CAPSIDA BIOTHERAPEUTICS

Systemic AAV Gene Therapy with CNS-Targeted Engineered Capsids Achieves Significant GCase Activity Increases in the Primate Brain to Support the Potential Treatment of GBA-PD

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Disclosures

- Nicholas Flytzanis is a co-founder and employee of Capsida Biotherapeutics

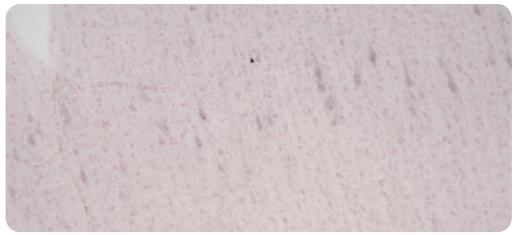
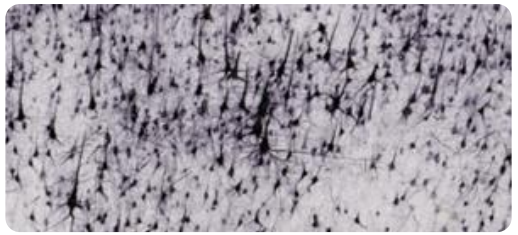
Capsida Biotherapeutics

Foundation in capsid engineering with focus on building a new class of targeted, non-invasive gene therapies

Pipeline of wholly owned and partnered programs in rare and more common Neurological and Ophthalmology diseases

Fully integrated capabilities: capsid engineering, cargo optimization, discovery, preclinical research, process development, manufacturing, and clinical development

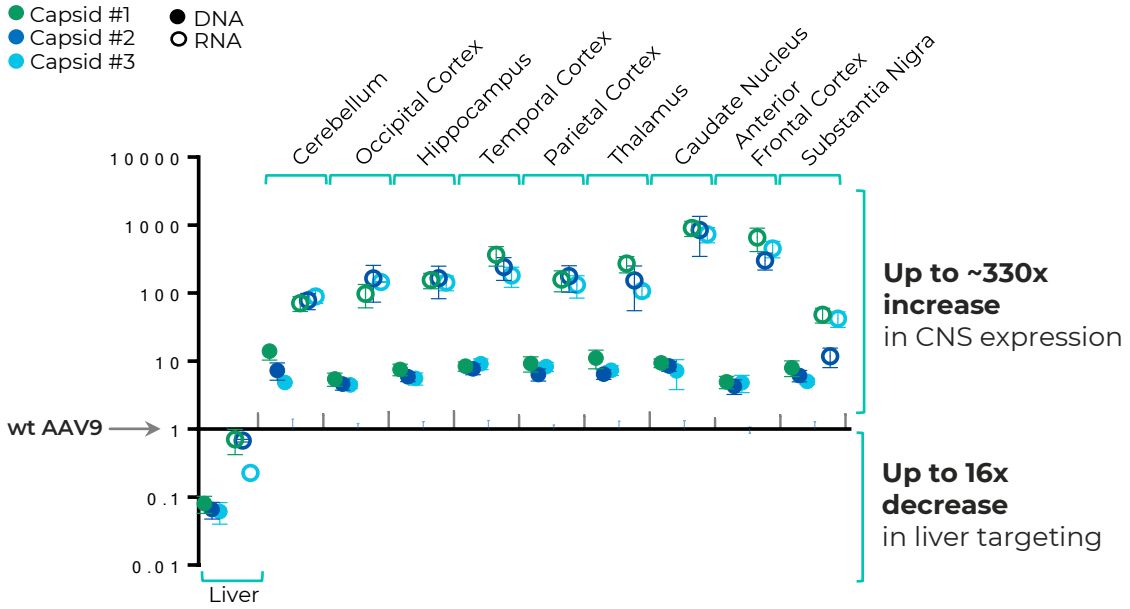
Capsida Addresses CNS Challenges Through our Engineered Gene Therapies

	CNS Challenges	Capsida Solutions
	Wild Type AAV9 (IV Delivery)	**Capsida Engineered Capsid** (IV Delivery)
	NHP Cortex 	NHP Cortex 
Neuronal Transduction	Limited ability to cross biological barriers, esp. BBB - < **1% transduction** with wild type AAV9 IV	Capsida engineered capsids cross BBB with high levels of neuronal transduction – **up to 70% neurons**
Safety Concerns	Safety concerns / **liver toxicity**	Enabling lower dosing and **~4000x difference** in CNS to liver targeting vs wild type AAV9
Patient Populations	Traditional gene therapies **primarily for ultra-rare/rare diseases**	**Access to more** common diseases across all ages
Risks	Direct injection into the brain or CSF is invasive with **significant risks**	Targeted IV admin **increases effectiveness** and **reduces risks**

Gen 5 Capsids Yield Breakthrough Expression Across the CNS and Significant Liver De-Targeting vs WT AAV9

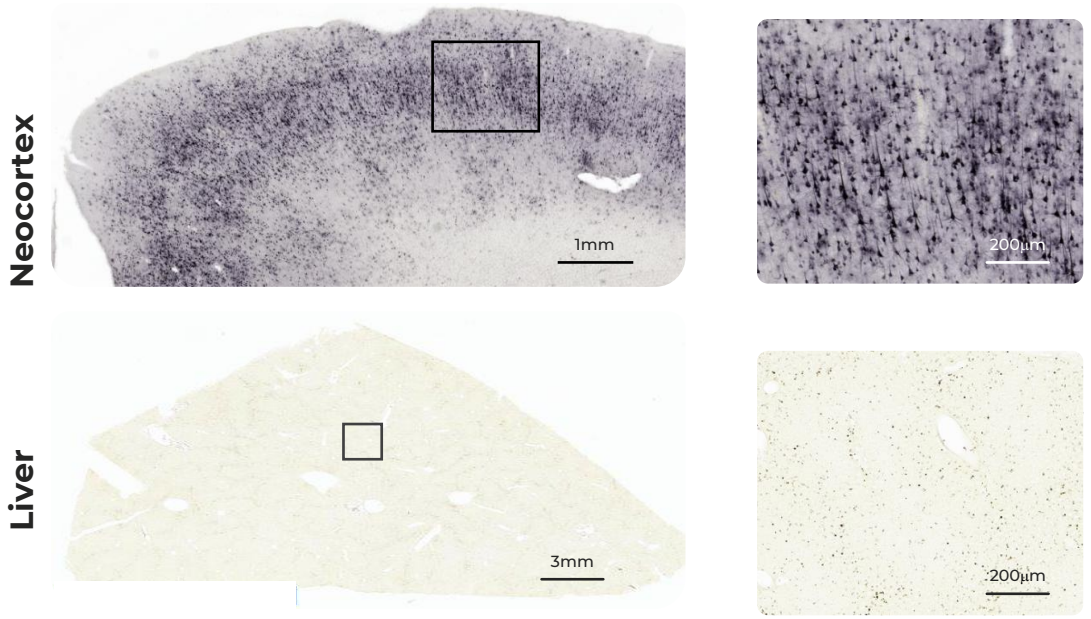
IV Delivery

DNA and RNA Enrichment over AAV9 From Individual Capsid Characterization Studies In Cynos



IV Delivery

Protein localization (HA tagged GOI)



~4000X difference in CNS expression vs liver targeting with Capsida's breakthrough capsids relative to wtAAV9

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Lower efficacious doses
Wider Therapeutic Index

Pipeline for Rare and Common Diseases Across All Ages

Capsida Wholly Owned Programs

Disease / Target	Cargo	Discovery	IND-Enabling	Clinical
Genetic Epilepsy due to STXBP1 mutations	Gene Supplementation	CAP-002		
Parkinson's disease associated with GBA mutations	Gene Supplementation	CAP-003		
Undisclosed	Gene Supplementation	CAP-004		

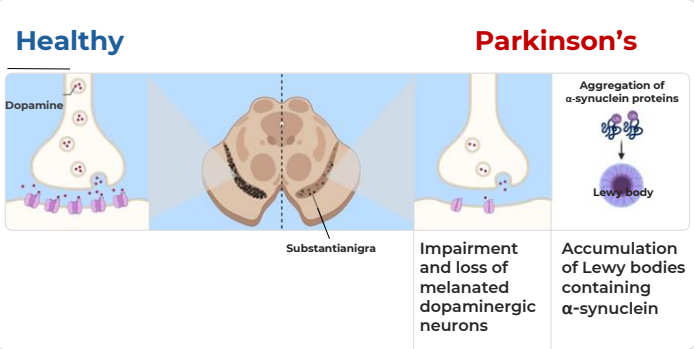
Partnered Programs

Disease / Target	Cargo	Partner	Co/Co Option
Neurological Diseases & Disorders (3)	Undisclosed	abbvie	One Program, U.S. Profit Share
Neurological Diseases & Disorders	Undisclosed	Prevail Therapeutics, A Wholly Owned Subsidiary of Eli Lilly and Company; Lilly	One Program, U.S. Margin Share
Ophthalmology Diseases & Disorders (3)	Undisclosed	abbvie	
Friedreich's Ataxia	Editing	CRISPR Therapeutics	CRISPR owned, Capsida Co/Co Option

Parkinson's Disease Associated with GBA Mutations

PD-GBA1

Mutations in GBA result in decreased GCase activity (25-30% in symptomatic PD-GBA1 patients) and lysosomal dysfunction



Addressing motor and non-motor symptoms require **widespread** supplementation of enzyme activity, including in key brain regions of **substantia nigra, frontal cortex, putamen**

Debilitating Disease Manifestations

Second most common neurodegenerative disease

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

Extreme Unmet Need

No approved disease-modifying therapies

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

CAP-003 Data in Primates

Protein Levels	GCase Enzyme Activity
59% of neurons transduced in substantia nigra	**45%** increase over wildtype in substantia nigra
Up to **70%** in other brain regions	Average brain-wide increase of **36%**

Commercial Opportunity Potential >$1B

Potential to be first IV delivered gene therapy

Nearly **1M** prevalent PD population in US[2]

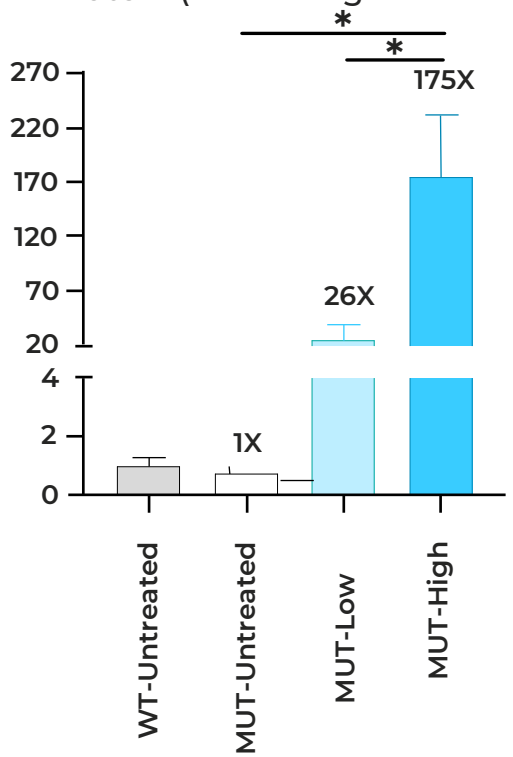
Up to **15%** of PD patients have mutations in the GBA gene[1]

[1]Smith and Schapira 2022; [2]Parkinson's Foundation
Created with BioRender.com

In Vivo Target Engagement in GBA1 LOF Mouse Model

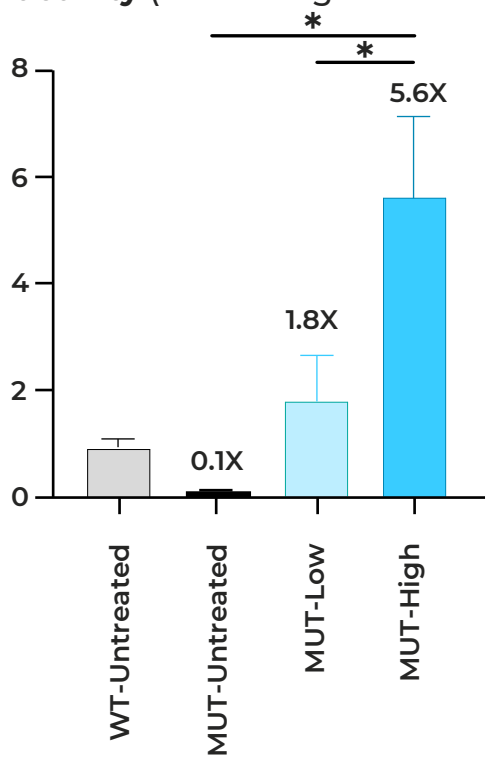
Brain - GBA1 Protein

GBA1 Protein (fold change over WT)



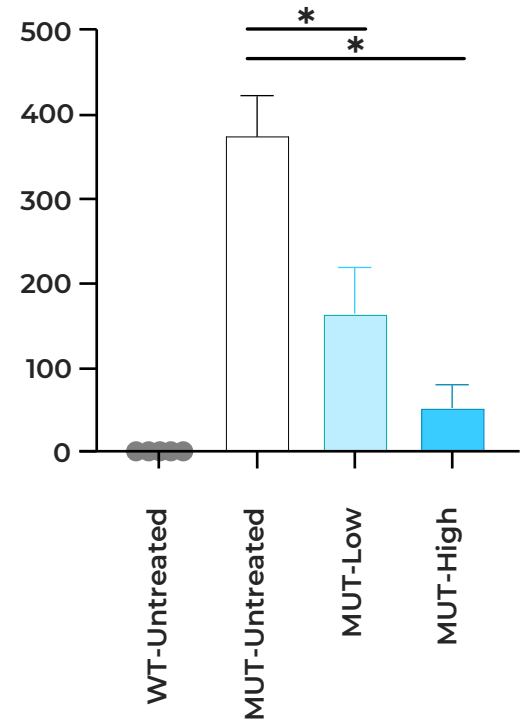
Brain - GCase Activity

Gcase activity (fold change over WT)



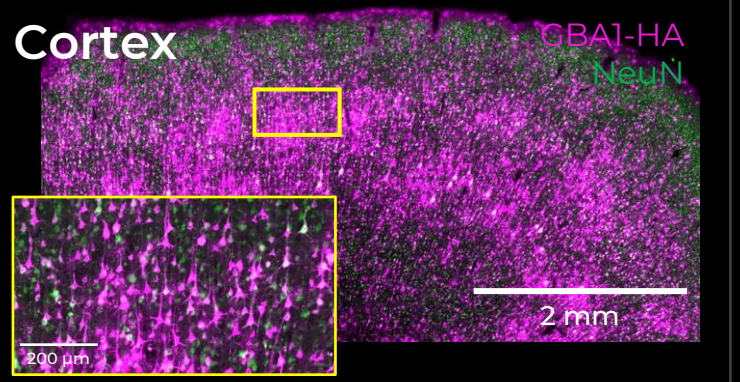
Brain - Glucosylsphingosine

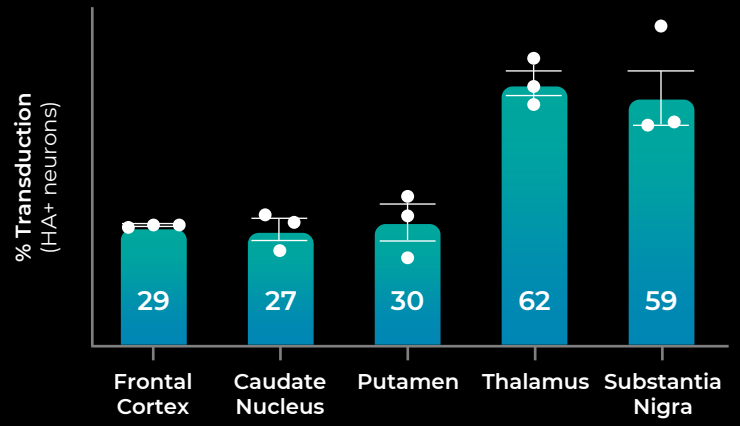
GluSph 18:1 (ng/ml)

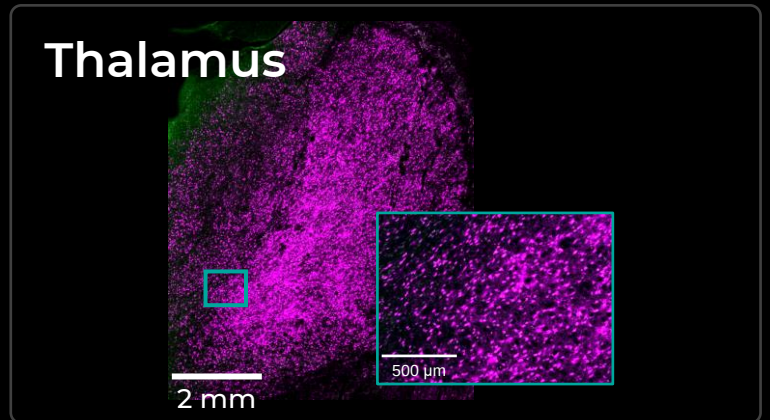


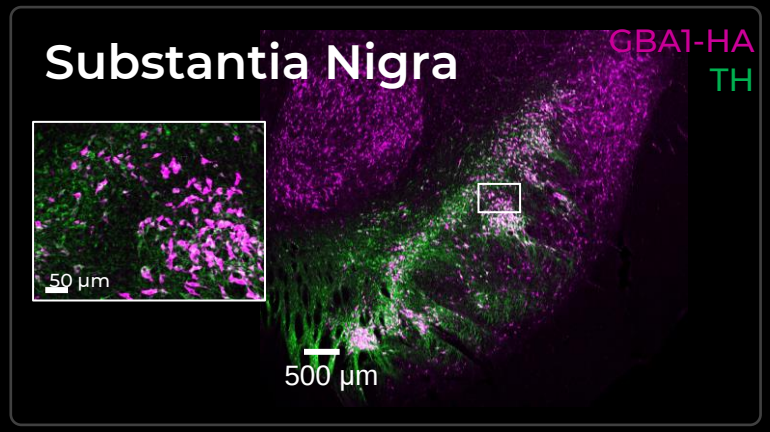
AAV Treatment Correlates with Dose-dependent **Increases in GBA1 Protein and Gcase Activity** in the Brain as Well as **Significantly Reduced Glusph Levels**

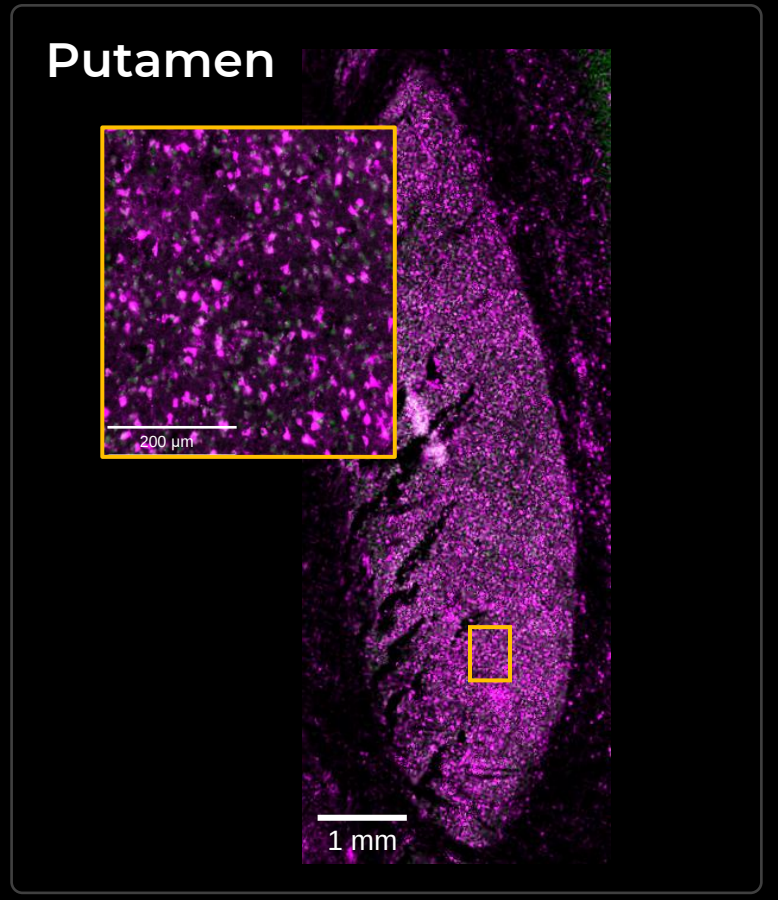
CAP-003 IV Results In Widespread Expression of GBA1-HA In Brain Areas Impacted by Neurodegeneration





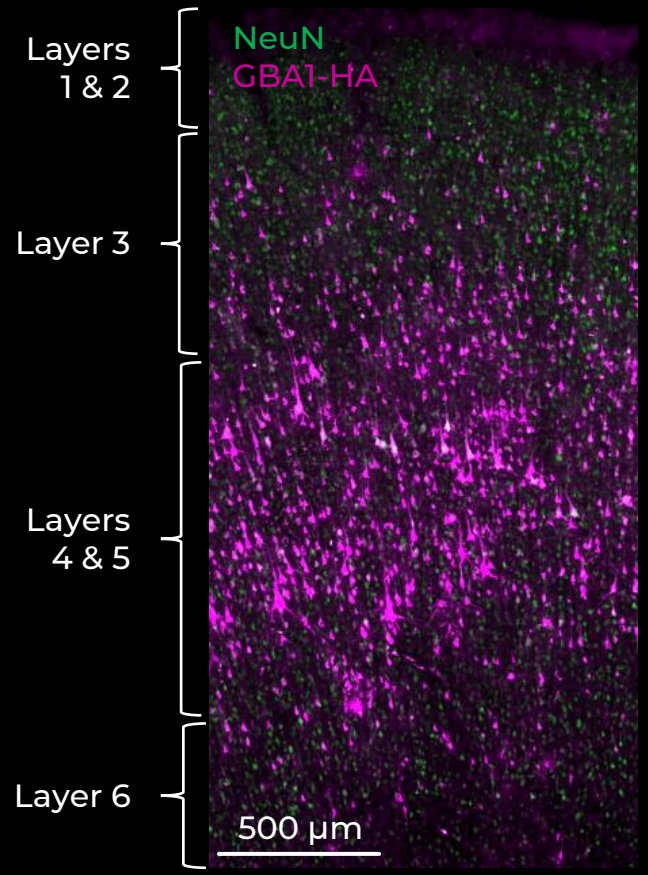






Capsid: Gen 5; **Dose:** 1.25E13 vg/kg
Cargo: hGBA1-HA; **In-life:** 6 weeks
Species/Age: N = 3 cynomolgus macaques, ~42mo

Sampling Across Cortical Layers Shows Neuronal Transduction up to 50% Following IV Delivery



» **10-20%**

» **28-41%**

» **49-50%**

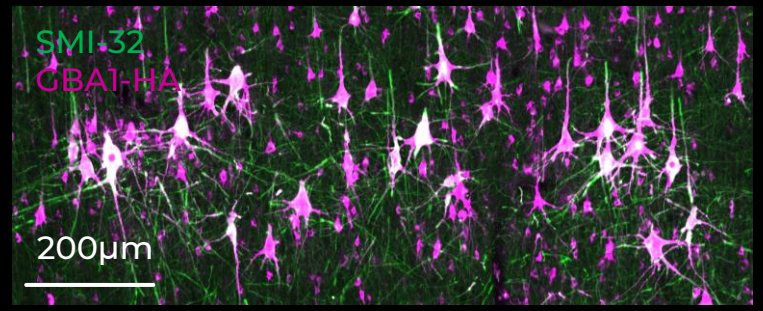
» **18-29%**

An average **neuronal transduction of 30%** was determined by quantifying the full depth of the cortex (pia to white matter)

Representative image to the left highlights the **range of neuronal transduction** observed **throughout the cortical layers**

Neuronal transduction observed in all layers of the NHP cortex, with the **highest transduction levels observed in Layers 4-5 at 50%**

Representative image below highlights **nearly 100% transduction of motor neurons** within Layer 5 of the cortex



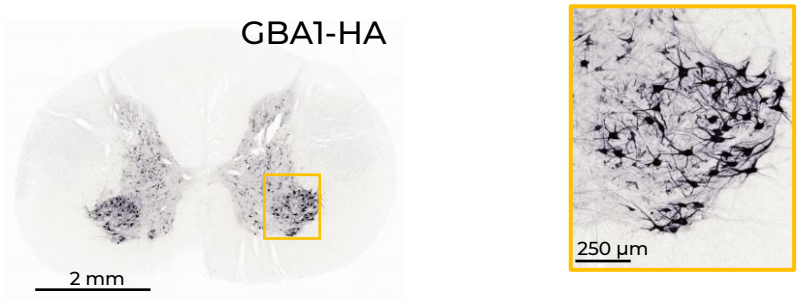
» **96-97%**

Capsid: Gen 5; **Dose:** 1.25E13 vg/kg
Cargo: hGBA1-HA; **In-life:** 6 weeks
Species/Age: N = 3 cynomolgus macaques/ ~42mo

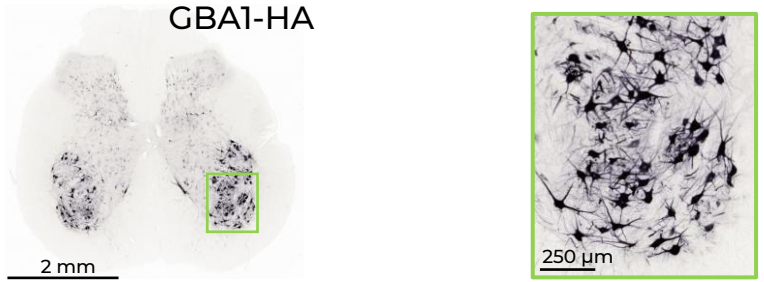
CAP-003 Expression Extends to Spinal Cord and is Markedly De-Targeted from the Liver and Well Tolerated Following IV Delivery

Spinal Cord

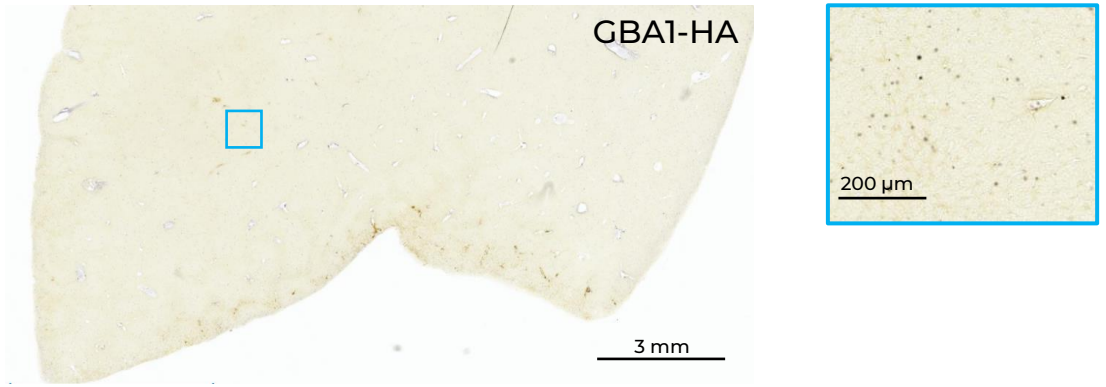
Cervical



Lumbar



Liver



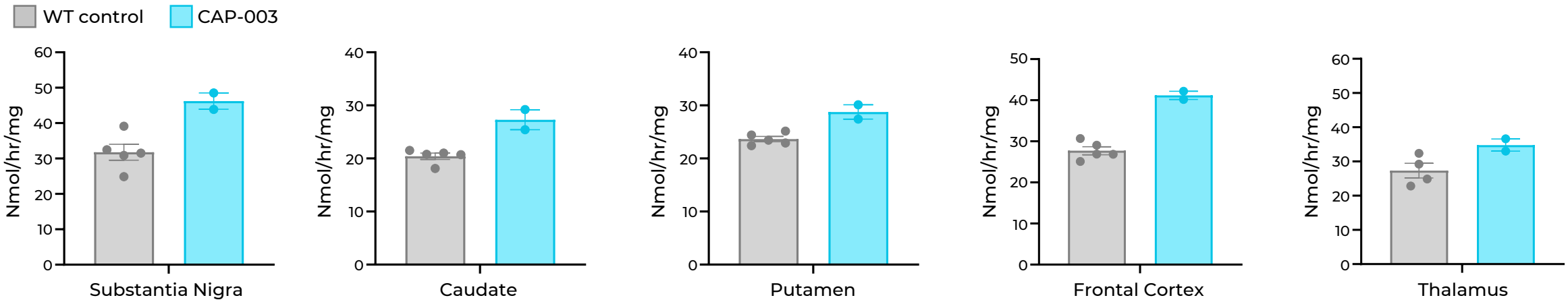
16X de-targeted compared to AAV9

Capsid: Gen 5; **Dose:** 1.25E13 vg/kg; **Cargo:** hGBA1-HA; **In-life:** 6 weeks
Species/Age: N = 3 cynomolgus macaques/ ~42mo

CAP-003 is **well tolerated** with no clinical pathology or immunogenicity findings.
Unremarkable histopathology across the body, including **liver** and **DRGs.**

CAP-003 IV Results in Substantial GCase Activity throughout the NHP Brain

GCase Activity in Key Regions of Interest



% increase vs WT[1]	Substantia Nigra	Caudate	Putamen	Frontal Cortex	Thalamus
	45%	**34%**	**22%**	**49%**	**27%**

IV delivered development candidate shows a significant increase in GCase activity in NHPs in majority of individual key brain regions, with a **45% increase** in the substantia nigra

Estimates of GCase activity increases within transduced neurons reach **82%** over wild-type levels in the substantia nigra and up to **102% across the whole brain**

These GCase increases are expected to normalize enzyme activity levels and provide clinically meaningful benefit for patients with PD-GBA1

[1] Reflects exogenous and endogenous protein

Capsida Manufacturability Assessment: CAP-003 Scales Well in Suspension to Meet Quantity and Quality for the Clinic

Characteristic	Method	Criteria	CAP-003 (2L)	CAP-003 (50L)
Productivity in crude lysate	**ddPCR**	**Good:** 1-3E+11 vg/ml **Better:** 3-5E+11 vg/ml **Best:** >5E+11 vg/ml	**3.45E11**	**3.35E11**
% Full, out of bioreactor	DLS + UV or vg/cp titer	**Good:** >5% Full **Better:** >15% Full **Best:** >30% Full	8%	8%
Binding to AAV9 resin	Affinity step, ddPCR	Recovery >50%, by ddPCR	56%	75%
Host cell DNA (encap), DS	qPCR	<1E3 ng per 1E13 VG	526	779
Aggregation, DS	SEC-FLD	Aggregation < 10%	3.3	1.5
Packaging, DS	Alkaline agarose gel or electrophoresis method	Dominant band at predicted size	Dominant band as expected	Dominant band as expected
VP1:VP2:VP3 ratio, DS	CE-SDS	Comparable to reference	1.3:1:5.8	1.1:1:4.8
Overall Yield, DS	**ddPCR**	**DS: Vg/L of cell culture**	**8.20E13**	**1.5E14**

Overall yield is in line with wild type AAV9

Summary

Capsida's CAP-003 candidate efficiently crosses the blood-brain barrier in NHPs after intravenous injection and achieves breakthrough levels of transduction throughout the NHP brain while significantly de-targeting the liver compared to AAV9

GCase enzyme activity is raised significantly throughout the therapeutically relevant areas of the NHP brain, exceeding levels needed to restore GCase function in patients with PD-GBA1

This efficacy can be achieved at doses as low as 1.25E13 vg/kg that are well tolerated without yielding any overt clinical pathology or immunogenicity and unremarkable histopathology findings across the body, including liver and DRGs

Capsida's PD-GBA1 program is currently in IND-enabling studies with the goal of supporting initiation of clinical trials in the first half of 2025

Acknowledgements

Capsida's PD-GBA1 Team

Kimberly McDowell

Reed Ressler

Alexander Armendariz

Maeve Flynn

Lubov Grigoryeva

Brandon Wheeler

Amanda Woodbury

Swati Tole

Hari Acharya

Paul Denis

Pasha Tchourilov

Other Capsida Oral Presentations

AAV Gene Therapy Corrects Neurological Phenotypes with Clinically Relevant Doses in a Mouse Model of STXBP1-Related Development and Epileptic Encephalopathy; **Wu Chen (BCM) - Abs # 38**

Directed Evolution of AAV9 Libraries in Non-Human Primates Identifies a Capsid Family with Enhanced Central Nervous System Tropism and Liver De-Targeting Following Systemic Delivery; **Xiaojing Shi - Abs # 122**

Capsida Poster Presentations

CAP-002: Systemic AAV Gene Therapy with Next Generation Capsida for Treatment of STXBP1 Encephalopathy; **Allison Knoll - Abs # 504**

Directed Evolution of AAV2 Libraries Yields Capsids with Improved Performance in the Central Nervous System and Cross-species Translatability; **Sean Gross– Abs # 992**

Characterization of engineered AAV capsids from different HEK293 cell culture fractions, crude lysate versus cell pellet material; **Heidy Morales – Abs # 529**

Alternative Plasmid Designs Including Two Plasmid Transfection Systems for Improved Production and Packaging of Engineered AAV Capsids; **Lysa-Anne Volpe – Abs # 530**

Separation of Empty and Full Engineered Adeno-Associated Virus Capsids Using a Weak Anion Exchanger; **Varun Gejji – Abs # 1038**

CAPSIDA BIOTHERAPEUTICS

Our Pipeline is Making the Impossible Possible

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