Systemic AAV Gene Therapy with CNS-targeted Engineered Capsid Significantly Increases GCase Activity to Support the Potential Treatment of PD-GBA

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Disclosures

- Kimberly McDowell is an employee of Capsida Biotherapeutics

Solving the Challenges of Gen-1 Genetic Medicines

Starting in CNS and Ophthalmology with applicability across all therapeutic areas

	CNS Challenges	Capsida Solutions
Crossing the BBB	Limited ability to cross BBB; < 1% neuronal transduction	>70% of neurons transduced in NHPs
Safety Concerns	Liver and dorsal root ganglia (DRG) toxicity	>16x liver & >50x DRG detargeting; lower dosing
Patient Populations	Narrow therapeutic index (TI) limits to ultra-rare/rare diseases	Broader TI = more common diseases across ages
Route of Administration	Direct injection to brain or CSF causes significant risks and inconsistent expression	IV limits risks and allows consistent expression
	IV delivery increases risk of off-target effects (esp. liver) and triggering immune response	Well-tolerated safety profile with no adverse histopathological findings

Capsida Has Developed Best-In-Class Platform

Leverages rigorous drug development principles and high-throughput automation to identify capsids that meet Target Capsid Profile (TCP) for each indication

Engineered Capsids that Meet or Exceed TCP

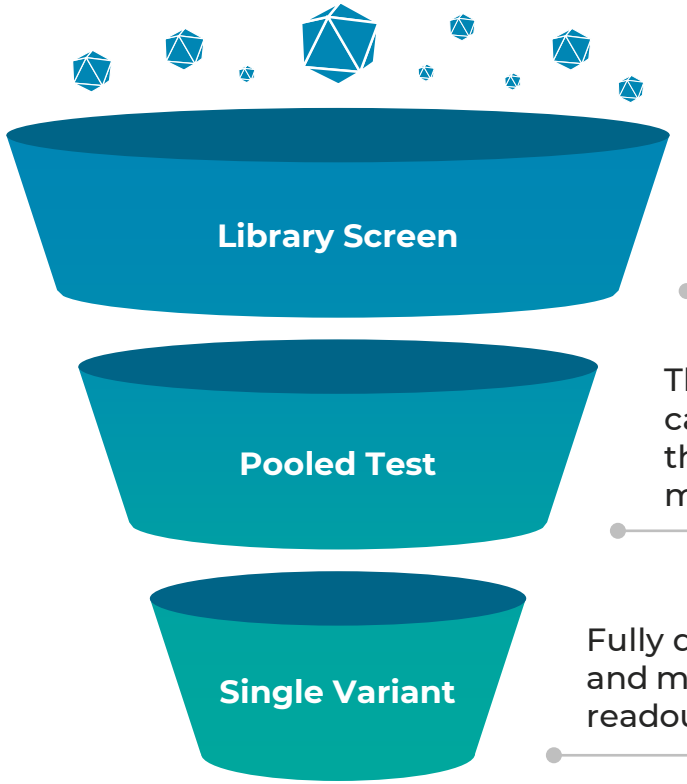
Evolved from engineering in mice to NHPs and screening in human cells to improve human translatability

Industrialized process built around customized robotics platform

Engineer capsids to meet TCP criteria including:

- Targeted tissues and cell type specificity
- High expression levels
- >10x off-target tissue detargeting
- Superior immunogenicity profile
- Superior manufacturability profile

Industrialized Capsid Development



Use directed evolution to create billions of variants screened directly in NHPs and human cells

Thousands of Candidate capsids are assessed for therapeutic expression and manufacturability

Fully quantitative efficacy, safety, and manufacturing scalability readouts for each single variant

Advance development candidates that meet or exceed TCP for each indication

Parkinson's Disease Associated with GBA Mutations

CAP-003 potential to be best-in-class disease modifying therapy

PD-GBA

Mutations in GBA result in decreased GCase activity (25-30% in symptomatic PD-GBA patients) and lysosomal dysfunction

Up to **15%** of PD patients have mutations in the GBA gene[1]

	Limitations of Investigational Therapies	CAP-003 Differentiators
Protein Levels	− Low neuronal transduction, especially in substantia nigra	+ Up to 70% of neurons transduced (57% in substantia nigra)
GCase Elevation	− Limited GCase elevation	+ GCase increases > levels needed to treat PD-GBA; reaching >200% on average across key brain regions
Delivery	− Direct injection to the brain or CSF is invasive and results in inconsistent expression	+ IV delivery limits risks and allows for broad coverage across the CNS
Safety	− Liver and DRG toxicity risks	+ No adverse histopathology findings, including liver and DRGs

Disease Manifestations

PD is second most common neurodegenerative disease

Motor Symptoms (e.g., resting tremor, rigidity, slowness of movement) and non-motor symptoms (e.g., cognitive decline, psychiatric)

Unmet Need

No approved disease-modifying therapies

Potential for earlier age of onset, more frequent cognitive impairment, more rapid progression vs idiopathic PD[1]

Impact

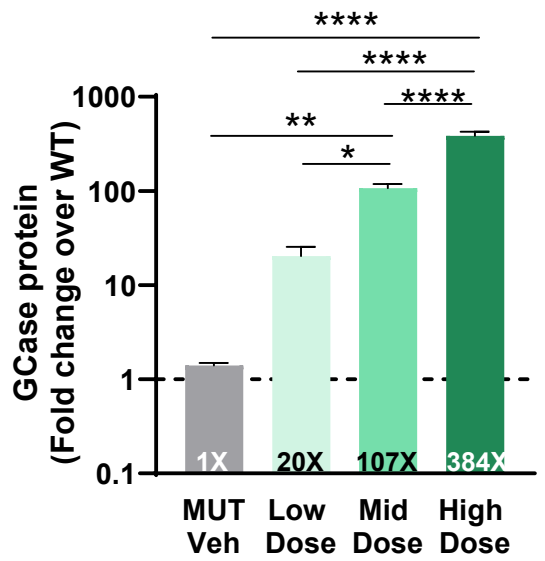
Potential to be first IV delivered gene therapy

Up to **150K** prevalent PD-GBA population in US[2] and up to **180K** in the EU[3]

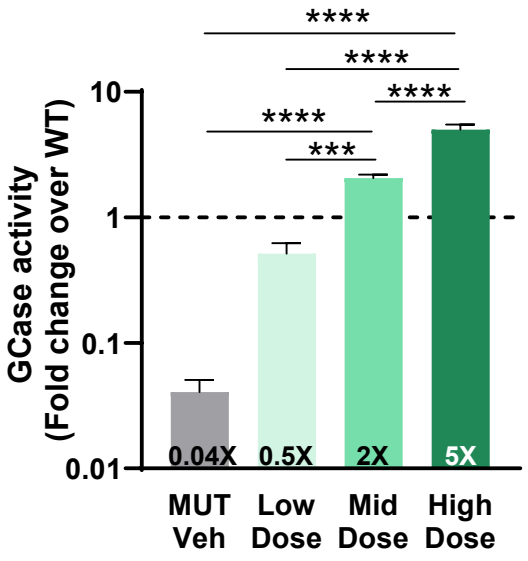
[1]Smith and Schapira 2022; [2]Parkinson's Foundation; [3]Deuschl G The Lancet Public Health 2020

Mouse model correction supports disease-modifying potential of *hGBA1* clinical cargo

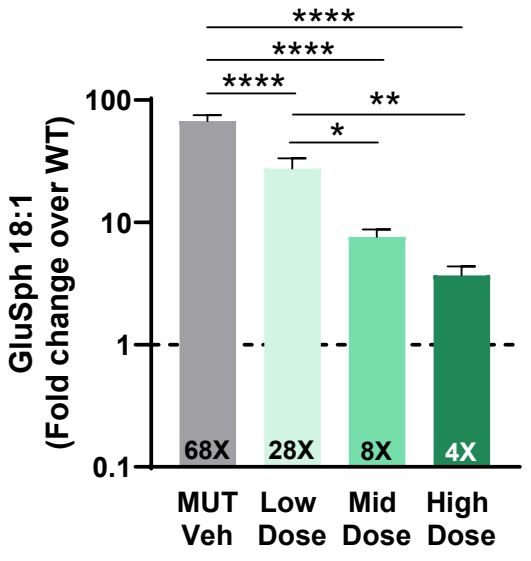
GCase Protein



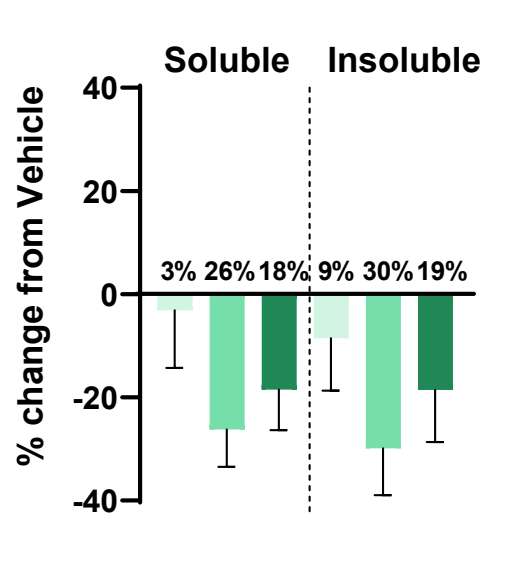
GCase Activity



GluSph



α - Synuclein

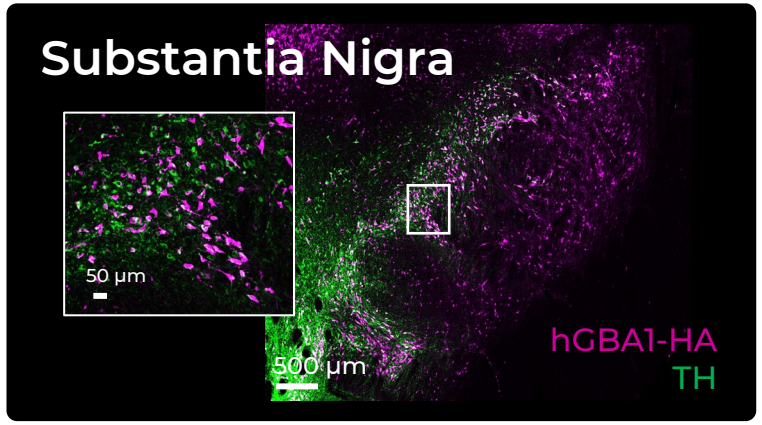


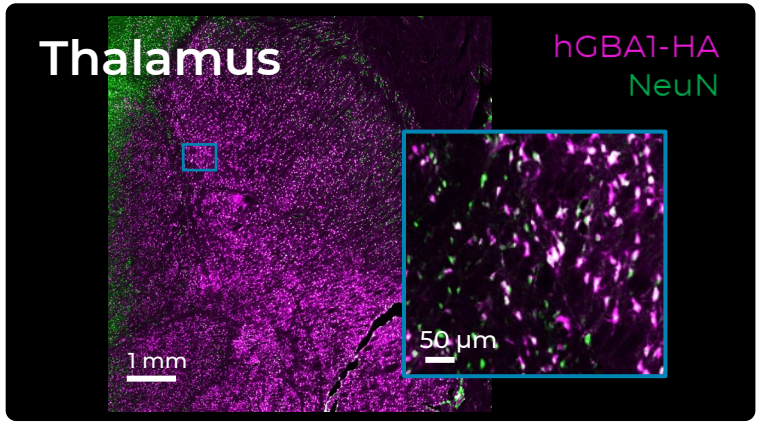
- The disease model exhibits a more severe phenotype (>90% GCase activity reduction, ~6800% GluSph increase) compared to PD-GBA patients (~30% GCase activity reduction[1], ~40% GluSph increase[2])
- Delivery of *hGBA1* via surrogate capsid results in dose-dependent increases in GCase protein and activity in the brain
- Increased activity coincides with significant decreases in GluSph levels, and reductions in α-synuclein

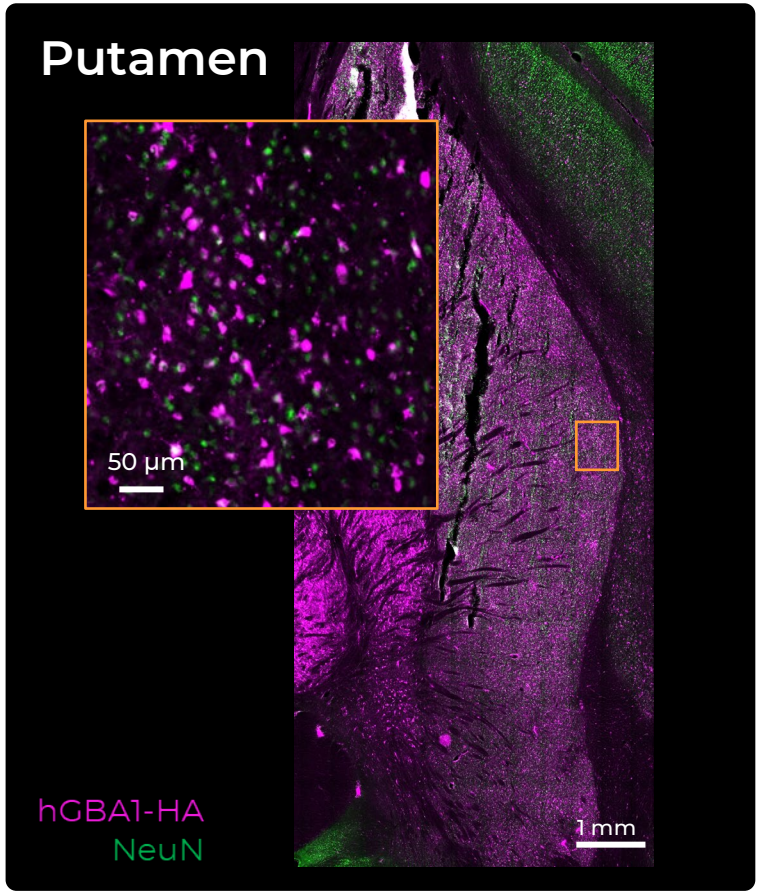
Pharmacology Study
In-life: 6 months
Species: Mus musculus (n=10/grp)

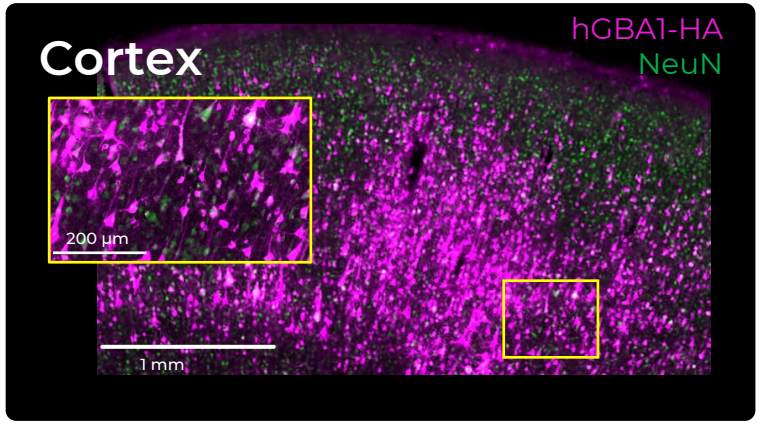
[1] Leyns et al., 2023; [2] Sanz Munoz et al., 2021

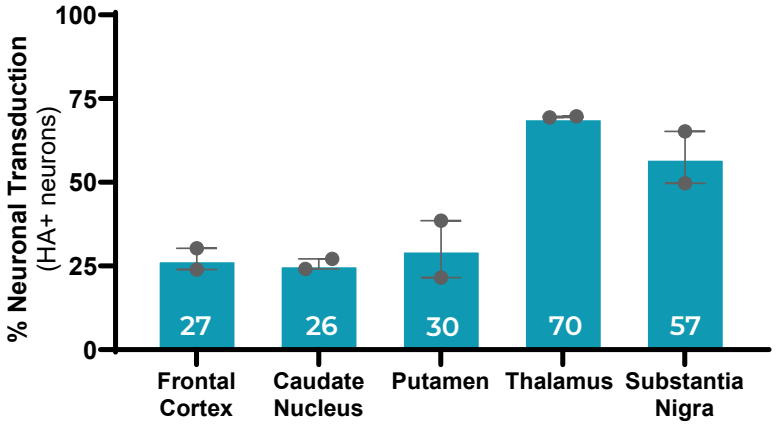
IV Dosing Yields Widespread Expression of hGBA1-HA in Relevant NHP Brain Regions, including Substantia Nigra







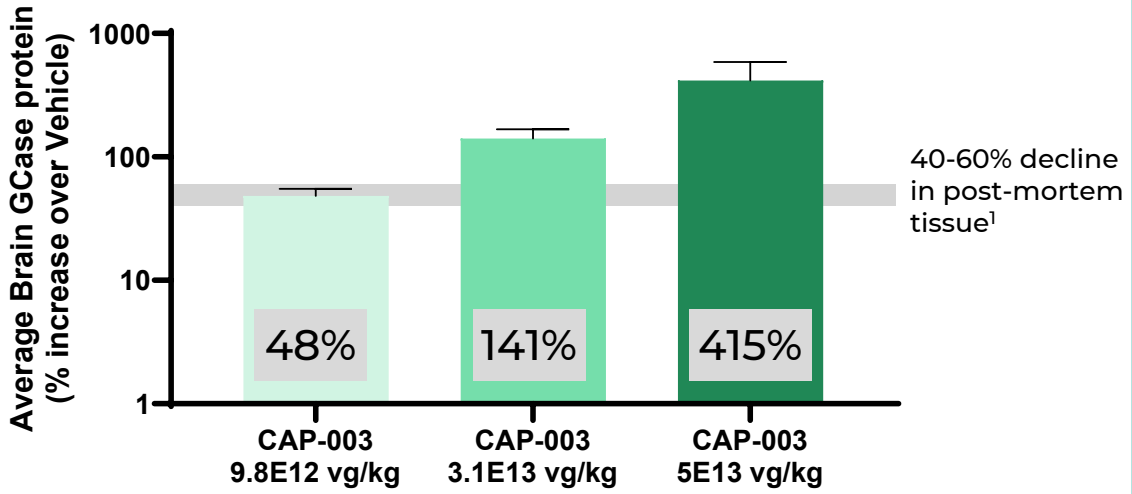




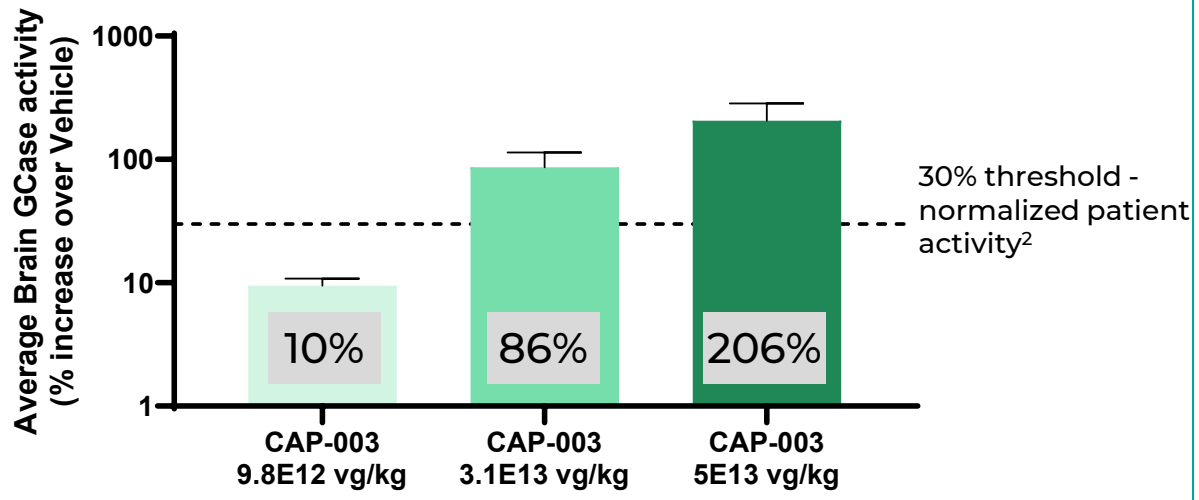
PD-GBA Development Candidate Study
Dose: 2.8E13 vg/kg; **In-life:** 6 weeks
Species/Age: Cynomolgus macaques, ~42 mo

CAP-003 maintains significant increased brain GCase protein and activity at 3 months post-dosing in NHP GLP Tox study

Brain GCase Protein



Brain GCase Activity



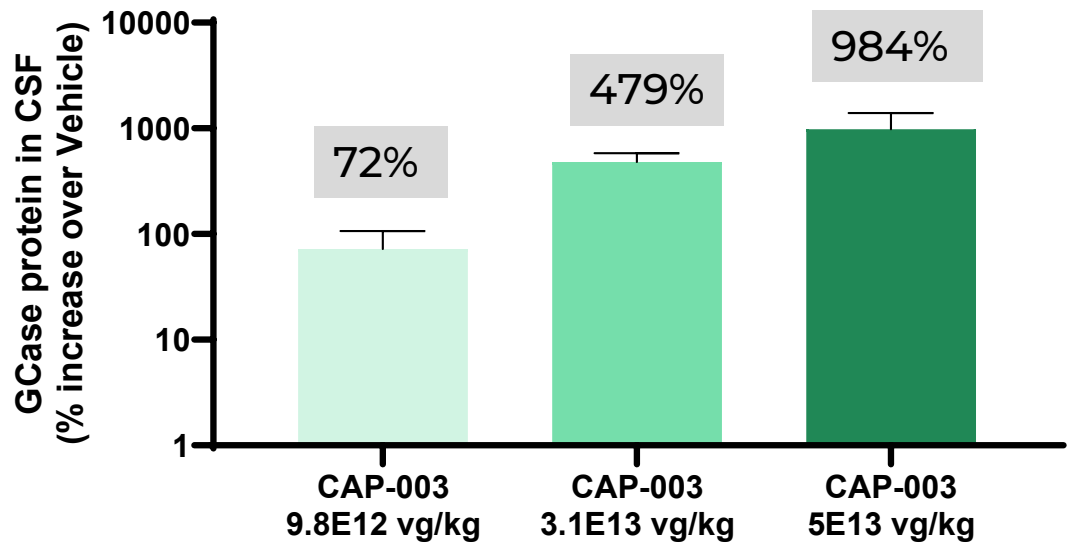
- Administration of CAP-003 resulted in a dose-dependent increases in average brain GCase protein and activity when normalized to the vehicle control (i.e., endogenous GCase levels)
- CAP-003-mediated increases in GCase activity are expected to provide clinically meaningful benefits to PD-GBA patients

GLP Tox Study
In-life: 3 months
Species: Cynomolgus macaques (n=3/grp)

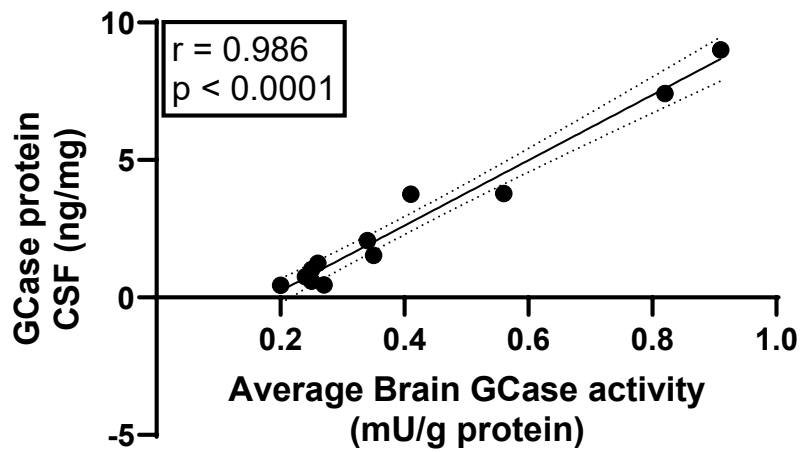
[1] Sanz Munoz et al., 2021; [2] Leyns et al., 2023

GCase protein levels in CSF serve as best biomarker for GCase activity in the brain

GCase Protein in CSF



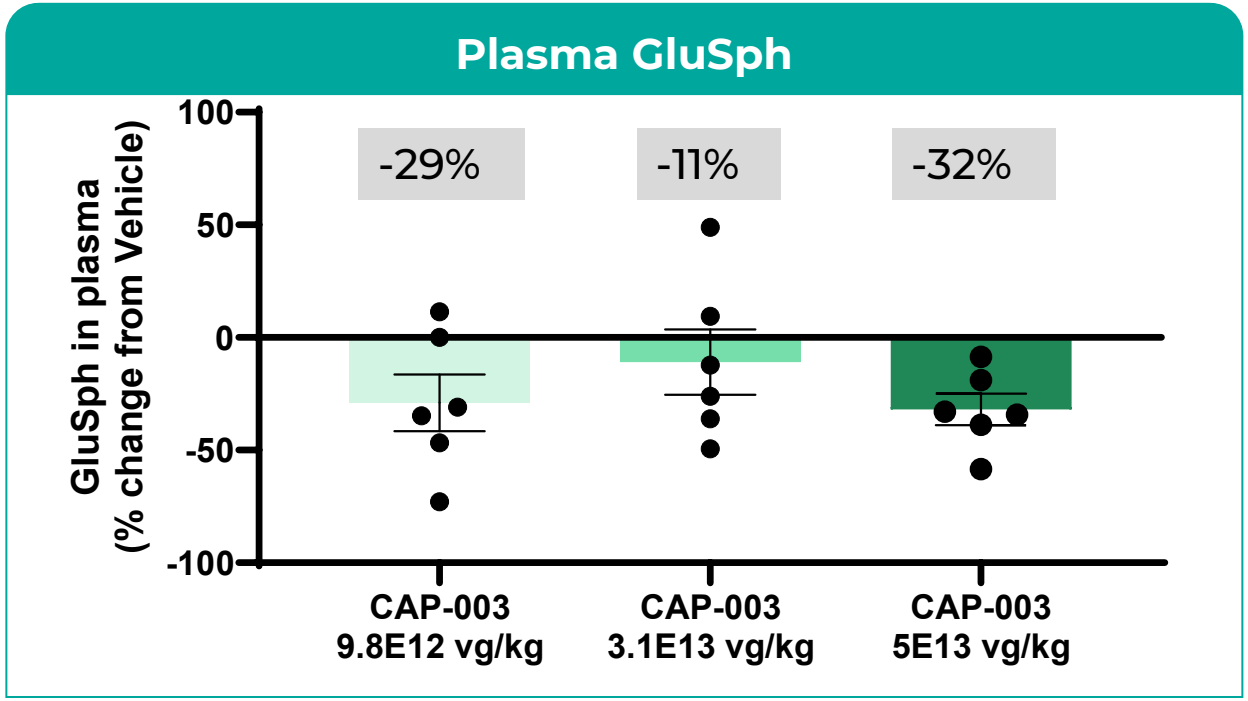
Correlation of CSF GCase Protein & Brain GCase Activity



- Administration of CAP-003 resulted in a dose-dependent increase in GCase protein levels in the CSF when normalized to the vehicle control
- Significant positive correlation between CSF GCase protein levels and brain GCase activity

GLP Tox Study
In-life: 3 months
Species: Cynomolgus macaques (n=3/grp)

Decreased GluSph levels in plasma confirm target engagement in WT NHPs

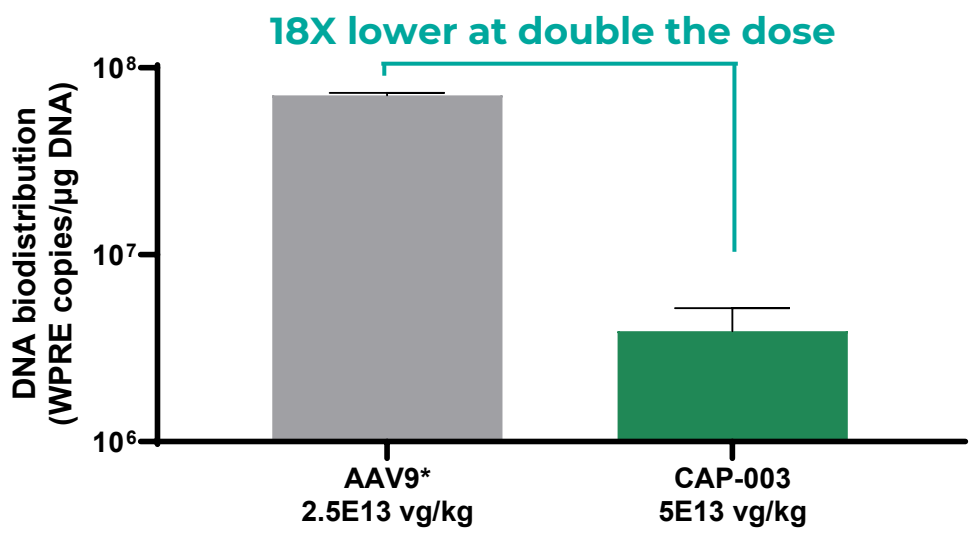


- Even in healthy wildtype NHPs, CAP-003 administration shows target engagement via decreases in GluSph levels when normalized to the vehicle control
- In healthy NHPs, GluSph levels are already low in the plasma and undetectable in the CSF; however, these data support the strong target engagement and dose-dependent decrease of GluSph observed in PD-GBA mouse models after *hGBA1* gene supplementation

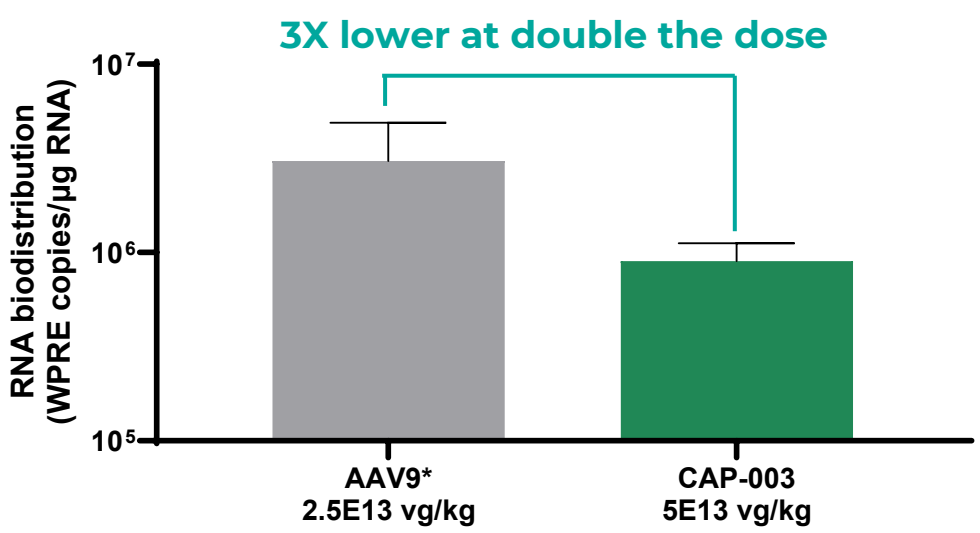
GLP Tox Study
In-life: 3 months
Species: Cynomolgus macaques (n=3/grp)

CAP-003 is Substantially Detargeted from Liver and DRGs in NHPs Compared to AAV9

Liver DNA



DRG RNA



Well-tolerated safety profile with no adverse histopathological findings

*Historical IV-delivered AAV9 2.5E13 vg/kg (non-GBA cargo control)

GLP Tox Study
In-life: 3 months
Species: Cynomolgus macaques (n=3/grp)

CAP-003 potential as best-in-class gene therapy for PD-GBA

- Capsida's PD-GBA candidate efficiently crosses the blood-brain barrier in NHPs after intravenous injection and achieves breakthrough levels of transduction throughout the brain while significantly de-targeting the liver (>15-fold) compared to AAV9
- GCase enzyme activity is raised significantly (>200% over endogenous levels) in therapeutically relevant areas of the NHP brain, exceeding levels needed to restore GCase function in patients with PD-GBA
- Significant phenotypic correction in a *GBA1* loss-of-function mouse model supports disease-modifying potential of *hGBA1* clinical cargo
- In the GLP Toxicology study, this efficacy was achieved at low to moderate doses that are well tolerated in NHPs without remarkable changes in clinical pathology or immunogenicity, with no adverse histopathology findings across the body, including liver and DRGs
- CAP-003 scales well in suspension manufacturing platform to meet quantity and quality for the clinic
- We have characterized a human receptor that binds our engineered capsids; this receptor has complete homology between humans and macaques in the predicted binding pocket
- Capsida's PD-GBA program is currently on track for IND filing in Q2 2025 and FIH in Q3 2025

CAPSIDA BIOTHERAPEUTICS

Our Pipeline is Making the Impossible Possible

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