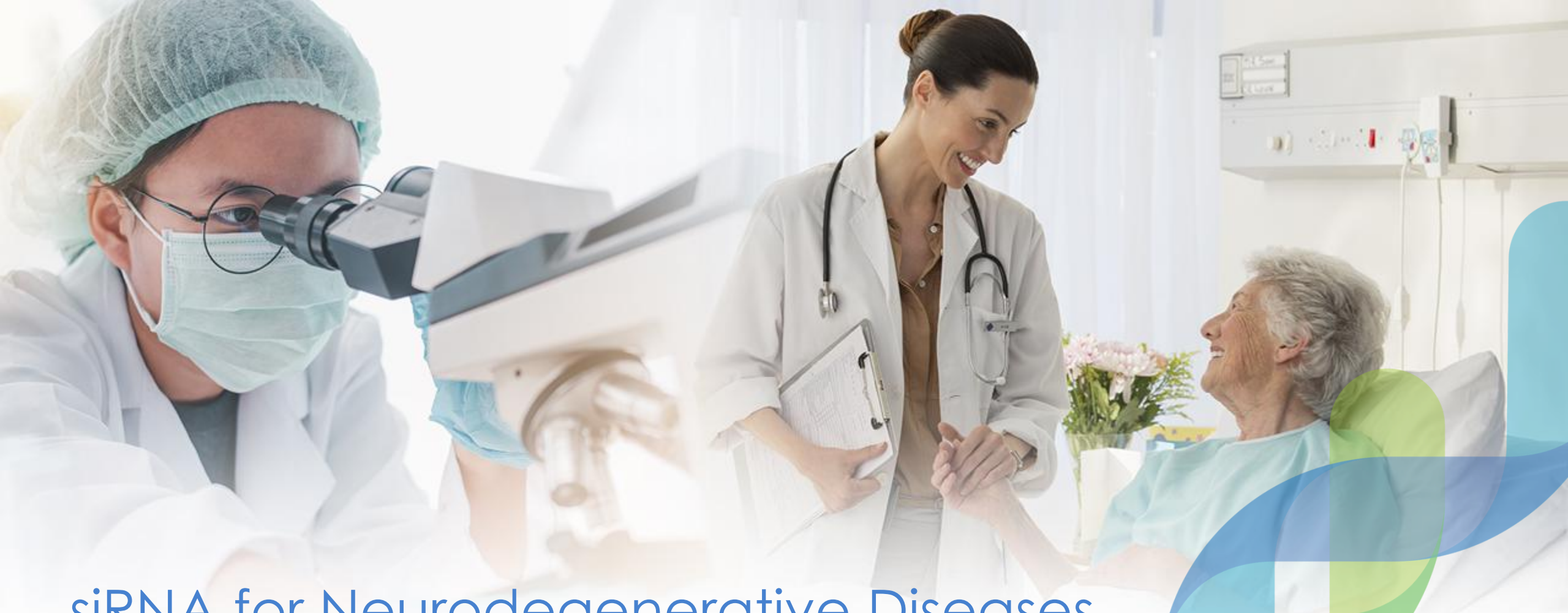

siRNA for Neurodegenerative Diseases

Christine Esau, Ph.D.,

RNA Leaders USA Congress 2025

September 10, 2025

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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, entering into new collaborations and achieving existing projected milestones, rapid technological changes 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.

Breaking the Mold of Medicine with RNA Interference

Arrowhead Pharmaceuticals is an **RNAi therapeutics platform company** with a **broad pipeline** of **wholly owned and partnered** product candidates on track for its **first commercial launch in 2025**.

Commercial Launch Planned in 2025

- **Plozasiran** for familial chylomicronemia syndrome US FDA **PDUFA date 11/18/25**
- Additional global regulatory submissions and review are ongoing
- Commercial leadership, sales and marketing, market access, and medical science liaisons from medical affairs are in place

Broad Pipeline

- **16 clinical stage programs** (8 wholly-owned; 8 partnered)
- Mix of **early, mid, and late-stage** candidates targeting **rare and high prevalence diseases**
- Growing pipeline with **2-3 new clinical programs planned per year**

Proprietary Platform

- **Targeted RNAi Molecules** platform (**TRiM™**) designed for **deep and durable gene silencing**
- **Fulfilling the promise** of bringing RNAi therapeutics to diseases **outside of the liver**
- Potential to be **best-in-class** across tissue types

Financial Resources

- **Strong balance sheet** with **funding into 2028** to push candidates to commercialization
- **Additional non-dilutive capital expected** from Novartis, Sarepta, Amgen, Takeda, GSK, and Royalty Pharma as milestones are achieved
- Potential for **additional** product and/or platform **deals**

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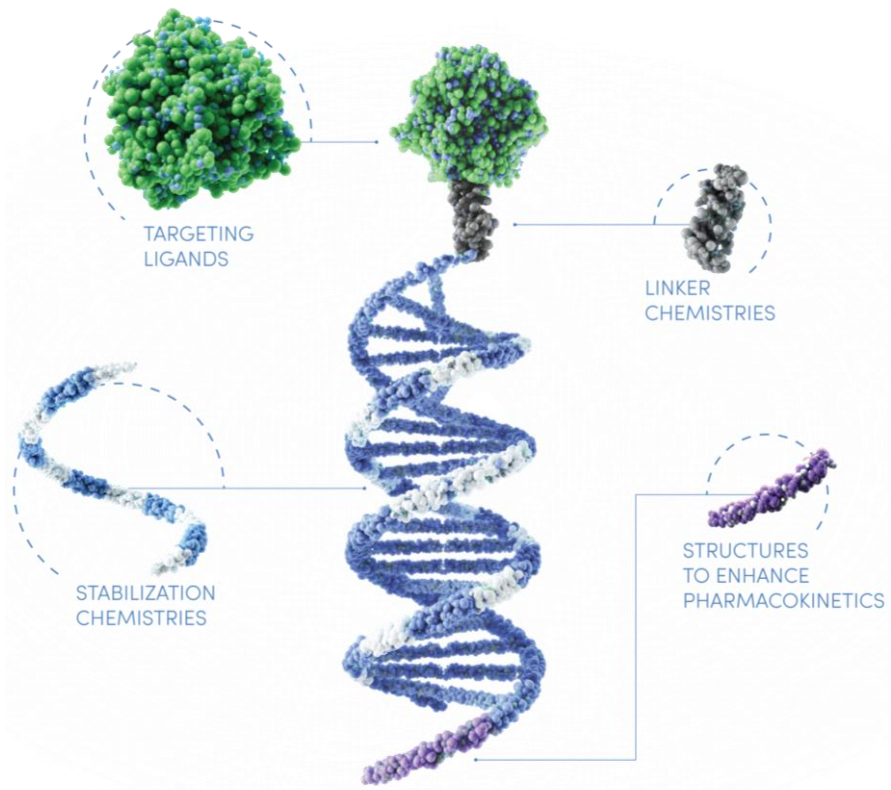
Arrowhead's Targeted RNAi Molecule (TRiM™) Platform: The Broadest and Most Versatile in the Field



Optimized Delivery of siRNA to Multiple Cell Types

TRiM™ also has rules and algorithms to optimize siRNA sequence and modification patterns

Activity

Characterized by depth & duration of effect

- Ability to unlock previously undruggable targets

Specificity

To maximize activity and innate stability with the potential for reduced off-target effects

Versatility

In structure and design offers multiple routes of administration and access to multiple tissues

- Facilitates rapid drug development and speed to patients

Simplicity

In design translates to relatively lower costs, and production at scale

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TRiM™ Platform Enables Delivery to Seven Target Tissues

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

Systemic Delivery to CNS Potentially Disruptive

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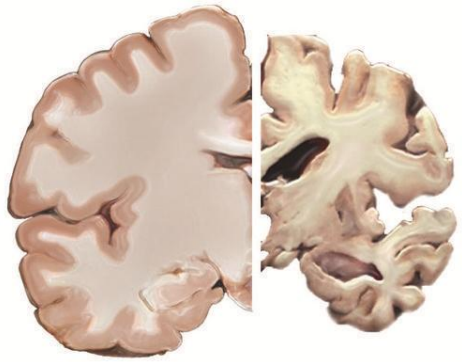
Neurodegenerative Diseases Are an Enormous Burden Uniquely Addressable by RNA Therapeutics

Over **50 million** neurodegeneration patients worldwide[1] and few disease modifying therapies

Healthy Brain



Diseased Brain

- Common feature is abnormal protein aggregation and neurotoxic gain of function: difficult mechanism to drug but RNAi approach knocks out disease-causing protein
- Recent progress in genetics and biomarker development are enabling clinical development in a broad range of neurodegenerative diseases, increasing probability of success

1. *Lancet Neurology* 2019, 18:459

TDP-43 proteinopathies
- Amyotrophic Lateral Sclerosis (ALS)
- Fronto-temporal dementia (FTD)

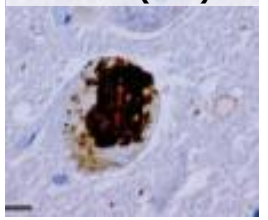
Tauopathies
- Alzheimer's disease (AD)
- Fronto-temporal dementia (FTD)
- Progressive Supranuclear Palsy
- Corticobasal Degeneration

Amyloidoses
- Alzheimer's disease (AD)
- Prion diseases

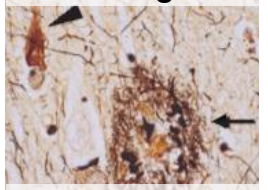
Synucleinopathies
- Parkinson's disease (PD)
- Lewy body dementia
- Multiple system atrophy

Expansion Repeat Disorders
- Huntington's disease (HD)
- Spinocerebellar ataxias (SCA)

SOD1 (ALS)

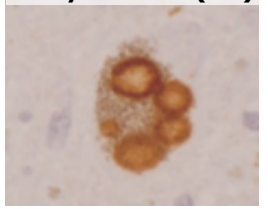


Tau tangles

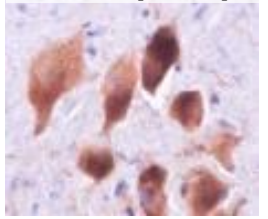


Amyloid plaques

Lewy bodies (PD)



ATXN2 (SCA2)



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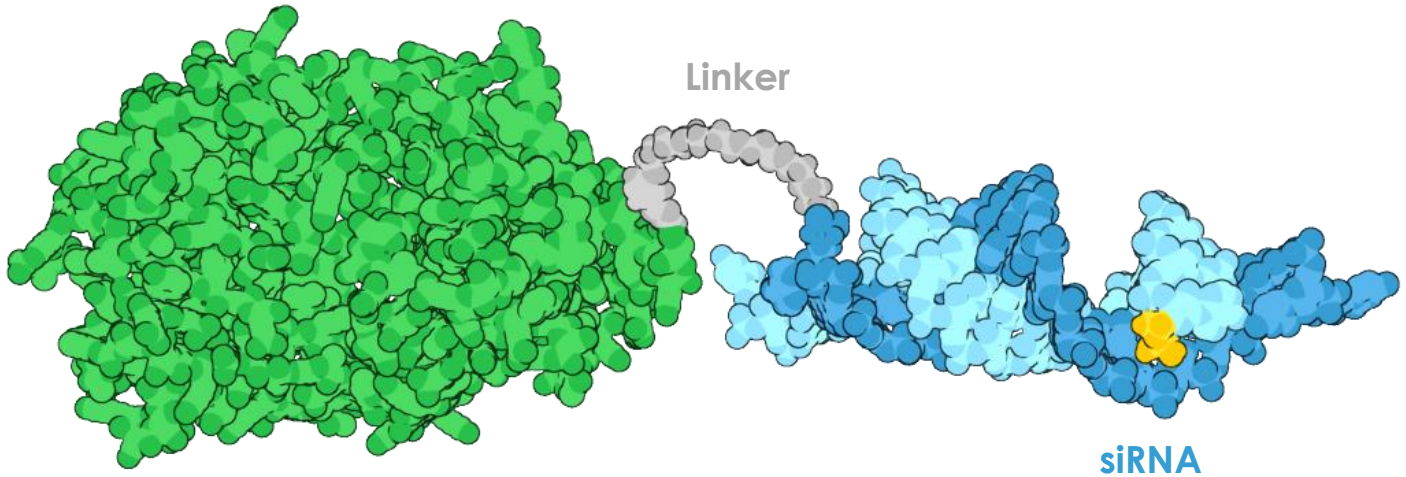
CNS Portfolio Programs

Program	Indication	Stage	Product Rights
ARO-ATXN2 (IT)	Spinocerebellar Ataxia 2	Phase 1	Sarepta
ARO-MAPT (SC)	Alzheimer's disease & Tauopathies	CTA Filed	Arrowhead
ARO-HTT (SC)	Huntington's disease	Preclinical	Sarepta
ARO-SNCA (SC)	Parkinson's disease & Synucleinopathies	Preclinical	Novartis
ARO-ATXN3 (SC)	Spinocerebellar Ataxia 3	Preclinical	Sarepta
ARO-ATXN1	Spinocerebellar Ataxia 1	Discovery	Sarepta

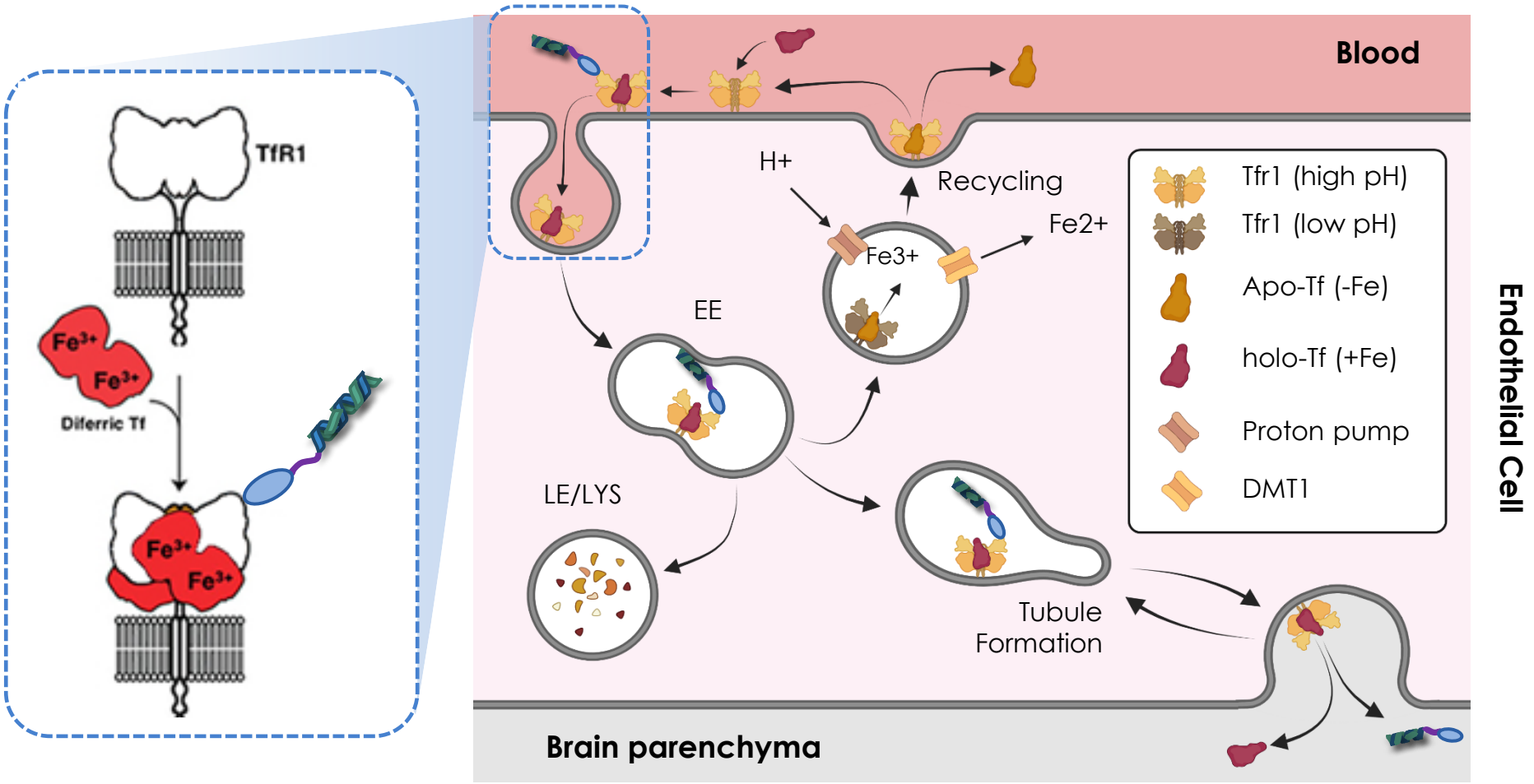
Next Gen. CNS-Targeting TRiM™ Platform via Subcutaneous Administration



We Have Developed an Optimized Systemic Delivery Platform for CNS

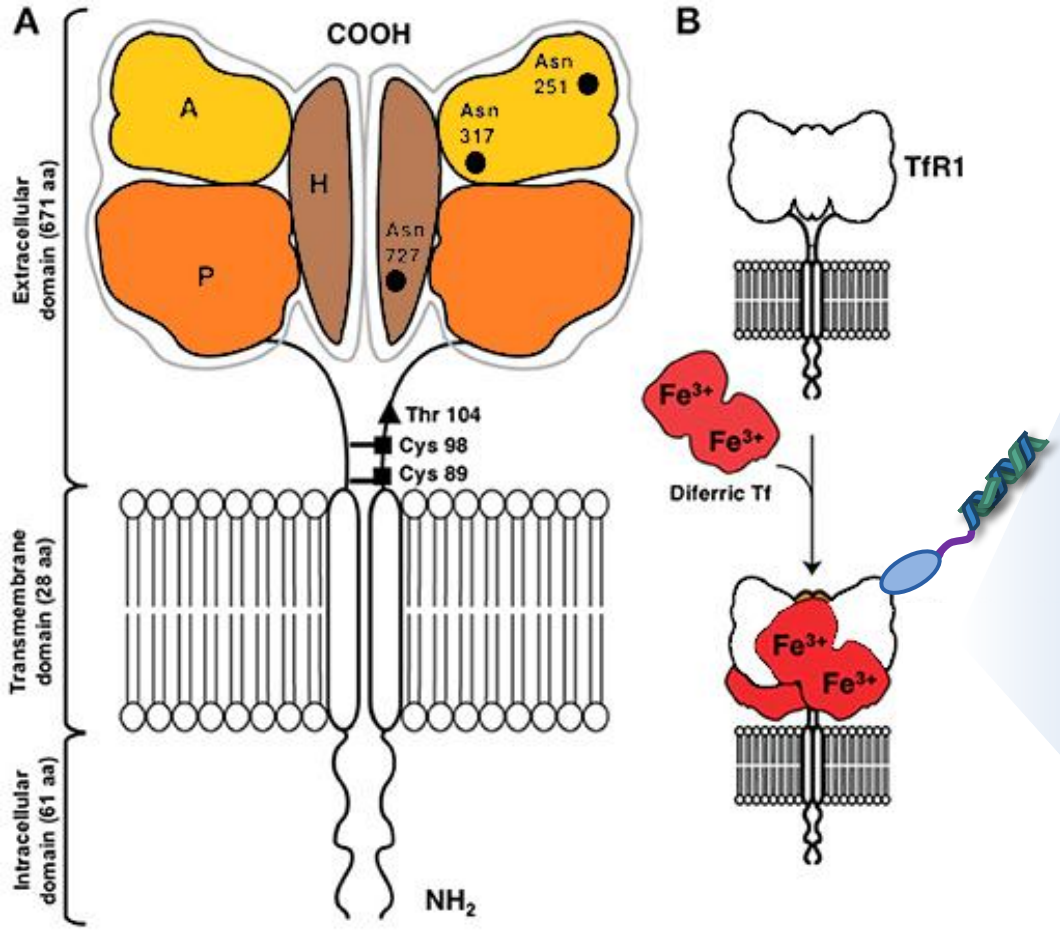
- **Ligand-driven** delivery via noninvasive BBB penetration and cellular uptake in brain tissue
- **Effective** and durable reduction in expression levels of therapeutically-relevant gene targets
- **Convenient** dosing via subcutaneous (SC) administration with potential for monthly to quarterly dosing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

TRiM™ CNS-SC Platform Leverages Noninvasive TfR1-Binding for CNS Delivery

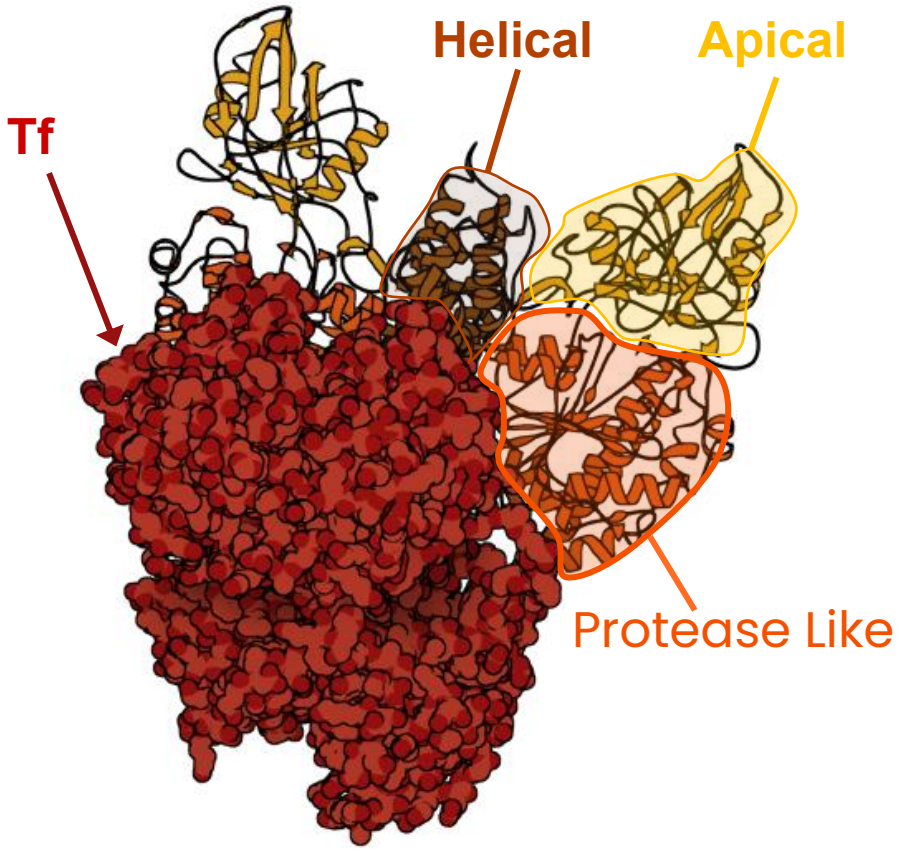


- TfR1 highly enriched in endothelium of the blood-brain barrier (BBB)
- Fast kinetics of internalization and recycling

TRiM™ CNS-SC Platform's TfR1-Binding Does Not Interfere with Binding of Endogenous Ligand



Front Immunol. 2021; 12: 607692.



Transferrin (up to 4 mg/mL in serum) occludes helical and protease like domains

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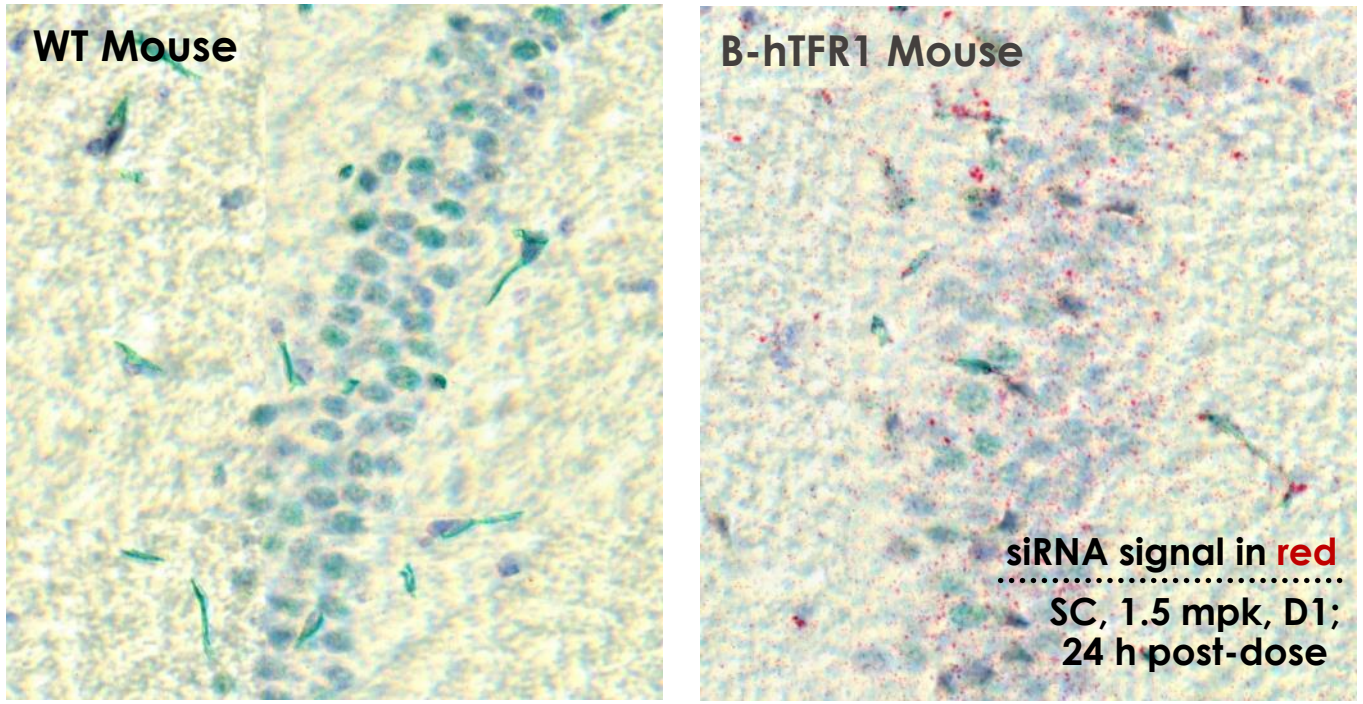
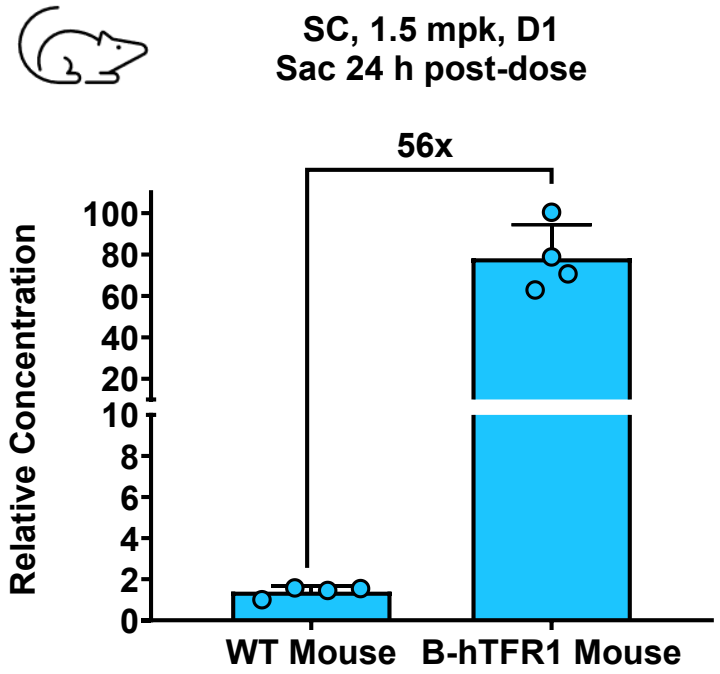
TRiM™ CNS-SC Platform Demonstrated to Achieve BBB Penetration in Mouse

siRNA Visualization in Hippocampus



siRNA Concentration in Half Brain



- Tissue-staining shows greater accumulation of siRNA in B-hTFR1 mouse brain than WT
- siRNA quantitation in mouse brain shows over 50x difference between TfR1-expressing and non-expressing groups

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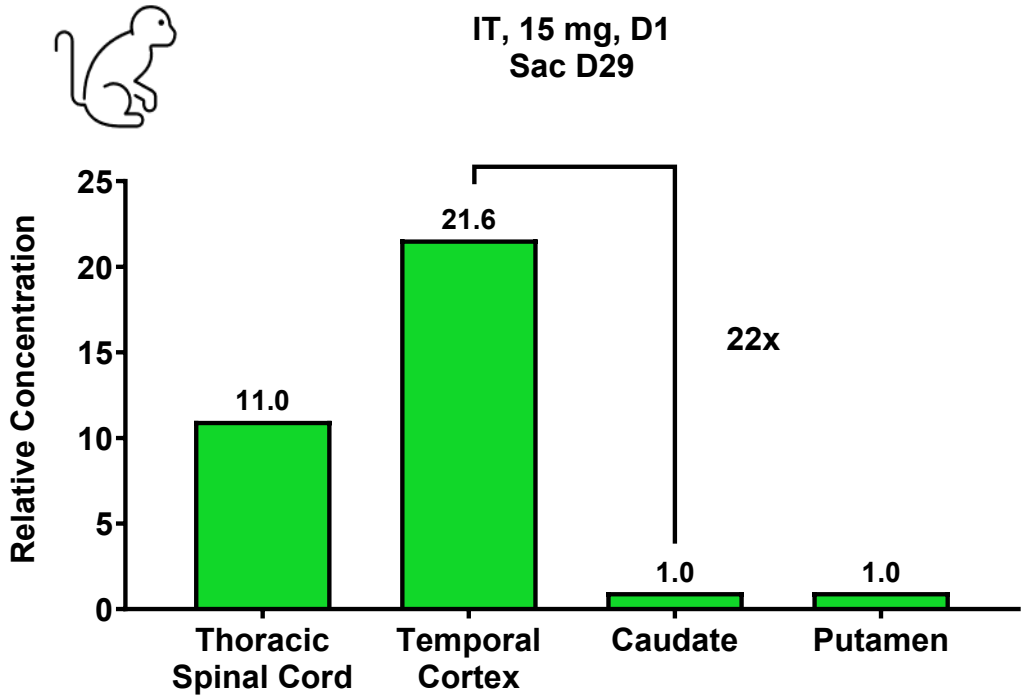
TRiM™ CNS-SC Platform Achieves Improved Delivery to Deep Brain Region

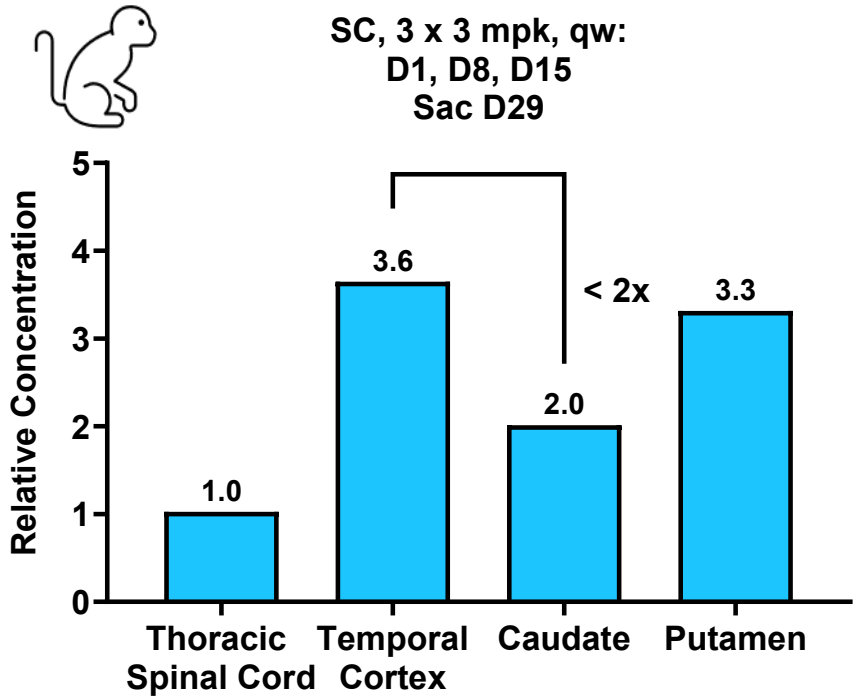
siRNA Concentrations in NHP Brain Regions by IT



By IT administration:

- Relatively limited delivery to deep brain regions

siRNA Concentrations in NHP Brain Regions by SC



By subcutaneous administration:

- Higher distribution to brain regions versus TSC
- Good distribution of siRNA across brain regions

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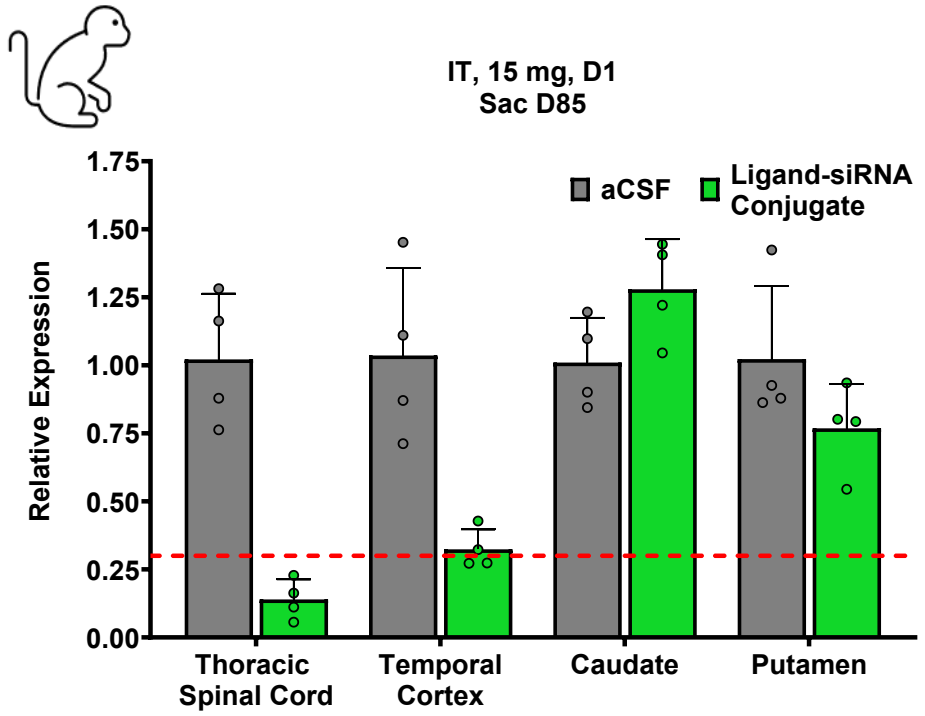
TRiM™ CNS Delivery Platforms Show Different Knockdown Profiles in Deep Brain Regions in NHP

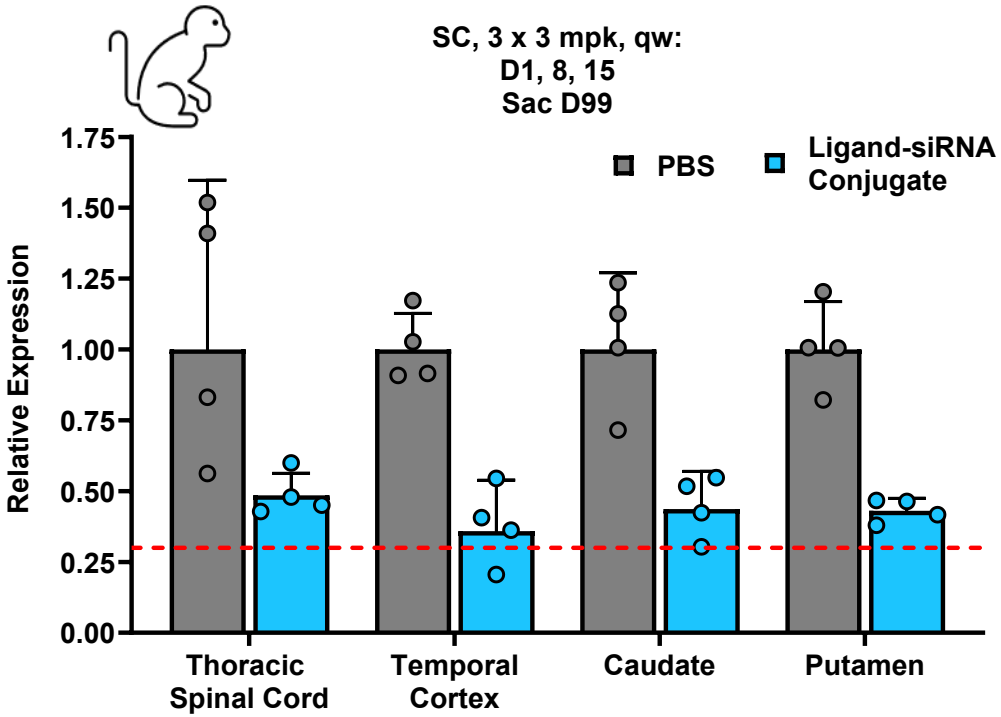
MAPT mRNA Reduction in NHP Brain Regions by IT



By IT administration:

- Minimal mRNA reduction in deep brain region

MAPT mRNA Reduction in NHP Brain Regions by SC



By subcutaneous administration:

- Even mRNA reduction across brain regions, including deep brain

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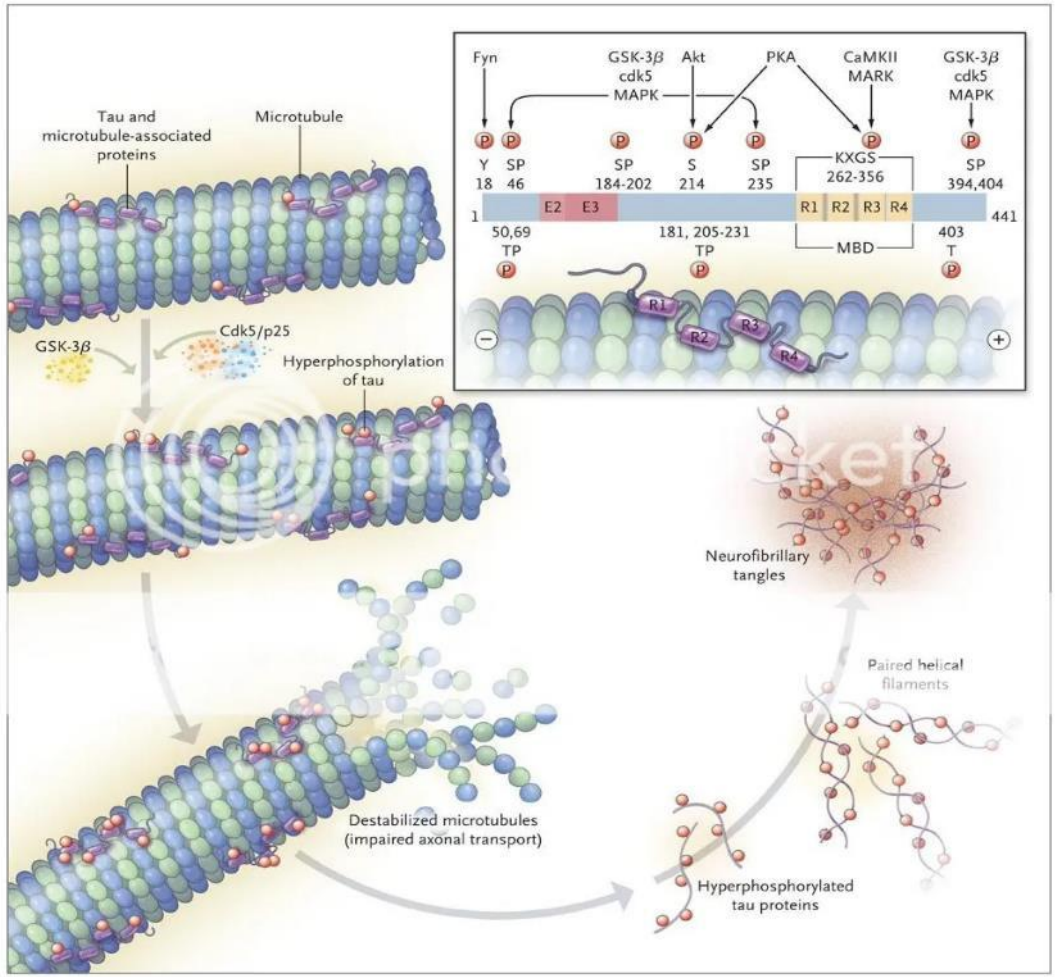
Toxic Tau Protein Aggregation: Key Driver in Tauopathies Including Alzheimer's Disease

Tau Protein:

- Encoded by the MAPT gene
- Abundant in neurons, where it promotes stabilization of microtubules in axons
- Intrinsically disordered and subject to many post-translational modifications
- Hyperphosphorylation promotes intracellular formation of neurofibrillary tangles which can be visualized with PET imaging and are correlated with neurodegeneration



Querfurth & LaFerla, *NEJM* 2010;362:329-44

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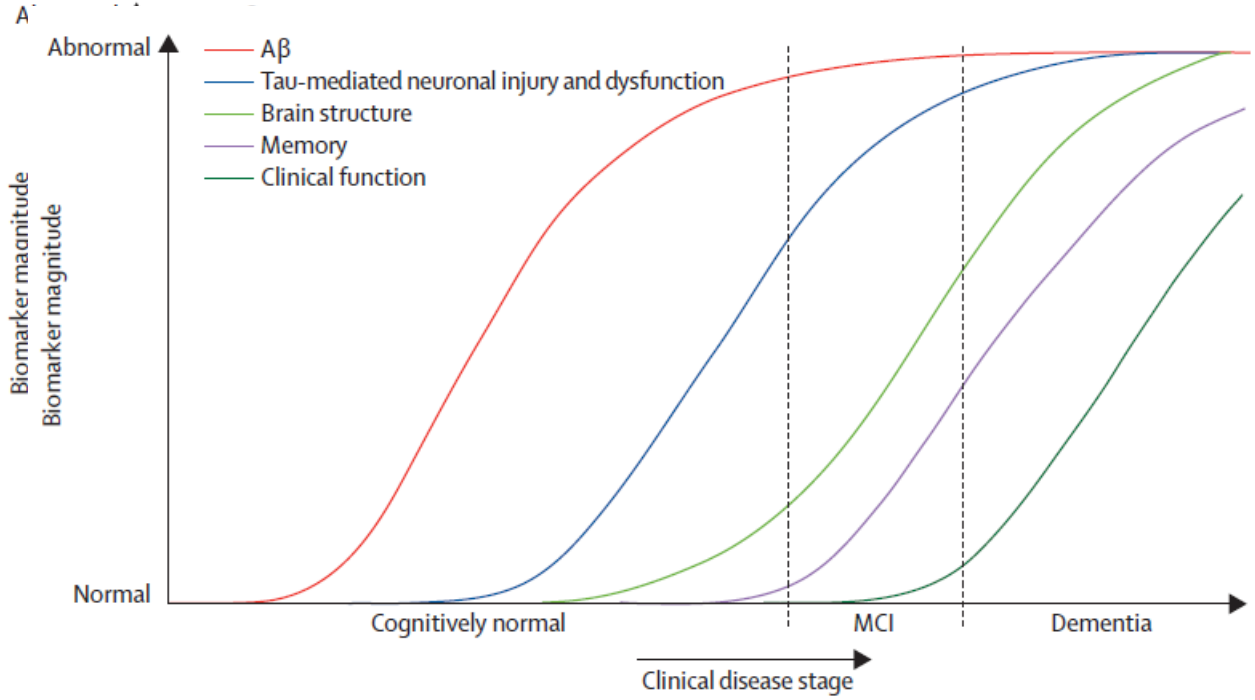
ARO-MAPT SC for Alzheimer's Disease

Amyloid Plaque Precedes Tau Pathology in Alzheimer's Disease



- In Alzheimer's disease, Tau neurofibrillary tangle pathology but not amyloid predicts cognitive decline
- Anti-amyloid therapies have shown minimal Tau reduction, are less effective in patients with high Tau burden, and have significant safety risks
- Biogen MAPT-ASO/BIIB080 treatment reduced Tau-PET signal in Alzheimer's patients' brains, clinical proof of concept for the approach
- **siRNA Tau reduction has potential for benefit in broader patient population with better safety profile compared to amyloid immunotherapy**

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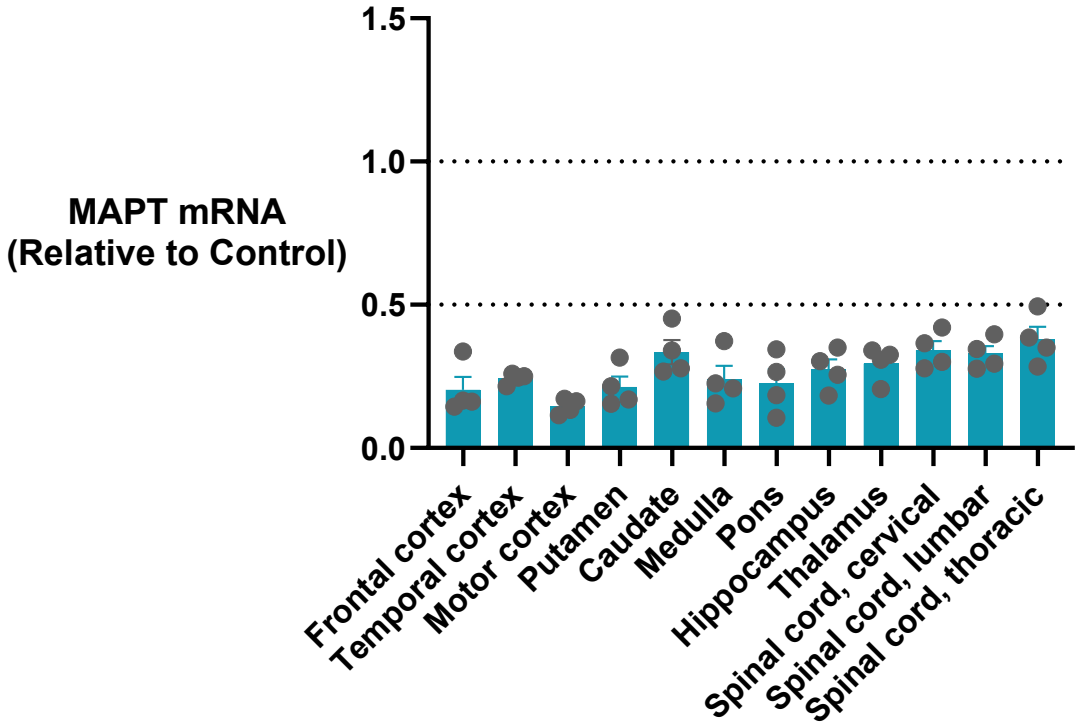
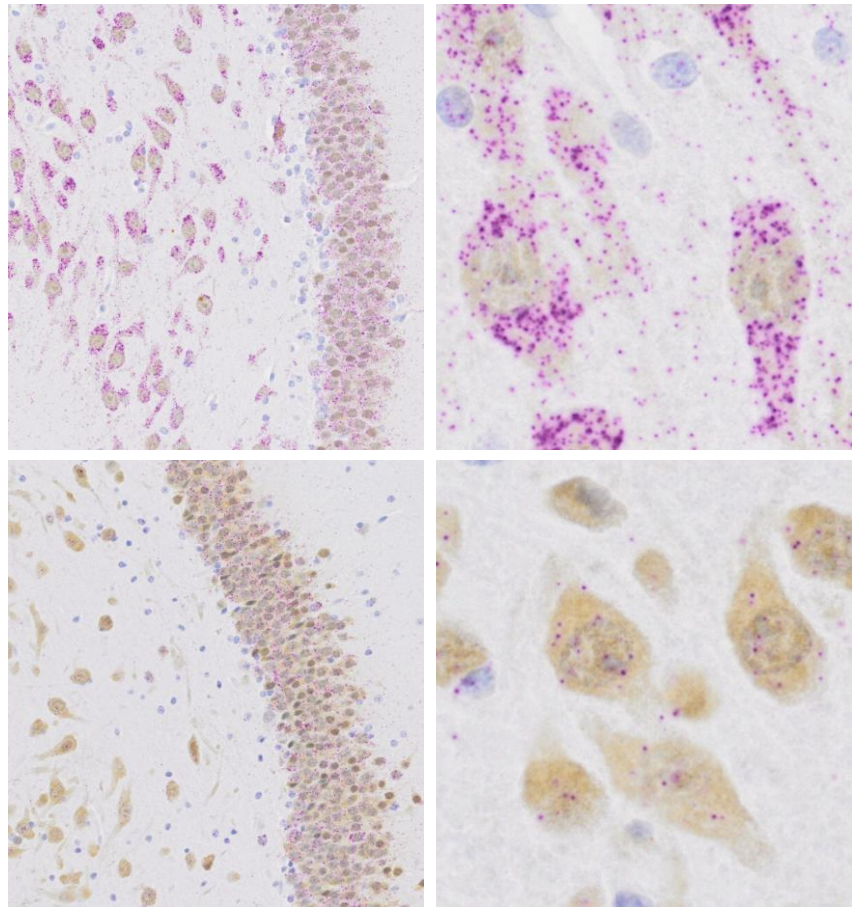
ARO-MAPT SC Achieves Deep Knockdown of MAPT mRNA Throughout the CNS with Subcutaneous Administration

MAPT mRNA in NHP



3 x 3mg/kg weekly subcutaneous doses
Day 29, n=4/group, mean±SEM

RNAscope for MAPT mRNA in Hippocampus



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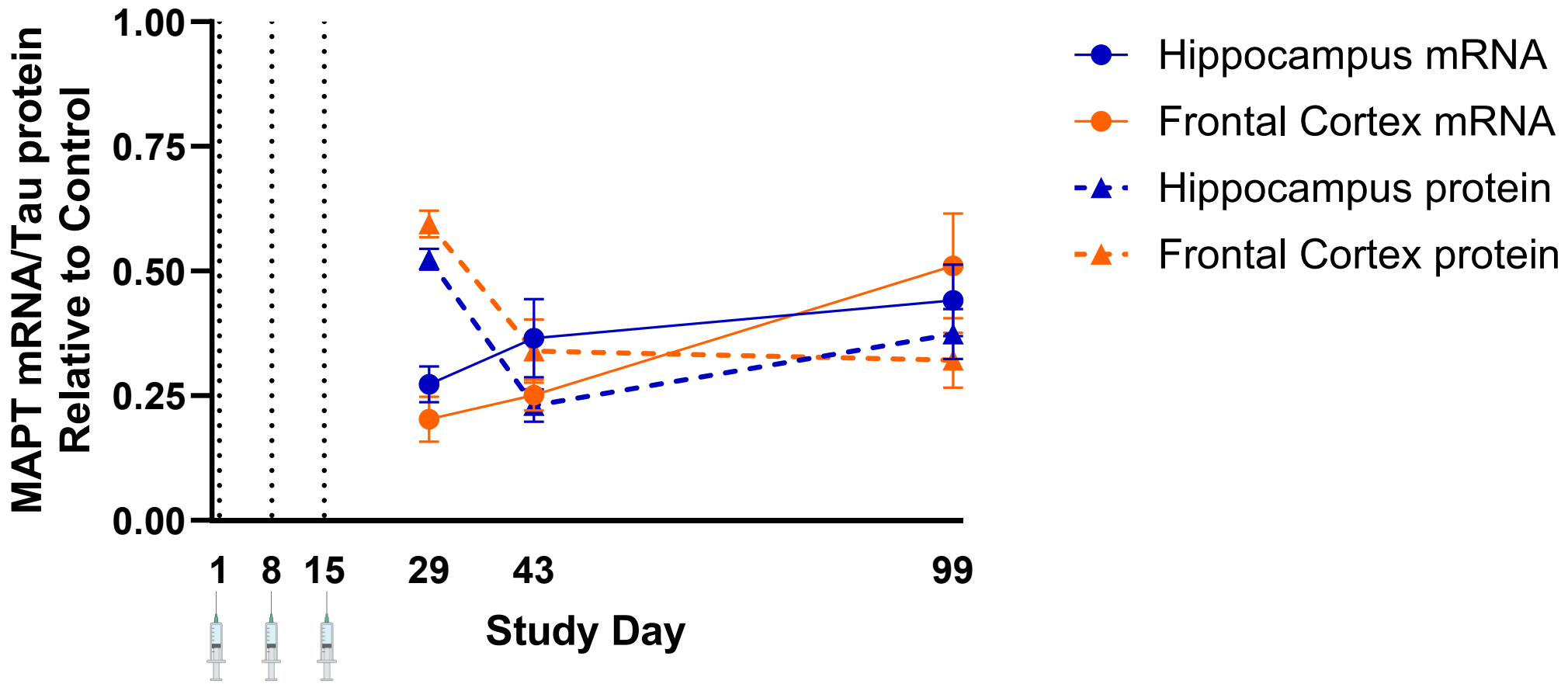
MAPT mRNA Reduction Translates into Long-Lasting Tau Protein Reduction After ARO-MAPT SC Treatment in NHP

MAPT/Tau Reduction in NHP



3 x 3mg/kg qw s.c.; n=4/group, mean±SEM

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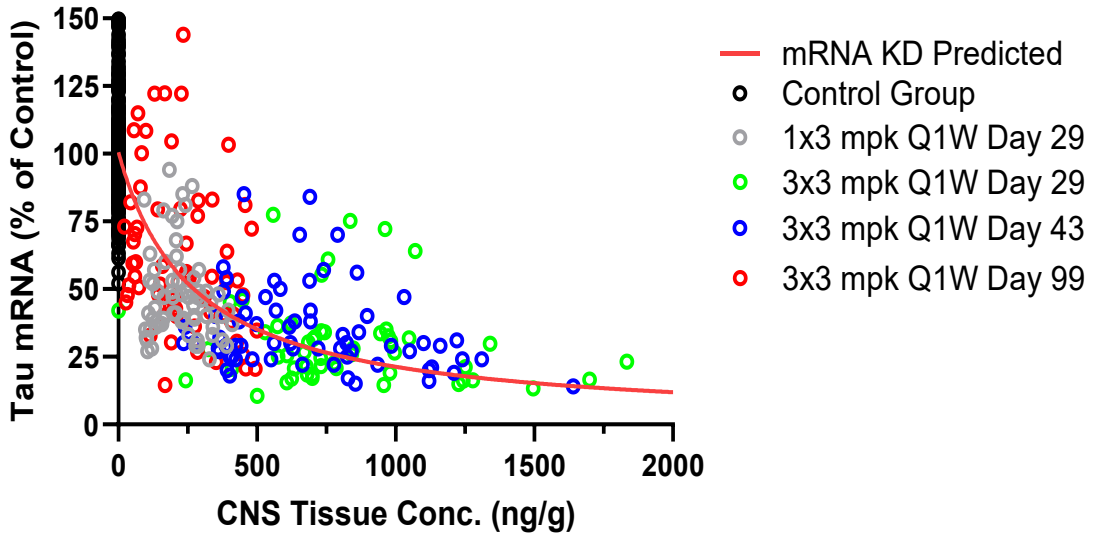
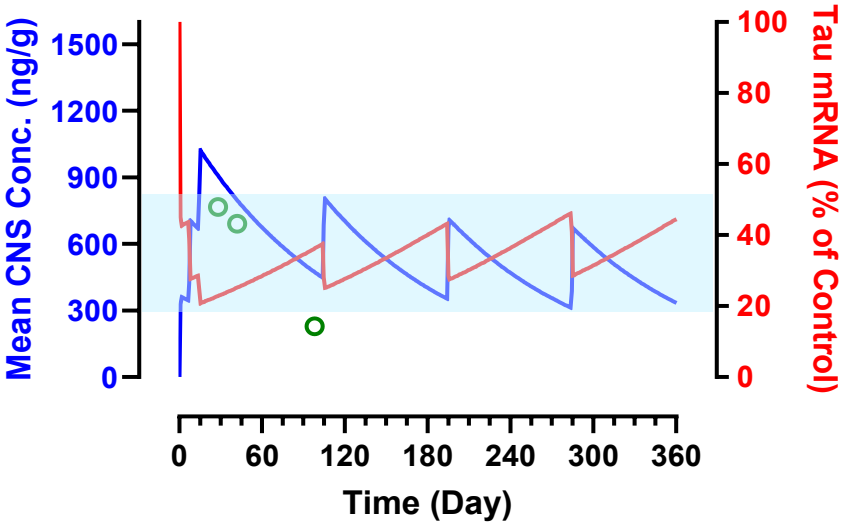
PK/PD Modeling Projects Sustained Tau Inhibition with Quarterly Dosing of ARO-MAPT SC

NHP Tissue Conc. vs Tau mRNA Level



- Calculated IC_{50} for mRNA KD in NHP CNS tissue ~270 ng/g
- Observed 3M postdose 3x3 mg/kg QW NHP CNS ~230 ng/g
- Longer CNS $t_{1/2}$ projected for human based on allometric scaling
- Assuming similar peak CNS exposure and a longer $t_{1/2}$ in humans:
  - 3x3 mg/kg QW with 3 mg/kg Q1M SC to maintain ~80% mRNA KD
  - **3x3 mg/kg QW with 3 mg/kg Q3M SC to maintain ~50-70% mRNA KD**

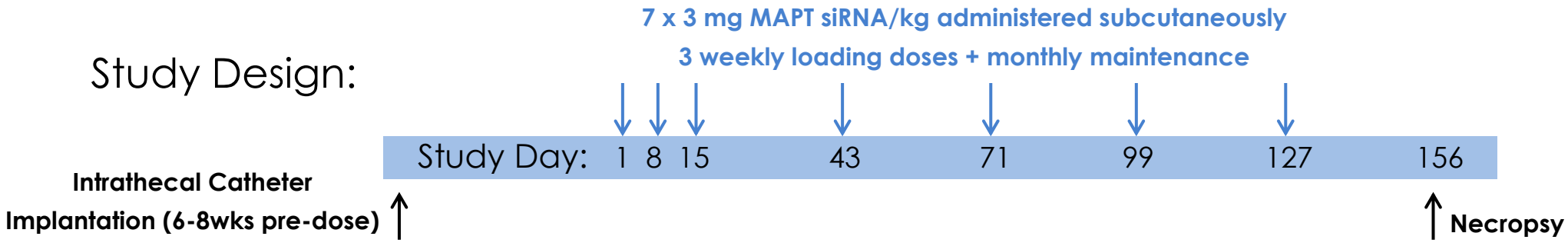
ARO-MAPT-SC 3x3 mg/kg Q1W SC with Q3M SC



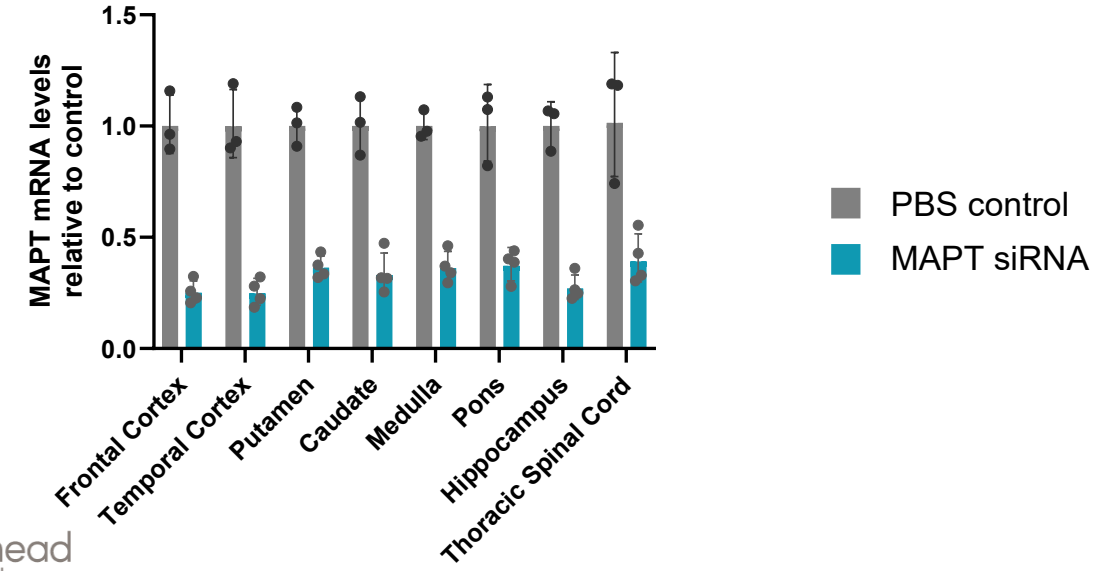
Blue Box represents 50-80% mRNA KD

Sustained Inhibition of Tau Protein After Repeat Dosing in NHP

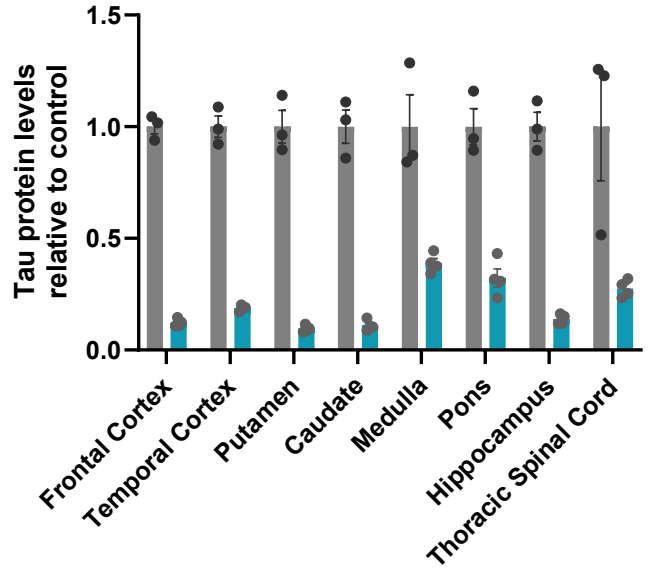
Study Design:



MAPT mRNA in NHP Brain Tissues Study Day 156



MAPT Protein in NHP Brain Tissues Study Day 156



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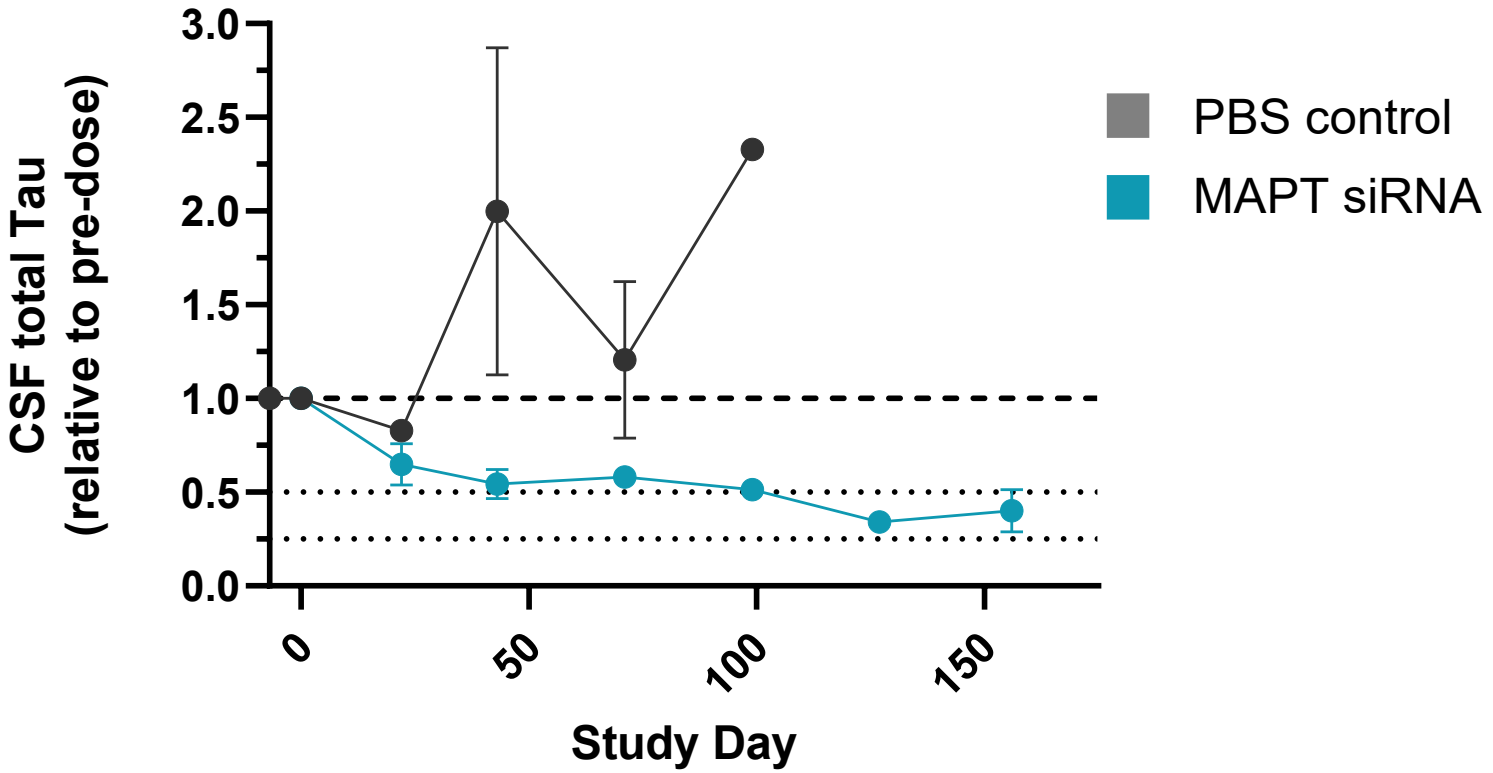
Tau Protein Reduction in Cerebrospinal Fluid Follows Reduction in CNS Tissues

65% Reduction in CSF Tau Protein after Four Months Repeat Dosing in NHP



mean±SEM, n=1-5.
2 timepoints post-catheter repair excluded

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ARO-MAPT SC Program Status

- siRNA targeting of MAPT has potential to treat most common (Alzheimer's) and rare forms of neurodegeneration caused by tauopathy
- Systemically delivered ARO-MAPT showed potent and long-lasting MAPT suppression in NHP, with potential for monthly or less frequent dosing
- Current formulation supports subcutaneous administration of 150mg siRNA in total volume of ≤ 4 ml, with optimization efforts ongoing
- GLP toxicology in NHP and mice completed, NOAEL is highest dose tested
- **ARO-MAPT Phase 1/2a CTA Filed, first dose planned before YE 2025**

ARO-MAPT-SC-1001 Phase 1/2a Clinical Study in Patients with Early Alzheimer's Disease †

Primary Endpoint

Safety and tolerability of ARO-MAPT-SC

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 (CTA submitted 9/2/2025)


Australia


Taiwan


Thailand


Canada


United Kingdom

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† Defined as MCI due to AD or Mild AD Dementia

Key Takeaways

Expanding portfolio in neurodegenerative diseases, targeting well-validated, difficult to drug disease-causing proteins

- First intrathecal clinical program underway for SCA2
- MAPT CTA filed

Two CNS TRiM™ delivery platforms with compelling preclinical data

- Intrathecal – Preferential distribution to spinal cord, cortex and cerebellum
- Systemic – Uniform and tunable distribution throughout the CNS

Subcutaneous delivery platform expands CNS-targeting feasibility to include larger patient populations and diseases with deep brain involvement

Arrowhead Teamwork

- Corporate headquarters
- Clinical & Regulatory

Corporate Headquarters

177 East Colorado Boulevard, Ste 700
Pasadena, CA 91105

Research and Development

502 South Rosa Road
Madison, WI 53719

- Discovery Chemistry
- Discovery Biology
- Toxicology

- CNS Discovery Biology
- Discovery Chemistry
- Translational Genetics & Data Sciences
- Clinical & Regulatory

Research and Development

10102 Hoyt Park Drive
San Diego, CA 92131

Research and Manufacturing

1080 Arrowhead Way
Verona, WI 53593

- CMC
- GMP Manufacturing

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Thank You!

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