2024 Summer Series of R&D Webinars
Part V – CNS Programs

October 07, 2024

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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.

CNS Programs Webinar – October 7, 2024

Welcome and Introductions

Vince Anzalone, CFA
Vice President, Finance and IR

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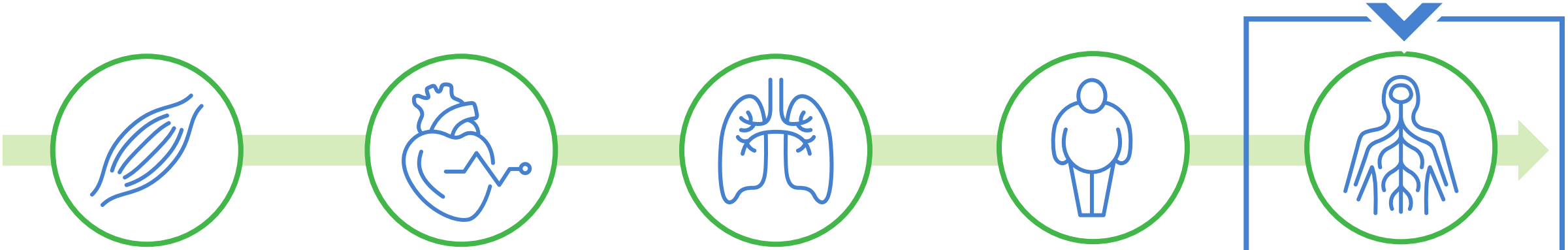
2024 Summer Series of R&D Webinars



Muscle

ARO-DM1 and ARO-DUX4

May 23, 2024

Cardiometabolic

Plozasiran and Zodasiran

June 25, 2024

Pulmonary

ARO-RAGE, ARO-MUC5AC, ARO-MMP7

July 16, 2024

Obesity/ Metabolic

ARO-INHBE and New Adipose Target

August 14, 2024

Central Nervous System

Platform and Pipeline Updates

Oct. 07, 2024

2024 Summer Series Goals

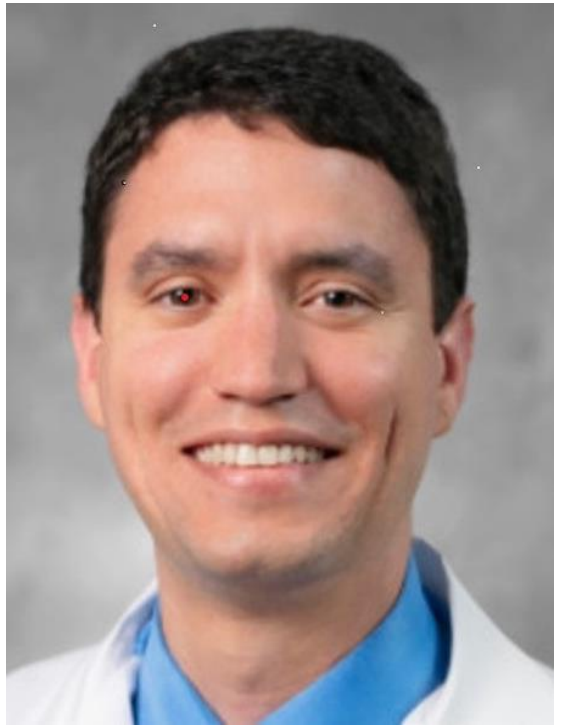
- Provide focused time to cover underappreciated parts of our pipeline
- Detail advances in the TRiM™ platform
- Hear directly from the Arrowhead team that worked on the programs
- Get external physician perspective on each disease area

CNS Webinar Agenda

Topic	Presenter
Introductions and Agenda	Vince Anzalone, CFA
CNS Portfolio Overview and IT Platform	Christy Esau Ph.D.
ARO-ATXN2	James Hamilton M.D., MBA
Subcutaneous Administration for CNS	Tao Pei Ph.D.
Targeting Tau for Neurodegenerative Disease	Christy Esau Ph.D.
Early CNS Pipeline Programs	Christy Esau Ph.D.
Clinical Evaluation and Unmet Needs in Alzheimer's	Jose Soria, M.D.
Key Takeaways	Vince Anzalone, CFA
Q&A	Panel

Neurology Key Opinion Leader

Jose Soria, M.D.



Director of Clinical Research, The Neuron Clinics

Assistant Clinical Professor of Neurosciences and Attending Neurologist, UC San Diego

Dr. Jose Soria is a board-certified neurologist specializing in Alzheimer's disease and cognitive impairments. He currently serves as the Director of Clinical Research and Memory Program at The Neuron Clinics, which operate in San Diego and Riverside Counties, California. In addition, he is an Assistant Clinical Professor of Neurosciences and an attending neurologist at the Adult Down Syndrome Clinic at the University of
California, San Diego.

Dr. Soria obtained his Bachelor of Science degree in Biological Sciences from Florida International University in Miami, Florida. He then earned his medical degree from the Johns Hopkins University School of Medicine in Baltimore, Maryland. Following this, he completed his neurology residency at the University of California, San Diego (UCSD), and pursued a fellowship specializing in memory and neurodegenerative diseases at the VA San Diego Healthcare System

With a research focus on the diagnosis and treatment of Alzheimer's disease, Dr. Soria serves as a scientific advisor to the Alzheimer's Association and collaborates with several pharmaceutical companies dedicated to developing early therapeutic interventions for the disease

CNS Programs Webinar – October 7, 2024

CNS Portfolio Overview
IT Platform

Christy Esau, Ph.D.
Vice President, Biology

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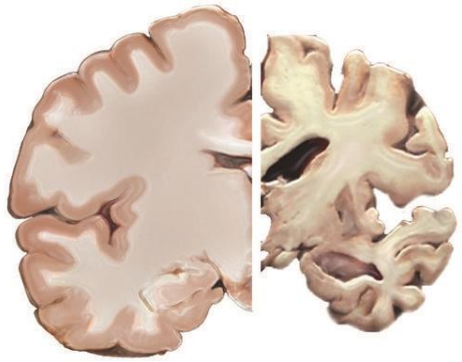
Neurodegenerative Diseases Are an Enormous Burden Uniquely Addressable by RNA Therapeutics

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)

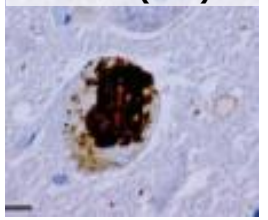
Tauopathies
- Alzheimer's disease (AD)
- Fronto-temporal dementia (FTD)
- Progressive Supranuclear Palsy
- Corticobasal Degeneration

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

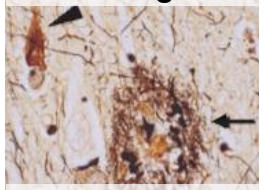
Synucleinopathies
- Parkinson's disease (PD)
- Lewy body dementia
- Multiple system atrophy

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

SOD1 (ALS)

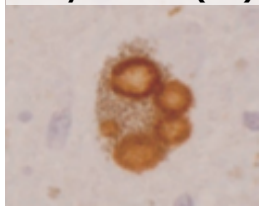


Tau tangles

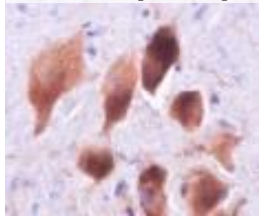


Amyloid plaques

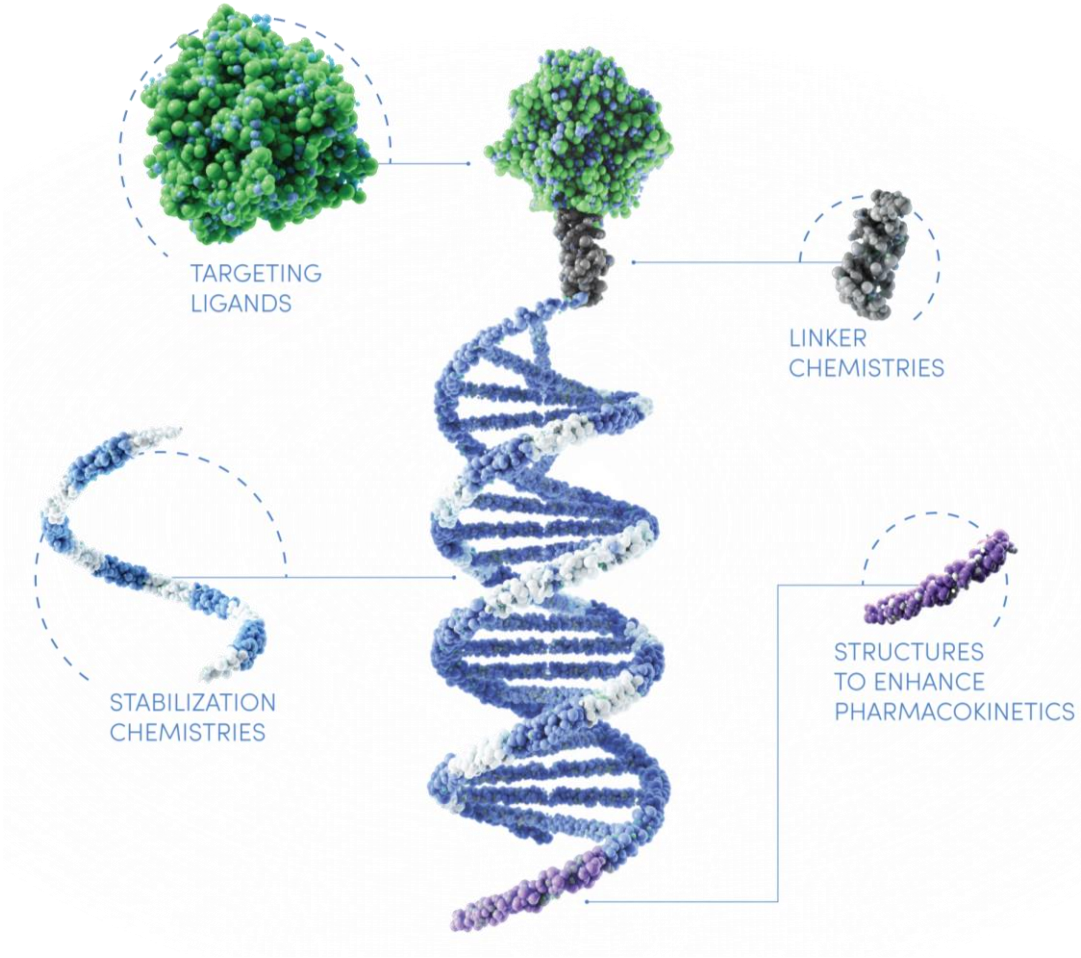
Lewy bodies (PD)



ATXN2 (SCA2)



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



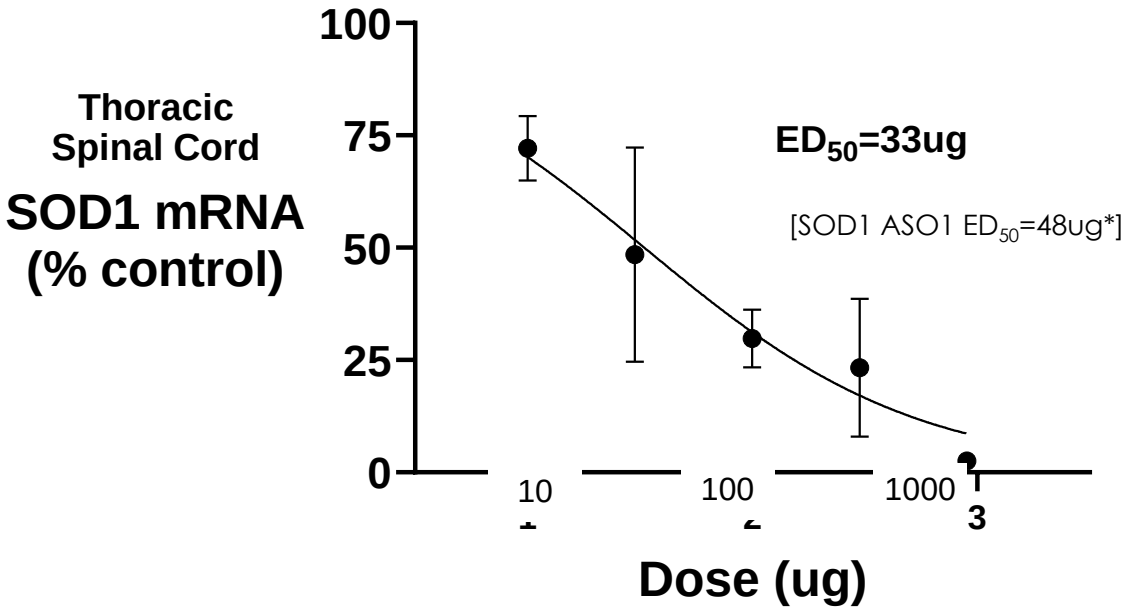
We Have Developed an Optimized Intrathecal Delivery Platform for CNS

- **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

Potent Reduction of Target mRNA in Rodent Models

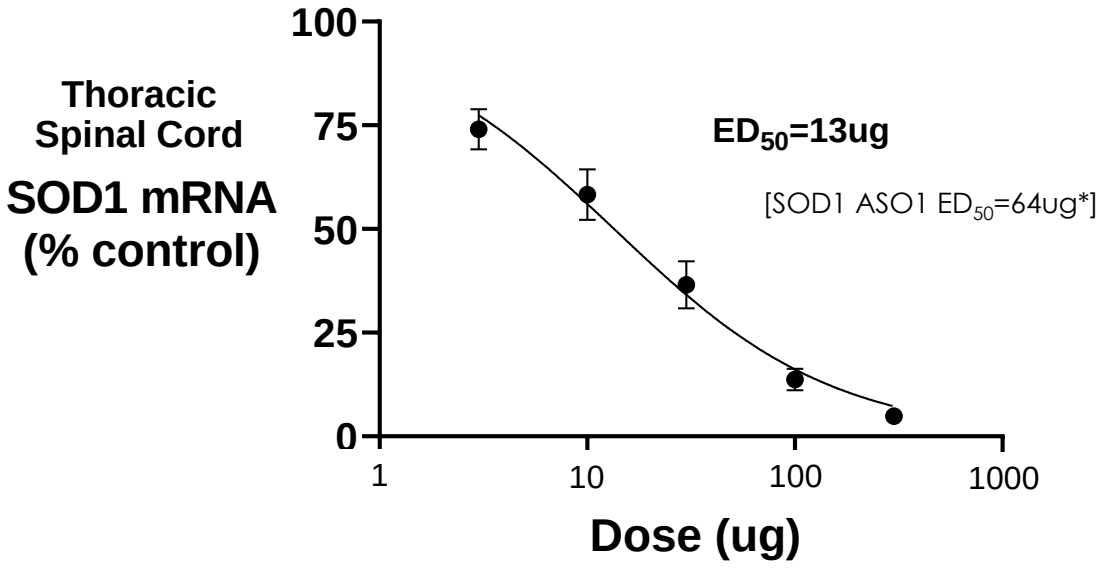
Transgenic Rat

Single Dose IT – 4 Weeks Post Dose



Transgenic Mouse

Single Dose ICV – 2 Weeks Post Dose

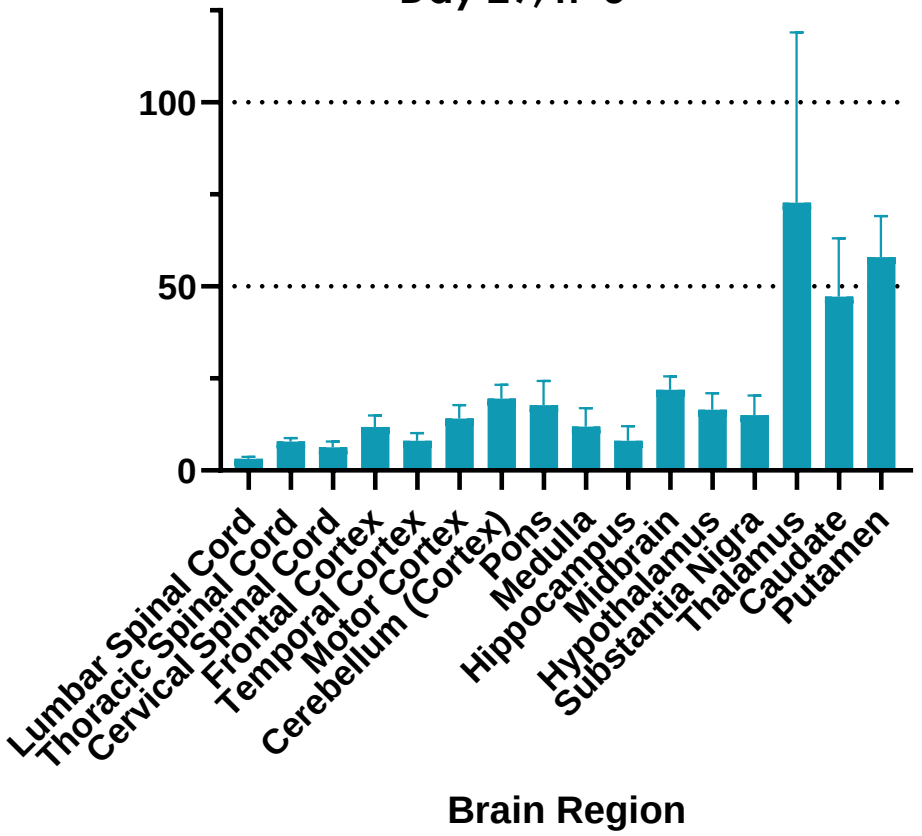


*McCampbell et. al. 2018

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

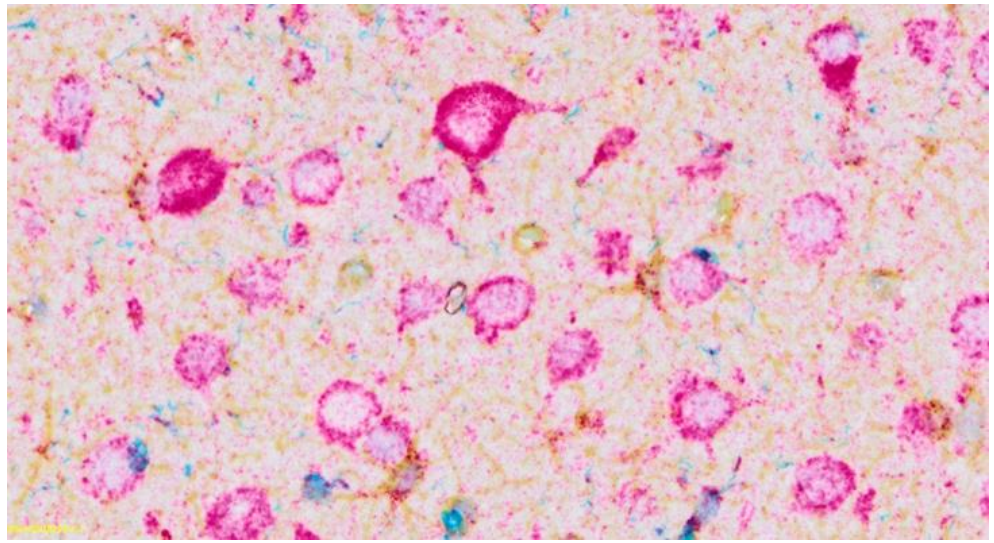
SOD1 mRNA Reduction in NHP

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

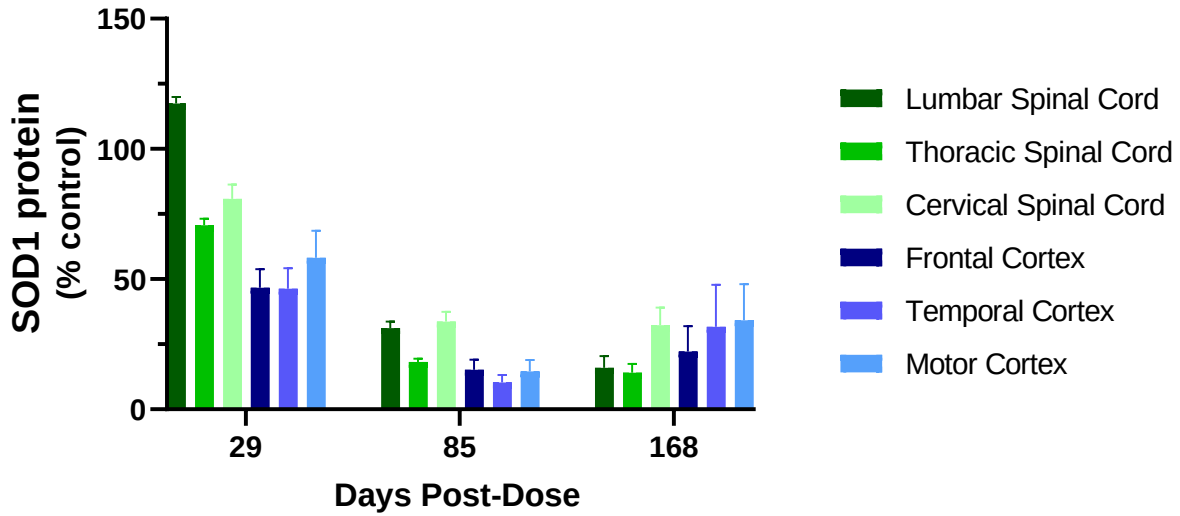
Yellow = astrocytes (GFAP)

Blue = microglia (IBA1)

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

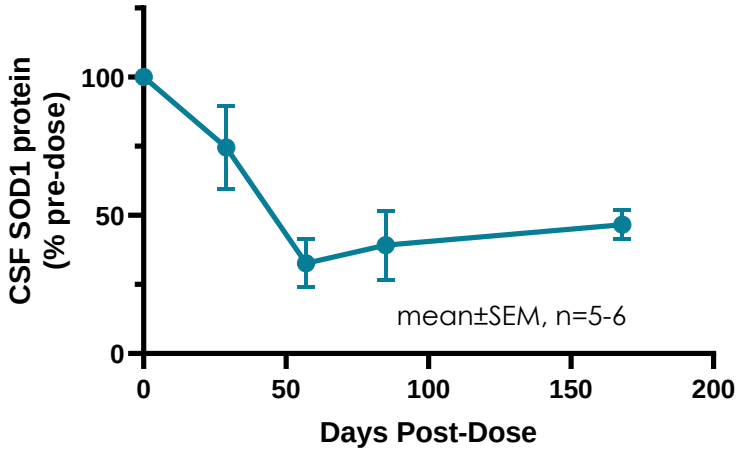
SOD1 Protein Reduction

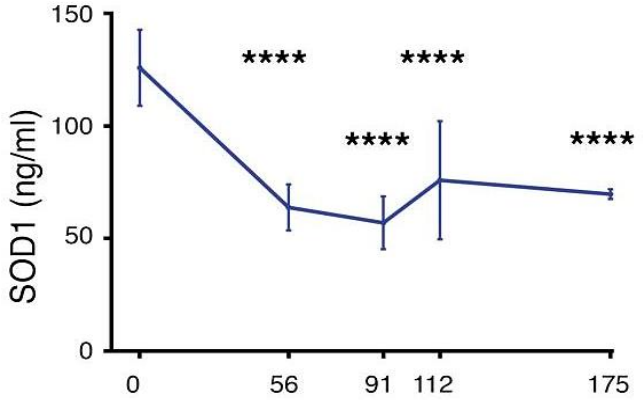
Single 45mg IT dose, n=3-5/group, mean±SEM



*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

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ARO-ATXN2 for Spinocerebellar Ataxia 2 - IT Administration

James Hamilton, M.D., MBA
Chief of Discovery and Translational Medicine

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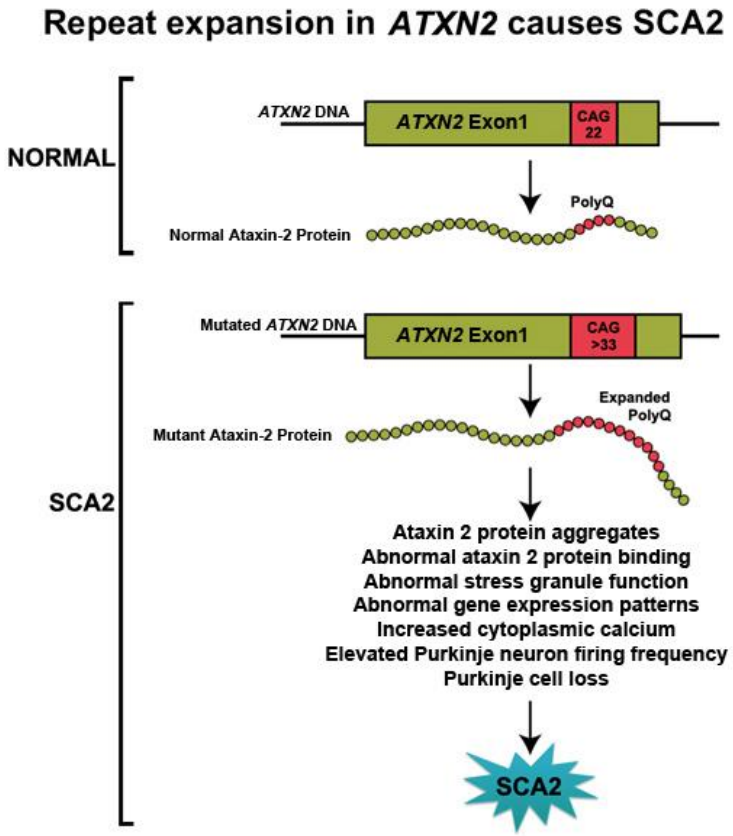
ARO-ATXN2 for Spinocerebellar Ataxia 2 (SCA2)



- 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 walking aid or wheelchair 8-10 years after symptom onset
- SCA2 patients typically survive 10-20 years after symptom onset
- Management is supportive care. There are no disease modifying therapies available.
- **RNAi targets production of toxic ATXN2 protein that causes the disease, and has potential to be disease modifying**

Stefan Pulst Lab

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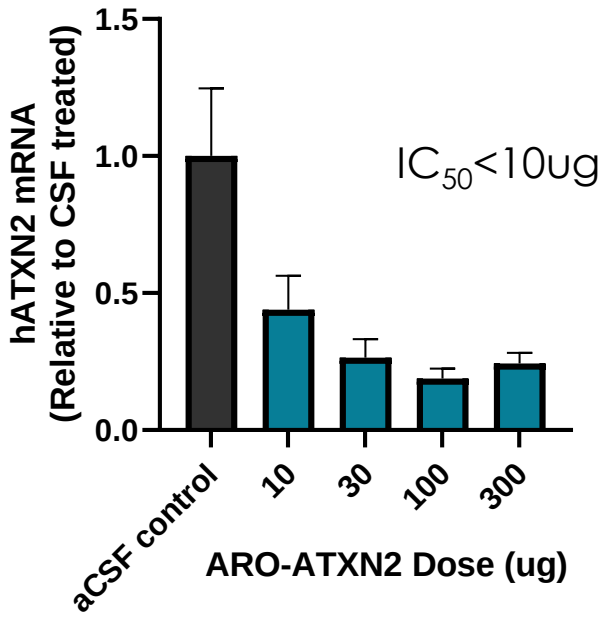
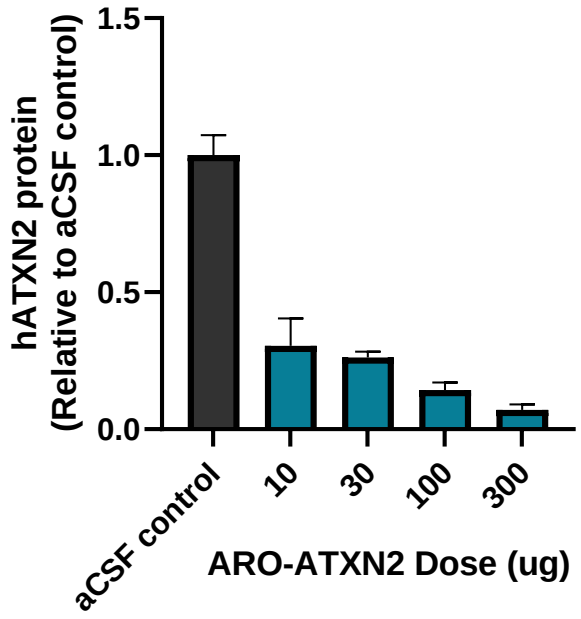
ARO-ATXN2 Potency in Cerebellum of BAC-Q22 ATXN2 Transgenic Mouse

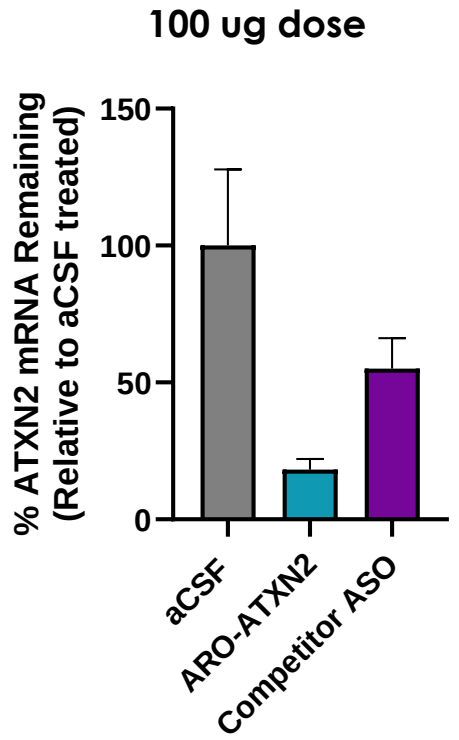
Human ATXN2 mRNA



Human ATXN2 protein



ARWR vs ASO



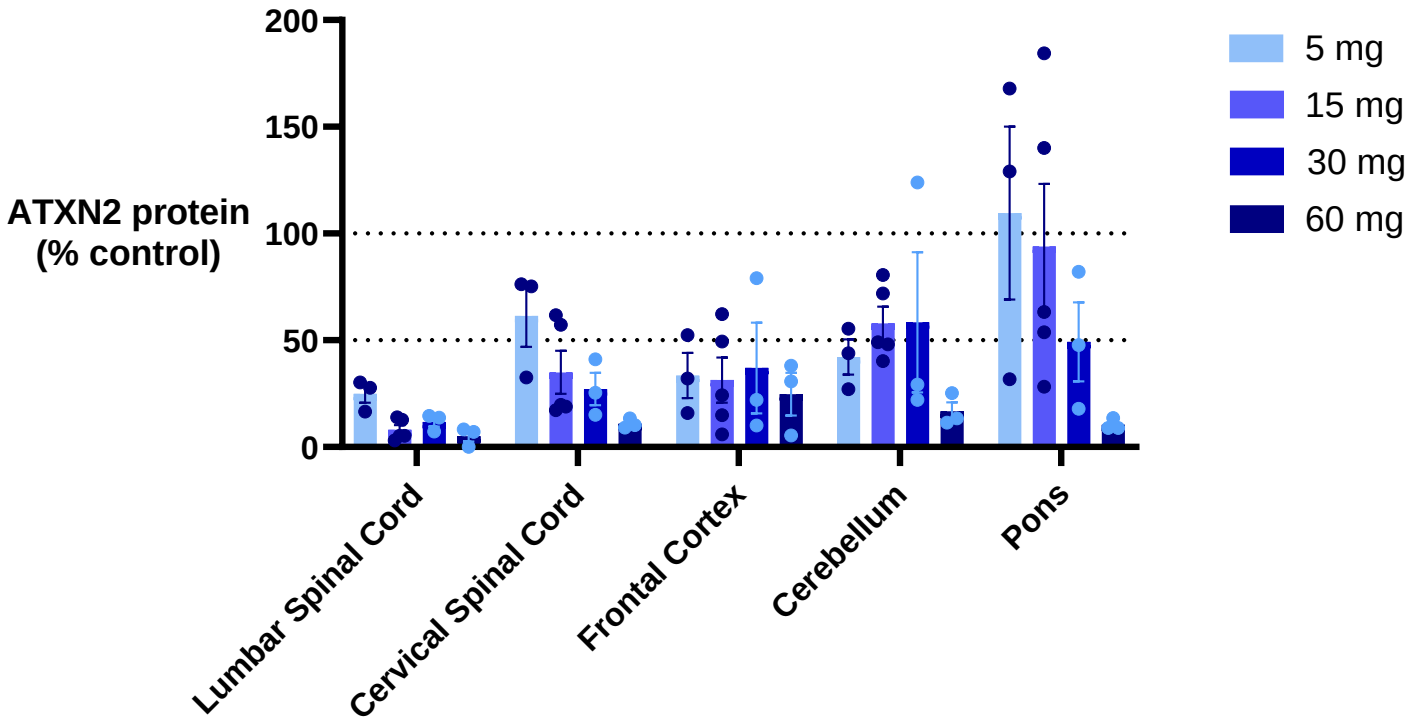
Two weeks after single ICV dose. n=4, mean ±SEM
BAC-Q22 ATXN2 Transgenic Mouse Model

Data in collaboration with Pulst Lab, University of Utah

ARO-ATXN2 Shows Dose-Dependent ATXN2 Protein Reduction in Relevant NHP CNS Regions

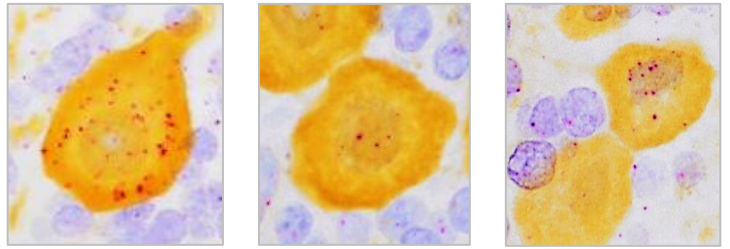
Non-Human Primate

Day 29 Post-IT Dose, n=3-5/Group



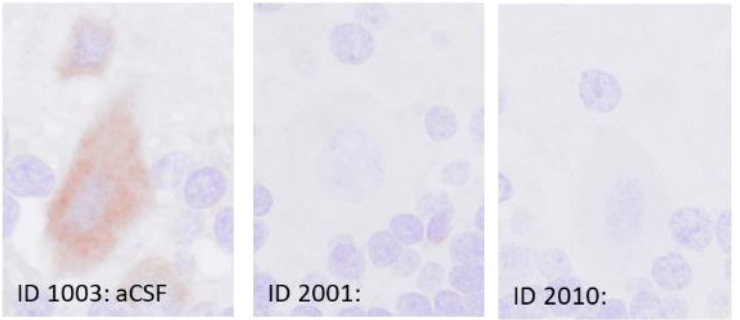
83% ATXN2 reduction in cerebellum

ATXN2 RNAscope in Purkinje Cells:



Yellow: calbindin stain for Purkinje Neurons
Purple: ATXN2 mRNA

ATXN2 Protein IHC:

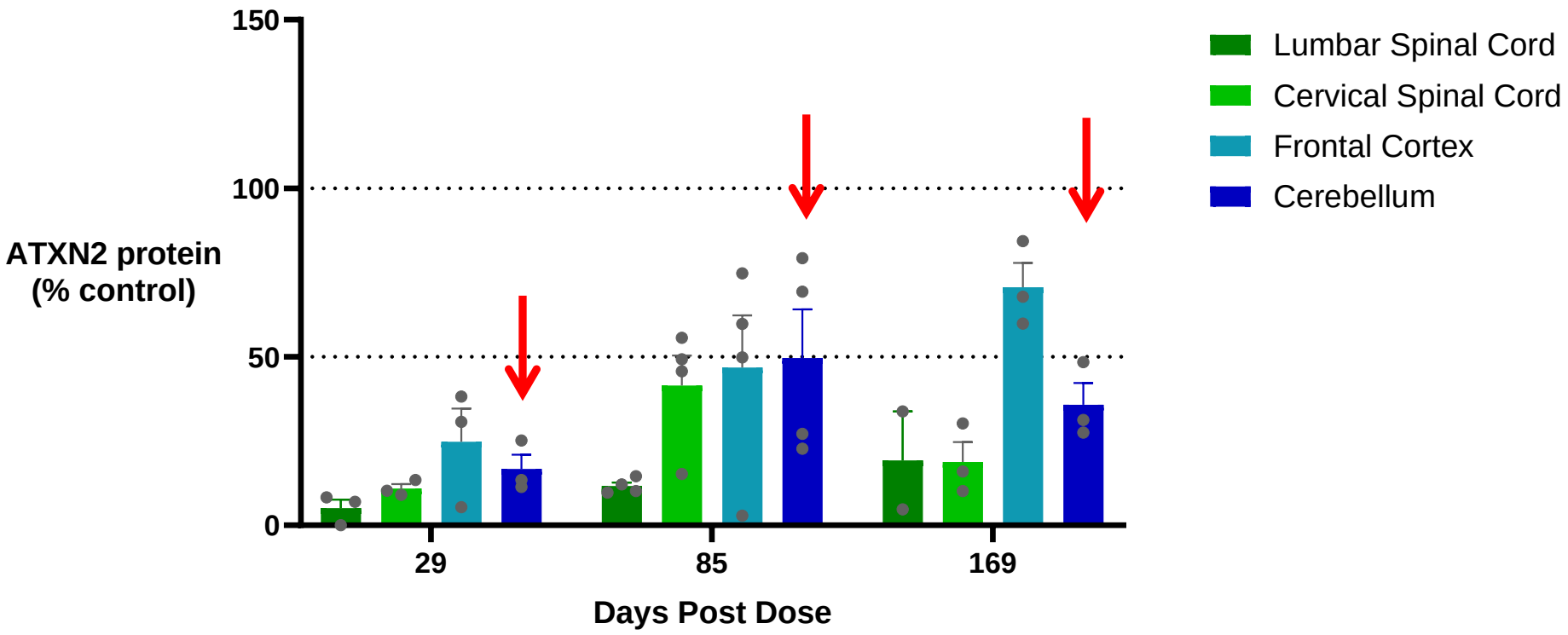


aCSF Control | 60mg ARO-ATXN2 Day 29 | 60mg ARO-ATXN2 Day 85

ARO-ATXN2 Long Duration of Action in NHP Supports Up to Half-Yearly IT Dosing

ATXN2 Protein Reduction

Single 60mg IT Dose, n=3-4/Group, Mean±SEM



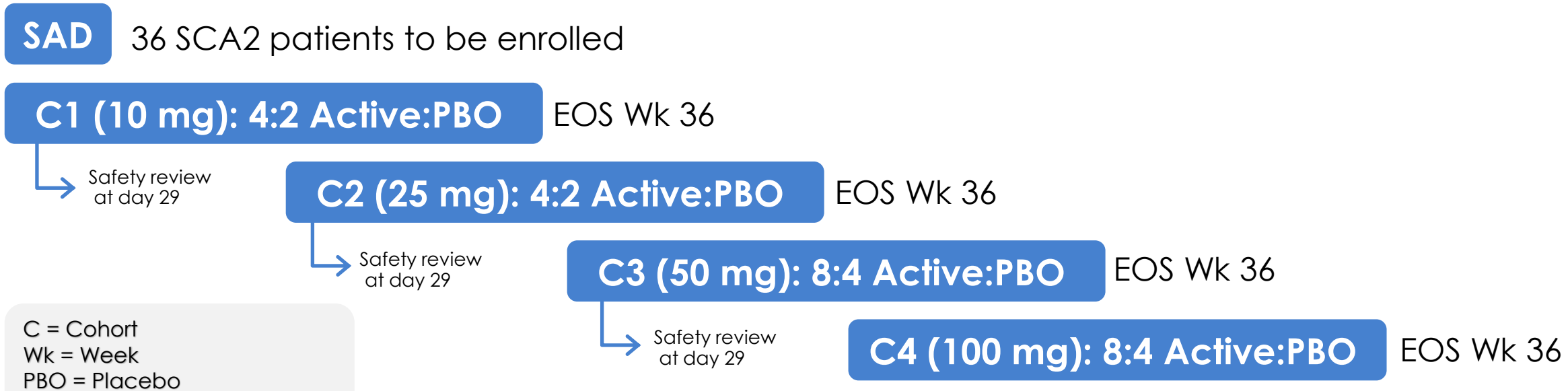
- Reproducible PK/PD profile
- CTA has been filed

Phase 1 Study Planned for ARO-ATXN2

Placebo-Controlled Single Ascending Dose in SCA2 Patients

Key Objectives:

- Safety, PK
- Proof of target engagement: ATXN2 protein in CSF
- Proof of mechanism: Serum and CSF Neurofilament light (NfL)



ARO-ATXN2 Clinical Trial Endpoints and Sites

Primary Endpoint

Safety and tolerability of ARO-ATXN2 in patients with SCA2

Secondary Endpoints

PK profile of ARO-ATXN2

Key Exploratory Endpoints

- **CSF ATXN2 protein levels**
- **CSF and plasma NfL levels**
- **Functional Testing**
  - Scale for Assessment and Rating of Ataxia (SARA)
  - Composite Cerebellar Functional Severity (CCFS)
- **Imaging**
  - Magnetic Resonance Imaging (MRI) brain volumetry

Sites

New Zealand (received regulatory approval)

Australia

Taiwan

Canada

European Union (ES, FR, DE, IT)

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Next Generation CNS TRiM™ Platform Subcutaneous Administration

Tao Pei, Ph.D.
Senior Vice President, Discovery Chemistry

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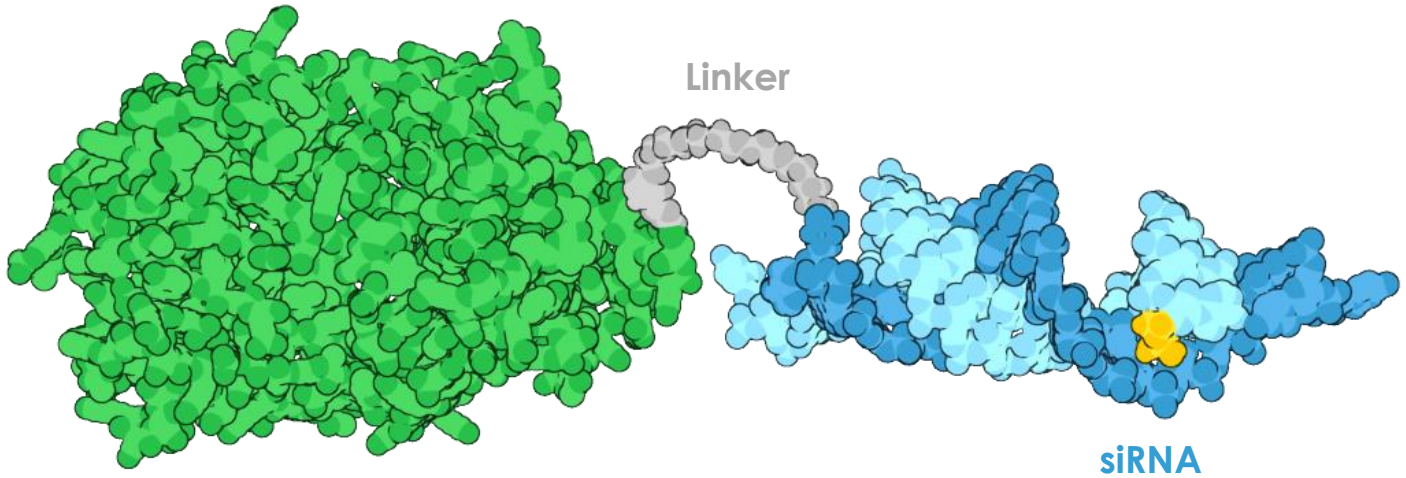
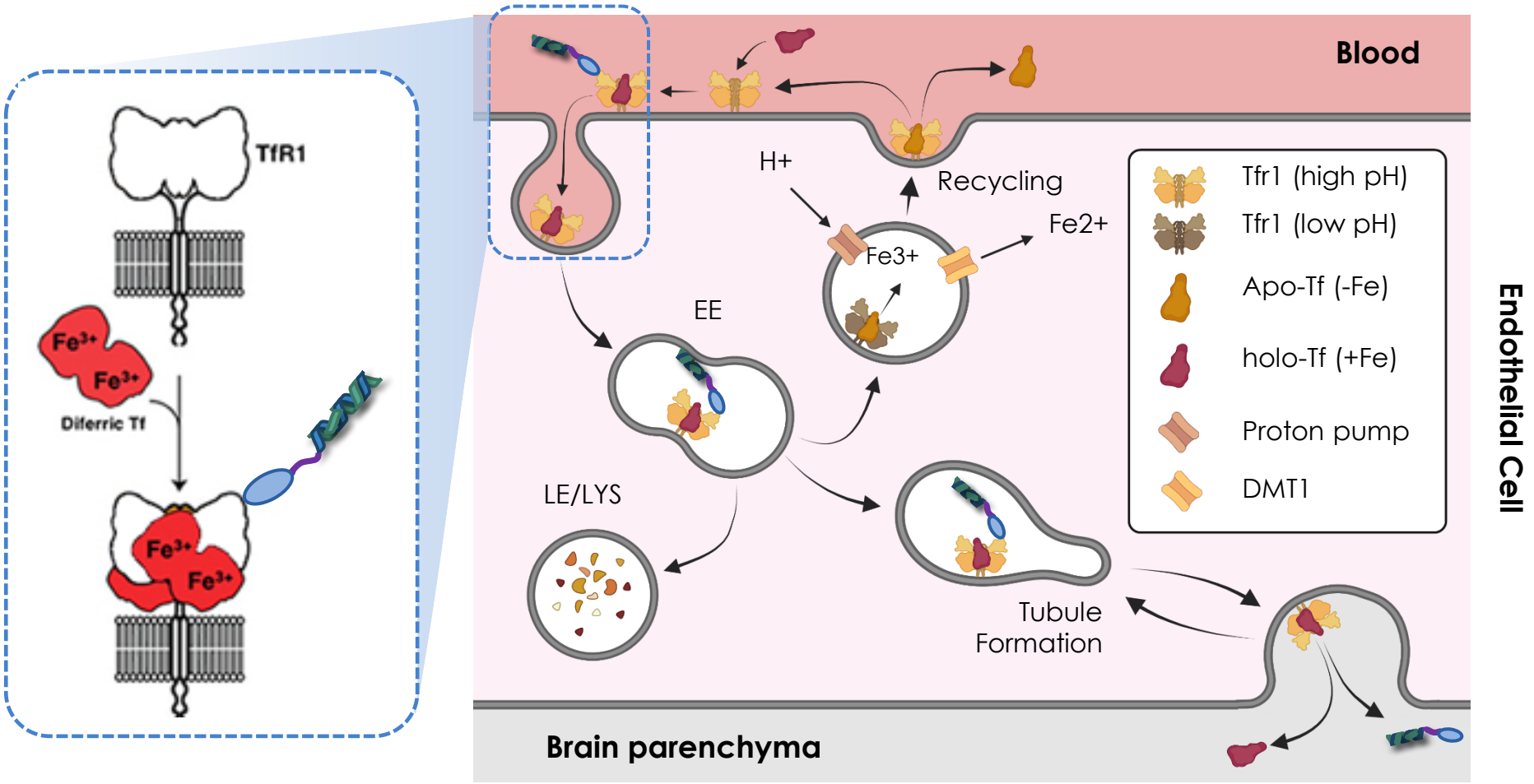
Next Gen. CNS-Targeting TRiM™ Platform via Subcutaneous Administration



We Have Developed an Optimized Systemic Delivery Platform for CNS

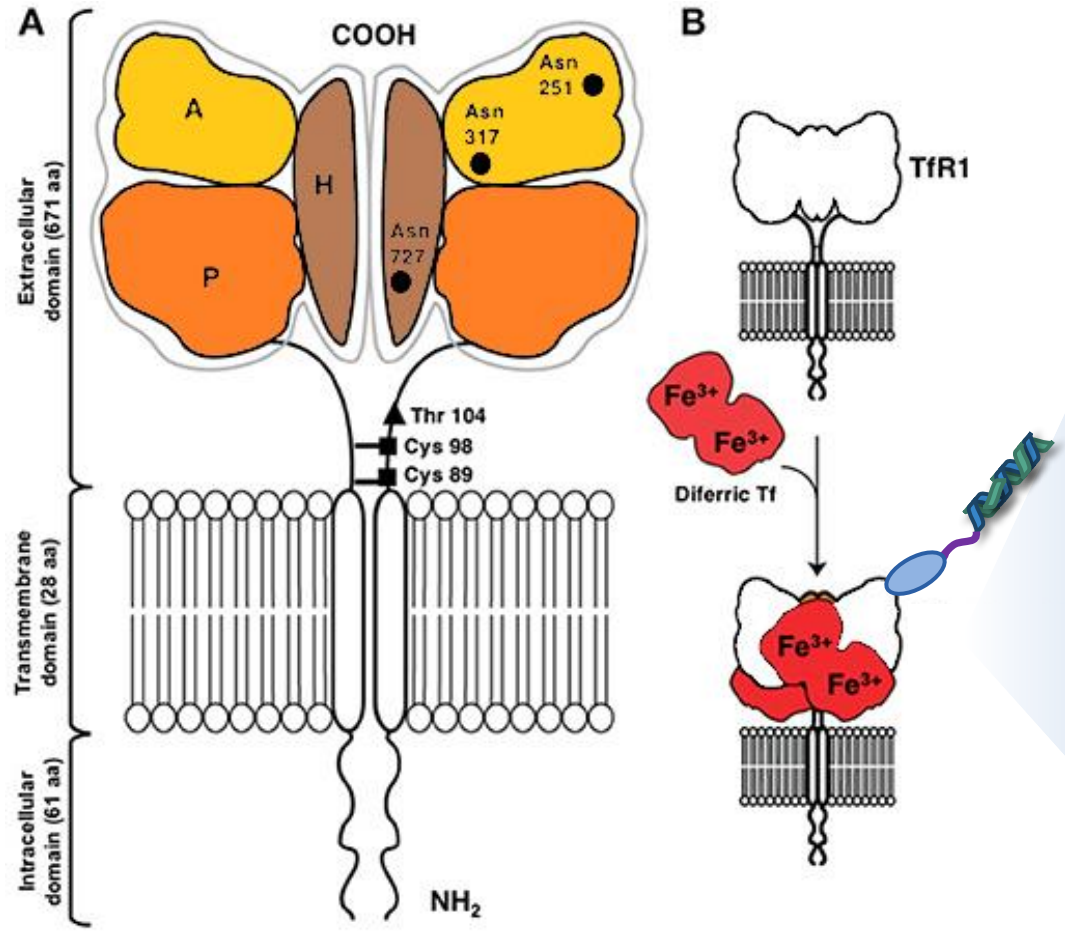
- **Ligand-driven** delivery via noninvasive BBB penetration and cellular uptake in brain tissue
- **Effective** and durable reduction in expression levels of therapeutically-relevant gene targets
- **Convenient** dosing via subcutaneous (SC) administration with potential for monthly to quarterly dosing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

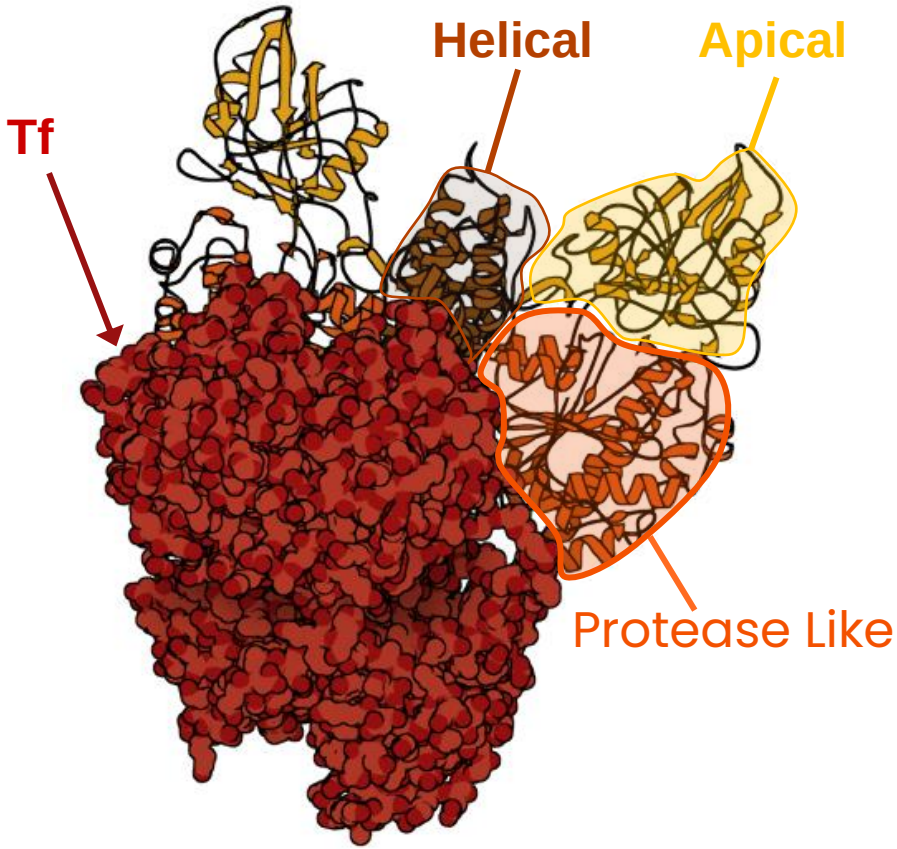
TRiM™ CNS-SC Platform Leverages Noninvasive TfR1-Binding for CNS Delivery



- 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



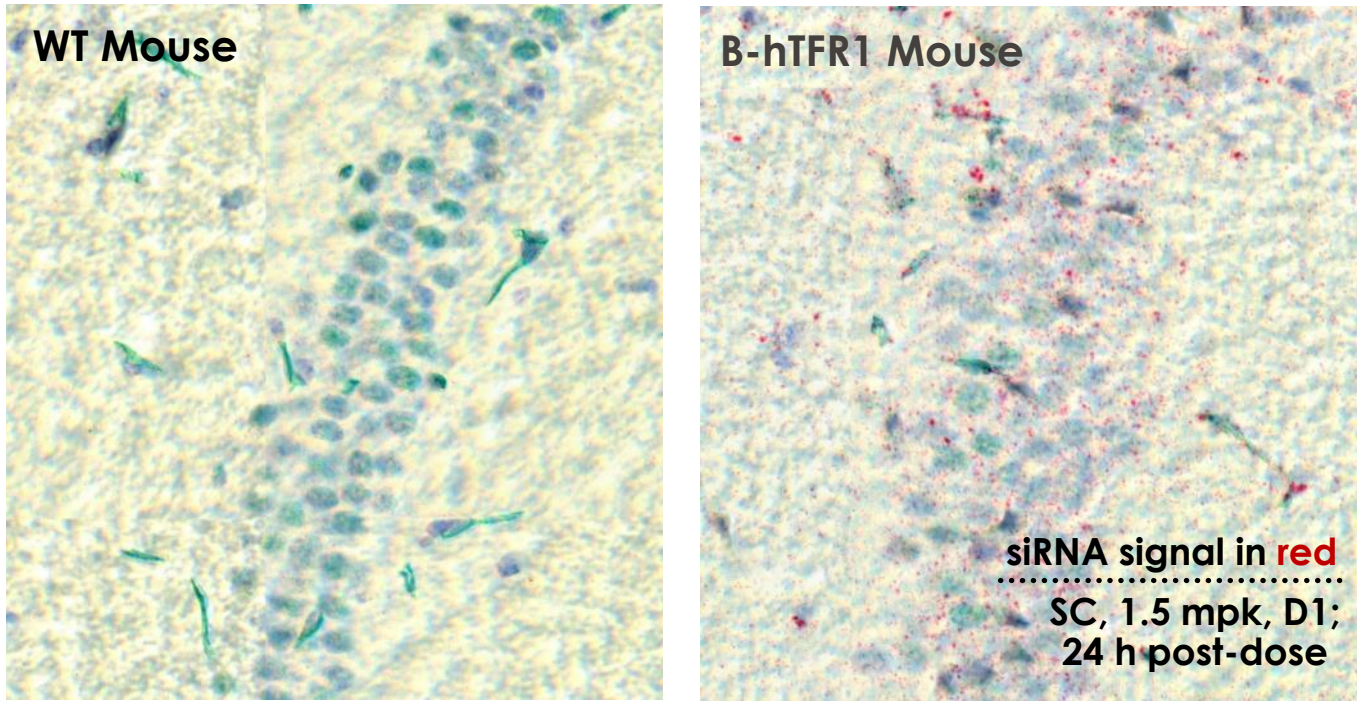


Trans**f**errin (up to 4 mg/mL in serum) occludes helical and protease like domains

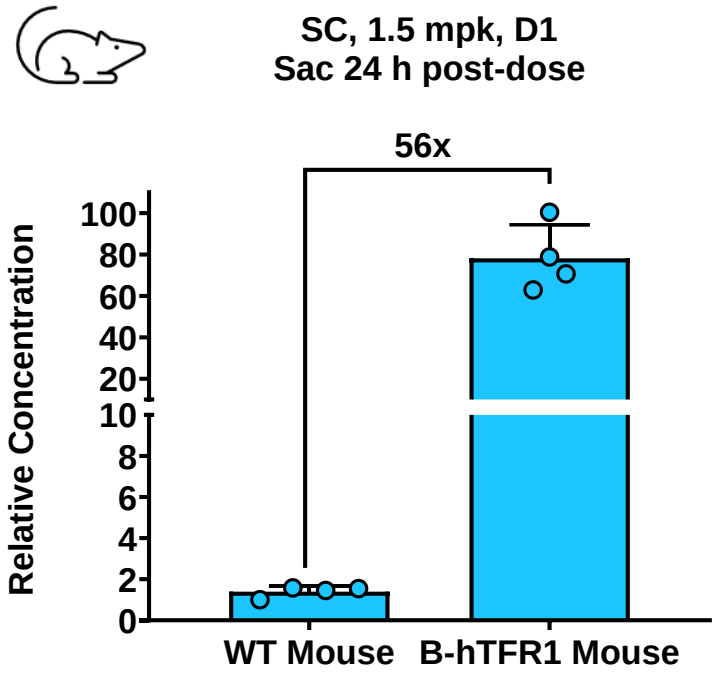
Front Immunol. 2021; 12: 607692.

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

siRNA Visualization in Hippocampus



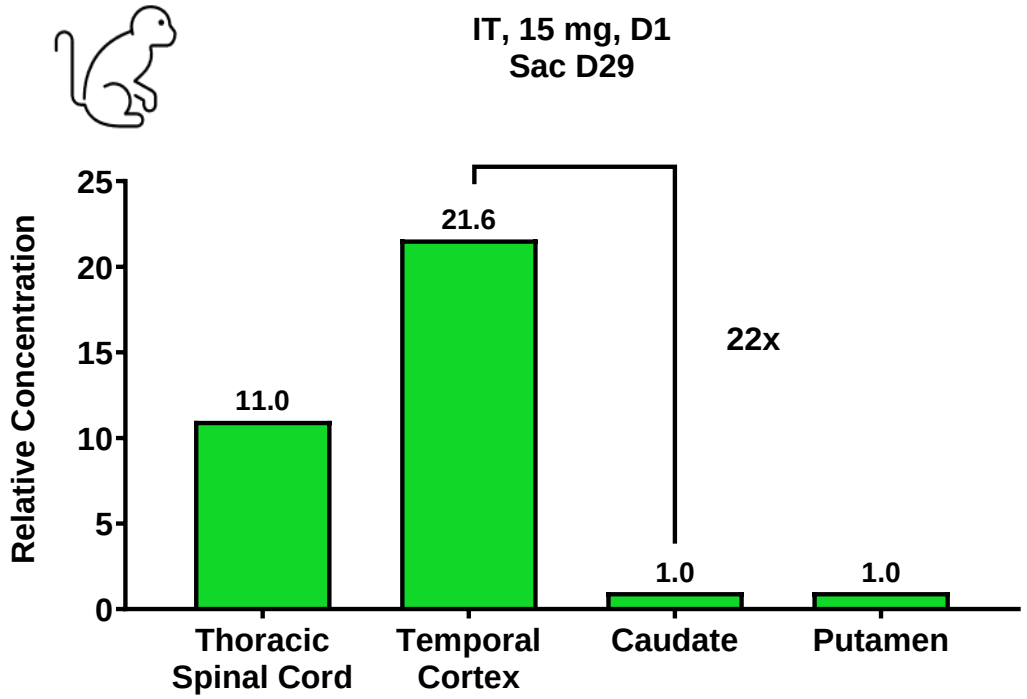
siRNA Concentration in Half Brain



- 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

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

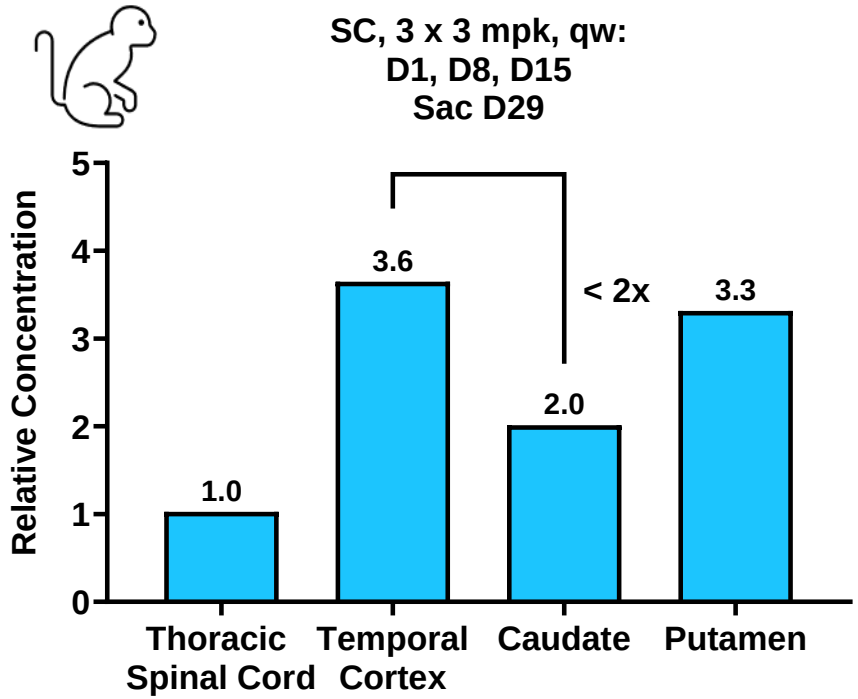
siRNA Concentrations in NHP Brain Regions by IT



By IT administration:

- Relatively limited delivery to deep brain regions

siRNA Concentrations in NHP Brain Regions by SC

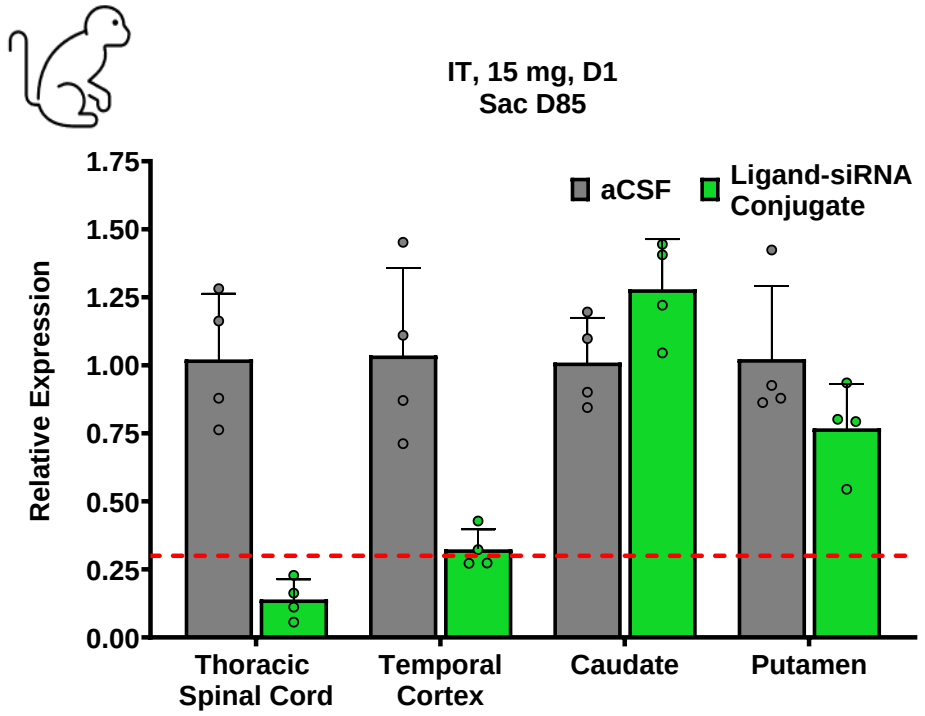


By subcutaneous administration:

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

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

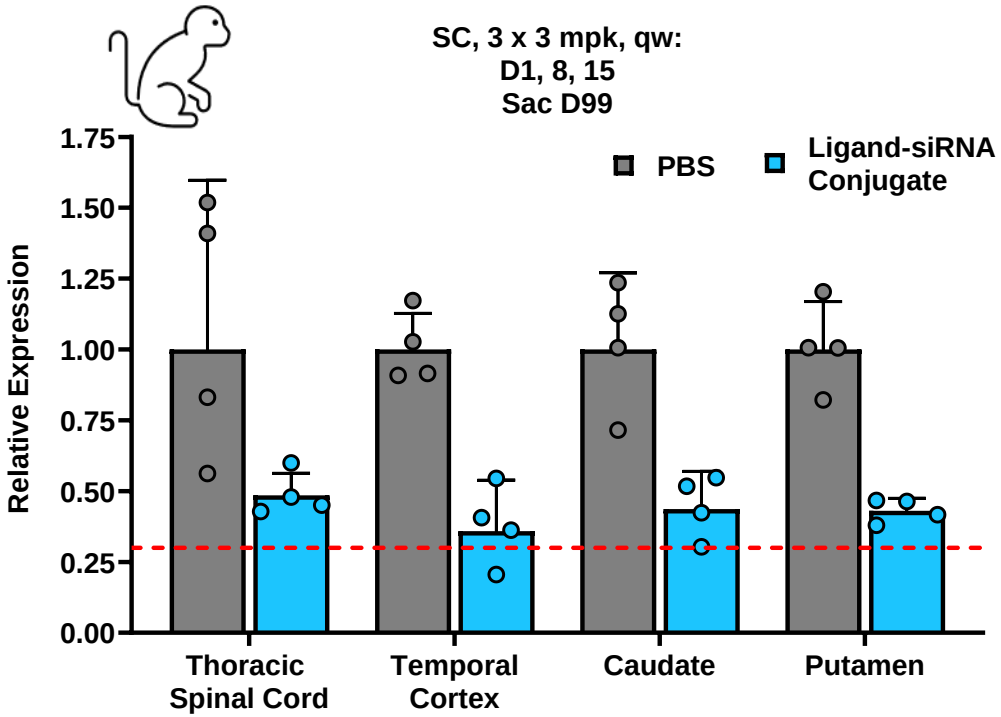
MAPT mRNA Reduction in NHP Brain Regions by IT



By IT administration:

- Minimal mRNA reduction in deep brain region

MAPT mRNA Reduction in NHP Brain Regions by SC

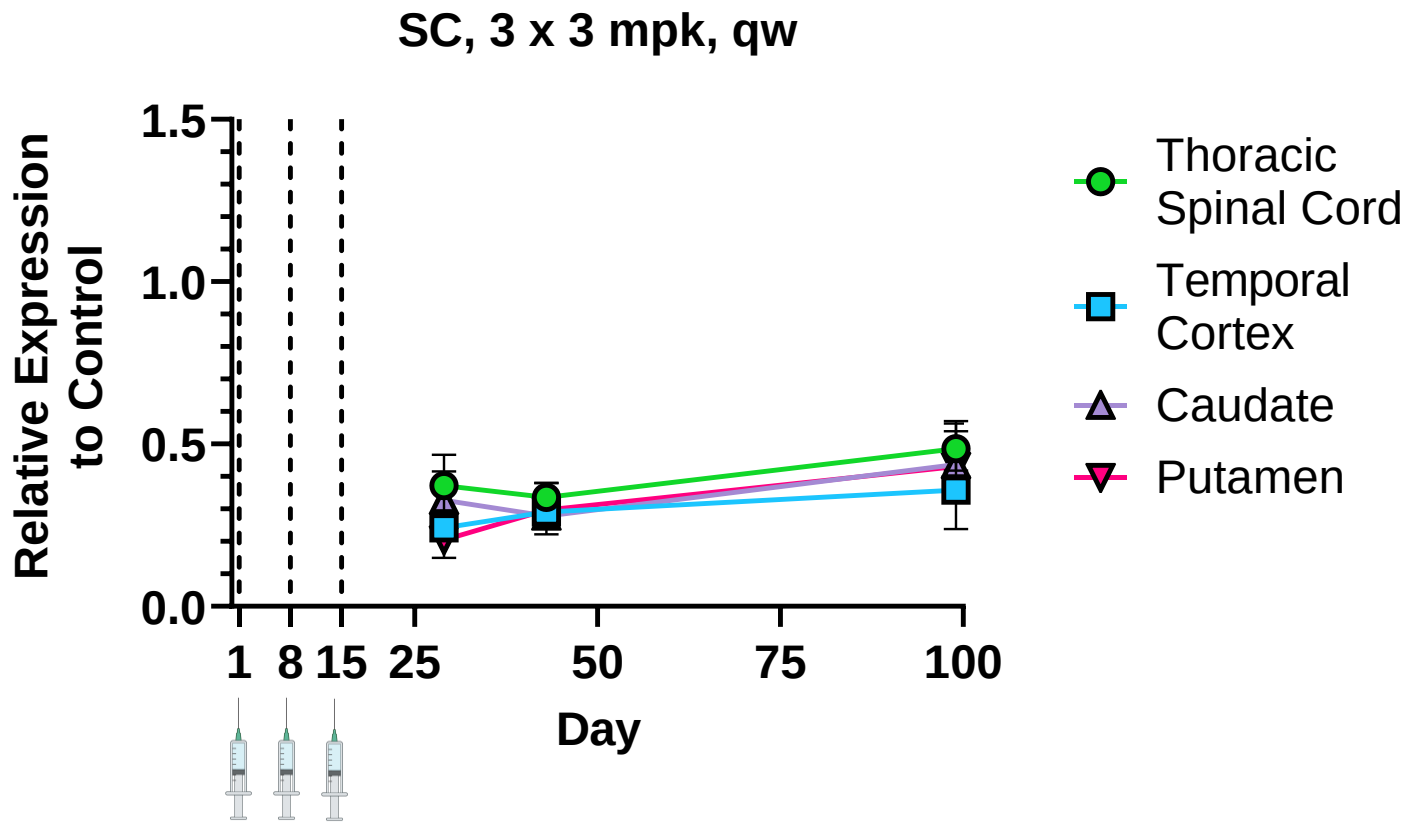


By subcutaneous administration:

- Even mRNA reduction across brain regions, including deep brain

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

CNS Programs Webinar – October 7, 2024

ARO-MAPT SC for Alzheimer's Disease/Tauopathies

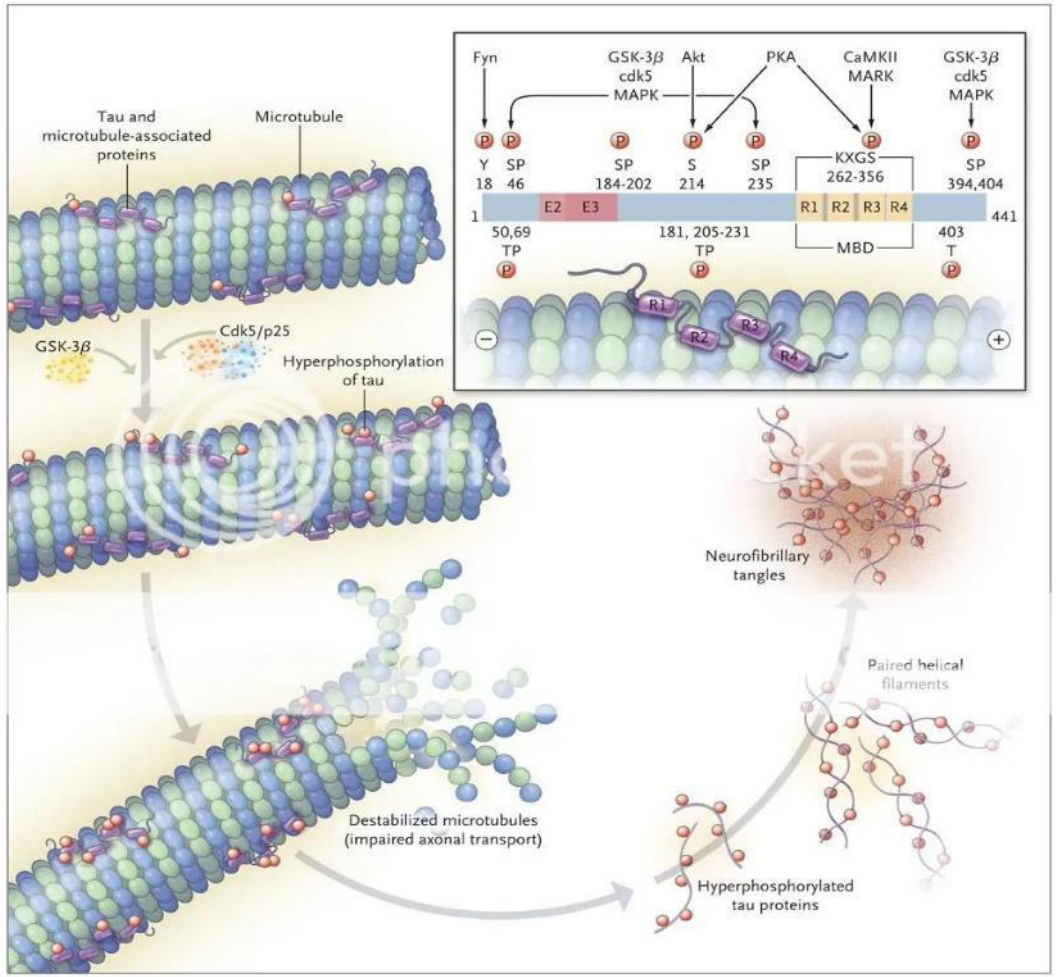
Christy Esau, Ph.D.
Vice President, Biology

arrowhead pharmaceuticals

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

Tau Protein:

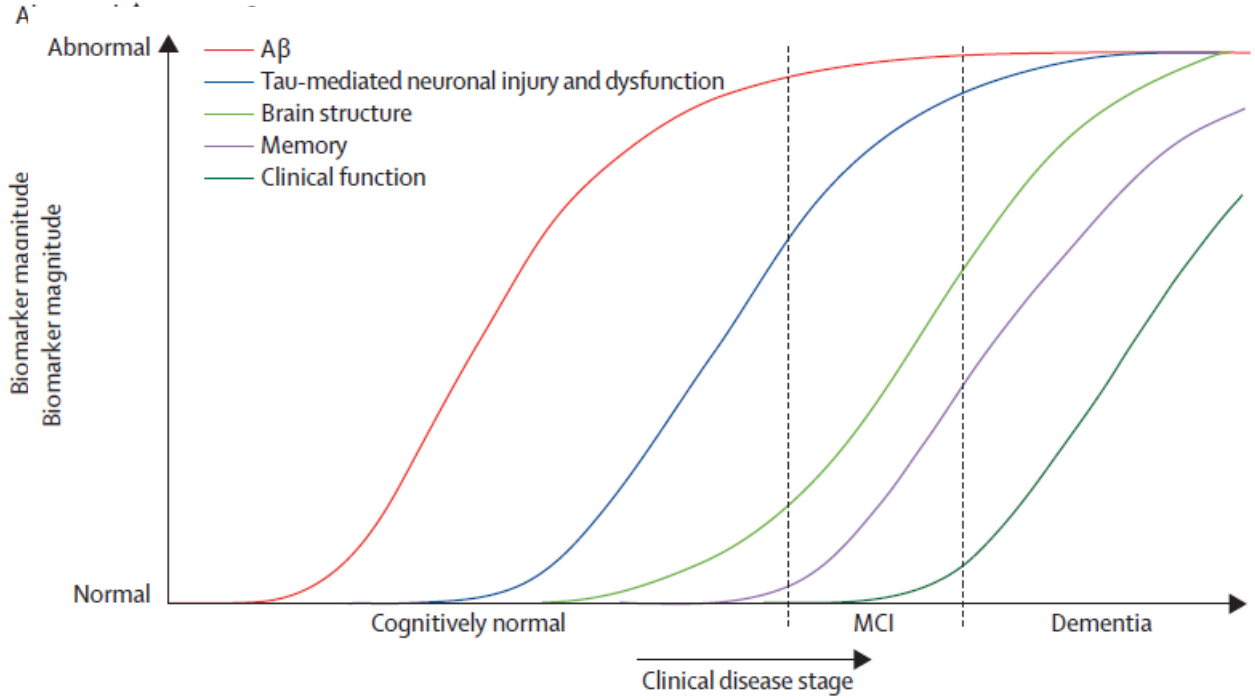
- Encoded by the MAPT gene
- Abundant in neurons, where it promotes stabilization of microtubules in axons
- Intrinsically disordered and subject to many post-translational modifications
- Hyperphosphorylation promotes intracellular formation of neurofibrillary tangles which can be visualized with PET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



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

ARO-MAPT SC for Alzheimer's Disease

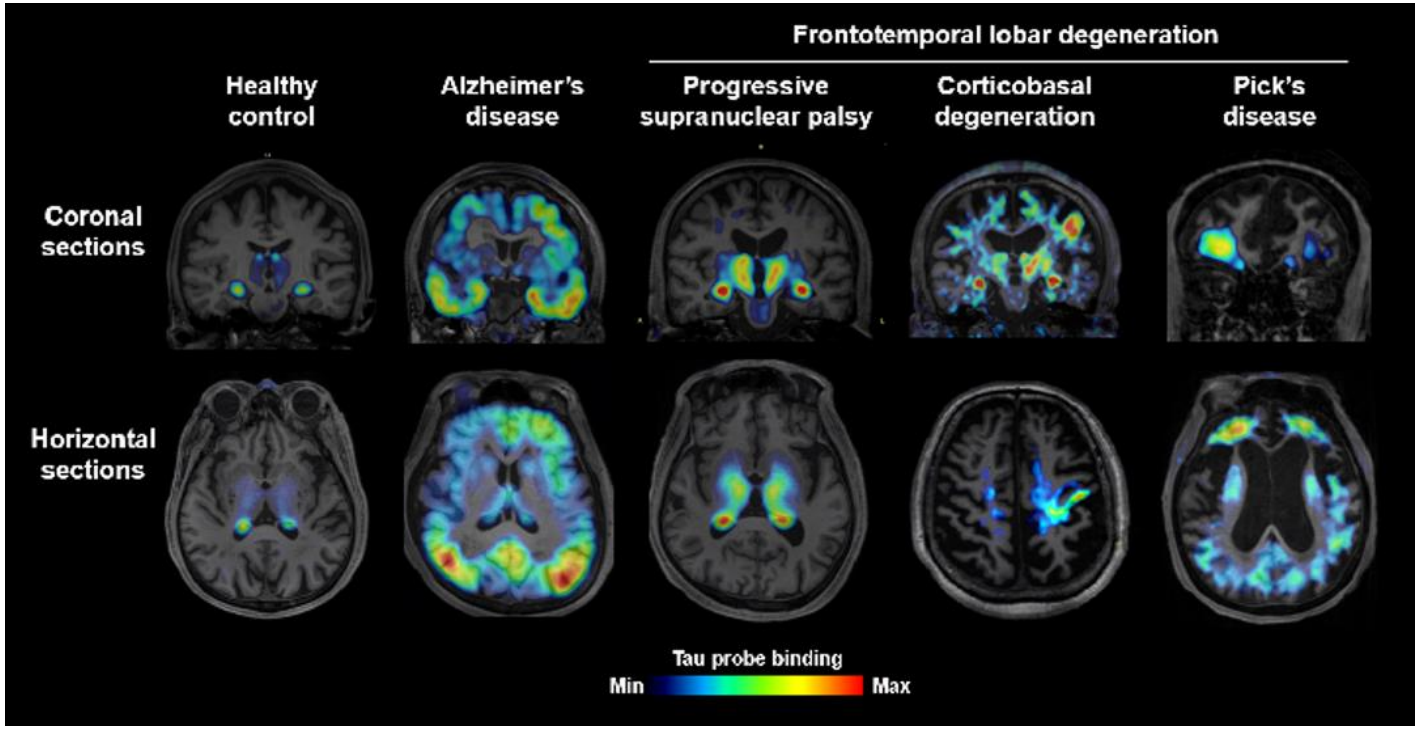
Amyloid Plaque Precedes Tau Pathology in Alzheimer's Disease



- 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**

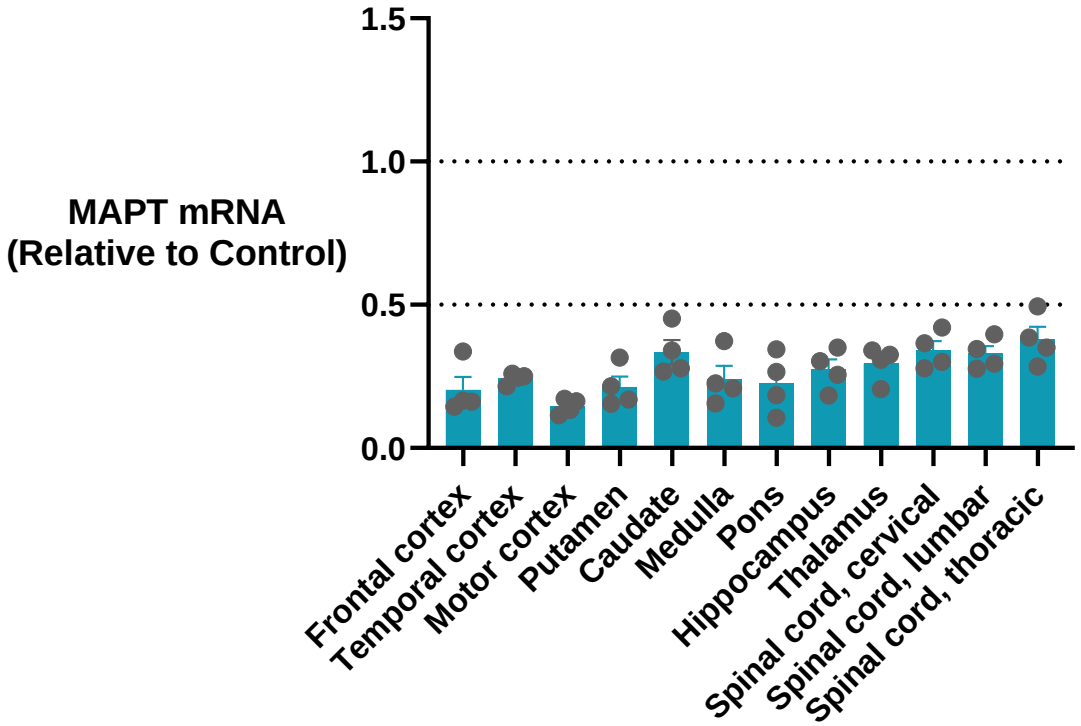
ARO-MAPT SC Targets All Tauopathies

- Intracellular tau neurofibrillary tangles in the CNS cause a range of tauopathies in addition to Alzheimer's
- Each tauopathy affects different brain regions and functions and are associated with different Tau isoforms – making it difficult to drug with other therapeutic modalities
- **siRNA approach targets intracellular Tau and all isoforms associated with different tauopathies**



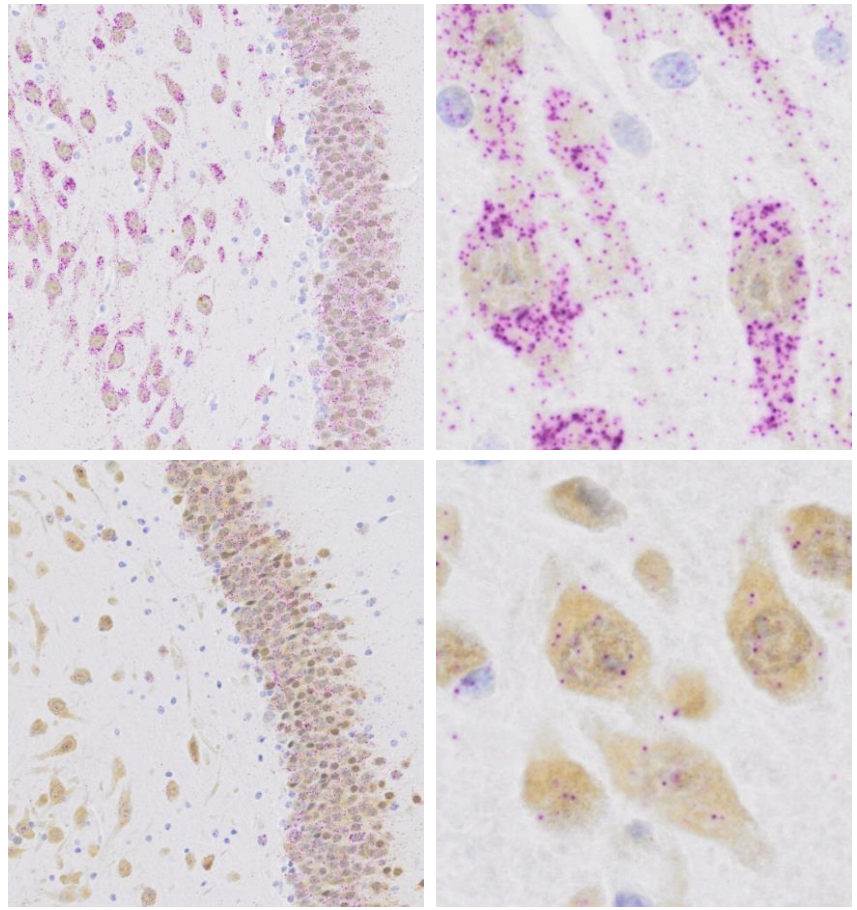
ARO-MAPT SC Achieves Deep Knockdown of MAPT mRNA Throughout the CNS with Subcutaneous Administration

MAPT mRNA in NHP



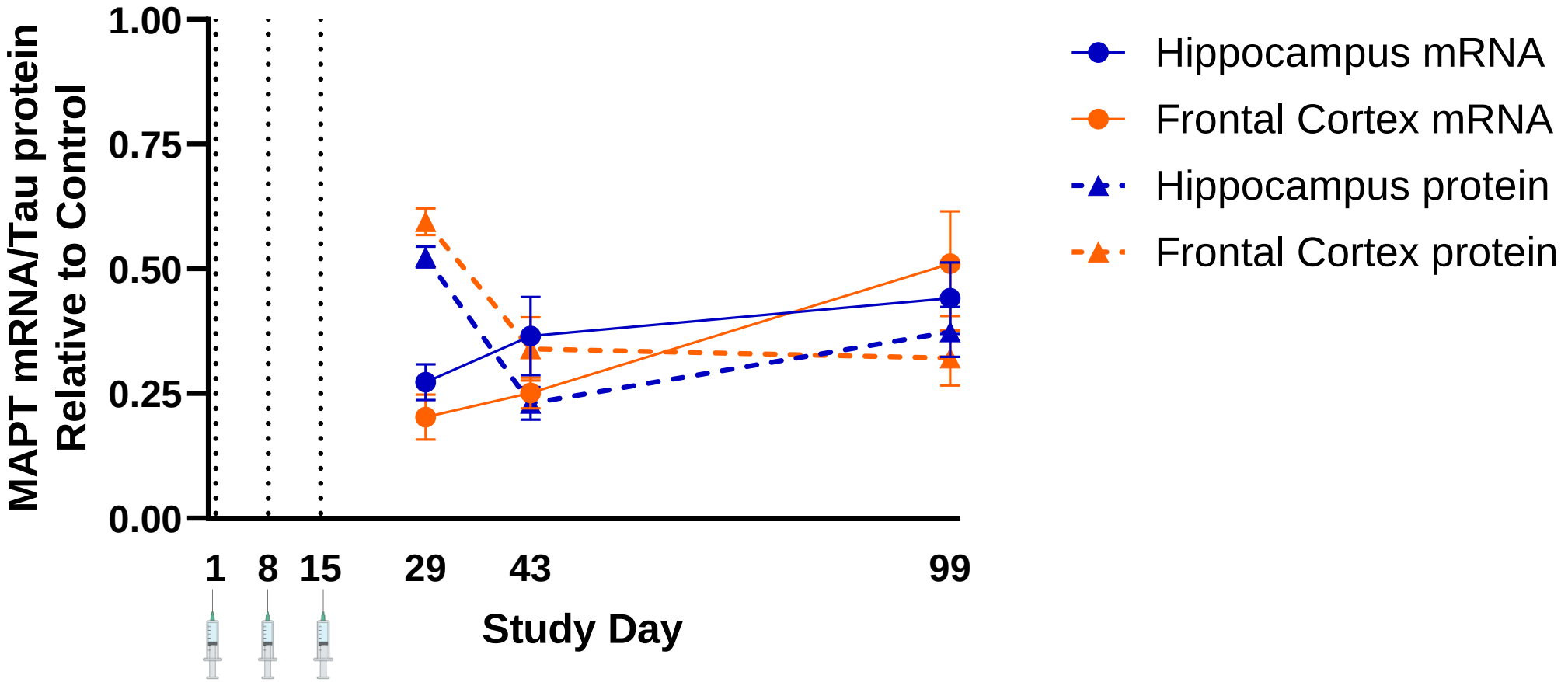
3 x 3mg/kg weekly subcutaneous doses
Day 29, n=4/group, mean±SEM

RNAscope for MAPT mRNA in Hippocampus



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

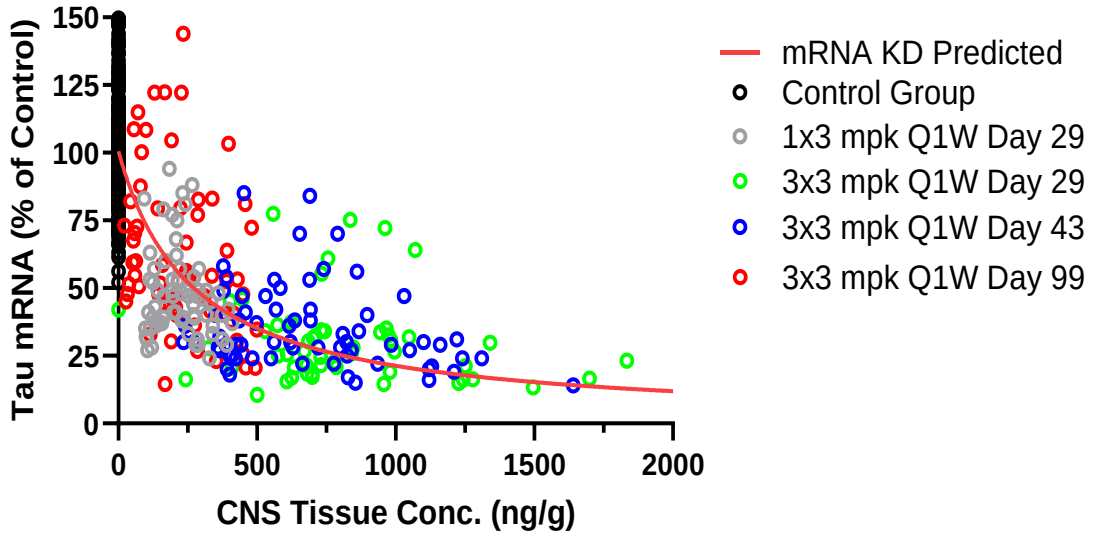
MAPT/Tau Reduction in NHP



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

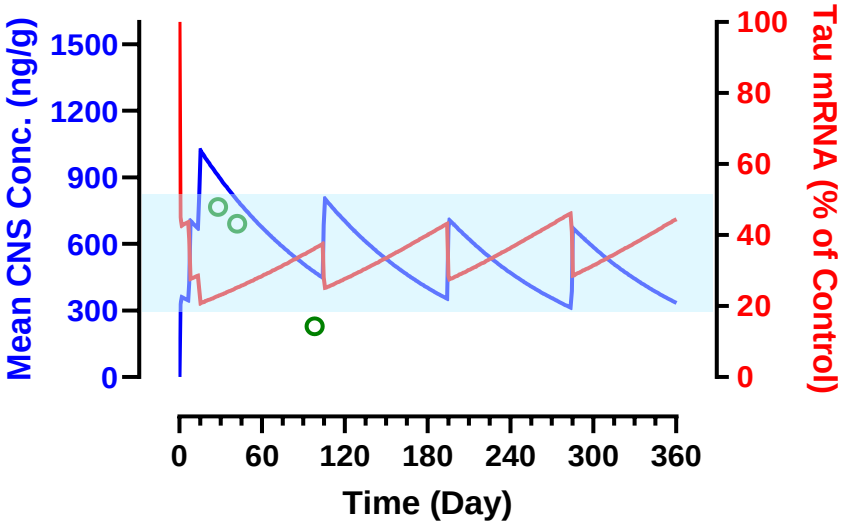
PK/PD Modeling Projects Sustained Tau Inhibition with Quarterly Dosing of ARO-MAPT SC

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**

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CNS Early Pipeline Programs

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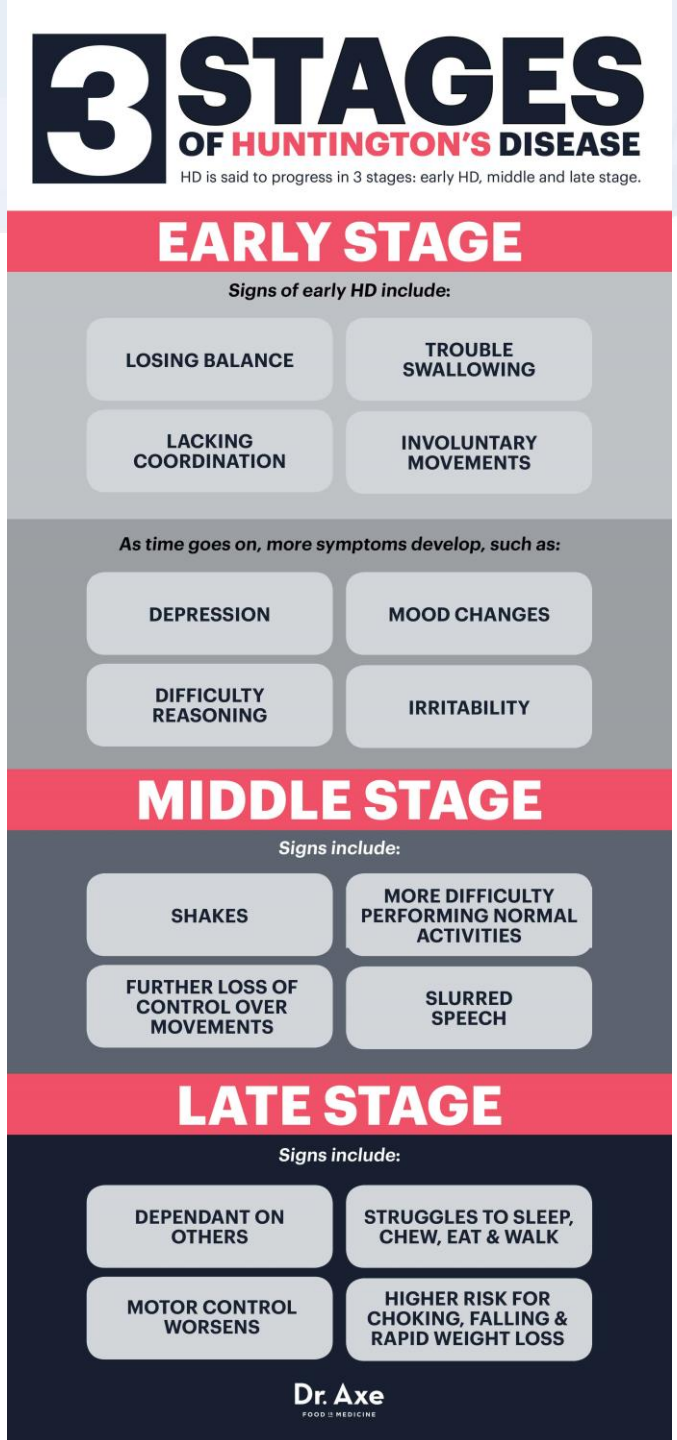
Huntington's Disease

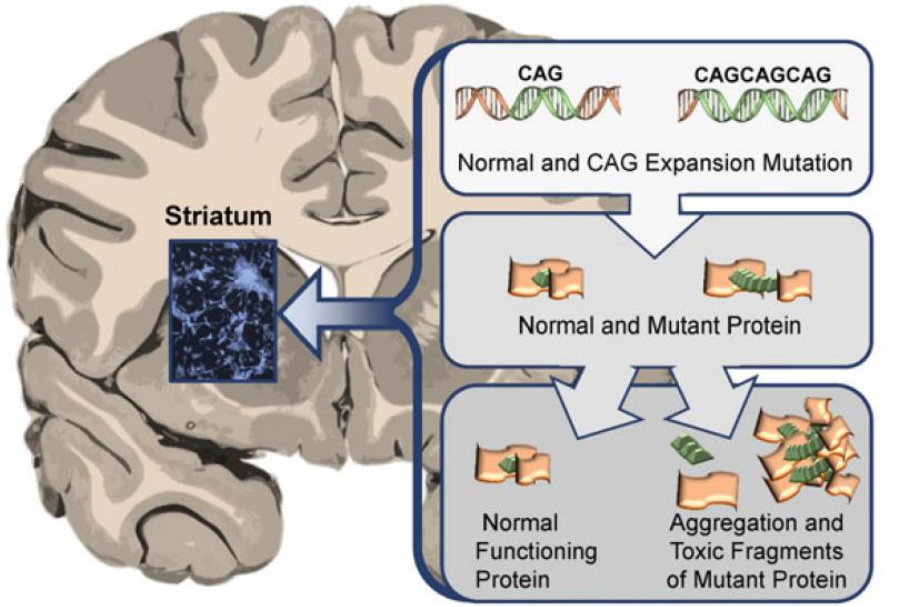
- Huntington's disease is the most common monogenic neurological disorder in the world with a prevalence of 8–13 per 100,000 in the US and Europe
- Symptoms include motor dysfunction, cognitive impairment, and neuropsychiatric problems. There are no disease modifying treatments available
- Symptom onset is typically between 30–50 yrs. Age of onset and disease progression correlates with CAG repeat number but genetic modifiers (e.g. somatic repeat expansion) have been identified
- Median survival from onset of motor symptoms is ~15 years
- Established target engagement biomarker (mutant HTT protein in CSF)



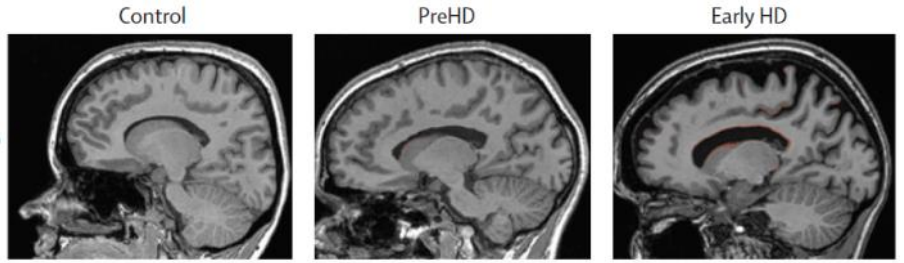
ARO-HTT SC for Huntington's Disease

Effective Delivery to Disease-Relevant Deep Brain Regions with CNS-SC TRiM™

- Huntington's disease is caused by expansion of the CAG repeat (>36) in exon 1 of the HTT gene
- The expanded polyglutamine (polyQ) in the HTT protein leads to protein aggregation and neuronal damage – initially in the striatum, then spreading to cortex regions
- HTT is an excellent target for siRNA therapeutics but has high hurdle for delivery to deep brain regions
- CNS-SC TRiM™ effectively targets HTT in striatum without excessive tissue accumulation in spinal cord and cortex – **potential for better efficacy with improved safety profile compared to tominersen/intrathecal approaches**



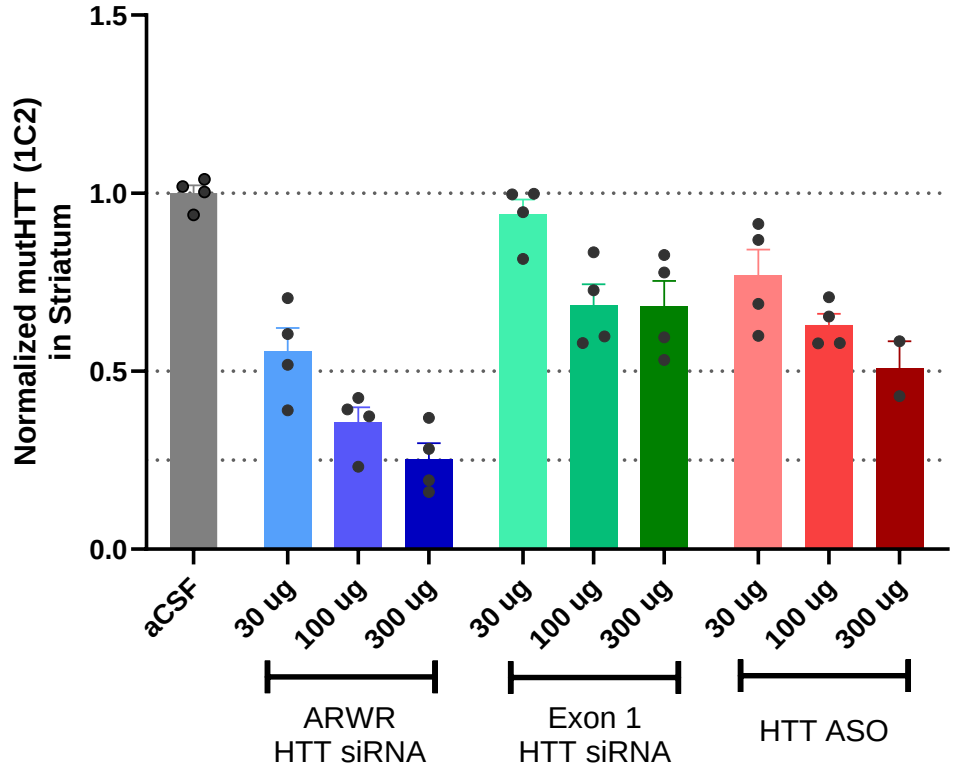
Bailus et. al., 2017



Tabrizi et. al., *Lancet Neurol* 2011;10:31-42

Potency of ARWR HTT Lead Compound Superior to Competing RNA Approaches

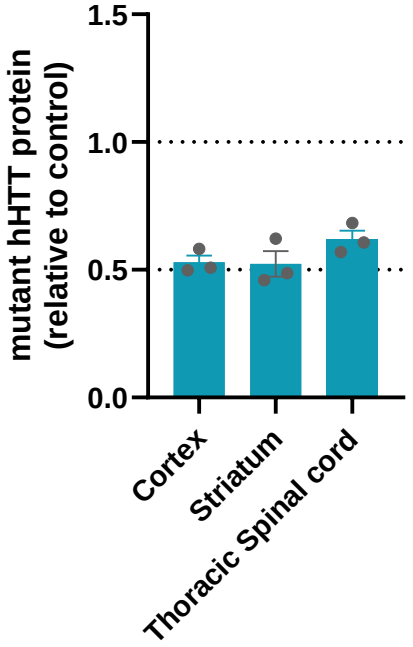
Intrathecal Delivery YAC128 HD Mice



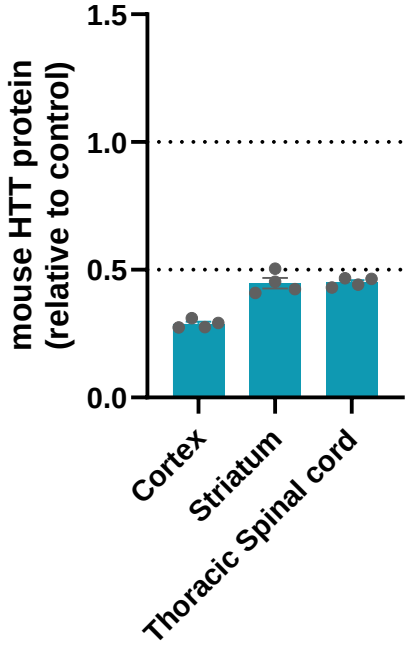
Single ICV Administration
Day 29, n=4/Group, Mean±SEM

Systemic Delivery of Lead HTT siRNA

Model: YAC128 HD Mice
Tfr Ligand: Mouse



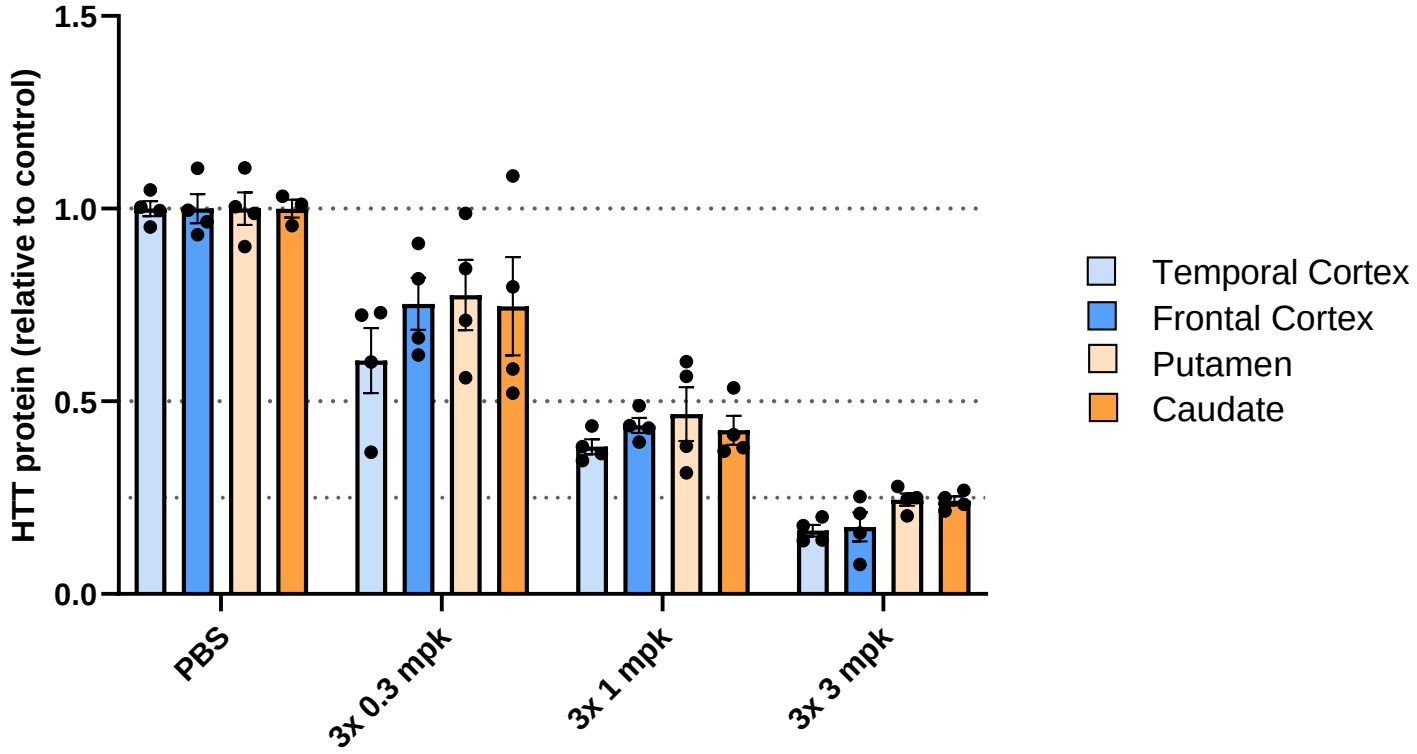
Model: hTfr Transgenic Mice
Tfr Ligand: Human



4 x 3mg/kg qd Subcutaneous Doses
Day 29, n=4/Group, Mean±SEM

HTT Protein Reduction Throughout the NHP CNS After Treatment with ARO-HTT SC >75% KD in Disease Relevant Brain Regions

HTT Protein in NHP



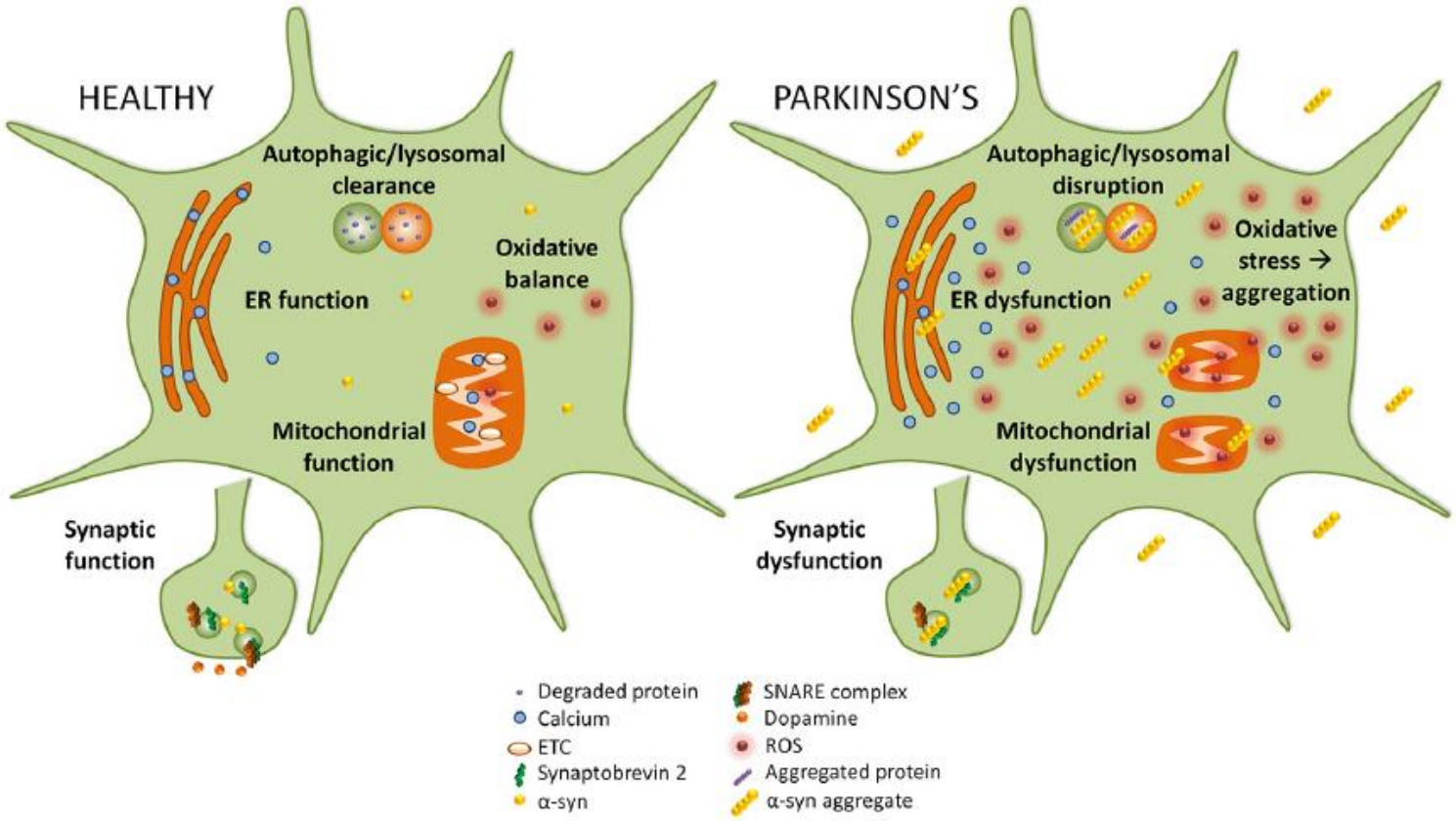
3 qw subcutaneous doses
Day 43, n=4/group, mean±SEM

ARO-HTT SC:

- Effectively targets deep brain regions important for Huntington's disease pathogenesis
- Targets both mutant and wildtype HTT mRNA
- CTA planned in 2H 2025

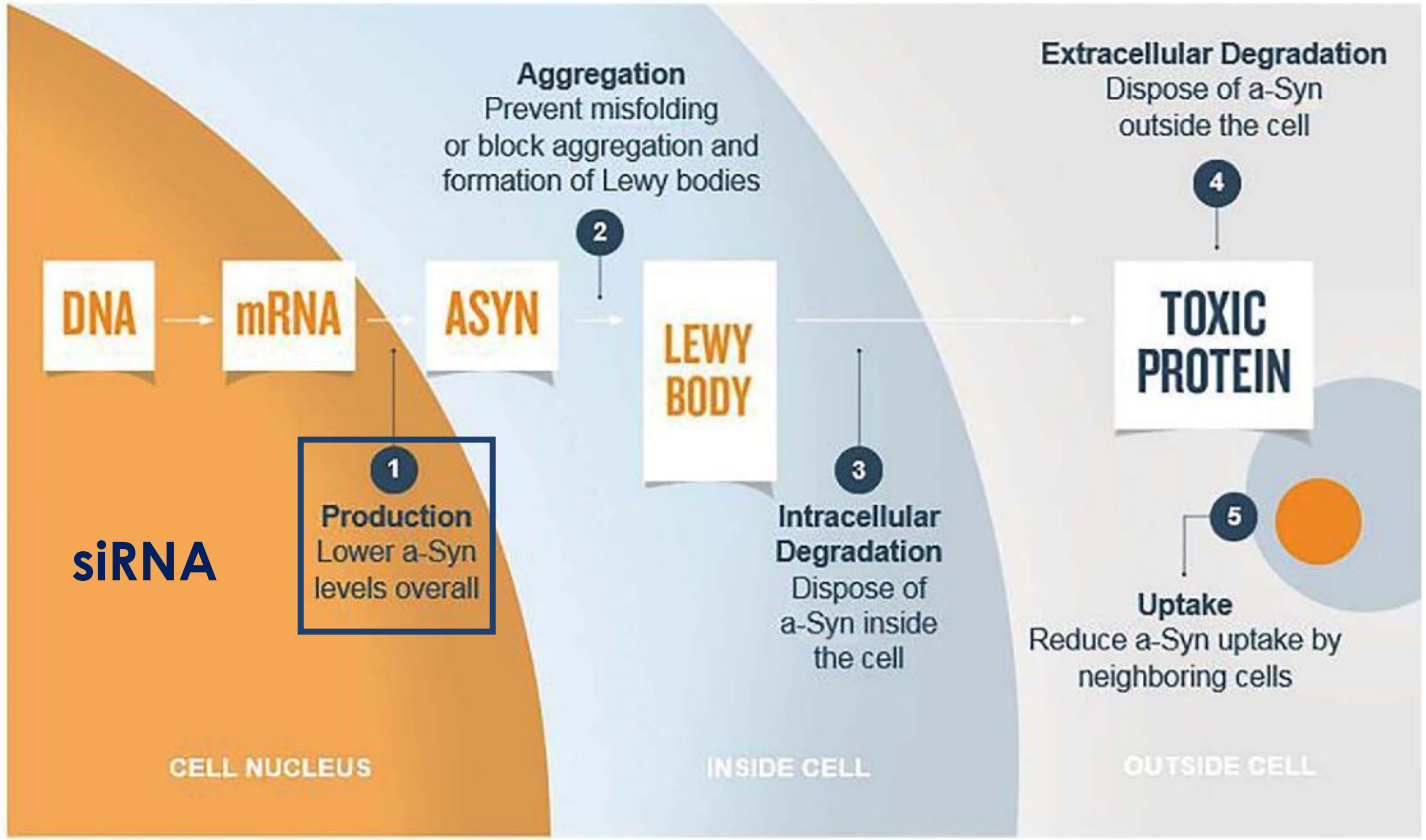
Toxic Aggregation of α-synuclein Causes Parkinson's Disease and a Range of Synucleinopathies

- α-synuclein is encoded by the SNCA gene
- Mutations or gene duplication of SNCA cause an autosomal dominant form of Parkinson's disease
- Abundant in neurons, α-synuclein is normally involved in synaptic vesicle trafficking and neurotransmitter release
- Accumulation of misfolded α-syn intracellularly in Lewy bodies is pathogenic in Parkinson's disease, Lewy body dementia, and multiple system atrophy



Fields et al, 2019. *Front Mol Neuro* 12:299

ARO-SNCA SC for Synucleinopathies

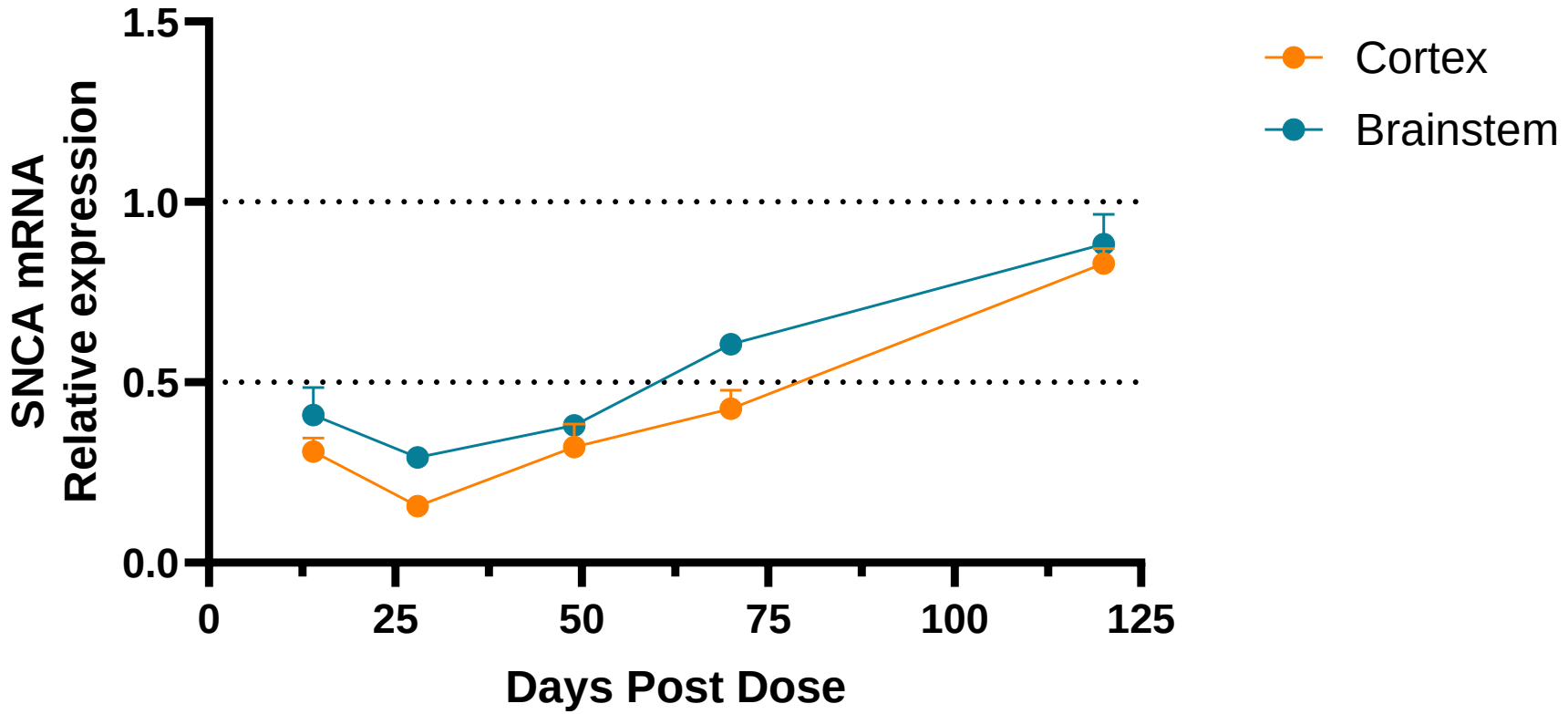


- As synucleinopathies are caused by a toxic gain of function, inhibition of α-synuclein protein production by siRNA has potential to be disease-modifying
- Targeting α-syn with other modalities has been unsuccessful to date, due to intracellular localization and structural diversity of aggregates
- One siRNA approach suitable for Parkinson's disease, Lewy body dementia, and Multiple system atrophy

Brundin, P. et al, 2017. *Experimental Neurology*

Deep Reduction of SNCA mRNA with Systemically Delivered siRNA in Mouse

SNCA mRNA in Mice



4 x 2.5mg/kg qd subcutaneous doses
n=4/group, mean±SEM
Surrogate mouse Tfr ligand

- Lead candidate selection expected end of 2024

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

CNS Programs Webinar – October 7, 2024

Clinical Evaluation and Unmet Needs in Alzheimer's

Jose Soria, M.D.
Director of Clinical Research, The Neuron Clinics
Assistant Clinical Professor of Neurosciences and Attending Neurologist, UC San Diego

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Clinical Evaluation and Unmet Needs in Alzheimer's Disease Treatment

Jose Soria MD

- Director of Clinical Research at The Neuron Clinic
- Assistant Clinical Faculty at UC San Diego Neuroscience

10.07.2024

Disclosures

Membership on Biogen, Eisai, Lilly, Merck and Genentech Advisory Boards.

Arrowhead, Biogen, Eisai, and Lilly Speaker.

Clinical Trial Research Support from Biogen, AriBio, Karuna/Bristol Myers Squibb, and Alzheimer's Association.

Objectives

Review	• Review definitions of Alzheimer's Disease
Discuss	• Discuss clinical aspects of care and treatment
Explain	• The impact of Tau pathology
Summarize	• Unmet needs, challenges, and opportunities

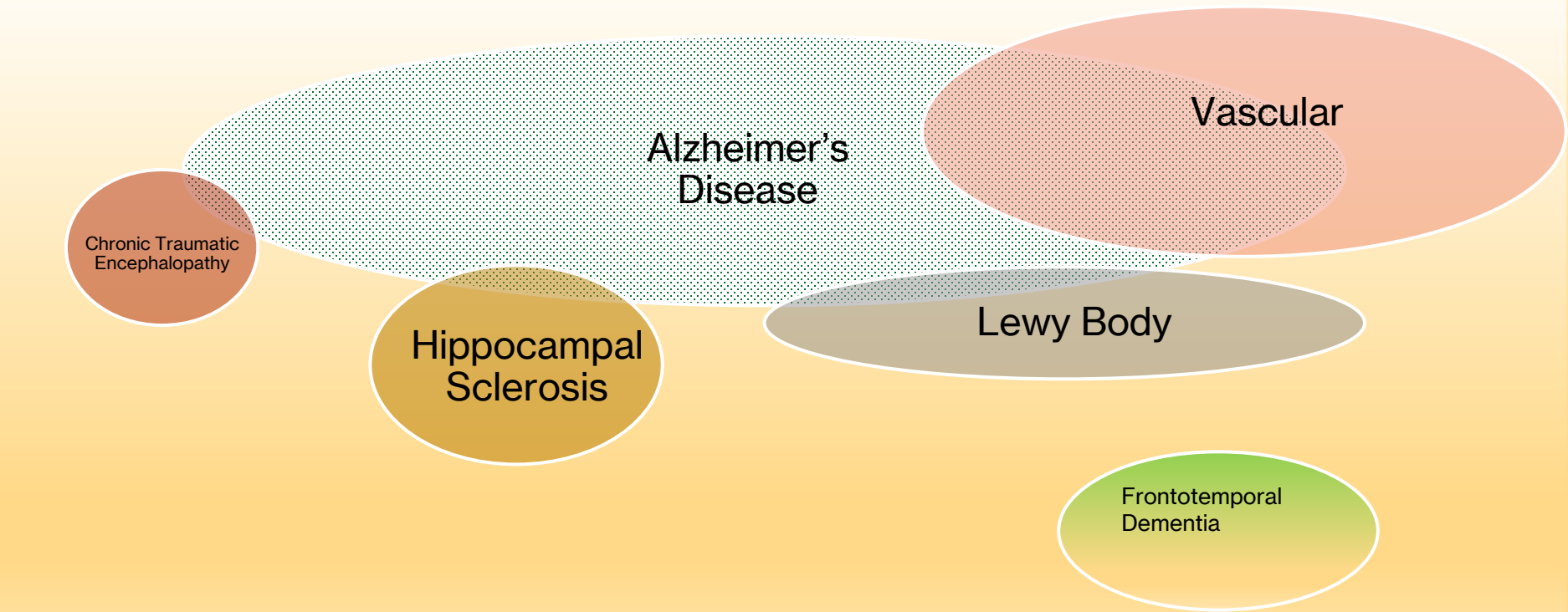
What is dementia?

- **Dementia** refers to decline in cognitive abilities leading to impaired daily function compared to a previously established baseline.
- There are many different causes of dementia
- Cognitive or behavioral impairment involves a minimum of two of the following domains
  - Impaired ability to acquire and remember new information
  - Impaired reasoning and handling complex task, poor judgment
  - Impaired visuospatial abilities
  - Impaired language function
  - Changes in personality or behavior

- Probable AD Dementia
  - Meets criteria for dementia
  - Insidious onset
  - “Clear-cut” history of worsening cognition by report or observation
  - Amnestic and non amnestic presentations
- Possible AD Dementia
  - has a sudden onset of cognitive impairment or demonstrates insufficient historical detail or objective cognitive documentation of progressive decline
  - Concomitant cerebrovascular disease, dementia with Lewy bodies or evidence of another neurological disease

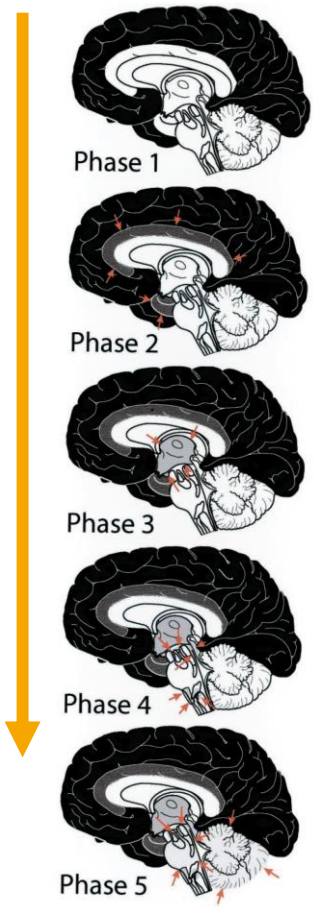
G.M. McKhann et al. / Alzheimer’s & Dementia 7 (2011) 263–269

The Most Common Form of Dementia

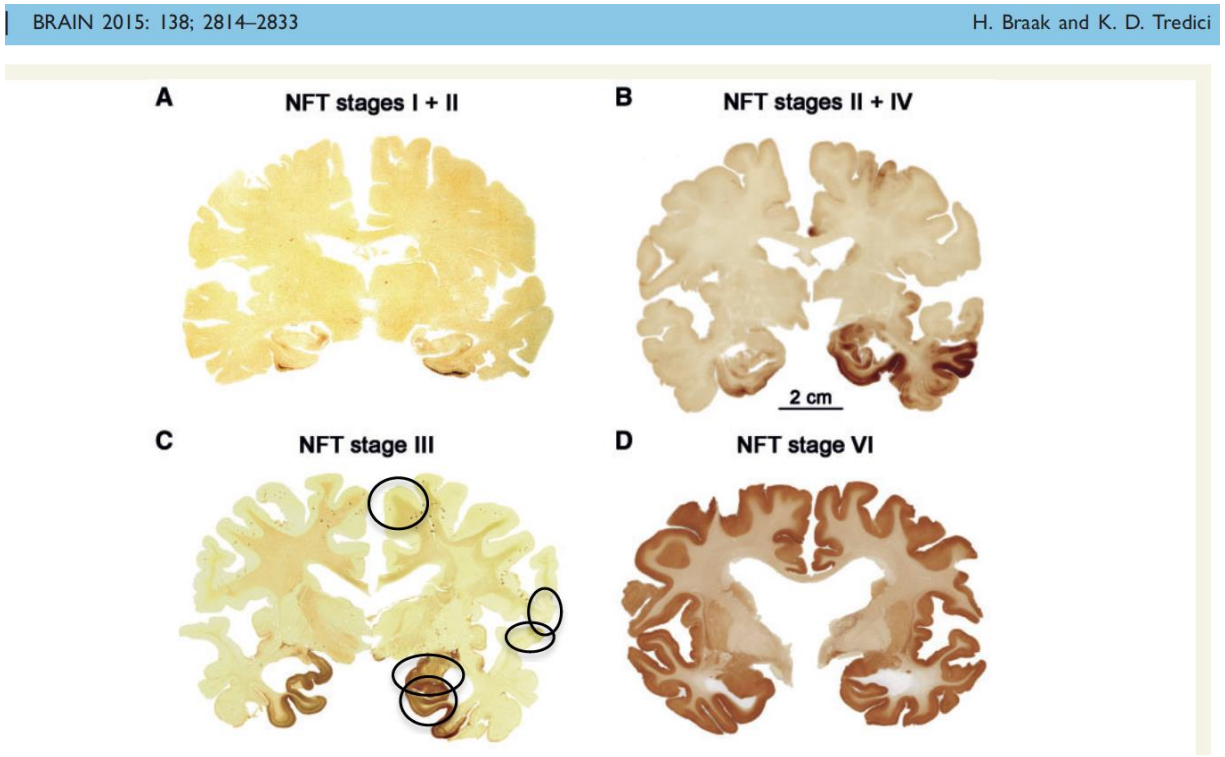


Alzheimer's Association. Alzheimers Dement. 2020;16(3):391-485. 2. Zarow C et al. Brain Behav. 2012; 2(4):435-442.

Underlying Neuropathologic Changes: Phases Of Beta Amyloidosis And Neurofibrillary Tangles



Thal et al. Neurology. 2002



Braak and Del Tredici. *BRAIN 2015: 138; 2814–2833*

Neuropathologic criteria and assessment for AD were updated in 2012 to be more specific and inclusive of comorbid neuropathologies that may also contribute to clinical dementia.

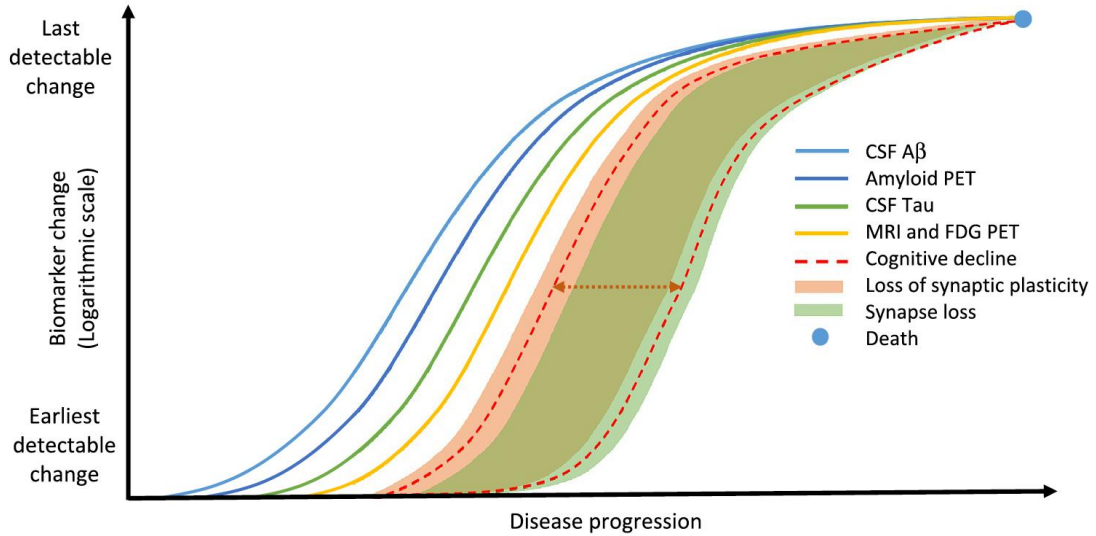
It established protocols for the neuropathologic assessment of Lewy body disease, vascular brain injury, hippocampal sclerosis, and TDP-43 inclusions, and recommend standard approaches for the workup of cases and their clinic-pathologic correlation

Additional concomitant neurodegenerative diseases accompanying AD are common and age related

B.T. Hyman et al. / Alzheimer's & Dementia 8 (2012) 1–13

The Alzheimer's Disease Continuum

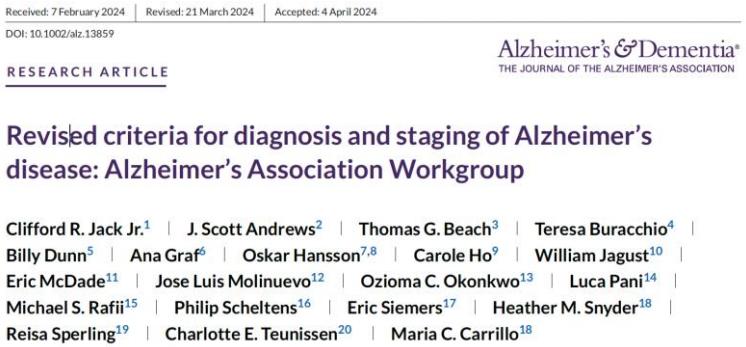
- **Preclinical** — Cognitively Unimpaired
- **Mild Cognitive Impairment** — Independent in Activities of Daily Living
- **Mild Dementia** — Functional Impact on Daily Life
- **Moderate and Severe Dementia** — Extensive functional impact



Jack CR et al. Alzheimers Dement. 2018;14(4):535-562. Alzheimer's Association. Alzheimers Dement. 2020;16(3):391-460.
Sperling R et al. Alzheimers Dement. 2011;16(3):280-292.

Revised Criteria

- Definition of Alzheimer's Disease as a "biological process"
- Disease progresses through a preclinical period
- Inclusion of blood-based biomarkers
- Treatment Related Amyloid Clearance (TRAC)
- Biological Staging of Disease (The impact of **Tau pathology**)



Received: 7 February 2024 | Revised: 21 March 2024 | Accepted: 4 April 2024
DOI: 10.1002/alz.13859

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup

Clifford R. Jack Jr.[1] | J. Scott Andrews[2] | Thomas G. Beach[3] | Teresa Buracchio[4] | Billy Dunn[5] | Ana Graf[6] | Oskar Hansson[7,8] | Carole Ho[9] | William Jagust[10] | Eric McDade[11] | Jose Luis Molinuevo[12] | Ozioma C. Okonkwo[13] | Luca Pani[14] | Michael S. Rafii[15] | Philip Scheltens[16] | Eric Siemers[17] | Heather M. Snyder[18] | Reisa Sperling[19] | Charlotte E. Teunissen[20] | Maria C. Carrillo[18]

Comment

https://doi.org/10.1038/s41591-024-02988-7

Revised criteria for the diagnosis and staging of Alzheimer's disease

Clifford R. Jack Jr, Scott J. Andrews, Thomas G. Beach, Teresa Buracchio, Billy Dun[illegible], Ana Graf, Oskar Hansson, Carole Ho, William Jagust, Eric McDade, Jose Luis Molin[illegible], Ozioma C. Okonkwo, Luca Pani, Michael S. Rafii, Philip Scheltens, Eric Siemers, Heather M. Snyder, Reisa Sperling, Charlotte E. Teunissen & Maria C. Carrillo

nature medicine

Check for updates

Received: 8 January 2024 | Accepted: 12 January 2024
DOI: 10.1111/jgs.18793

COMMENTARY

Journal of the American Geriatrics Society

Who gets to decide on what it means to have Alzheimer's disease?

Eric Widera MD[1,2]

[1]Department of Medicine, Division of Geriatric Medicine, University of California San Francisco, San Francisco, California, USA
[2]San Francisco Veterans Affairs Healthcare System, San Francisco, California, USA

	Initial-stage biomarkers (A)	Early-stage biomarkers (B)	Intermediate-stage biomarkers (C)	Advanced-stage biomarkers (D)
PET	Amyloid PET	Tau PET medial temporal region	Tau PET moderate neocortical uptake	Tau PET high neocortical uptake
	$A+T_2-$	$A+T_{2MTL}+$	$A+T_{2MOD}+$	$A+T_{2HIGH}+$

Jack CR, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimer's Dement*. 2024; 20: 5143–5169. https://doi.org/10.1002/alz.13859

Biological and Clinical Staging

	Stage 0	Clinical Stage 1	Clinical Stage 2	Clinical Stage 3	Clinical Stages 4–6
Initial biological stage (A)	X	1A	2A	3A	4-6A
Early biological stage (B)	X	1B	2B	3B	4-6B
Intermediate biological stage (C)	X	1C	2C	3C	4-6C
Advanced biological stage (D)	X	1D	2D	3D	4-6D

Jack CR, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimer's Dement*. 2024; 20: 5143–5169. https://doi.org/10.1002/alz.13859

Aging Population Continues To Grow And Burden Of Disease Is Substantial

2024 Alzheimer's Disease Facts and Figures

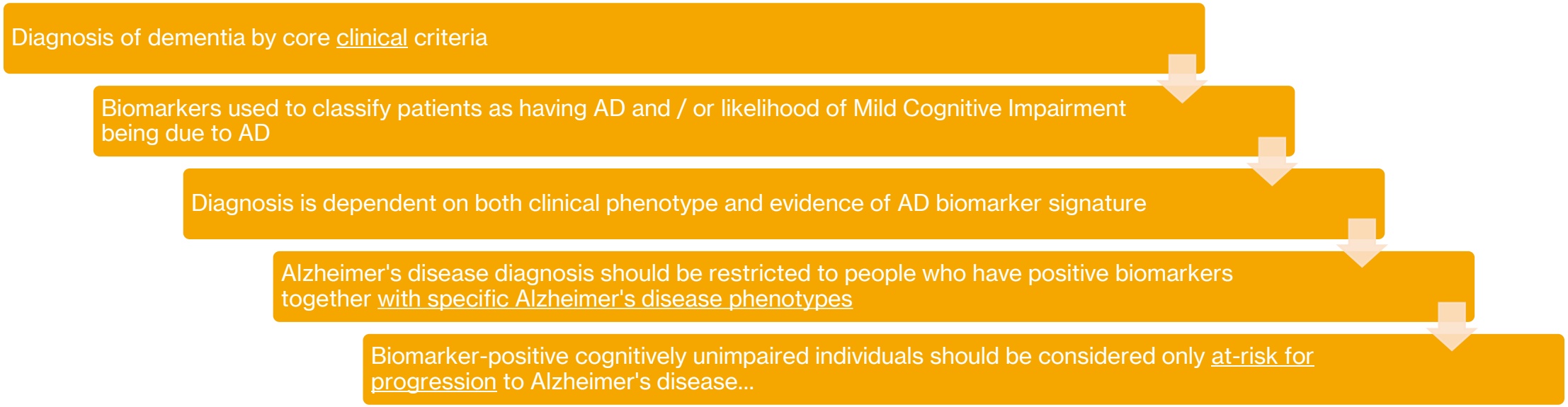
Clinical Practice: Evaluation Of Cognitive Decline

The clinical diagnosis of AD dementia (Alzheimer's clinical syndrome) or amnestic MCI (mostly likely due to AD) does not require measuring biomarkers (not yet)

The presence of functional impairment, amnestic clinical profile, deficit in another cognitive domain, and absence of other causes/contributors (through routine blood tests, neuroimaging, and failure to meet criteria for other diagnoses) are sufficient to make a diagnosis of probable AD

Disease is characterized by impaired consolidation or storage of information with relatively spared registration and recall. Impaired short-term memory along with impaired naming and diminished semantic fluency can help discriminate between AD and overlapping syndromes

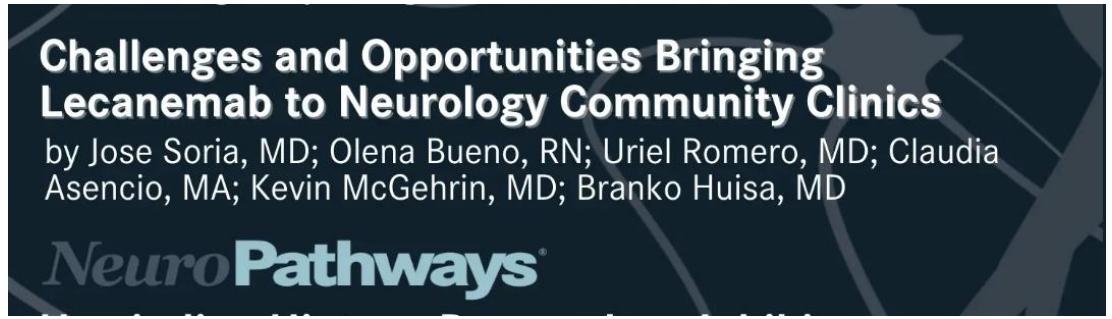
Diagnostic Guidelines Using Biomarkers: Framework for AD Based on Biomarkers (Clinical Practice)



G.M. McKhann et al. / Alzheimer's & Dementia 7 (2011) 263–269

Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. The Lancet Neurology. PERSONAL VIEW| VOLUME 20, ISSUE 6, P484-496, JUNE 01, 2021

Challenges and Opportunities Bringing New Therapies to Clinical Practice



J Prev Alz Dis 2022;
Published online March 18, 2022, http://dx.doi.org/10.14283/jpad.2022.30

Original Research

Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease

S. Budd Haeberlein[1], P.S. Aisen[2], F. Barkhof[3,4], S. Chalkias[1,], T. Chen[1], S. Cohen[5], G. Dent[1], O. Hansson[6,7], K. Harrison[1], C. von Hehn[1,*], T. Iwatsubo[8], C. Mallinckrodt[1,*], C.J. Mummery[9], K.K. Muralidharan[1], I. Nestorov[1], L. Nisenbaum[1,*], R. Rajagovindan[1,*], L. Skordos[1,*], Y. Tian[1], C.H. van Dyck[10], B. Vellas[11], S. Wu[1], Y. Zhu[1], A. Sandrock[1,*]*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lecanemab in Early Alzheimer's Disease

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Research

JAMA | Original Investigation

Donanemab in Early Symptomatic Alzheimer Disease
The TRAILBLAZER-ALZ 2 Randomized Clinical Trial

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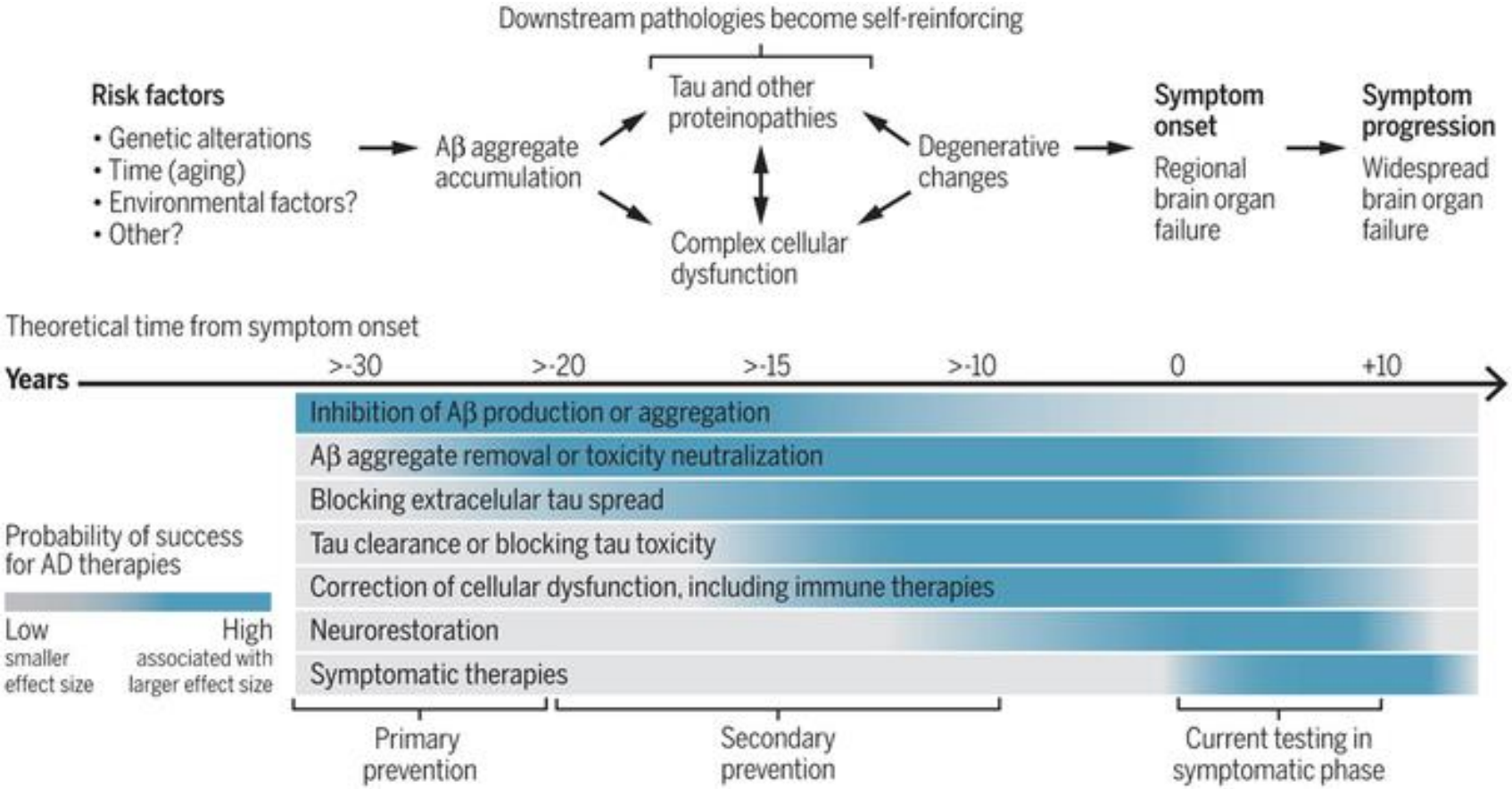
Science | AAAS



Alzheimer's disease: The right drug, the right time, Volume: 362, Issue: 6420, Pages: 1250-1251, DOI: (10.1126/science.aau0437)

Impact of Tau Pathology on the Efficacy of Anti-Amyloid Monoclonal Antibodies

CLARITDY AD STUDY

- Over 50% of participants with no or low tau had no decline in measures of cognition and function at 36 months in the open label extension study.
- Lecanemab slowed spread of tau relative to placebo in temporal lobe region over 18 months in the core study.

TRAILBLAZER-ALZ 2

- Donanemab slowed clinical progression at 76 weeks in participants with low/medium tau and in the combined low/medium and high tau pathology groups.
- Donanemab slow spread of tau relative to placebo in temporal, parietal, and frontal lobes over 76 weeks.

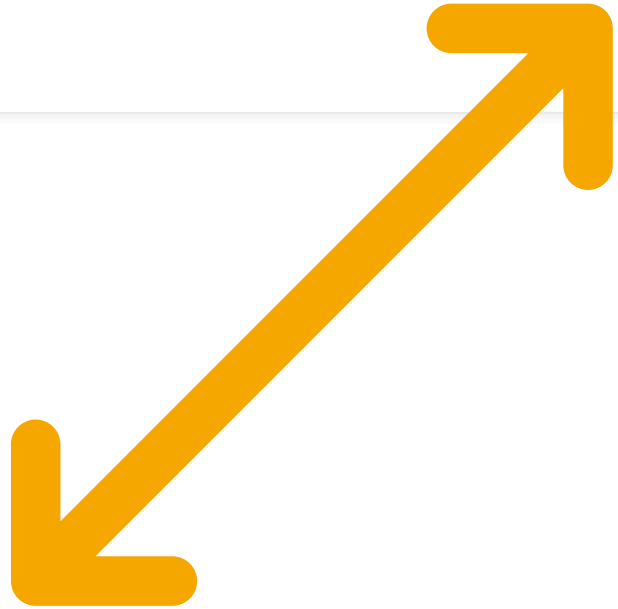
July 30, 2024. Alzheimer's Association International Conference (AAIC) 2024. July 28 - August 1, 2024 / Philadelphia, PA, USA + Online.
Sims JR, Zimmer JA, Evans CD, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA. 2023;330(6):512–527. doi:10.1001/jama.2023.13239.

How Are Tau-Targeted Therapies Expected to Differ from Current Treatment Approaches?

- There is limited efficacy of amyloid beta targeting therapies
- Tau is more likely to be efficacious once cognitive decline begins
- Targeting Tau pathology is anticipated to shorten the time needed to reach primary cognitive and functional decline endpoints in clinical trials, leading to **faster trial completion** and potentially reducing participant enrollment requirements
- No amyloid-related imaging abnormalities **(ARIA)** associated with amyloid-targeting therapies

How Might Tau-Targeted Therapies Be Utilized in Clinical Practice?

- **Expand treatment** to include patients with moderate stage of disease (large patient population)
- **Leverage biological stage** of disease to identify window for therapy (Tau PET Imaging)
- Allow treatment of patients with comorbid vascular disease including cerebral amyloid angiopathy (CAA)
- **Alternative treatment** option for patients taking anticoagulant medications and Apolipoprotein E4 (APOE4) homozygotes
- **Combination treatment** with anti amyloid targeting therapies and other therapies
- **Follow up sequential therapy** for patients with ”treatment related amyloid clearance” (TRAC) and others
- Expand the options for induction and maintenance therapy of this chronic relentless disease



Current Clinical Practice

The Alzheimer's disease definitions have evolved to include biomarkers and identify patients early in the disease process

Early clinical detection begins with MCI due to AD (Tau correlates with decline)

Treatment options are needed for patients with mild to moderate dementia state of disease (temporal & neocortical Tau stages)

The right medication at the right time, considering side effects (ARIA)

Mechanism of action, route of administration, combination therapy

CNS Programs Webinar – October 7, 2024

Key Takeaways and Timelines

Vince Anzalone, CFA
Vice President, Finance and IR

arrowhead pharmaceuticals

Key Takeaways

Two Routes of Administration

- Intrathecal – Broad distribution to cord and brain
- Subcutaneous – Better distribution to deep brain regions

Growing Pipeline and Compelling Data

Addressing Previously Difficult to Drug Targets

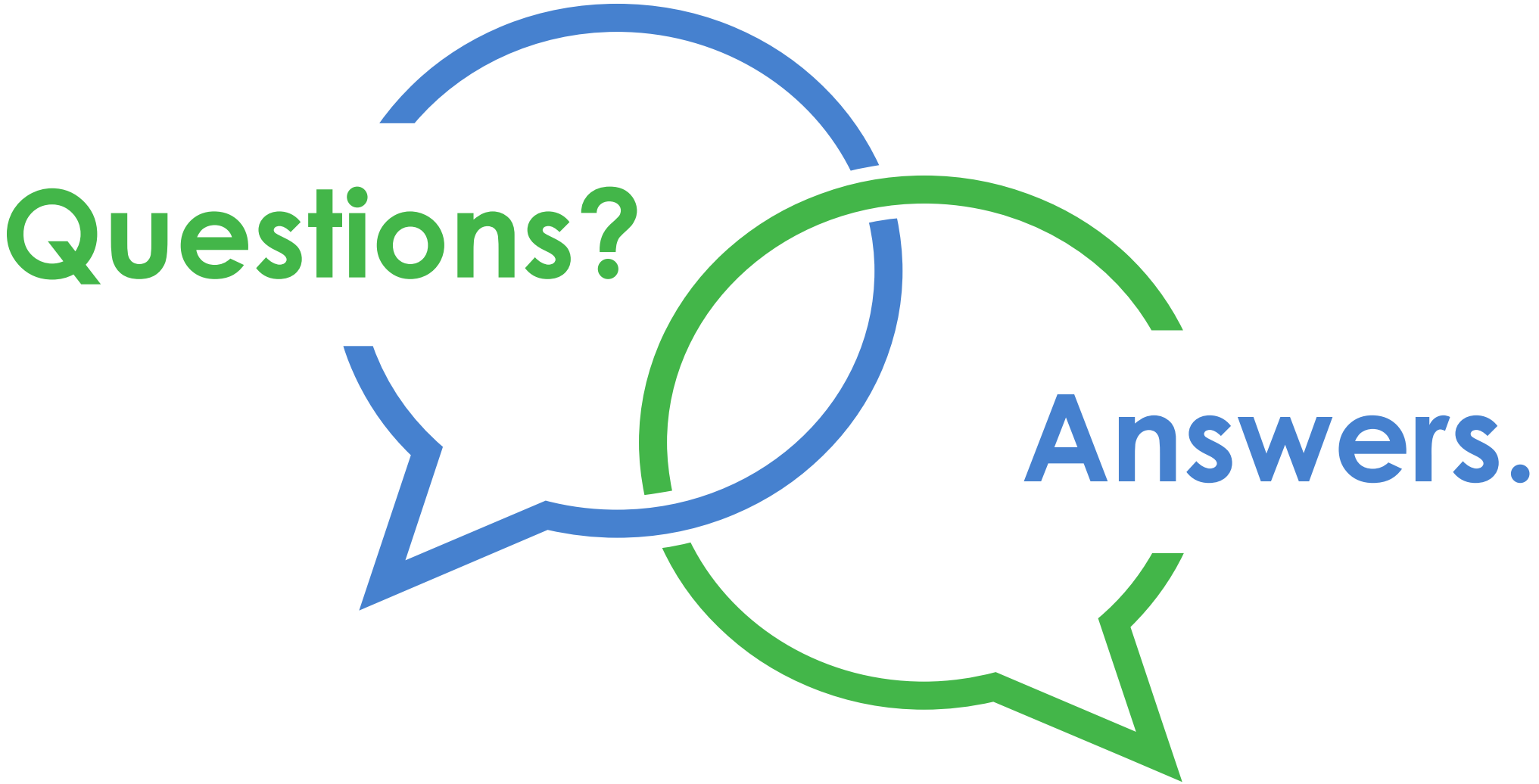
Arrowhead Has First Mover Advantage

siRNA is Promising Mechanism for Many CNS Targets

- High specificity
- Long durability of response

CNS Pipeline and Timelines

Route	Program	Next Milestone
Intrathecal	**ARO-ATXN2** Spinocerebellar Ataxia 2	First Patient Dosed 1st Quarter 2025
Subcutaneous	**ARO-MAPT** Alzheimer's Disease and tauopathies	CTA 2nd Half 2025
	ARO-HTT Huntington's Disease	CTA 2nd Half 2025
	ARO-SNCA Parkinson's Disease and Synucleinopathies	Candidate Selection YE 2024


Questions?
Answers.