# TRiM™ Platform for Delivery of RNAi Therapeutics to Central Nervous System via Subcutaneous Administration

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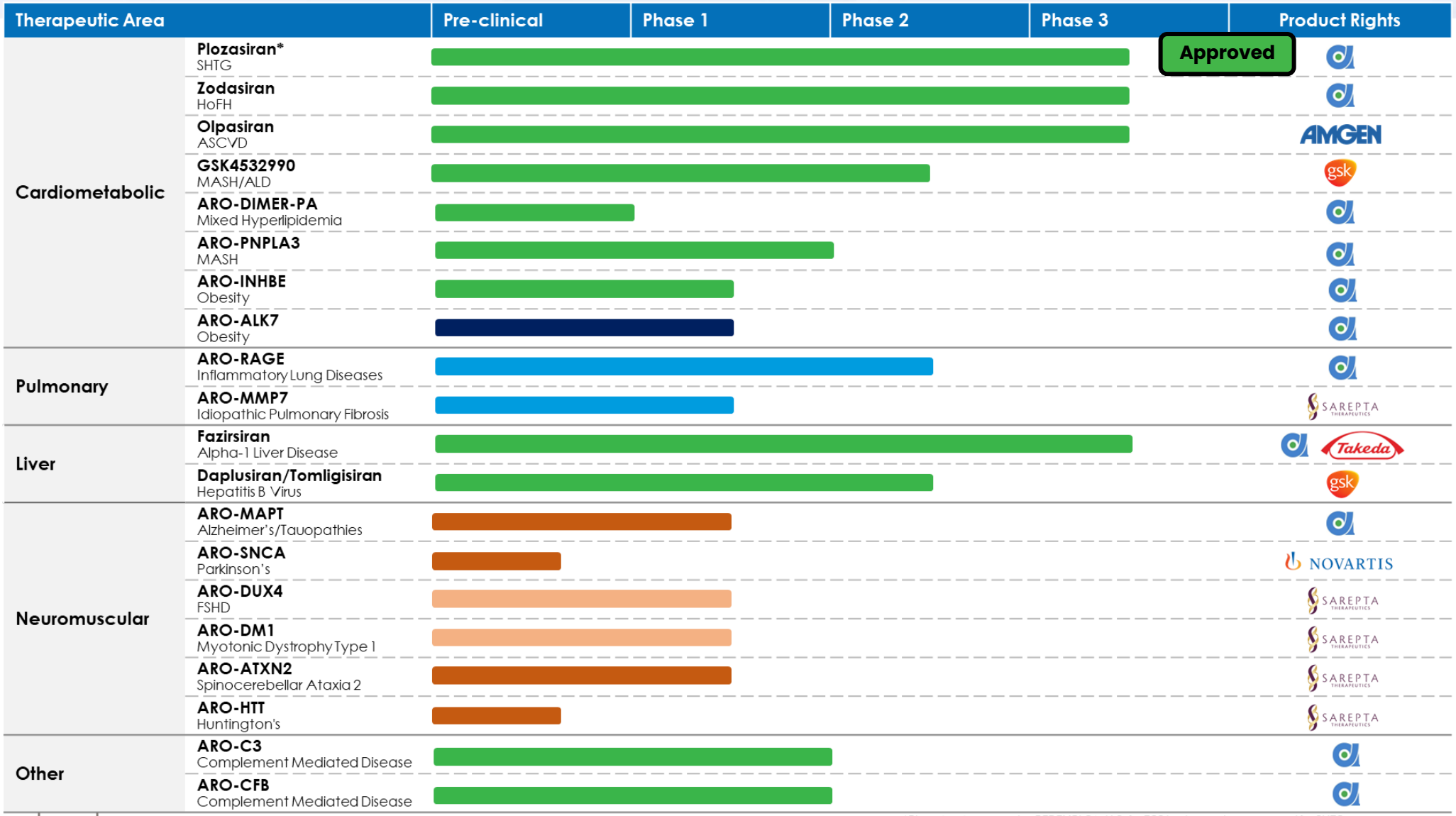
# Safe Harbor Statement

This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of various factors and uncertainties, including, without limitation, our developmental stage and limited operating history, our ability to successfully and timely develop products, enter into collaborations and achieve other projected milestones, rapid technological change in our markets, demand for our future products, legislative, regulatory and competitive developments and general economic conditions. Our Annual Report on Form 10-K, recent and forthcoming Quarterly Reports on Form 10-Q, recent Current Reports on Forms 8-K, and other SEC filings discuss some of the important risk factors that may affect our ability to achieve the anticipated results, as well as our business, results of operations and financial condition. Readers are cautioned not to place undue reliance on these forward-looking statements. Additionally, Arrowhead disclaims any intent to update these forward-looking statements to reflect subsequent developments.

# Robust Pipeline with Near-term Commercial Opportunities

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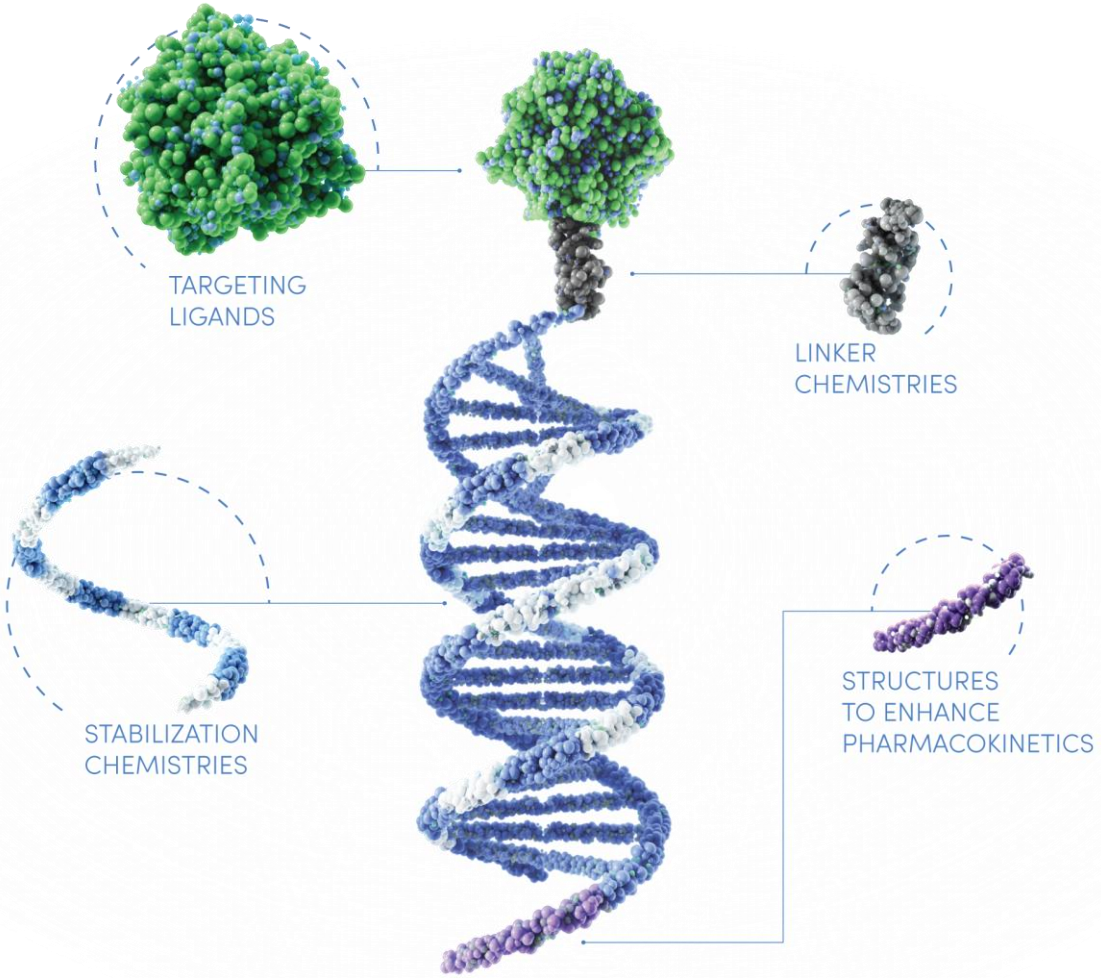
# TRiM™ Platform: Targeted RNAi Molecule




A modular system comprising:

- Unique RNAi chemistry insights and expertise
- Powerful platform technology to maximize activity and stability employing:
  - Algorithmic approach to sequence selection and design
  - Stabilization chemistry
  - Targeting ligand
  - Linker chemistry
  - PK and PD enhancers

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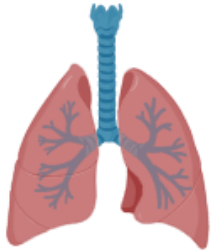
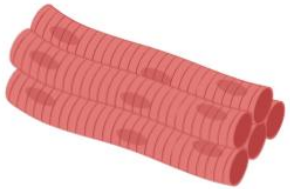
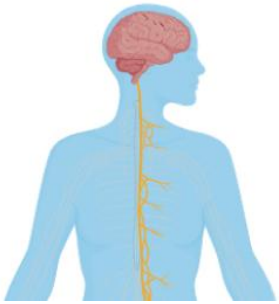
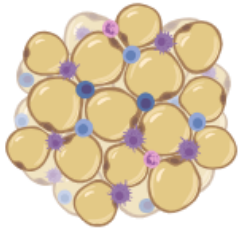
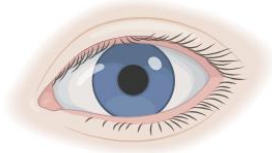
# TRiM™ Platforms Drive Robust Pipeline for Multiple Tissue Types

| Liver | Lung | Skeletal Muscle | CNS | Adipose | Ocular | Cardio-myocyte |
|---|---|---|---|---|---|---|
|  |  |  |  |  |  |  |
| Strong clinical validation | Deep lung clinical validation (RAGE) | Early clinical stage | Early clinical stage | Early clinical stage | Preclinical stage | Preclinical stage |

- ❖ Arrowhead is leading the field in extrahepatic delivery of the siRNA drug modality
- ❖ We have built experience and tools to achieve productive RNAi in new tissues and cell types

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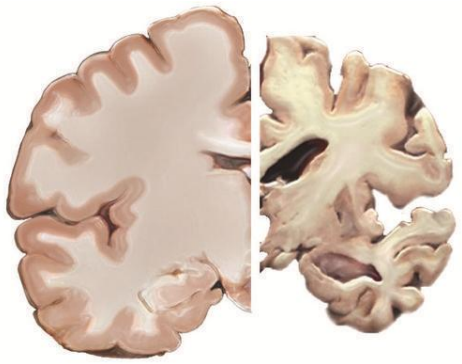
# Neurodegenerative Diseases Are an Enormous Burden Uniquely Addressable by RNAi Therapeutics

Over **50 million** patients with neurodegenerative diseases worldwide[1] and few disease-modifying therapies

**Healthy Brain**



**Diseased Brain**

- Common feature of CNS diseases: neurotoxic gain of function due to abnormal protein aggregation
- siRNA can be an effective modality to suppress further target protein expression and halt disease progression

| Disease | Cases in the US | Projections (U.S.) | Implications |
|---|---|---|---|
| Huntington's Disease | 41,000 | 1.3-2.3k new cases per year[2] | Growing loss of voluntary motor function and complete reliance on caregiver for daily tasks requiring around-the-clock care |
| Parkinson's Disease | 1 million | ~90k new cases per year[3] | $24.5 billion in direct medical costs[4] |
| Alzheimer's Disease | 6.9 million | Nearly double by 2050 | Unpaid family caregiving for dementia is valued at nearly $350 billion[5] |

[1]Lancet Neurology 2019, 18:459. [2]Prevalence and Incidence of Huntington. NIH National Library of Medicine. PMC10086981. [3]Statistics. Parkinson's Foundation.
[4]Current and projected future economic burden of Parkinson. Nature. DOI: 10.1038/s41531-020-0117-1.[5]Facts and Figures. Alzheimer's Association.

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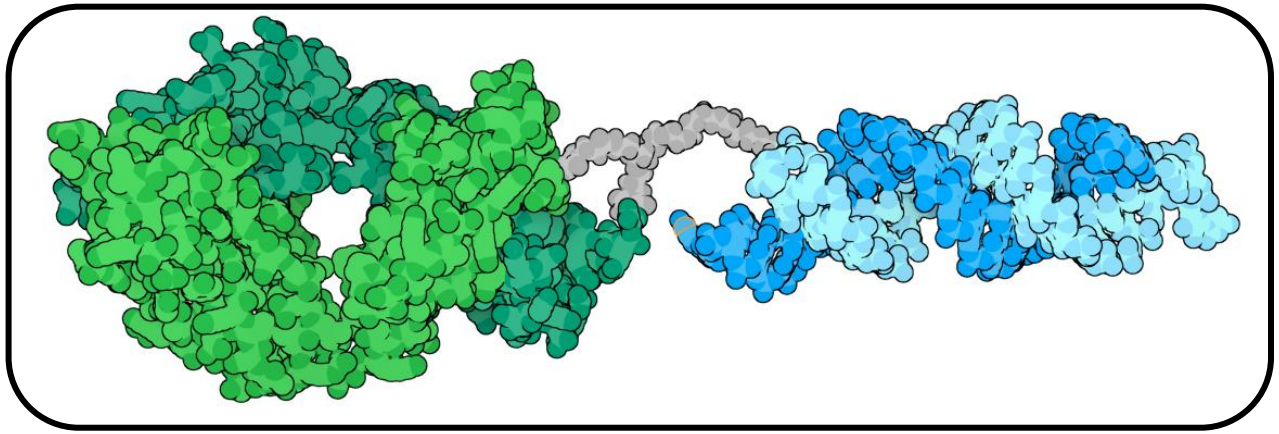
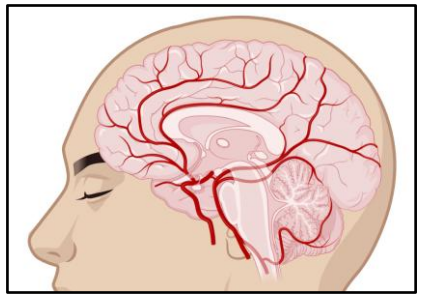
# Agenda

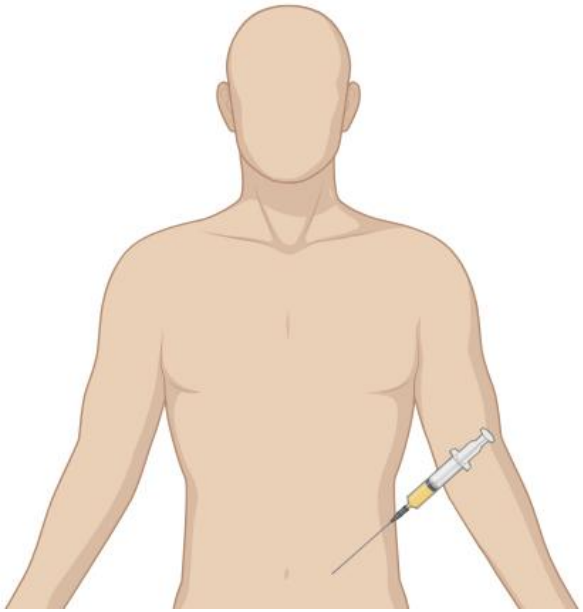
- TRiM™ BBB platform introduction
- TRiM™ BBB platform efficacy in rodent
- TRiM™ BBB platform efficacy in NHP
- Therapeutic programs

# TRiM™ BBB Platform for siRNA Delivery to CNS

Systemic Delivery Platform







- Subcutaneous (SC) administration for crossing blood-brain barrier (BBB)
- siRNA conjugated to a TfR-targeting ligand through a stable, non-reversible covalent linkage
- Stable in circulation

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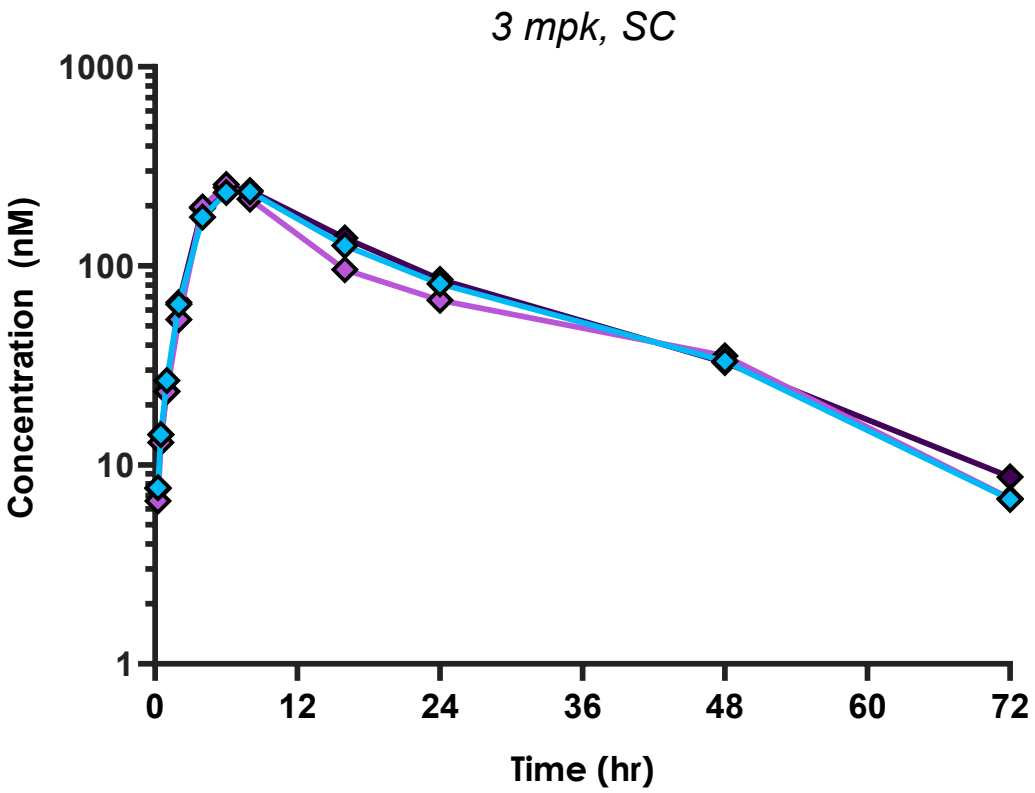
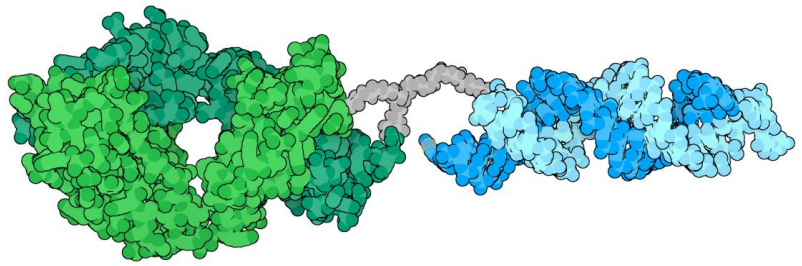
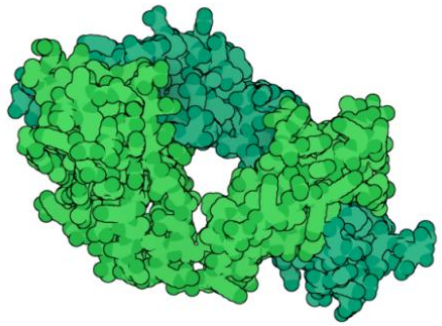
# TRiM™ BBB Conjugate Is Stable in Circulation

## Plasma PK in NHP



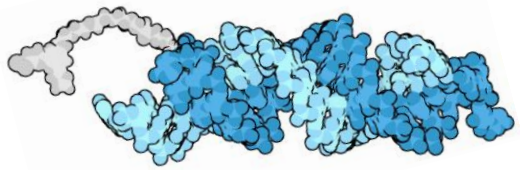



# High-Yielding and Economical Conjugation Process

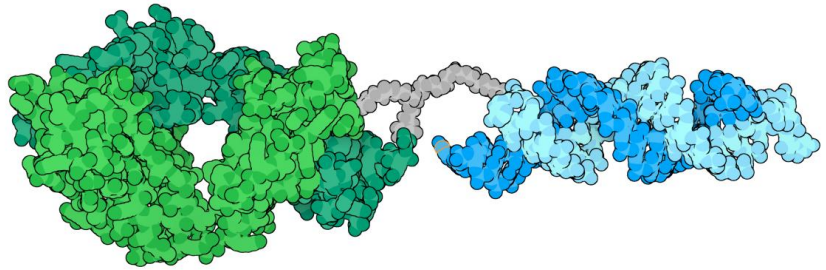


1 eq

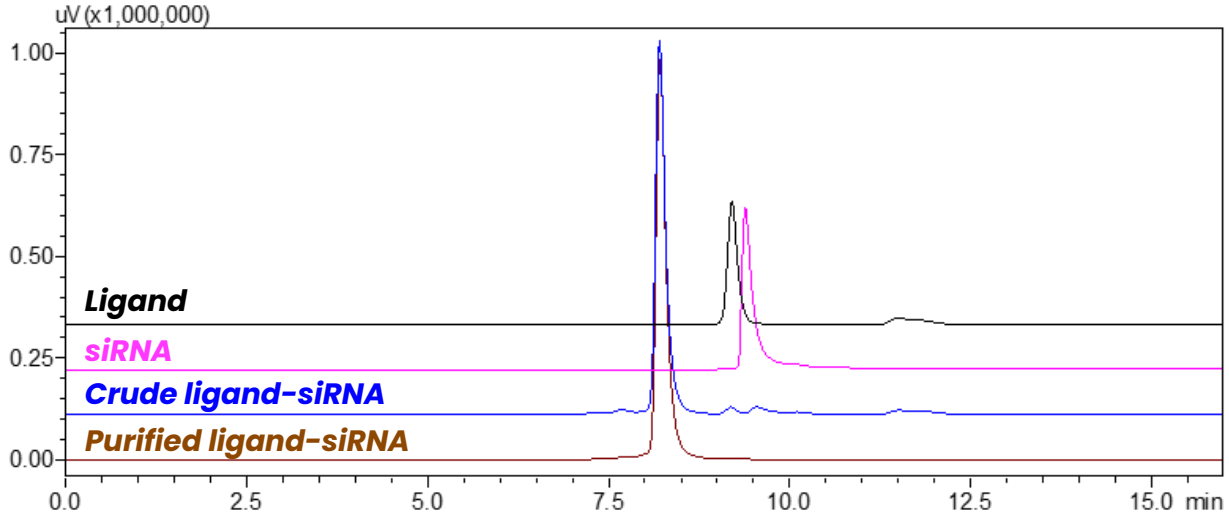
+



1.03 eq



75-80% total conjugation yield




- Economical process with equimolar amounts of ligand and oligo used in conjugation
- 75-80% yield achieved consistently at discovery stage at scale ranging from milligram to multi-gram

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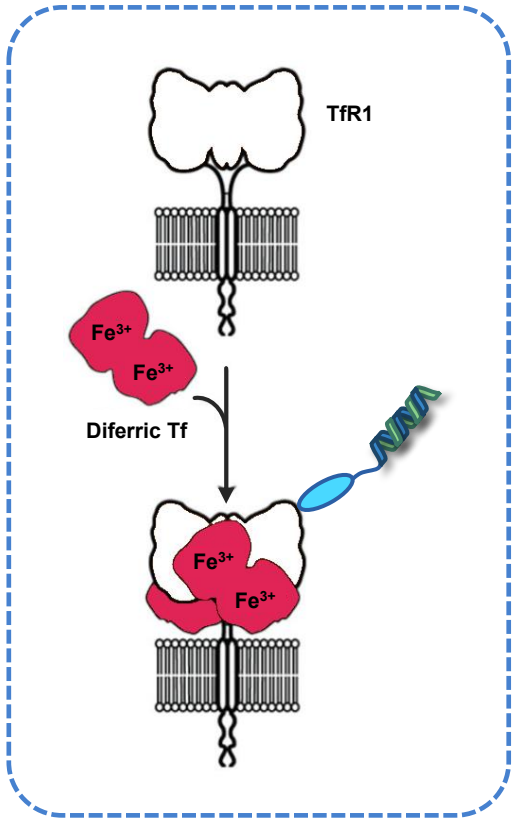
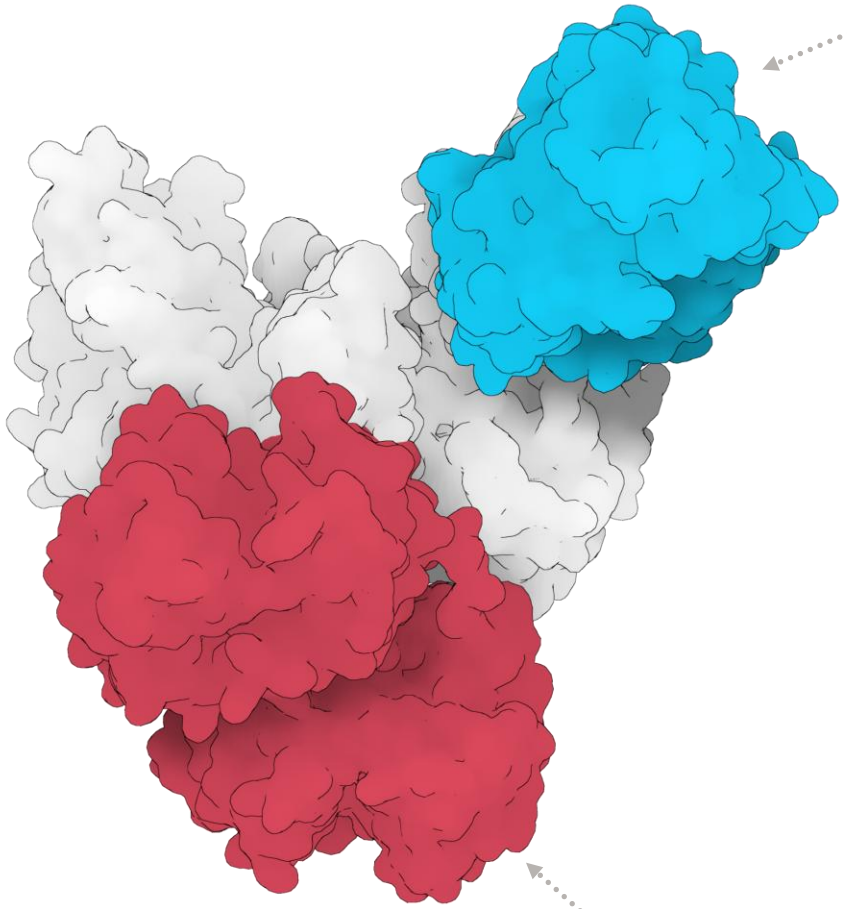
# TRiM™ BBB Platform Binds to Apical Domain of TfR1




- Cryo-EM structure comprising TRiM™ BBB ligand, human TfR, and endogenous Tf, shows apical domain binding
- TRiM™ BBB ligand does not interfere with endogenous Tf binding

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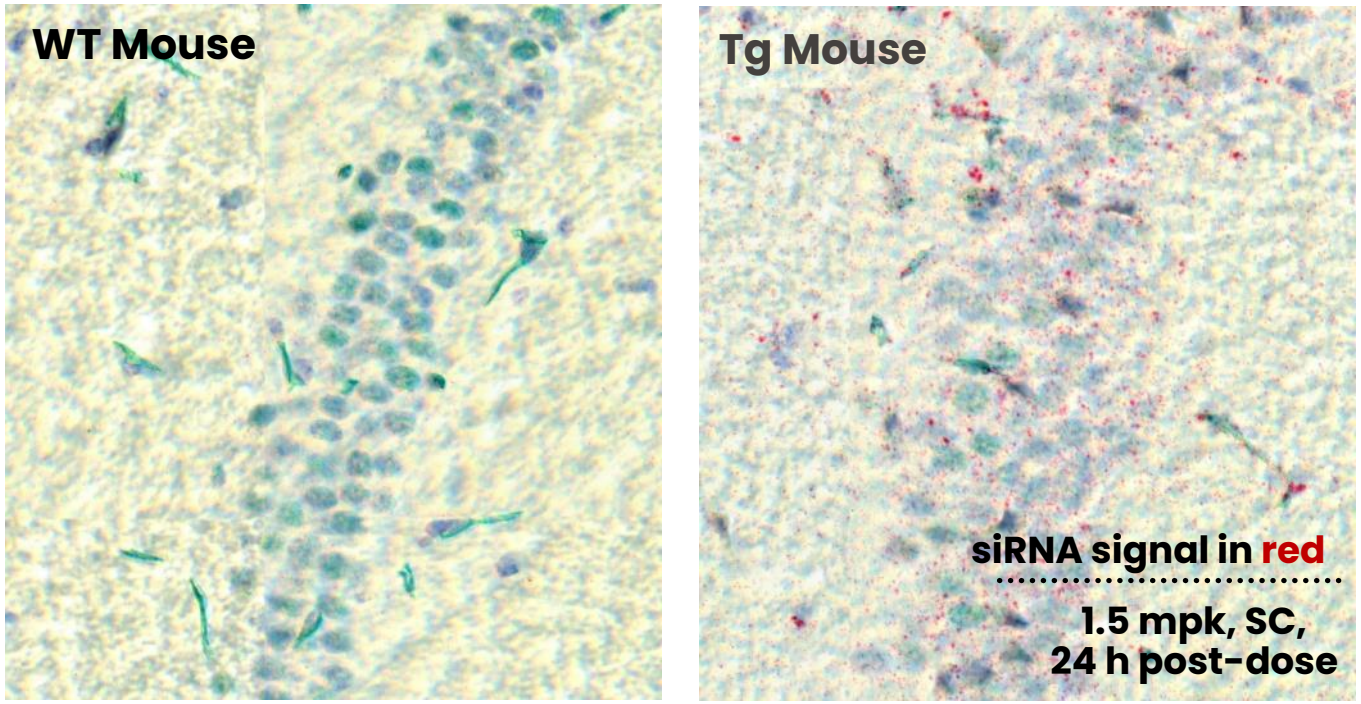
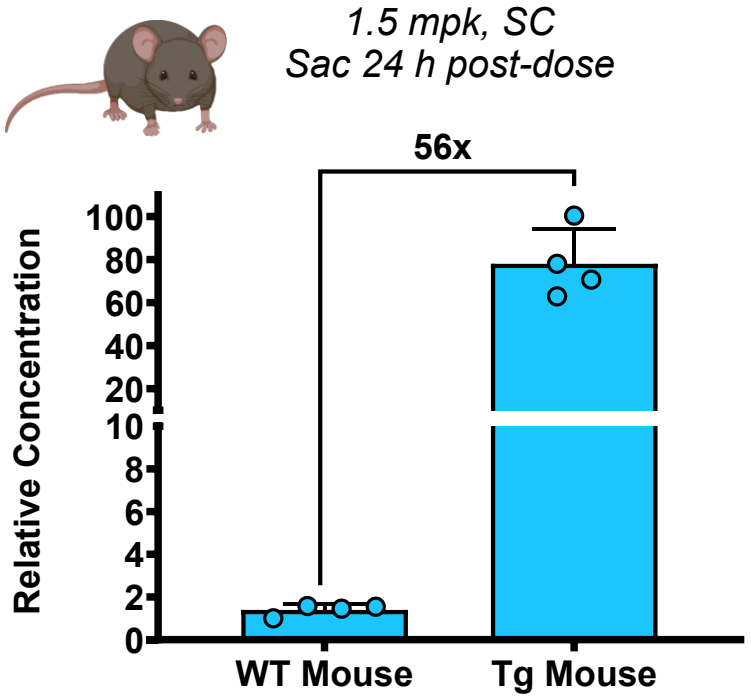
# BBB Platform Demonstrated to Cross BBB in hTfR Tg Mouse

## siRNA Delivery in Hippocampus




## siRNA Concentration in Half Brain




- TRiM™ BBB platform is human/cyno cross-reactive
- Delivery assessed in transgenic (Tg) mice expressing human Transferrin receptor
- siRNA quantitation shows over 50x difference between Tg and control group

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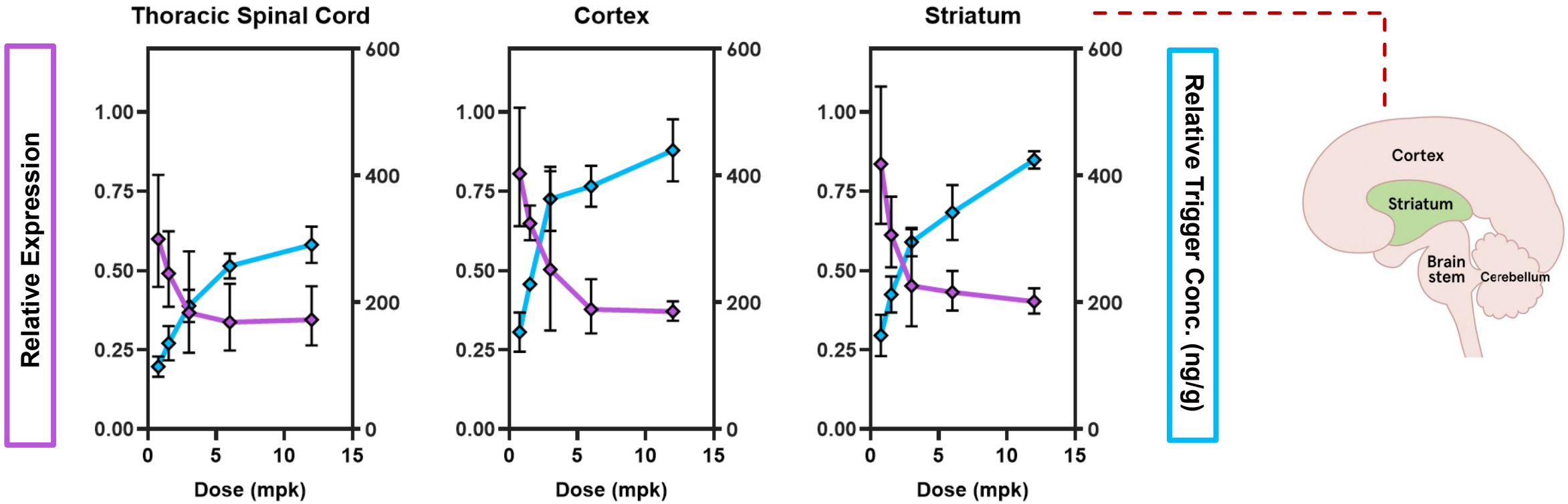
# BBB Platform Displays Dose-Dependent Delivery and mRNA Target Engagement in Mouse CNS

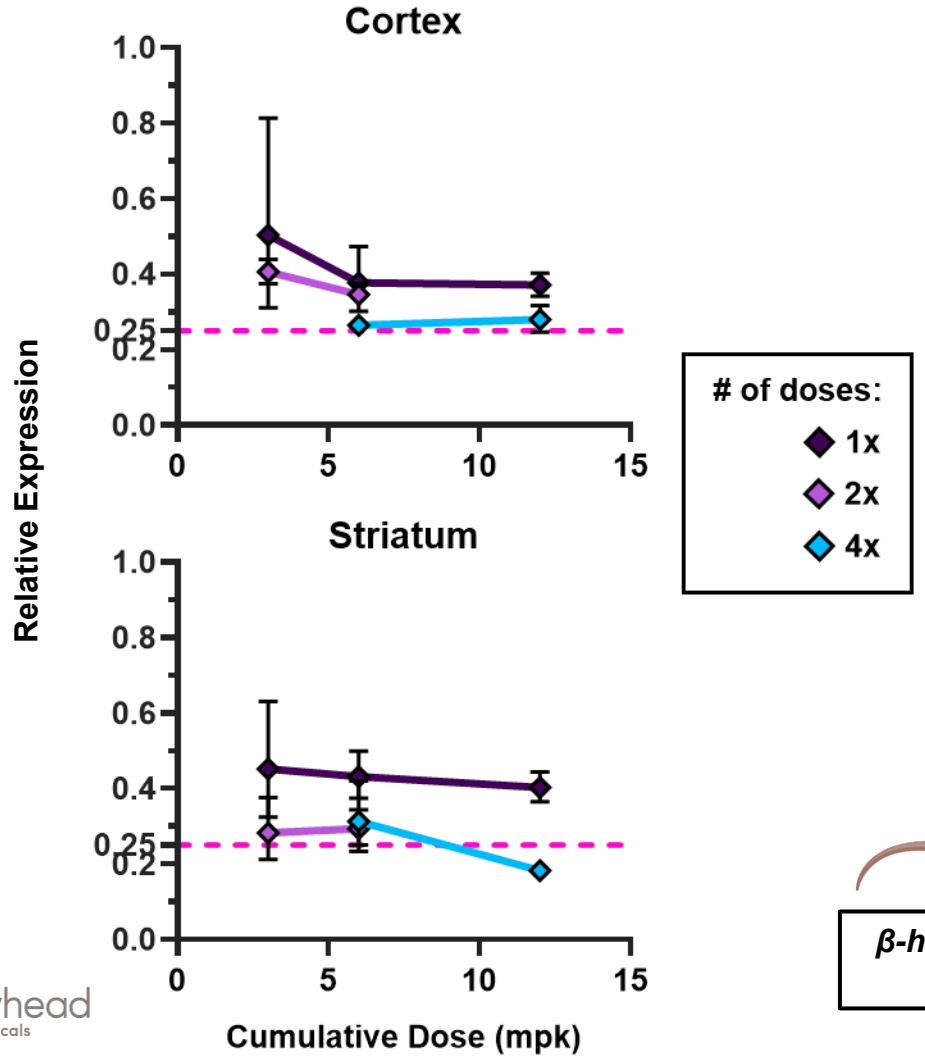
## Single Dose Response Effect on Target mRNA Reduction by CNS Region




*Tg Mouse: single SC dose, D15*

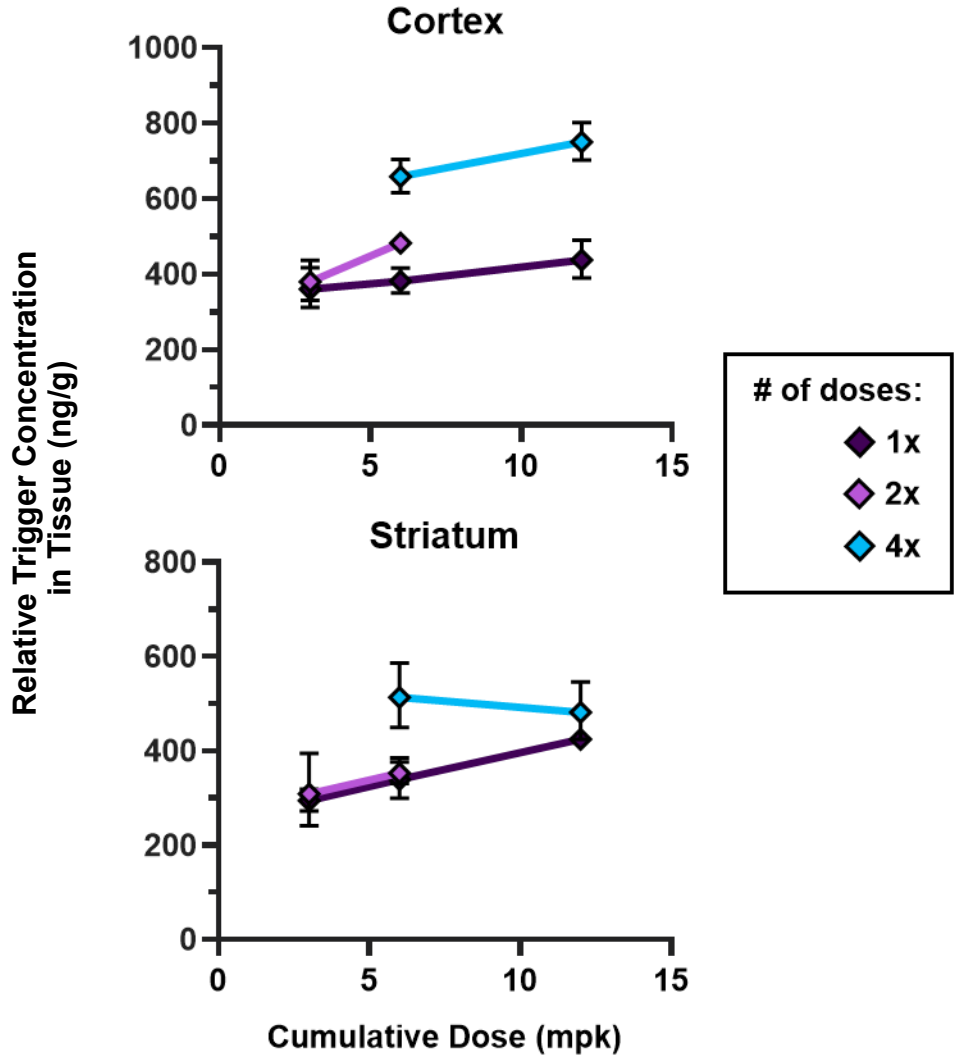
# Subcutaneous Multi-Dosing Paradigm Enables Clinically Relevant Efficacy

## Multi-Dose Effect on Target mRNA Reduction




*β-hTfR1 mouse, Day 15*

## Multi-Dose Effect on Delivery

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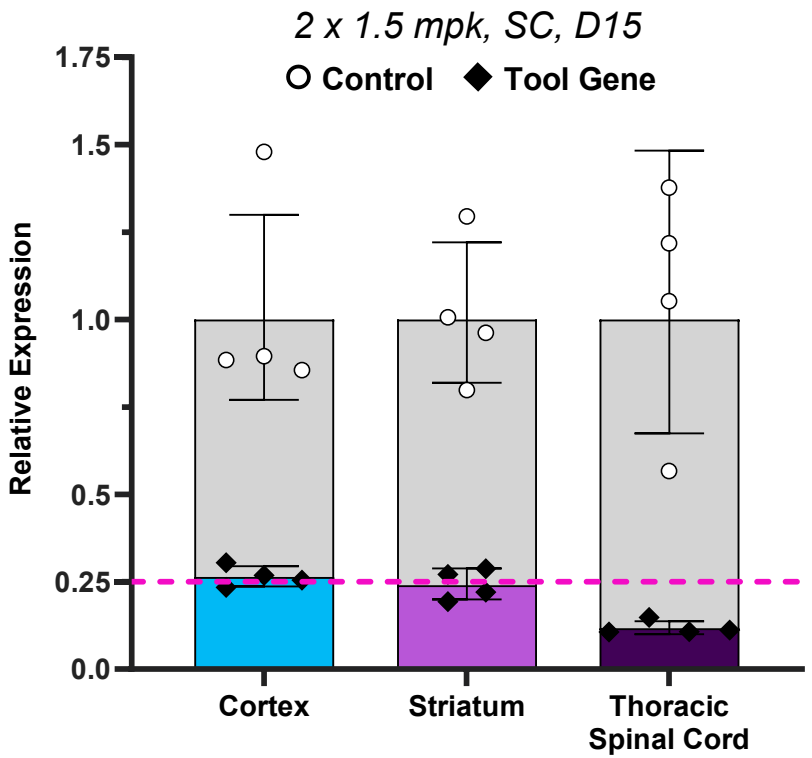
# BBB Platform Achieves Improved Knockdown via Multi-Dosing

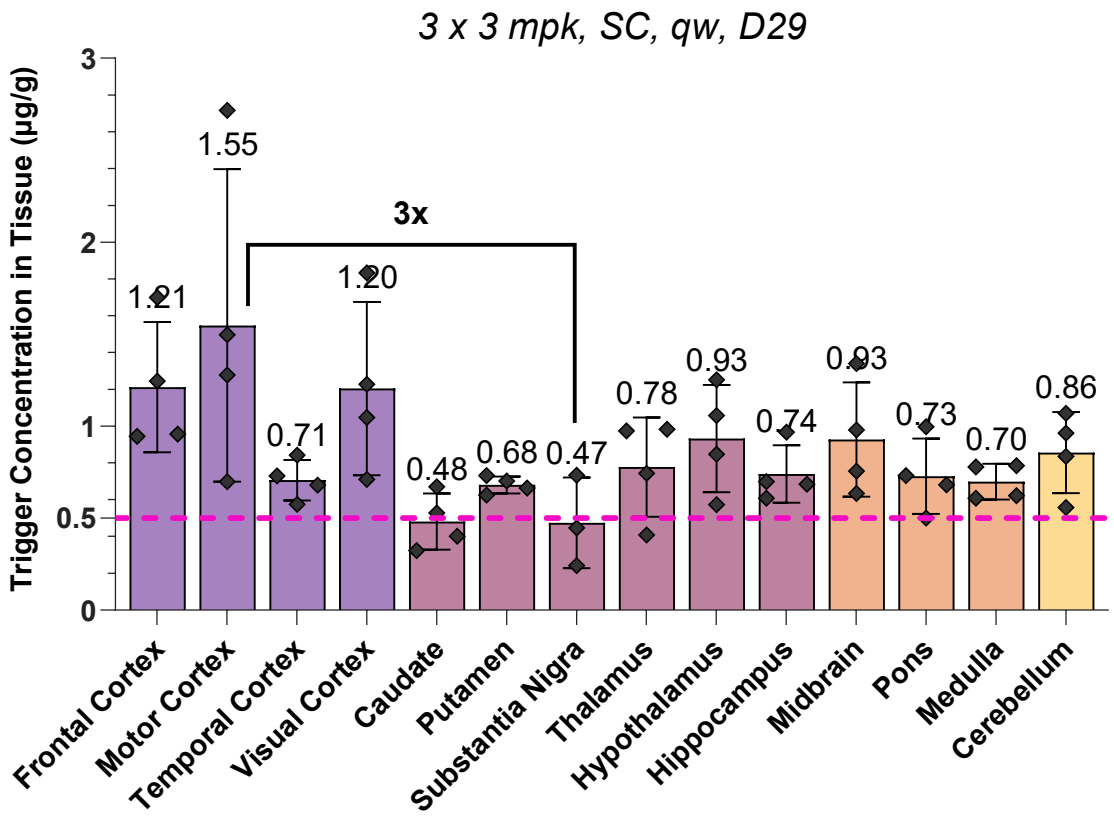
## Multi-Dose Effect on Target Engagement




- Two doses of 1.5 mpk achieved ≥75% KD across CNS regions including deep brain

# TRiM™ BBB Conjugates Effectively Deliver siRNA to CNS Tissue in NHP

## Trigger Accumulation in NHP Brain Regions




- ✓ Therapeutically relevant siRNA accumulation in the brain
- ✓ Relatively even distribution across all regions
- ✓ Overcomes IT limitation in deep brain delivery
- ✓ 0.5-1.5 µg/g across the brain on day 29

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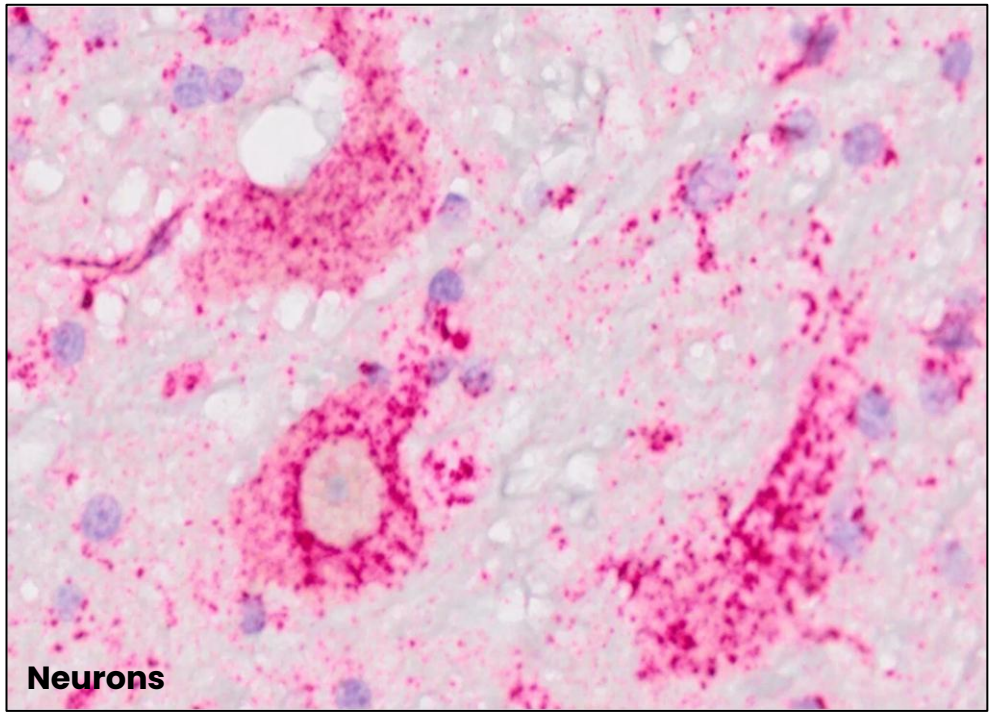
# TRiM™ BBB Achieves Efficient Delivery to Deep Brain Neuronal Cells in NHP

## Trigger Accumulation in Deep Brain Neurons in NHP

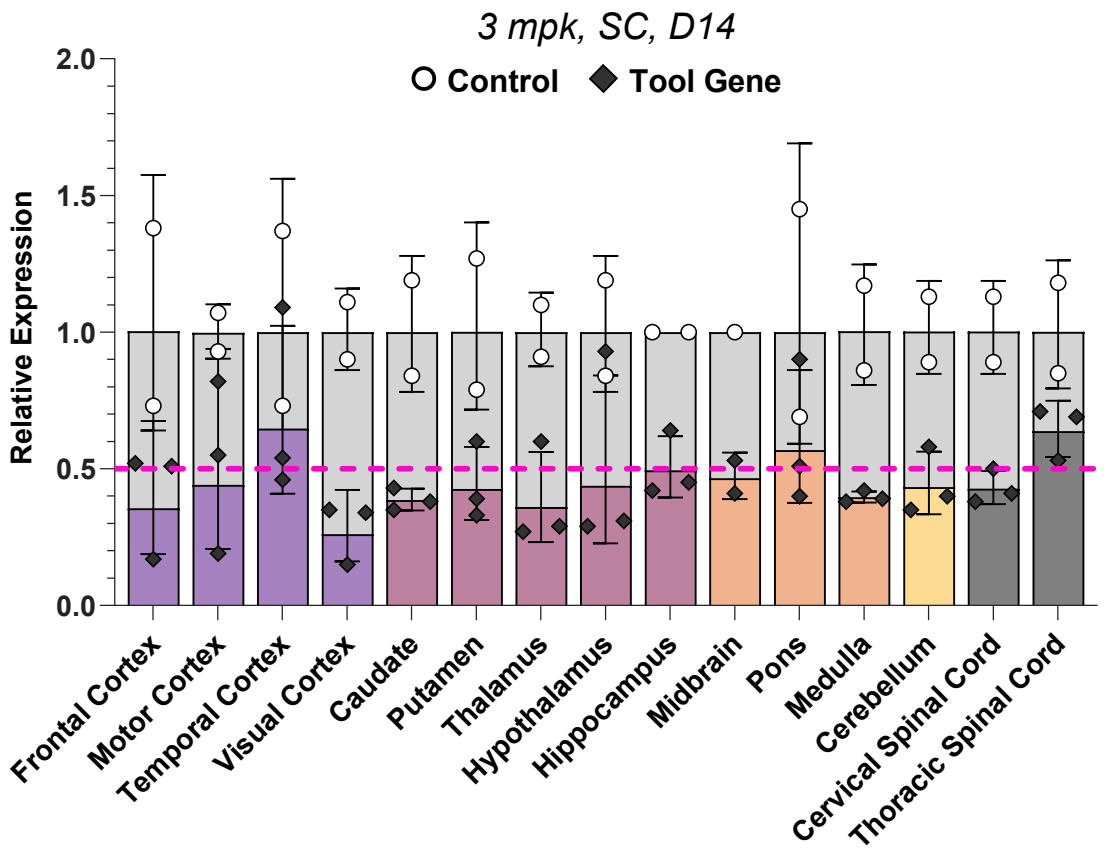



*siRNA shown in pink*

- 1 x 6 mpk, SC, D15
- Notable deep brain neuronal accumulation after single 6 mpk dose in NHP

# TRiM™ BBB Platform Achieves Efficacious Target Engagement in NHP

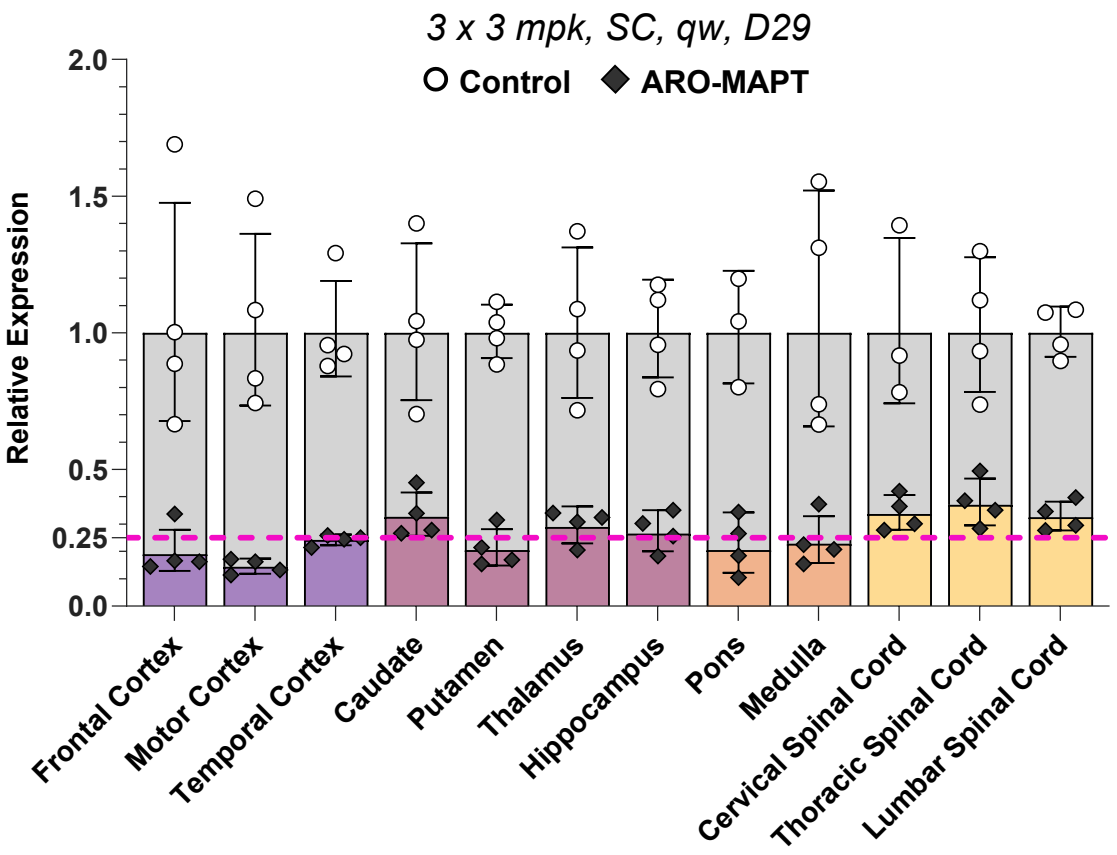
## Tool Gene mRNA Reduction in CNS Regions




- Greater than 50% mRNA reduction across brain regions at single 3 mpk dose
- Up to 75% knockdown

# ARO-MAPT Achieves Deep Knockdown of MAPT mRNA Throughout the CNS with Subcutaneous Administration

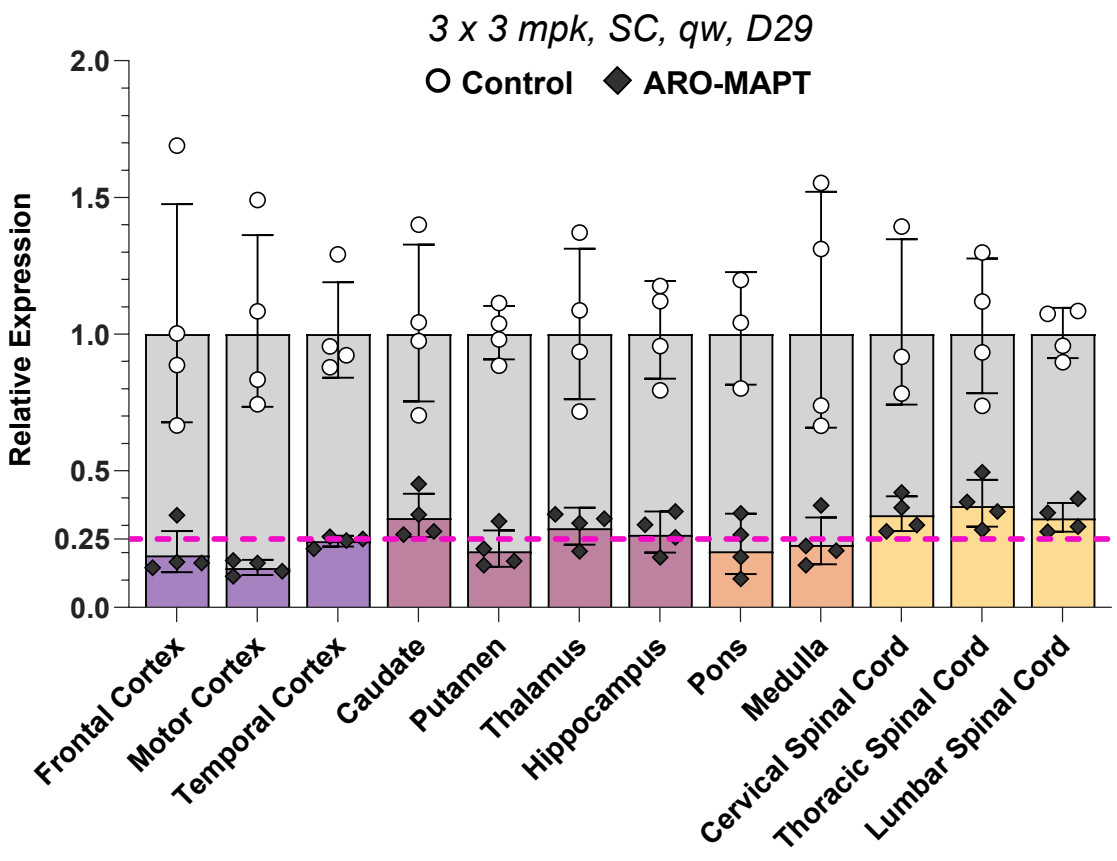
## MAPT mRNA Reduction in NHP CNS Regions



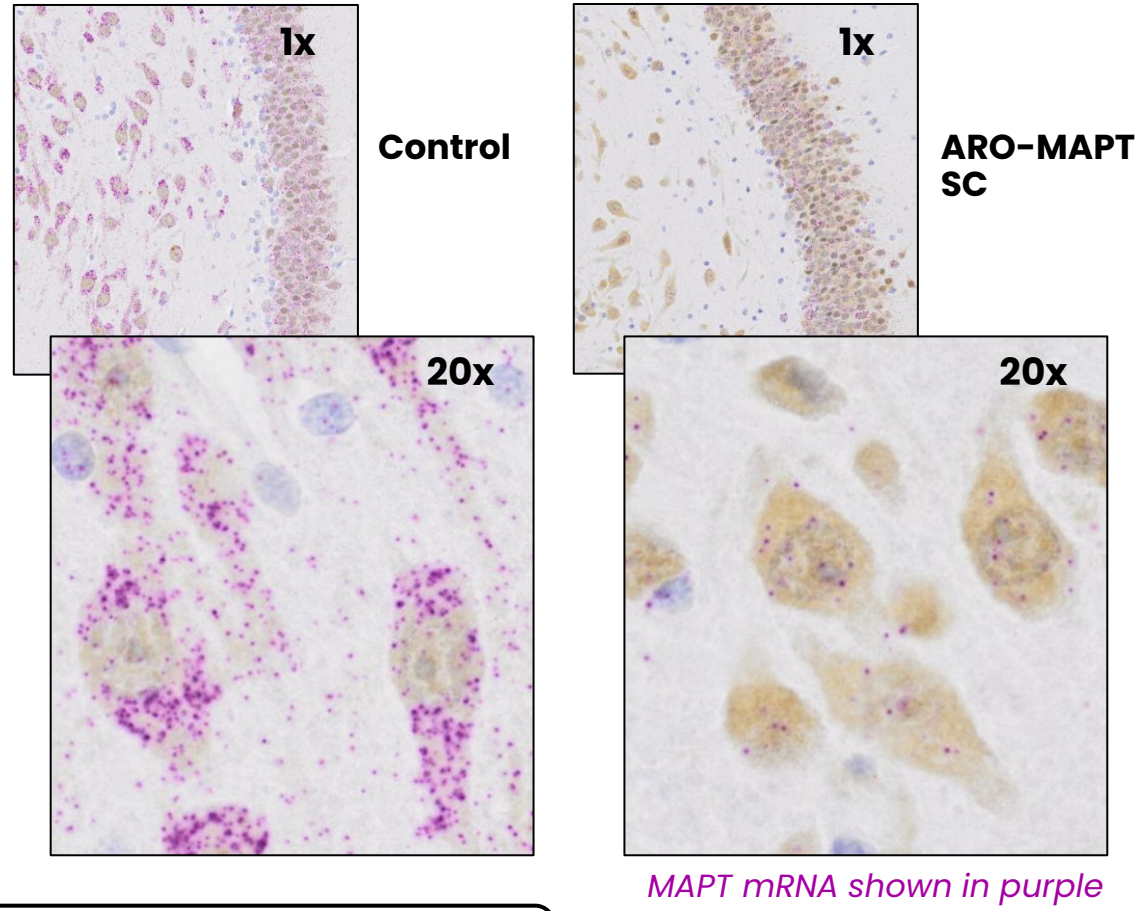

- At 3 x 3 mpk, 70-80% MAPT mRNA reduction was achieved across all brain regions, including brain stem and deep brain
- Up to 85% knockdown in some cortex regions

# ARO-MAPT Achieves Deep Knockdown of MAPT mRNA Throughout the CNS with Subcutaneous Administration

## MAPT mRNA Reduction in NHP CNS Regions




## MAPT mRNA Depletion in Hippocampus




*MAPT mRNA shown in purple*

- mRNA knockdown corroborated by tissue-staining

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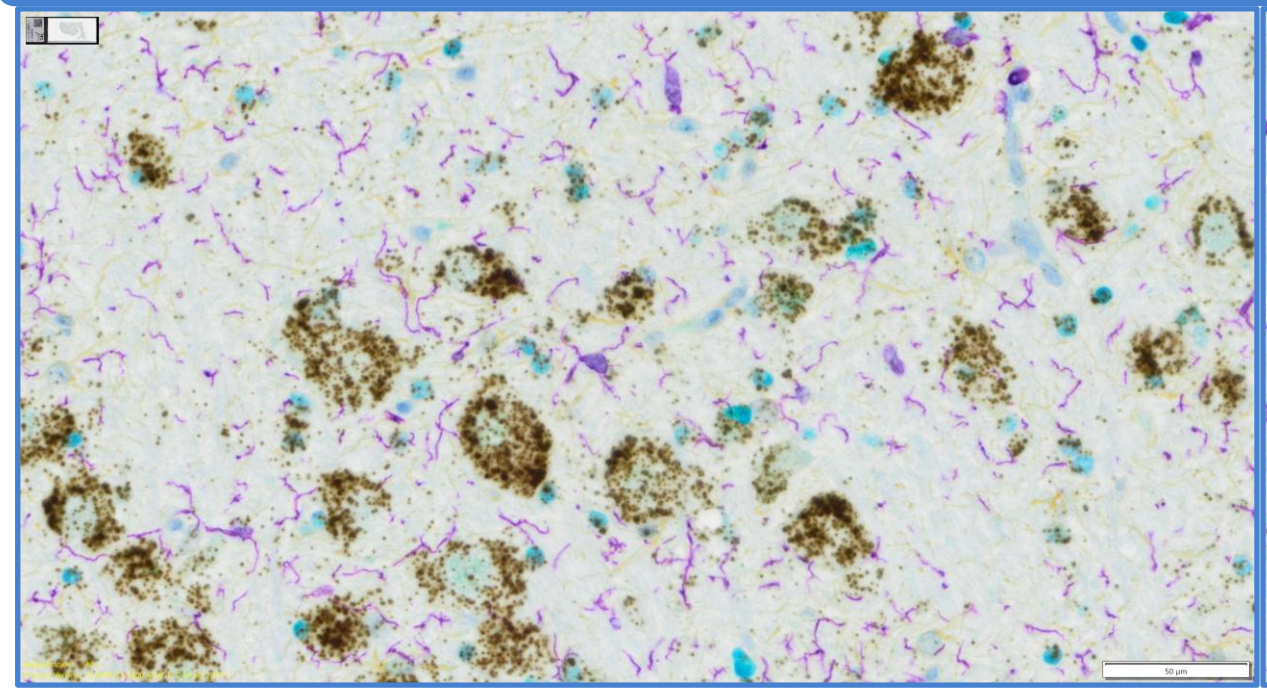
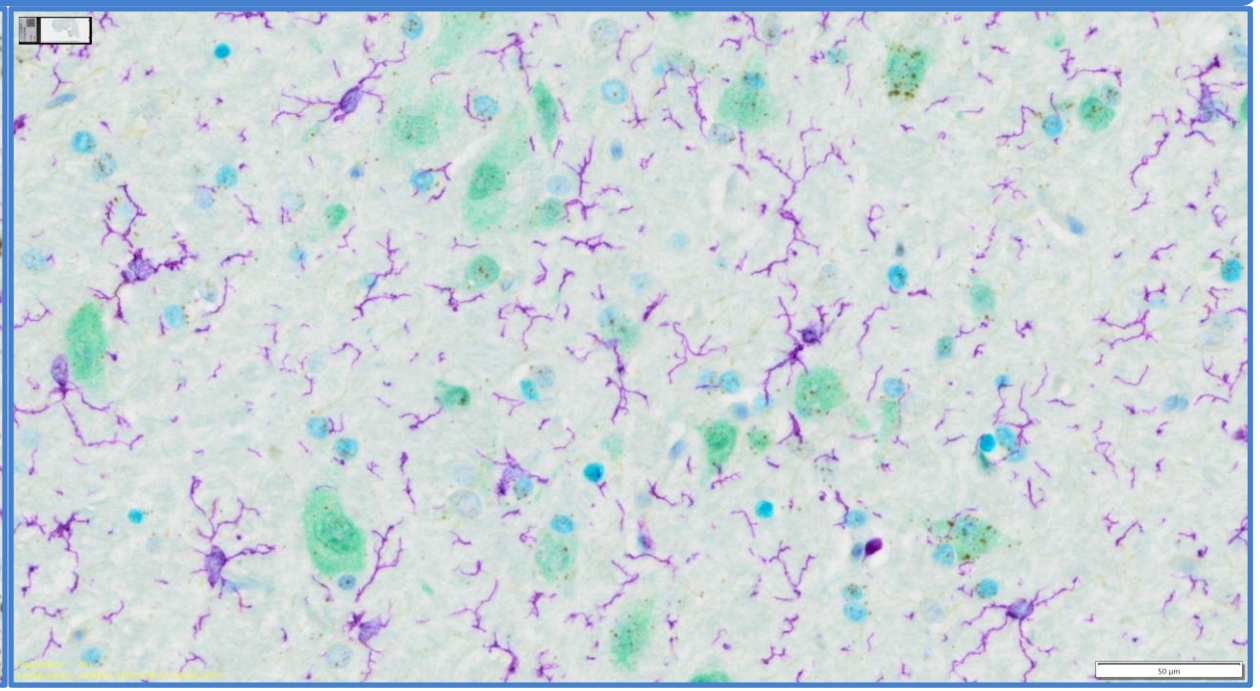
# ARO-MAPT Achieves Great Target mRNA Reduction Across All Major CNS Cell Types

RNAscope™ Detection of MAPT mRNA with Multiplex Cell-Type IHC in NHP Brainstem



***Control***



***ARO-MAPT dosed 3 x 3 mpk, SC, D29***

- **MAPT: brown puncta**
- **Neurons: green**
- **Astrocytes: yellow**
- **Microglia: purple**
- **Oligodendrocytes: teal**

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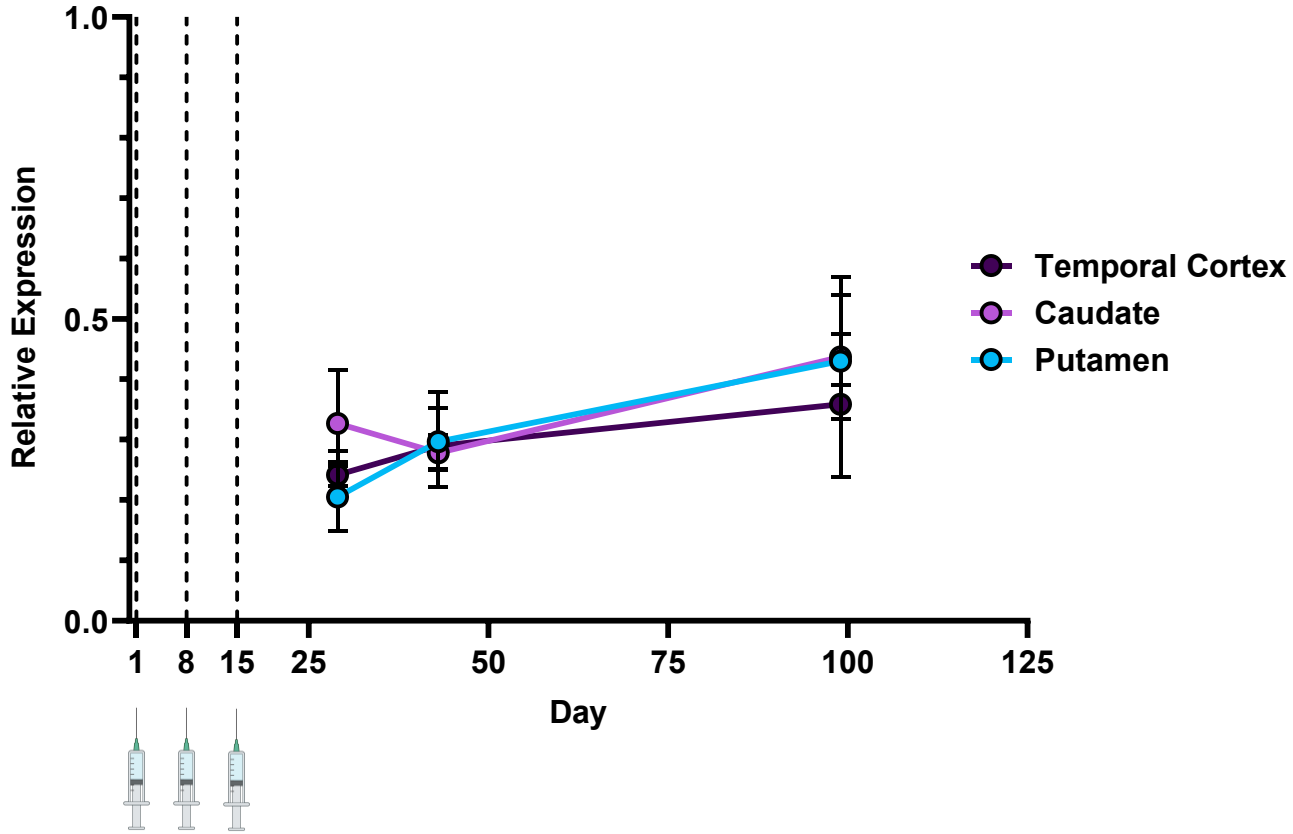
# ARO-MAPT Maintains 3 Months of Durable Knockdown Throughout CNS Regions in NHP

## Duration of MAPT mRNA Reduction in CNS

*3 x 3 mpk, SC, qw*




Days: 1, 8, 15; N=4

- Durable target engagement with ≥50% knockdown over 3 months in CNS regions including deep brain

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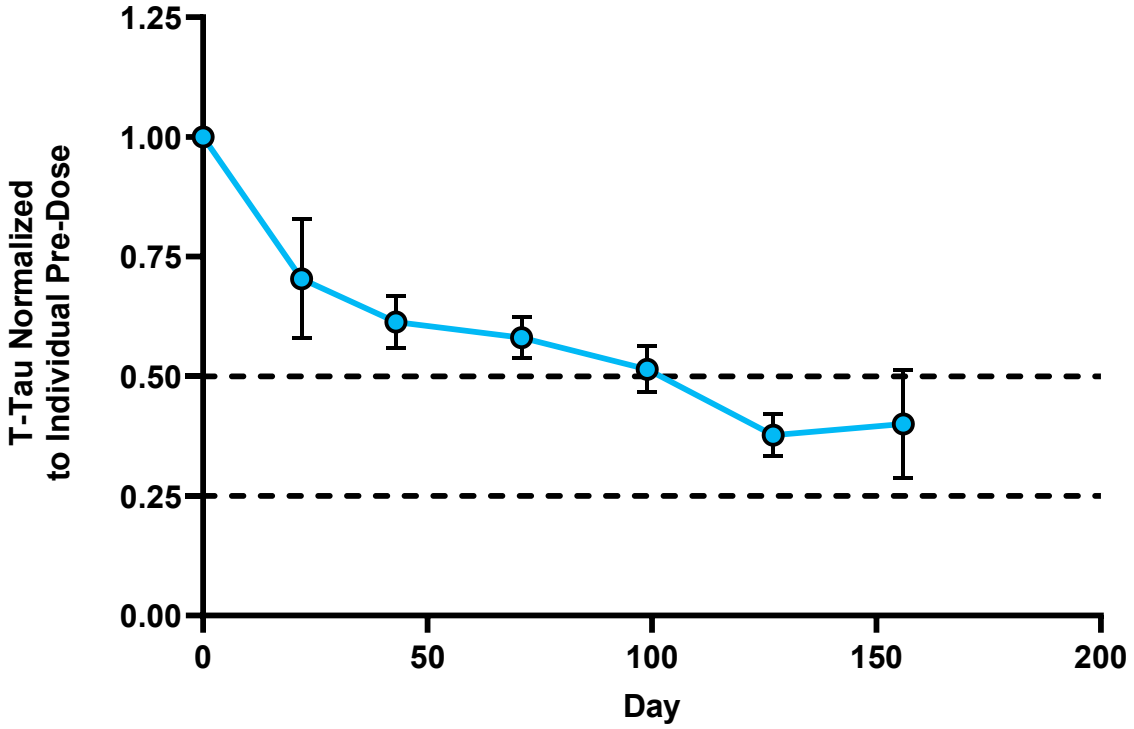
# ARO-MAPT Achieved 50-60% Total-Tau Reduction in CSF in NHP

## T-Tau Levels in CSF

*Dosed 3 mpk, SC*
*on D1, 8, 15, 26, 71, 99, and 127*




*N=1 to 5 at each timepoint*

- Tau protein reduction maintained at 50-60% up to 5 months with single 3 mpk monthly dose

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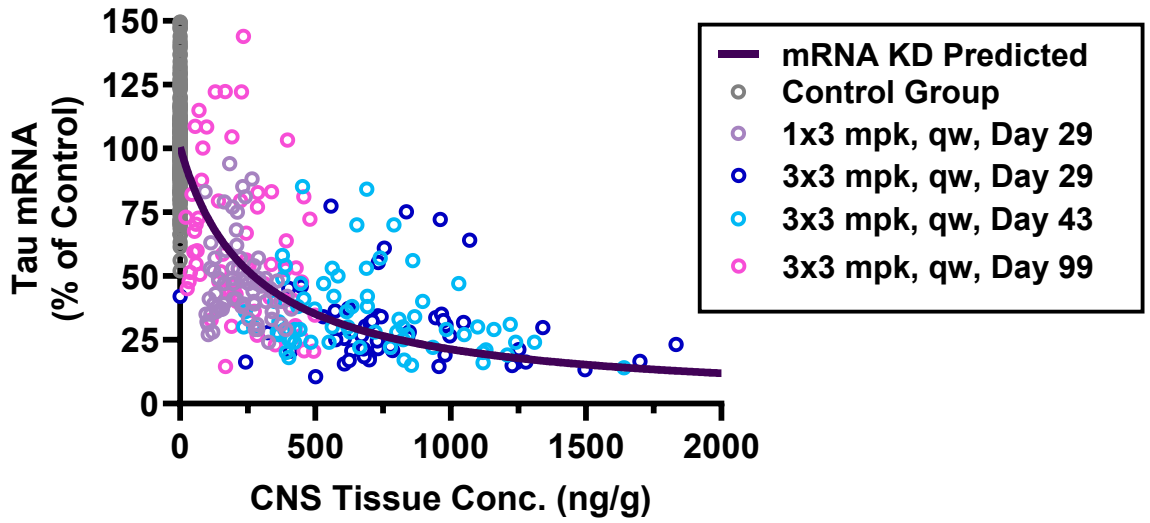
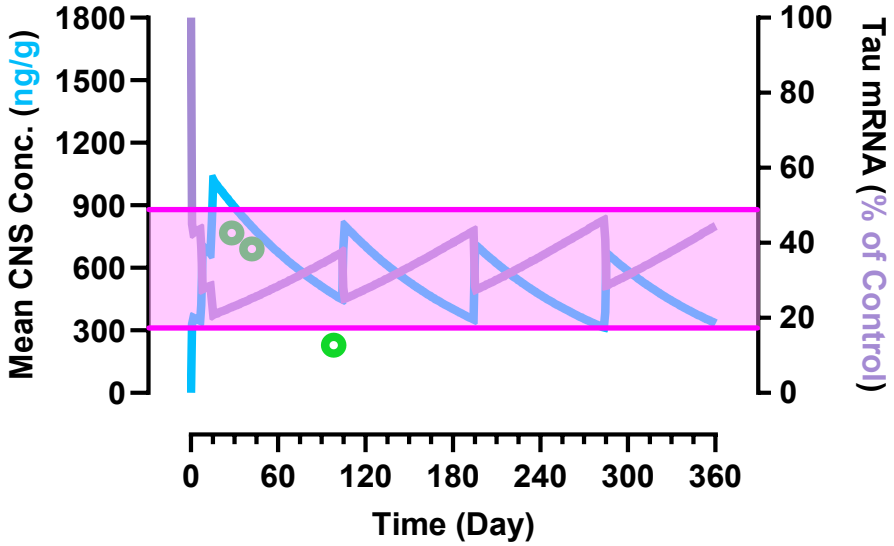
# PK/PD Modeling Projects Sustained Tau Inhibition with Quarterly Dosing of ARO-MAPT

## NHP Tissue Conc. vs Tau mRNA Level




## Projection of ARO-MAPT PK/PD with Quarterly Dosing




- PK/PD profile in NHP
- Monthly booster after initial 3 x 3 mpk weekly dose projected to maintain 80% KD
- Quarterly dosing projected to maintain 50-70% knockdown

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# ARO-MAPT Profile

| Productive Delivery Across BBB | Efficacy & Activity Profile in NHP | Duration & Dosing Schedule | Formulation | Safety Profile |
|---|---|---|---|---|
| | | | | |

# ARO-MAPT Profile

| Productive Delivery Across BBB | Efficacy & Activity Profile in NHP | Duration & Dosing Schedule | Formulation | Safety Profile |
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|  | | | | |

- siRNA delivery demonstrated by tissue-staining & quantitation
- Productive delivery shown by target reduction

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- Deep and durable target reduction across CNS regions
- Limited target engagement in peripheral tissues

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|---|---|---|---|---|
| ✓ | ✓ | ✓ | | |

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- Deep and durable target reduction across CNS regions
- Limited target engagement in peripheral tissues

- Duration of target reduction ≥ 3 months
- Duration supports monthly-to-quarterly dosing regimen

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| ✓ | ✓ | ✓ | ✓ | |

- siRNA delivery demonstrated by tissue-staining & quantitation
- Productive delivery shown by target reduction

- Deep and durable target reduction across CNS regions
- Limited target engagement in peripheral tissues

- Duration of target reduction ≥ 3 months
- Duration supports monthly-to-quarterly dosing regimen

- Formulation capacity enables 150 mg of siRNA in ≤ 4 mL total volume
- Formulation supports SC administration in human

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# ARO-MAPT Profile

| Productive Delivery Across BBB | Efficacy & Activity Profile in NHP | Duration & Dosing Schedule | Formulation | Safety Profile |
|---|---|---|---|---|
| ✓ | ✓ | ✓ | ✓ | ✓ |
| ➢ siRNA delivery demonstrated by tissue-staining & quantitation<br>➢ Productive delivery shown by target reduction | ➢ Deep and durable target reduction across CNS regions<br>➢ Limited target engagement in peripheral tissues | ➢ Duration of target reduction ≥ 3 months<br>➢ Duration supports monthly-to-quarterly dosing regimen | ➢ Formulation capacity enables 150 mg of siRNA in ≤ 4 mL total volume<br>➢ Formulation supports SC administration in human | ➢ Exploratory tox: safety profile in rodent and NHP at >10x margin over efficacious dose |

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|---|---|---|---|---|
| ✓ | ✓ | ✓ | ✓ | ✓ |
| ➢ siRNA delivery demonstrated by tissue-staining & quantitation<br>➢ Productive delivery shown by target reduction | ➢ Deep and durable target reduction across CNS regions<br>➢ Limited target engagement in peripheral tissues | ➢ Duration of target reduction ≥ 3 months<br>➢ Duration supports monthly-to-quarterly dosing regimen | ➢ Formulation capacity enables 150 mg of siRNA in ≤ 4 mL total volume<br>➢ Formulation supports SC administration in human | ➢ Exploratory tox: safety profile in rodent and NHP at >10x margin over efficacious dose<br>➢ **CTA filed** |

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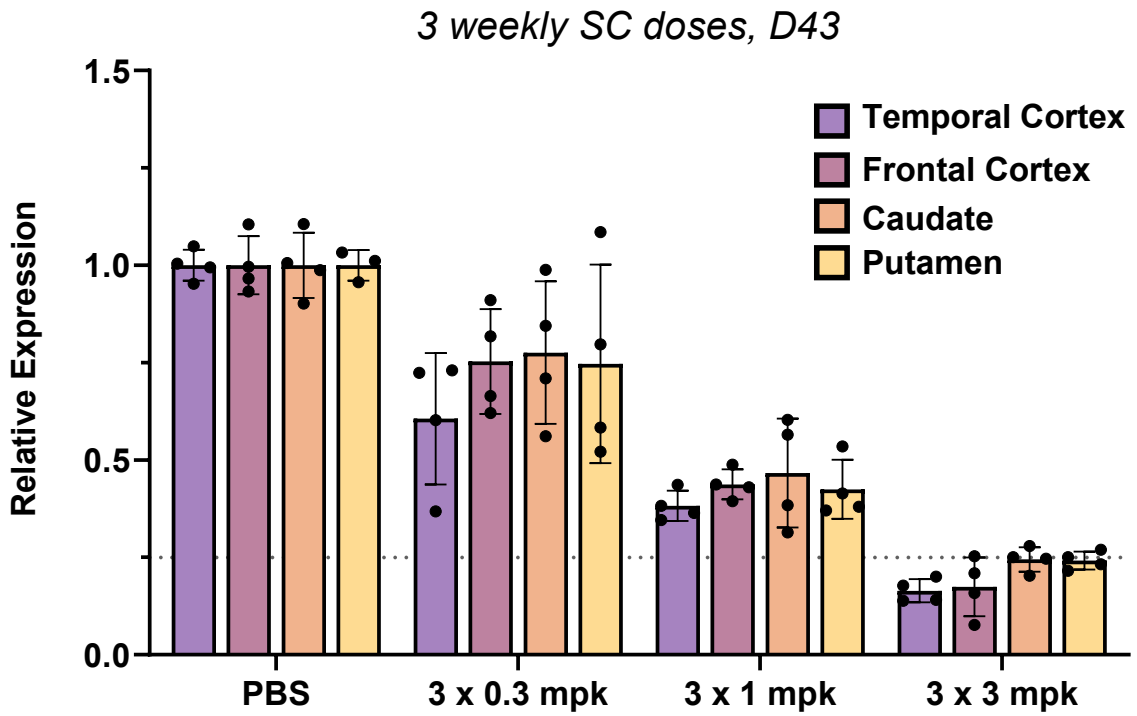
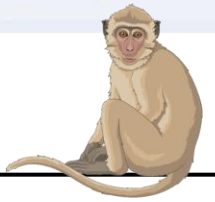
# ARO-HTT Achieves >75% Htt Protein Reduction Throughout NHP Brain Regions

## Htt Protein in NHP Brain Regions



**ARO-HTT SC:**

- Effectively targets deep brain regions important for Huntington's disease pathogenesis
- Targets both mutant and wildtype HTT mRNA
- Partnered with Sarepta Therapeutics

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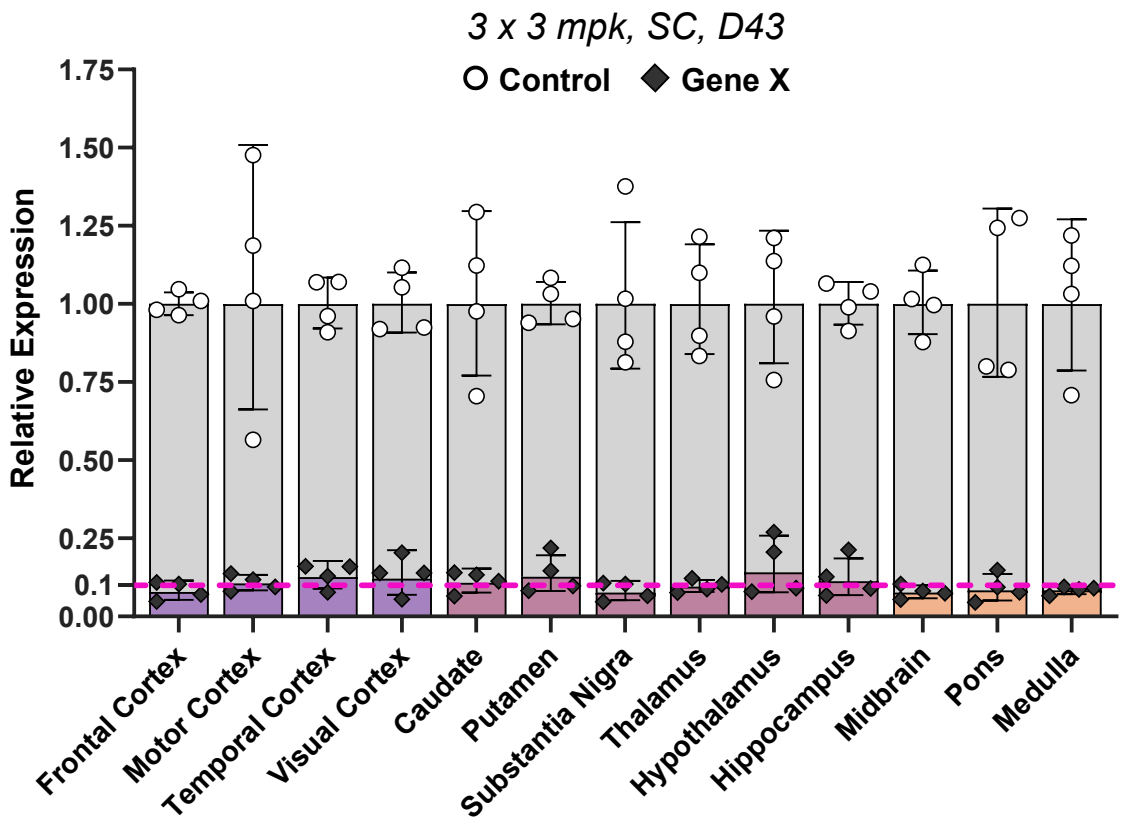
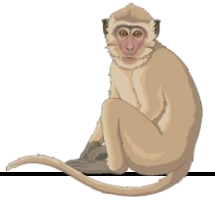
# TRiM™ BBB Platform Achieves ~90% KD Across the Brain for a New Cardiometabolic Target

## Target X mRNA Reduction in NHP Brain Regions



- ~90% target mRNA knockdown achieved across all brain regions for a new cardiometabolic target

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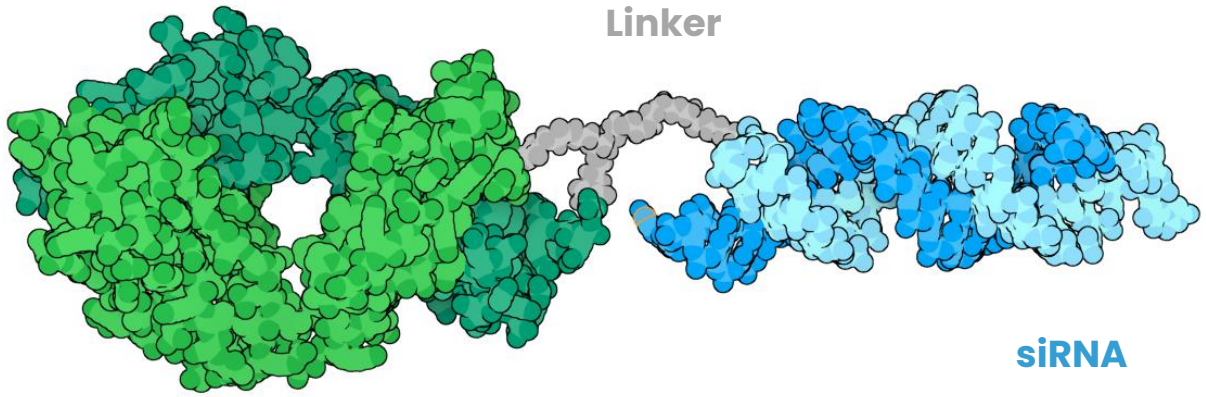
# TRiM™ BBB Platform via Subcutaneous Administration




**We Have Developed an Optimized Systemic Delivery Platform for CNS**

- ✓ **Ligand-driven** delivery via noninvasive BBB penetration and cellular uptake in brain tissue
- ✓ **Effective** and durable reduction in expression levels of therapeutically relevant gene targets
- ✓ **Convenient** dosing via subcutaneous (SC) administration with potential for monthly to quarterly dosing
- ✓ **Favorable** safety profile in rodent and NHP >10x margin over efficacious dose

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# Thank you!



Questions?

Answers.

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