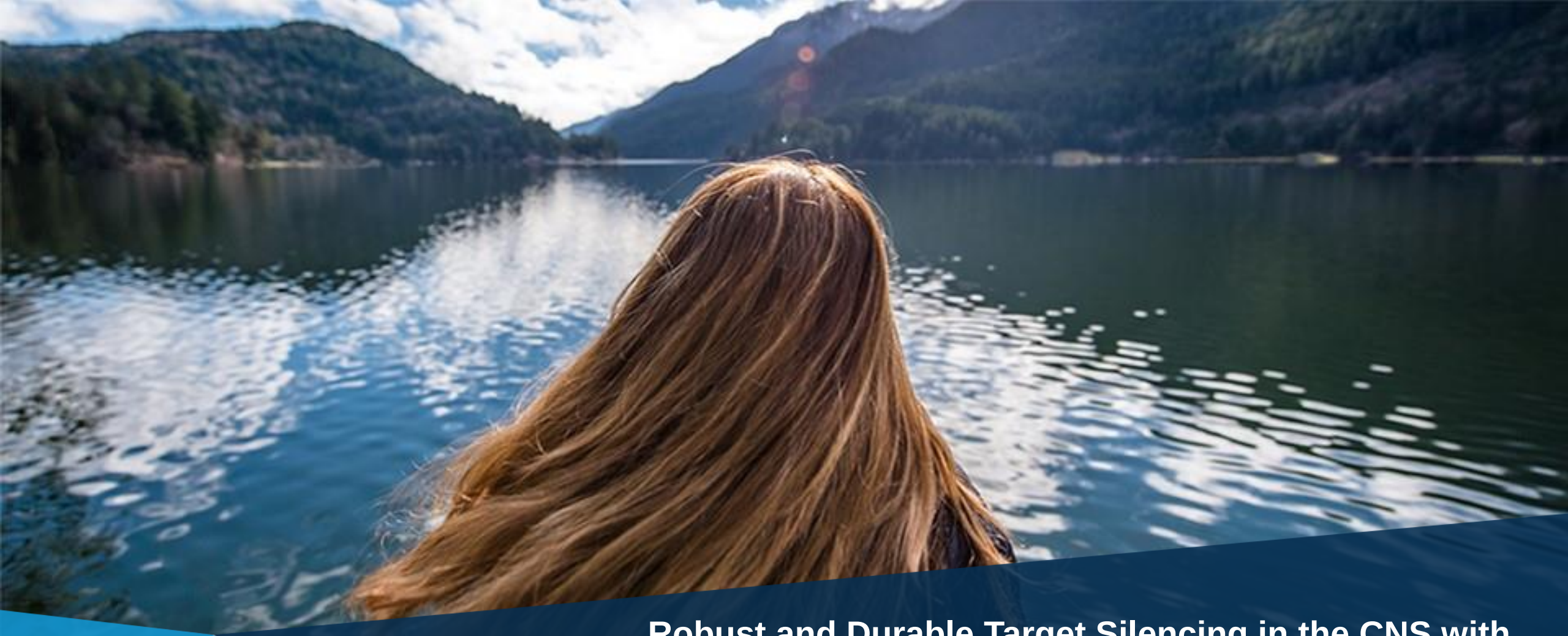


Robust and Durable Target Silencing in the CNS with siRNA Conjugates

Stuart Milstein

October 2, 2018

Alnylam® PHARMACEUTICALS

Alnylam Forward Looking Statements

This presentation contains forward-looking statements, within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. There are a number of important factors that could cause actual results to differ materially from the results anticipated by these forward-looking statements. These important factors include our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates; pre-clinical and clinical results for our product candidates; actions or advice of regulatory agencies; delays, interruptions or failures in the manufacture and supply of our product candidates; our ability to obtain, maintain and protect intellectual property, enforce our intellectual property rights and defend our patent portfolio; our ability to obtain and maintain regulatory approval, pricing and reimbursement for products; our progress in establishing a commercial and ex-United States infrastructure; our ability to successfully launch, market and sell our approved products globally; our ability to successfully expand the indication for ONPATTRO™ (patisiran) in the future; competition from others using similar technology and developing products for similar uses; our ability to manage our growth and operating expenses, obtain additional funding to support our business activities and establish and maintain business alliances; the outcome of litigation; and the risk of government investigations; as well as those risks more fully discussed in our most recent report on Form 10-Q under the caption “Risk Factors.” If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.

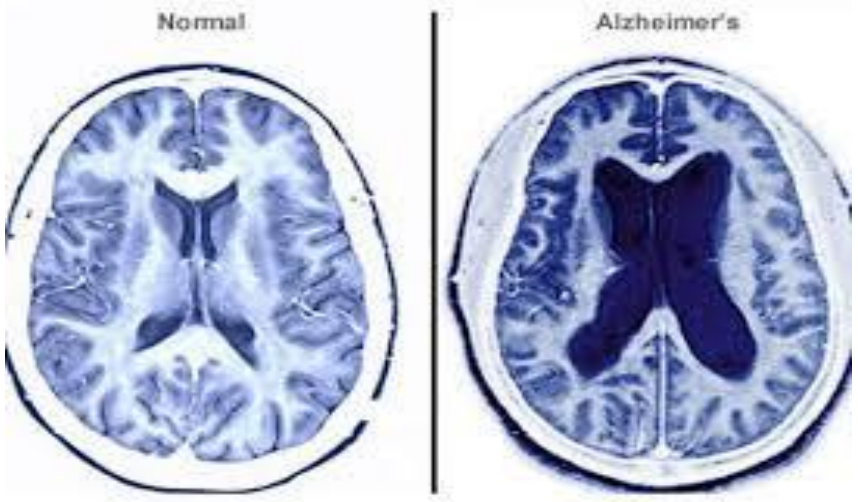
Conflicts of Interest

I am an employee of Alnylam Pharmaceuticals

Investigational RNAi Therapeutics for CNS Diseases

No current therapies to prevent or reverse neurodegenerative disease

- Dominantly inherited neurodegenerative diseases include
  - Alzheimer's disease
  - Parkinson's disease
  - Frontotemporal dementia
  - Huntington's disease
  - Amyotrophic lateral sclerosis (ALS)
  - Spinocerebellar ataxia
  - Prion disease
  - Many other orphan genetic diseases with CNS component

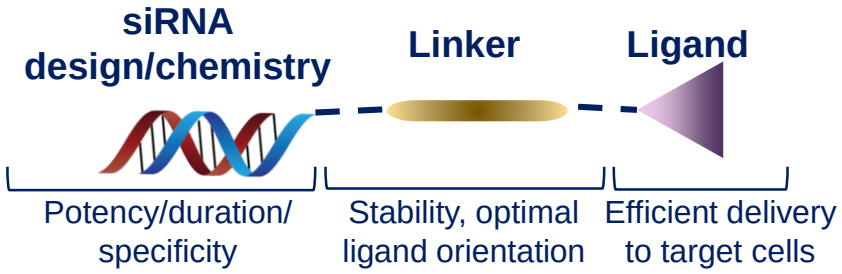


- Number of genetically validated targets known but few disease modifying therapies for these devastating, life threatening disorders
- RNAi therapeutics directed to disease-causing, CNS-expressed genes represent an opportunity to address diseases with some of the greatest unmet need.

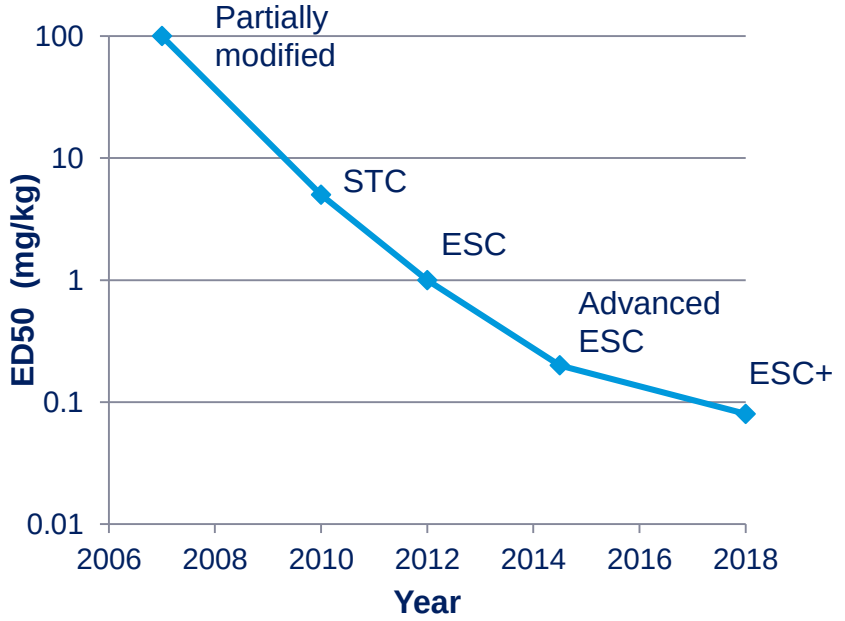
Alnylam PHARMACEUTICALS

Transformative Advancements in Conjugate-Based Delivery

siRNA designs with enhanced potency and stability may extend to extrahepatic tissues



Evolution of conjugate potency (mouse, SD ED_{50})

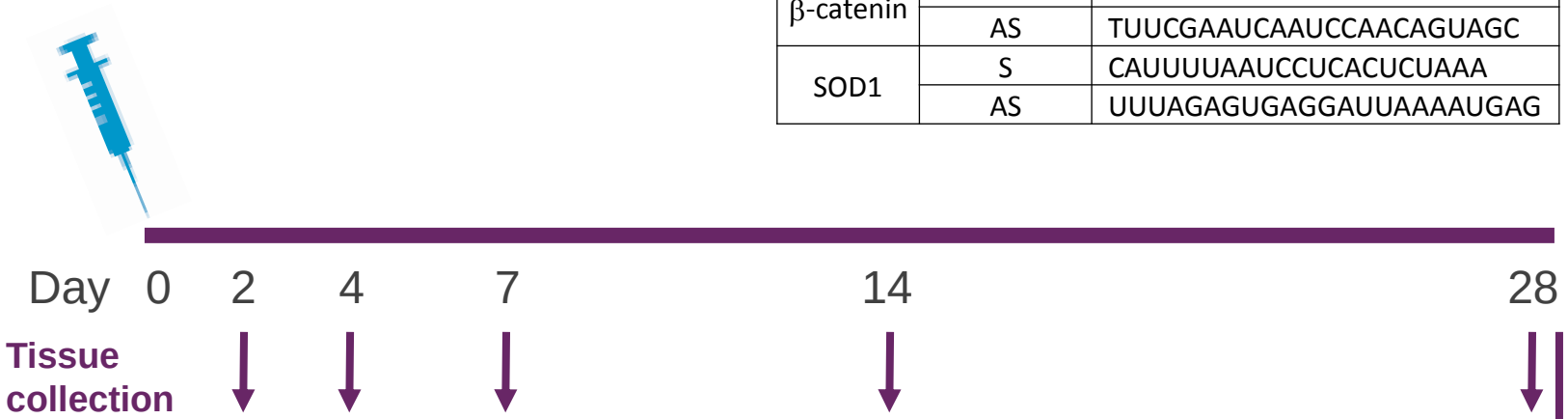


Intrathecal Delivery of siRNA Conjugates

Single dose time course in rat

- siRNAs targeting β-catenin and SOD1 tested to demonstrate efficacy and sequence specificity
- siRNA conjugate dose of 0.9 mg

	Strand (5'-3')	Sequence
β-catenin	S	UACUGUUGGAUUGAUUCGAAA
	AS	TUUCGAAUCAAUCCAACAGUAGC
SOD1	S	CAUUUUAAUCCUCACUCUAAA
	AS	UUUAGAGUGAGGAUUAAAAUGAG



Tissues: Spinal cord: Lumbar, thoracic and cervical

Brain: prefrontal cortex, cerebellum and remaining brain

Fluids: CSF and plasma

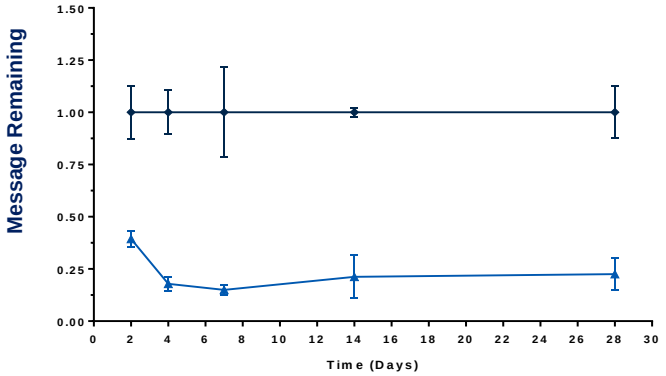
Assays: mRNA, tissue siRNA levels

Histology

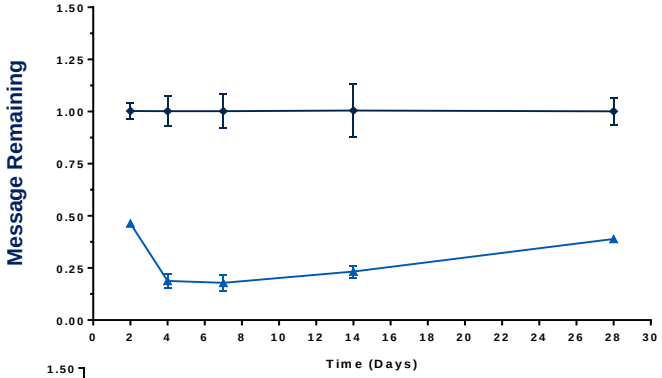
IT Dosing of SOD1 siRNA Conjugate to Evaluate CNS RNAi activity

Spinal cord regions

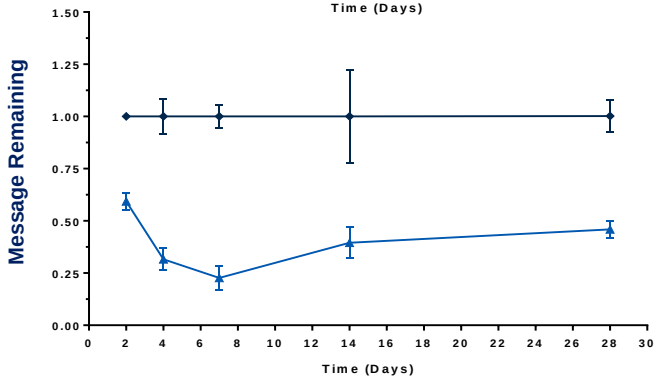
Lumbar

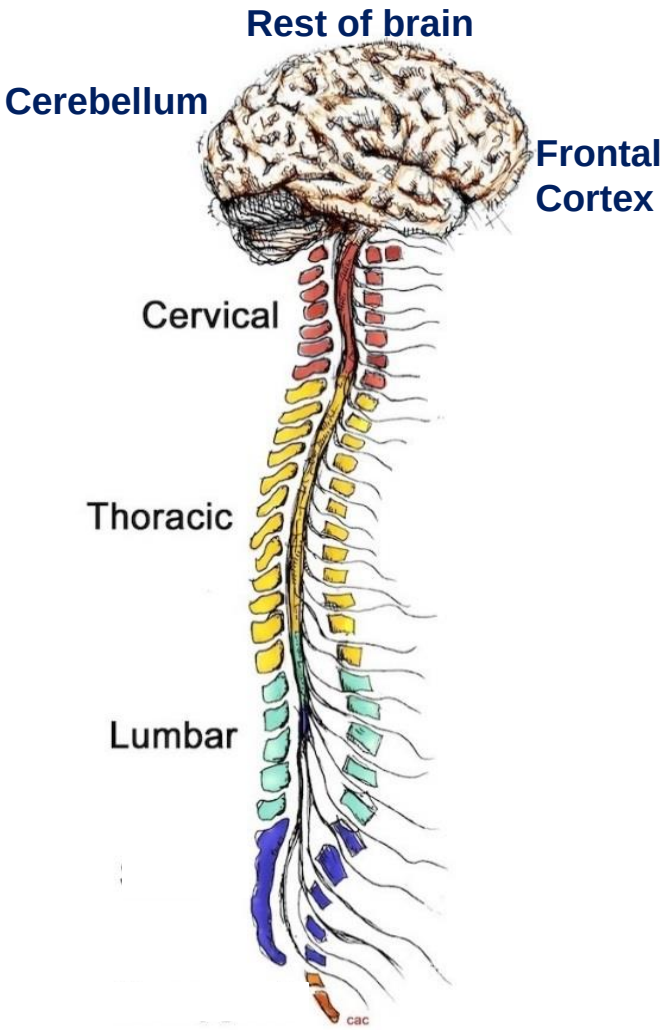


Thoracic

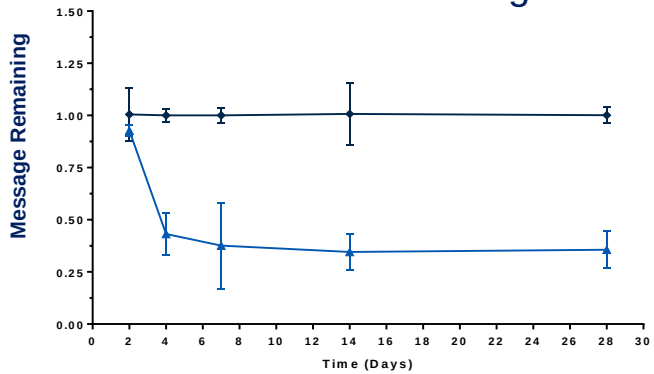


Cervical

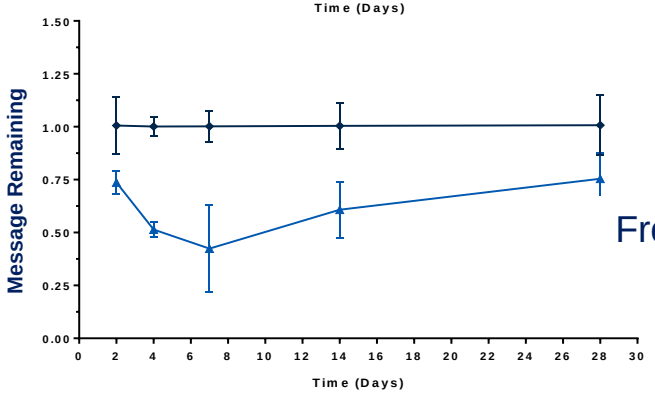




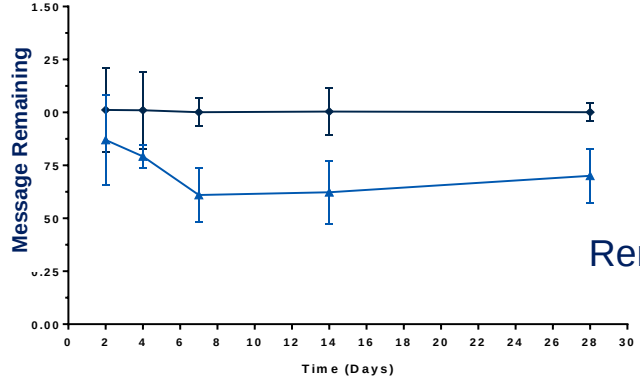
Brain regions



Cerebellum



Frontal Cortex



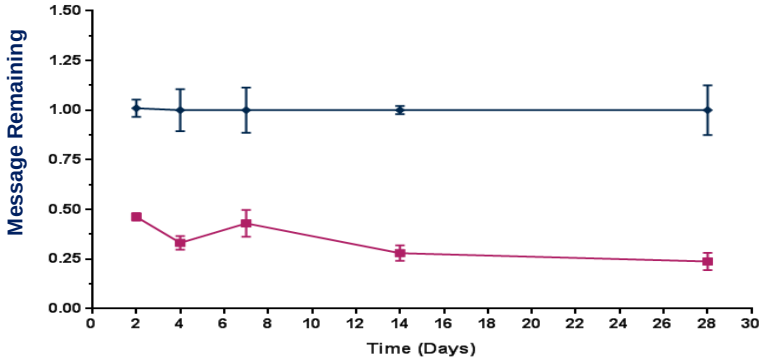
Remaining Brain

Durable SOD1 mRNA silencing is seen in all regions of the brain and spinal cord tested

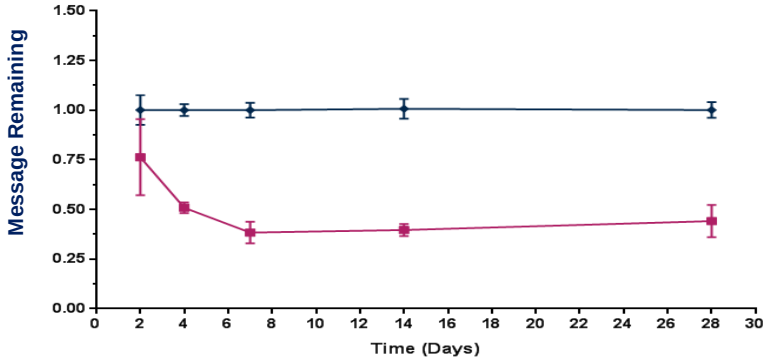
Robust and Durable Silencing is Consistent Across Targets

Silencing of β-catenin following a single IT dose

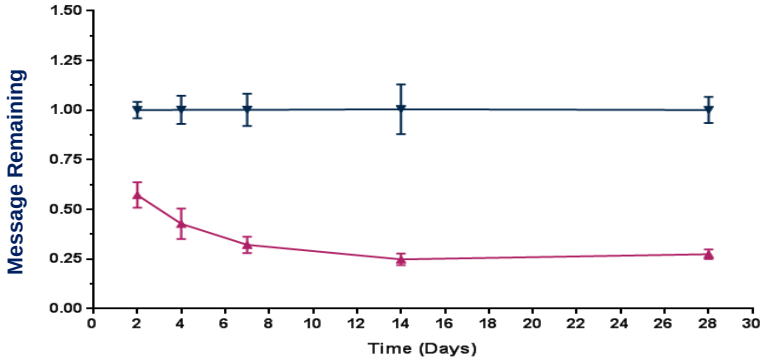
Lumbar



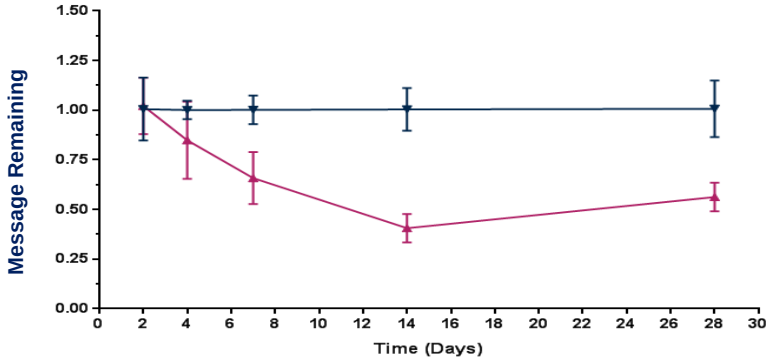
Cerebellum



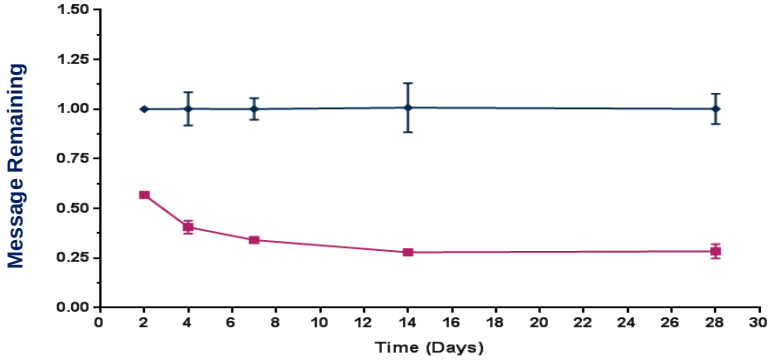
Thoracic



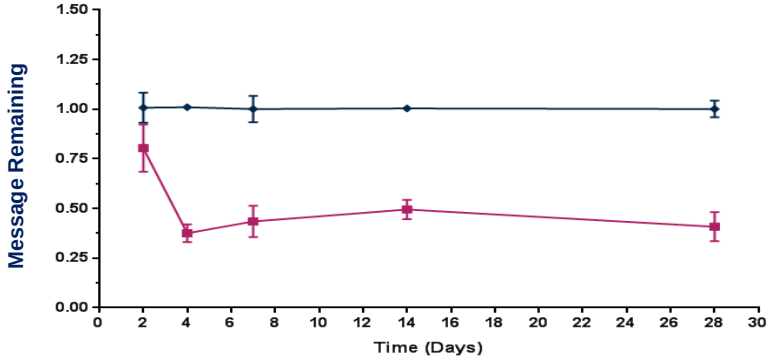
Frontal Cortex



Cervical

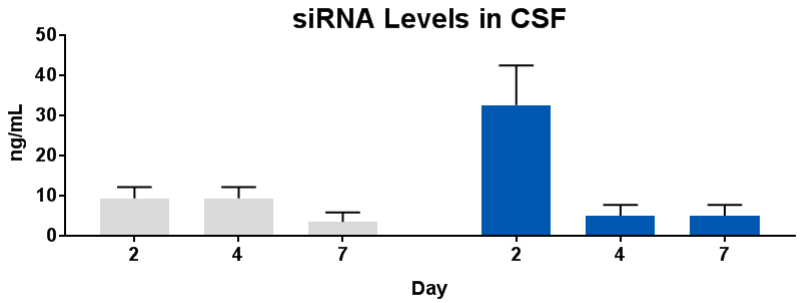


Remaining Brain

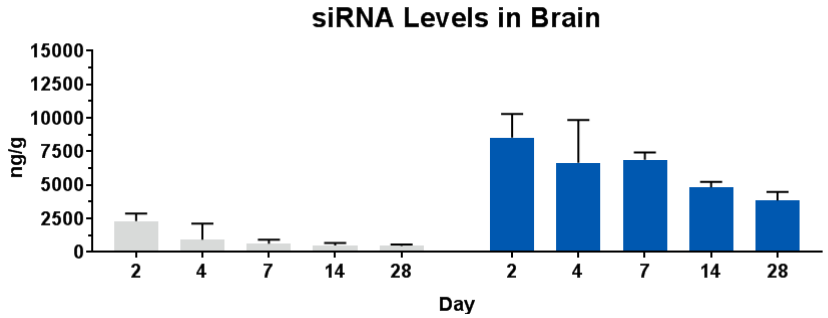


siRNA Conjugates Show Enhanced Uptake and Activity

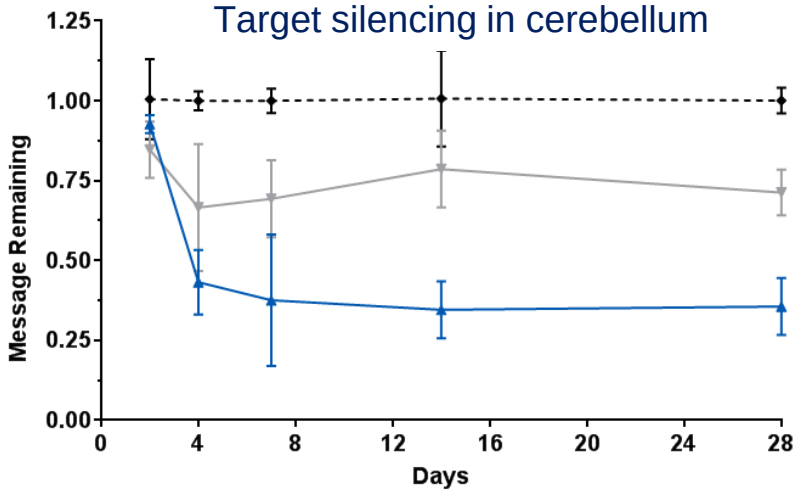
Higher drug levels and robust silencing observed in brain with SOD1 siRNA conjugate

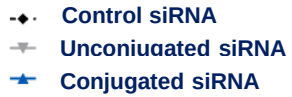


- Rapid siRNA clearance from CSF



- Conjugate reveals superior uptake and stability in brain over unconjugated siRNA

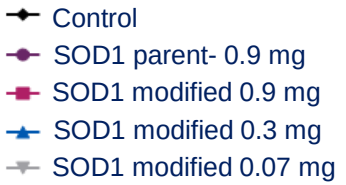




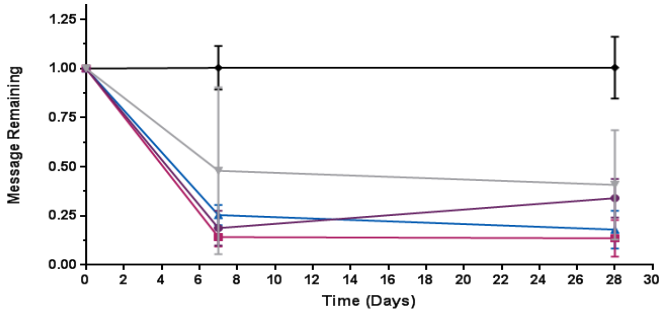
- Increased uptake in brain results in substantial improvement in mRNA knockdown

Further Optimization of SOD1 siRNA Demonstrates Best in Class Silencing

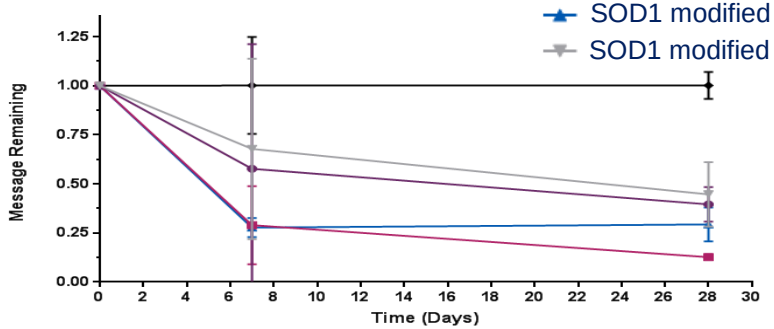
Superior Silencing to Parent at 10-fold Lower Dose



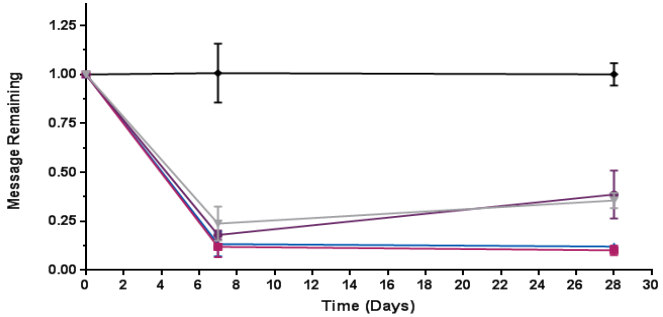
Lumbar



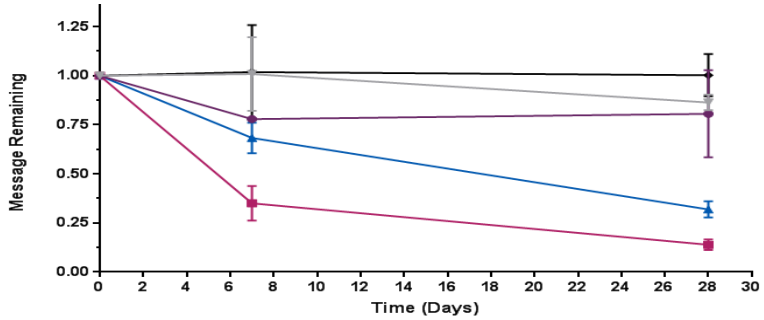
Cerebellum



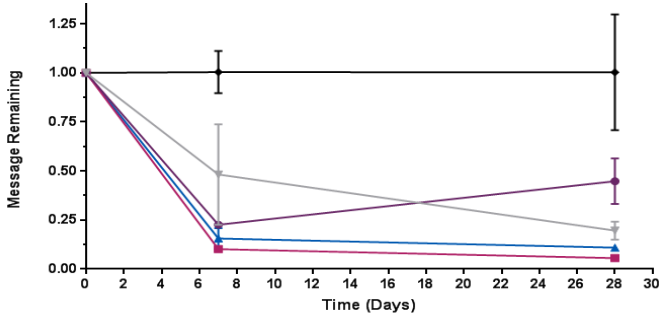
Thoracic



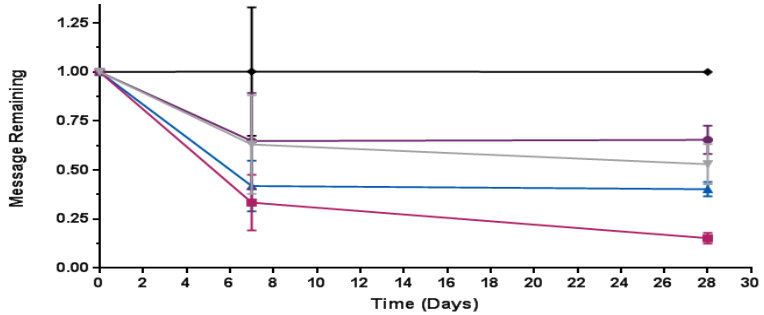
Frontal Cortex



Cervical



Temporal Cortex



Evaluating Translation of CNS siRNA Conjugate Delivery to NHP

Single dose NHP study design

- siRNA conjugate dosed at 72 mg – IT bolus
- Evaluated a single target – β-catenin

	Strand (5'-3')	Sequence
β-catenin	S	UACUGUUGGAUUGAUUCGAAA
	AS	TUUCGAAUCAAUCCAACAGUAGC

Tissue collection

Tissues: Spinal cord: Lumbar, thoracic and cervical

Brain: Prefrontal cortex, temporal cortex, cerebellum, brain stem hippocampus

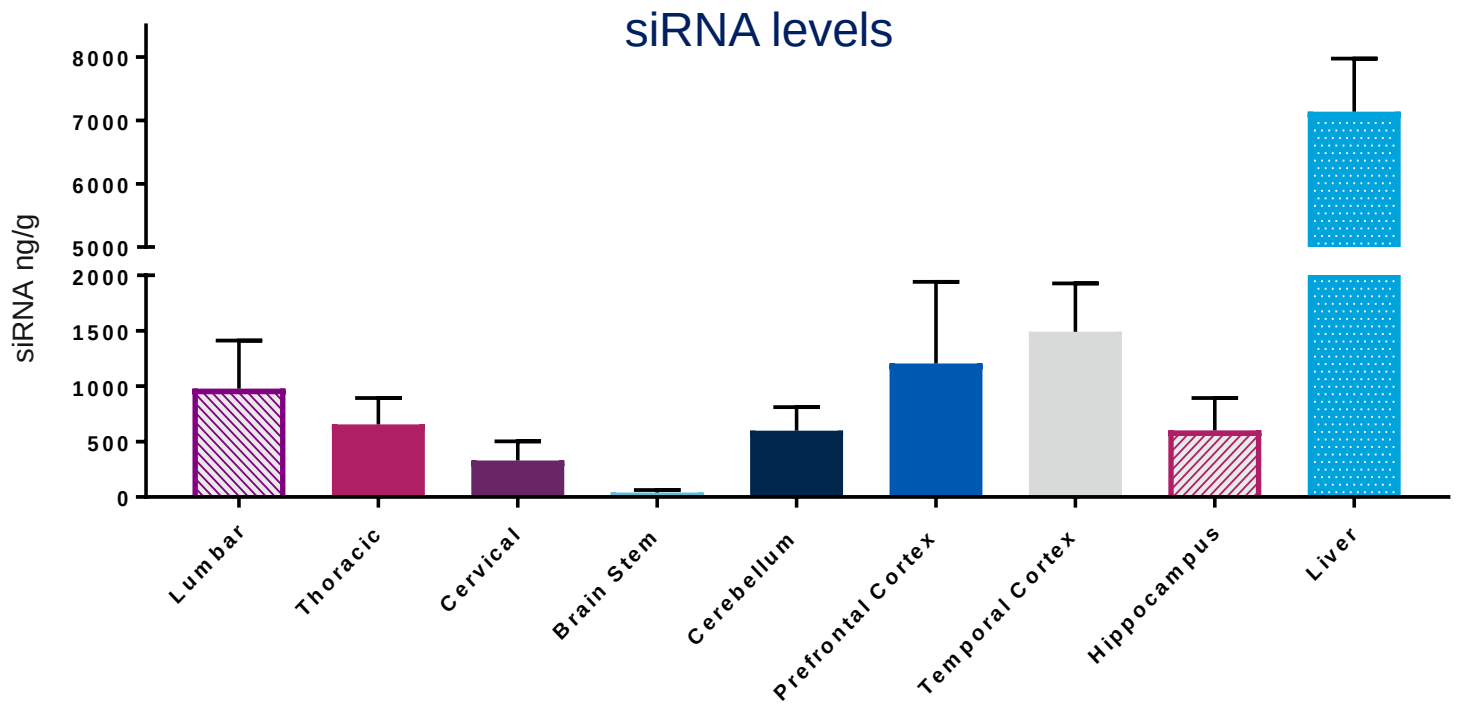
Fluids: CSF and plasma

Assays: mRNA, siRNA levels

Histology

IT Dosed β-catenin siRNA is Detected Throughout the Spinal Cord and Brain Regions of NHP

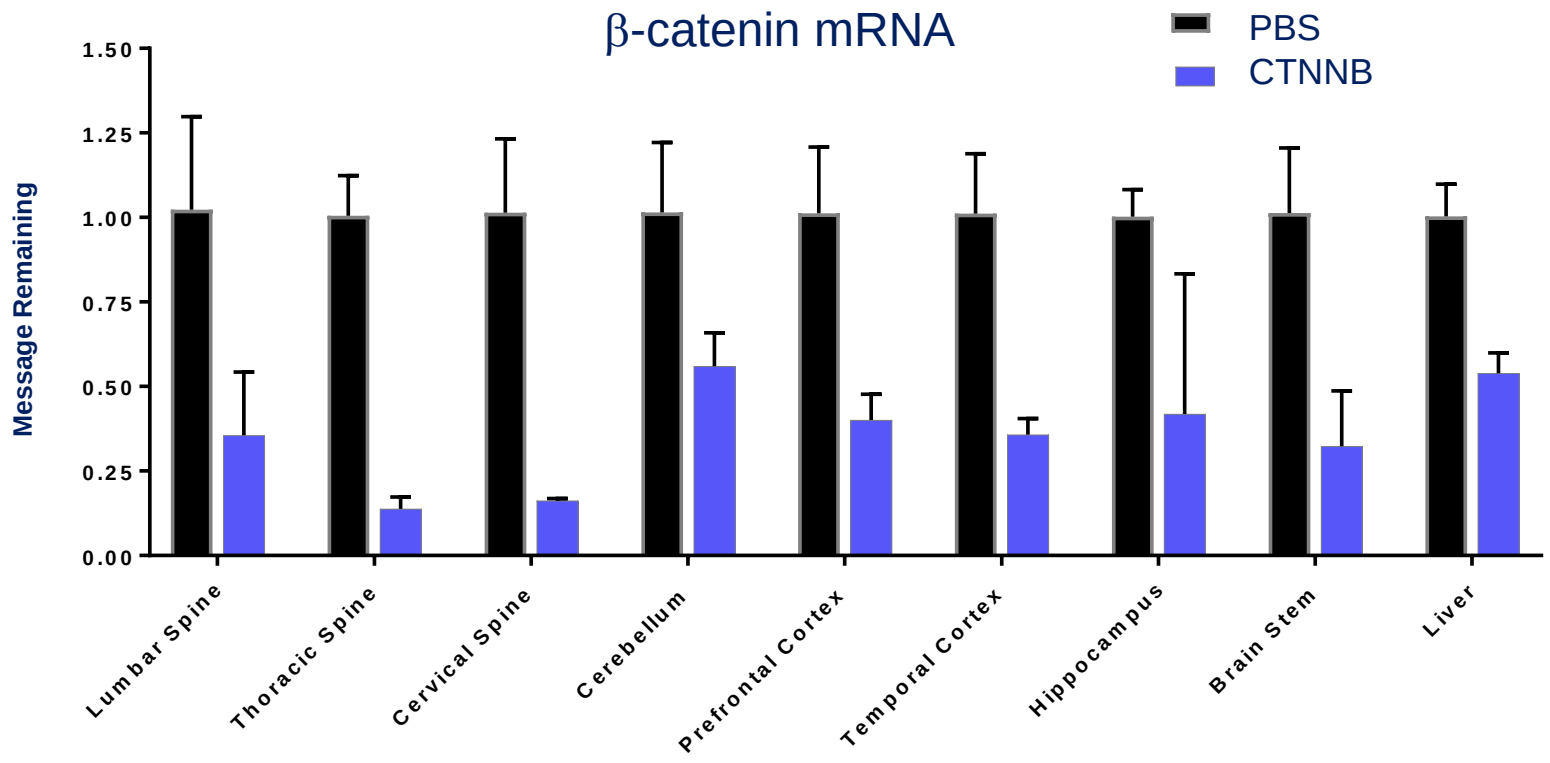
siRNA uptake varies between CNS regions and is also seen in liver



The day 31 time point shows the presence of significant siRNA levels across all tissues tested

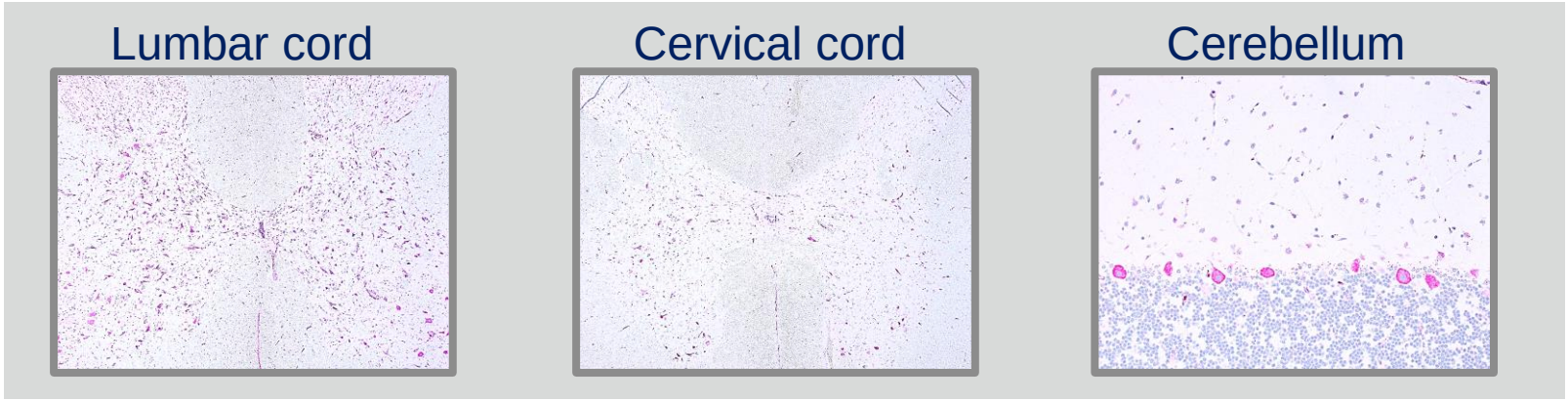
Robust Silencing Across CNS Demonstrating Successful Translation NHP

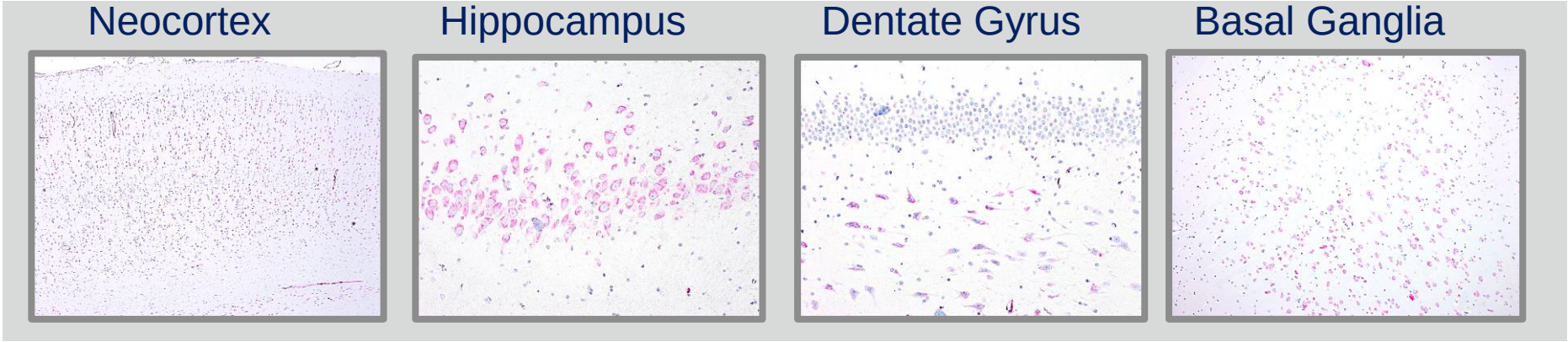
β-catenin mRNA Knockdown by Tissue, Day 31



- The conjugate targeting β-catenin produces robust knockdown throughout the spinal cord and brain at the 31 day time point.

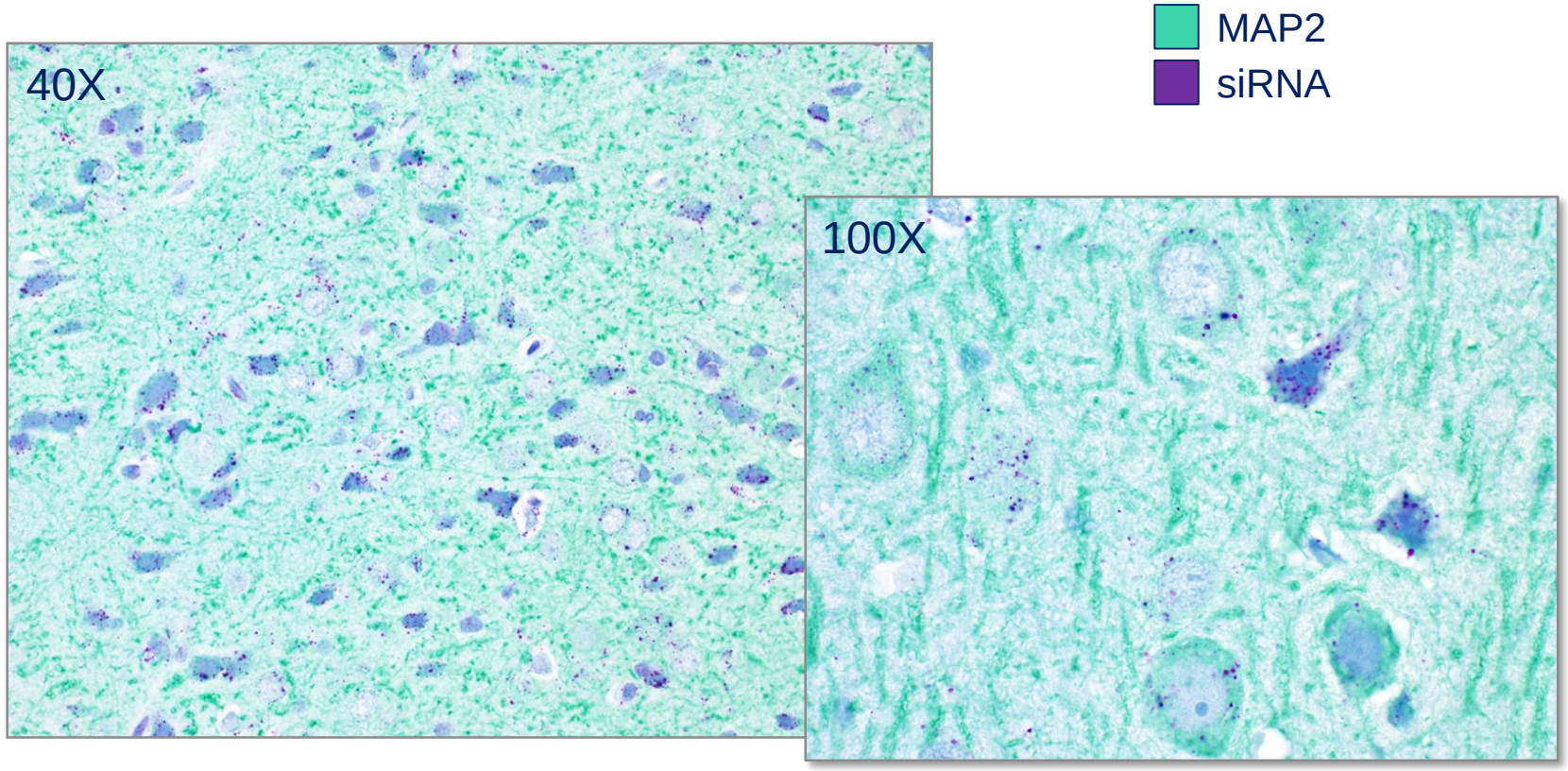
siRNAs Distribute Throughout the CNS in NHP Following IT Dosing





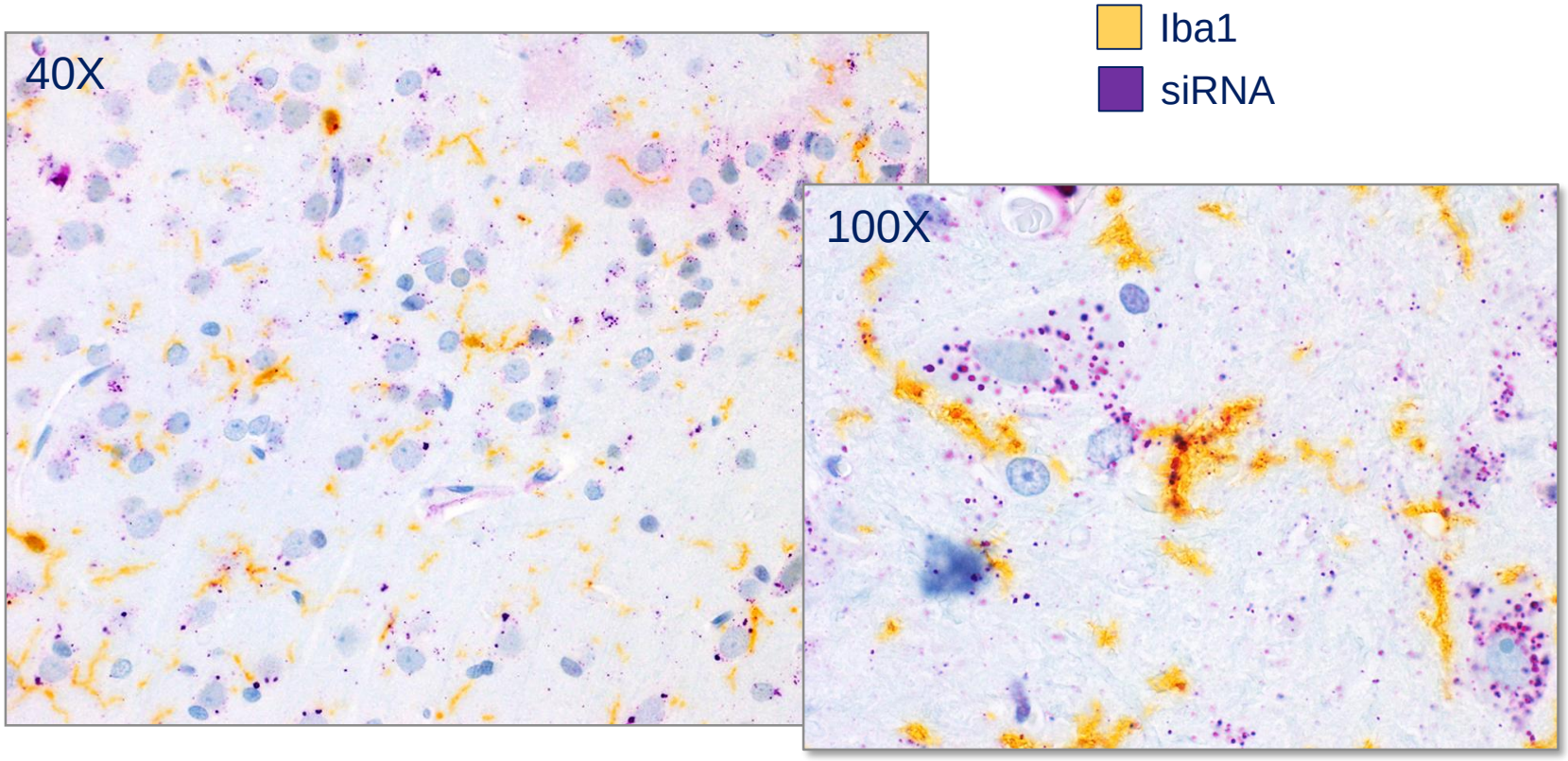
siRNA Conjugates are Localized to Neurons Following IT Dosing

Most neurons show siRNA uptake



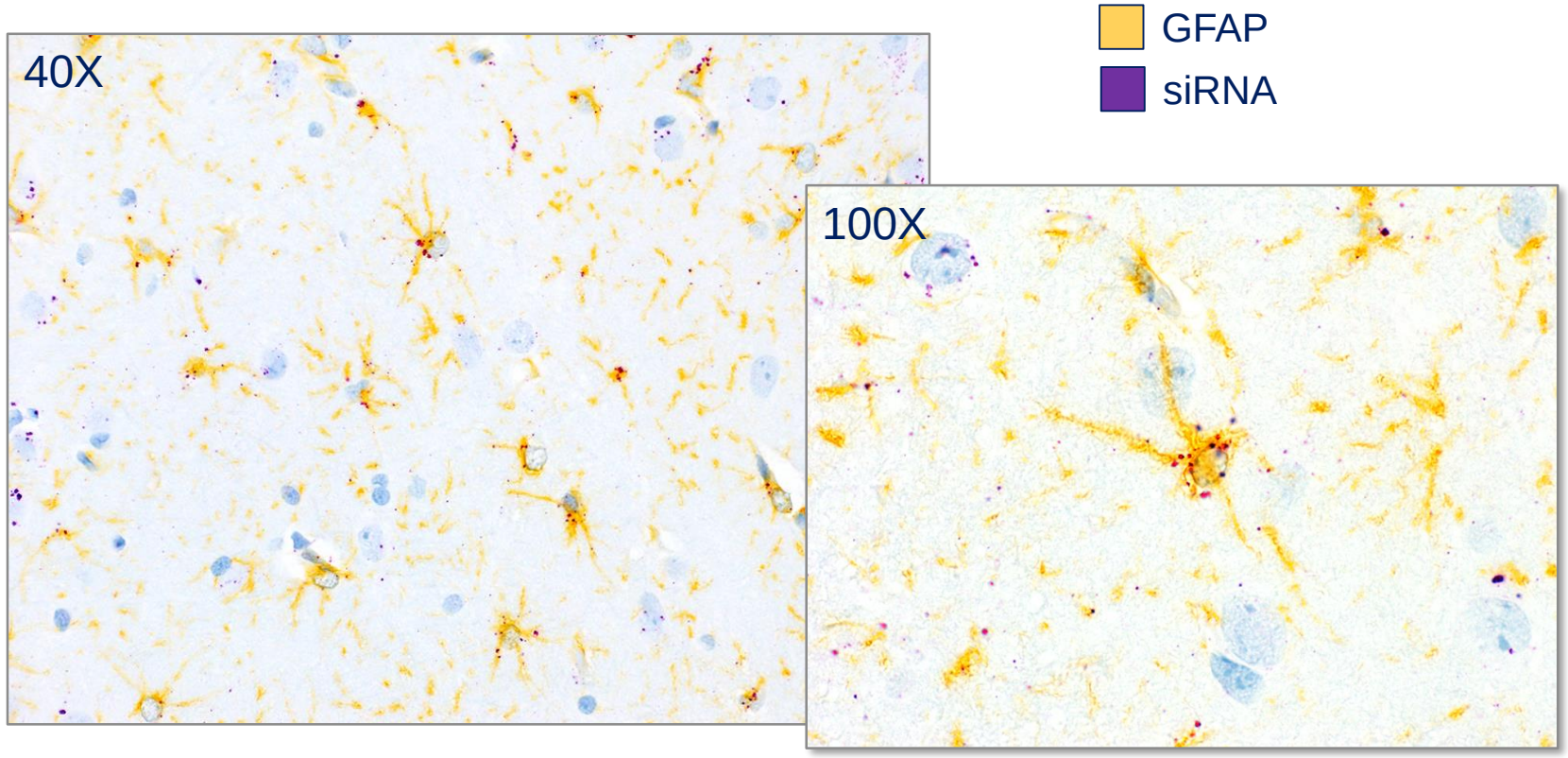
MAP2 is a neuronal marker
CTNNB siRNA probed with siRNA antibody

siRNA Conjugates are Localized to Microglia Following IT Dosing



Iba1 is a microglia marker
β-catenin siRNA probed with siRNA antibody

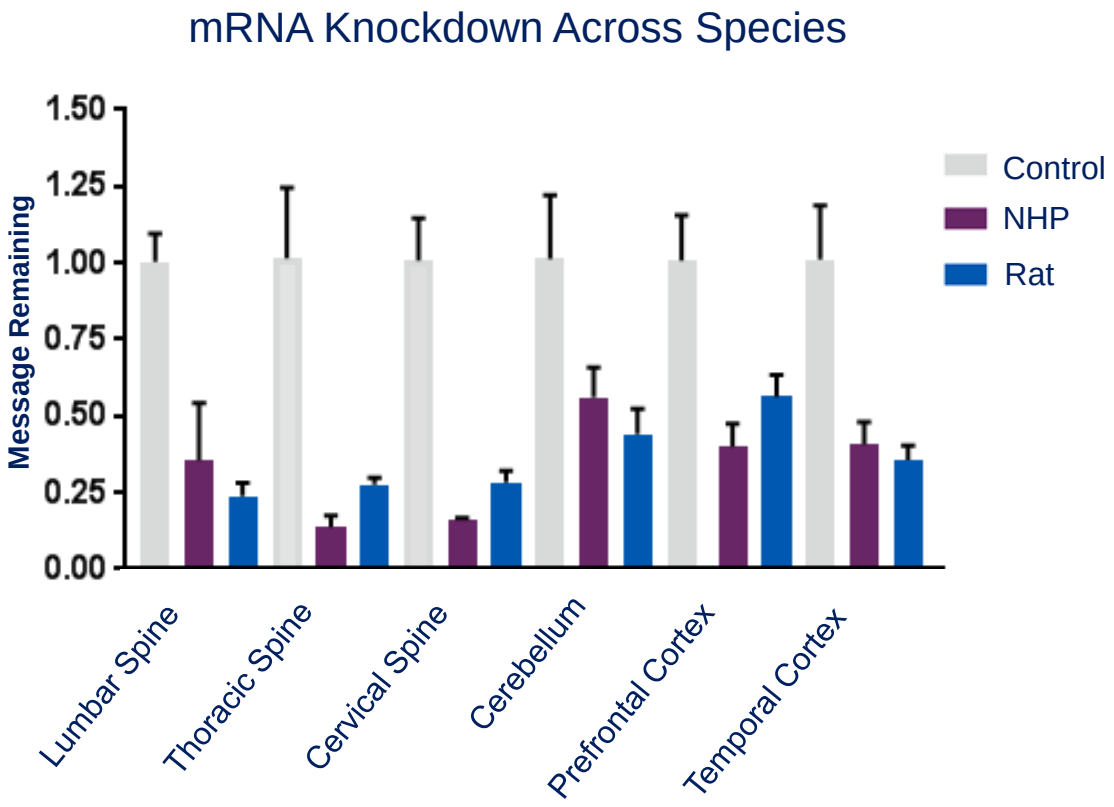
siRNAs Conjugates are Localized to Astrocytes Following IT Dosing



GFAP is an Astrocyte marker
β-catenin siRNA probed with siRNA antibody

Consistent Silencing Observed Across Pre-clinical Species

Successful Delivery of siRNA Conjugate Across CNS



Comparable activity seen between rats and NHP at compartment scaled dose

Summary

- Durable silencing of target mRNA observed across the CNS of rat and NHP following IT administration
  - Silencing extends through the end of study
  - Further optimized designs with >-10-fold improved potency
- Tissue uptake was observed in all CNS tissues examined with drug levels in the ng/g to μg/g range
- In both rat and NHP studies, intrathecal administration of the novel siRNA conjugates was found to be generally well tolerated
- As seen with liver target gene silencing, we anticipate a highly competitive profile for our siRNA conjugates with increased potency, extended duration of action, and encouraging safety margins
- We plan to select first CNS program Development Candidate (DC) by the end of 2018 with an initial Investigational New Drug (IND) or equivalent application in late 2019 or early 2020