Apertura GENE THERAPY

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Open Aperture: An express MTA framework enabling academic evaluation of an hTfR1-targeting AAV capsid for systemic CNS delivery

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References

- Guidance for Industry, Preclinical Assessment of Investigational Cellular and Gene Therapy Products. FDA (November 2013)
- Qin Huang et al. An AAV capsid reprogrammed to bind human transferrin receptor mediates brain-wide gene delivery. Science 384, 1220-1227 (2024).

Introduction

Academic investigators continue to generate promising CNS gene therapy payloads, but translational progress often slows when programs move beyond natural serotypes or mouse-adapted CNS-tropic capsids and require access to clinically relevant delivery tools. In parallel, manufacturability, nonclinical study design, and regulatory planning can create additional barriers for groups without dedicated translational infrastructure. Open Aperture was developed to help address these bottlenecks by pairing access to a clinically intended, hTfR1-targeting AAV capsid with a structured support package that includes translational roadmap guidance, CMC resources, and referrals to experienced external partners. Building on prior work describing hTfR1-targeting vectors and a streamlined, primate-sparing nonclinical strategy, this framework is intended to help academic researchers translate their preclinical progress into actionable steps towards the clinic.

Open Aperture: A structured access pathway for translational CNS gene therapy studies

1 Unmet translational need

Promising academic CNS gene therapy programs often begin with natural serotypes or mouse-adapted capsids. Progress can slow when access to clinically relevant delivery tools and translational development guidance is limited.

2 Application and program review

Qualified academic investigators submit institution and tech transfer office (TTO) details, indication, development stage, and research plan that outlines the intended studies to be performed with TfR1 CapX.

3 Eligibility confirmation and MTA execution

Eligible non-commercial academic programs proceed through a standardized review process and CDA/MTA workflow. If an institutional agreement is already in place, additional laboratories can be added efficiently via amendments.

4 Access to capsid and translational package

After execution, investigators receive TfR1 CapX-related materials, including access to starting material for TfR1 CapX rep/cap plasmid along with the sequence, plus a preclinical roadmap, CMC and analytics resources, and introductions to experienced vendors.

Translational roadmap, CMC guidance, and development support

Open Aperture includes a translational support package designed to help academic investigators generate data that are more actionable for downstream development.

Translational roadmap

- Preclinical strategy guidance to help align early studies with downstream regulatory expectations
- Study design support, including dose selection, histology approaches, analytical readouts, and development strategies to transition to TfR1 CapX
- Considerations tailored to different therapeutic modalities, including gene replacement, gene editing, and gene silencing

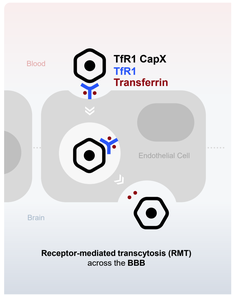
CMC guidance

- Fit-for-purpose CMC and analytics resources to support forward-compatible development planning
- Reference process descriptions and process flow materials for TfR1 CapX production using standard materials and unit operations
- Analytical method compatibility guidance and QC recommendations based on intended material use

Experienced vendor network

- Connection to vendors with prior experience supporting TfR1 CapX-based programs
- Access to partners supporting rep/cap plasmid production, AAV manufacturing, *in vivo* study execution, and access to hTfR1 knock-in mouse models
- For qualified licensees, information may also include scalable GMP starting points, including a TfR1 CapX rep/cap plasmid master cell bank hosted at Viralgen

Human Transferrin Receptor and TfR1 CapX™



Well-Understood BBB Receptor

TfR1 is a well-studied receptor **highly expressed on the BBB**. The receptor cycles rapidly and is expressed consistently throughout life. There are no known SNPs in the critical regions for TfR1 CapX binding.

Efficent Brain-Wide Delivery

All brain cells are **within 20μm of a blood vessel across mammalian species**, RMT via endothelial cells enables efficient, brain-wide CNS delivery, making IV-delivery an ideal route of administration.

Scalable Across Species

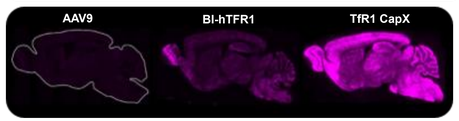
IV administration avoids diffusion scaling challenges seen with intraparenchymal and intrathecal injections. This facilitates direct translational relevance from preclinical models (e.g., hTFR1 mouse) to humans.

Validated Clinical Target

Clinical efficacy has been demonstrated by studies of TfR1-binding antibodies from multiple companies. JCR, Denali, and Roche all have shown promising clinical data with their TfR1-binding antibody programs, validating our MOA in humans.

Pardridge, W. M. (2023); Duvernoy, H. et al (2002); Galvan, A. et al. (2021); NCT03568175; NCT06181136; NCT05661125

TfR1 CapX Demonstrates Superior Biodistribution vs Other Vectors

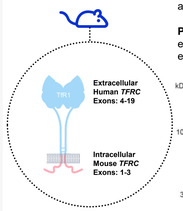


Compared to AAV9 and the first-generation BI-hTFR1 capsid, TfR1 CapX demonstrates transduction of **>80% of neurons** at a low dose of 2E12 vg/kg, as well as superior **175-fold brain enrichment** relative to AAV9.

Payload	ssAAV-CAG-NLS-mScarlet-2A-luc-WPRE-pA
Dose	2.0 x 10^{12} vg/kg
Readout	21 days post injection
Age of Mice	10 – 16 weeks (adult)

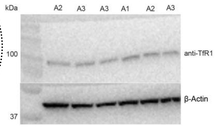
	AAV9	BI-hTFR1	TfR1 CapX
Receptor	Galactose AAVR	hTfR1, Galactose, AAVR	
Species			
Dose (vg/kg)		2E12	
Brain Delivery (vg/dg)	0.02	1.43	2.80
Liver Sequestration (vg/dg)	14.38	21.01	4.74
Brain-to-Liver Ratio (1 vg : vg)	1:899	1:14.7	1:1.7
Brain enrichment over AAV9	1	89.4	175
Cortical neuron transduction (%)	N/A	15.0%	82.2%

FDA-Endorsed Surrogate Capsid Approach Enables Efficient and Scalable Preclinical Development

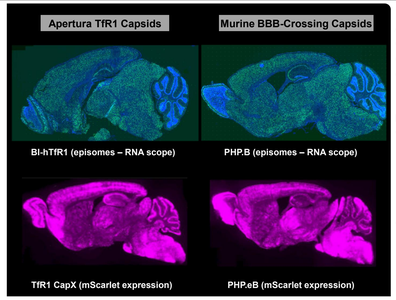


Human-Relevant Expression: B-hTFR1 mice express a chimeric transferrin receptor with human extracellular domains, enabling accurate biodistribution and toxicology assessments for TfR1 CapX gene therapies.

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



Similar expression of TFRC between WT and KI



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 crosing.

	Payload Feasibility	Surrogate Capsid Evaluation	Mouse Model Correlation	Capsid Correlation	Safety, Distribution & Toxicology Study
	Proof of concept of payload	Correlation of PHP.eB between diseased vs. non-diseased mice	Evaluation of PHP.eB in hTfR1 KI mice compared to non-disease mice	Assess correlation of PHP.eB and TfR1 CapX in hTfR1 KI mice	TfR1 CapX dose equivalency between hTfR1 KI mice and humans
PROCESS	A: Disease Mice + PHP.eB + Therapeutic Gene	B: Non-Disease Mice + PHP.eB + Therapeutic Gene	C: hTfR KI Mice (non-disease mice) + PHP.eB + Reporter Transgene	D: hTfR KI Mice (non-disease mice) + TfR1 CapX + Reporter Transgene	E: hTfR1 KI Mouse ≈ Human Patient + TfR1 CapX + Therapeutic Payload
OUTCOME	A	A ∝ B	A ∝ B ∝ C	A ∝ B ∝ C ∝ D	D = E
ANALYSIS	Assessments by immunofluorescence & RNAscope (spatial resolution) and ddPCR analysis (bulk tissue measurement)				

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	✓	✓	✓	✓	⊘	✓	✓

Conclusions

Open Aperture illustrates a practical model for reducing structural barriers to next-generation CNS gene therapy development. By coupling an MTA framework with access to a clinically intended hTfR1-targeting capsid, development documentation informed by FDA discussions, translational roadmap support, CMC guidance, and vendor referrals, the program is designed to help academic investigators align early research with downstream translational requirements. Broader use of access models grounded in clinically relevant capsids and regulator-informed development planning may help improve reproducibility, manufacturability readiness, and early regulatory alignment, particularly for rare and ultra-rare CNS indications.

Call to Collaboration

No single organization can address every disease. Apertura recognizes that partnering with driven organizations can help expand our reach and hopefully drive research forward from bench to bedside. It is our intention that the tools, technologies, and know-how we develop can be leveraged by partners across patient advocacy groups, foundations, academia, as well as biotechnology & pharmaceutical companies.

Connect with us – info@aperturagtx.com