Identification of Multiple Novel Blood-Brain-Barrier Receptors for CNS Gene Therapy and Other Drug Modalities via an Integrated AAV Capsid Engineering Platform

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Disclosures

- Nick Goeden, 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, Parkinson's disease associated with GBA mutations, or Friedreich's ataxia, 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 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

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[1]
- IND clearance
- ODD granted

CAP-003: PD-GBA[2]
- Human POC in Q4

Third clinical program in 2026

CAP-004: Friedreich's ataxia[3]

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 #123; Wednesday, 3:45-4:00p in NOLA Theater B presented by Nicholas Flytzanis, Ph.D.
[2]Abstract #1435, Wednesday Poster Session, presented by Kim McDowell, Ph.D.
[3]Abstract #75, Wednesday, 1:45-2 pm, presented by Celeste Stephany, Ph.D.

Capsida is Uniquely Positioned to Lead Gene Therapy

Capsid Engineering Scale

Fully industrialized and roboticized platform

Screening capabilities across cell types in NHPs and human cells

CNS Tropism

>99% specific to neurons at the capsid level

>70% neurons transduced

Broad IP portfolio protecting capsids and capsid/cargo

Peripheral De-targeting

>16x liver detargeted and >50x DRG detargeting

Superior off-target safety profile

Broad IP portfolio protecting de-targeting

Safe Therapeutic Expression

Expression levels in NHPs with potential to achieve full disease correction

Safety demonstrated in GLP toxicology studies for both CAP-002 and CAP-003

Clinical Translatability

Identified and patented novel human receptor with complete homology in NHPs and humans

Validated expression in NHPs including primates >20 years old

Manufacturability

In-house process development and GMP manufacturing

Productivity surpassing AAV9

Quality specs exceeding FDA requirements

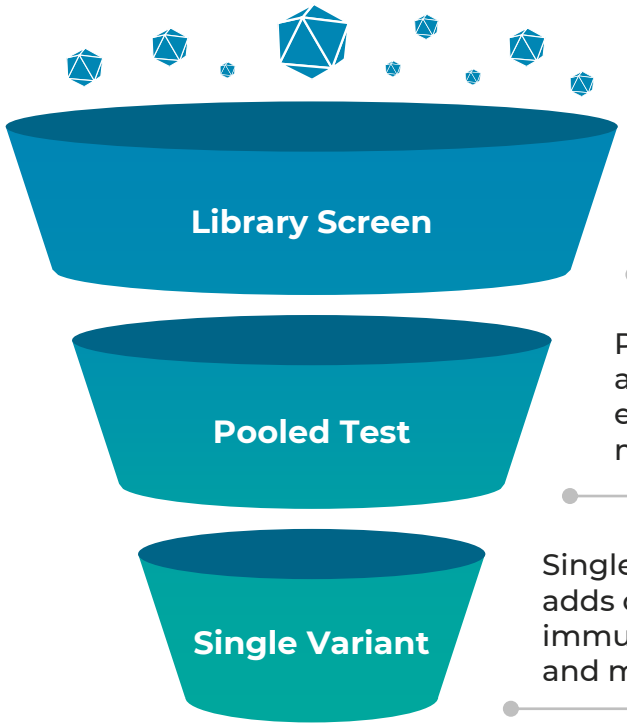
Only Capsida has created all the capabilities and results needed to deliver on the promise of gene therapy

GMP = Good Manufacturing Practice

Capsida Has Built a Field-leading Capsid Engineering Platform

High-throughput Automated Process Identifies Multiple Capsid Families with Efficient CNS Targeting

Evolving Capsids to Meet **Target Capsid Profile**



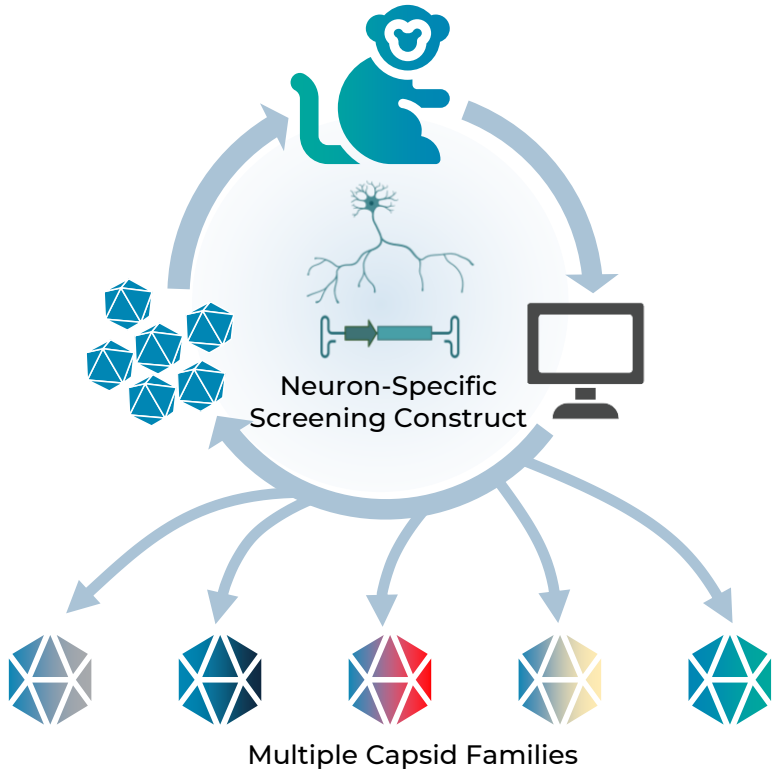
Billions of variants screened via Next Gen sequencing for enriched DNA and RNA

Pools with tens of variants adds assessment of protein expression and preliminary manufacturability

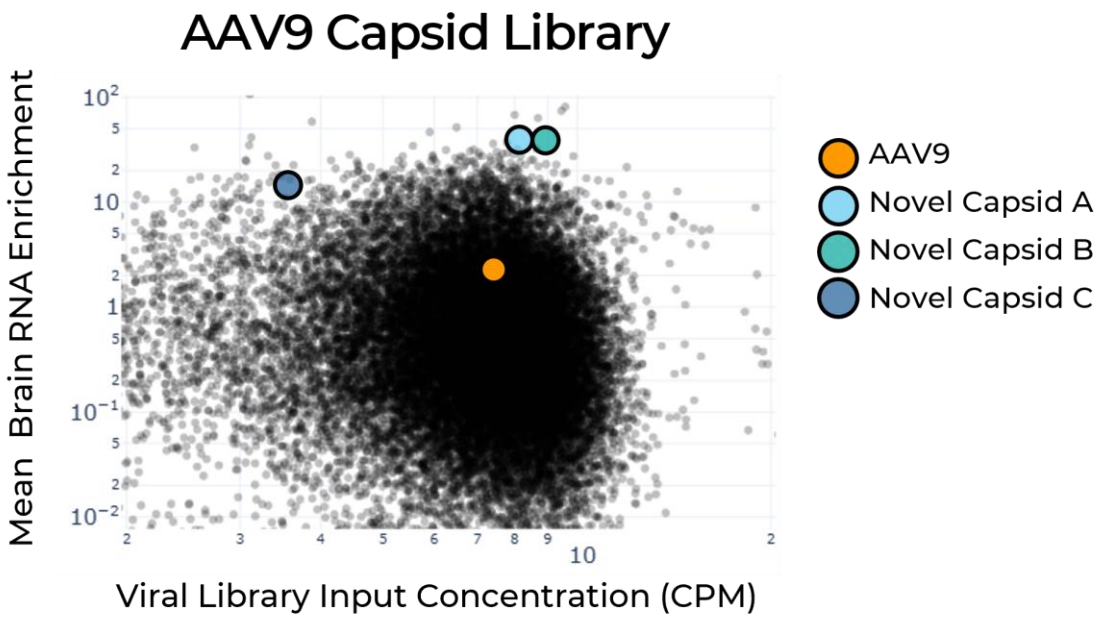
Single variant characterization adds cell-type distribution, immunogenicity / toxicity profile, and manufacturing scalability

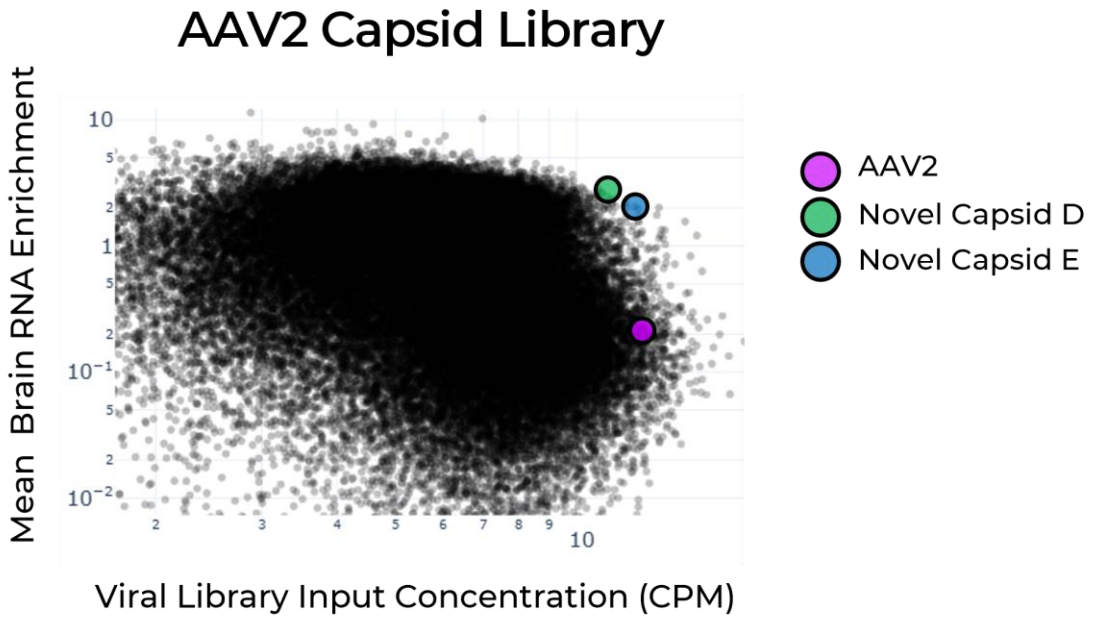
IND-enabling

Iterative Screenings Yield **Multiple High-performing** Capsids



Capsida's Platform Delivers Multiple Novel Capsids that Exceed Target Capsid Profiles for CNS



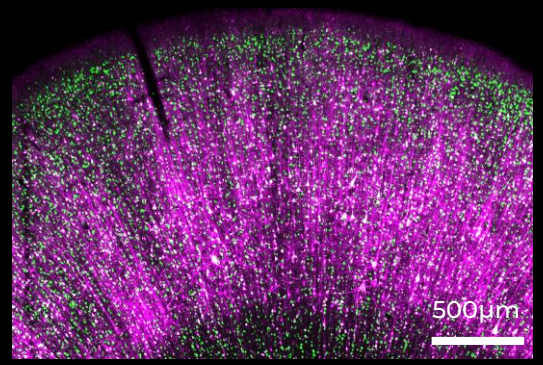


Multiple independent screens have identified >5 distinct novel capsids with breakthrough CNS performance

Lead Capsid Transduces Majority of Neurons Throughout the CNS Across 3 Wholly-Owned Programs at Low E13 vg/kg Dose

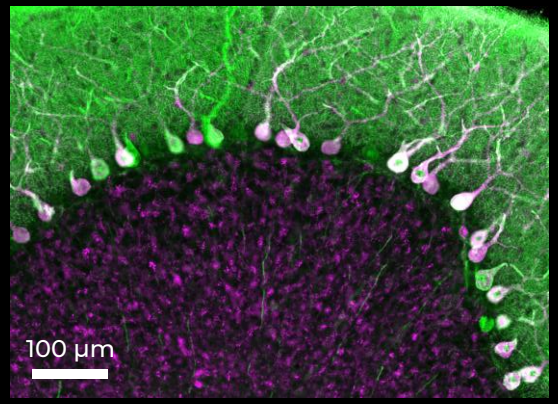
Cortex: Genetic Epilepsy Motor neurons and deep cerebellar nuclei: Friedreich's Ataxia

Frontal Cortex



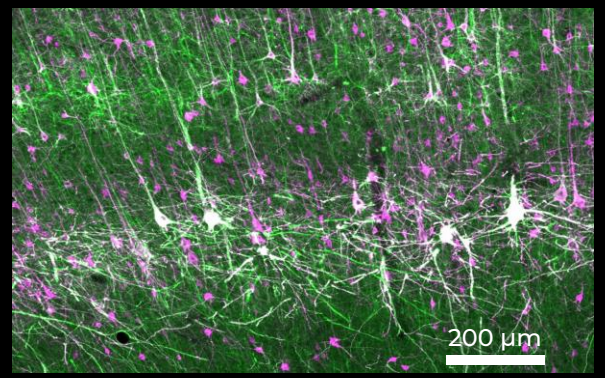
HA-GOI NeuN

Cerebellum



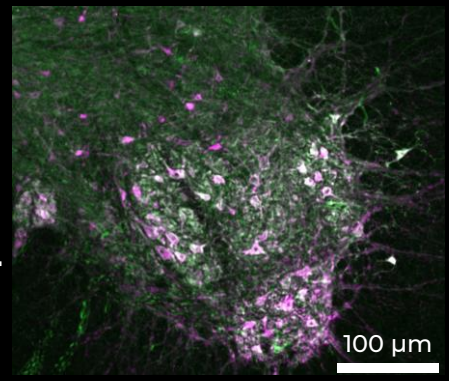
HA-GOI CALBINDIN

Motor Cortex



HA-GOI SMI32

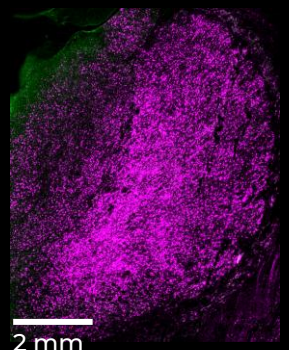
Spinal Cord



HA-GOI SMI32

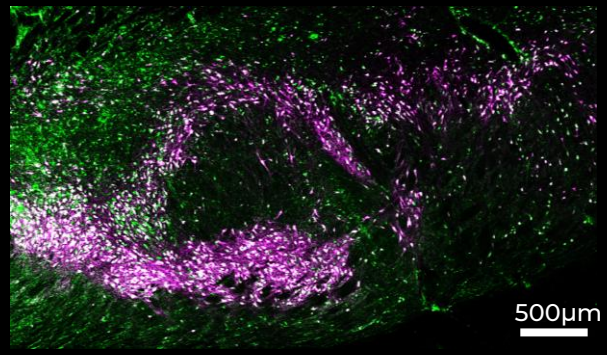
Deep brain structures: Parkinson's Disease

Thalamus

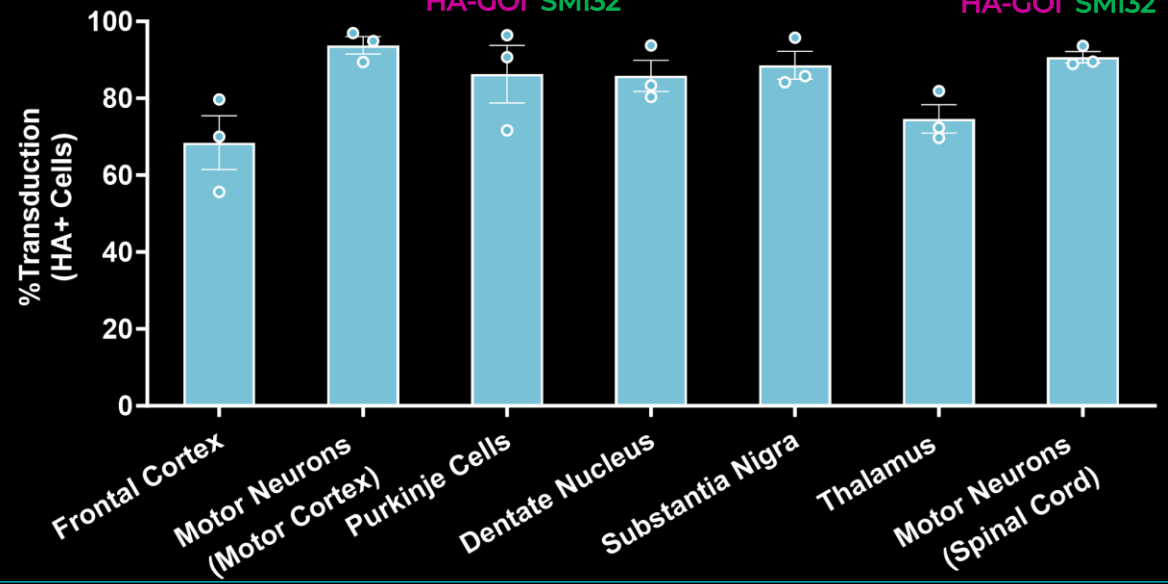


HA-GOI NeuN

Substantia Nigra



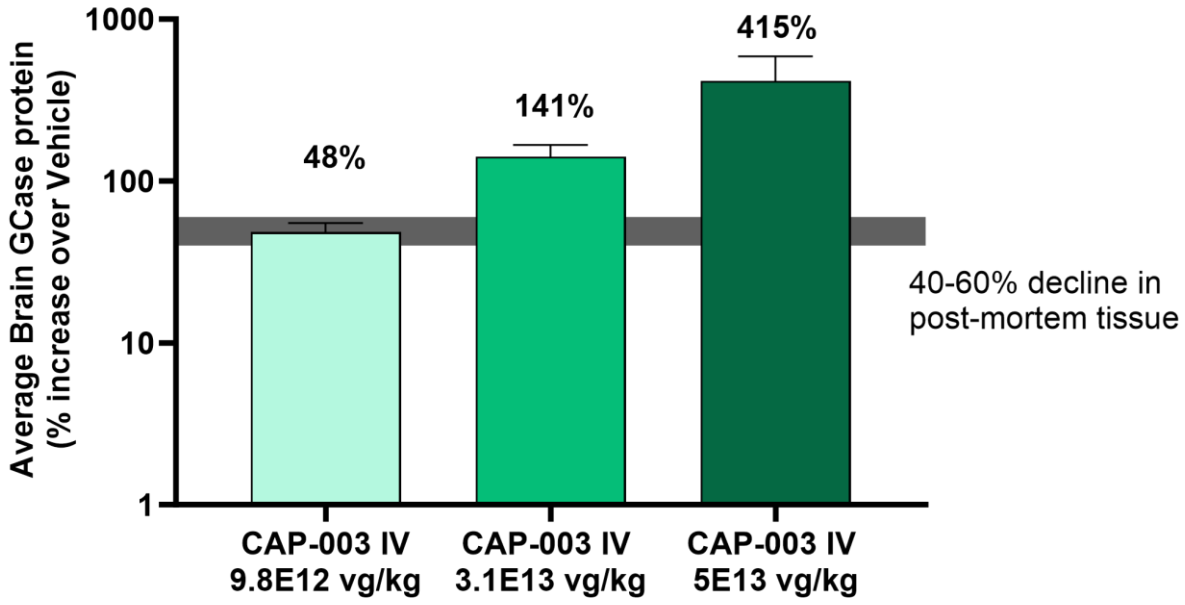
HA-GOI TH



Lead Capsids Enable Robust Therapeutic Expression

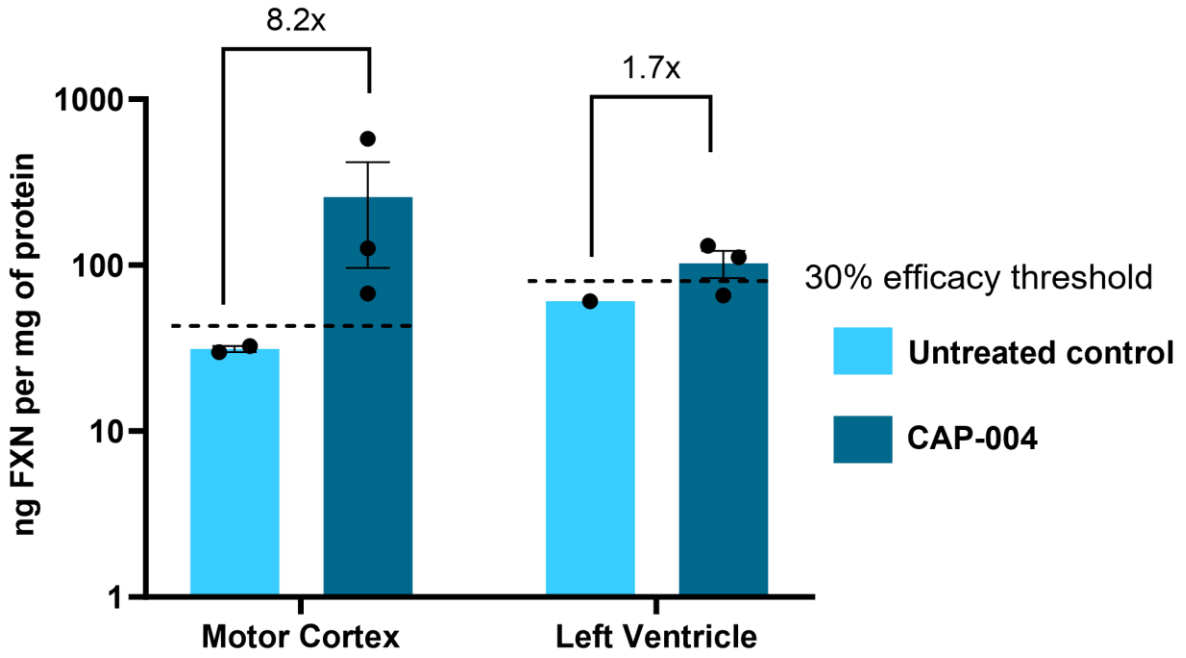
CAP-003

GCase Protein Expression



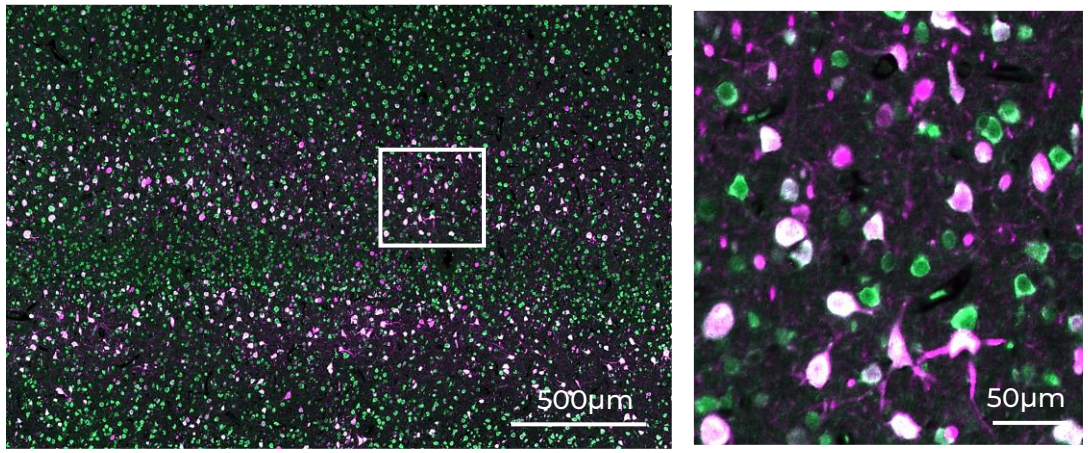
CAP004

Frataxin Protein Expression



Therapeutic expression levels exceed clinically relevant thresholds – IND Clearance of CAP-002 provides the strongest validation of lead capsid's therapeutic potential

Neuronal-Specific Transduction Enables Safer and More Effective CNS Gene Therapies

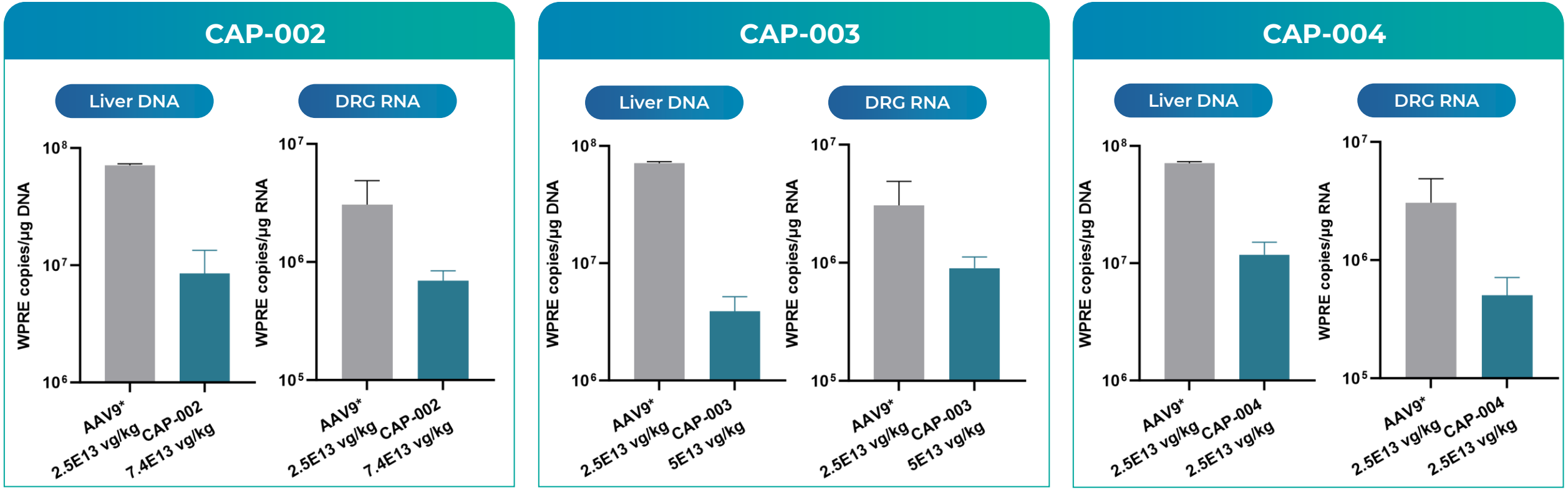


Capsida's lead CNS capsid achieved **high neuronal specificity**, **minimizing off-target transduction** and improving the safety profile of CNS-targeted gene therapies.

- **99% neuronal specificity** across the CNS
- Specificity achieved via **cell type-specific selection pressure**
- **Minimized off-target cell transduction** reduces toxicity risk
- Achieved efficient, cell-type-targeted delivery across 3 programs

Neuron-specific transduction across 3 wholly-owned programs improves safety and efficacy

Reduced Off-target Biodistribution Improves Safety Profile



- All three programs show peripheral detargeting from key off-target tissues (liver and DRG) of first-generation gene therapies using wild-type AAV
- No adverse clinical pathology or histopathological findings throughout the CNS, DRGs, or peripheral organs (including the liver) at all doses tested

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

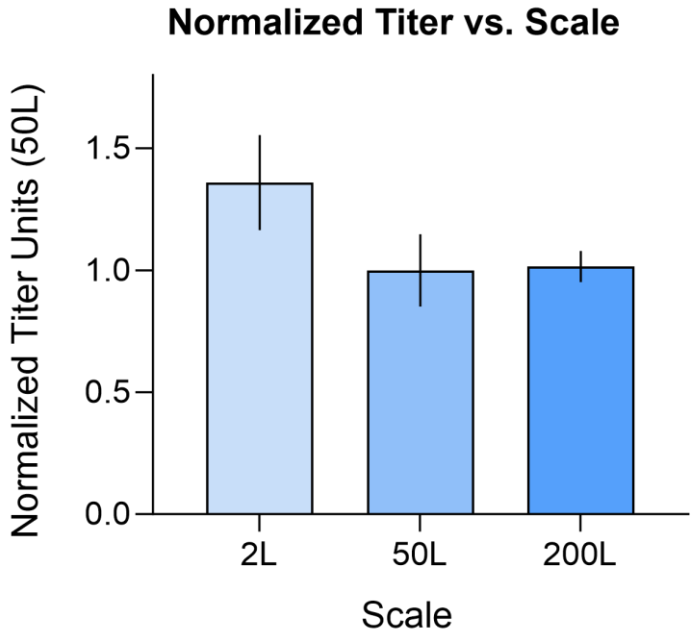
Capsida's Lead Capsid Has Favorable Manufacturability, Well Positioned for Clinical Success

Manufacturability

Characteristic	Industry Standard AAV9	Capsida Lead Capsid
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

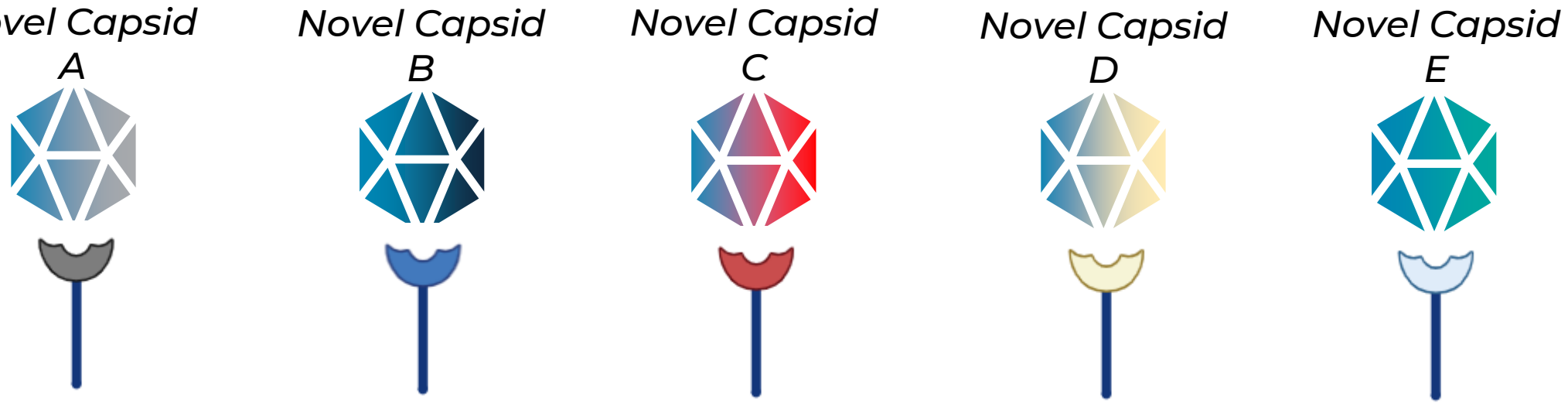
Scalability



In-house PD and GMP manufacturing capabilities enable seamless scale-up from preclinical to commercial supply

Clinical supply for CAP-002 and CAP-003 has been produced and released
Clinical trial start-up activities have initiated for CAP-002

Identification of Distinct Novel Receptors with High Cross-Species Conservation Significantly De-Risks Clinical Translatability



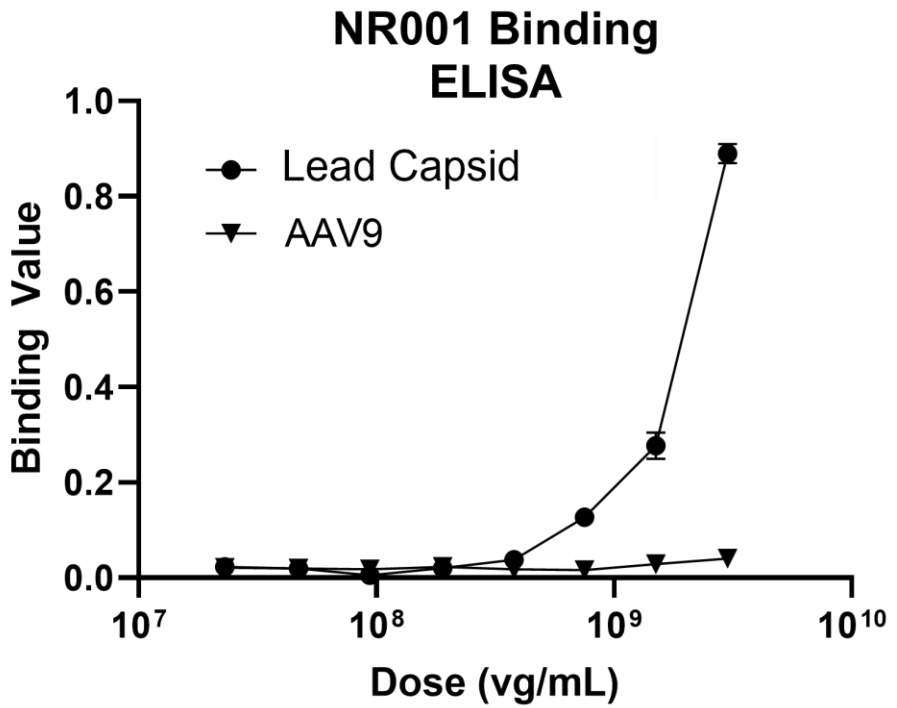
Sequence Identity to Human	NR001	NR002	NR003	NR004	NR005
NHP	96%	99%	96%	98%	93%

**Sequence identity is calculated across full protein and is not restricted to predicted binding site*

Capsida Biotherapeutics has successfully filed patents for all five of these groundbreaking novel receptors and is focused on further expanding the IP portfolio surrounding them

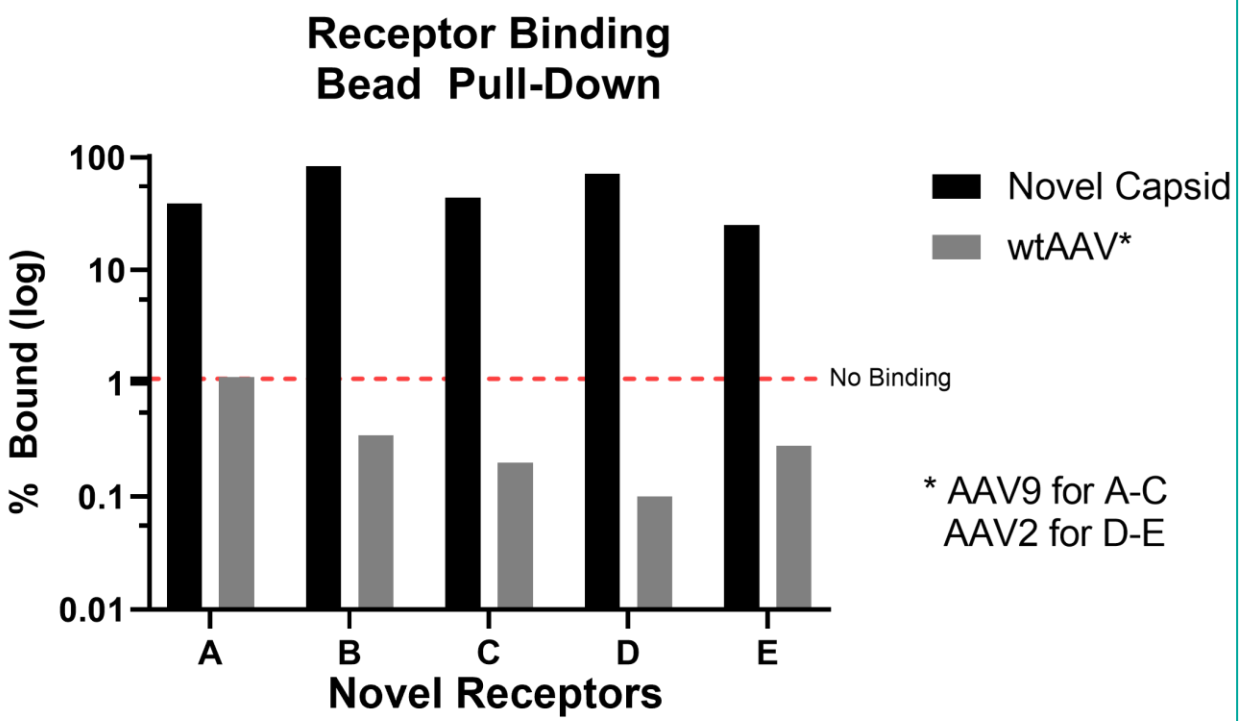
In Vitro Binding Platform Demonstrates Reproducible Capsid/Receptor Binding Data Consistent with Expression Profiles

Plate-Based Receptor Binding Detection



Binding also confirmed for NR002-5

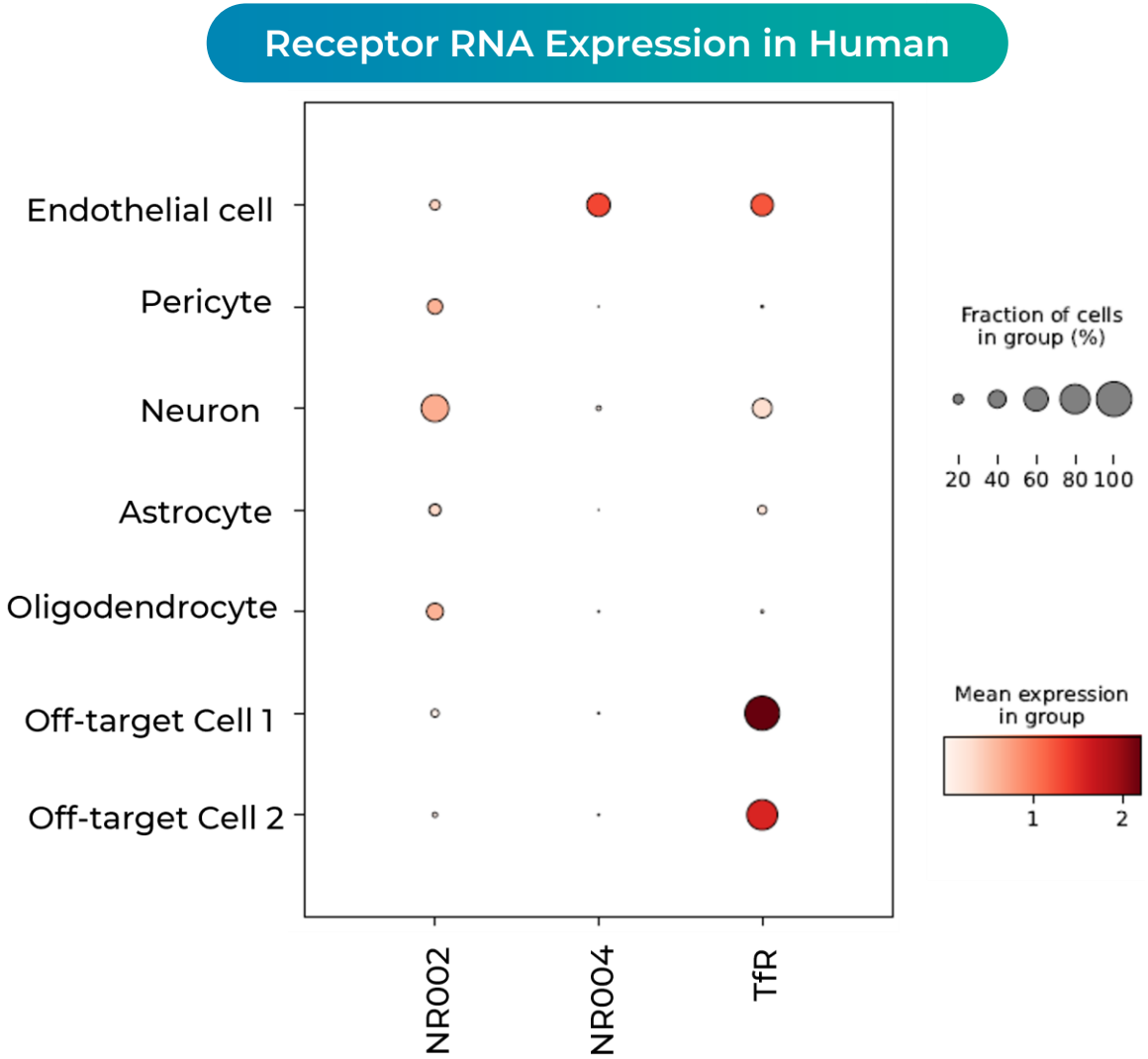
Bead-Based Receptor Binding Detection



Human and NHP ortholog binding confirmed

The predictive power of in vitro receptor binding is confirmed by AAV transduction in cell lines with receptor expression

Novel Receptors Highly Expressed in Neurons and Brain Endothelial Cells Enable More Specific Delivery to the CNS

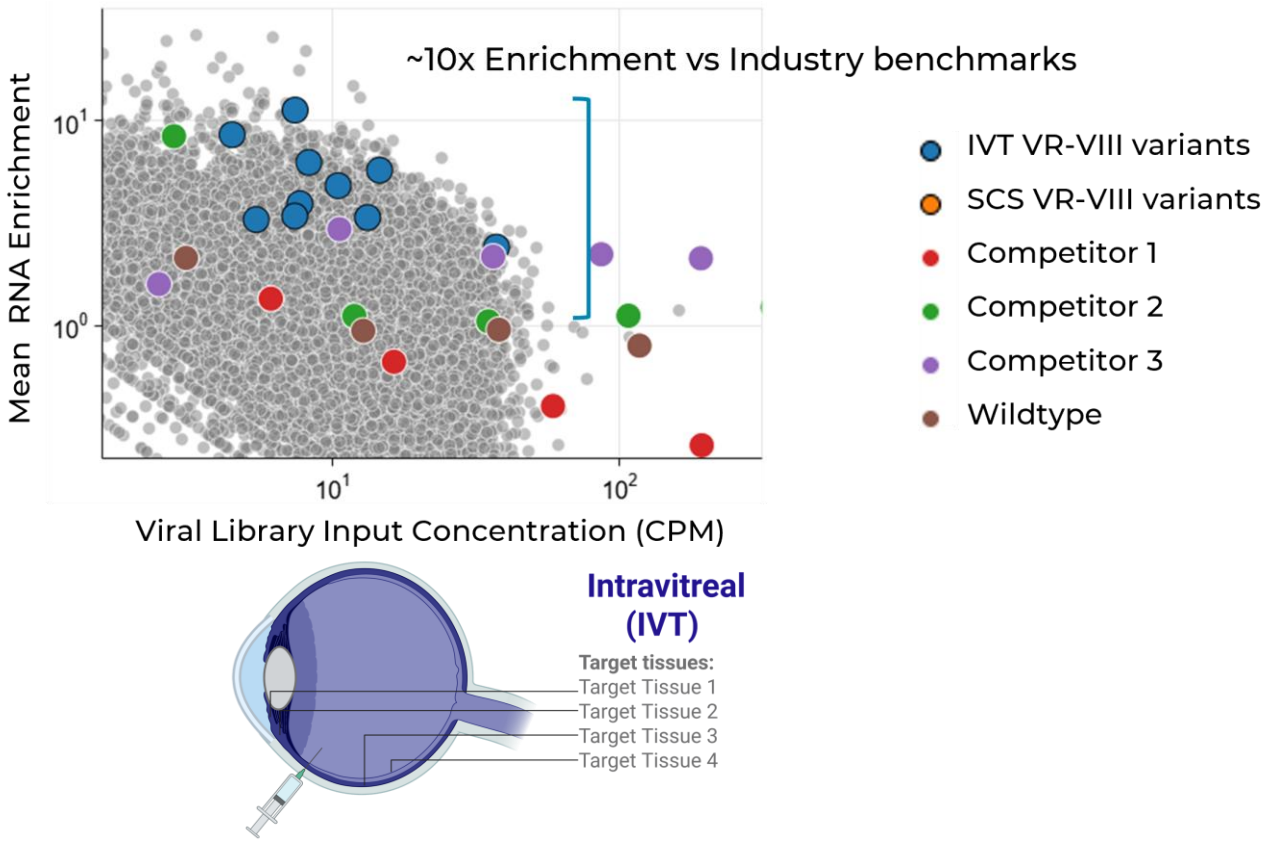


- **Improved safety profile**
  - Lower expression in off-target cell types relative to TfR
- **Differentiated CNS delivery mechanisms**
  - **NR004**: endothelial-specific
  - **NR002**: broad expression across CNS cell types, enabling intracellular delivery
- **Broad IP protection**

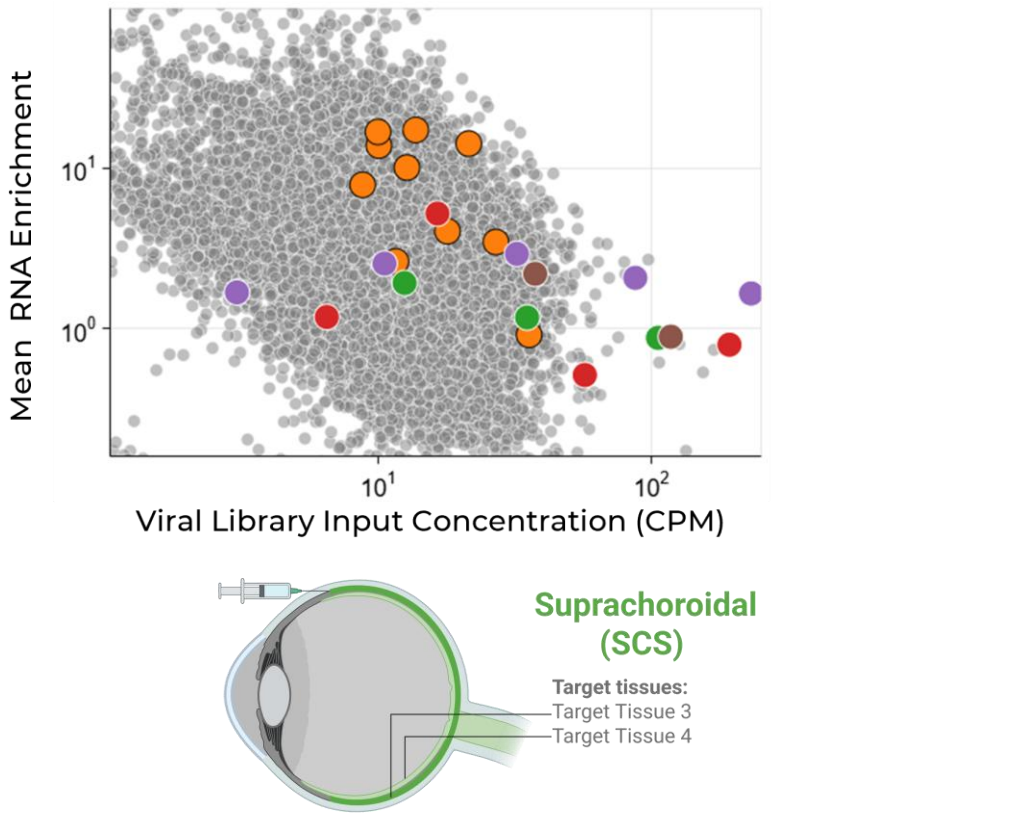
Engineered Ocular Capsids Poised to Be Best-in-Class

Our engineered capsids target multiple ocular tissues with differentiated enrichment profiles

Intravitreal (IVT) Injections in Ocular Tissue



Suprachoroidal (SCS) Injections in Ocular Tissue



Capsida's Platform Enables Rapid Entry Into New Therapeutic Areas

Summary

Built a **field-leading capsid engineering platform** that enables rapid, at-scale capsid discovery

Identified **> 5 breakthrough CNS capsids,** each leveraging a distinct mechanism, expanding the BBB-crossing playbook

Lead capsid drives **three differentiated CNS programs into the clinic**, with CAP-002 STXBP1-DEE having received **FDA IND clearance**

In-house GMP manufacturing ensures high-quality, scalable capsid production, accelerating development and enabling IND success

Expanded into ophthalmology with potential best-in-class capsids; broad IP portfolio and platform capabilities position us to enter any therapeutic area

Acknowledgements

Thank you to the entire Capsida team for your dedication and innovation.

Together, we're unlocking the power of gene therapy for all.

CAPSIDA BIOTHERAPEUTICS

Our Pipeline is Making the Impossible Possible

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