Systemic Gene Therapy CAP-002 Demonstrates Potential for Disease-Modifying Treatment of Seizures and Motor and Cognitive Deficits of STXBP1-DEE Using an Engineered, CNS-Targeted AAV

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Founder, Chief Research and Innovation Officer

Capsida Biotherapeutics

ASGCT May 14, 2025

Disclosures

- Nicholas Flytzanis, Ph.D. is an **employee of Capsida Biotherapeutics, Inc.**

- This Presentation contains information regarding the research and development programs of Capsida Biotherapeutics, Inc. that are based on or derived from preclinical data. Clinical trial results may differ. Capsida does not have an approved therapy presently available for *STXBP1* Developmental and Epileptic Encephalopathy, nor is there any promise or guarantee that Capsida's research and development will produce any potential therapy in the future.

Solving the Challenges of Gen-1 Genetic Medicines

	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 delivery 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

*For more details, see Abstract #93; Wednesday May 14, 2:45-3:00p in NOLA Theater C presented by Nick Goeden

Next-generation Genetic Medicines Company

Unlocking the full potential of gene therapy for all

Wholly-owned Pipeline

Two clinical programs in 2025

CAP-002: STXBP1-DEE
- ✓ IND clearance
- ✓ ODD granted

CAP-003: PD-GBA[1]
- Human POC in Q4

Third clinical program in 2026

CAP-004: Friedreich's ataxia[2]

Fully-integrated Capabilities

- » **Capsid engineering**
- » **Cargo optimization**
- » **Clinical development**
- » **In-house GMP manufacturing**
- » **Protected by expansive IP portfolio**

External Validation

Strategic partnerships

abbvie » 1st AbbVie opt-in achieved

Lilly Prevail THERAPEUTICS — A Wholly Owned Subsidiary of Eli Lilly and Company

CRISPR THERAPEUTICS®

Contract manufacturing

KATE THERAPEUTICS — A NOVARTIS COMPANY

Capsida is the first genetic medicines company with FDA IND clearance for an engineered IV-delivered gene therapy that crosses the blood-brain-barrier and detargets liver

[1]Abstract #1435, Wednesday Poster Session, presented by Kim McDowell, Ph.D.
[2]Abstract #75, Wednesday 1:45-2 pm, presented by Celeste Stephany, Ph.D.

STXBP1 Developmental and Epileptic Encephalopathy

Disease Background

- DEE (like LGS and Dravet) with no approved treatments
- Seizures, developmental delays, and motor impairment
- ~5,000 patients in US and Europe
- Genetic validation and potential for FDA approval after Ph2

CAP-002

- ✓ First and best in class IV-administered program
- ✓ Industry-leading brain wide STXBP1 expression
- ✓ Potential for correction of all phenotypes
- ✓ Safety demonstrated in GLP-Toxicology study in NHPs, including liver and DRGs
- ✓ Successful IND clearance and ODD granted
- ○ Q2 Fast Track filing

CAP-002 IND cleared, Orphan Drug Designation was granted, and SYNRGY clinical trial start up activities have initiated

Background on STXBP1 Function

STXBP1 Function & Disease Etiology

- STXBP1-DEE is an autosomal dominant disorder caused by *de novo* heterozygous mutations
- STXBP1 (Munc18-1) is present in *every* neuron and synapse in the CNS and mediates synaptic vesicle exocytosis
- STXBP1 binds syntaxin-1 and helps scaffold correct formation of SNARE complexes
- Reduced STXBP1 protein results in dysregulated synaptic vesicle release and impaired neuronal communication

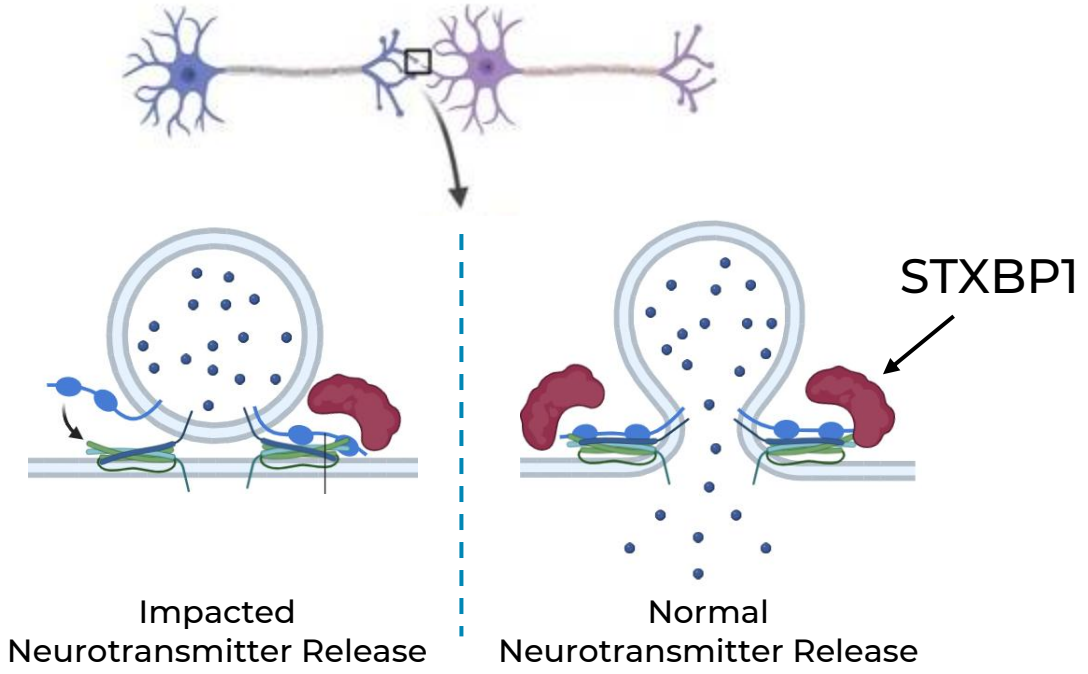


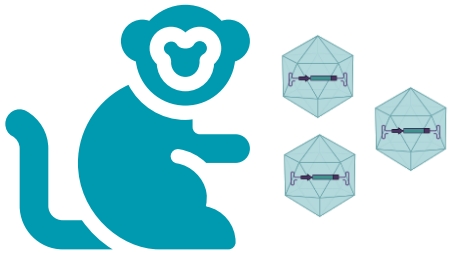
Figure created with BioRender.com

Dysregulated neuronal communication due to *STXBP1* haploinsufficiency results in the major clinical features of the disorder: seizures and motor and cognitive deficits

Capsida's Approach to Drug Development

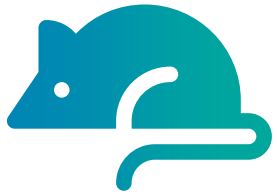
Capsida's proprietary drug development begins and ends with studies in NHPs, supporting identification of best-in-class capsids and potential therapies

Capsid Engineering
- Identify capsids with improved CNS tropism in NHPs

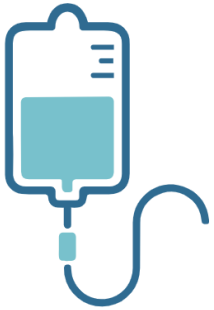


In Vitro Model
- Confirm CAP-002 corrects deficits in human STXBP1 diseased neurons

Mouse Model
- Define efficacy threshold of *hSTXBP1* expression in Stxbp1+/- mouse model to support prospect of direct benefit



Manufacturing
- In-house vector production and Process & Analytical Development, supporting cGMP-MFG



GLP Toxicology
- Confirm CAP-002 safety and *hSTXBP1* expression level to support clinical dose selection

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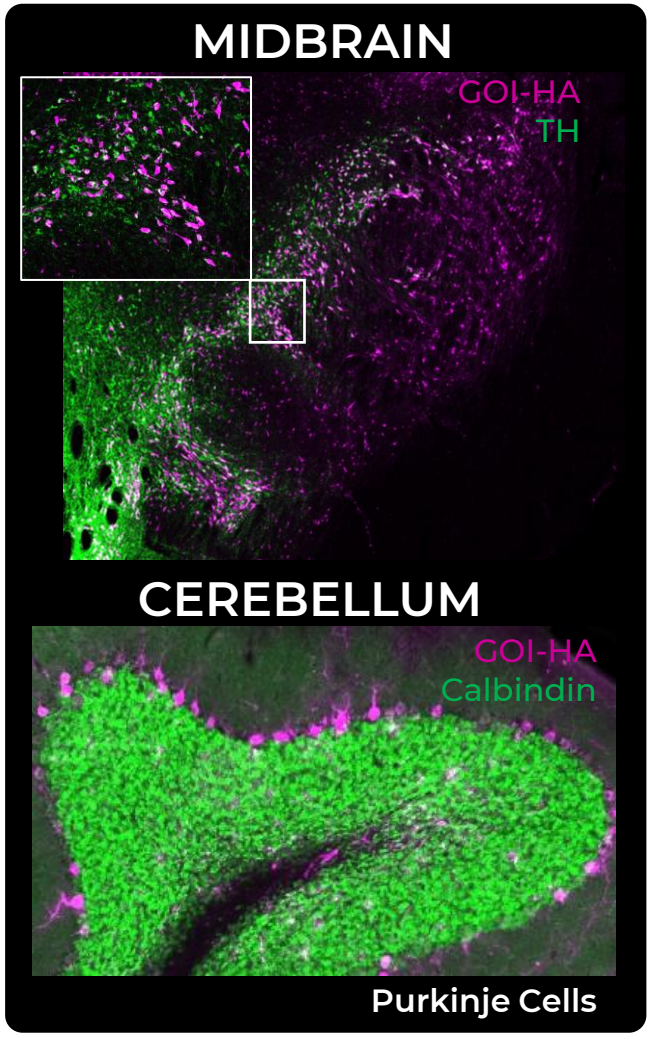
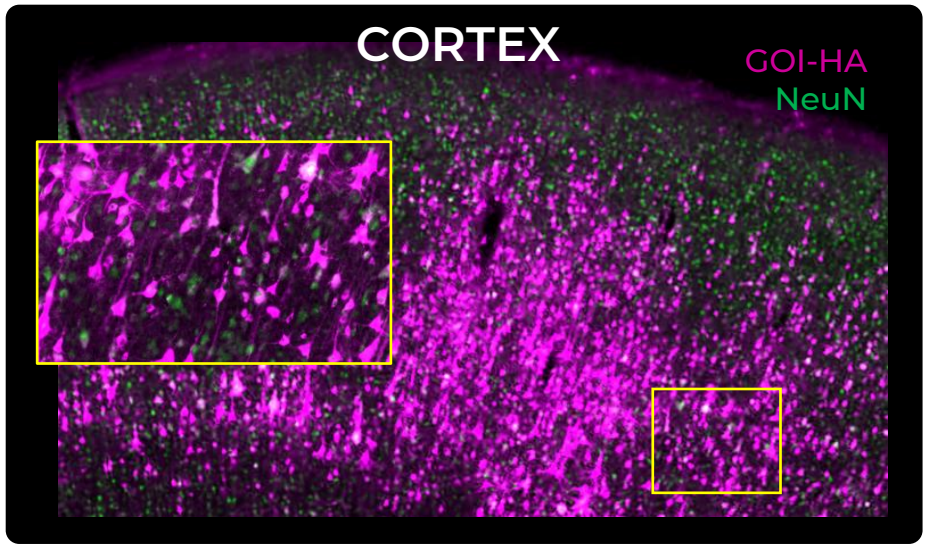
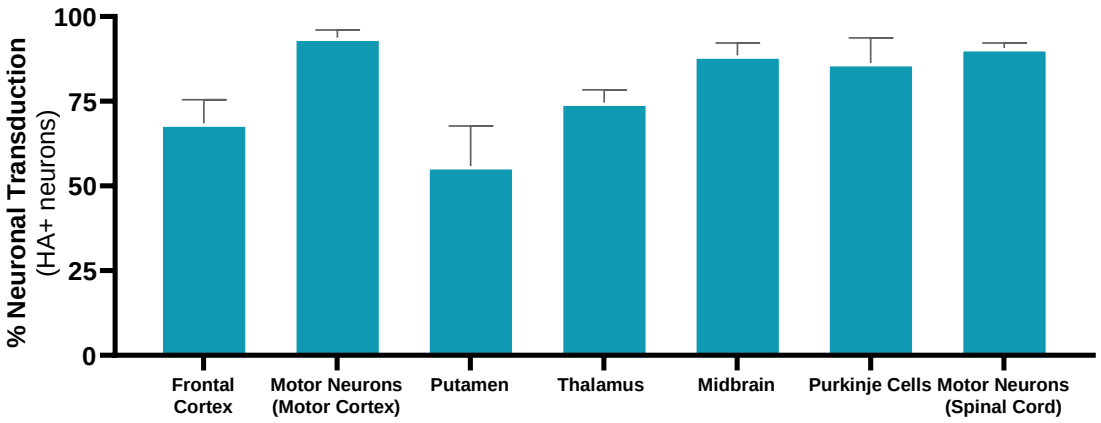
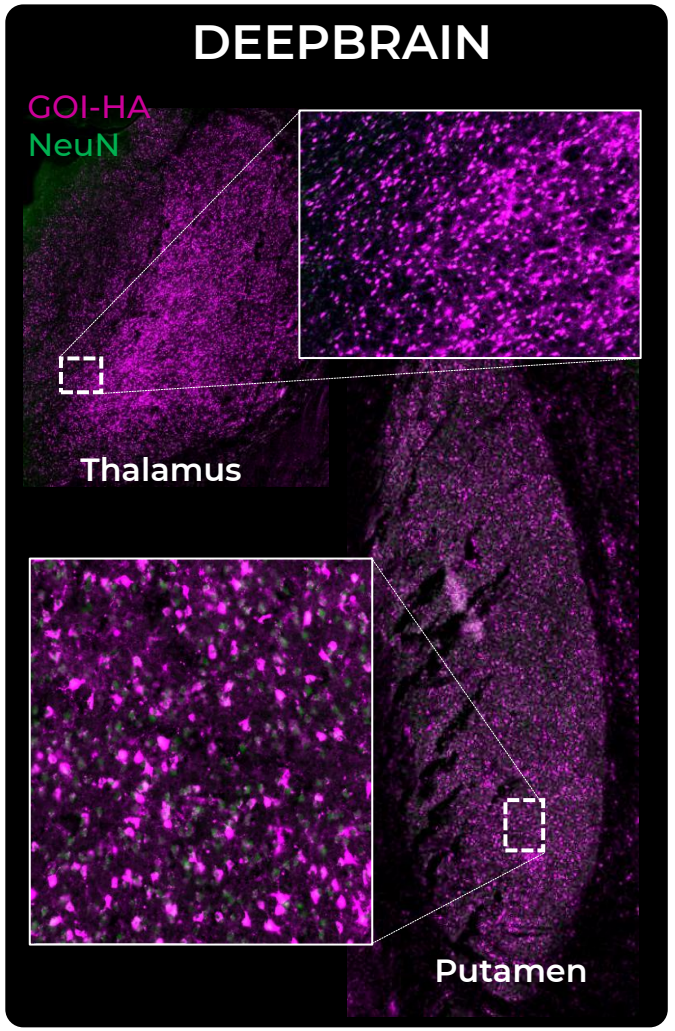
Capsida's Novel Engineered Capsids Transduce the Majority of Neurons across the Brain



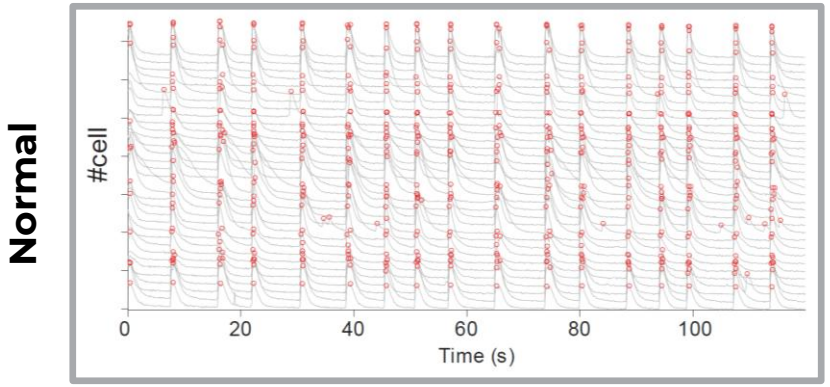


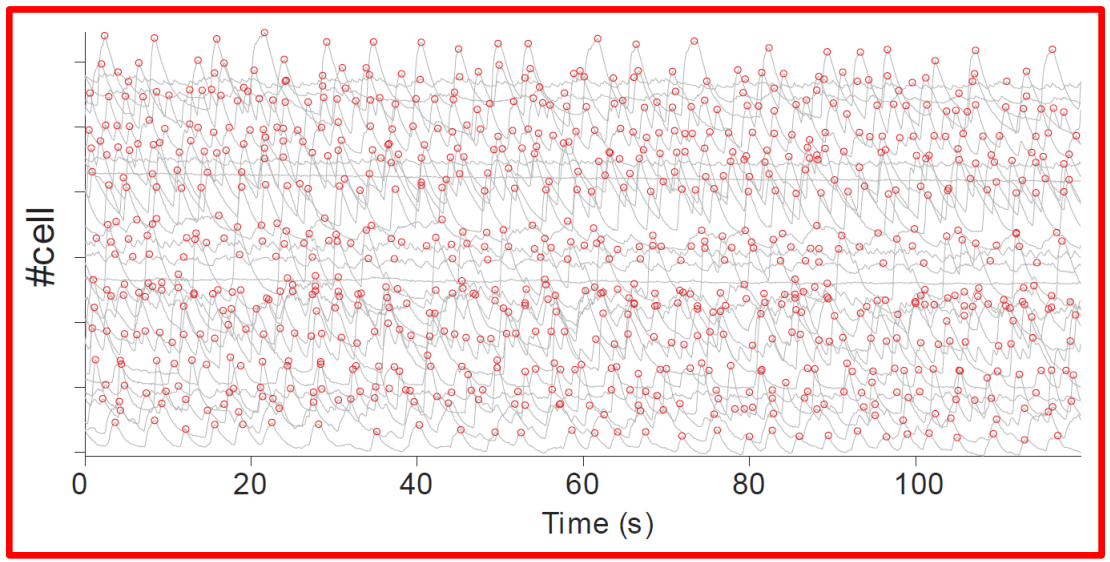




Capsid: CAP-002 capsid; **Cargo:** GOI-HA; **Dose:** 2.5E13 vg/kg; **In-life:** 4 weeks; **Species/Age:** Cynomolgus macaques, ~32-38 mo

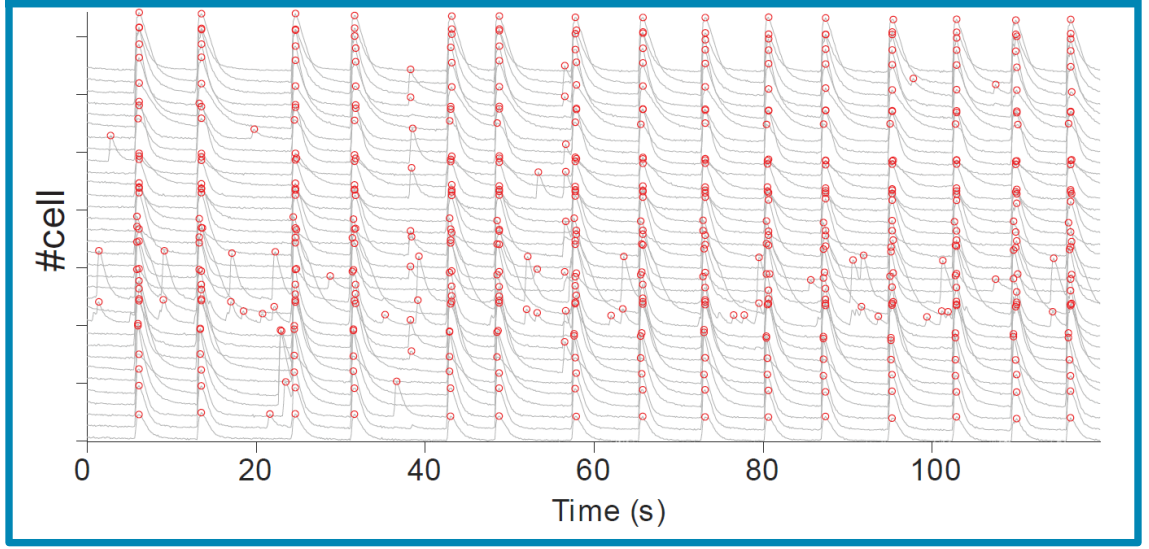
CAP-002 Restores Normal STXBP1 Expression and Neuronal Firing in Human Knock Out Neurons





***STXBP1* Knock Out**

CAP-002 restores neurons to normal firing



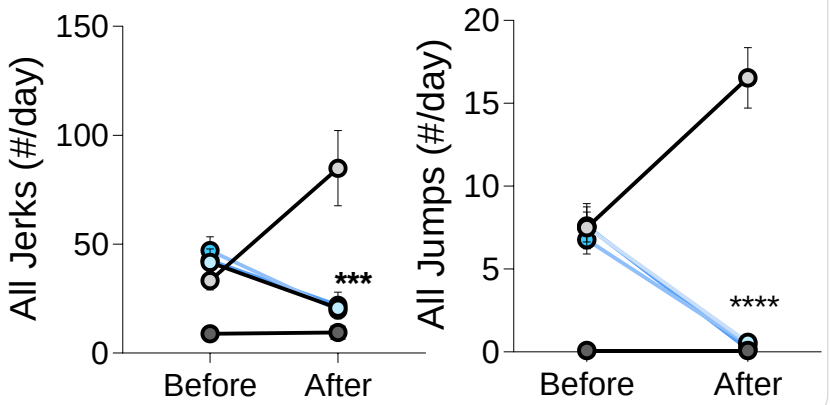
***STXBP1* Knock Out with CAP-002**

Generated in collaboration with Neurospector, a CRO established by Matthijs Verhage's laboratory at VUmc Research BV, part of Foundation Stichting Amsterdam UMC

Brain-wide STXBP1 Expression Enables Dose-Dependent Correction of Seizures, Cognitive, and Motor Dysfunction in Mouse Model

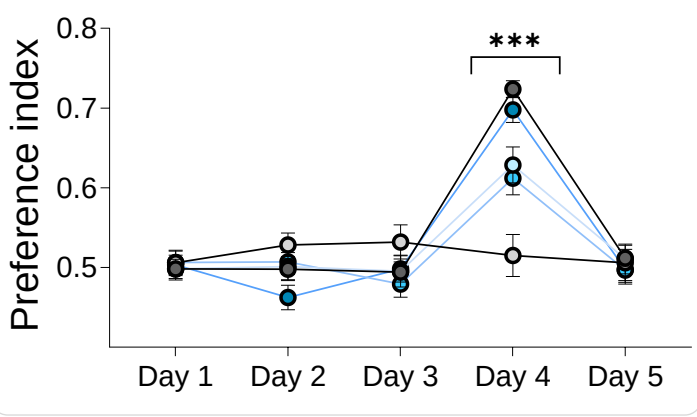
Epilepsy

Myoclonic Seizures



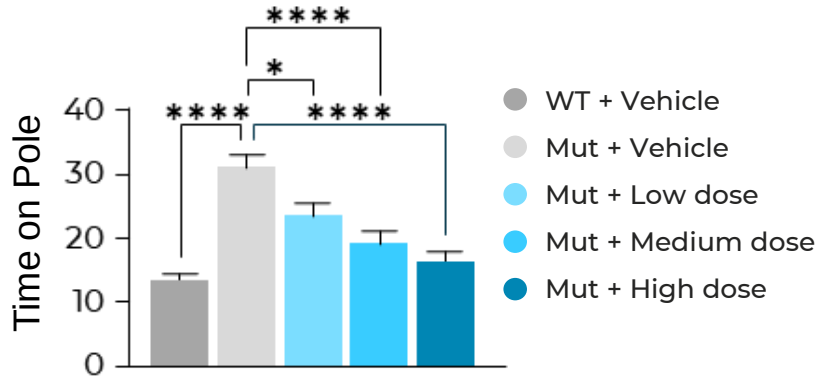
Cognitive Dysfunction

Novel Object Recognition



Motor Dysfunction

Vertical Pole

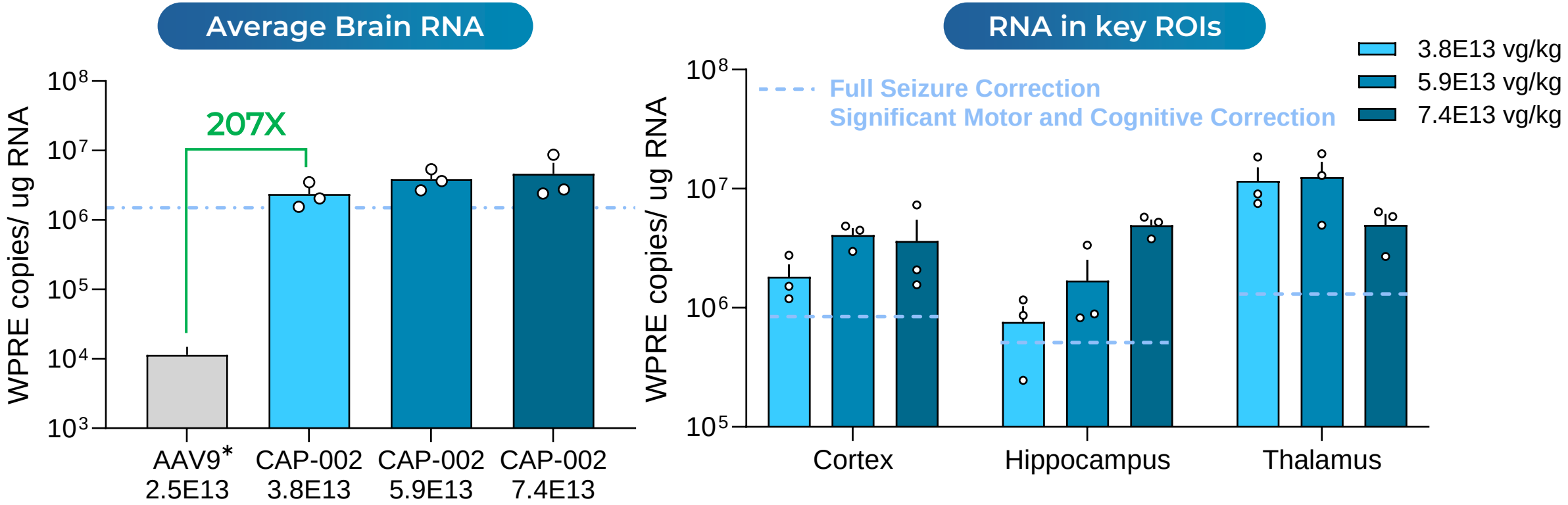


Difference from Het (Mut) + VEH: * $p < 0.05$, *** $p < 0.001$, **** $p < 0.0001$.
Seizures and Vertical Pole: Kruskal-Wallis Test with Dunn's Multiple Comparisons Test; NOR: 2-way ANOVA with Tukey's Multiple Comparisons Test

- IV delivery of a surrogate capsid with *hSTXBP1* achieves significant and long-lasting correction of all phenotypes at all doses, with no histopathology findings
- Low dose provides meaningful correction, defining levels of *hSTXBP1* needed for prospect of direct benefit
- Reversal of symptoms in mature mice demonstrates the disease-modifying potential of this therapy

Mouse data generated in collaboration with lab of Mingshan Xue, Baylor College of Medicine

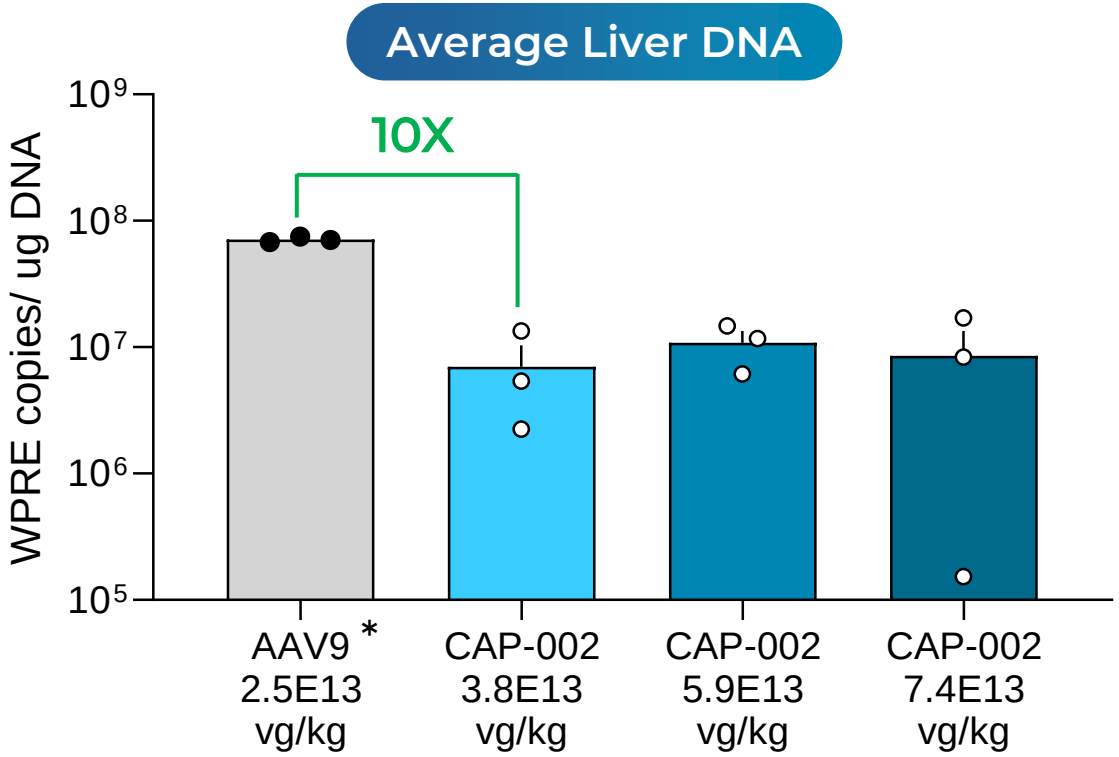
GLP Tox Study Shows Durable Expression of hSTXBP1 that Exceeds Levels Expected to Improve Disease Symptoms

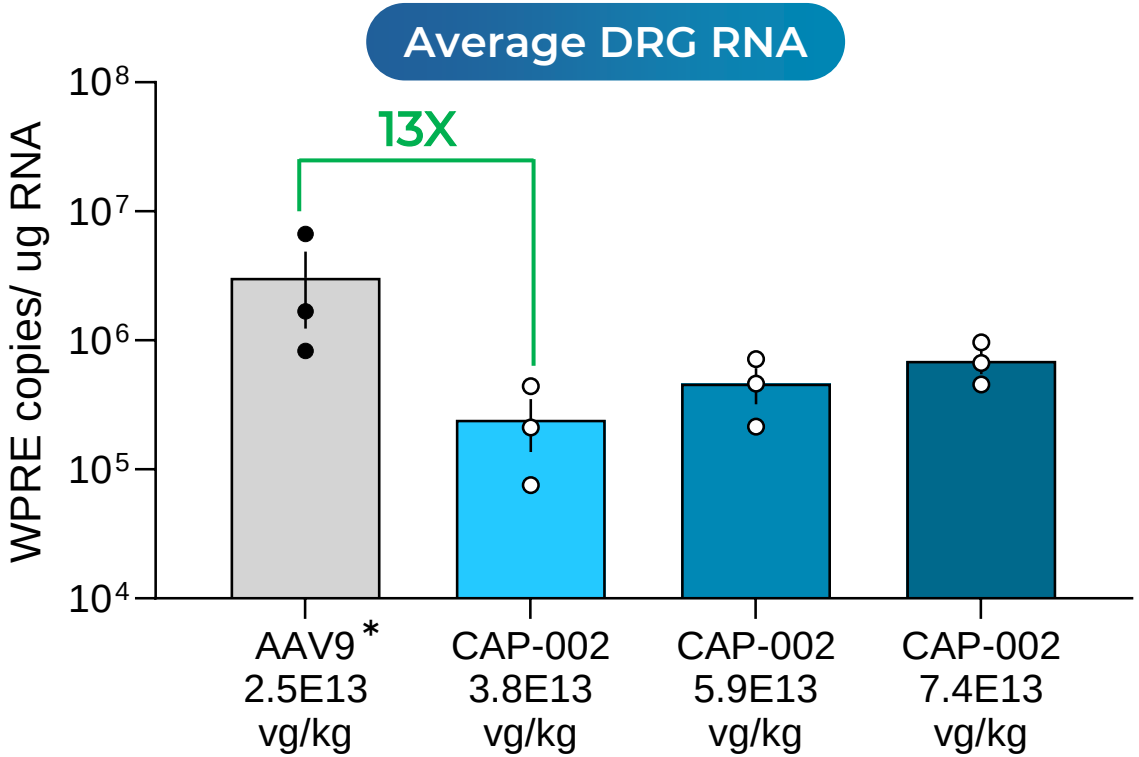


- Mouse pharmacology study defines cargo RNA thresholds associated with meaningful improvement of all disease domains
- All doses of CAP-002 surpass this efficacy threshold in NHPs. The 5.9E13 and 7.4E13 vg/kg doses achieve RNA levels expected to provide further improvements to motor and cognitive function than 3.8E13 vg/kg

* Historical IV-delivered AAV9 2.5E13 vg/kg (non-STXBP1 cargo control); 4 weeks expression

CAP-002 is Well-Tolerated and Demonstrates Robust Liver and DRG Detargeting Compared to AAV9





- Despite being delivered at higher doses, CAP-002 remains detargeted compared to AAV9 in liver and DRGs
- CAP-002 is safe and well-tolerated in GLP-Tox, with no adverse clinical pathology or histopathological findings throughout the CNS, DRGs, or peripheral organs (including liver) up to CAP-002 NOAEL, 7.4E13 vg/kg

* Historical IV-delivered AAV9 2.5E13 vg/kg (non-STXBP1 cargo control); 4 weeks expression

CAP-002 Clinical Material Produced Using In-House cGMP Manufacturing Capabilities

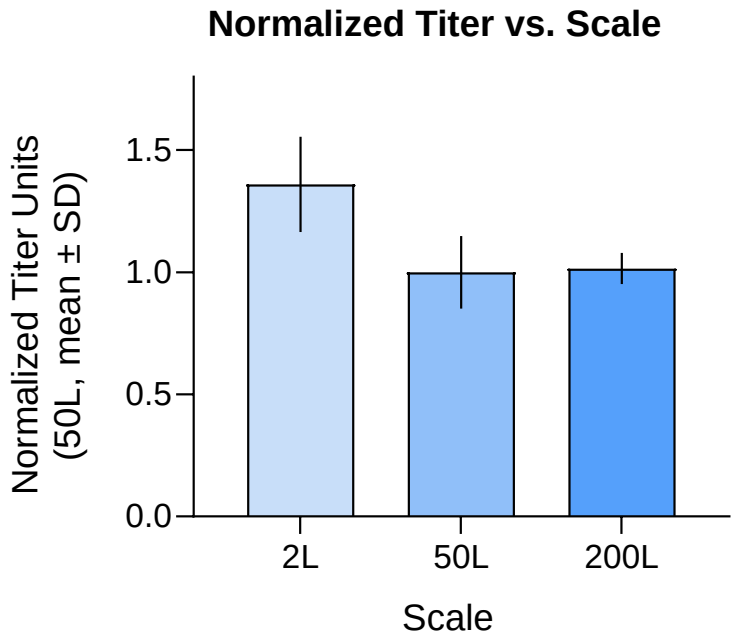
End-to-end **manufacturing** capabilities enable control of quality, timelines, and costs

Manufacturability

Characteristic	Industry Standard AAV9	CAP-002
Productivity in crude lysate	1E11 vg/ml	6.2E11 vg/ml
Packaging (Empty/Full)	>70%	~90%
Aggregation	< 10%	5%
Overall Recovery	~25%	36%

Capsida's lead capsid outperforms AAV9 with higher yield, improved purity, and greater recovery, overcoming key manufacturability hurdles for engineered AAVs

Scalability



In-house PD and cGMP manufacturing capabilities enable seamless scale-up from preclinical to clinical supply

CAP-002 has excellent yields and meets clinical supply needs

CAP-002 Phase 1/2a SYNRGY Study

Potential for approval after Phase 2 study

Clinical Ph1/2a Planning

Population

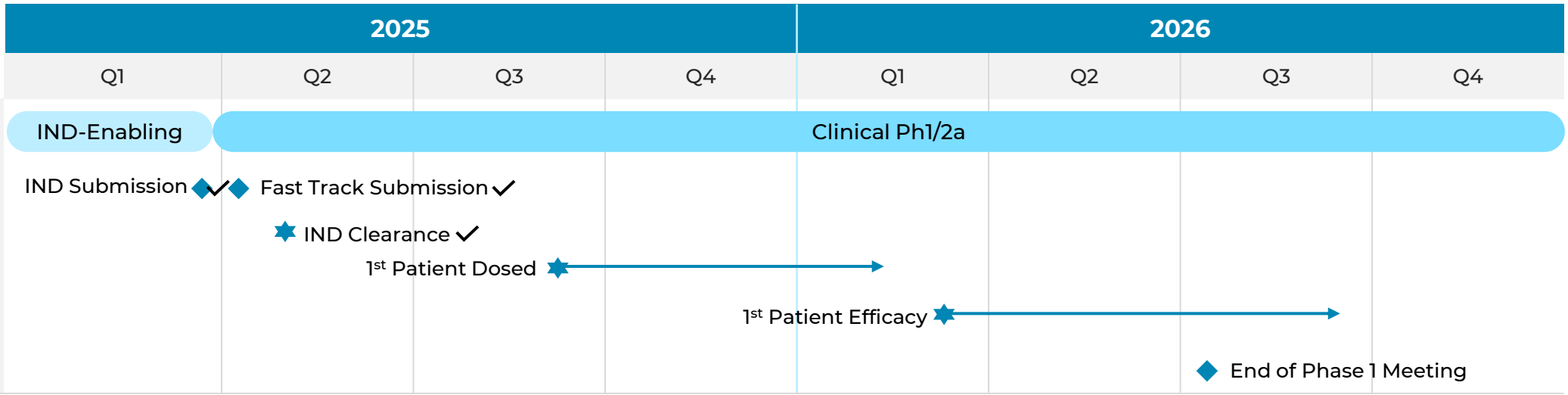
- 18 months – 7 years inclusive
- Potential expansion to broader ages
- Ph1: 6 patients

Key Measurements

- Safety
- Motor, language, neurocognitive, seizure, and EEG
- Clinical scales consistent with STARR natural history study

Plan to leverage ODD and other designations to accelerate approval

CAP-002 (STXBP1-DEE) Program Overview



EEG = electroencephalogram; STARR = STXBP1 Clinical Trial Ready

CAP-002 is first-in-class treatment for STXBP1-DEE

- CAP-002 utilizes a novel engineered capsid that efficiently crosses the BBB in NHPs after IV administration and delivers the *hSTXBP1* therapeutic cargo to neurons brain-wide
- The potential efficacy and safety of the *hSTXBP1* therapeutic cargo and CAP-002 is demonstrated in nonclinical studies:
  - **Knockout Human Neurons → S**TXBP1 expression and functional correction in target cell-type
  - **Heterozygous Mouse Model →** establishes cargo RNA levels required to enable phenotypic correction
  - **Wild-Type NHPs →** supports safety and clinical dose selection based on cargo RNA levels
- Capsida has characterized a human receptor that binds our engineered capsids; this receptor has complete homology between humans and macaques in the predicted binding pocket
- **CAP-002 received FDA IND clearance**
- **SYNRGY Phase 1/2a clinical trial start-up activities have initiated**

CAPSIDA BIOTHERAPEUTICS

Our Pipeline is Making the Impossible Possible

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