Systemic RNAi Targeting MAPT: Advancing Tau Suppression Across the CNS with TRiM™ SC

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TIDES USA 2026

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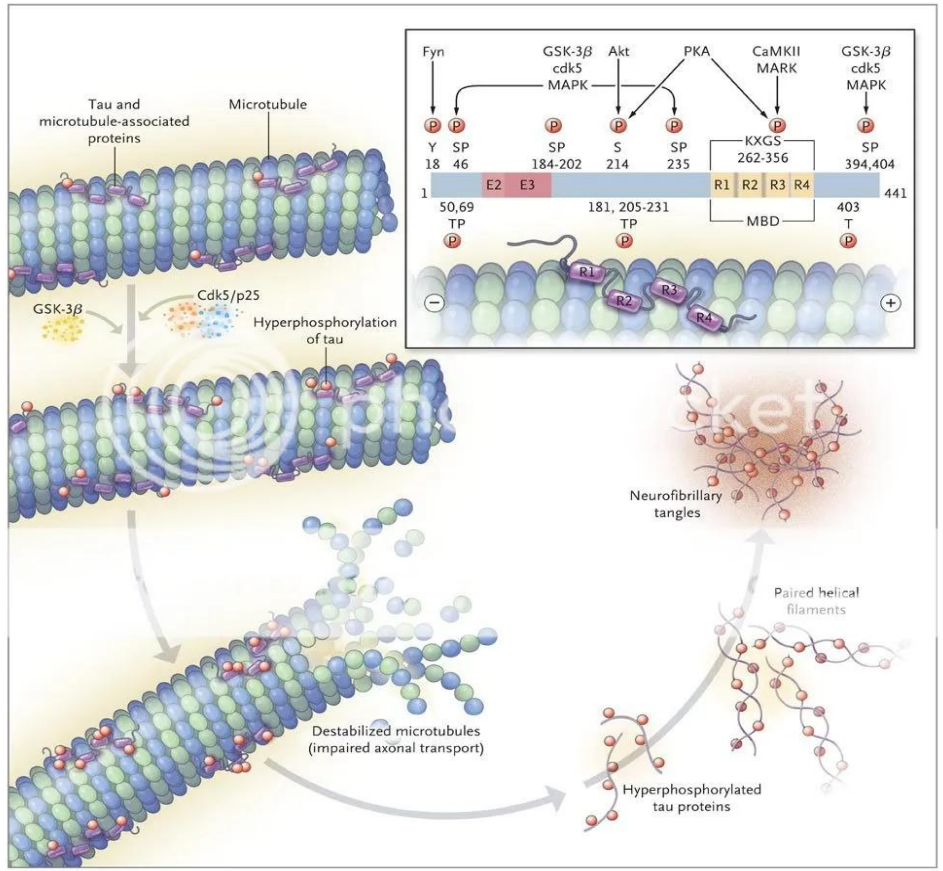
Toxic MAPT/Tau protein aggregation: Key driver in Tauopathies including Alzheimer's Disease

Microtubule-associated protein tau (MAPT) gene encodes tau protein:

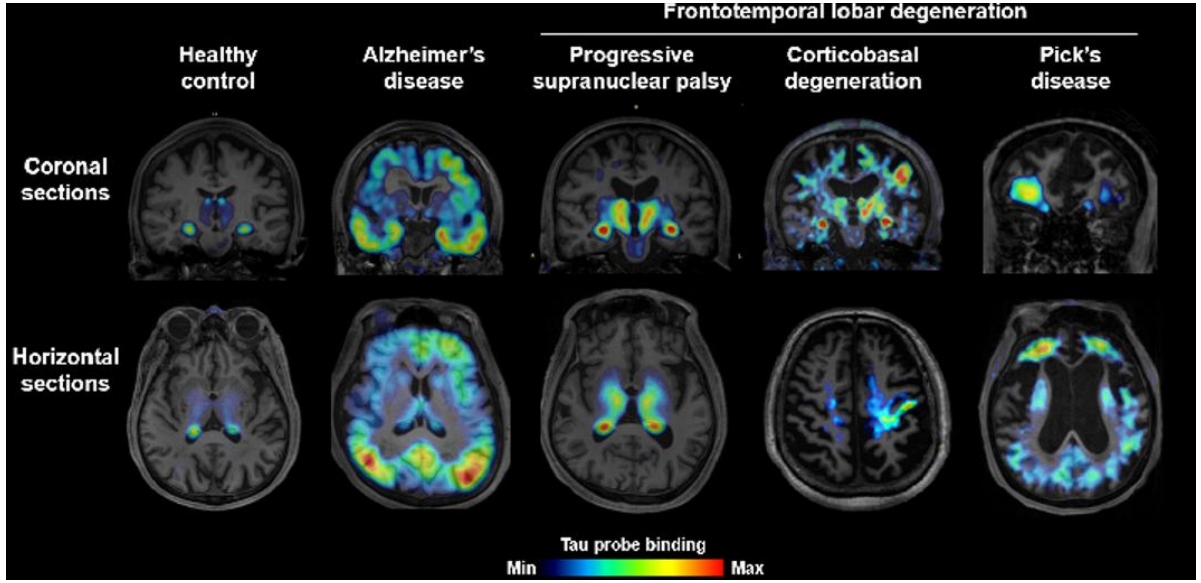
- Abundant in neurons of CNS, less in astrocytes and oligodendrocytes
- Promotes stabilization of microtubules in axons
- Intrinsically disordered and subject to many post-translational modifications
- Hyperphosphorylation promotes intracellular formation of neurofibrillary tangles which are correlated with neurodegeneration



Querfurth & LaFerla, N Engl J Med, 2010

Tauopathies: A spectrum from Common to Rare

- Heterogeneous group of ~20 neurodegenerative diseases characterized by abnormal intracellular deposition of tau in neurons and glial cells
- Further classified by the relative balance of 3R & 4R tau isoforms found in pathological inclusions and morphological/ ultrastructural features of inclusions.
- Major tauopathies:
  - Alzheimer's disease (>7M in U.S.)
  - Frontotemporal lobar degeneration dementia (FTLD) associated with Tau (~25-30K)
    - Progressive supranuclear palsy (PSP) (~20K)
    - Familial FTLD-MAPT due to MAPT mutation (1-5K)



Adapted from Tagai et al., Neuron, 2021.

A single siRNA targeting MAPT has the potential to address all these diseases.

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Tau Pathology Correlates with Cognitive Decline in Alzheimer's Disease

- Amyloid cascade hypothesis is:

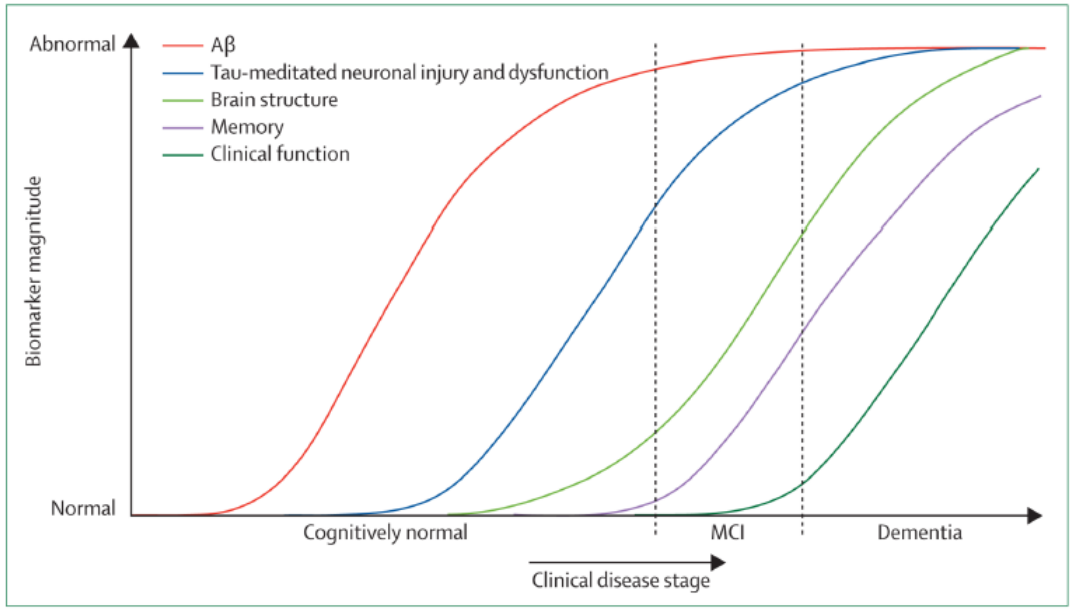
  amyloid plaque → Tau tangles → cognitive decline

- Tau neurofibrillary tangle pathology but not amyloid predicts cognitive decline

- Anti-amyloid therapies have shown no Tau reduction, are less effective in patients with high Tau burden, and have significant safety risks

- Tau reduction has potential for benefit in broader patient population with better safety profile

Amyloid plaque precedes Tau pathology



Jack et al., Lancet Neurol, 2010.

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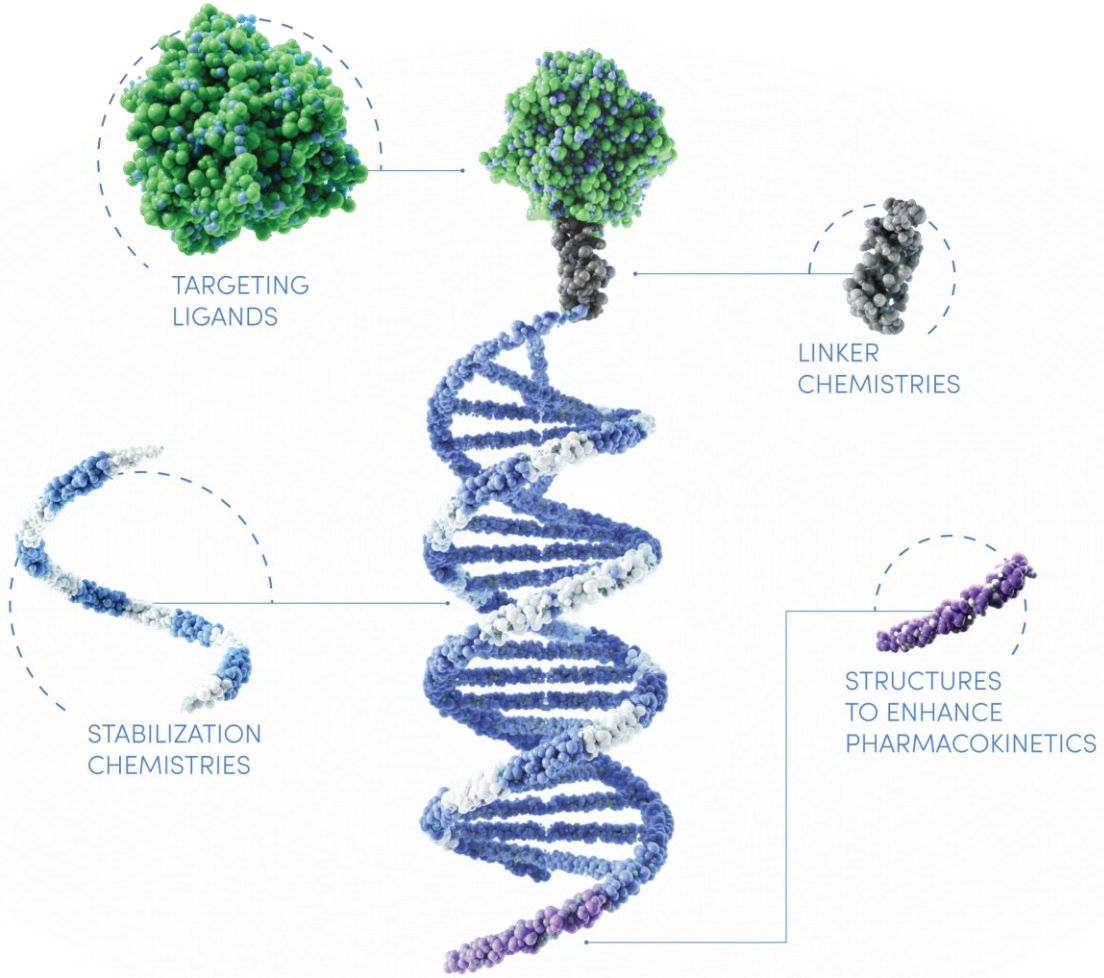
TRiM™ Platform: Targeted RNAi Molecule



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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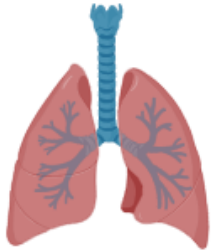
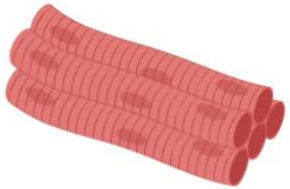
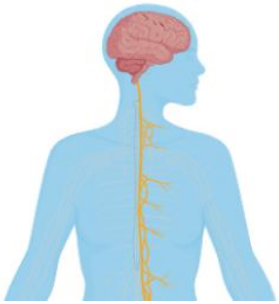
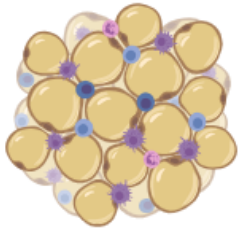
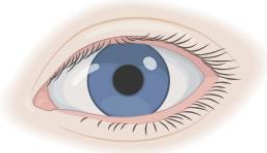
TRiM™ Platforms Drive Robust Pipeline for Multiple Tissue Types

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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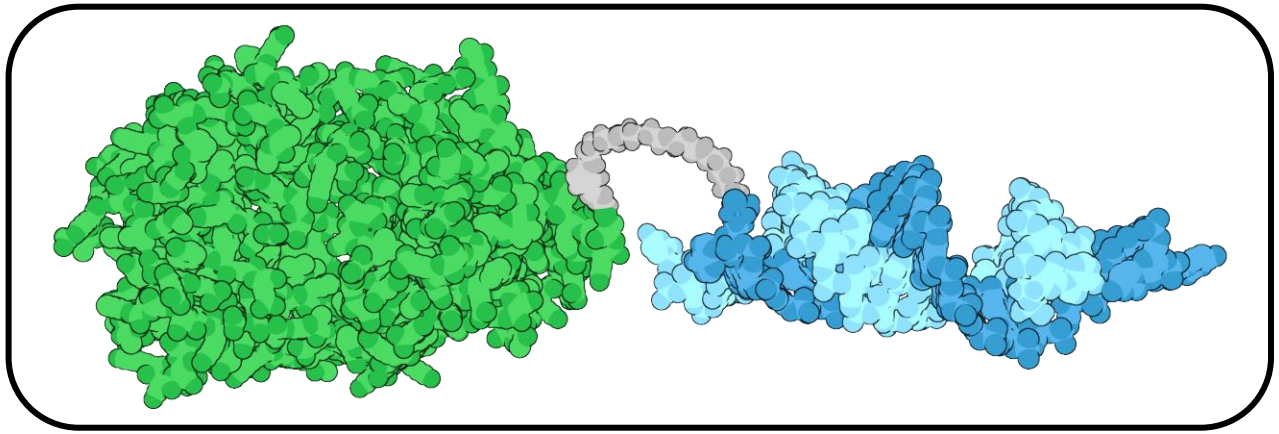
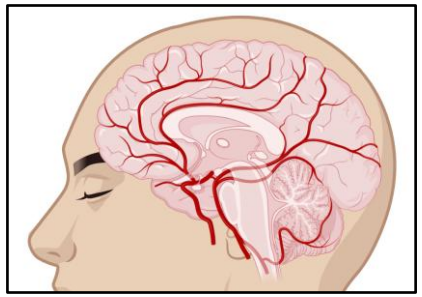
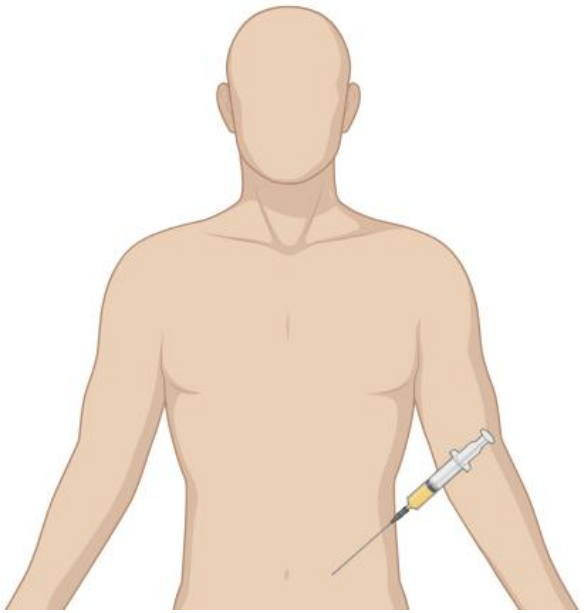
TRiM™ BBB Platform for siRNA Delivery to CNS

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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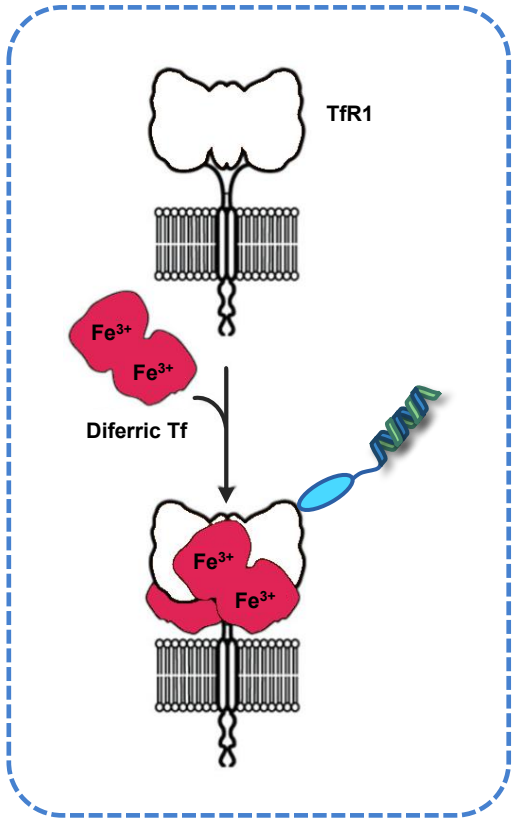
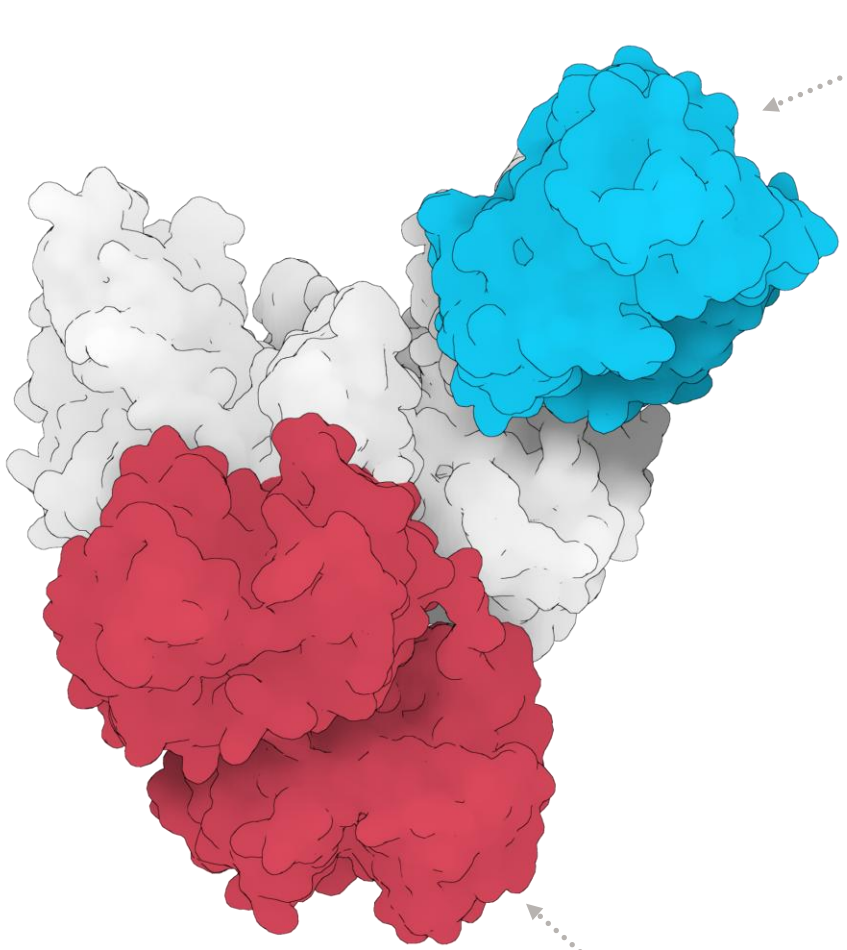
TRiM™ BBB Platform Binds to Apical Domain of TfR1





- 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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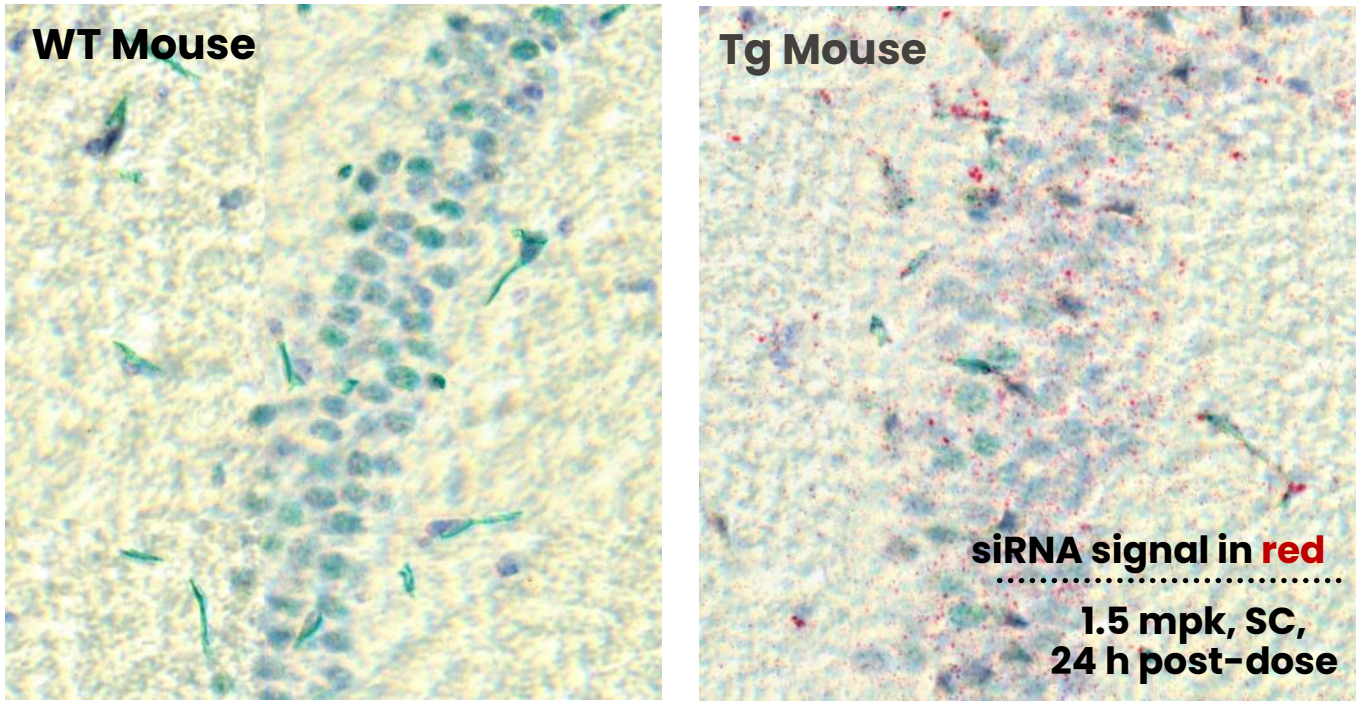
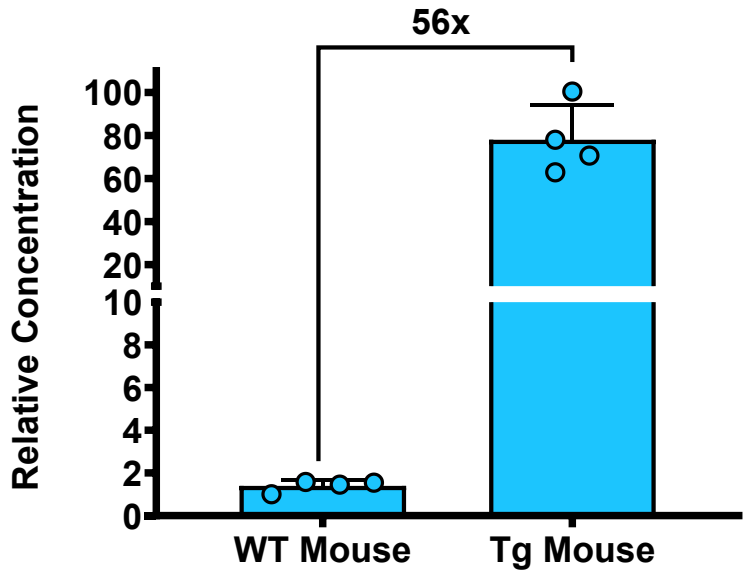
BBB Platform Demonstrated to Cross BBB in hTfR Tg Mouse

siRNA Delivery in Hippocampus



siRNA Concentration in Half Brain

1.5 mpk, SC
Sac 24 h post-dose



- 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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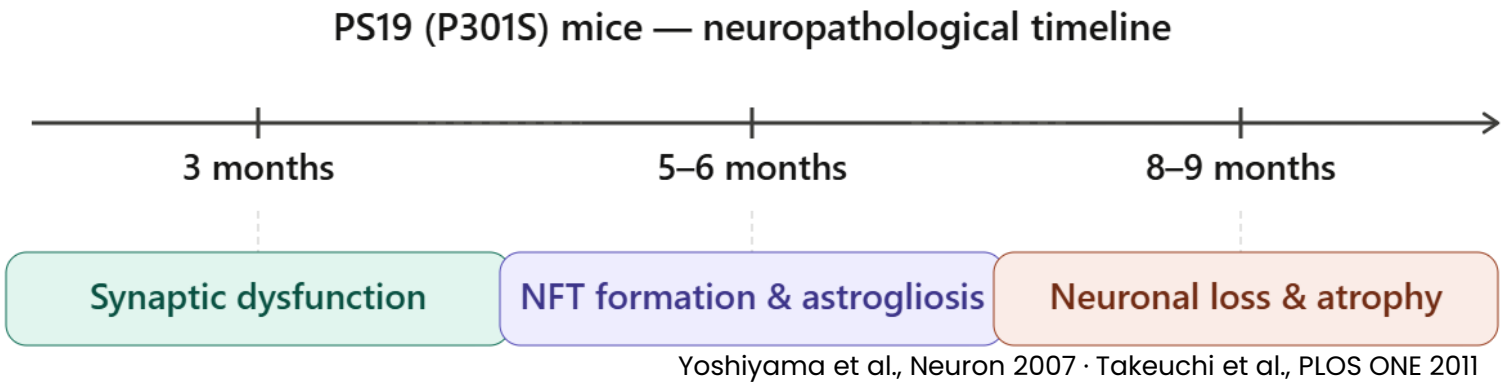
PS19 × hTFR1: A Tauopathy Model with Human TfR1-Mediated CNS Delivery

➢ PS19 mice express human P301S mutant tau:

- Develop progressive neurofibrillary tangle pathology from ~6 months.



Yoshiyama et al., Neuron 2007 · Takeuchi et al., PLOS ONE 2011

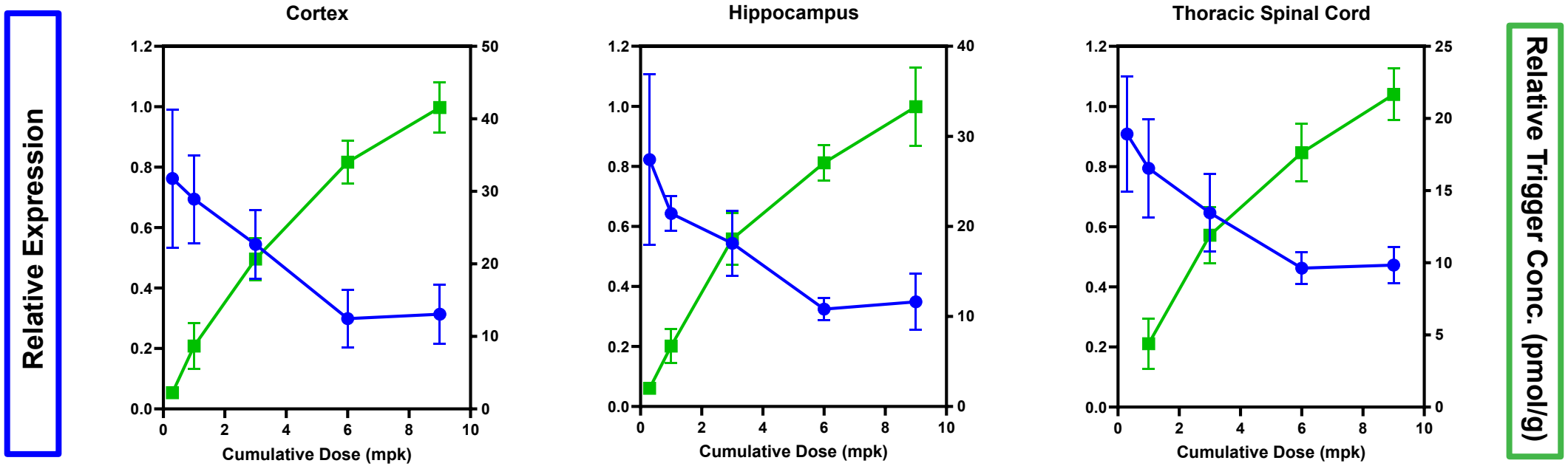
➢ Crossed with hTFR1 transgenic mice to enable TfR1-dependent siRNA delivery.

➢ Model allows assessment of both MAPT knockdown and reduction of pathological phospho-tau species in the same animal.

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

Dose Response Effect on MAPT mRNA Reduction by CNS Region

PS19 × hTFR1 tauopathy model: D15 post last-dose



Increasing siRNA tissue concentration drives proportional MAPT mRNA reduction across all CNS regions

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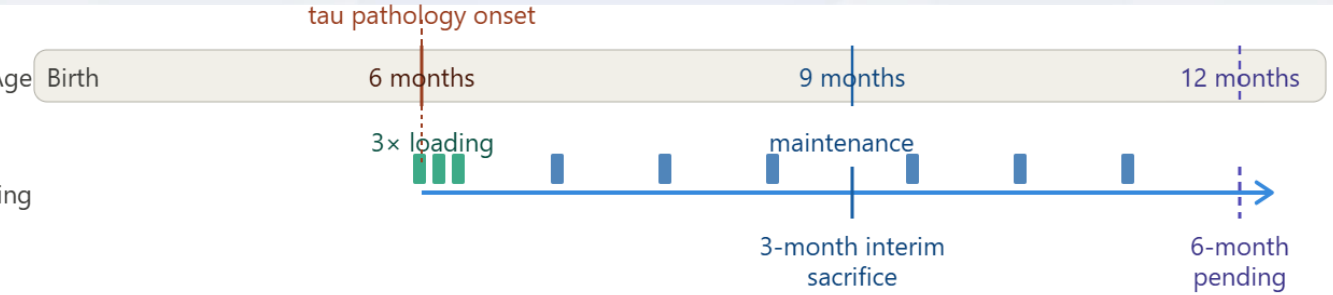
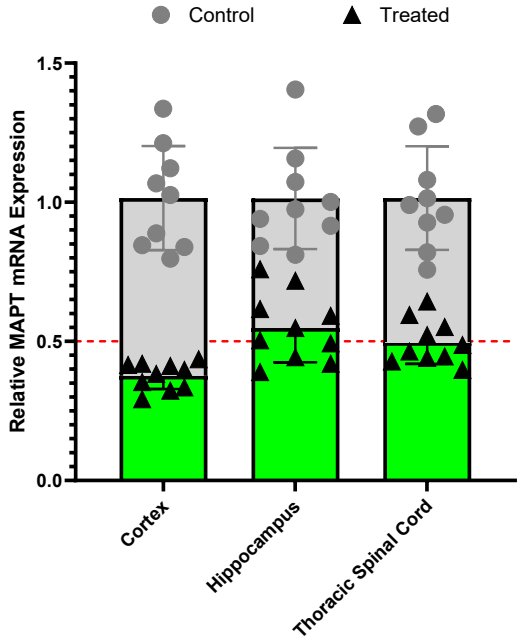
MAPT mRNA Knockdown Translates to Reduced AT8-Positive Tau Pathology

PS19 x hTfR1 mice:

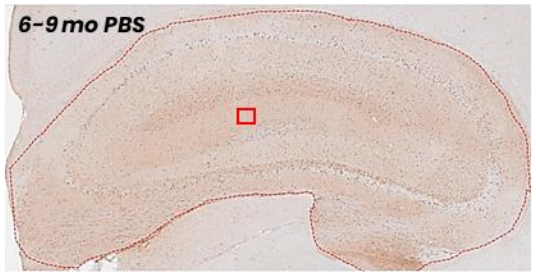


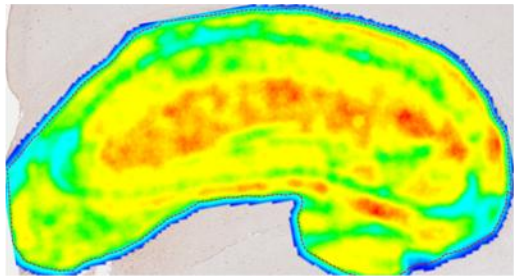
3mg/kg: Dosing

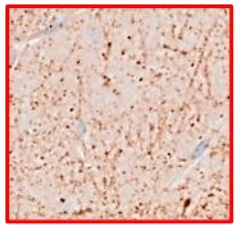
MAPT mRNA reduction

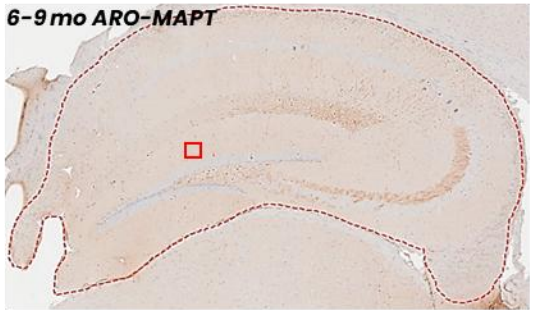


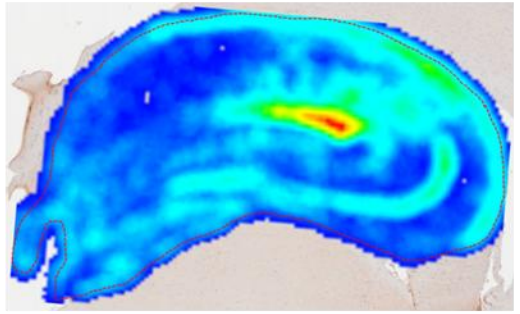
Phospho-Tau reduction in the Hippocampus

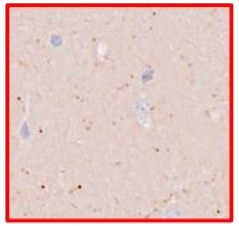


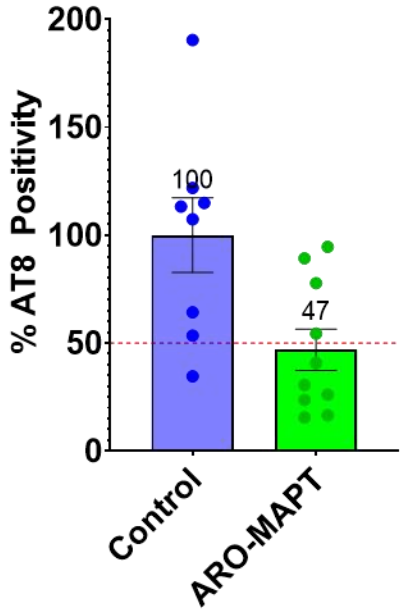












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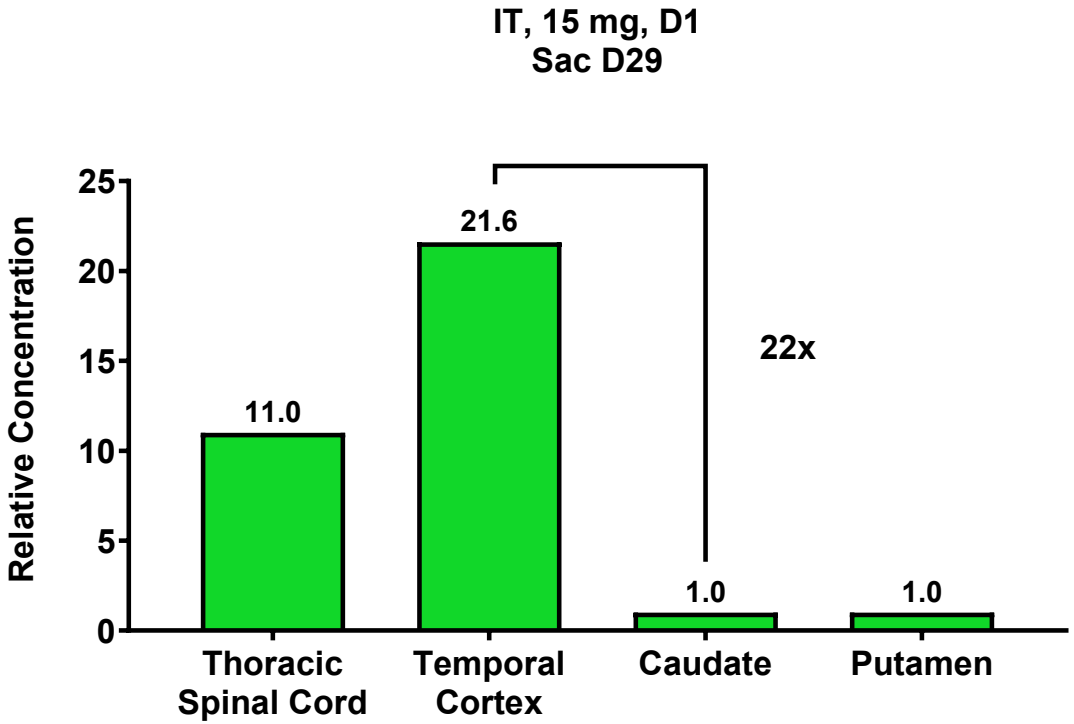
BBB Platform Achieves Improved Delivery to Deep Brain Regions

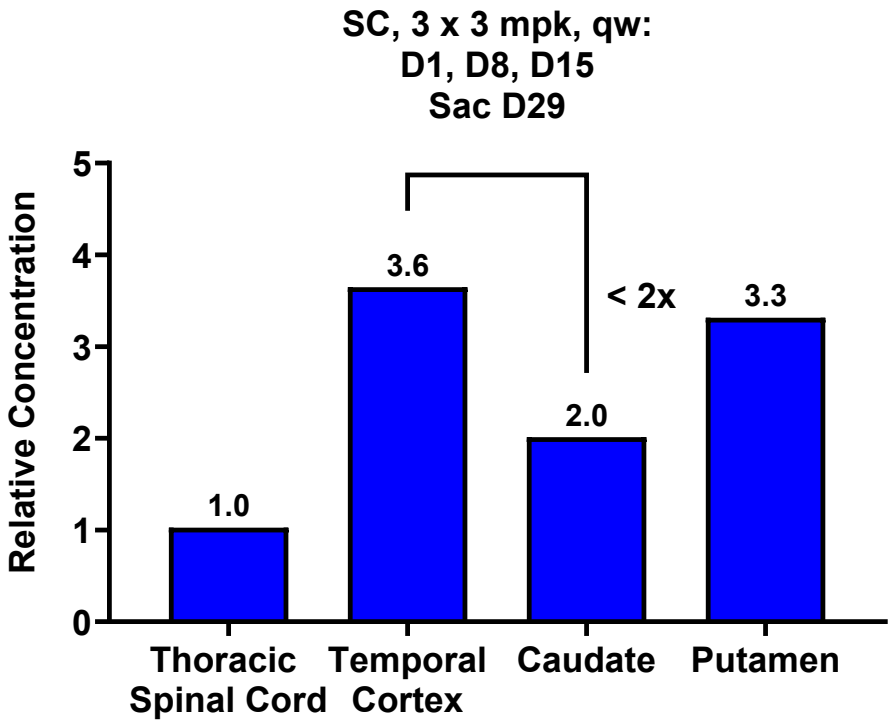
siRNA Concentrations in NHP Brain regions by IT



Intrathecal administration:

- Relatively limited delivery to deep brain regions

siRNA Concentrations in NHP Brain regions by SC



Subcutaneous administration:

- Good distribution of siRNA across different brain regions.

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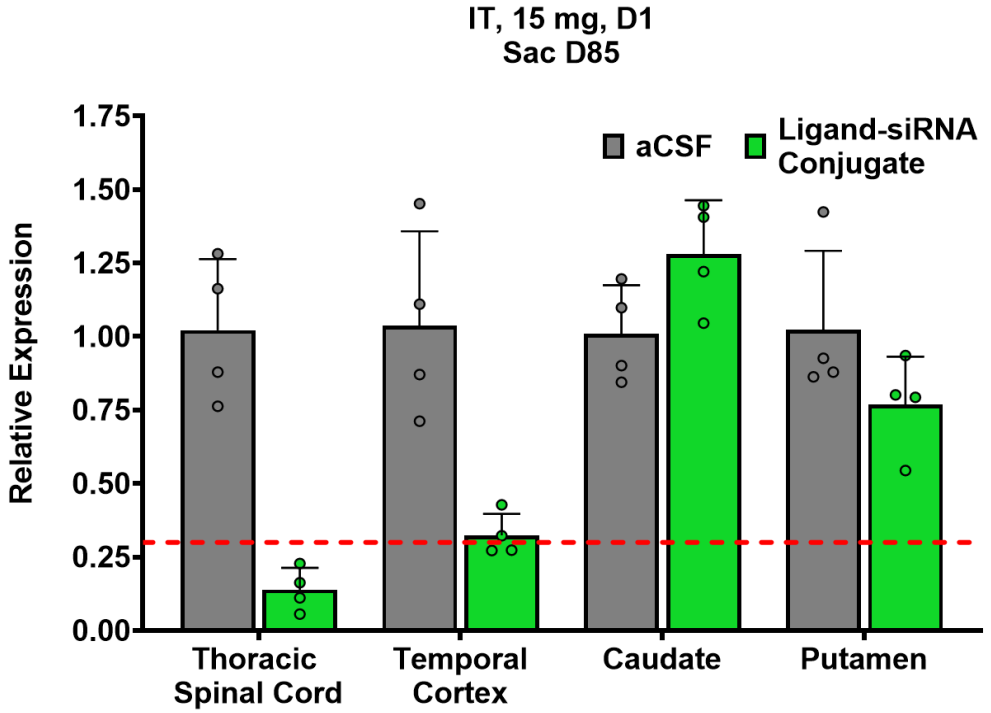
BBB Platform Achieves Uniform Reduction Across the Brain

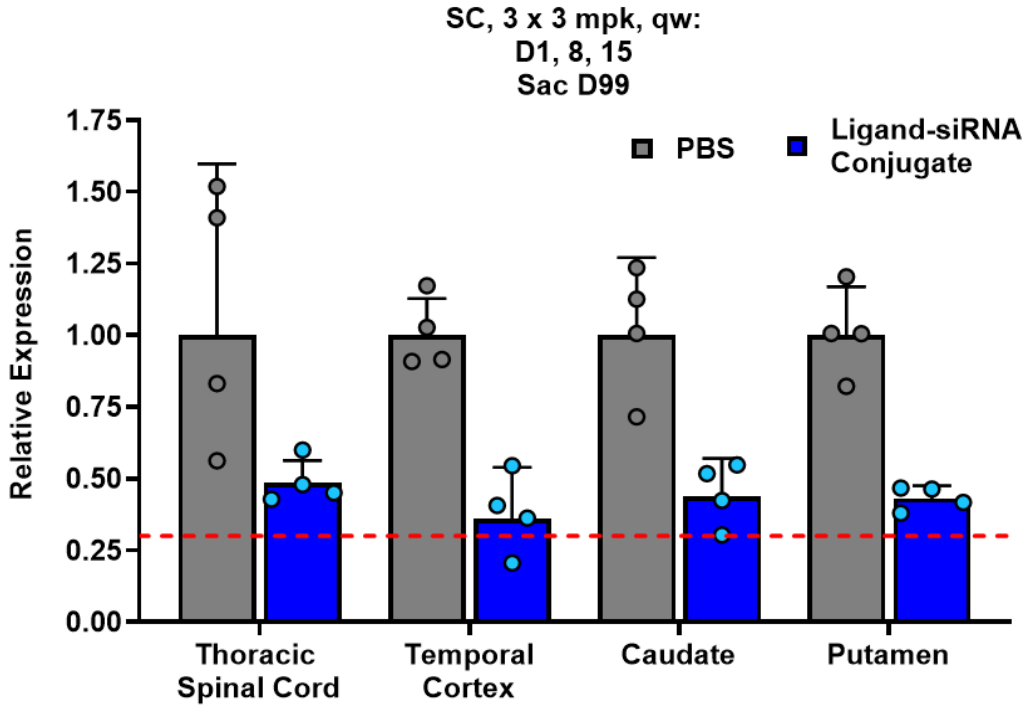
MAPT mRNA reduction in NHP Brain regions by IT



Intrathecal administration:

- Minimal mRNA reduction in deep brain regions

MAPT mRNA reduction in NHP Brain regions by SC



Subcutaneous administration:

- Even mRNA reduction across brain regions, including deep brain.

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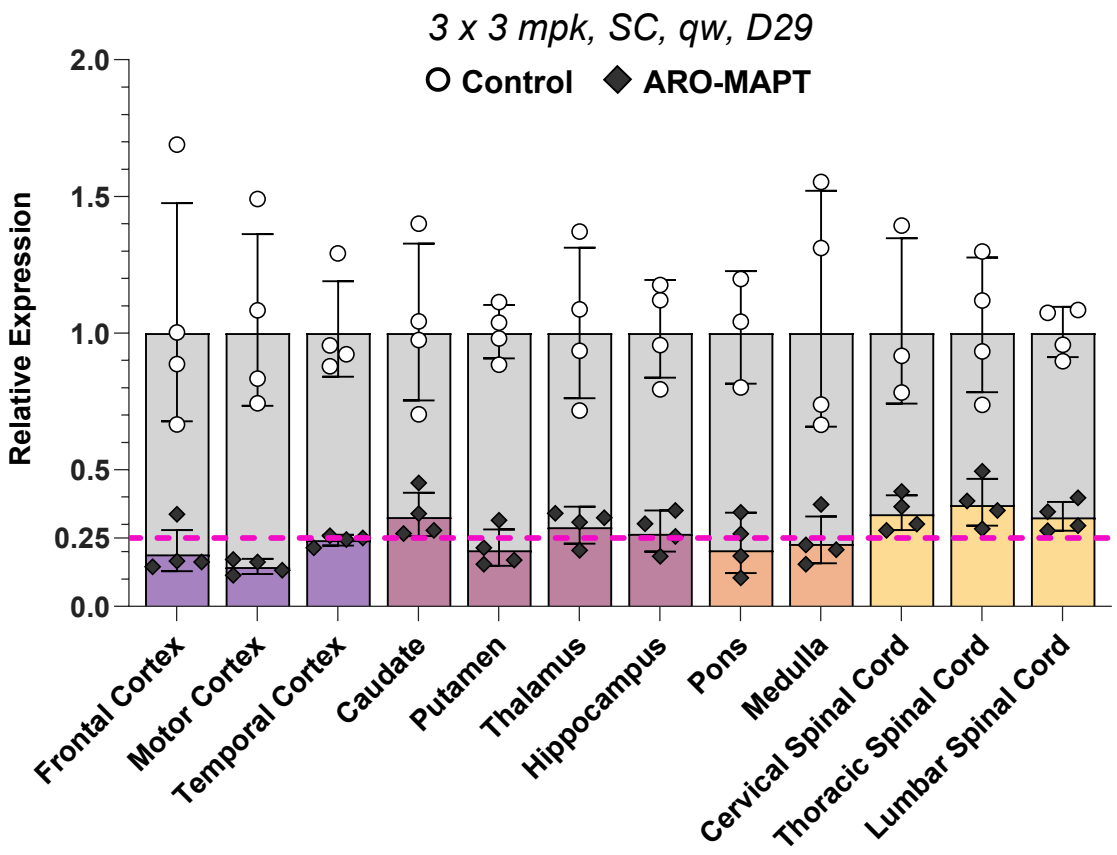
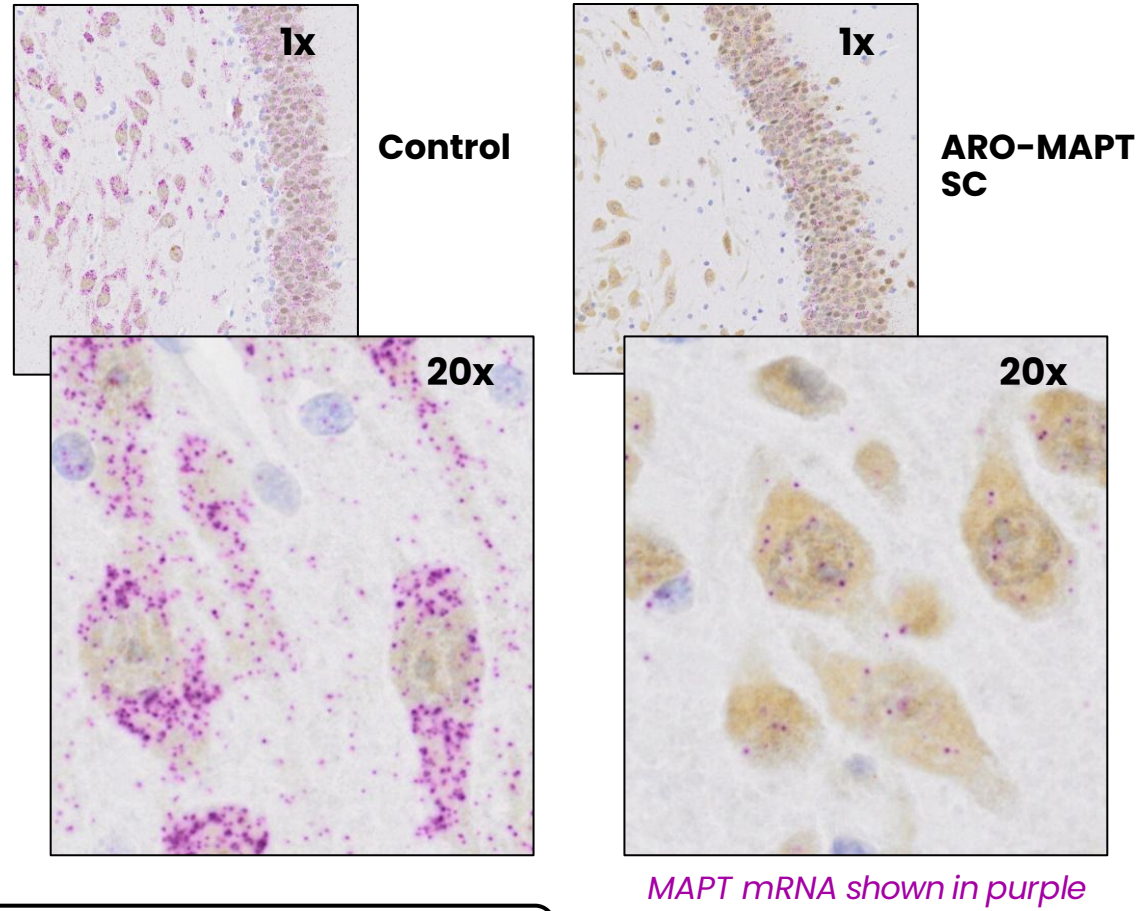
ARO-MAPT Achieves Deep Knockdown of MAPT mRNA Throughout the CNS with Subcutaneous Administration

MAPT mRNA Reduction in NHP CNS Regions



MAPT mRNA Depletion in Hippocampus



MAPT mRNA shown in purple

- mRNA knockdown corroborated by RNAscope

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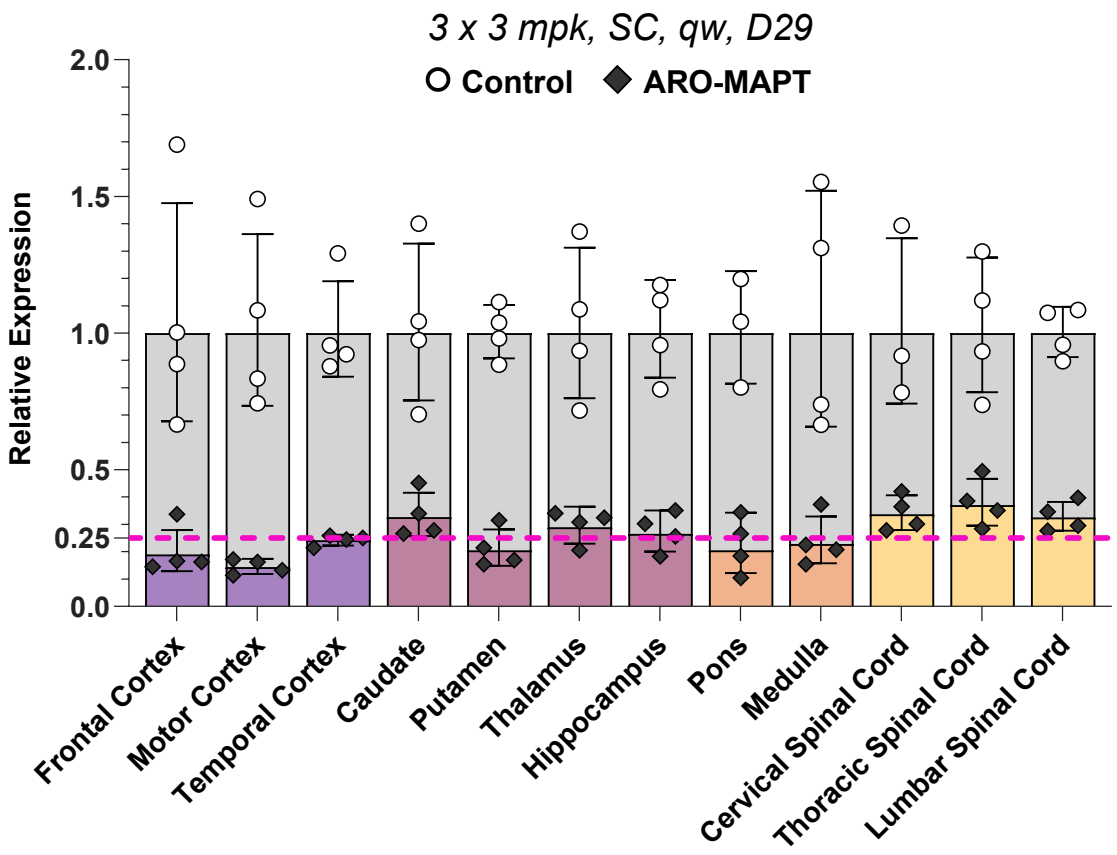
ARO-MAPT Achieves Deep Knockdown of MAPT mRNA Throughout the CNS with Subcutaneous Administration

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

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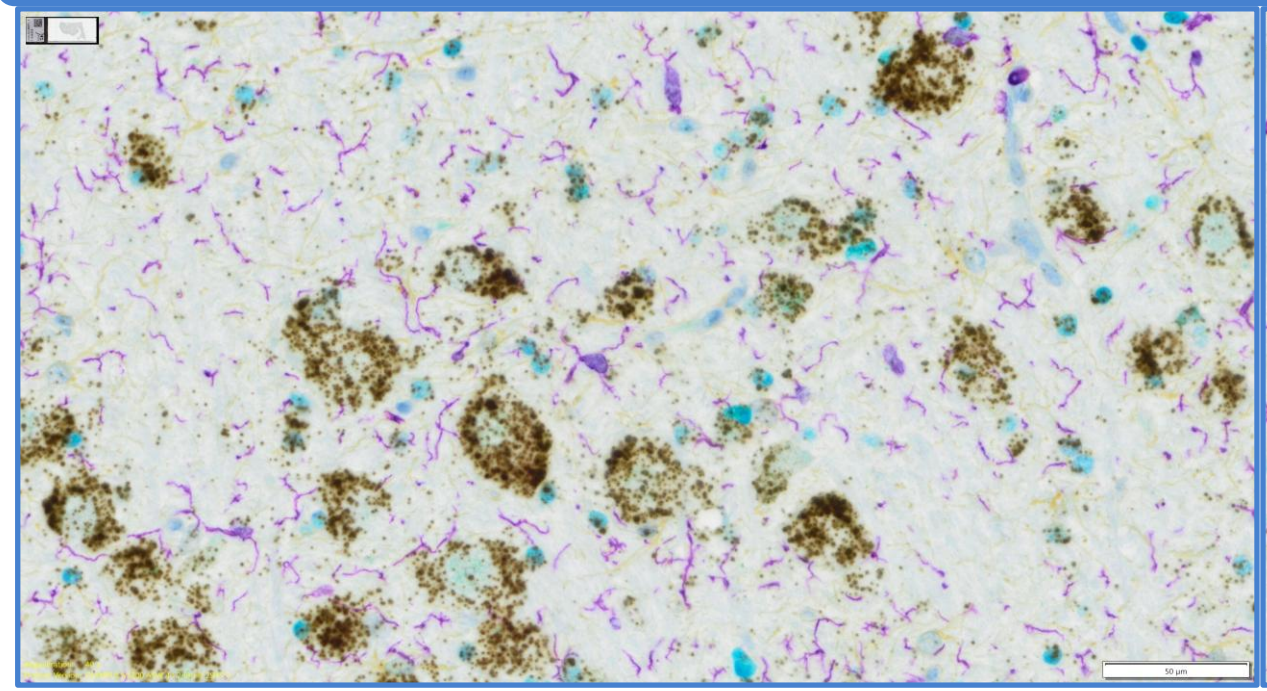
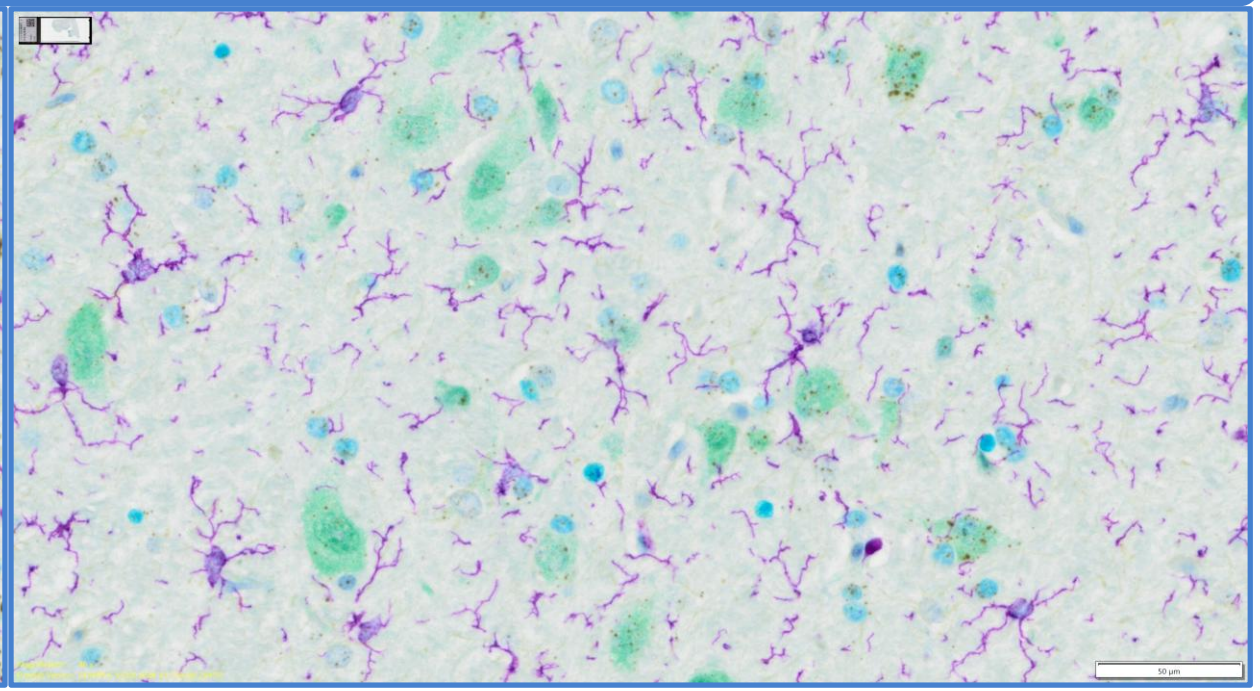
ARO-MAPT Achieves MAPT mRNA Reduction Across All Major CNS Cell Types

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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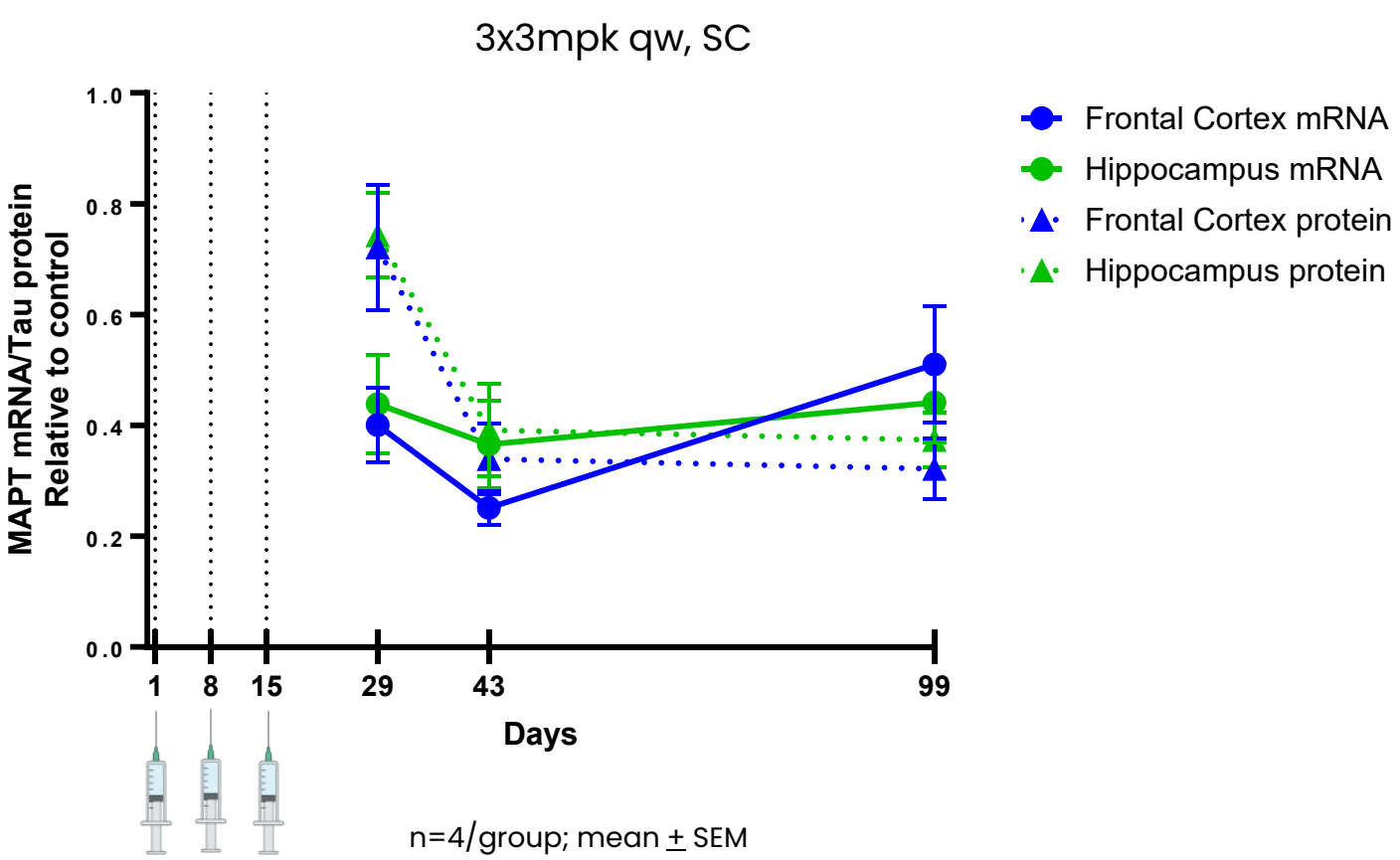
ARO-MAPT maintains 3 months of durable knockdown throughout the brain in NHP

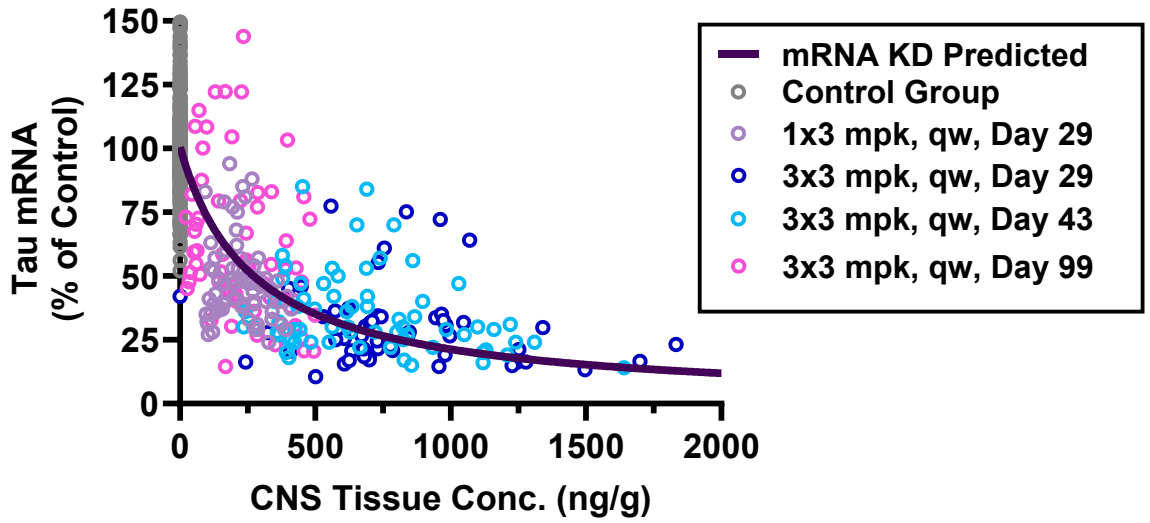
Duration of MAPT mRNA/ Tau protein Reduction in NHP



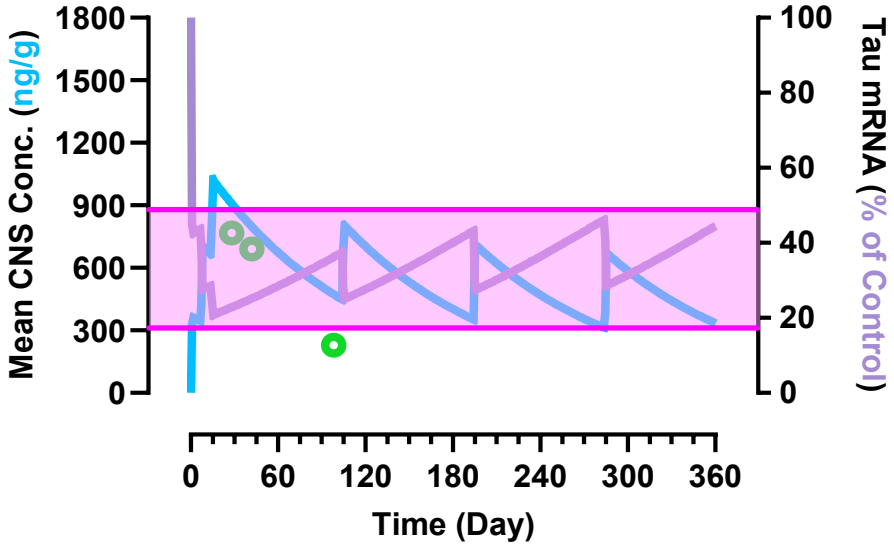
- Durable target engagement with ≥50% knockdown over 3 months in CNS regions including deep brain

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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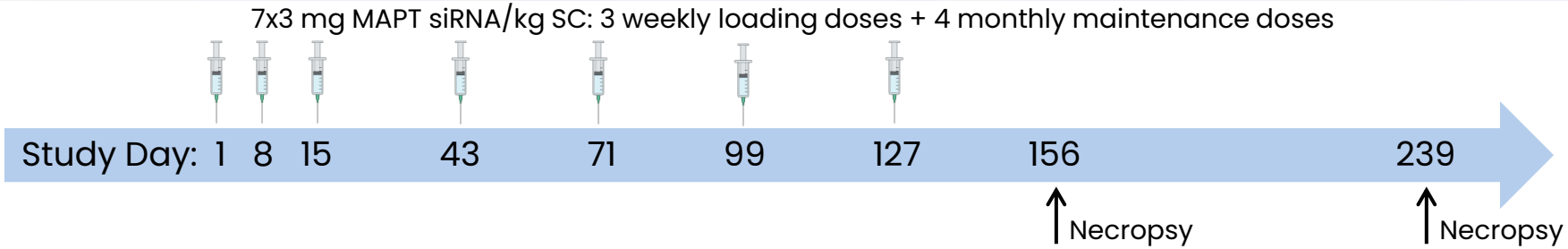
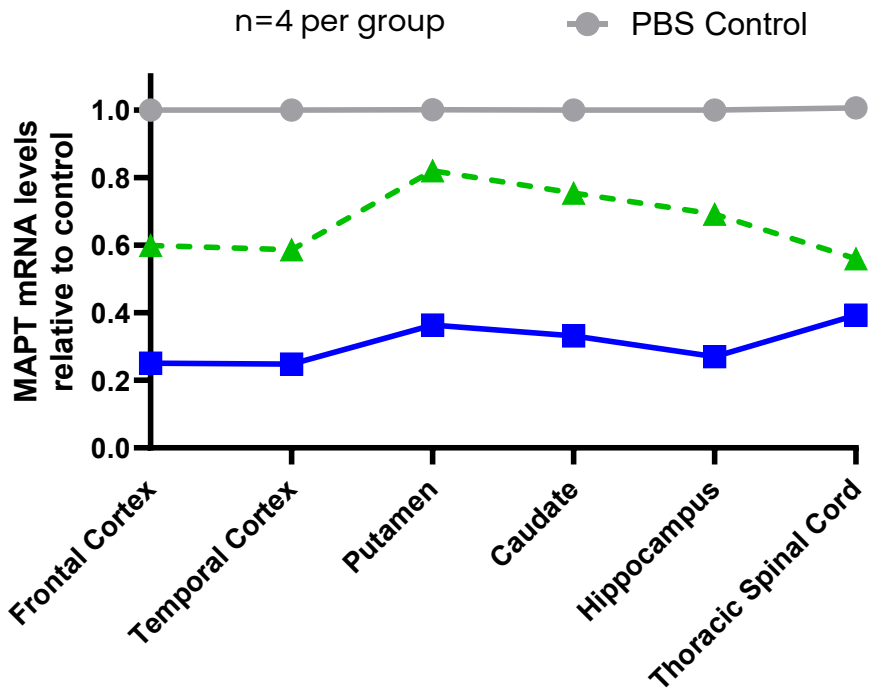
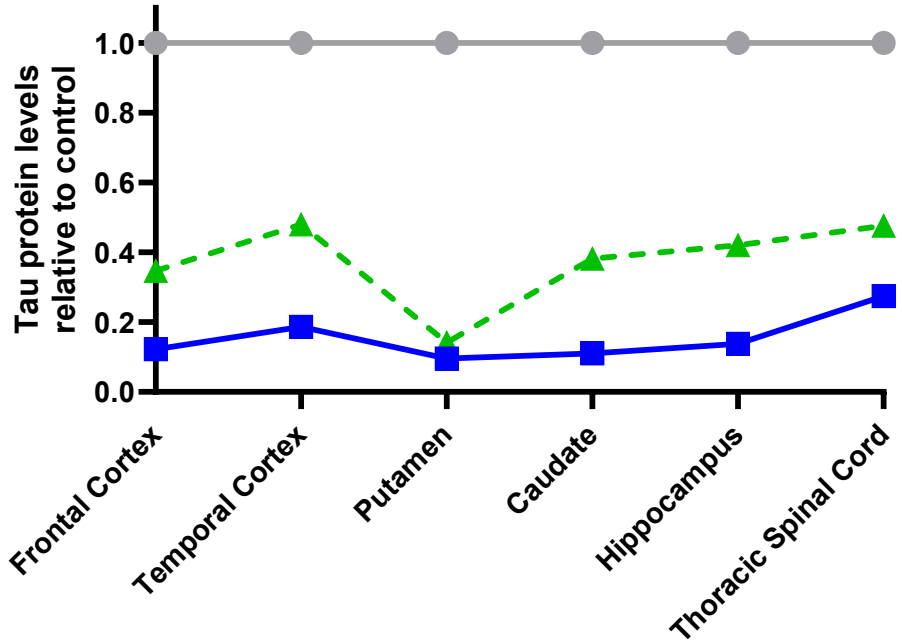
Sustained inhibition of Tau Protein After Repeat Dosing



Duration of MAPT mRNA Reduction in NHP



Duration of Tau protein Reduction in NHP



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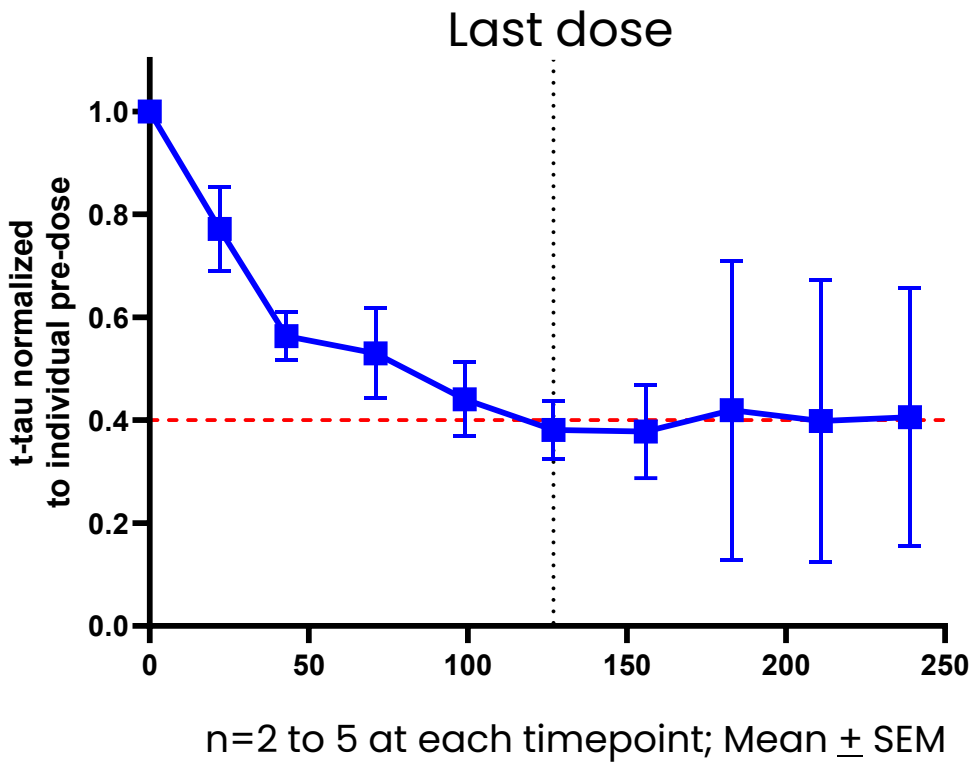
Tau protein suppression outlasts mRNA recovery — consistent with long protein half-life

Tau Protein reduction in Cerebrospinal Fluid Follows Reduction in CNS Tissues

T-Tau Levels in CSF



n=2 to 5 at each timepoint; Mean ± SEM

- Tau protein reduction maintained at 50-60% up to 4 months after last-dose.

CSF total tau validated as pharmacodynamic biomarker tracking tissue protein suppression.

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ARO-MAPT Profile

Productive Delivery Across BBB	Efficacy & Activity Profile in NHP	Duration & Dosing Schedule	Formulation	Toxicology Profile
✓	✓	✓	✓	✓
➢ 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 supports SC administration in human	➢ No changes ➢ CTA filed ➢ **FIH dosed**

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Study Design of Phase 1/2a Placebo-controlled Dose-escalating Study

Purpose: To evaluate the safety, tolerability, PK, and PD of ARO-MAPT-SC compared to placebo in adult healthy volunteers and in participants with early Alzheimer's disease, defined as mild cognitive impairment due to AD and mild AD dementia

NHV Cohort

18-80 years

BMI 18-35 kg/m^2

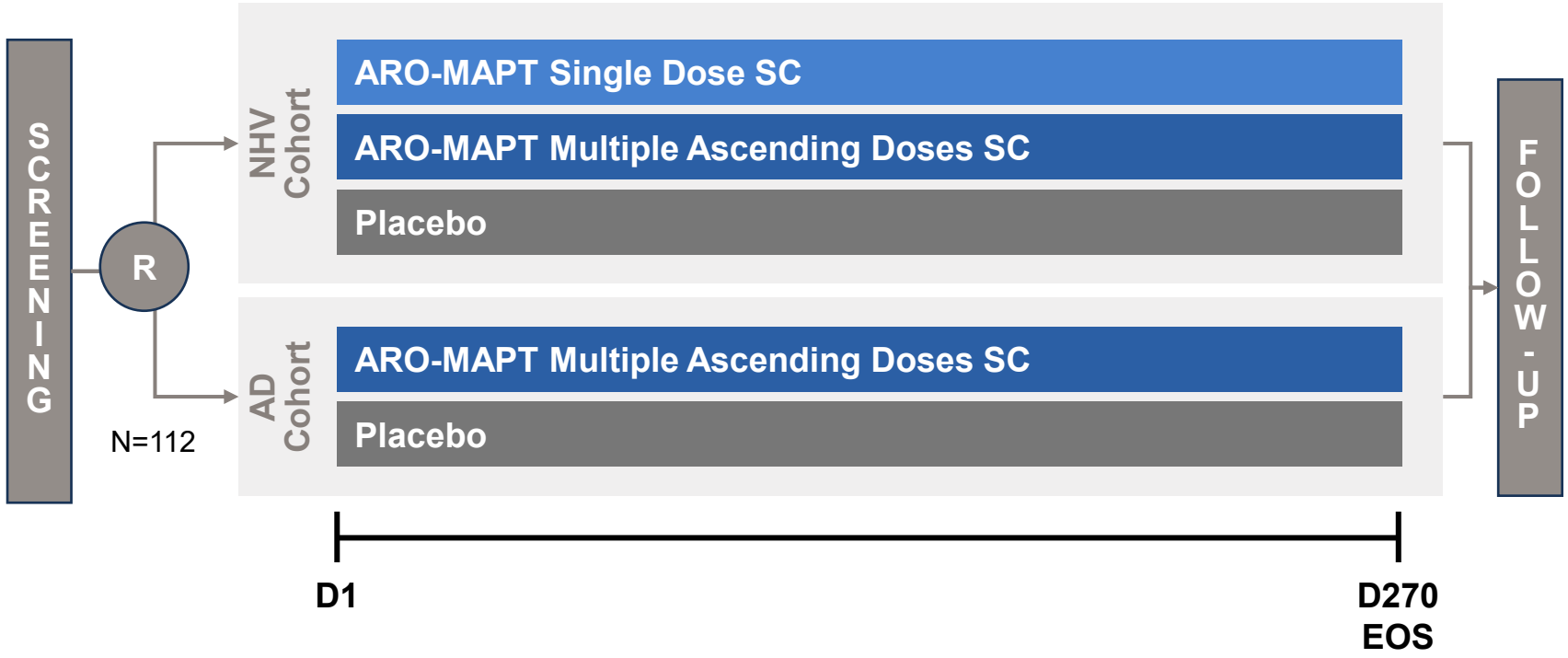
AD Cohort

18-80 years

Clinical diagnosis of early AD

Not receiving AD-related medications or on stable doses of such medications >= 8 weeks

Have reliable and competent caregiver ≥18 years



ARO-MAPT-SC-1001 Phase 1/2a Clinical Study

Primary Endpoint

Safety and tolerability of ARO-MAPT-SC in patients with Early AD†

Secondary Endpoints

PK profile of ARO-MAPT-SC

CSF cell count, glucose, and protein (safety)

Key Exploratory Endpoints

- **CSF t-tau, p-tau217, p-tau 181, MTBR tau**
- **Plasma p-tau 217**
- **Functional Testing**
  - CDR Global Score
  - ADAS-cog 13
- **Imaging**
  - Tau PET SUVR changes
  - MRI Brain volumetry

Sites

New Zealand
(Dosed Adult Healthy Volunteers – 12/2025)

United Kingdom

Canada

Australia

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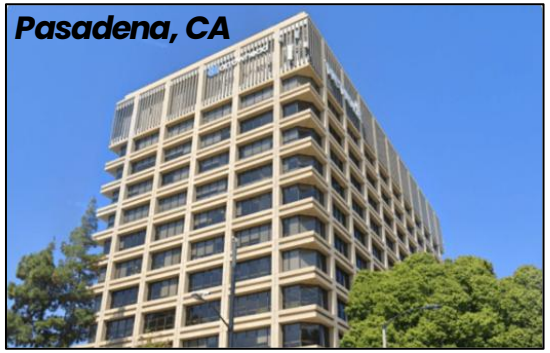
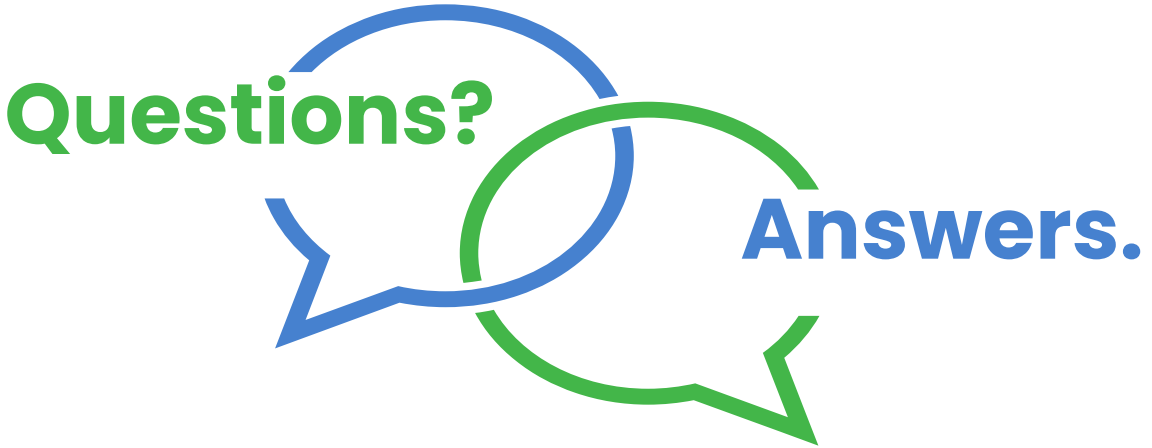
† Defined as MCI due to AD or Mild AD Dementia

Thank you!





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