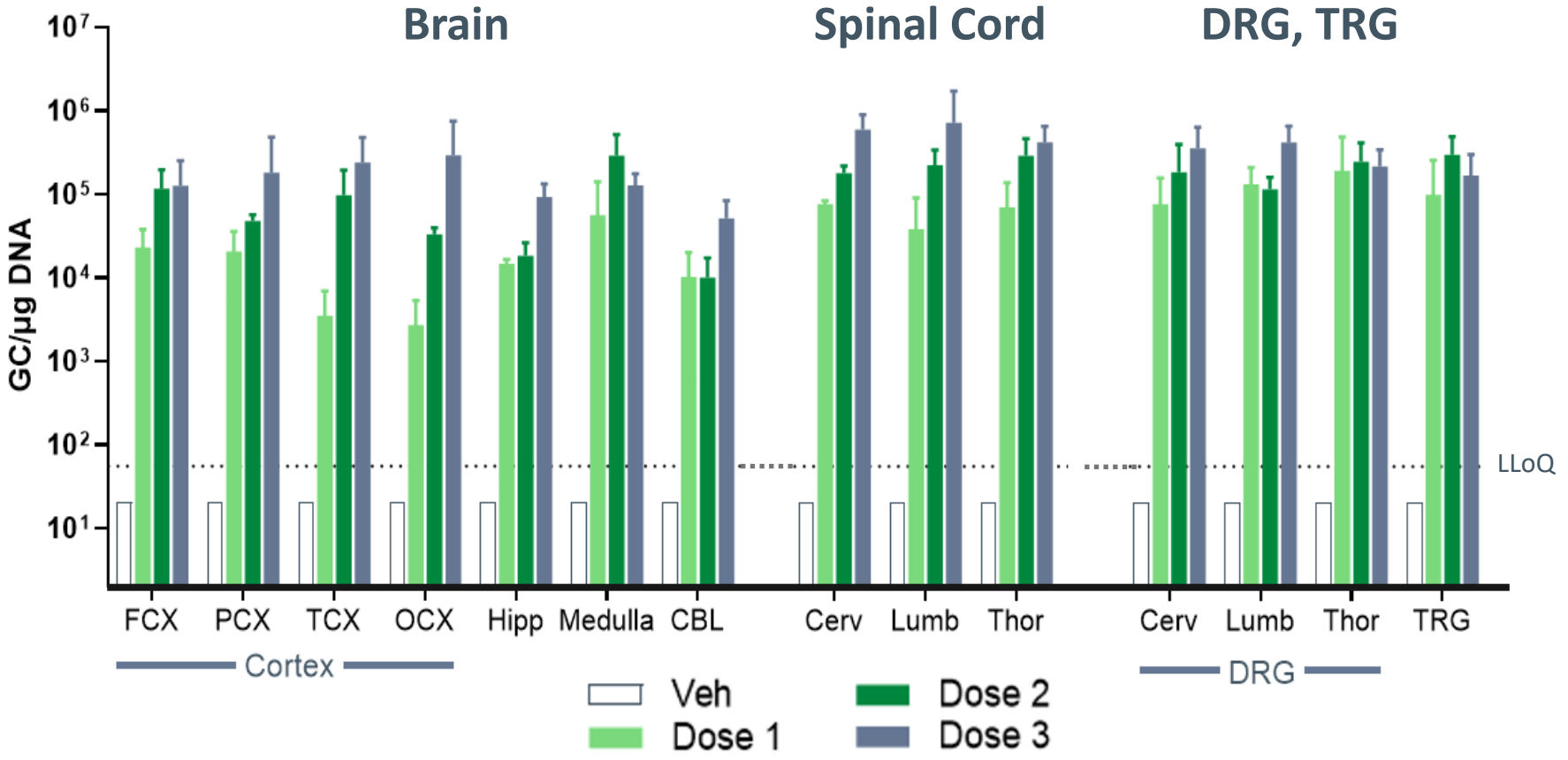
Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; h, hour; ICM, intra-cisterna magna; IV, intra-venous; PNS, peripheral nervous system; PGRN, progranulin.

Reference: [1]Hinderer et al, *Human Gene Therapy*. 2018, 29:15-24

ICM Administration to NHPs Achieved High Levels of Gene Distribution Throughout the Nervous System

- Robust vector delivery to cortical and sub-cortical brain regions affected in FTD
- NHP PBFT02 dose 1 (equivalent to upliFT-D clinical Dose 1) resulted in ~10e^4 GC/ug DNA throughout the brain

Vector Biodistribution 90 days post-PBFT02 to NHPs

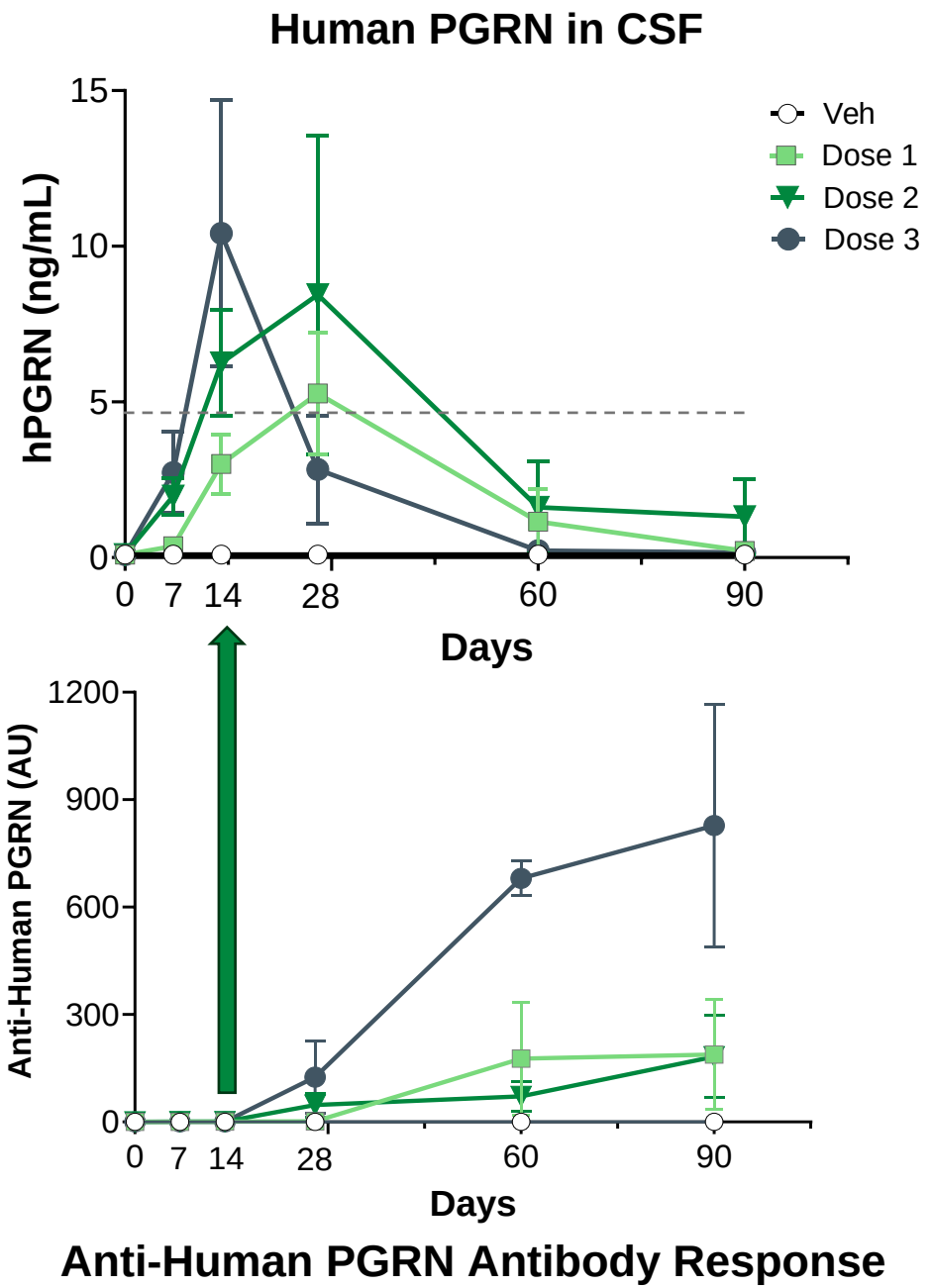


PBFT02, n=3/group; Veh, n=2/group. Data are mean +/- SEM.

Abbreviations: CBL, cerebellum; Cerv, cervical; DRG, dorsal root ganglion; FCX, frontal cortex; GC, genome copies; Hipp, hippocampus; ICM, intra-cisterna magna; LLoQ, lower limit of quantitation; Lumb, lumbar; NHP, non-human primate; OCX, occipital cortex; PCX, parietal cortex; TCX, temporal cortex; TRG, trigeminal root ganglio; Thor, thoracic; Veh, vehicle

PBFT02 Dose-Dependently Increased PGRN in NHP CSF

- Human PGRN was detected in NHP CSF shortly after ICM PBFT02 administration
- Dose-dependent increases in PGRN seen up to day 14
- Thereafter, an immune response to the human protein in NHPs attenuated PGRN levels
  - Not relevant when dosing FTD-*GRN* haploinsufficient individuals



14 PBT02, n=3/group; Veh, n=2. Data: mean +/- SEM. Dashed line is mean healthy adult human PGRN (n=61)

Abbreviations: AU, arbitrary units; CSF, cerebrospinal fluid; ICM, intra-cisterna magna; NHP, non-human primate; PGRN, progranulin; SEM, standard error of mean; Veh, vehicle

PBFT02 was Well Tolerated in NHPs

Followed for 90 days after a single ICM delivery of one of 3 doses

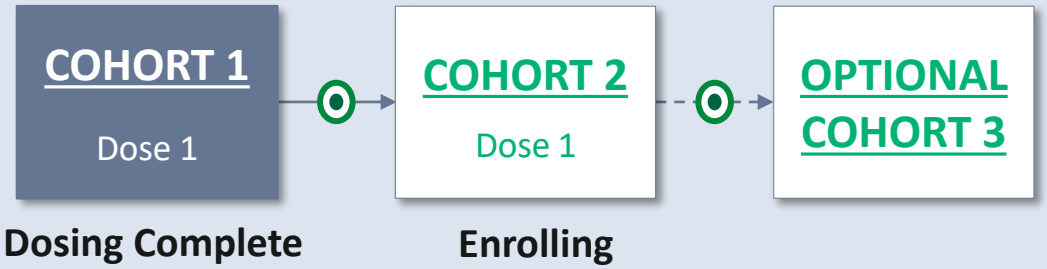
Assessments	Observations in NHPs
Abnormal clinical, neurological, or behavioral signs	None
Blood and CSF clinical pathology	Mild and transient increases in CSF leukocytes only
DRG, TRG, sensory nerve histopathology	Typically minimal to mild • Consistent with NHP AAV responses • No clinical correlates observed
NOAEL	Not reached

Dose 1 equivalent taken forward into a Ph1/2 clinical study, upliFT-D

Abbreviations: CSF, cerebrospinal fluid; DRG, dorsal root ganglion; ICM, intra-cisterna magna; NOAEL, no observed adverse effect level; TRG, trigeminal root ganglion

upliFT-D: Global Phase 1/2 Trial with PBFT02

- Phase 1/2 multi-center, open label dose-escalation study
- Primary endpoints: Safety and tolerability



Progress

- FTD-*GRN* Cohort 1 (n = 5) dosing complete
- Longest followed 12 months

Dose 1: 3.3e10 GC/g estimated brain weight. ◎ IDMC review

Safety Observations

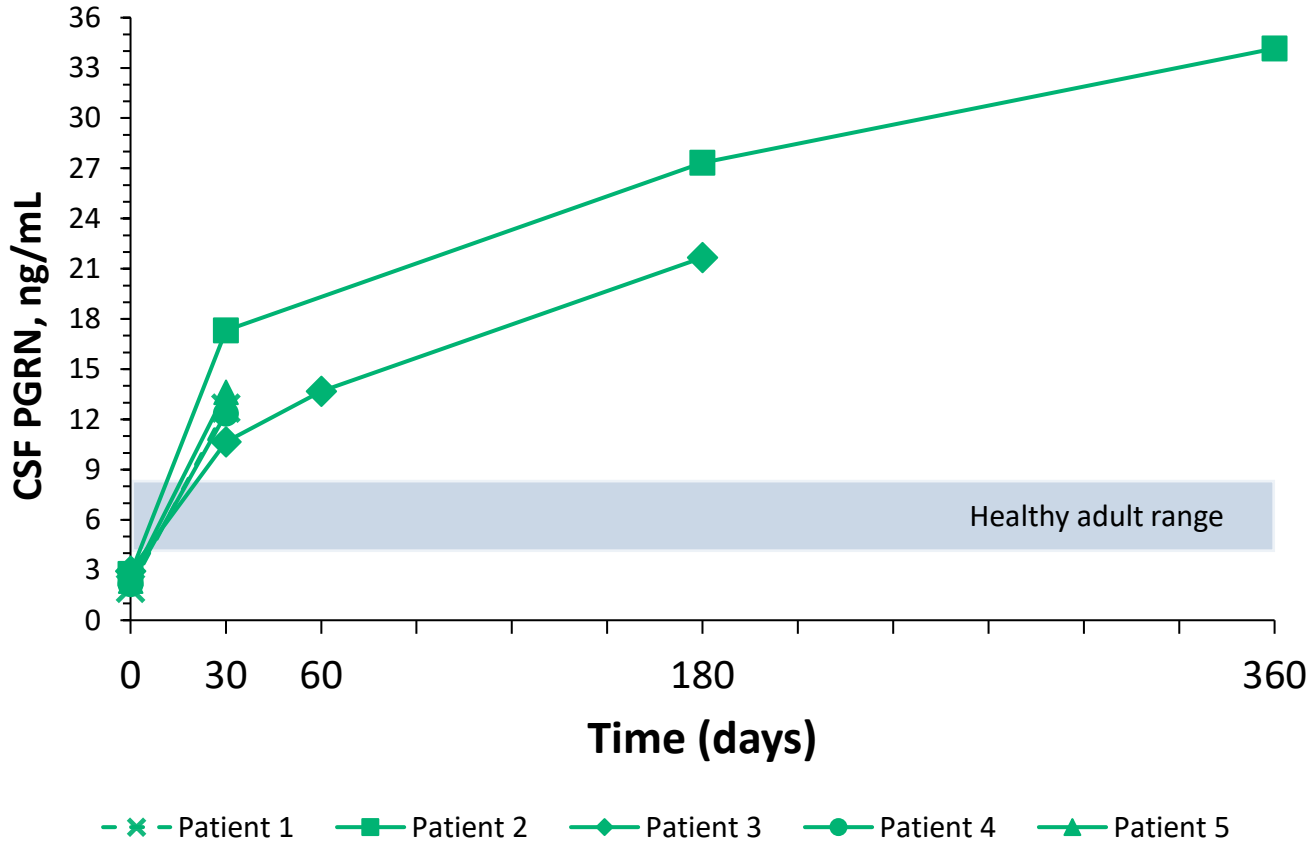
- All four Cohort 1 participants who received a revised immunosuppression regimen* had no SAEs or significant immune responses
- No patients showed evidence of DRG toxicity, as measured by nerve conduction studies
- No complications of ICM administration

*Revised steroid regimen: 1 g methylprednisolone IV daily to day 3, then 60 mg oral prednisone to day 60; Participant 1 received 60 mg oral prednisone to day 60 and had 2 SAEs. Safety cut-off: 08/20/2024

Abbreviations: DRG, dorsal root ganglion ICM, intra-cisterna magna; SAE, severe adverse event

Find more information on the upliFT-D trial here

Cohort 1 Interim Data: PBFT02 Administration Leads to Robust and Sustained Increases in CSF PGRN



- Continued elevation of CSF PGRN at 6 M (n=2) and 12 M (n=1)
  - Rate of increase slowing over time
- Consistent response across all five treated patients
- Plasma PGRN remained below healthy adult control levels
- Potential for best-in-class profile

Shading: Healthy adult human sample range of PGRN levels in CSF, n=61 (Passage Bio data)
Abreviations: CSF, Cerebrospinal fluid; M, month; PGRN, progranulin

PBFT02 Preclinical and Clinical Development Summary

Strong preclinical profile of PBFT02, a gene therapy to elevate PGRN in FTD-*GRN*

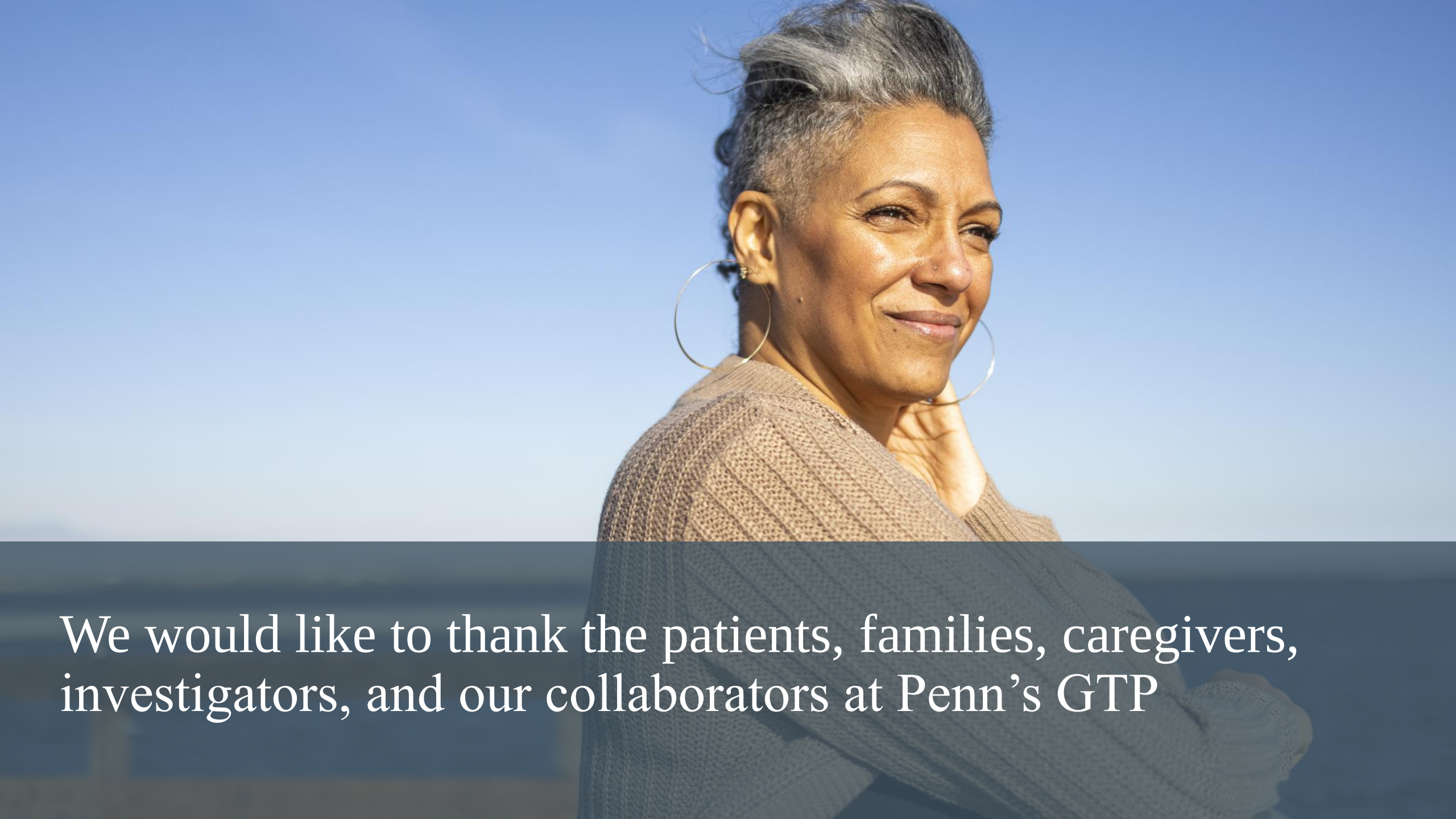
- PBFT02 improved lysosomal histopathology and neuroinflammation in *Grn*$^{-/-}$ mice
- Broad transduction across the brain and spinal cord in NHPs after ICM administration into the CSF
- Well-tolerated in NHPs with no clinical adverse effects

PBFT02 shows clinical potential as a one-time, CSF-delivered gene therapy approach

- Consistent, durable elevation of CSF PGRN at 6-months and 12-months
- Dose 1 well-tolerated among all Cohort 1 patients who received the revised steroid regimen*
- Continuing to assess Dose 1 in Cohort 2, given the robust effects on PGRN expression

*Revised steroid regimen: 1 g methylprednisolone IV daily up to day 3, followed by 60 mg oral prednisone to day 60. Safety cut-off: 08/20/2024

Abbreviations: CSF, cerebrospinal fluid; *GRN*/*Grn*, granulin gene; ICM, intra-cisterna magna; NHP, non-human primate; PGRN, progranulin



We would like to thank the patients, families, caregivers, investigators, and our collaborators at Penn’s GTP