Developing siRNA for Neurodegenerative Diseases

Christine Esau, Ph.D.

RNA at the Bench and Bedside IV

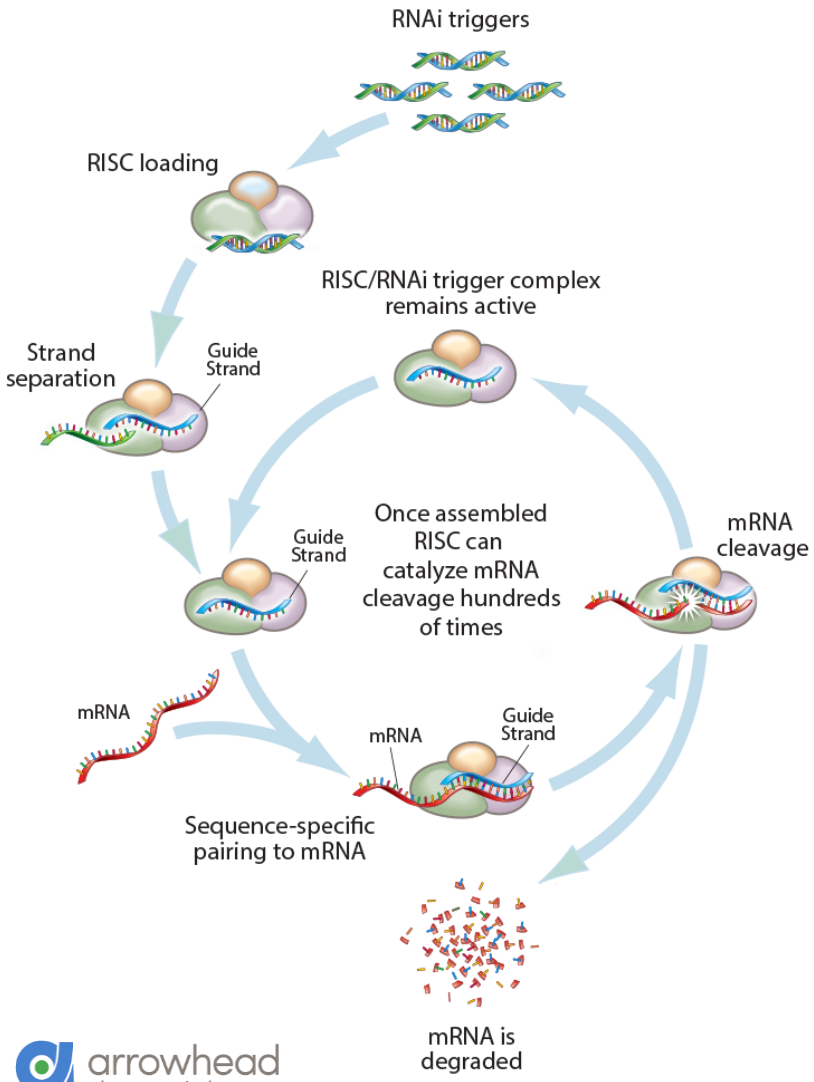
December 9, 2024

arrowhead pharmaceuticals

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.

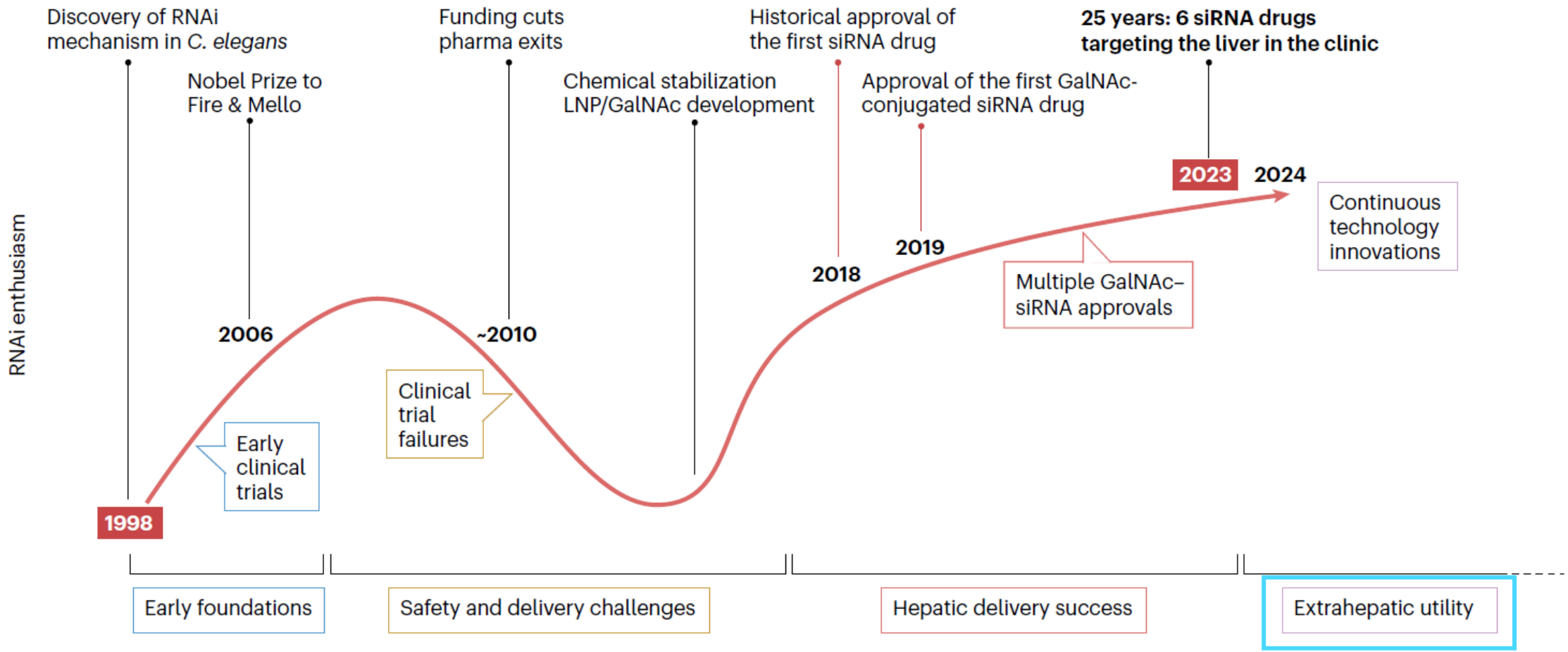
RNA Interference as a Therapeutic Modality



- RNAi co-opts the **natural pathway** for microRNA regulation of gene expression
- Double stranded RNAi triggers engage RNA-induced silencing complex (RISC) to sequence-specifically recognize and **potently** cleave target mRNAs
- Any protein-coding gene in the genome can be targeted - **all targets are druggable**
- **Rapid**, cost effective, and potentially lower risk relative to traditional approaches
- However, RNA requires chemical stabilization and facilitated delivery into cells to be a drug

arrowhead pharmaceuticals

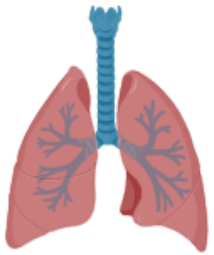
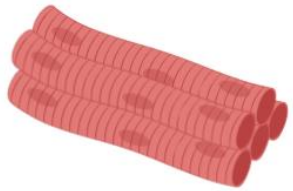
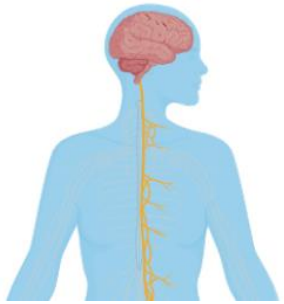
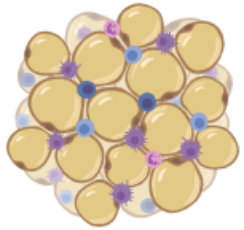
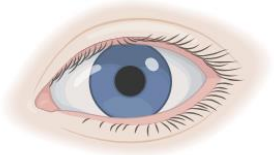
The Long Road to Establish siRNA as a Therapeutic Modality



Tang and Khvorova, 2024, Nature Rev Drug Discovery

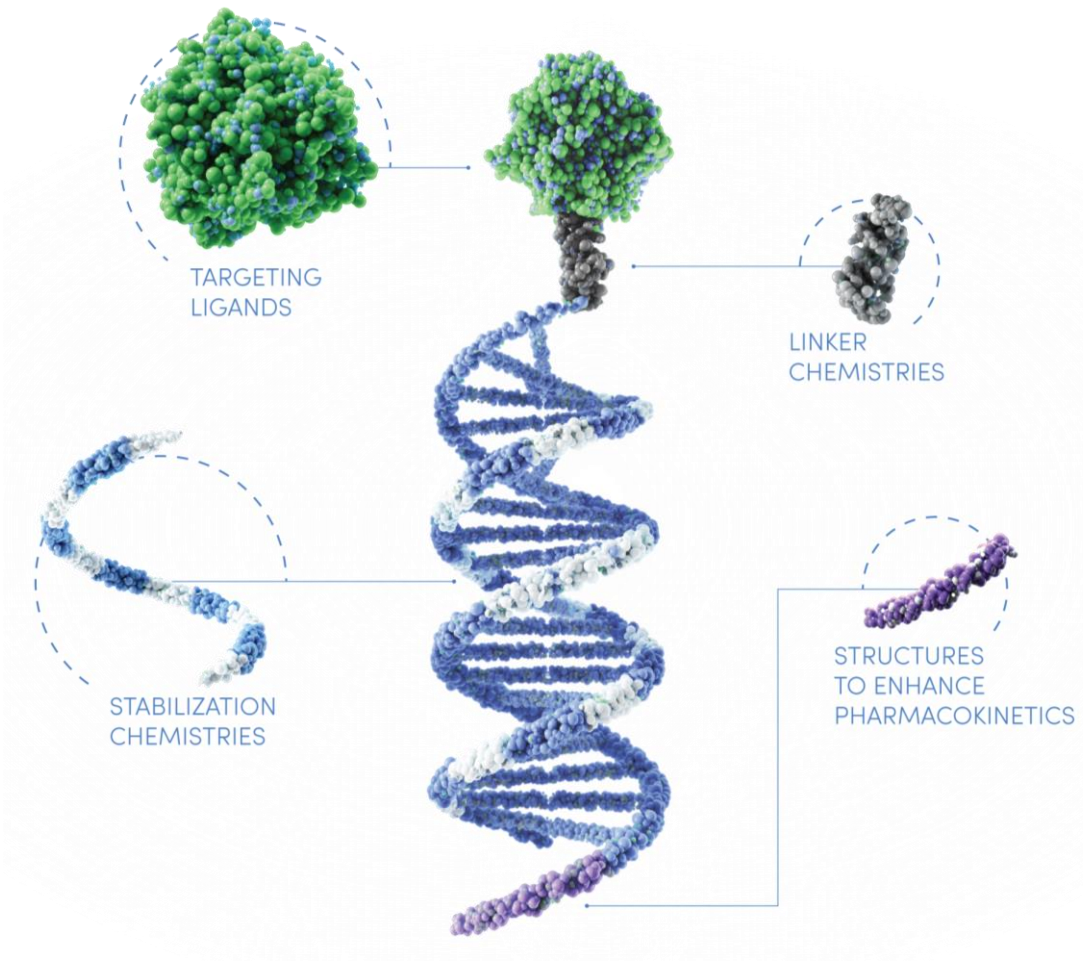
arrowhead pharmaceuticals

TRiM™ Platforms Drive Robust Pipeline for Multiple Tissue Types

Liver	Lung	Skeletal Muscle	CNS	Adipose	Ocular
					
Strong clinical validation	Deep lung clinical validation (RAGE)	Early clinical testing	Preclinical Stage FIH Q1, 25	Preclinical Stage FIH Q1, 25	Preclinical Stage

- TRiM™ technology enables oligonucleotide delivery to liver and multiple extrahepatic tissues

Arrowhead's TRiM™ Platform: Targeted RNAi Molecule



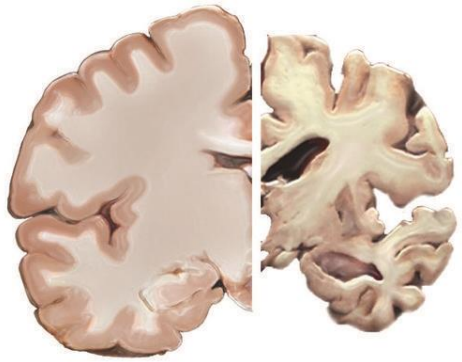
- A modular system
- Unique RNAi chemistry insights and experience
- Powerful platform technology to maximize activity and stability employing:
  - Algorithmic approach to sequence selection and design
  - Stabilization chemistry
  - Targeting ligands – small molecules, peptides, proteins
  - Linker chemistry
  - PK and PD enhancers

arrowhead pharmaceuticals

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)

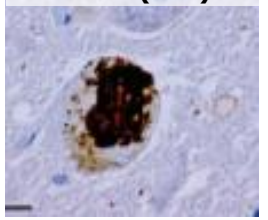
Tauopathies
- Alzheimer's disease (AD)
- Fronto-temporal dementia (FTD)
- Progressive Supranuclear Palsy
- Corticobasal Degeneration

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

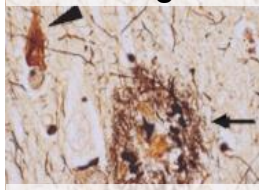
Synucleinopathies
- Parkinson's disease (PD)
- Lewy body dementia
- Multiple system atrophy

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

SOD1 (ALS)

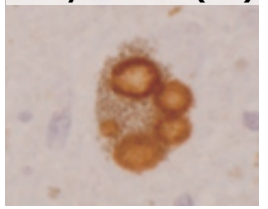


Tau tangles

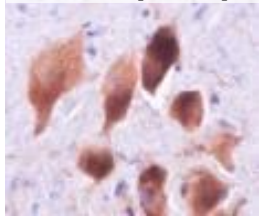


Amyloid plaques

Lewy bodies (PD)

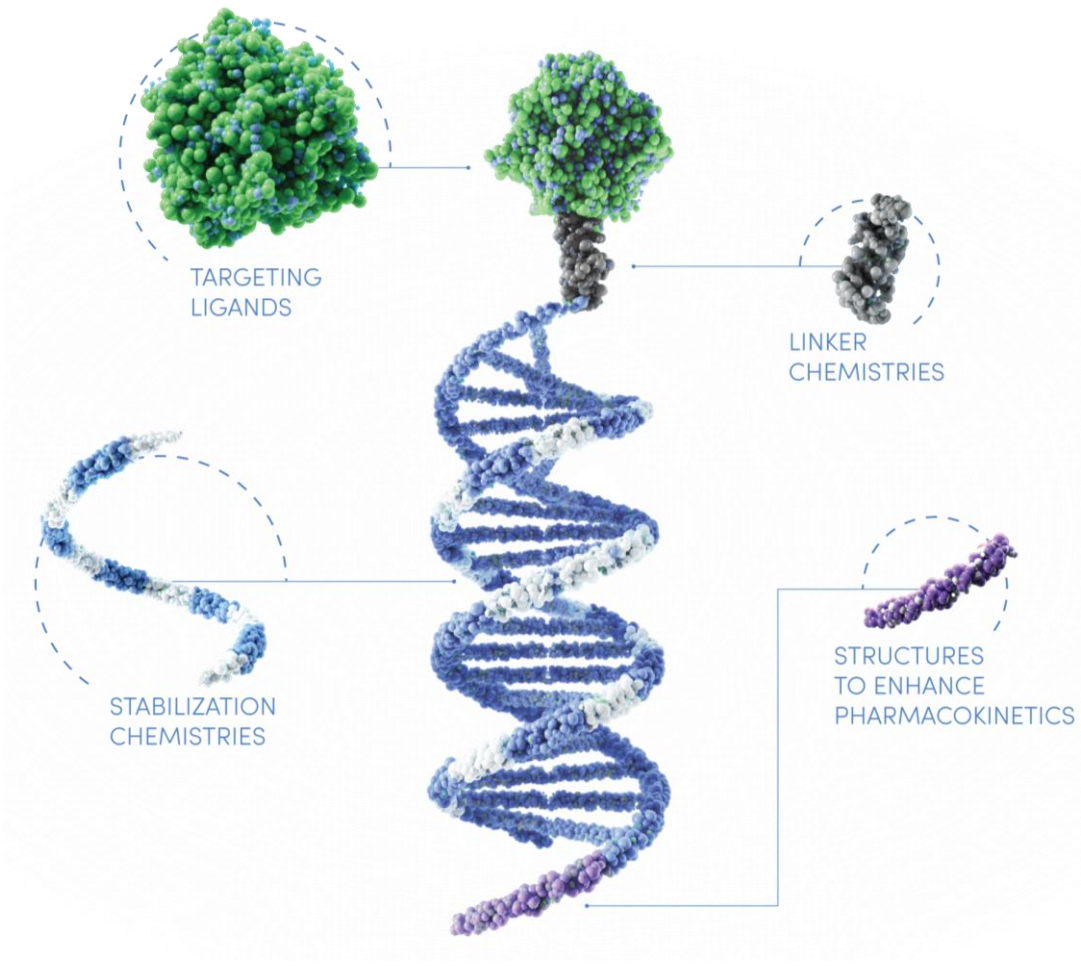


ATXN2 (SCA2)



arrowhead pharmaceuticals

First Gen CNS-Targeting TRiM™ Platform Intrathecal (IT) Administration



We Have Developed an Optimized Intrathecal Delivery Platform for CNS

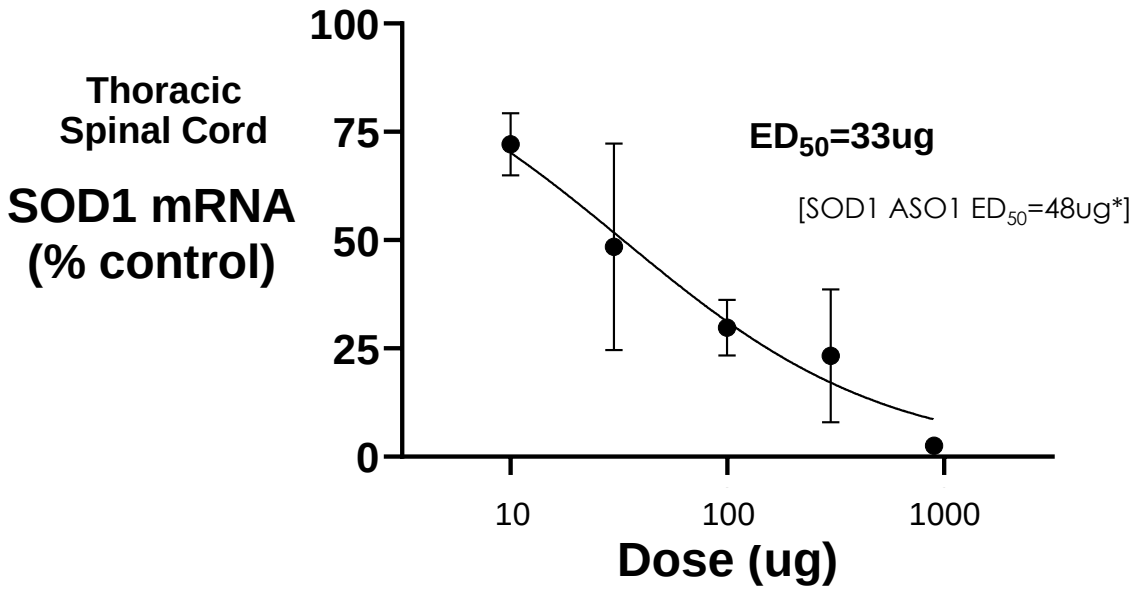
- **Simple** lipid-conjugate design
- **Potent** target mRNA reduction
- **Broad distribution** throughout the brain and to all relevant cell types in rodent and monkey
- **Long duration of action** with potential for infrequent (quarterly or half-yearly) dosing
- **Safety** Initial GLP tox complete with no serious adverse findings

arrowhead pharmaceuticals

Potent Reduction of Target mRNA in Rodent Models

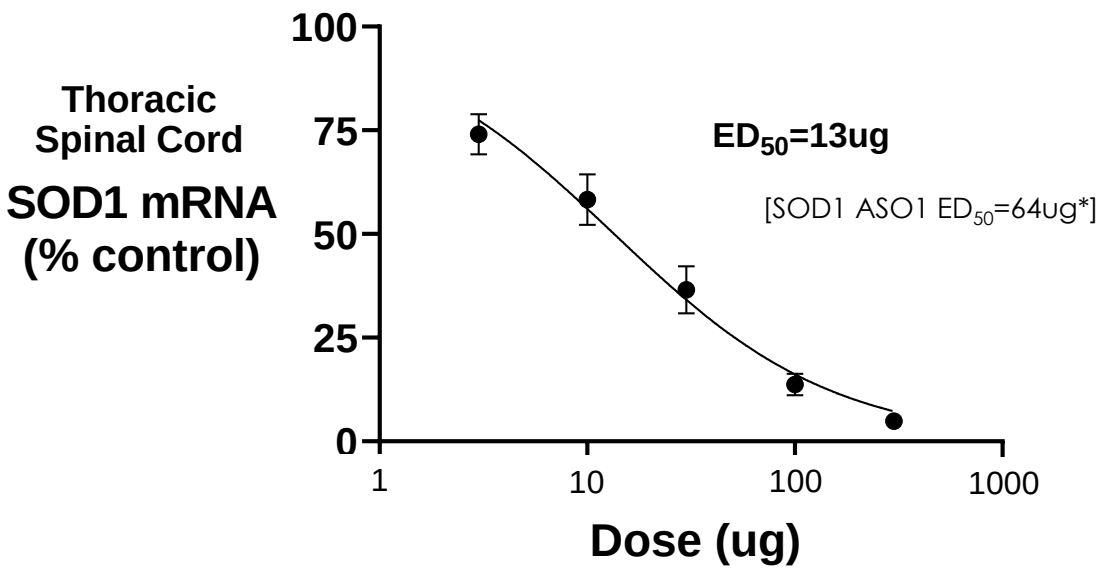
Transgenic Rat

Single Dose IT – 4 Weeks Post Dose



Transgenic Mouse

Single Dose ICV – 2 Weeks Post Dose



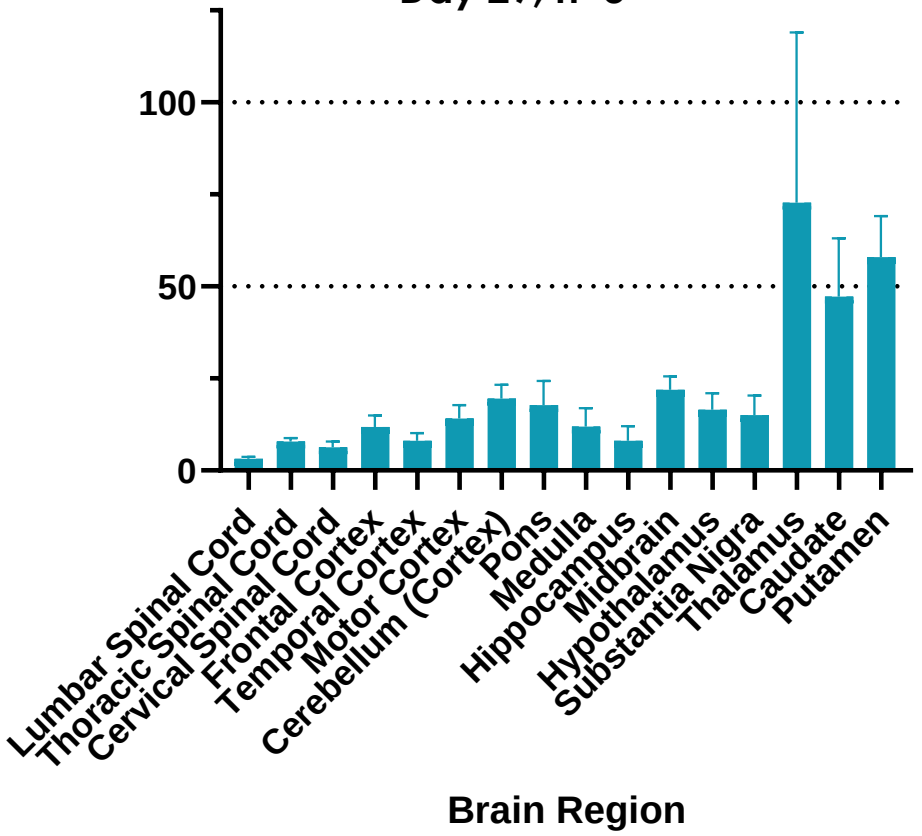
*McCampbell et. al. 2018

arrowhead pharmaceuticals

Target Knockdown Throughout the CNS and Distribution to All Relevant Cell Types in Non-Human Primate

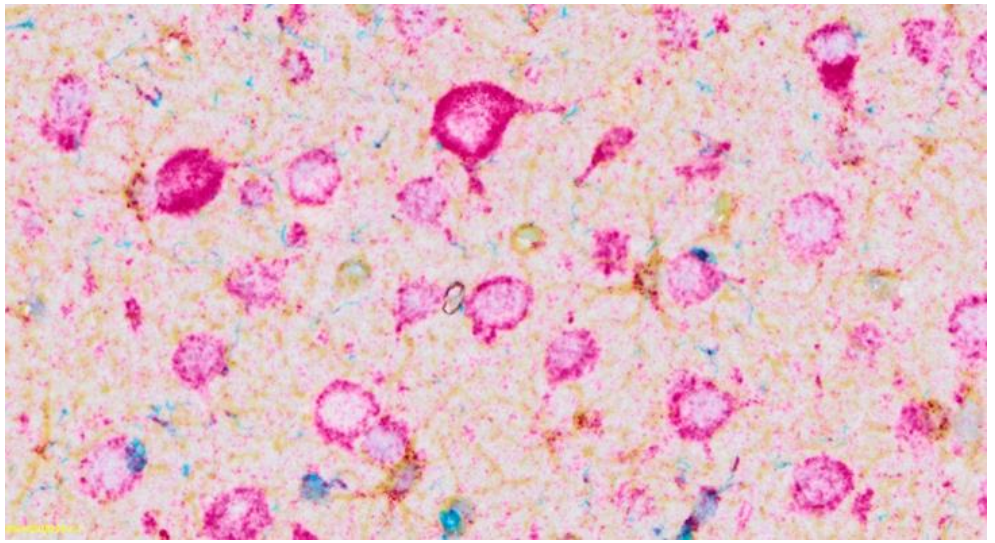
SOD1 mRNA Reduction in NHP

Single Intrathecal Dose of SOD1 siRNA, 45mg, Day 29, n=3



siRNA Delivery to Relevant Cell Types in NHP Cortex

Neurons, Astrocytes, Microglia



miRNAscope™ Detection of siRNA by in situ Hybridization

Red = siRNA

Yellow = astrocytes (GFAP)

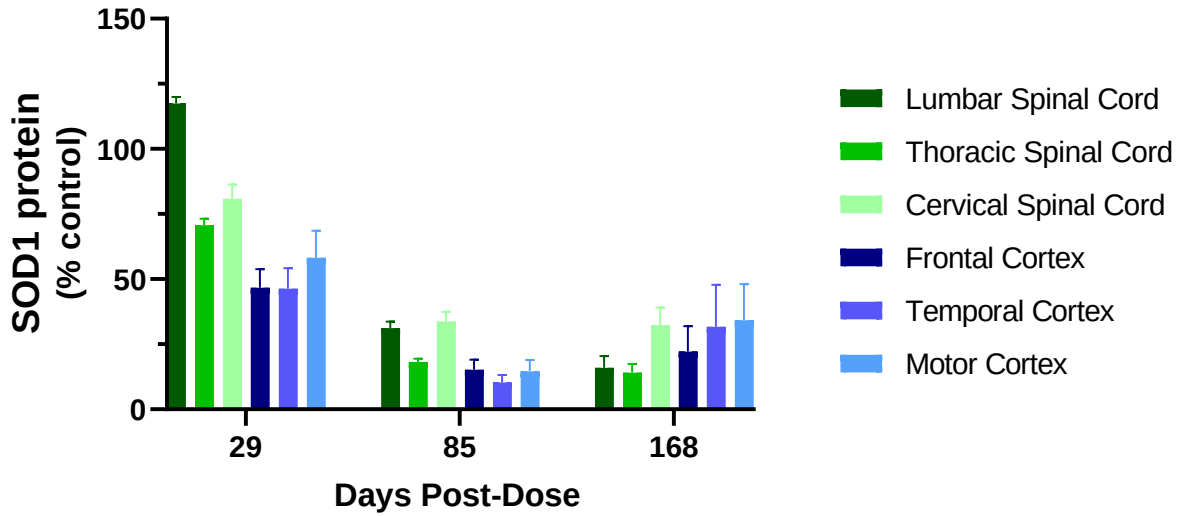
Blue = microglia (IBA1)

arrowhead pharmaceuticals

Long Duration of Action in NHP Supports Up to Half-Yearly Dosing

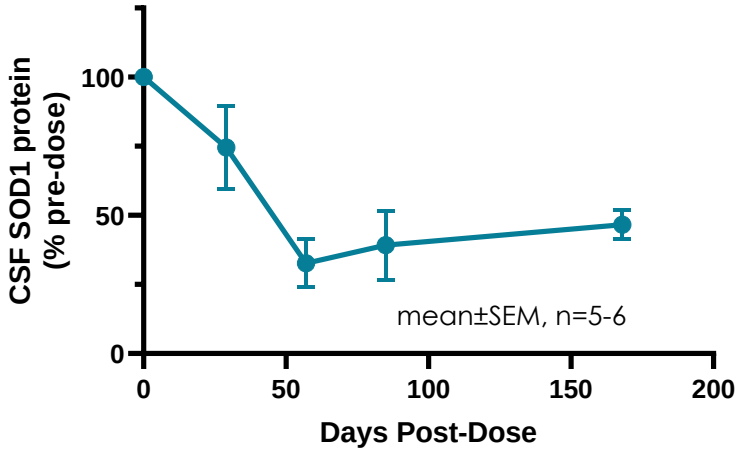
SOD1 Protein Reduction

Single 45mg IT dose, n=3-5/group, mean±SEM

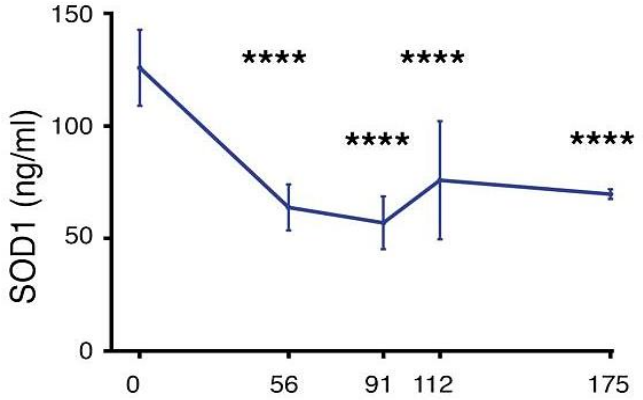


*McCampbell et. al. 2018

SOD1 Protein in CSF



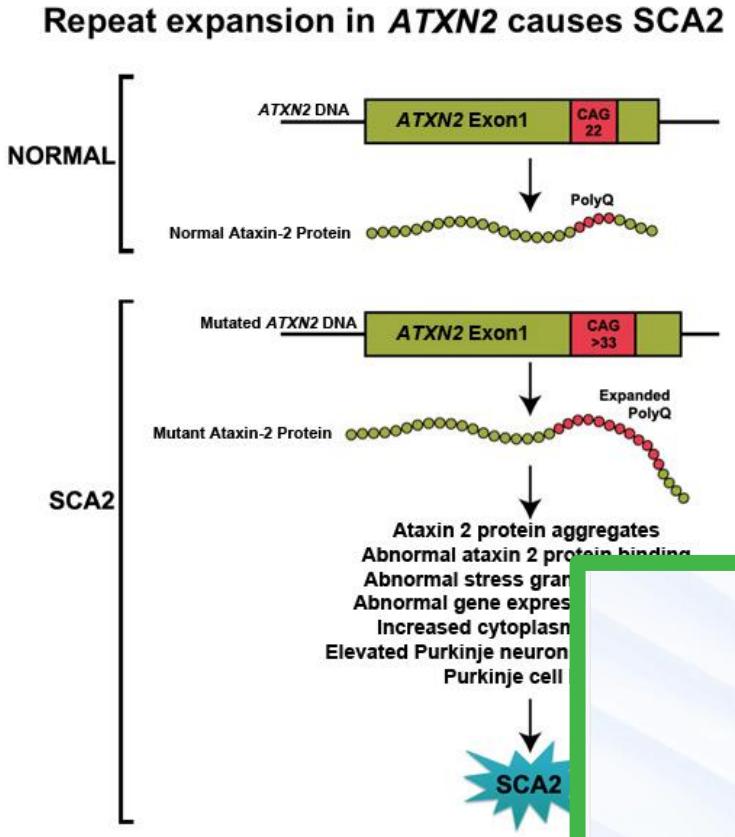
Up to 70% reduction after single 45mg dose



SOD1 ASO1* ~50% reduction in CSF SOD1 in NHP 5 x 35mg doses

arrowhead pharmaceuticals

ARO-ATXN2 for Spinocerebellar Ataxia 2 (SCA2)
First Intrathecal Clinical Program



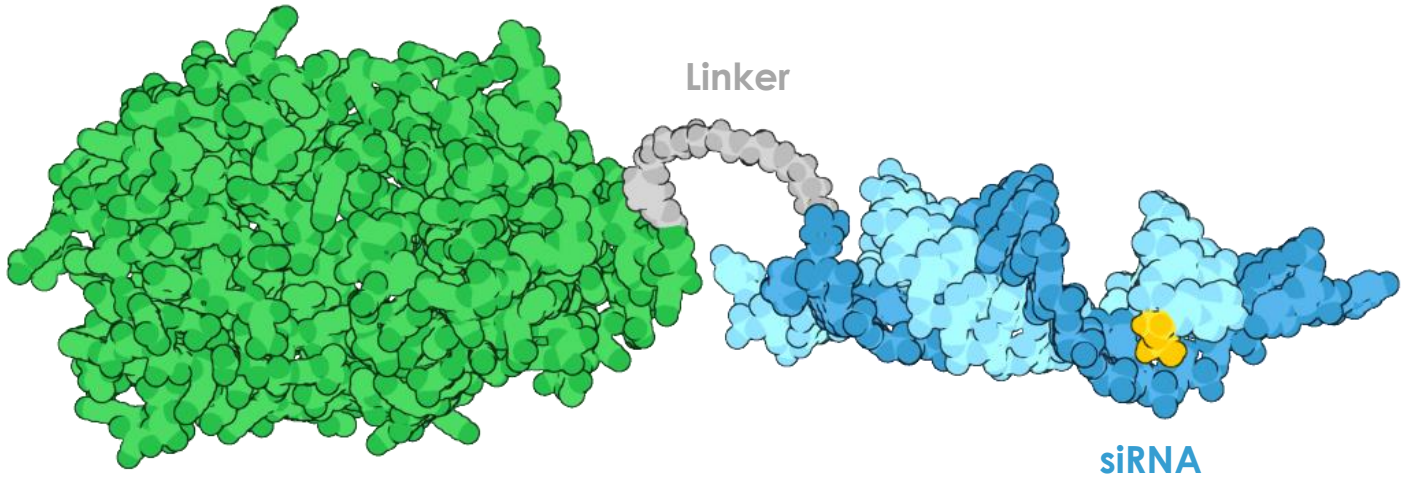
- SCA2 is a dominantly inherited repeat expansion disorder which makes up ~15-20% of all SCA cases (~5 people in 100,000)
- Caused by gain of function of mutant expanded polyQ ATXN2 protein
- It is a progressive cerebellar ataxia w/ instability of stance, speech and swallow disorder, pain, spasticity, and ocular signs - some also present parkinsonism or ALS phenotypes
- SCA2 patients develop symptoms at age 20-30, need a

Arrowhead Pharmaceuticals Announces Global License and Collaboration Agreement with Sarepta Therapeutics for Multiple Clinical and Preclinical Programs

Stefan Pulst Lab

arrowhead pharmaceuticals

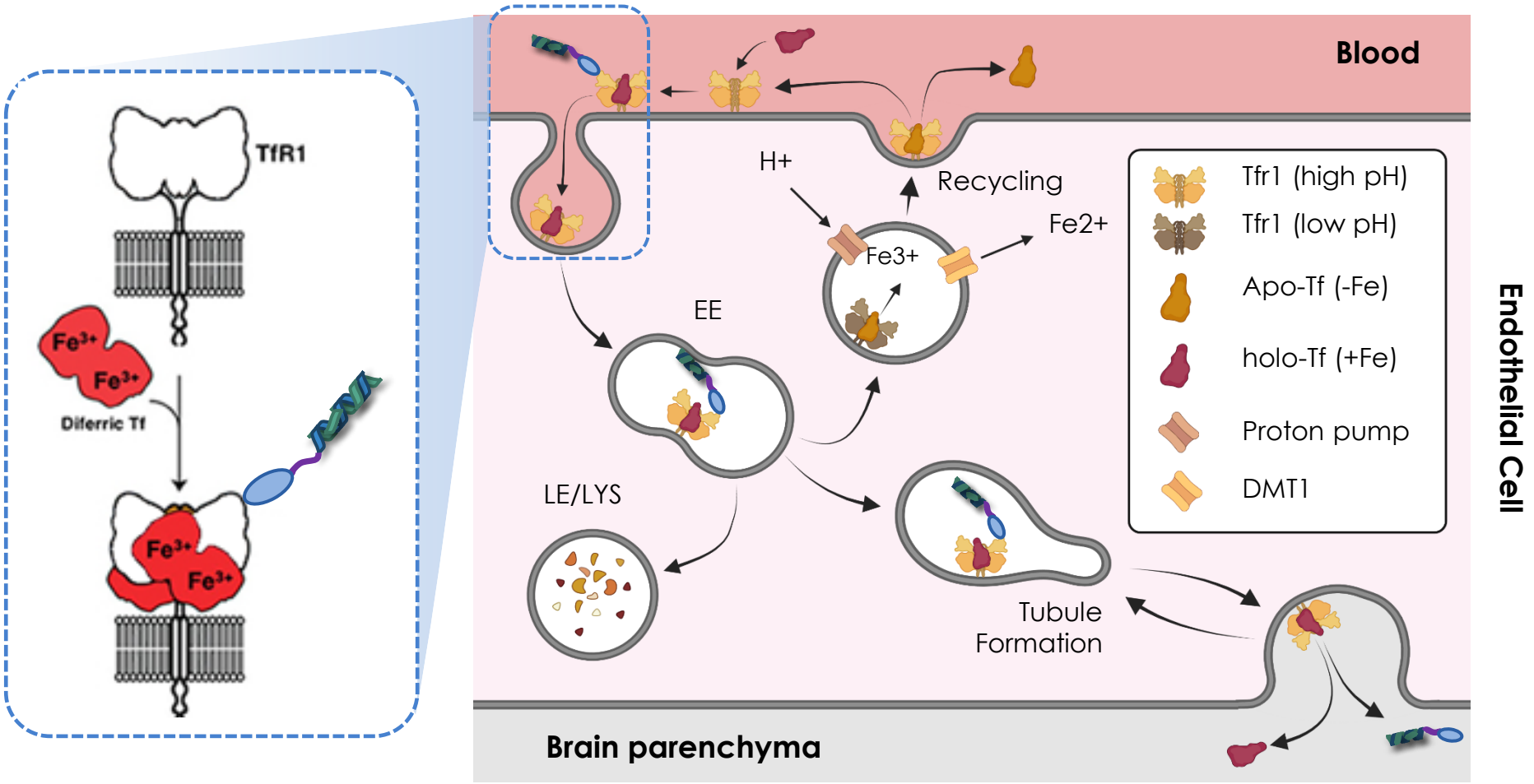
Next Gen. CNS-Targeting TRiM™ Platform via Subcutaneous Administration



We Have Developed an Optimized Systemic Delivery Platform for CNS

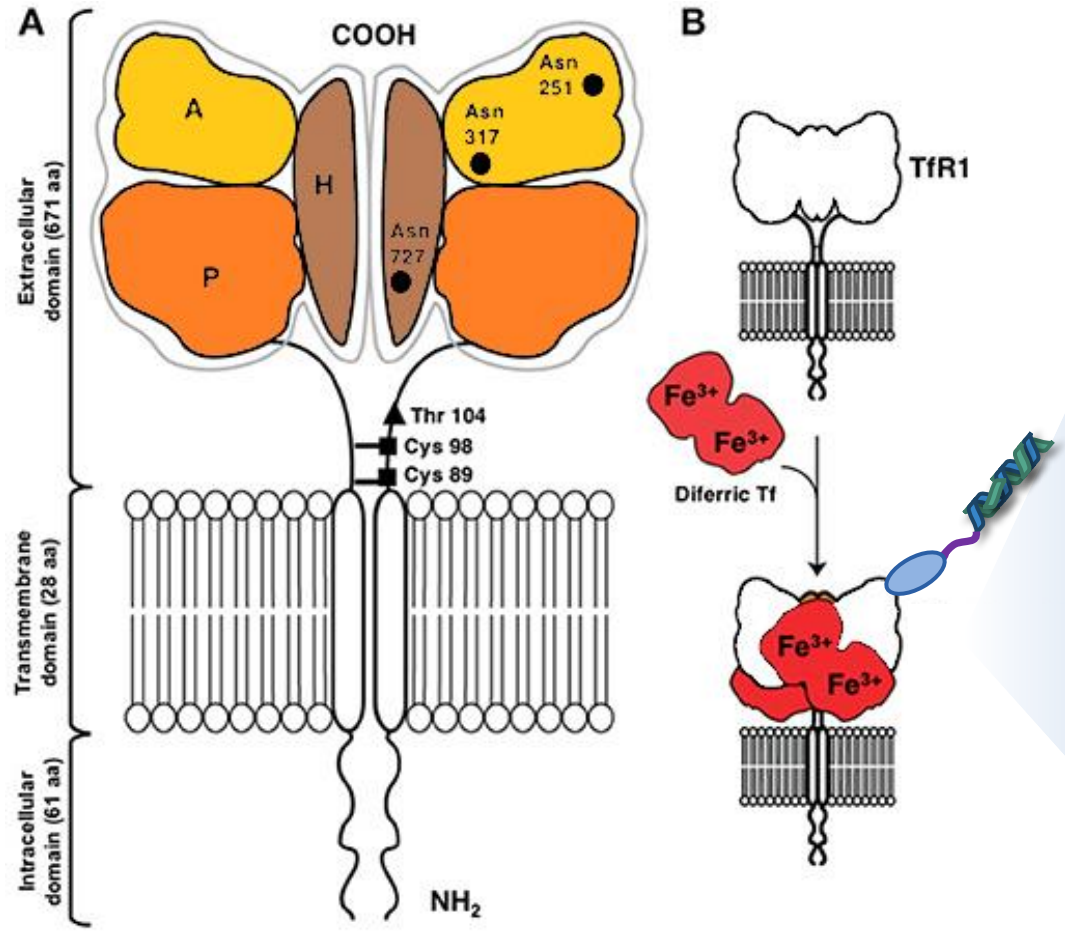
- **Ligand-driven** delivery via noninvasive BBB penetration and cellular uptake in brain tissue
- **Effective** and durable reduction in expression levels of therapeutically-relevant gene targets
- **Convenient** dosing via subcutaneous (SC) administration with potential for monthly to quarterly dosing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

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

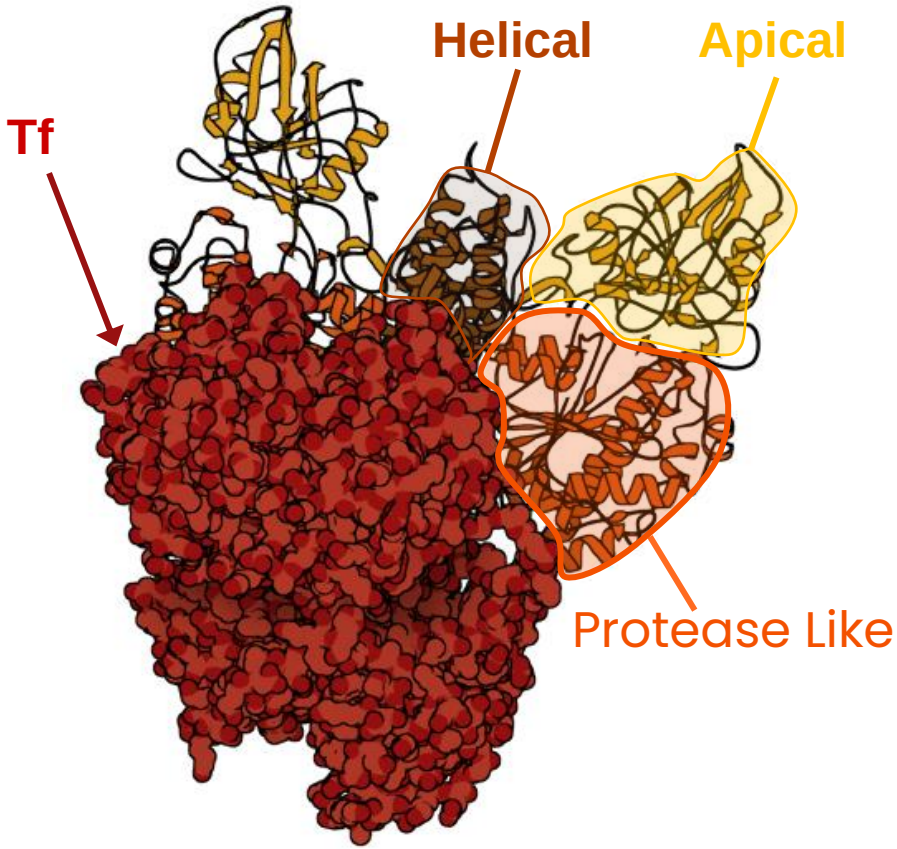


- TfR1 highly enriched in endothelium of the blood-brain barrier (BBB)
- Fast kinetics of internalization and recycling

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



Front Immunol. 2021; 12: 607692.

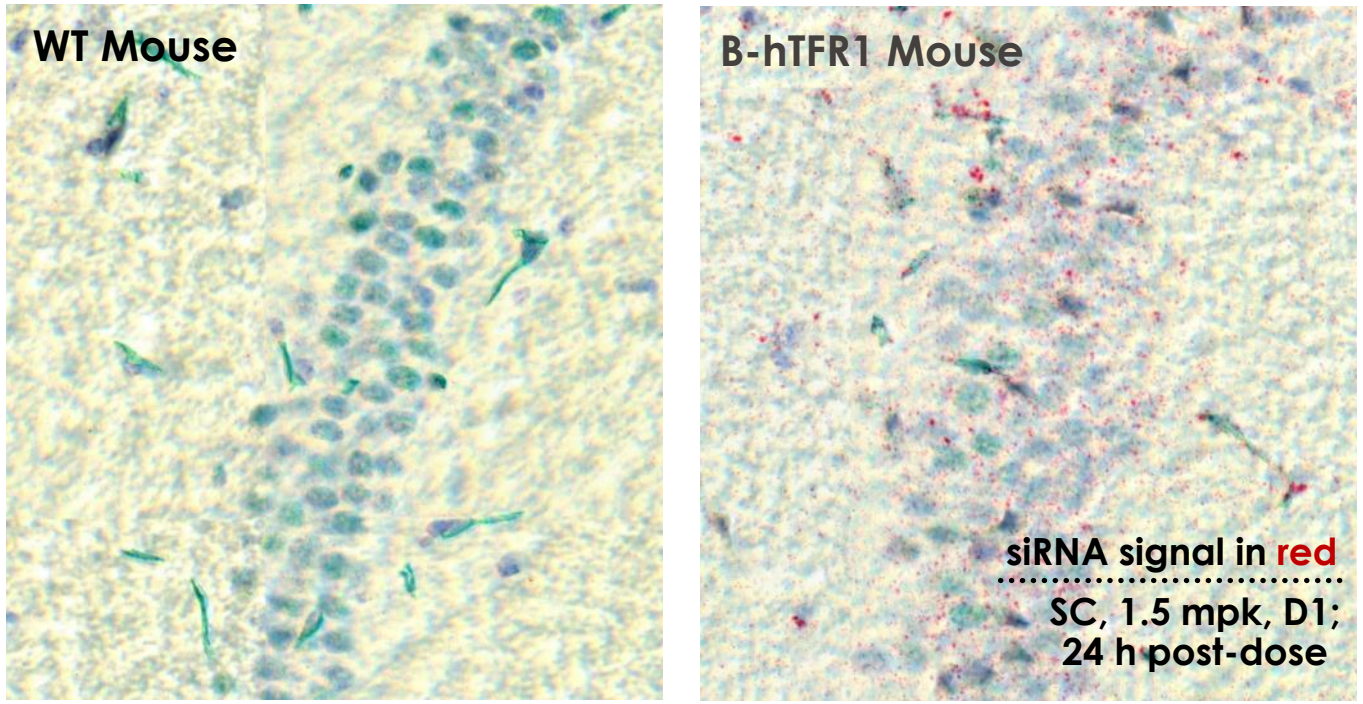


Transferrin (up to 4 mg/mL in serum) occludes helical and protease like domains

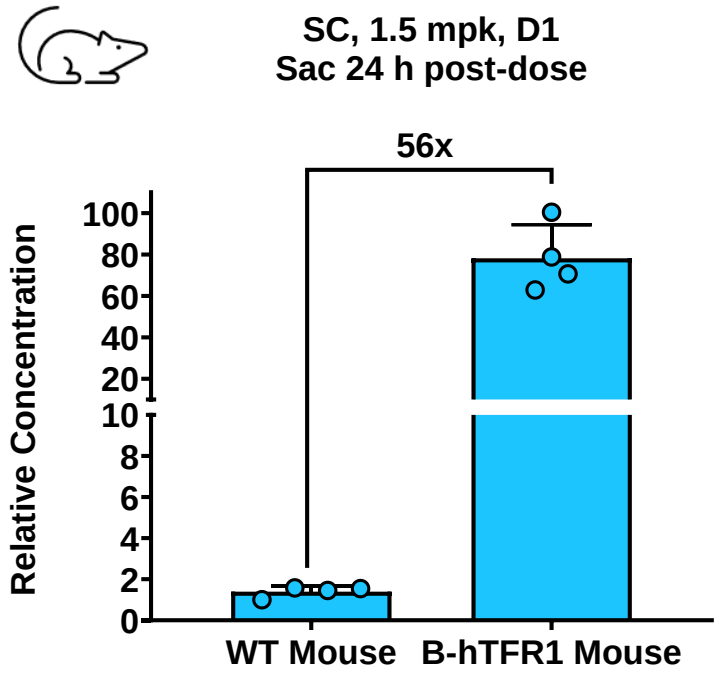
arrowhead pharmaceuticals

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

siRNA Visualization in Hippocampus



siRNA Concentration in Half Brain

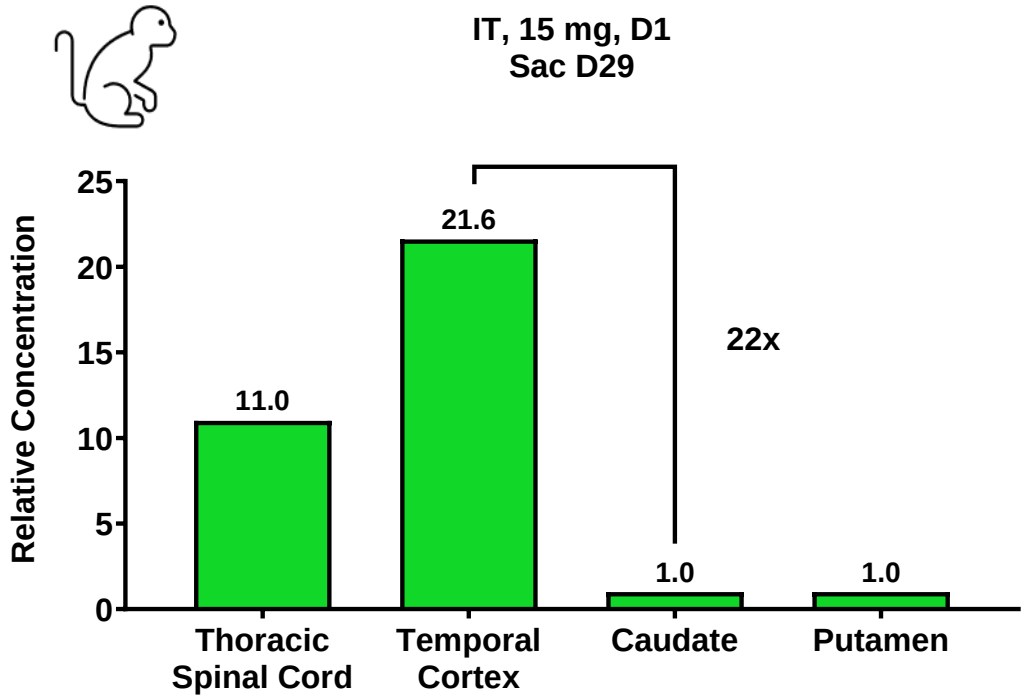


- Tissue-staining shows greater accumulation of siRNA in B-hTFR1 mouse brain than WT
- siRNA quantitation in mouse brain shows over 50x difference between TfR1-expressing and non-expressing groups

arrowhead pharmaceuticals

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

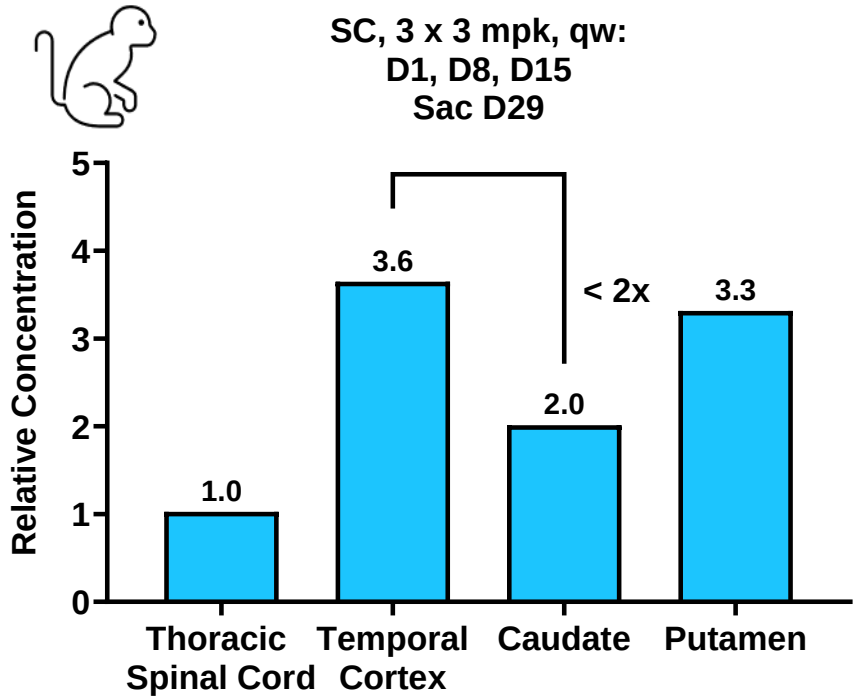
siRNA Concentrations in NHP Brain Regions by IT



By IT administration:

- Relatively limited delivery to deep brain regions

siRNA Concentrations in NHP Brain Regions by SC



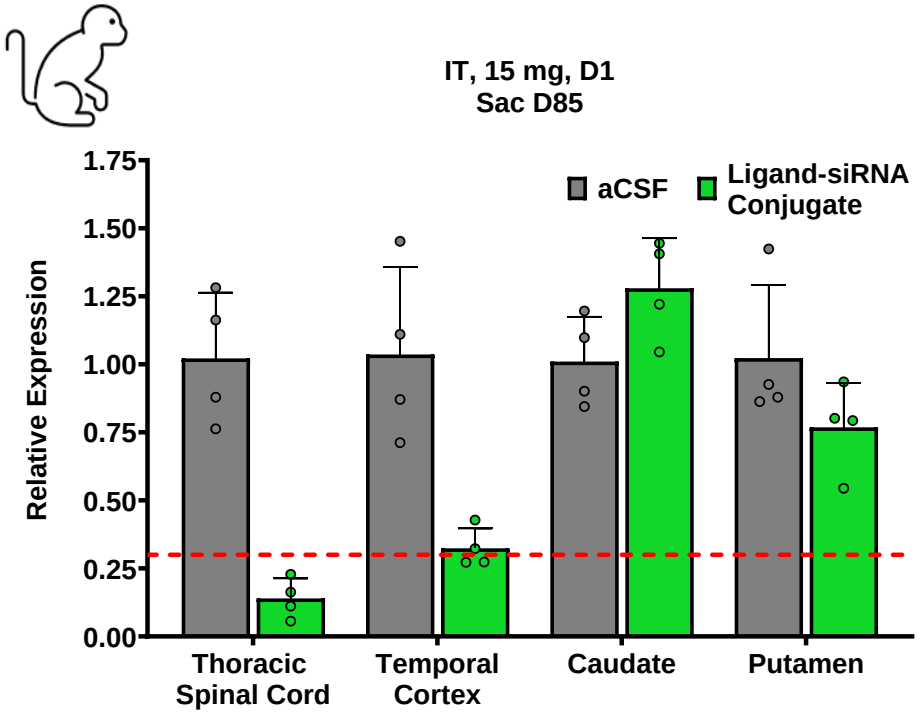
By subcutaneous administration:

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

arrowhead pharmaceuticals

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

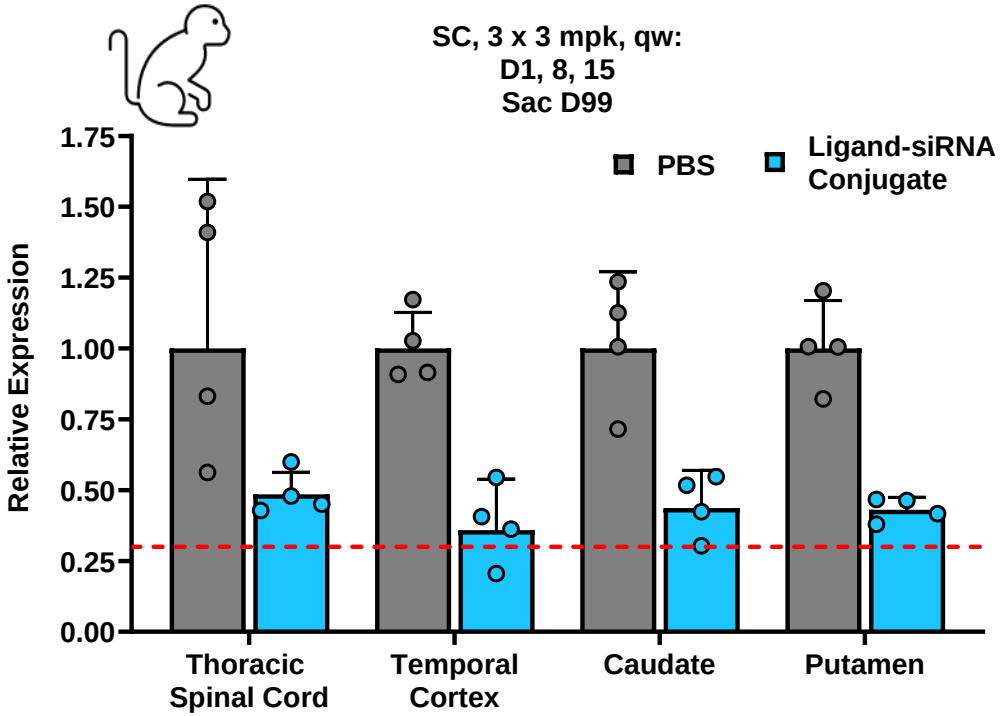
MAPT mRNA Reduction in NHP Brain Regions by IT



By IT administration:

- Minimal mRNA reduction in deep brain region

MAPT mRNA Reduction in NHP Brain Regions by SC



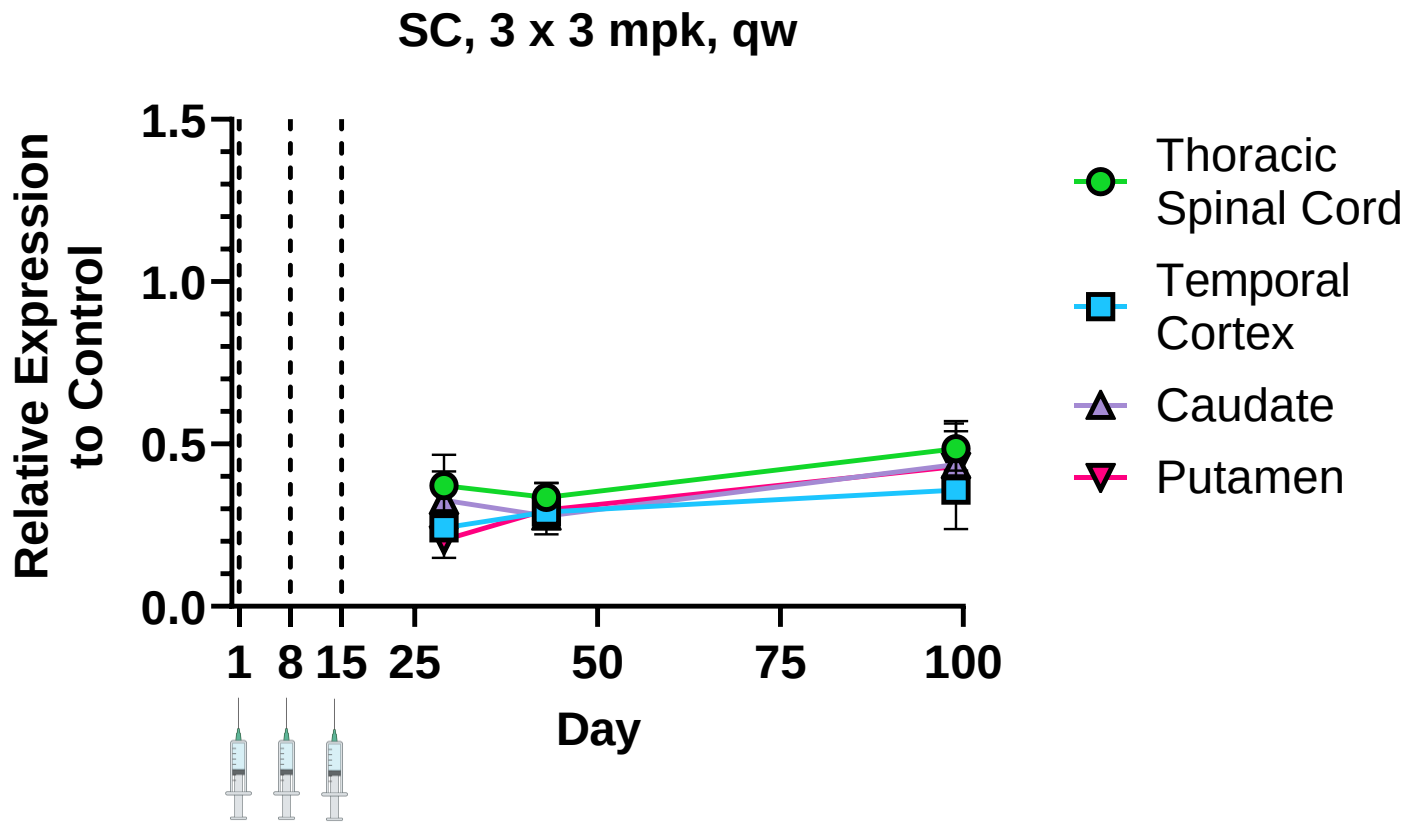
By subcutaneous administration:

- Even mRNA reduction across brain regions, including deep brain

arrowhead pharmaceuticals

TRiM™ CNS-SC Platform Maintains Knockdown Duration Throughout CNS Regions in NHP

KD Duration of MAPT mRNA in NHP



Days: 1, 8, 15; N=4

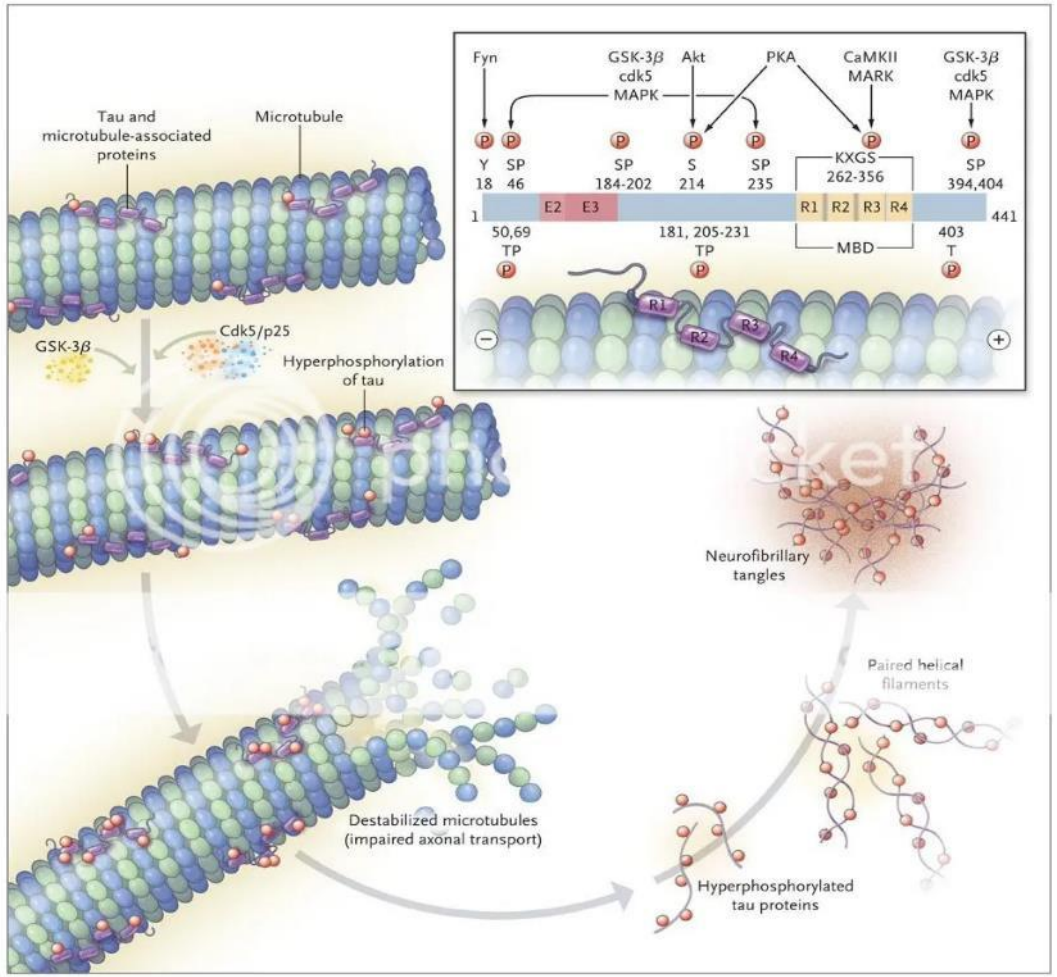
- Duration supports monthly to quarterly dosing regimen
- Formulation supports SC administration in human
  - 150 mg of siRNA in ≤ 4 mL total volume

arrowhead pharmaceuticals

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

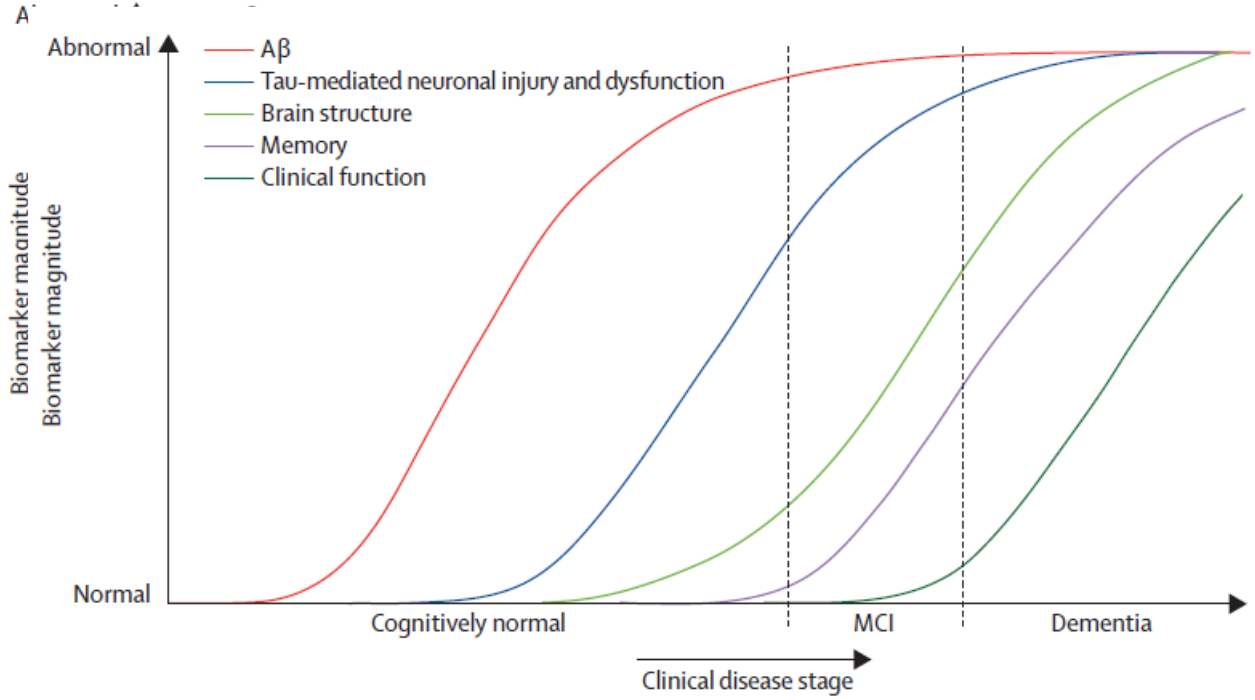


Querfurth & LaFerla, *NEJM* 2010;362:329-44

arrowhead pharmaceuticals

ARO-MAPT SC for Alzheimer's Disease

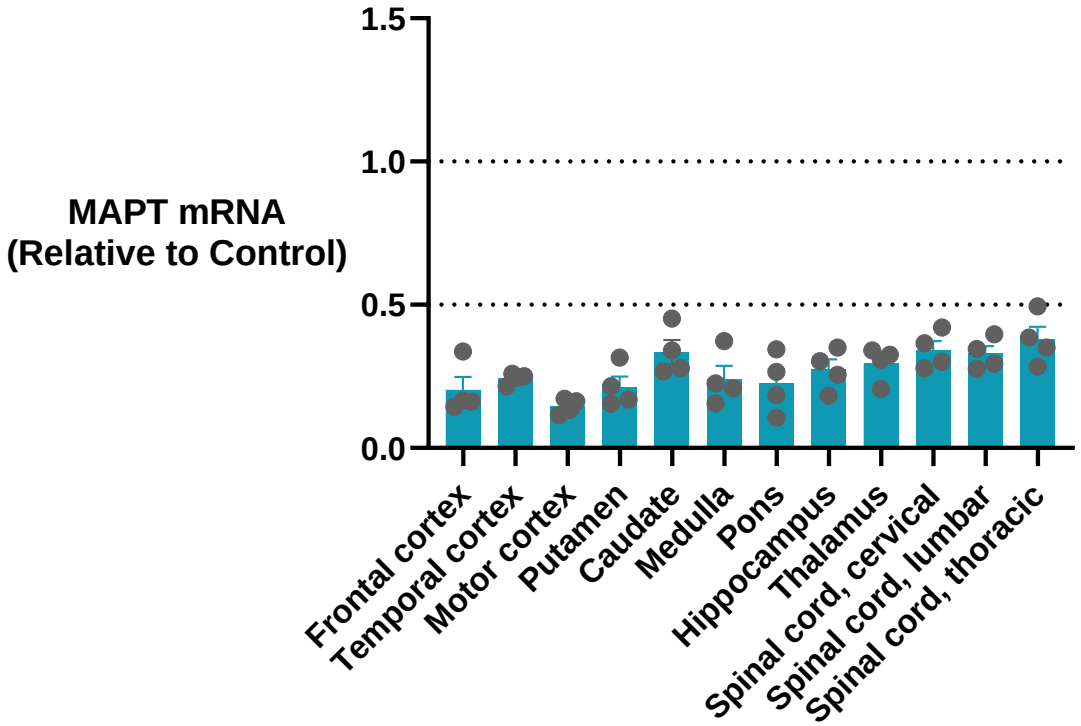
Amyloid Plaque Precedes Tau Pathology in Alzheimer's Disease



- 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**

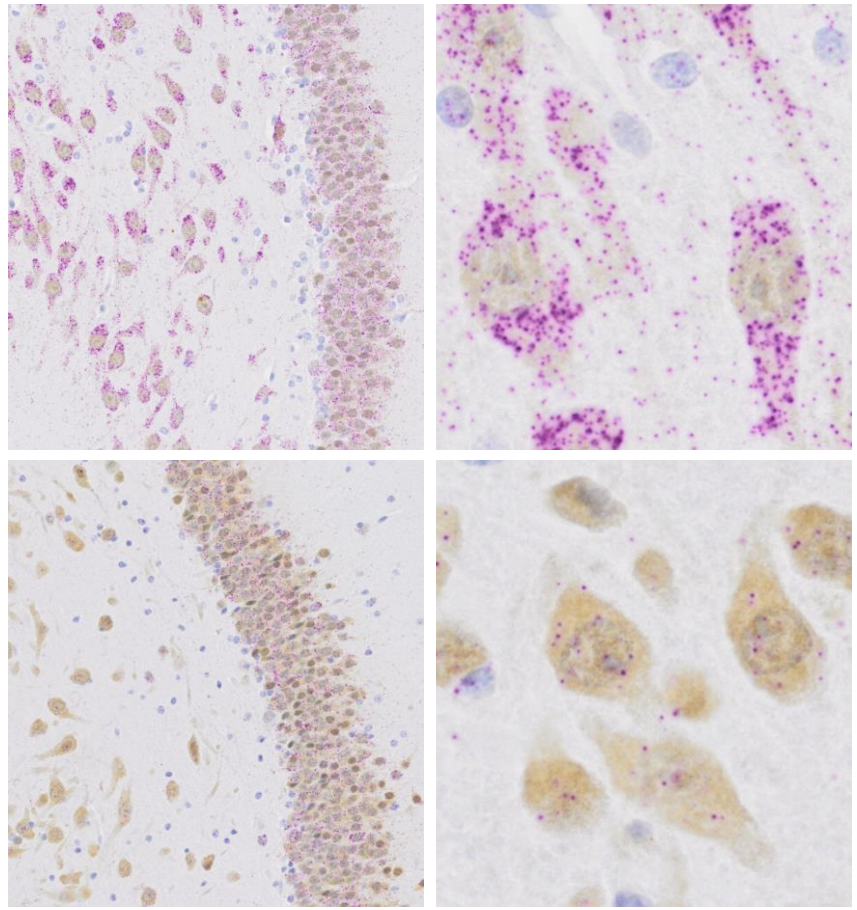
ARO-MAPT SC Achieves Deep Knockdown of MAPT mRNA Throughout the CNS with Subcutaneous Administration

MAPT mRNA in NHP



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

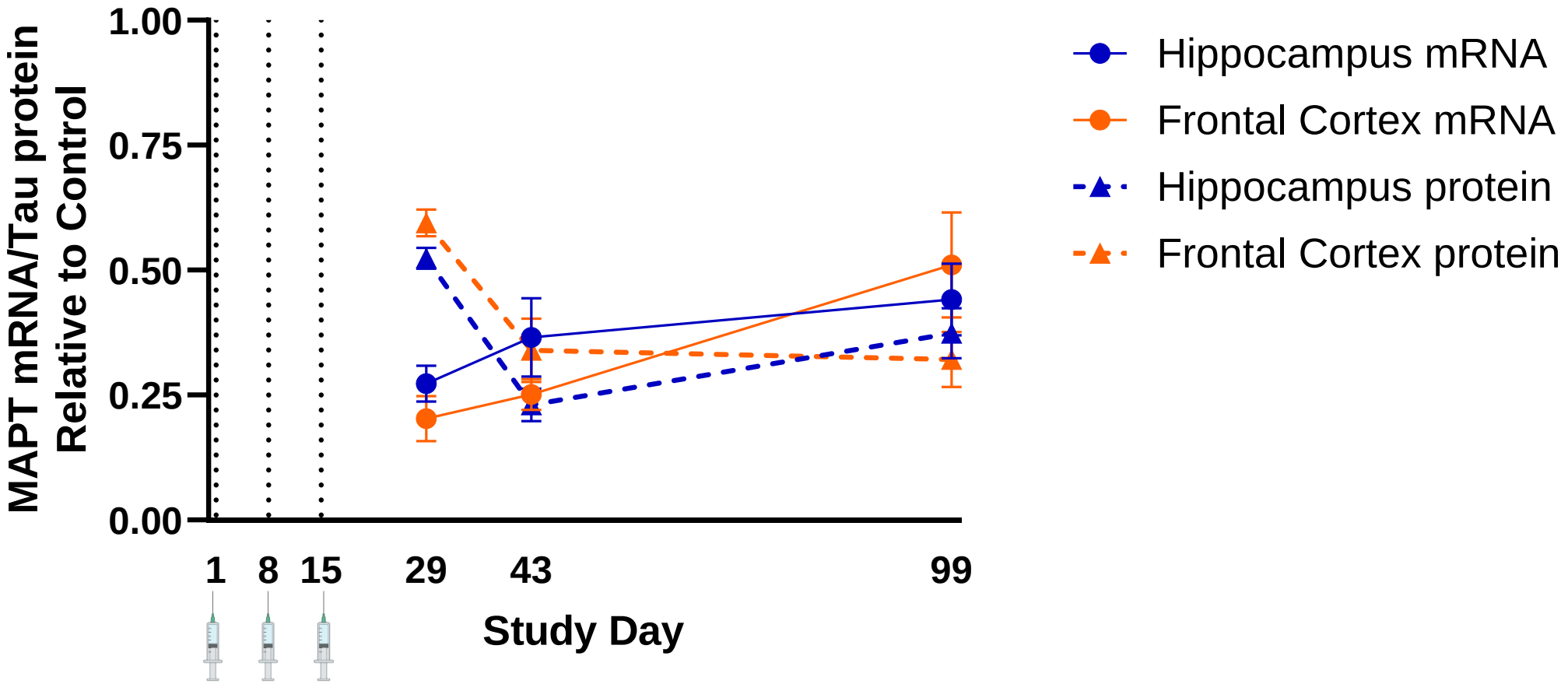
RNAscope for MAPT mRNA in Hippocampus



arrowhead pharmaceuticals

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

MAPT/Tau Reduction in NHP

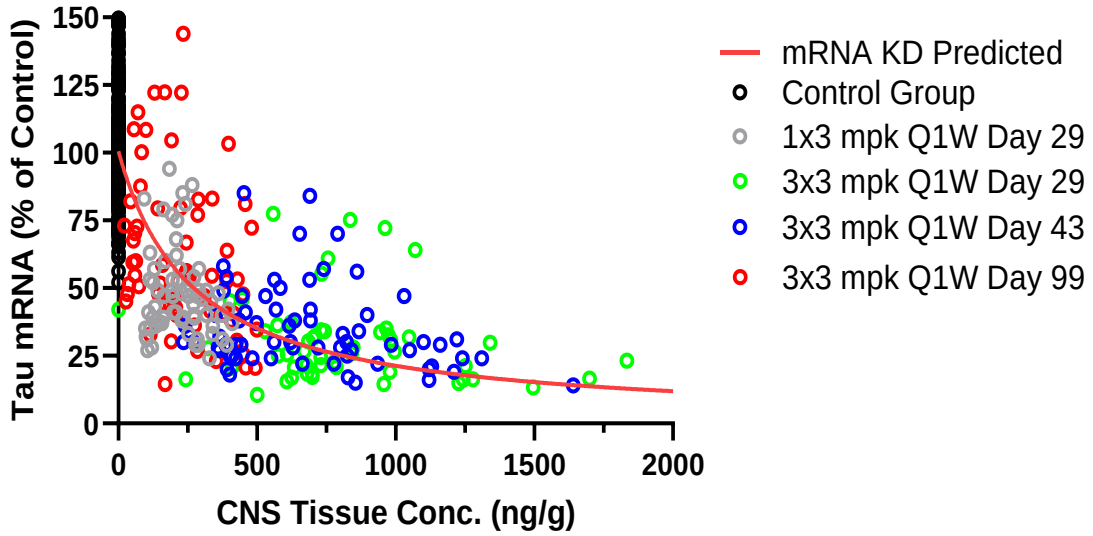


3 x 3mg/kg qw s.c.; n=4/group, mean±SEM

arrowhead pharmaceuticals

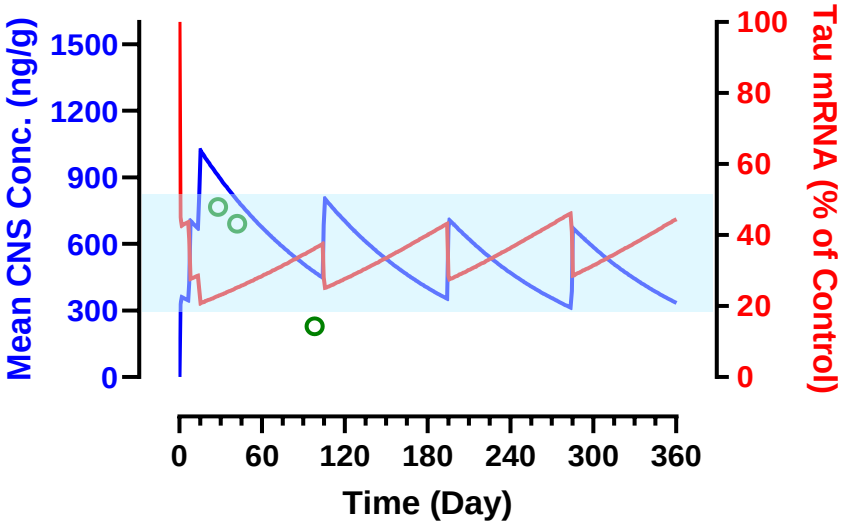
PK/PD Modeling Projects Sustained Tau Inhibition with Quarterly Dosing of ARO-MAPT SC

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

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
- Non-GLP toxicology in NHP and transferrin receptor transgenic mice at up to 10x efficacious dose is supportive of further development
- Expected CTA filing in **2H 2025**

CNS-SC TRiM™ Platform Expands Opportunity for siRNA Therapeutics

- Systemically delivered CNS-SC TRiM™ platform can achieve deep knockdown of multiple targets in non-human primates at clinically relevant dose levels
- Expands CNS-targeting feasibility to include larger patient populations (e.g., Alzheimer's disease) or diseases with deep brain involvement (e.g., Huntington's disease)
- Multiple programs are in preclinical development with expected CTA filings 2H 2025

Arrowhead Teamwork

- Corporate headquarters

Corporate Headquarters

177 East Colorado Boulevard, Ste 700
Pasadena, CA 91105

Research and Development

502 South Rosa Road
Madison, WI 53719

- Discovery Chemistry
- Toxicology

- CNS Discovery Biology
- Discovery Chemistry

Research and Development

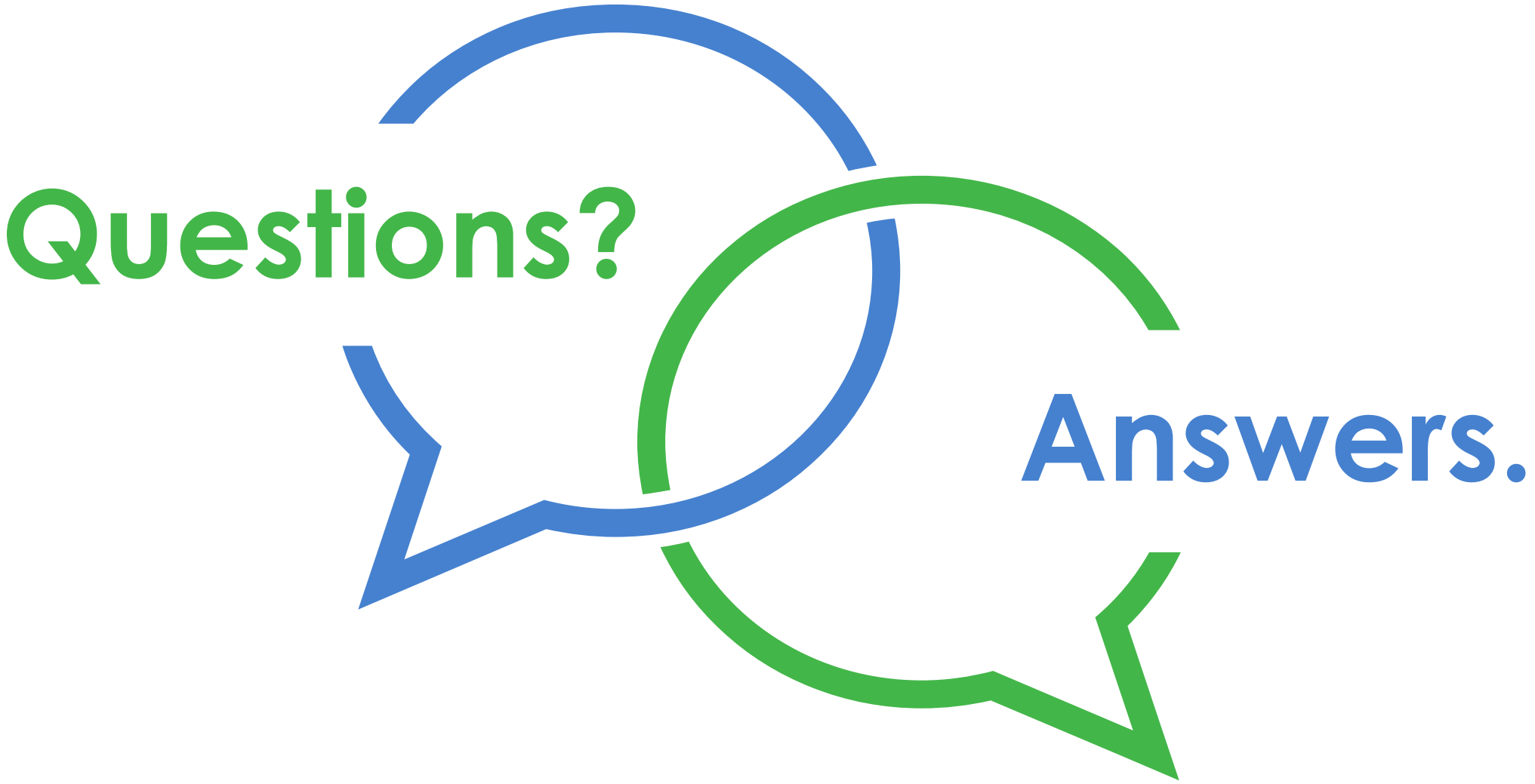
10102 Hoyt Park Drive
San Diego, CA 92131

Research and Manufacturing

1080 Arrowhead Way
Verona, WI 53593

- CMC
- GMP Manufacturing

arrowhead pharmaceuticals



arrowhead pharmaceuticals