

**Apertura**  
GENE THERAPY

# Advancing CNS gene therapies with manufacturable AAV capsids and an FDA-integrated regulatory approach

**Jorge Santiago-Ortiz, PhD**

Vice President, CMC & Regulatory Affairs; Apertura Gene Therapy

**Advanced Therapies Week 2026**

**February 10, 2026**



# Brief Introduction



Jorge Santiago-Ortiz, Ph.D.

Vice President, CMC & Regulatory Affairs

Apertura Gene Therapy

[Linkedin.com/in/jsantiagoortiz](https://www.linkedin.com/in/jsantiagoortiz)

[jso@aperturagtx.com](mailto:jso@aperturagtx.com)

# A Translational Capsid Platform with a CNS Clinical Lead in 2H'26

## Highlights

### Receptor-mediated engineering platform

Yielded promising capsids targeting the CNS via TfR1, a well-characterized and clinically validated receptor on the blood brain barrier

### Expanding to neutralizing antibody evasion

Developing NAb technology to both Apertura capsids and non-Apertura capsids to allow dosing in seropositive patients

### Pipeline positioned to move rapidly to clinic

Projecting FIH data using TfR1 CapX in 2H 2026 and 1H 2027 for two rare disease groups using our capsid

### Externally validated capability

TfR1 CapX biodistribution and manufacturability have been independently confirmed by multiple external groups

## Apertura is the leader in receptor-mediated delivery.

We design capsids to target human receptors of interest that we believe will better translate into the clinic and unlock better tropism to the tissues we need to address in gene therapy. Our lead capsid targeting the CNS (**TfR1 CapX**) will have a significant value inflection point in 2H 2026 and 1H 2027 when it enters the clinic. This capsid was designed as an improvement upon BI-hTfR1, which was the first capsid targeting the human transferrin receptor (TfR1) and described in the 2024 Science publication. This receptor has been extensively used by other non-capsid drug designers to shuttle therapeutics across the BBB for multiple CNS indications.

## Collaboration is our strength.

No single group can address the vast number of neurogenetic disorders that exist. We license our capsid technology for clinical use to enable treatments for diseases previously hindered by poor delivery to the CNS. We have licensed our technology to several industry partners and two rare disease groups, with active continuing discussions.

### Flexible Partnering Opportunities

Various licensing options arrangements available, which can include co-development along with flexible milestone arrangements.

### Consulting Services

Our team has extensive experience across manufacturing, regulatory, and preclinical development. We can provide these services in use with TfR1 CapX.



# The leader in receptor-targeted capsid development

Reach the right cells by targeting human receptors, using human-centric models

Humanized mice for translatable specificity and selectivity

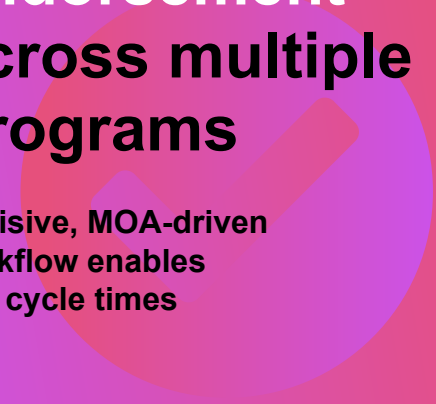


Proprietary approach to co-optimizing fitness and function

Developable modifications that can de-target liver and evade NAbs while maintaining core tissue tropism

Preclinical and regulatory roadmap with FDA endorsement across multiple programs

Decisive, MOA-driven workflow enables fast cycle times



Successfully engineered novel capsids targeting multiple human receptors.

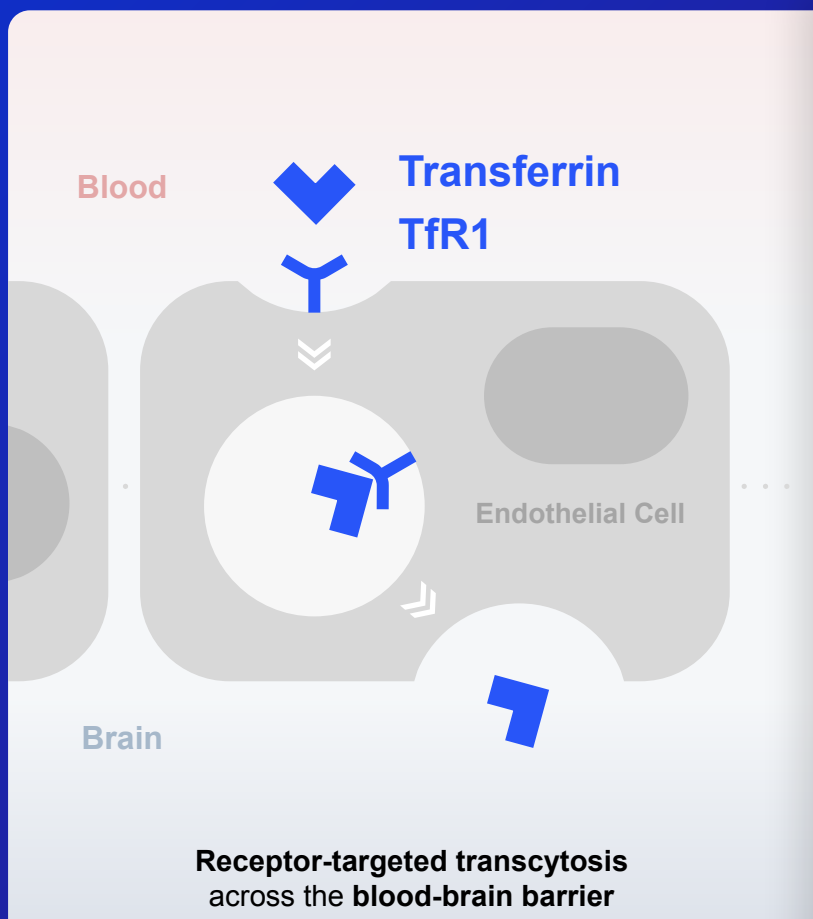
Pioneered by Scientific Co-Founder, Ben Deverman, PhD over the past 10 years.





Human transferrin receptor

# Human transferrin receptor 1 (TfR1) is well-validated as a valuable brain target on the blood brain barrier (BBB).



## Well-Understood BBB Receptor

- Over 40 years of research, with consistent and durable expression throughout life<sup>1</sup>, applicable for pediatric and geriatric dosing.
- **Highly expressed in the brain microvasculature** of mice, non-human primates (NHPs), and humans<sup>2,3</sup>.
- Expression pattern in the brain microvasculature is **well conserved between mice and humans**, supporting translational relevance<sup>3</sup>.
- TfR1 mediates rapid shuttling of transferrin from blood to the brain extracellular space (BES).
- Transit time for half of the TfR1 on the lumen surface to BES **10–15 minutes**<sup>4</sup>.

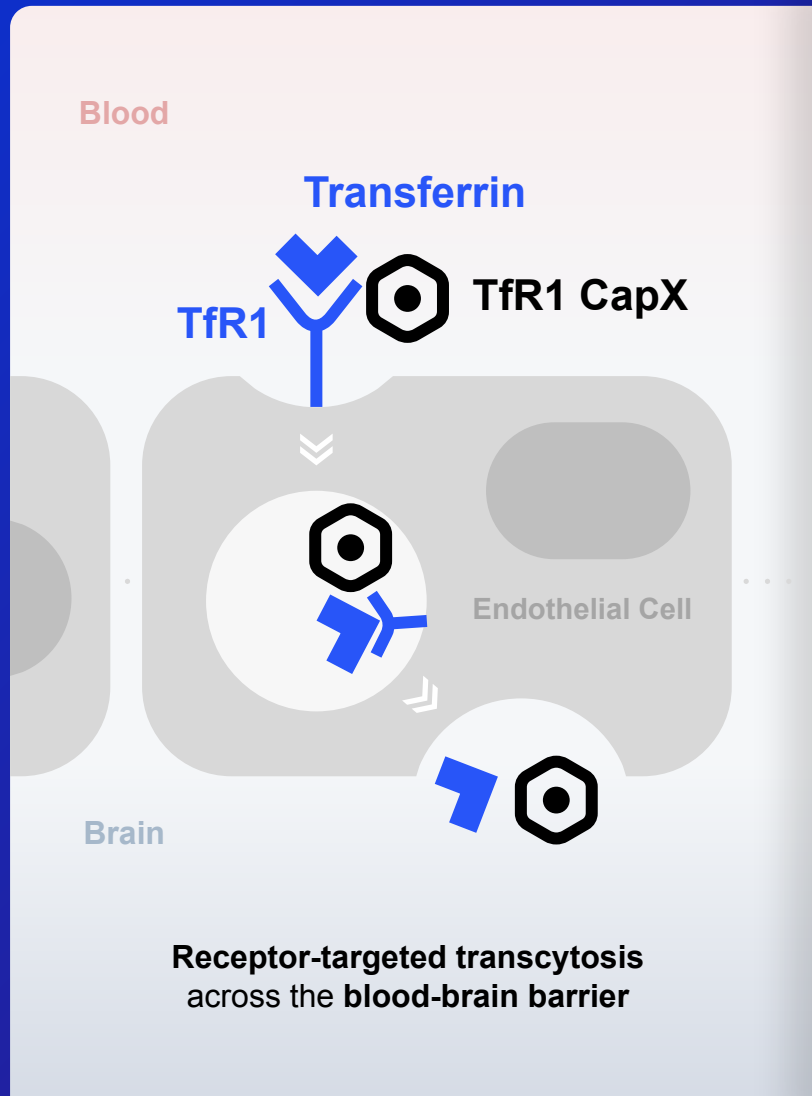
## Validated Clinical Target

**Clinical efficacy has been shown in peer antibody studies.**

JCR, Denali, and Roche all have shown promising clinical data with their TfR1-binding antibody programs, validating our MOA in humans.

No safety findings of significance in clinical programs using TfR1 to shuttle drugs to the brain, reflecting hundreds of pediatric and geriatric patients dosed.

# Advancing targeted delivery with human-specific TfR1 capsids, with first-in-human data projected 2H 2026.



## TfR1 CapX Interaction with TfR1 is Highly Characterized

### Extensive Characterization

- Apertura's AAV capsids, including **TfR1 CapX**, have been thoroughly studied.
- CapX binds the **apical domain** of TfR1 without interfering with natural transferrin binding.

### Human Specificity

- CapX binding is **exclusive to the human** form of TfR1.

### Molecular Determinant

- A **single amino acid** in human TfR1 dictates both binding and transduction.
- This site is **highly conserved**, with no known SNP variation in humans.

### Safety Profile

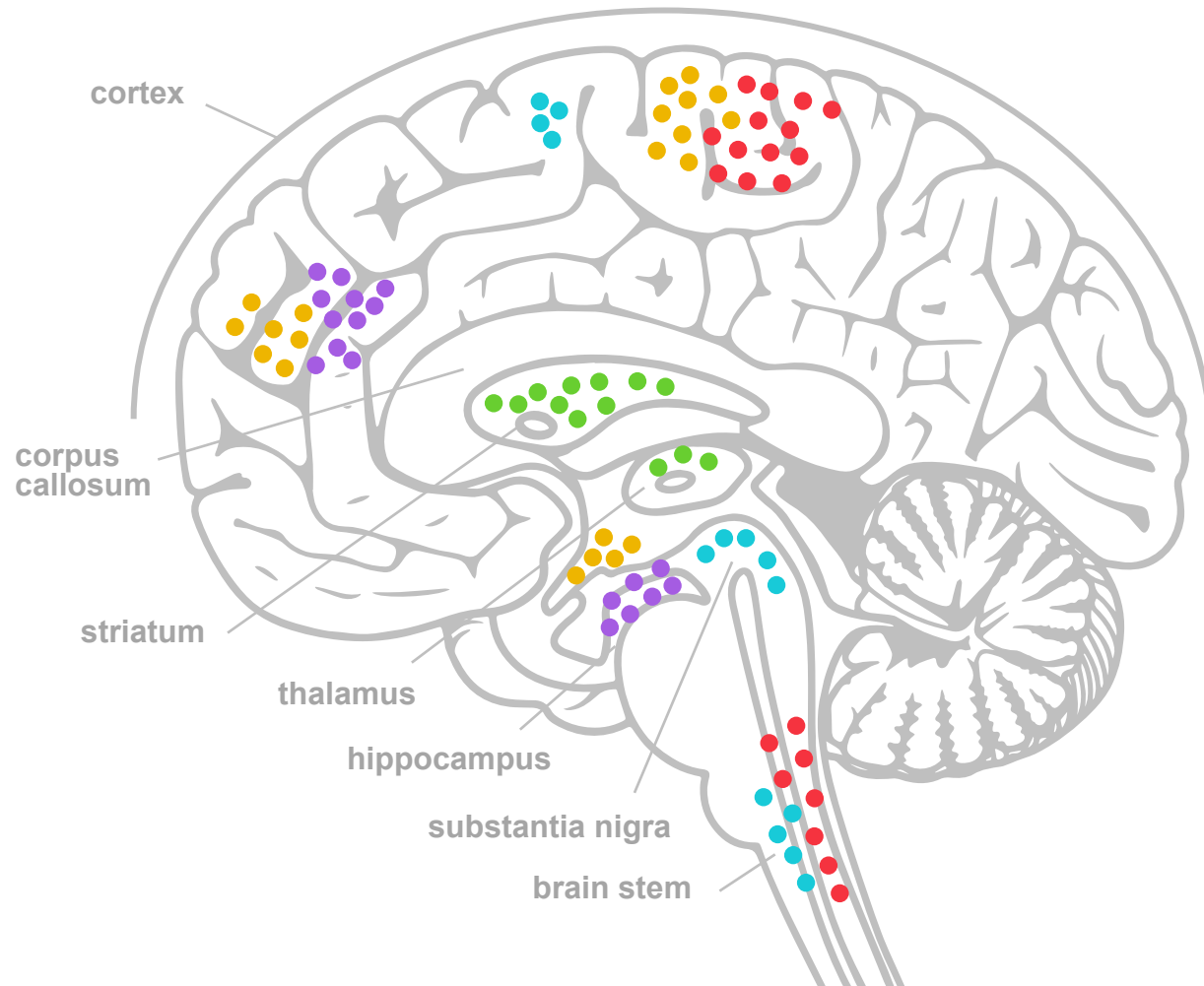
- **No evidence** of reticulocyte depletion in preclinical models.

### Clinical pathway

- Projecting **FIH data using TfR1 CapX in 2H 2026 and 1H 2027** for two rare disease groups using our capsid.
- Intravenous delivery does not require specialized neurosurgery, facilitating **scalable patient access** during trials and commercialization.



# Broad distribution of TfR1 CapX across the CNS expands reach of gene therapies for neurological disorders



## Regional Diseases (Key Regions)

- Parkinson's Disease
- Alzheimer's Disease
- Huntington's Disease
- Frontotemporal Degeneration
- ALS

## Global Diseases

### Lysosomal Storage Diseases

- Fabry
- Gaucher
- Niemann-Pick A/B/C
- GM1
- MPS I
- MPS II

### Neurogenetic Disorders

- Angelman
- CDKL5
- TSC1
- Rett
- SYNGAP1
- TSC2



# Pipeline positioned to move rapidly to clinic.

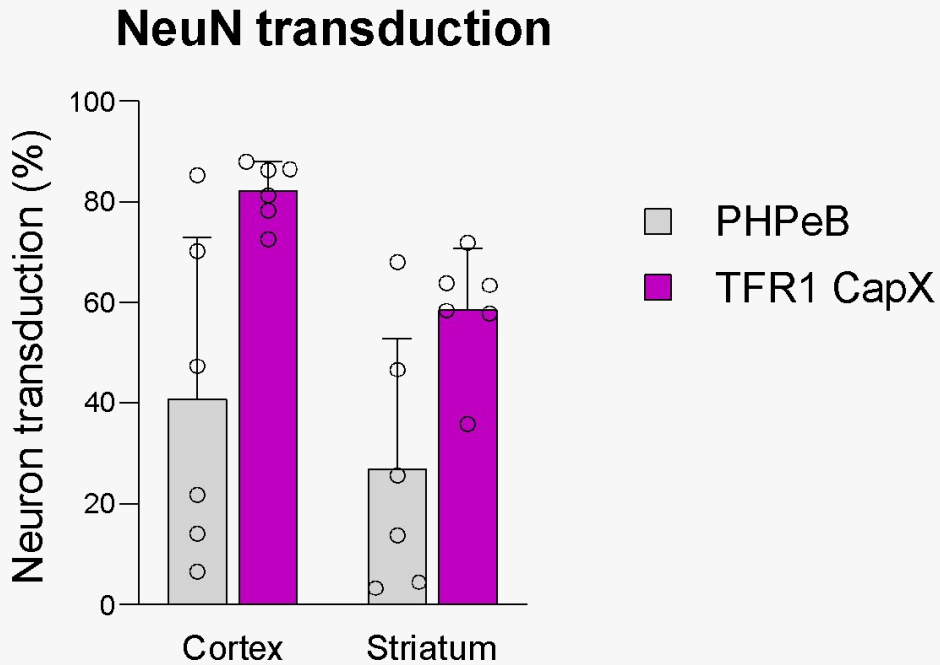
Indication	Target	Target Tissue	Indication Evaluation	Early Research	Late Research	IND-Enabling	FIH Target Date
<b>Undisclosed Rare Disease<sup>1</sup></b>	<b>Undisclosed</b>	<b>CNS</b>					<b>2H26</b>
<b>Prion Disease<sup>2</sup></b>	<b>PRNP</b>	<b>CNS</b>					<b>1H27</b>
<b>Tuberous Sclerosis Complex 1</b>	<b>TSC1</b>	<b>CNS</b>					<b>1H28</b>
<b>Tuberous Sclerosis Complex 2</b>	<b>TSC2</b>	<b>CNS</b>					<b>2H28</b>
<b>TfR1 Capsid Partnerships</b>						Undisclosed venture-backed biotech	

<sup>1</sup> Apertura is advising on preclinical development, regulatory strategy, and CMC.

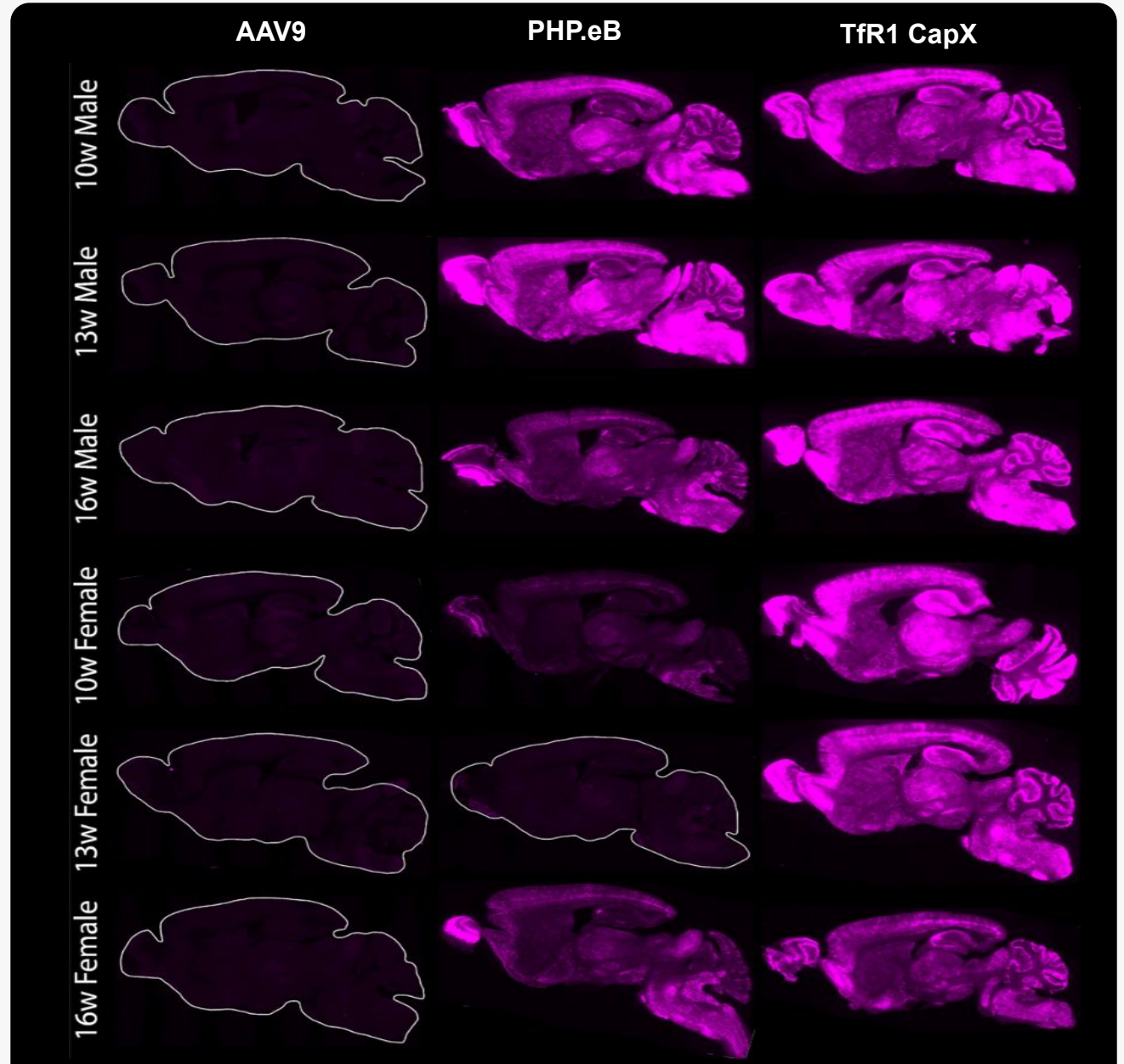
<sup>2</sup> The Broad Institute is developing a gene therapy for prion disease, utilizing TfR1 CapX, to reduce PRNP expression and slow neurodegeneration. Dr. Sonia Vallabh leads the program, with Apertura advising on preclinical development, regulatory strategy, and CMC.



# Breaking Through: Superior CNS targeting with TfR1 CapX versus PHP.eB



Payload	ssAAV-CAG-NLS-mScarlet-2A-luc-WPRE-pA
Dose	2.0 x 10 <sup>12</sup> vg/kg
Readout	21 days post injection
Age of Mice	10 – 16 weeks (adult), n=6/group (3M/3F)

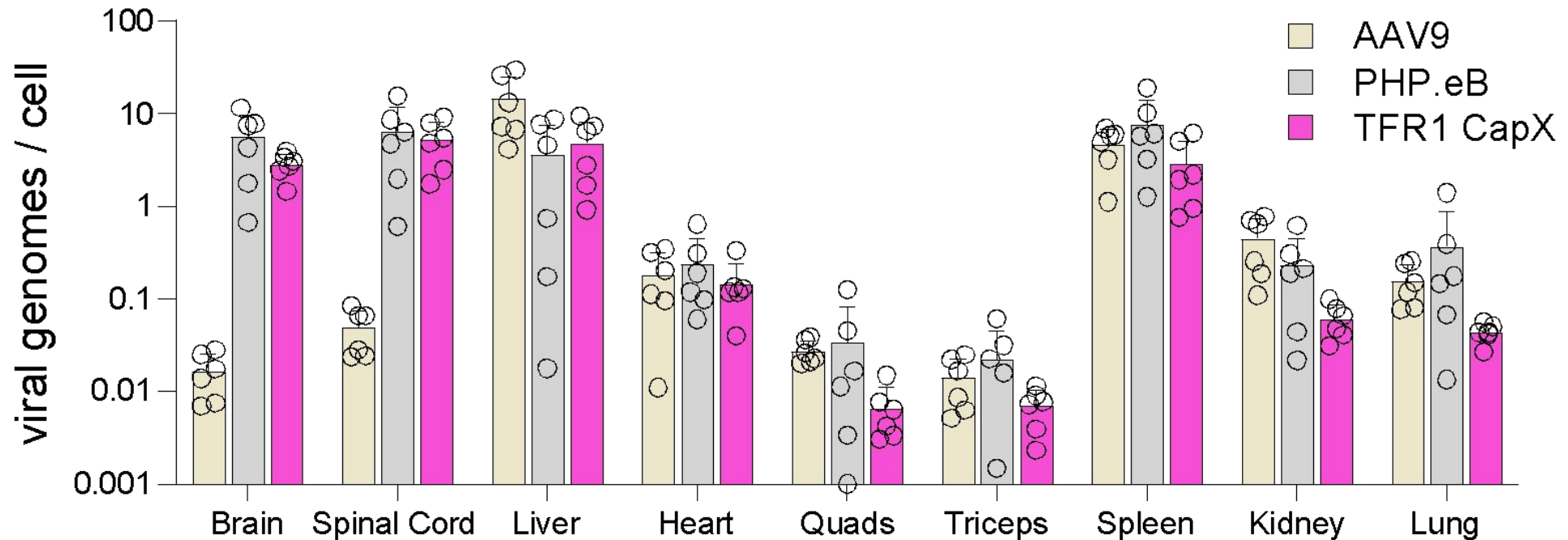




# Brain and spinal cord successfully targeted via IV-administered TfR1 CapX.

<b>Payload</b>	ssAAV-CAG-NLS-mScarlet-2A-luc-WPRE-pA
<b>Dose Level</b>	$2 \times 10^{12}$ vg/kg
<b>Readout</b>	21 days post injection
<b>Age of Mice</b>	10 – 16 weeks (adult), n=6/group (3M/3F)

**Biodistribution vg per cell at  $2 \times 10^{12}$  vg/kg**



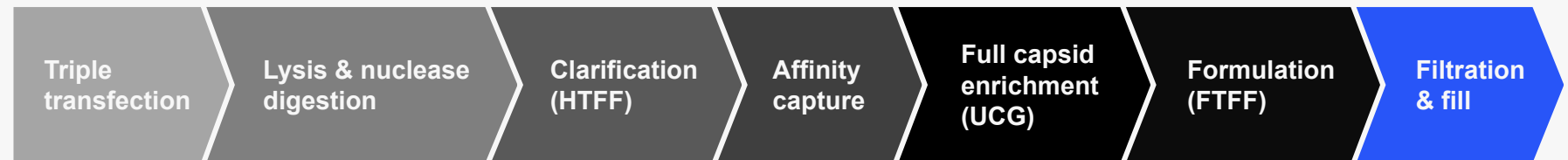


# TfR1 CapX is manufacturable using the same forward-compatible processes used for natural serotypes and other engineered capsids.

 **Manufacturability**

**Overcome challenges while leveraging existing infrastructure**

TfR1 CapX demonstrates compatibility with current practices with yields on par to AAV9.



- Forward-compatible manufacturing process
- Commercially available suspension HEK293 cells
  - AAVX affinity resin

Prior to any process optimization, obtained productivities and yields are comparable to AAV9 and other AAV9-based engineered capsids

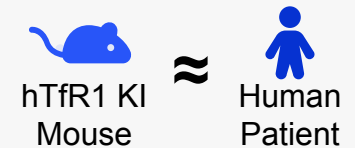
TfR1 has been produced internally and externally at scales up to 50L to support mouse and NHP studies

**A CDMO has manufactured a 50 L batch of TfR1 CapX using a process that is representative of clinical-scale production, confirming the capsid’s scalability and supporting future clinical manufacturing**



## Clear guidance from FDA on TfR1 CapX preclinical development.

- **The FDA supports using the TfR1 CapX capsid and the humanized TfR1 knock-in mouse model for distribution and safety evaluation, eliminating the need for NHP data for IND submission in both the TSC and PRNP programs. The agency has also endorsed the surrogate capsid strategy for dose range finding.**
- **Apertura is developing gene therapies for genetic epilepsy in tuberous sclerosis complex (TSC) using TfR1 CapX for broad CNS delivery.** The therapy targets TSC1/TSC2 mutations, with a focus on both pediatric and adult patients, in collaboration with the TSC Alliance.
- **The Broad Institute is developing a gene therapy for prion disease, also utilizing TfR1 CapX, to reduce PRNP expression and slow neurodegeneration.** Dr. Sonia Vallabh leads the program, with Apertura advising on preclinical development, regulatory strategy, and CMC.





# B-hTFR1 mice are an ideal tool for *in vivo* evaluation of hTfR1 capsids.

## B-hTFR1 Mouse: A Pharmacologically Relevant Model

**Human-Relevant Expression:** B-hTFR1 mice express a chimeric transferrin receptor with human extracellular domains, enabling accurate biodistribution and toxicology assessments for CapX gene therapies.

**Physiologically Comparable:** TfR1 expression in B-hTFR1 mice mirrors endogenous levels in the background strain.

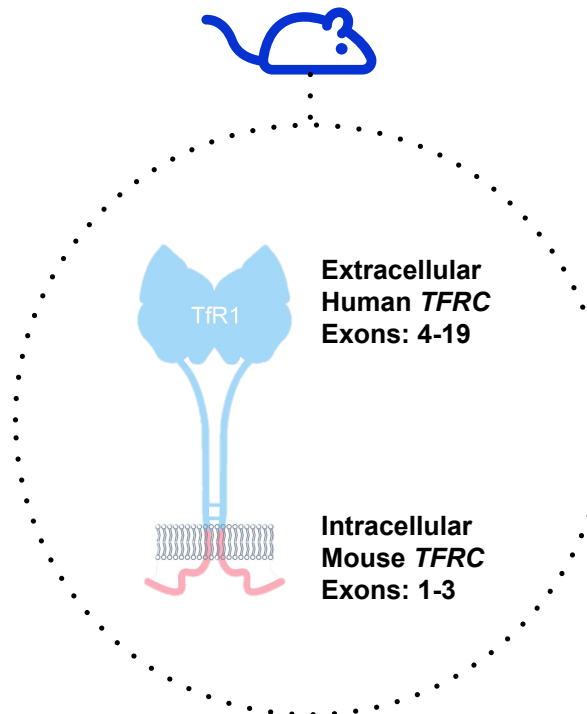
**CNS Targeting Validation:** Demonstrates enhanced TfR1 capsid distribution to the CNS due to human TfR1 expression.

### Regulatory & Industry Precedent:

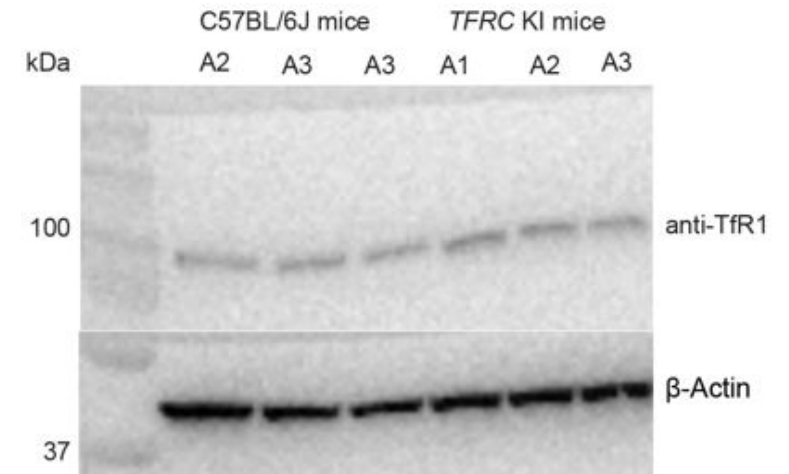
- **FDA-Endorsed Approach**
- **Industry Validation:** Similar successful strategies used with hTfR1 transgenic mice

## TFRC KI mice

B-hTFR1 mice (Biocytogen #110861)



## Similar expression of TFRC between WT and KI





# FDA-endorsed surrogate capsid approach for efficient preclinical development



## Regulatory Alignment:

- FDA endorsed the surrogate capsid approach, consistent with its published gene therapy guidance.

## Advantages of Surrogate Capsids:

- Eliminates additional breeding.
- Leverages existing data for future indications.
- Broad applicability across multiple gene therapy targets

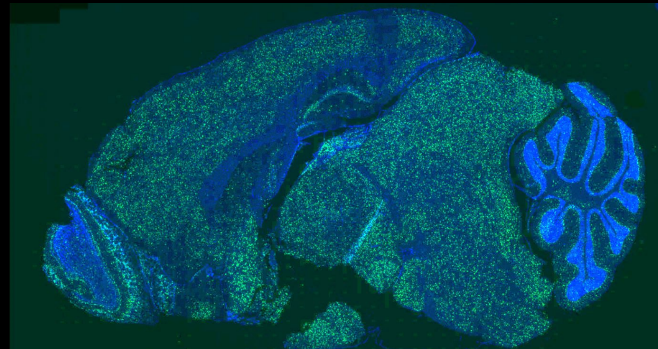
## Mouse BBB-Crossing Capsids

- Developed by Dr. Ben Deverman (Deverman et al., 2016), **PHP.B and PHP.eB capsids cross the BBB upon IV administration**, enabling robust transduction of astrocytes and neurons in LY6A-expressing mice. **Capsid BI-28** (Huang et al., 2023), leveraging the LY6C receptor, expands applicability across most mouse strains.
- **RMT Mechanism:** Both capsid families utilize receptor-mediated transcytosis (RMT) for BBB penetration.

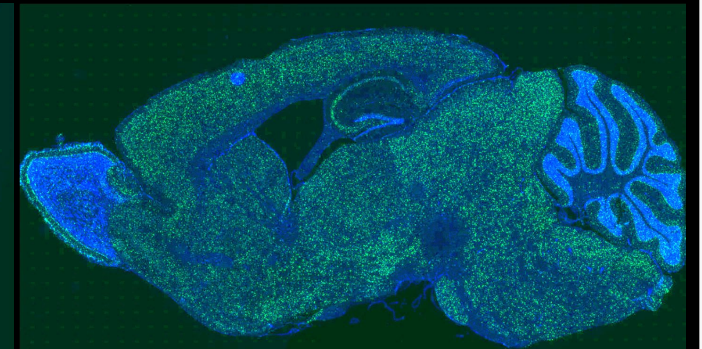
## Validated Across Models:

- Apertura: Used PHP.B and BI-28 in TSC1 preclinical studies (GFP & TSC1 payloads).
- Broad Institute: Used PHP.eB in PRNP studies (PRNP silencing payload).
- Confirmed distribution in TfR1 KI Model.

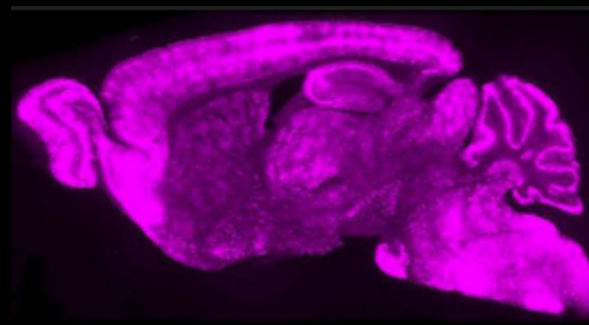
Apertura TfR1 Capsids



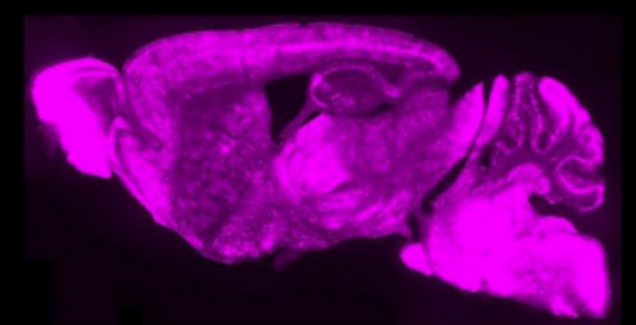
Murine BBB Crossing Capsids



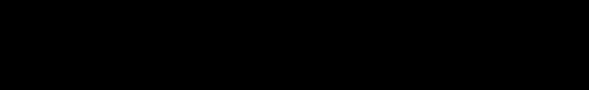
BI-hTfR1 (episomes – RNA scope)



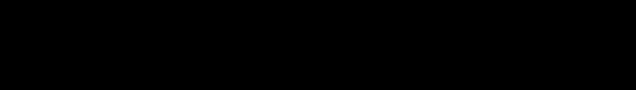
PHP.B (episomes – RNA scope)



TfR1 CapX (mScarlet expression)



PHP.eB (mScarlet expression)





# In vivo study roadmap for TfR1 CapX

## Pilot payload expression study



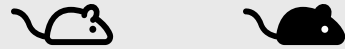
Wild type or hTfR1 KI Mice  
(non-disease mice)



Surrogate capsid (e.g. PHP.B, PHP.eB, BI-28) +  
Therapeutic Payload

- **Goal:** Express payload in wild type mice using surrogate capsid for preliminary safety readout
- **Readouts:** Survival (acute toxicity), distribution by ddPCR or in situ hybridization (ISH)

## Efficacy study



Non-Disease and Disease Mice



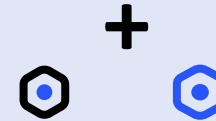
Surrogate capsid +  
Therapeutic Payload

- **Goal:** Express payload in disease model mice using surrogate capsid to assess improvement in disease phenotype
- **Readouts:** Survival, biomarkers, other phenotypic readouts, distribution by ddPCR or ISH

## Pilot distribution study



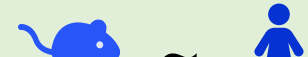
hTfR1 KI Mice  
(non-disease mice)



Surrogate and TfR1 CapX +  
Reporter or Therapeutic  
Payload

- **Goal:** Compare distribution of surrogate capsid and TfR1 CapX in hTfR1 KI mice for dose translation
- **Readouts:** Distribution by ddPCR and ISH

## Definitive toxicology and distribution study



hTfR1 KI Mice  $\approx$  Human Patient



TfR1 CapX +  
Therapeutic Payload

- **Goal:** Deliver clinical capsid and payload to hTfR1 KI mice to assess safety outcomes and distribution in key tissues
- **Readouts:** Survival, histopathology, immunogenicity, clinical chemistry, distribution by ddPCR and ISH



# Strengthened regulatory pathway: FDA INTERACT & Pre-IND feedback supports TfR1 CapX IND plan.



- **FDA Endorsement:** Human TfR1 KI model endorsed to assess **biodistribution & toxicology** to support initial human dose selection.
- **NHP Irrelevance Confirmed:** Preclinical data **validates the non-necessity of NHP studies** for TfR1 CapX.
- **Established Regulatory Alignment:** The use of the **TfR1 KI mouse model** aligns with **published FDA guidance**.
- **Cross-Species Translation:** Industry data confirm **dose equivalency from small species to humans** in IV dosed TfR1-targeting therapies, supporting clinical translation.
- **Surrogate Capsid Validation:** FDA supports **PHP.B/eB as surrogates for efficacy assessment** due to similar MOA and biodistribution profiles with TfR1 CapX.

Evaluation Method	Expresses hTfR1	Biological Rationale	Efficacy	Dose Response	Distribution	Safety	Immunogenicity
Human cell line models	✓	✓	⊘	⊘	⊘	⊘	⊘
Disease mice model	⊘	✓	✓	✓	⊘	⊘	⊘
hTfR1 KI mice	✓	⊘	⊘	✓	✓	✓	✓
Disease x hTfR1 KI mice	✓	✓	✓	✓	✓	✓	✓
NHP	⊘	⊘	⊘	⊘	⊘	⊘	✓
Clinical trials	✓	✓	✓	✓	⊘	✓	✓



# A focus on what matters for the field

**Next generation collaborations for the next generation of gene therapy.**

**Developed and deployed preclinical and regulatory roadmap with FDA endorsement across multiple programs**

**Collaborative and flexible licensing for pharma, biotech, foundations, and academia**

**Expertise in developing therapeutic programs, regulatory science, and managing CROs & CDMOs**

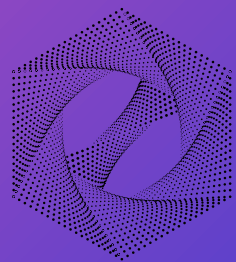


**Apertura aims to ensure that its technologies are accessible and utilized to their fullest extent possible.**

**Start a conversation with us: [info@aperturagtx.com](mailto:info@aperturagtx.com)**

# Acknowledgements

- **Apertura Gene Therapy Team**
  - Dave Greenwald, PhD
  - Andrew Steinsapir, MBA
  - Diego Garzón, PhD, MBA
  - Christopher Davis, PhD
  - Von Wiltman, BS
- **Ben Deverman, PhD**
- **Sonia Vallabh, PhD**
- **TSC Alliance Preclinical Consortium**
- **Apertura's TfR1 Capsid Partners**



**Apertura**  
GENE THERAPY

Contact: [info@aperturagtx.com](mailto:info@aperturagtx.com)



To be revised

# Contents

1. Apertura Gene Therapy
2. TfR1 CapX – characterization and manuf
3. TfR1 CapX preclinical roadmap
4. Closing