Platform Advances in RNAi Therapeutics

RNAi ROUNDTABLE 2018

June 26, 2018

Alnylam® PHARMACEUTICALS

Agenda

Welcome
- Christine Lindenboom, Vice President, Investor Relations & Corporate Communications

Introduction
- Martin Maier, Ph.D., Vice President, Research

Platform Advances in RNAi Therapeutics
- Advances in ESC+ Design for Improved Specificity and Therapeutic Index
  - Mark Schlegel, Ph.D., Senior Scientist, Research
- New Frontiers: CNS Delivery Update
  - Kirk Brown, Ph.D., Associate Director, Bioanalytical Sciences

Q&A Session
- Moderated by Vasant Jadhav, Ph.D., Senior Director, Research

Reminders

Event will run for approximately 60-75 minutes

Q&A session at end of presentation

- Questions may be submitted at any time via the ‘Ask a Question’ field on the webcast screen

Replay, slides and transcript available at www.alnylam.com/capella

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; 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.

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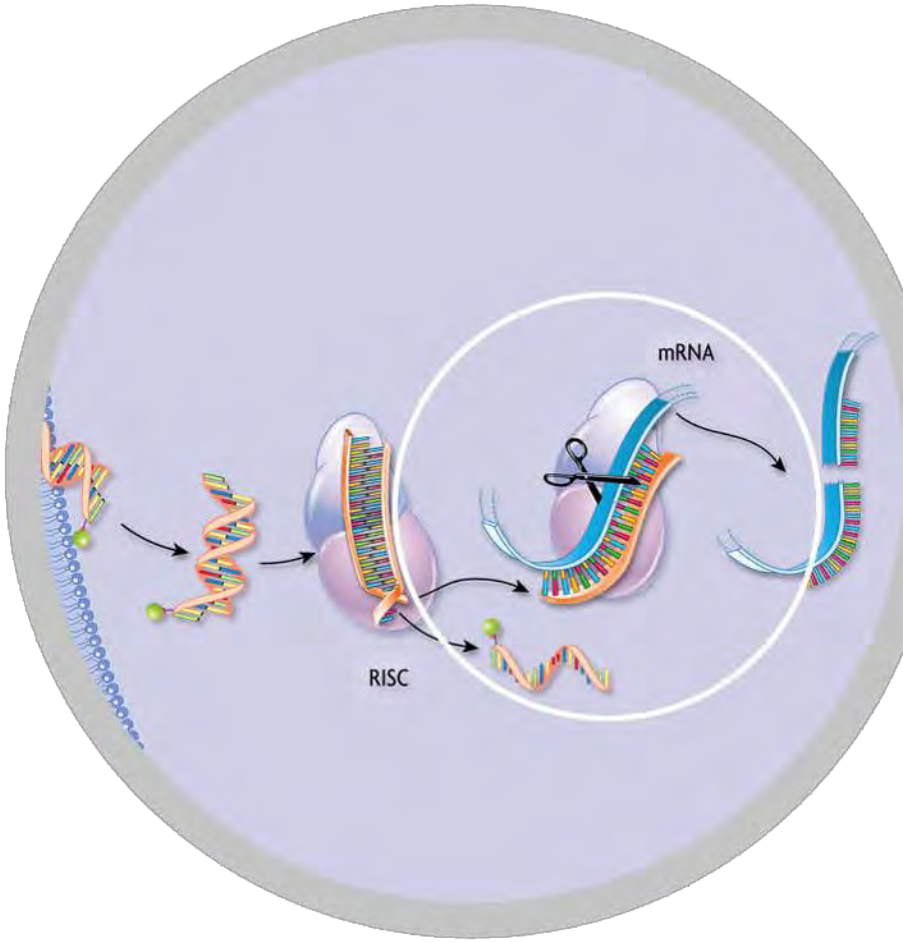
RNAi Therapeutics: New Class of Innovative Medicines

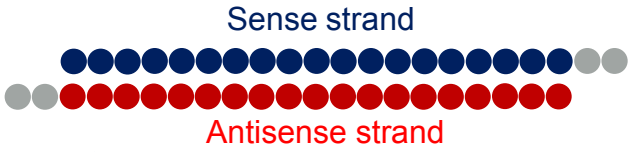
Clinically Proven Approach with Transformational Potential

- Nobel Prize-winning science
- Silence any gene in genome
- Potent and durable mechanism of action
- Product engine for sustainable pipeline
- Now entering commercial stages



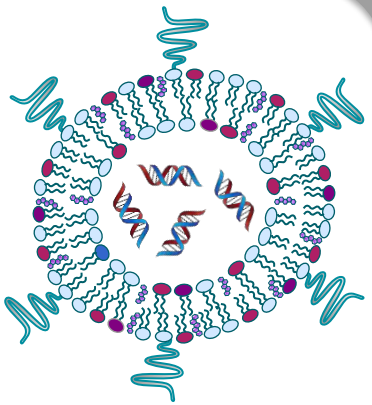
Addressing Delivery Challenge

Alnylam Platforms for Functional siRNA Delivery to Target Tissue

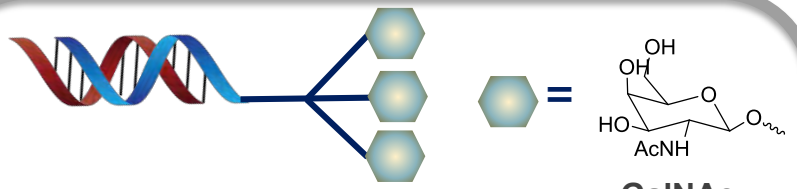


Lipid Nanoparticles (LNPs)

- Multi-component lipid formulation (~100 nm in size)
- Encapsulated siRNA
- Highly efficient for targeted delivery to liver
- Administered intravenously (IV)
- Clinically validated



Patisiran



GalNAc

GalNAc-siRNA Conjugates

- Single chemical entity
- GalNAc ligand conjugated to extensively modified siRNA
- Targeted delivery to liver
- Administered subcutaneously (SC)
- Clinically validated

Complementary Approaches for Efficient siRNA Delivery to Liver

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Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STARs):

- Genetic Medicines
- Cardio-Metabolic Diseases
- Hepatic Infectious Diseases
- CNS Diseases

		HUMAN POC[1]	BREAKTHROUGH DESIGNATION	EARLY STAGE *(IND or CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION/ COMMERCIAL[2]	COMMERCIAL RIGHTS
Patisiran	*Hereditary ATTR Amyloidosis*	✓	●			●	Global
Givosiran	*Acute Hepatic Porphyrias*	✓	●		●		Global
Fitusiran	*Hemophilia and Rare Bleeding Disorders*	✓			●		15-30% Royalties
Inclisiran	*Hypercholesterolemia*	✓			●		Milestones & up to 20% Royalties
ALN-TTRsc02	*ATTR Amyloidosis*	✓		●			Global
Lumasiran	*Primary Hyperoxaluria Type 1*	✓	●	●			Global
Cemdisiran	*Complement-Mediated Diseases*	✓		●			Global

[1]POC, proof of concept – defined as having demonstrated target gene knockdown and/or additional evidence of activity in clinical studies
[2]Includes marketing application submissions

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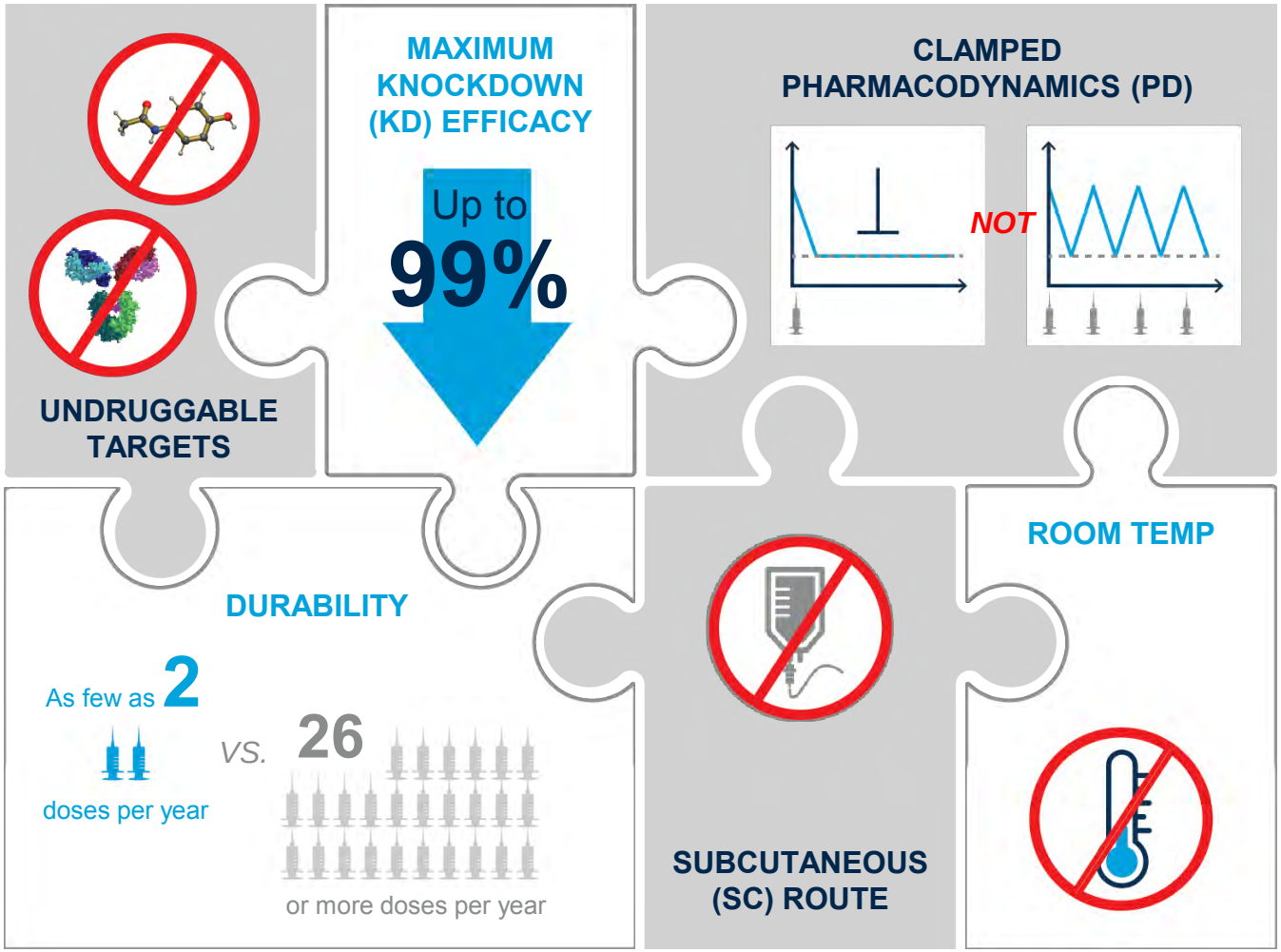
Key Features of Alnylam Investigational RNAi Therapeutics

Potential Attributes for Differentiation and Value



Extensive Human Safety Experience

Encouraging Results to Date

Number of Programs	Number of Clinical Studies	Total Patients or Volunteers Dosed	Greatest Duration of Exposure
>10	>25	>1200	>48 months

Minimal platform related findings*

- Low incidence (2.9%) of generally mild, asymptomatic, reversible LFT increases >3x ULN
- Injection site reactions (24%) generally mild, transient and rarely led to discontinuation
  - No events of ulceration, necrosis or tissue damage
- One report of anaphylaxis (<0.05%) in patient with prior history of atopy**
  - No anti-drug antibodies (ADA) detected against GalNAc-siRNA

Revusiran program discontinued in October 2016

- Extensive evaluation showed no clear reason for mortality imbalance
- While possible that imbalance was a chance finding, role for revusiran cannot be excluded
- Revusiran exposure is 12-140 times greater than other pipeline programs

Favorable emerging profile for ESC-GalNAc platform compared with competing oligo platforms†

- No evidence of thrombocytopenia, renal toxicity, or systemic inflammatory effects

* Experience as of December 2017 – Data estimated based on available safety data
** Givosiran OLE study, reported April 2018
† Not based on direct comparative studies

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GalNAc-Conjugate Platforms for Delivery to Liver

Next Gen ESC+ Conjugates Featuring Seed-Pairing Destabilization

STC-Conjugate

- Standard Template Chemistry GalNAc conjugate
- SC administration

Revusiran

ESC-Conjugate

- Enhanced Stability Chemistry GalNAc conjugate
- SC administration

- Fitusiran
- Inclisiran
- Givosiran
- ALN-TTRsc02
- Lumasiran
- Cemdisiran
- ALN-HBV

ESC+ Conjugate

- Enhanced Stability Chemistry GalNAc conjugate, ↑ specificity
- SC administration

- 2018 INDs and CTAs

First generation GalNAc conjugate, initial human POC → **Second generation GalNAc conjugate, human POC, greater potency and durability with lower exposures** → **Next generation GalNAc conjugate with further improvements to specificity and therapeutic index**

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Alnylam CNS Pipeline Strategy

Expanding a Pipeline of Potentially Transformative Medicines

Genetically validated, CNS-expressed target gene

Biomarker for POC in Phase 1

Definable path to approval and patient access

Alnylam CNS Objectives

- 1st DC in 2018
- 1st IND in late ’19/early ’20
- 1-2 INDs/yr starting in ’20

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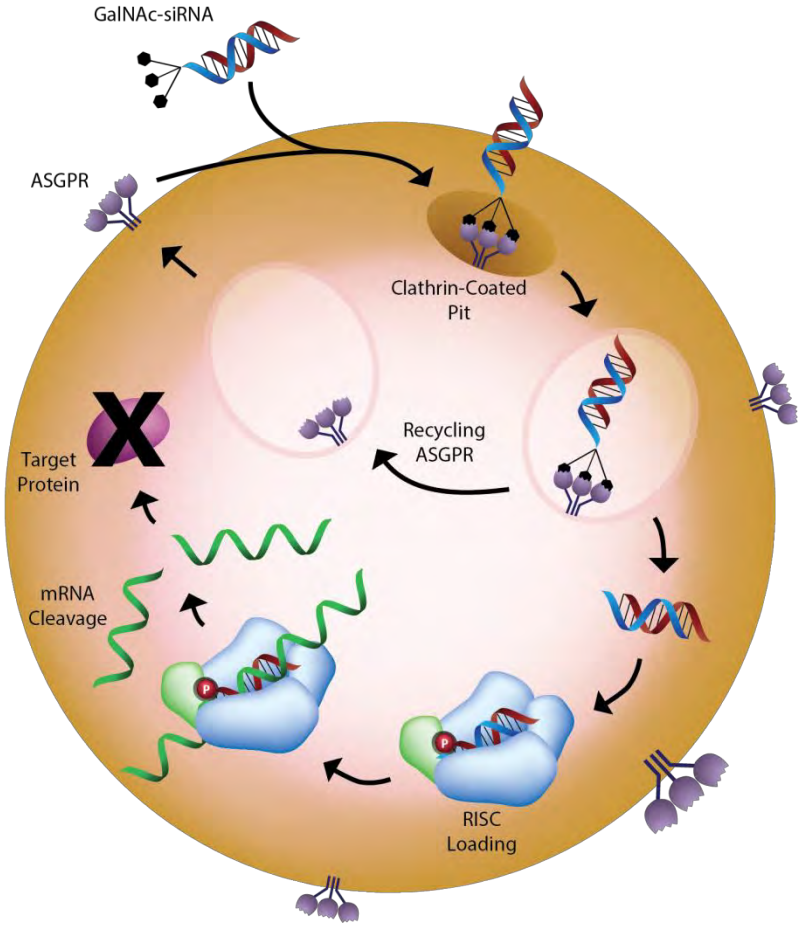
Enhanced Stabilization Chemistry (ESC) GalNAc-siRNAs

Subcutaneously-Administered Conjugate Platform for Targeted Delivery to Liver

siRNA

- Metabolic stability
- Intrinsic potency



Ligand

- Trivalent GalNAc
- High affinity and specificity

Asialoglycoprotein Receptor (ASGPR)

- Highly expressed in hepatocytes
- High capacity receptor
- Conserved across species

Nair et al. *JACS* **2014**
Matsuda et al. *ACS Chem. Bio.* **2015**
Rajeev et al. *ChemBioChem* **2015**
Nair et al. *NAR* **2017**
Foster et al. *Mol. Ther.* **2018**

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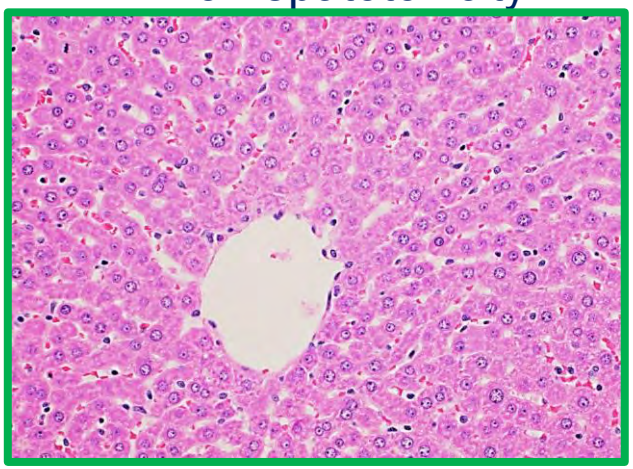
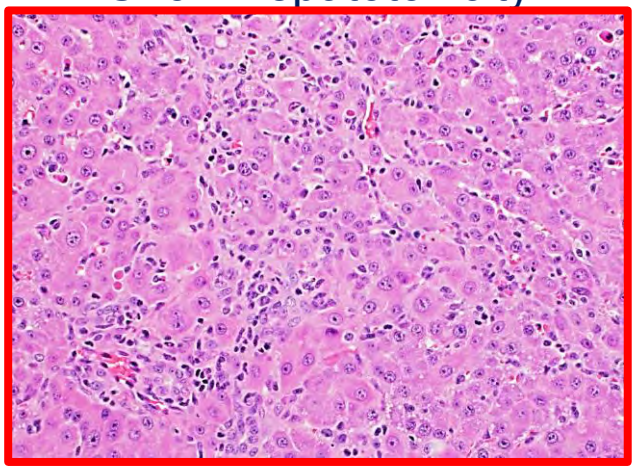
Subset of ESC Conjugates Show Rat Hepatotoxicity at Exaggerated Doses

In silico prediction & *In vitro* efficacy → *In vitro* screen for predicted off-targets → Rodent Knockdown → Rat Tox @ >100x PD dose → NHP Knockdown → DC

Good Actors
No hepatotoxicity



Bad Actors
Show hepatotoxicity



Single cell necrosis and/or hepatocellular degeneration with ↑LFT 2x upper limit of normal

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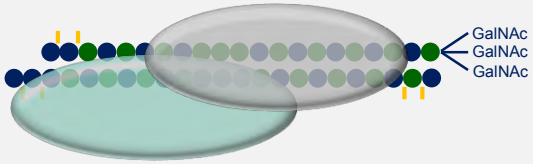
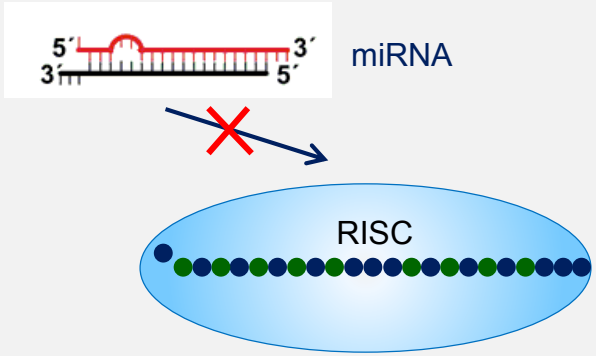
Seed-Based Off-Target Effects Are Important Drivers of Rodent Hepatotoxicity for Subset of Conjugates

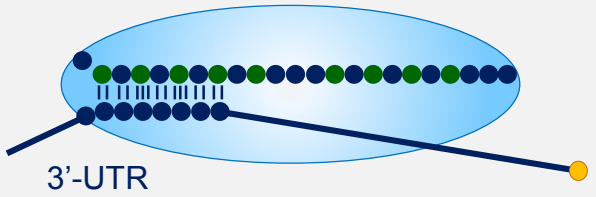
1. Non-RNAi effects
   e.g. siRNA chemistry, metabolites protein binding, drug accumulation



2. Competition for RISC loading with miRNAs



3. Undesired seed-based off-target activity



Off-target binding
Partial sequence match

nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-02989-4 OPEN

Selection of GalNAc-conjugated siRNAs with limited off-target-driven rat hepatotoxicity

Maja M. Janas[1], Mark K. Schlegel[1], Carole E. Harbison[1], Vedat O. Yilmaz[1], Yongfeng Jiang[1], Rubina Parmar[1], Ivan Zlatev[1], Adam Castoreno[1], Huilei Xu[1], Svetlana Shulga-Morskaya[1], Kallanthottathil G. Rajeev[1], Muthiah Manoharan[1], Natalie D. Keirstead[1], Martin A. Maier[1] & Vasant Jadhav[1]

Janas et al. *Nat Commun*. 2018 Feb 19;9(1):723

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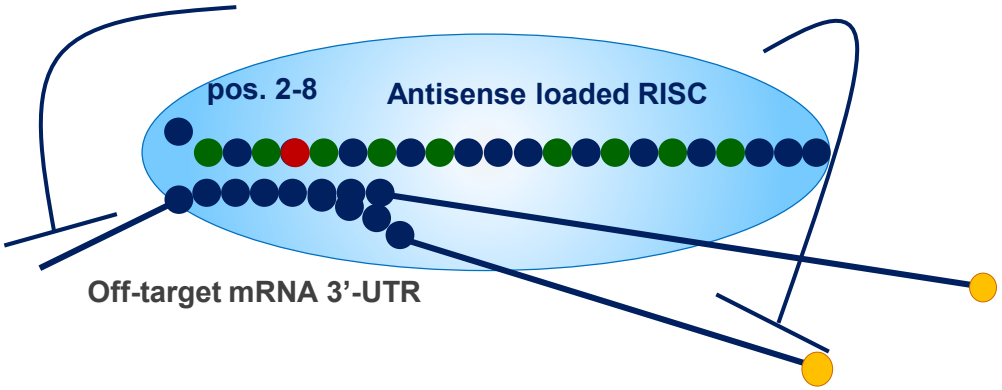
Strategy to Improve Specificity and Therapeutic Index

Utilize seed-pairing destabilization via novel chemical modifications to selectively destabilize off-target binding

Off-target binding
Partial sequence match



Undesired off-target activity

Important Considerations

1. **On-target potency must be maintained in vivo**
2. **Off-target activity should be minimized**

Bramsen et. al. *Nucleic Acids Res.* 2010, 38, 5761; Vaish et. al. *Nucleic Acids Res.* 2011, 39, 1823; Lee et. al. *Nat. Comm.* 2015, 6, 10154.

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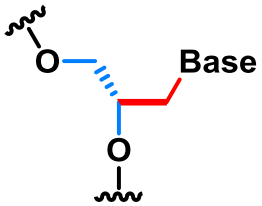
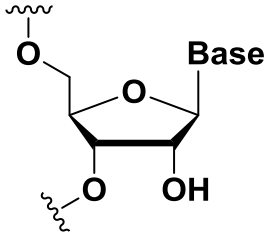
GNA – a Potential Solution

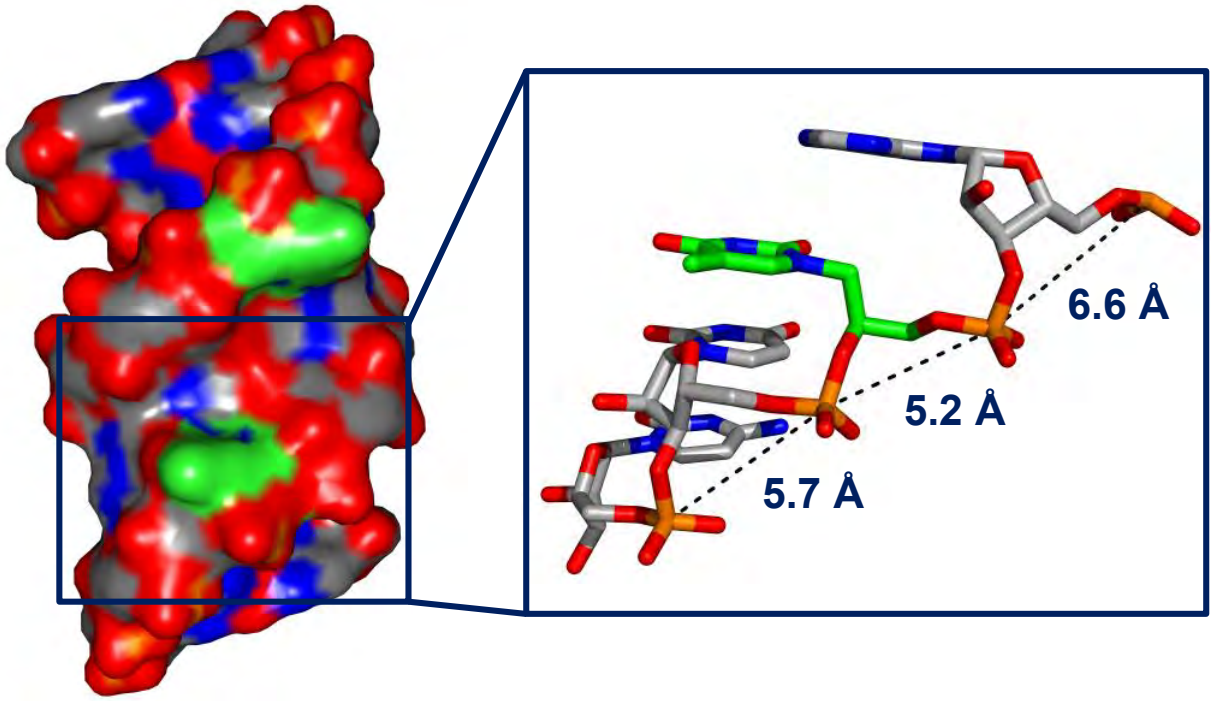
- Glycol Nucleic Acid (GNA) in seed region generally appears to be well-suited to minimize off-target effects via **seed-pairing destabilization** while maintaining potency
- GNA can be well accommodated within the RNA duplex despite shorter phosphate-phosphate and base-backbone distance



(*S*)-GNA



RNA



Schlegel et al. *J. Am. Chem. Soc.* 2017, 139, 8537.

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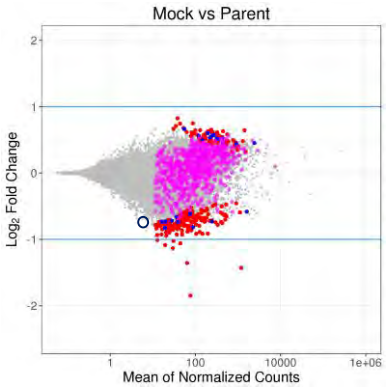
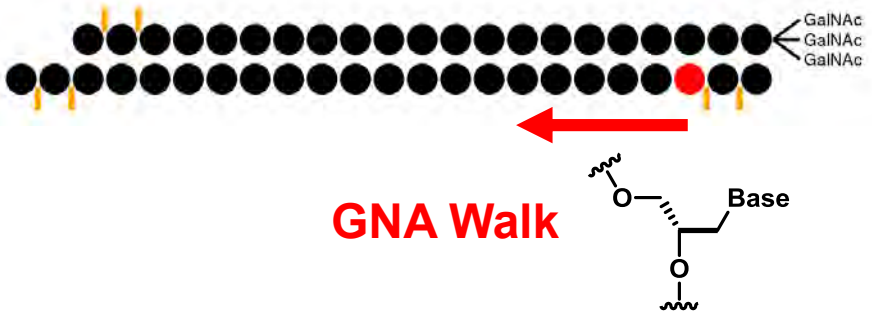
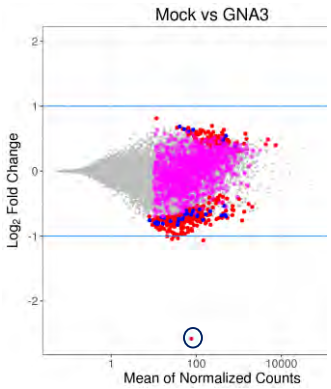
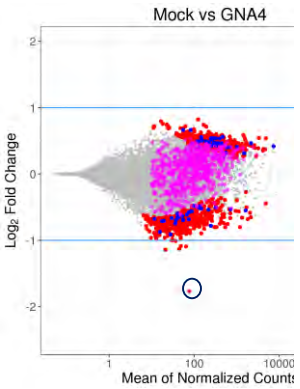
GNA at Positions 6-8 Demonstrates Superior Off-Target Mitigation Compared to Positions 3-5

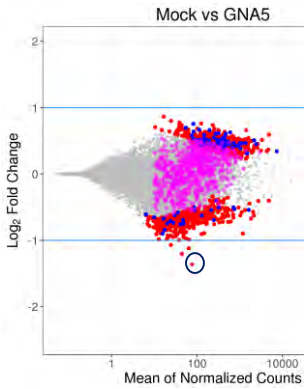
In Vitro RNAseq

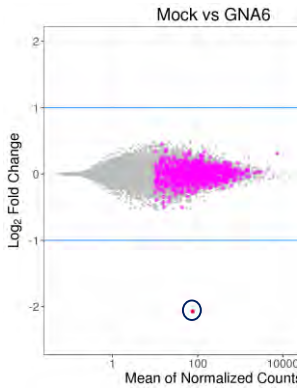


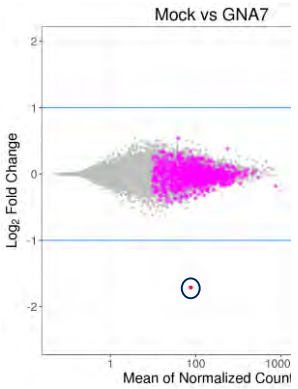


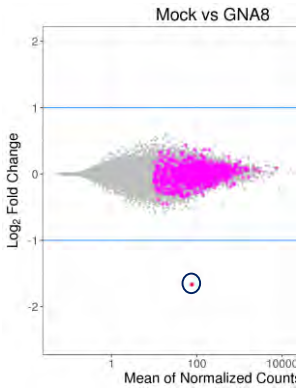












DEGs (Differentially Expressed Genes), significant

3'UTR match, significant

3'UTR match, not significant

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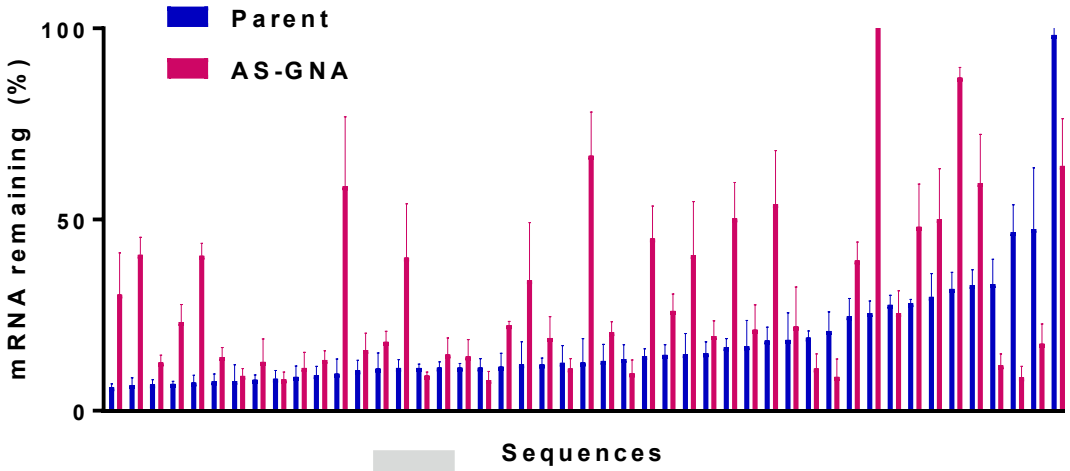
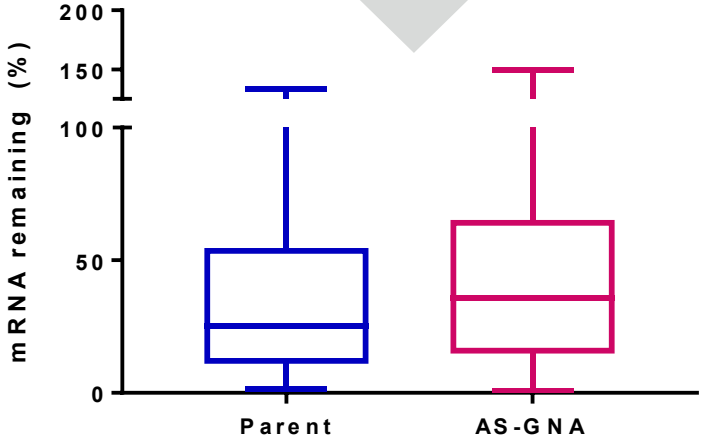
Sequence-Dependent Impact of GNA on Inherent Potency





- 315 Sequences, 6 Targets
- Transfection, 10 nM siRNA, 24 hours, PMH

Example Screen

- Screen of 47 sequences against single target
- Transfection, 10 nM siRNA, 24 hours, PMH

- Differential tolerance of GNA modification across a panel of sequences ranging from improved activity to decreased activity
- In those cases where potency reduced, individual sequence optimization can be successfully used to improve potency to the level of the parent ESC conjugate

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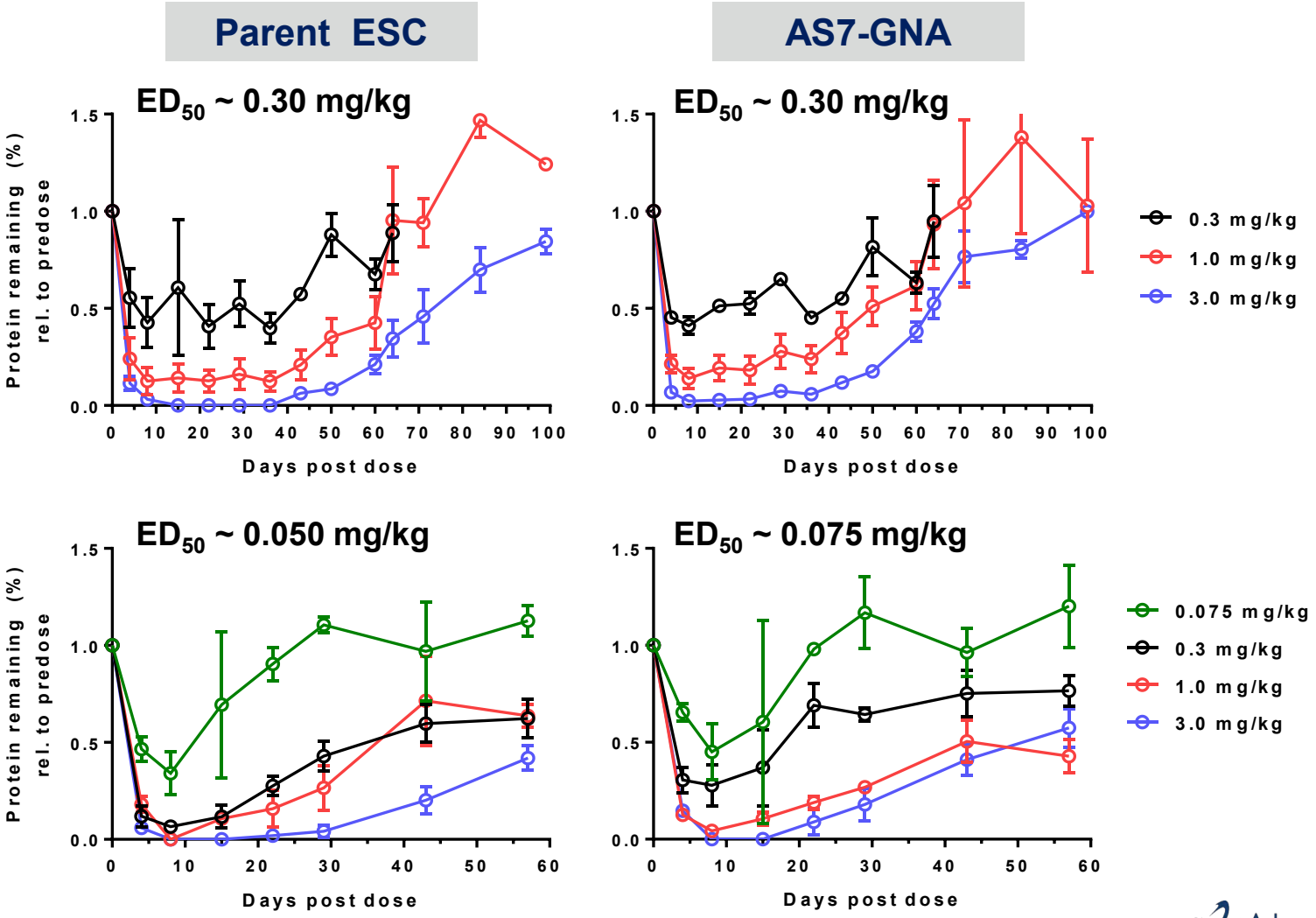
Comparable Potency in Rodents with GNA-Containing Conjugates

Mice

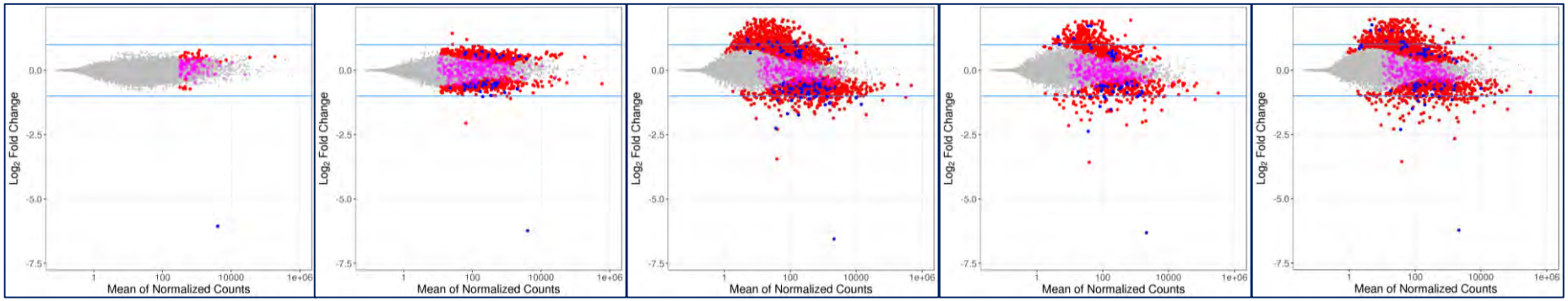
Rats



ESC+ Demonstrates More Quiescent Off-Target Signature Across Dose Levels in Rat Liver

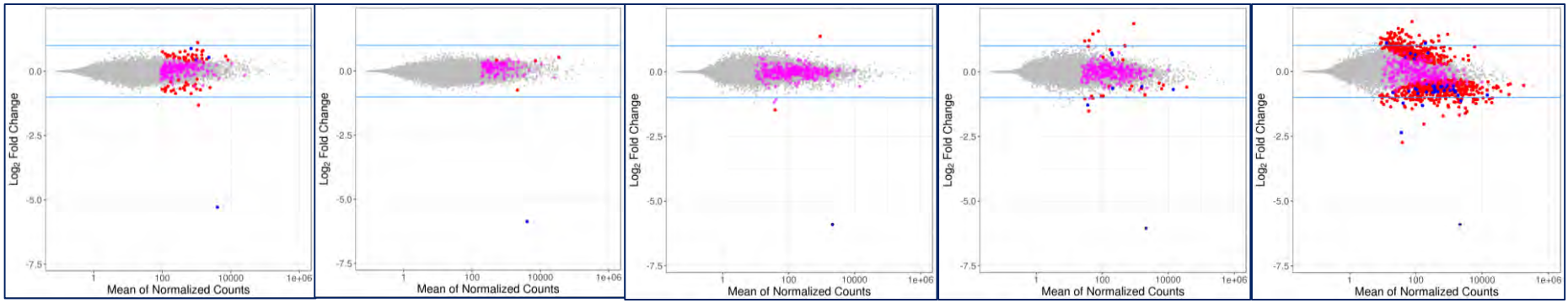
Dose: qw x 3
Necropsy: Day 16

ESC



3 mg/kg	10 mg/kg	30 mg/kg	60 mg/kg	120 mg/kg

ESC+



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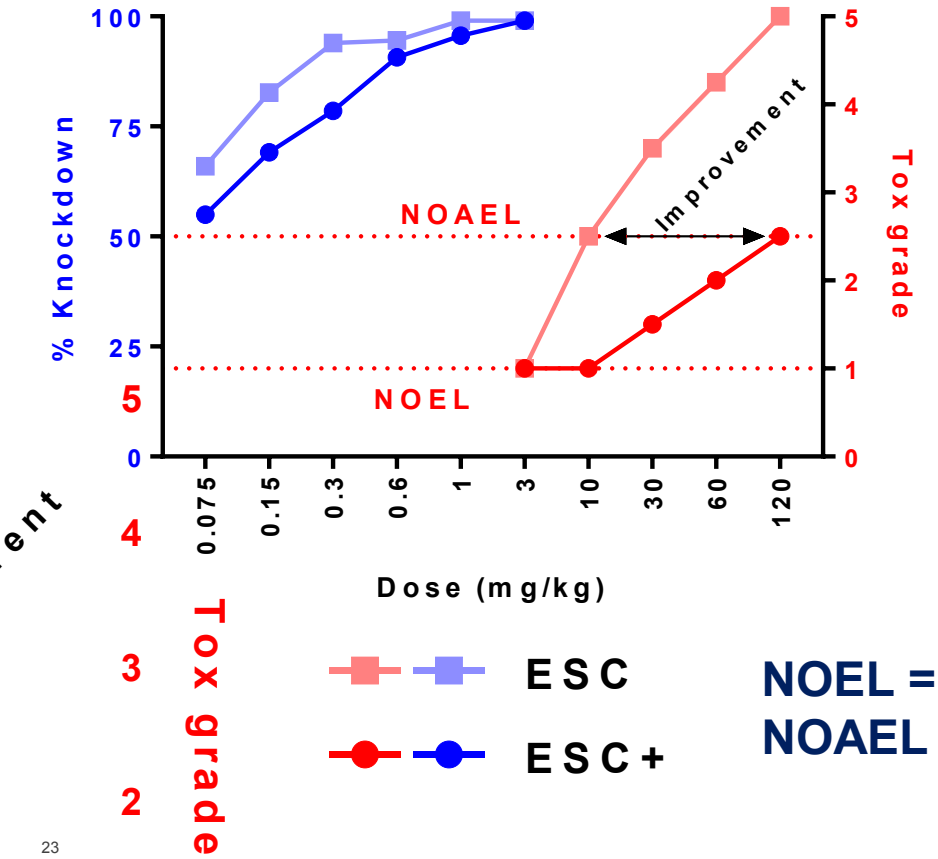
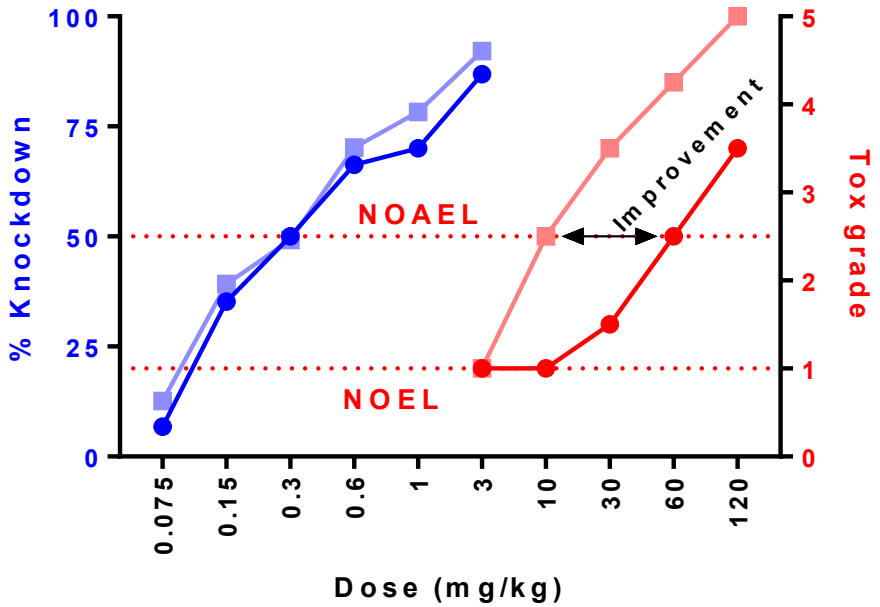
Therapeutic Index Improved Greater Than 5-fold with ESC+ Conjugates

$$\text{Therapeutic Index} = \frac{\text{NOAEL (qw x 3)}}{\text{ED}_{80}\text{(single dose)}}$$

Sequence 1



Sequence 2



NOEL = No observed effect level
NOAEL = No observed adverse effect level

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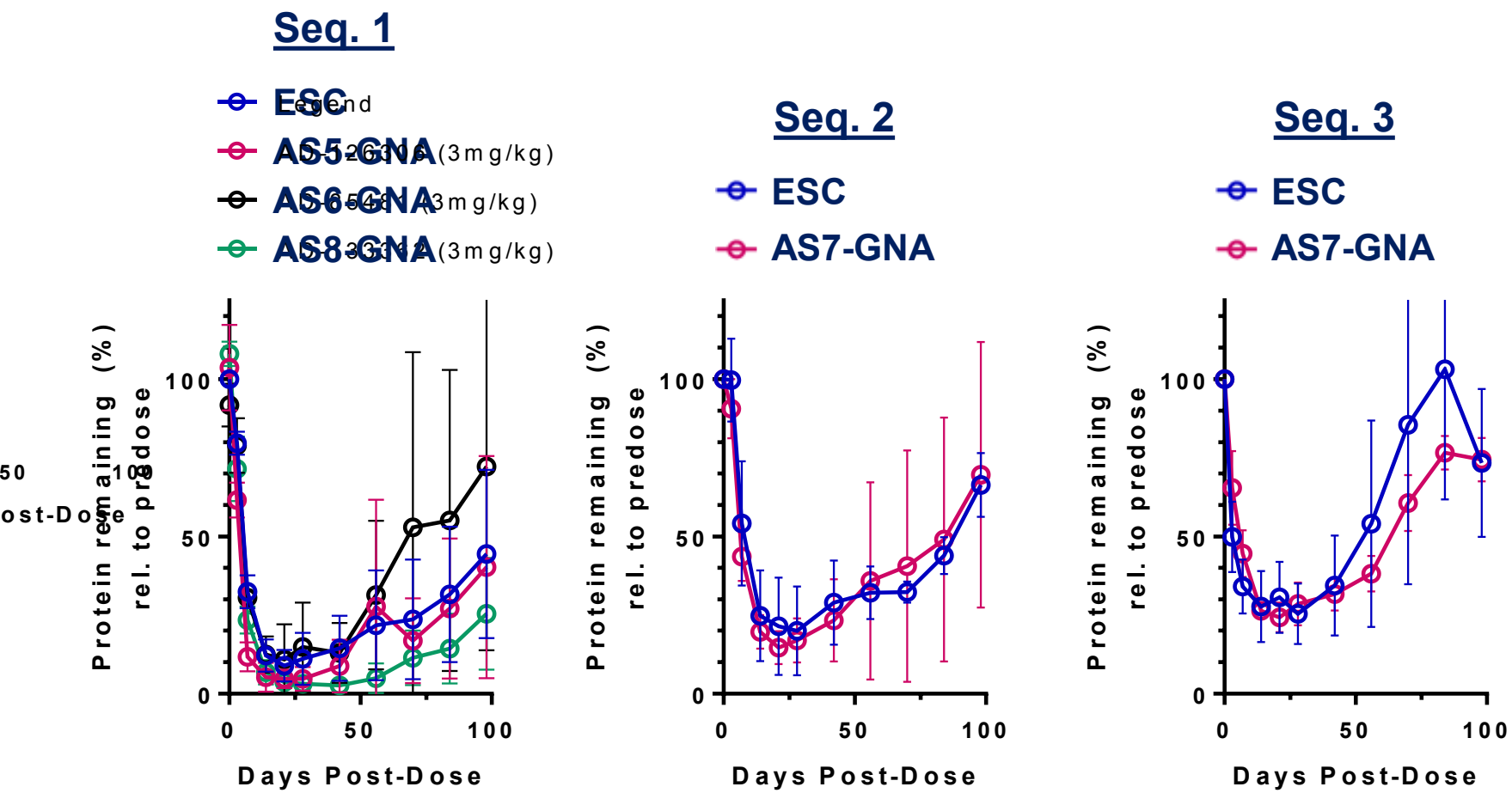
ESC+ Conjugates Containing GNA Translate to NHP



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Summary

- RNAi-mediated off-target effects are important drivers of hepatotoxicity observed for subset of ESC conjugates in rodent toxicity studies
  - No evidence for impact of chemical modifications on observed toxicity
- Developed ESC+ strategy to mitigate seed-mediated off-target effects and improve specificity of siRNA conjugates
  - Utilizes thermally destabilizing modifications, such as glycol nucleic acid (GNA), in the seed region of antisense strand
  - Pharmacodynamics of ESC+ design translates across species
  - Improves *in vitro* and *in vivo* specificity and further expands therapeutic index of conjugates
- Multiple ESC+ conjugates are advancing towards clinical development

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- New Frontiers: CNS Delivery Update
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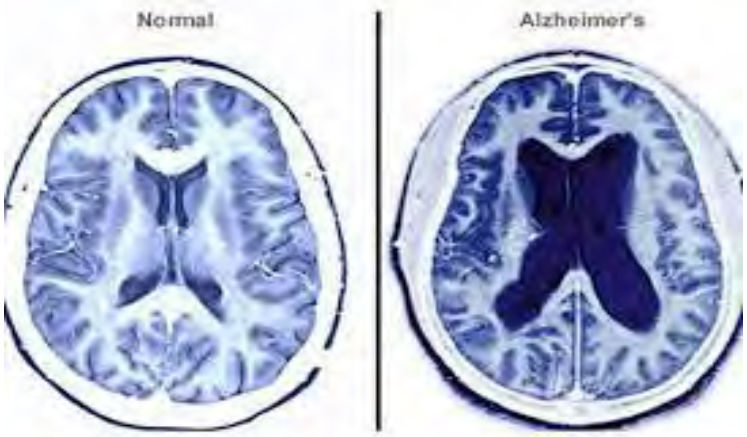
Q&A Session

- Moderated by Vasant Jadhav, Ph.D., Senior Director, Research

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 no current disease modifying therapies for these devastating, life threatening disorders
- RNAi therapeutics directed to disease-causing, CNS-expressed genes represent next great frontier
- Expect superior potency, duration and systemic safety profile vs. ASOs

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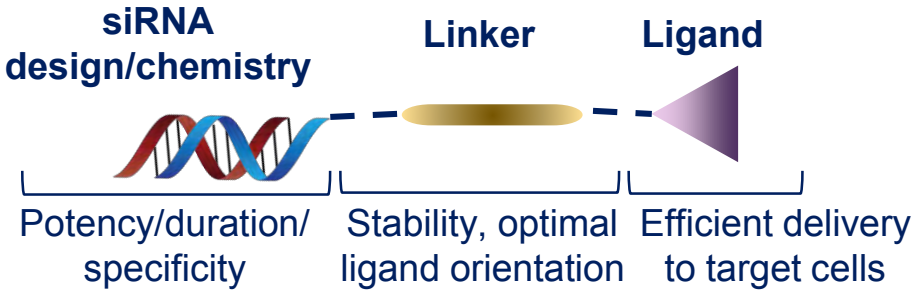
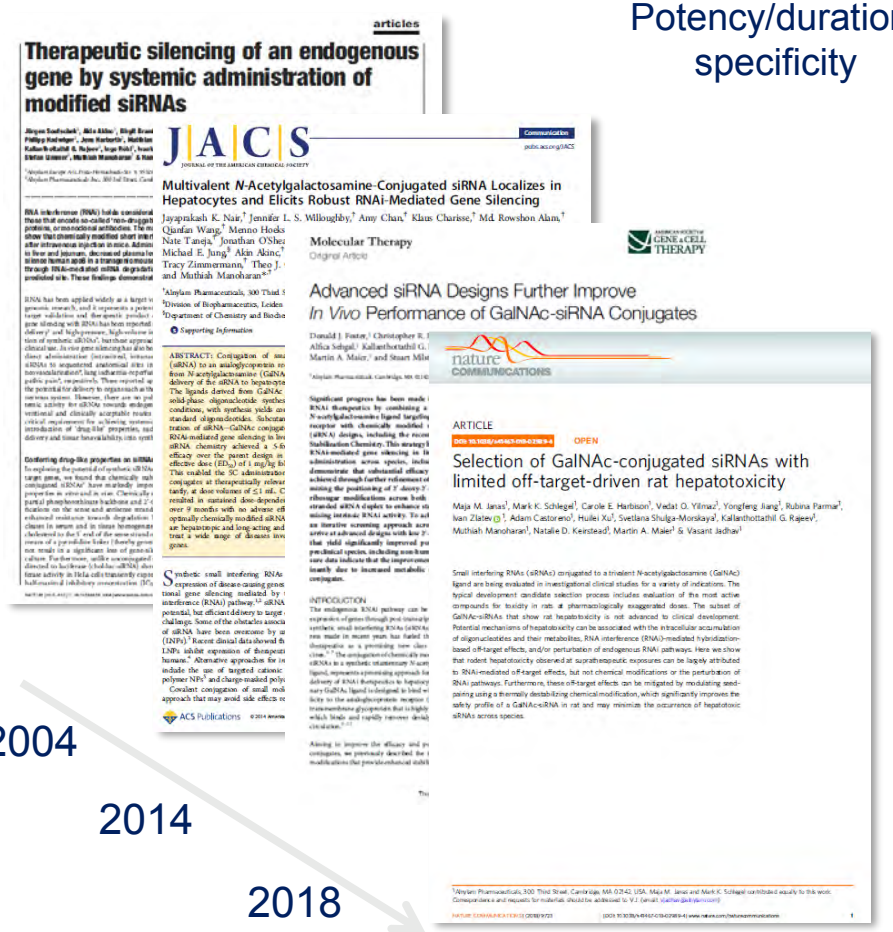
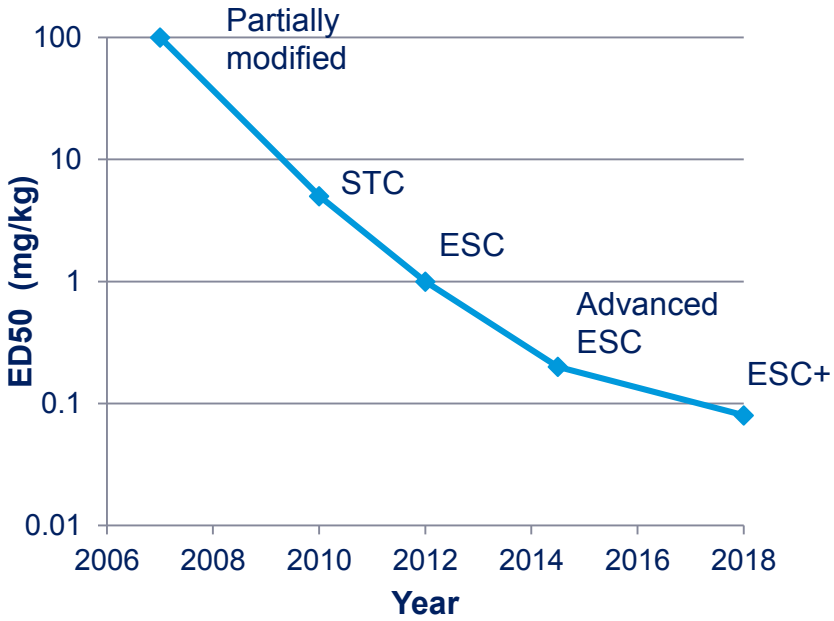
Alnylam Advancements in Conjugate-Based Delivery





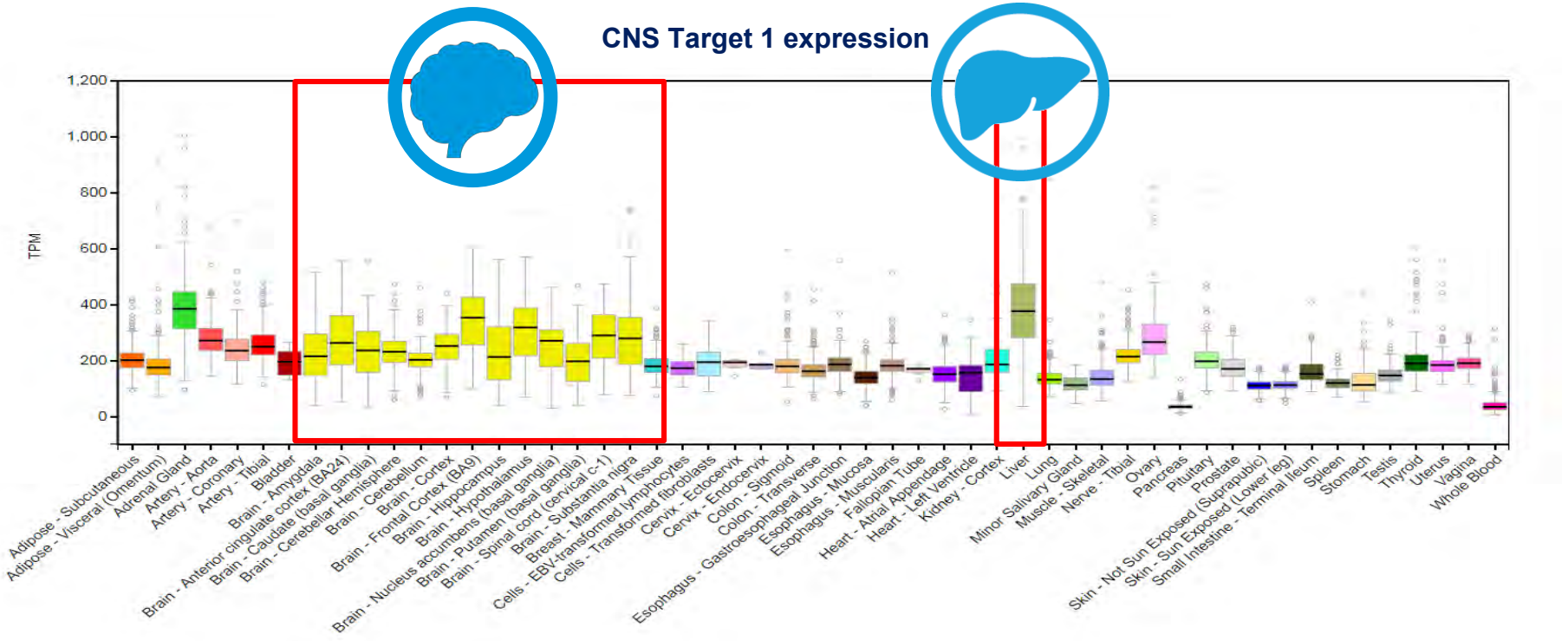
Evolution of conjugate potency (mouse, SD ED_{50})



CNS Target 1, an Optimal Target for CNS POC

Target 1 is broadly expressed

- Expressed ubiquitously in CNS and robustly expressed in liver
  - Lead selection can be performed *in vitro* and *in vivo* activity confirmed in liver utilizing GalNAc conjugate chemistry prior to triggering CNS studies



In vitro Results Identify Potent Duplexes for Mouse *in vivo* Study

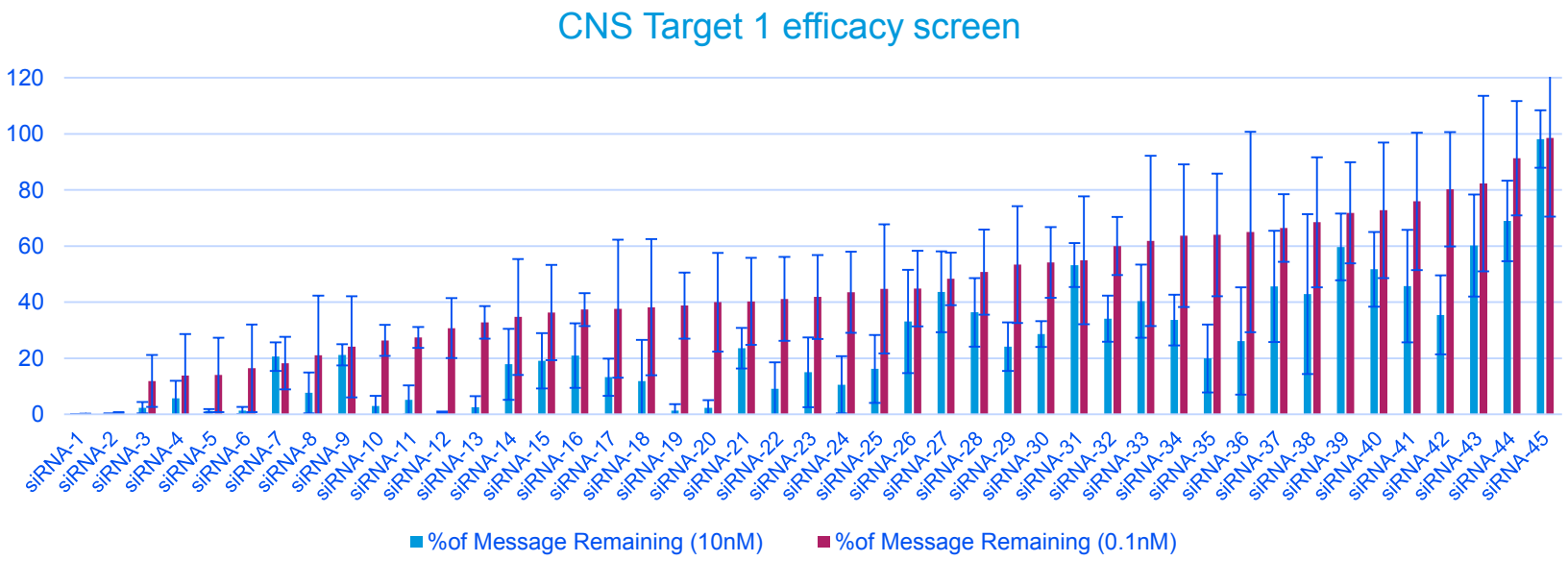
In vitro efficacy screen

Primary mouse hepatocytes

10 and 0.1 nM

24 hr time point

Assayed by qPCR

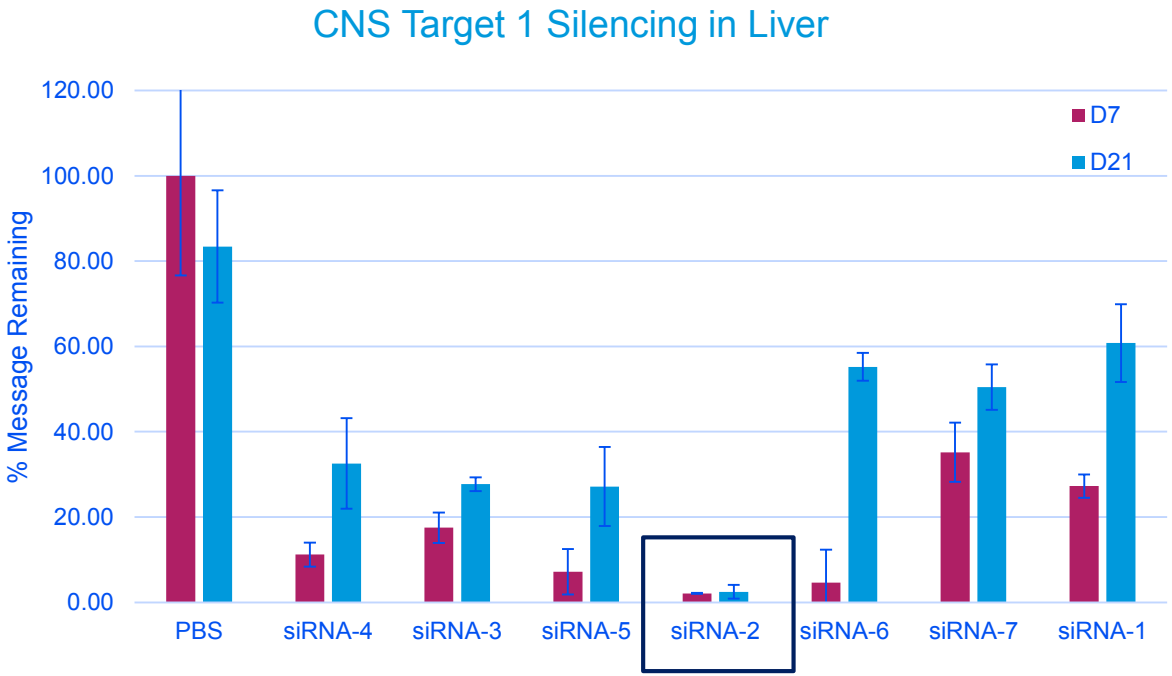


In vivo CNS Target 1 Screen Identifies Potent Candidate for IT Dosing

In vivo potency screen with GalNAc versions

7 duplexes selected for *in vivo* screen (target silencing in liver)

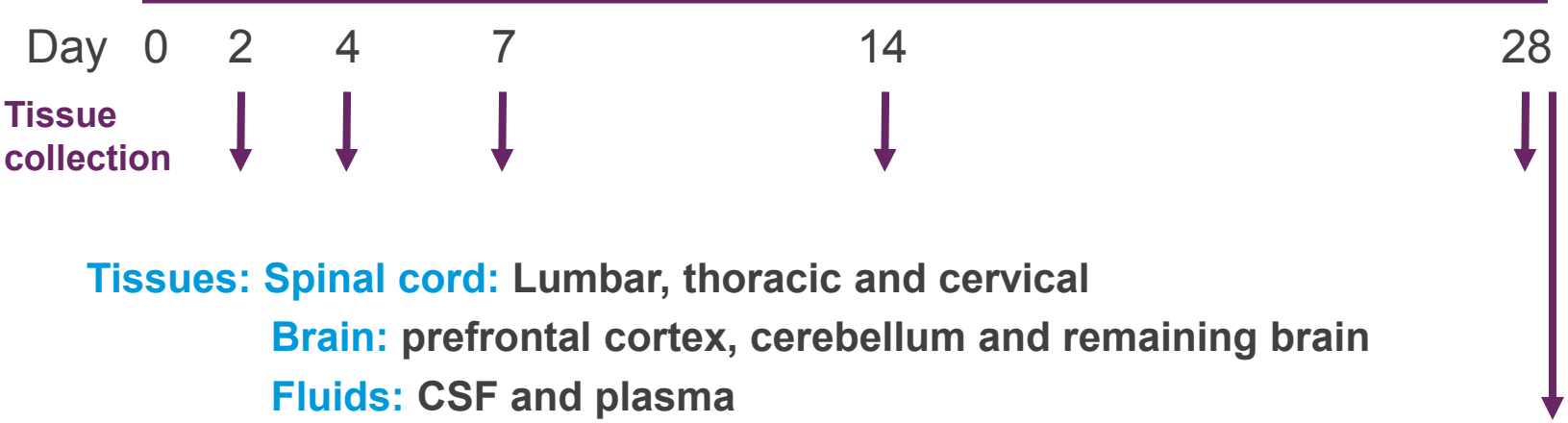
Single 2 mg/kg subcutaneous dose with two time points day 7 and 21



Intrathecal Delivery of Novel siRNA Conjugates

Single Dose Time Course in Rat

Two targets tested to demonstrate sequence specificity
siRNA conjugate dose of 0.9 mg



Tissues: Spinal cord: Lumbar, thoracic and cervical

Brain: prefrontal cortex, cerebellum and remaining brain

Fluids: CSF and plasma

Assays: mRNA, tissue siRNA levels, RISC loaded siRNA

Histology

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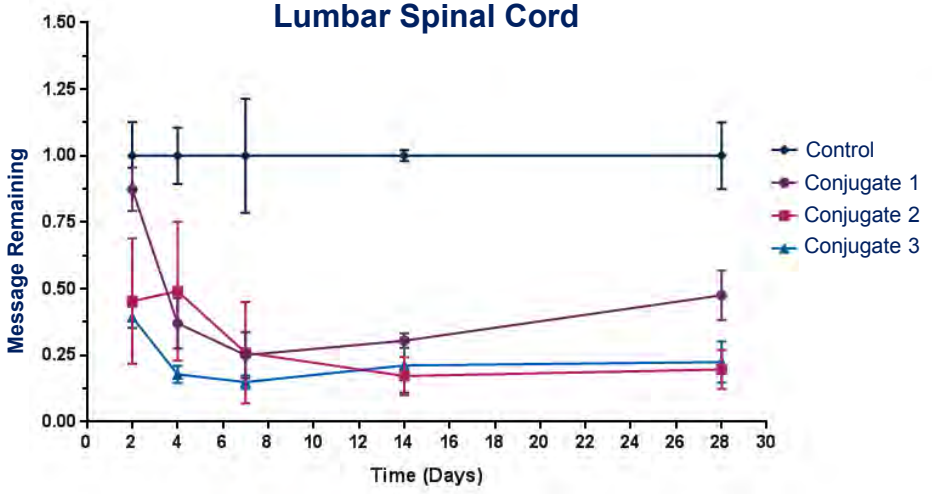
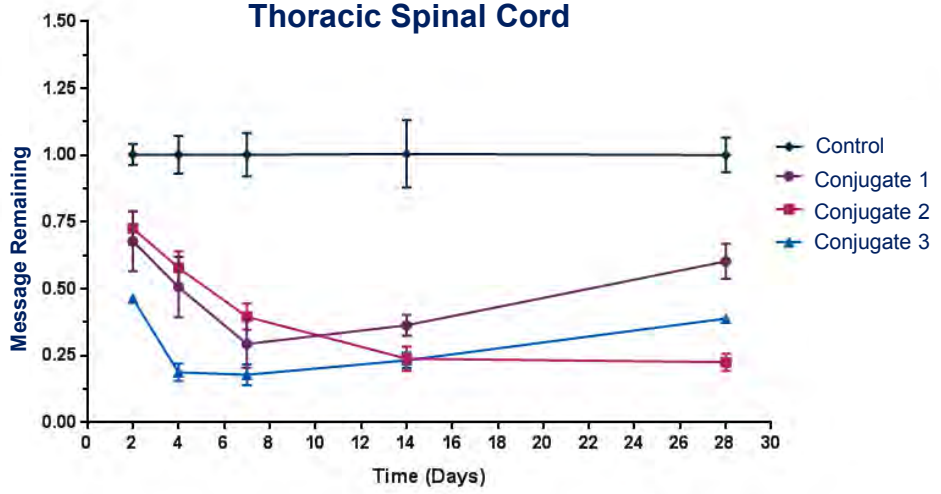
CNS Target 1 siRNA Shows Significant Target Knockdown Throughout Spinal Cord

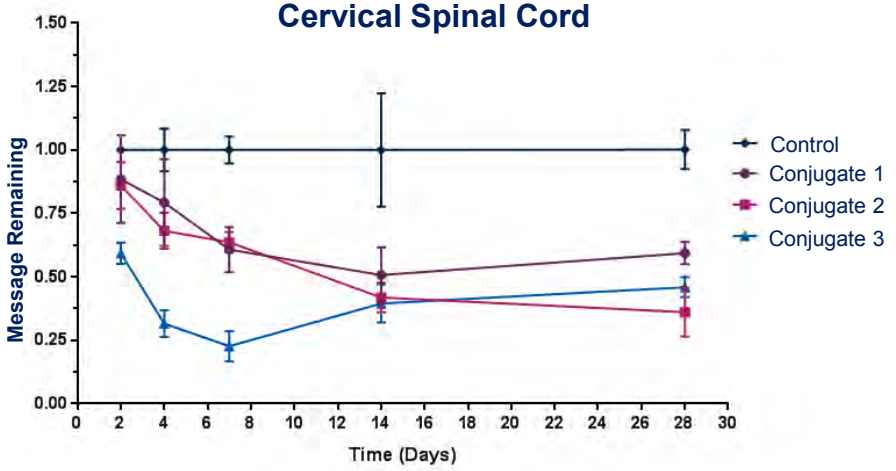
Lumbar Spinal Cord



Thoracic Spinal Cord



Cervical Spinal Cord



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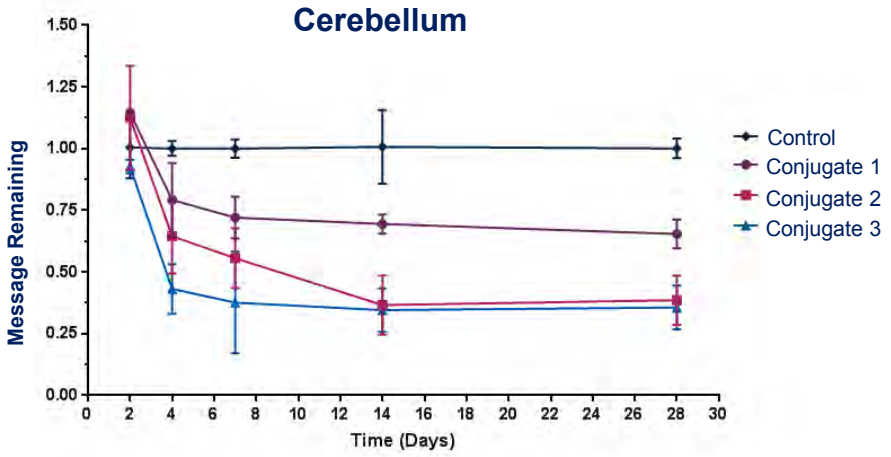
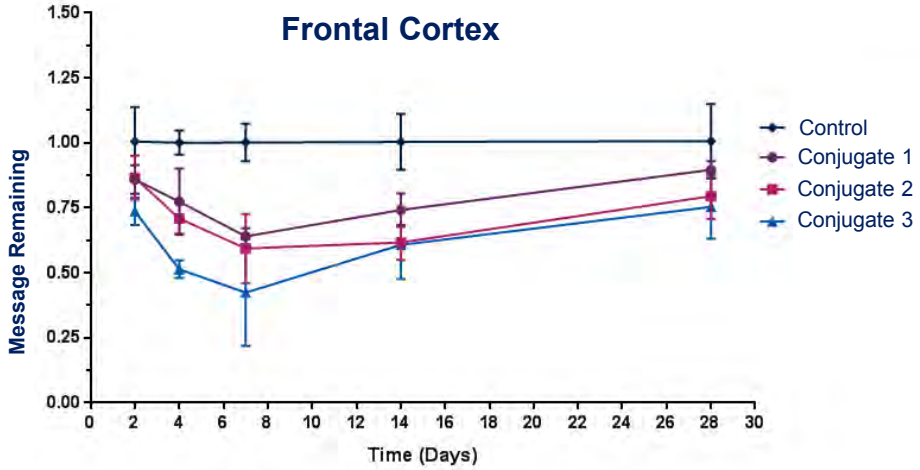
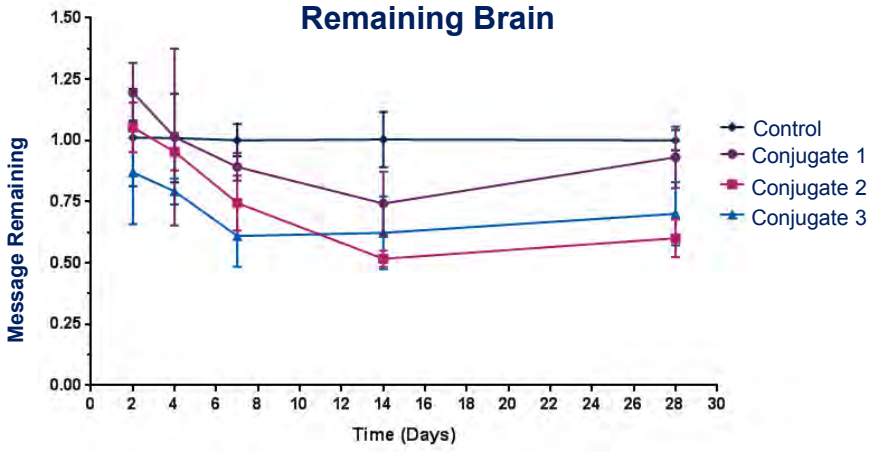
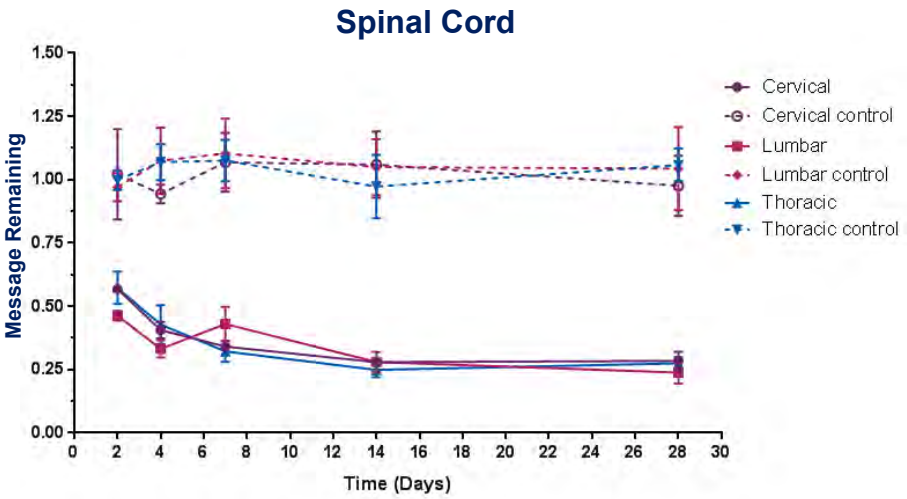
Differing Degrees of Knockdown Observed Across Brain

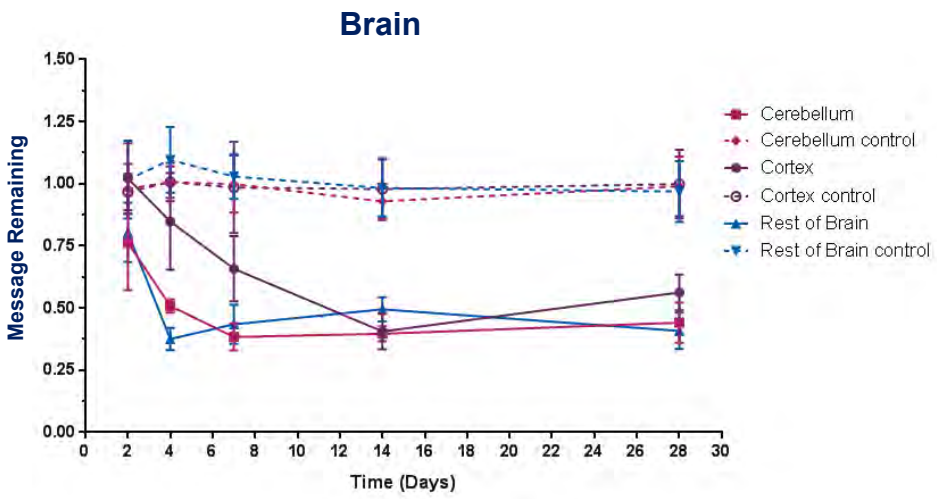






Potent Silencing Achieved by Second, Independent siRNA Conjugate Across Spinal Cord and Brain





- Significant knockdown observed in spinal cord and brain by a second siRNA conjugate targeting beta-catenin, which is ubiquitously expressed throughout the CNS

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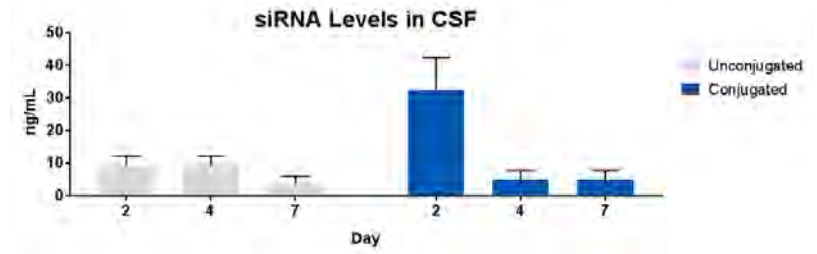
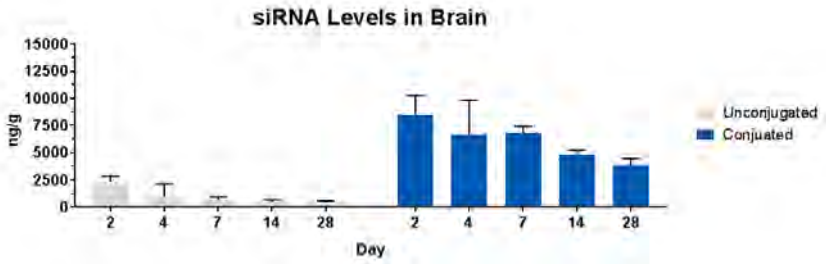
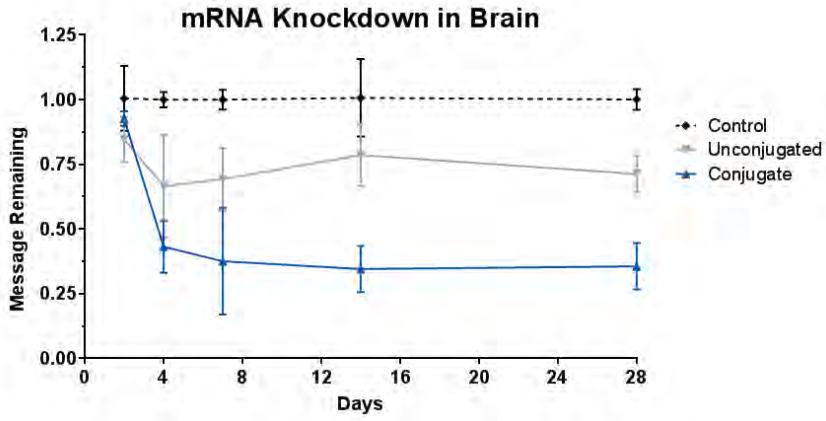
siRNA Conjugates Show Enhanced Uptake and Activity

Higher Drug Levels and Robust Silencing Observed in Brain with siRNA Conjugates







- 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

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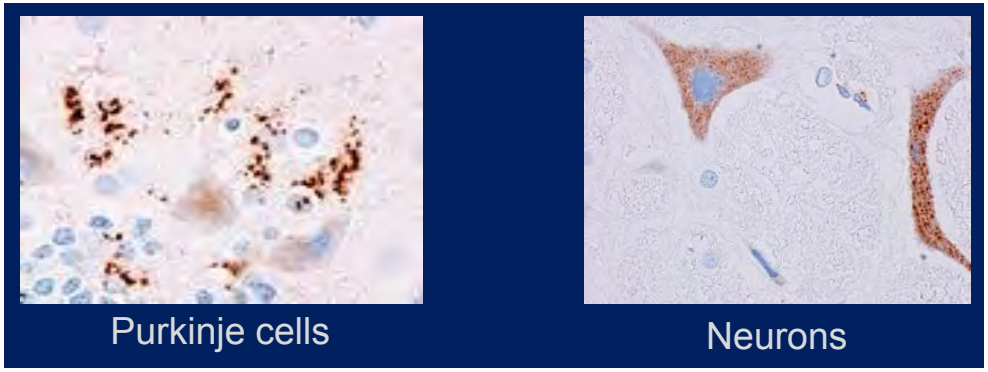
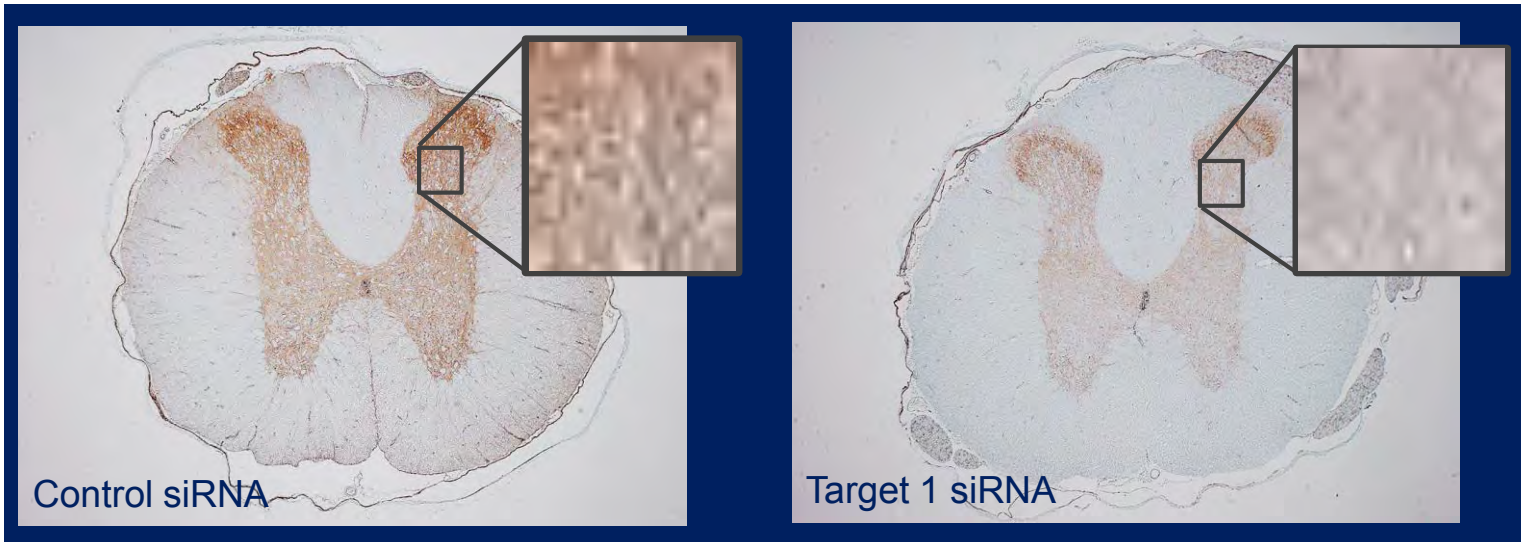
CNS Tissue Analysis Confirms Distribution of siRNA and Protein Knockdown

Intraneuronal and Purkinje cell siRNA uptake in spinal cord, cerebellum and brain (Day 28)



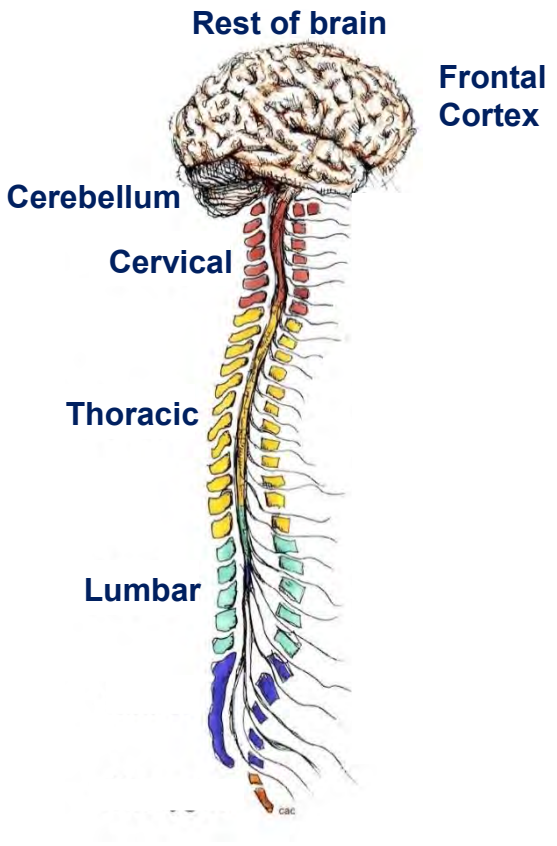
65% protein reduction in spinal cord detected by IHC (Day 28)



Anti-siRNA antibody and anti-Target 1 antibody used to identify cell uptake and activity

Rat Intrathecal Study Conclusions

Successful Delivery of siRNA Conjugate Across CNS



- CSF clearance is rapid following IT bolus injection
- Tissue uptake was observed in all CNS tissues examined with drug levels in the low to mid single digit μg/g range
- Robust, specific and durable silencing of target mRNA observed across the CNS following a single IT administration of siRNA conjugates
  - Silencing extends out through the end of study on Day 28
  - Enhanced tissue uptake and activity observed for siRNA conjugate compared to unconjugated siRNA
- Conjugate administered by IT dosing was well tolerated

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Alnylam CNS Pipeline Strategy

Expanding a Pipeline of Potentially Transformative Medicines

Genetically validated, CNS-expressed target gene

Biomarker for POC in Phase 1

Alnylam CNS Objectives

- 1st DC in 2018
- 1st IND in late ’19/early ’20
- 1-2 INDs/yr starting in ’20

Agenda

Welcome

- Christine Lindenboom, Vice President, Investor Relations & Corporate Communications

Introduction

- Martin Maier, Ph.D., Vice President, Research

Platform Advances in RNAi Therapeutics

- Advances in ESC+ Design for Improved Specificity and Therapeutic Index
  - Mark Schlegel, Ph.D., Senior Scientist, Research
- New Frontiers: CNS Delivery Update
  - Kirk Brown, Ph.D., Associate Director, Bioanalytical Sciences

Q&A Session

- Moderated by Vasant Jadhav, Ph.D., Senior Director, Research

Upcoming RNAi Roundtables

Givosiran, in Development for the Treatment of Acute Hepatic Porphyrias

- Tuesday, July 24, 10:00 am ET

Lumasiran, in Development for the Treatment of Primary Hyperoxaluria Type 1

- Wednesday, August 15, 10:30 am ET

Patisiran & ALN-TTRsc02, for the Treatment of Transthyretin-Mediated Amyloidosis

- Tuesday, September 11, time TBD

Additional details for upcoming RNAi Roundtables, including speakers, dates and times, will be provided on the Capella section of the Company's website, www.alnylam.com/capella.

Thank You

RNAi ROUNDTABLE 2018

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