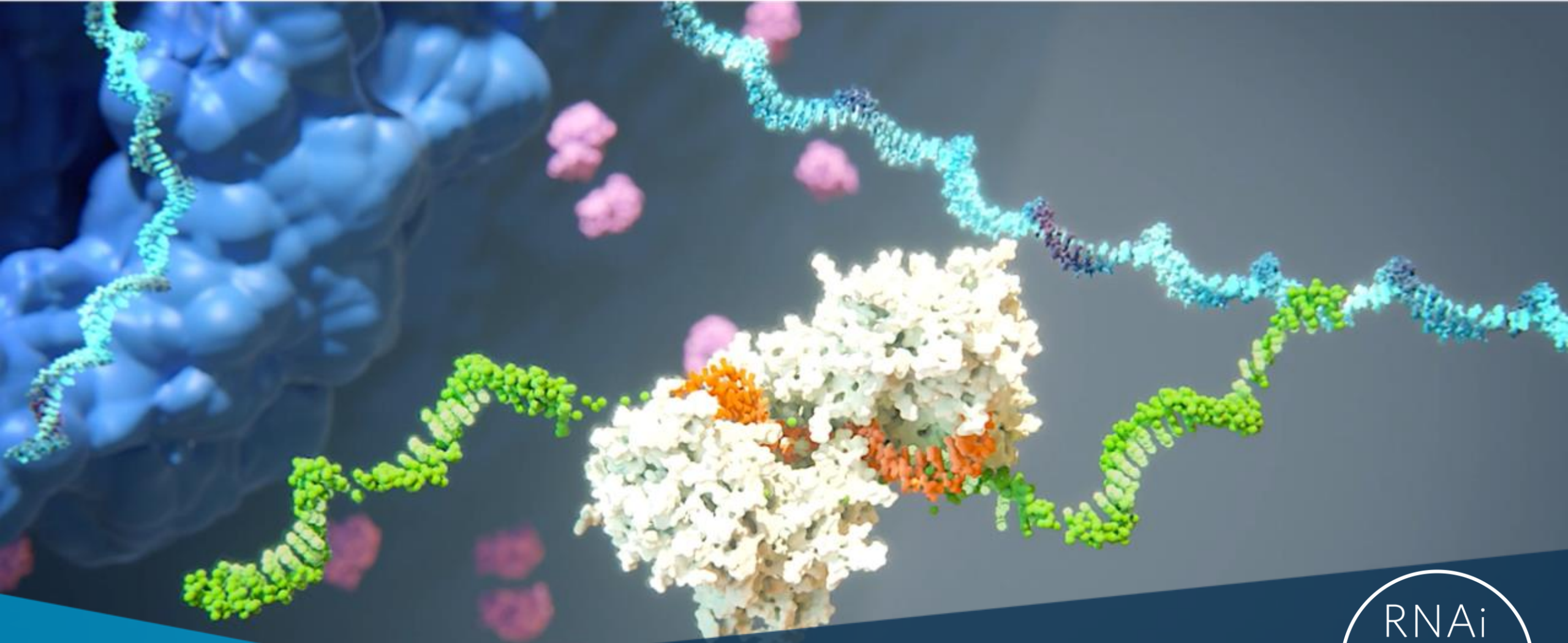

CNS & Extrahepatic RNAi Pipeline Programs

October 1, 2021

RNAi ROUNDTABLE 2021

Alnylam PHARMACEUTICALS

Agenda

Welcome
- Joshua Brodsky – Senior Director, Investor Relations & Corporate Communications

Introduction & Extrahepatic Platform Overview
- Vasant Jadhav, Ph.D. – SVP, Research

RNAi Therapeutics for CNS Disorders
- CNS Delivery
  - Kirk Brown, Ph.D. – Senior Director, CNS Program
- CNS Pipeline
  - Bret Bostwick, M.D. – Director, Clinical Research

Advancing RNAi Therapeutics into Ocular and Lung Disorders
- Vasant Jadhav, Ph.D. – SVP, Research

Q&A Session

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 interface

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, including expectations regarding our aspiration to become a leading biotech company, and the planned achievement of our “Alnylam P5x25” strategy, the potential of our platform to enable RNAi therapeutics for the treatment of large indications and the extension into extrahepatic tissues, including the CNS, eye and lungs, the potential of RNAi therapeutics to demonstrate superior potency, duration and systemic safety profile versus ASOs, the potential of ALN-APP to treat Alzheimer’s disease and other indications and expectations regarding the timeline for the initiation of clinical development, and expectations regarding our long-term pipeline opportunities and growth. Actual results and future plans may differ materially from those indicated by these forward-looking statements as a result of various important risks, uncertainties and other factors, including, without limitation: the direct or indirect impact of the COVID-19 global pandemic or any future pandemic on our business, results of operations and financial condition and the effectiveness or timeliness of our efforts to mitigate the impact of the pandemic; our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates; the pre-clinical and clinical results for our product candidates; actions or advice of regulatory agencies and our ability to obtain and maintain regulatory approval for our product candidates, including lumasiran, as well as favorable pricing and reimbursement; successfully launching, marketing and selling our approved products globally; delays, interruptions or failures in the manufacture and supply of our product candidates or our marketed products; obtaining, maintaining and protecting intellectual property; our ability to successfully expand the indication for ONPATTRO (and potentially vutrisiran) in the future; our ability to manage our growth and operating expenses through disciplined investment in operations and our ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; our ability to maintain strategic business collaborations; our dependence on third parties for the development and commercialization of certain products, including Novartis, Sanofi, Regeneron and Vir; the outcome of litigation; the potential impact of current and risk of future government investigations; and unexpected expenditures; as well as those risks more fully discussed in the “Risk Factors” filed with our most recent Quarterly Report on Form 10-Q filed with the SEC and in our other SEC filings. If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance, timelines 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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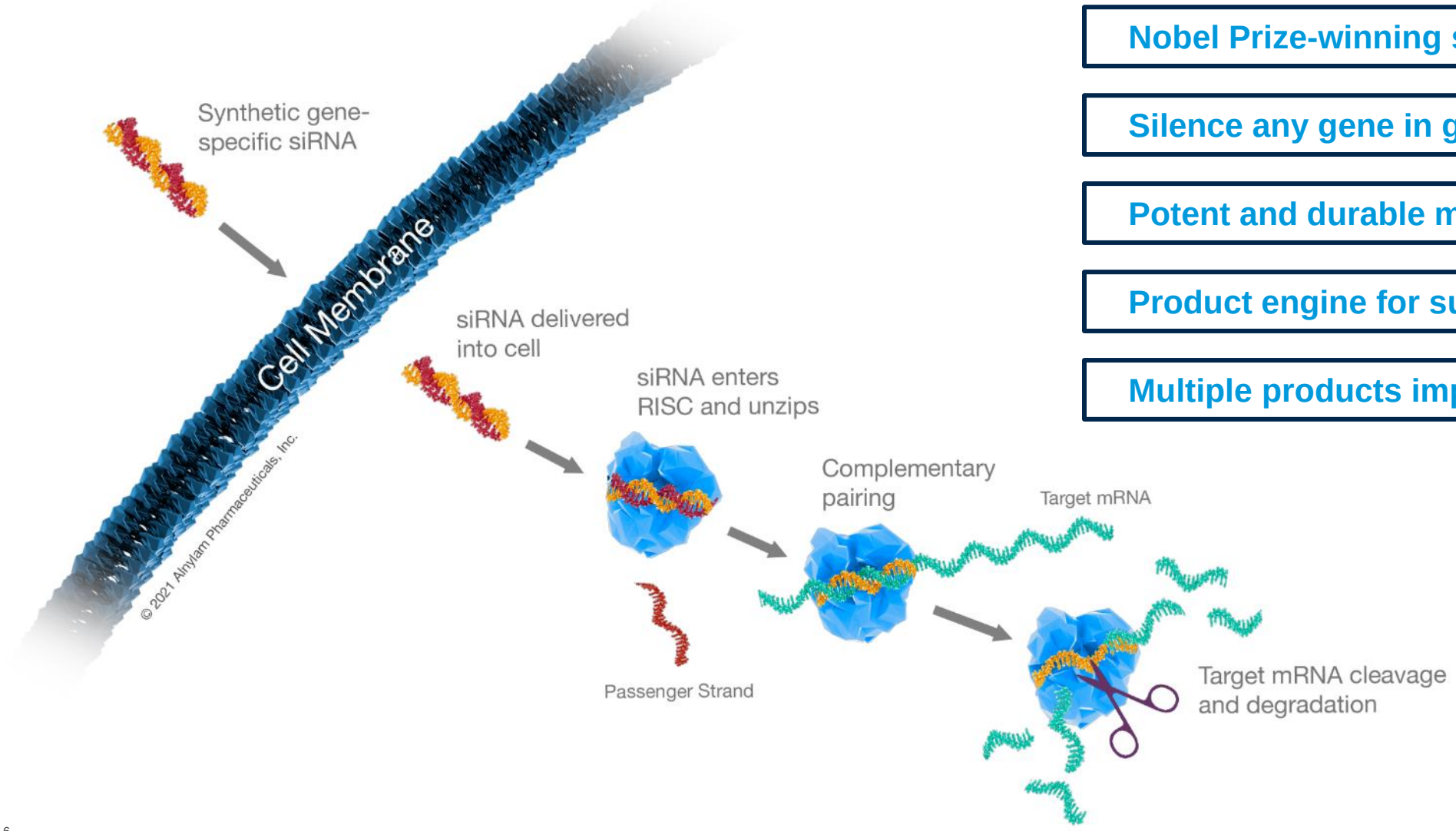
Q&A Session

RNAi Therapeutics: New Class of Innovative Medicines

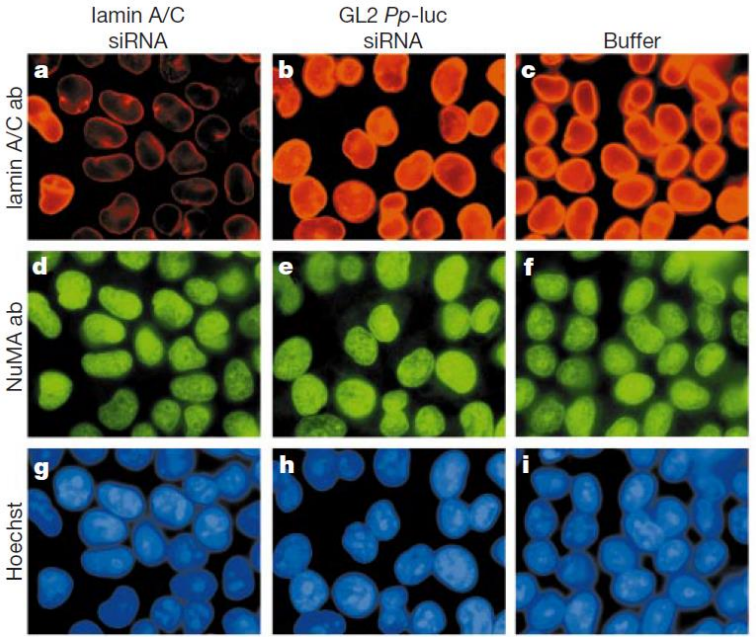
Clinically and Commercially Established Approach with Transformational Potential

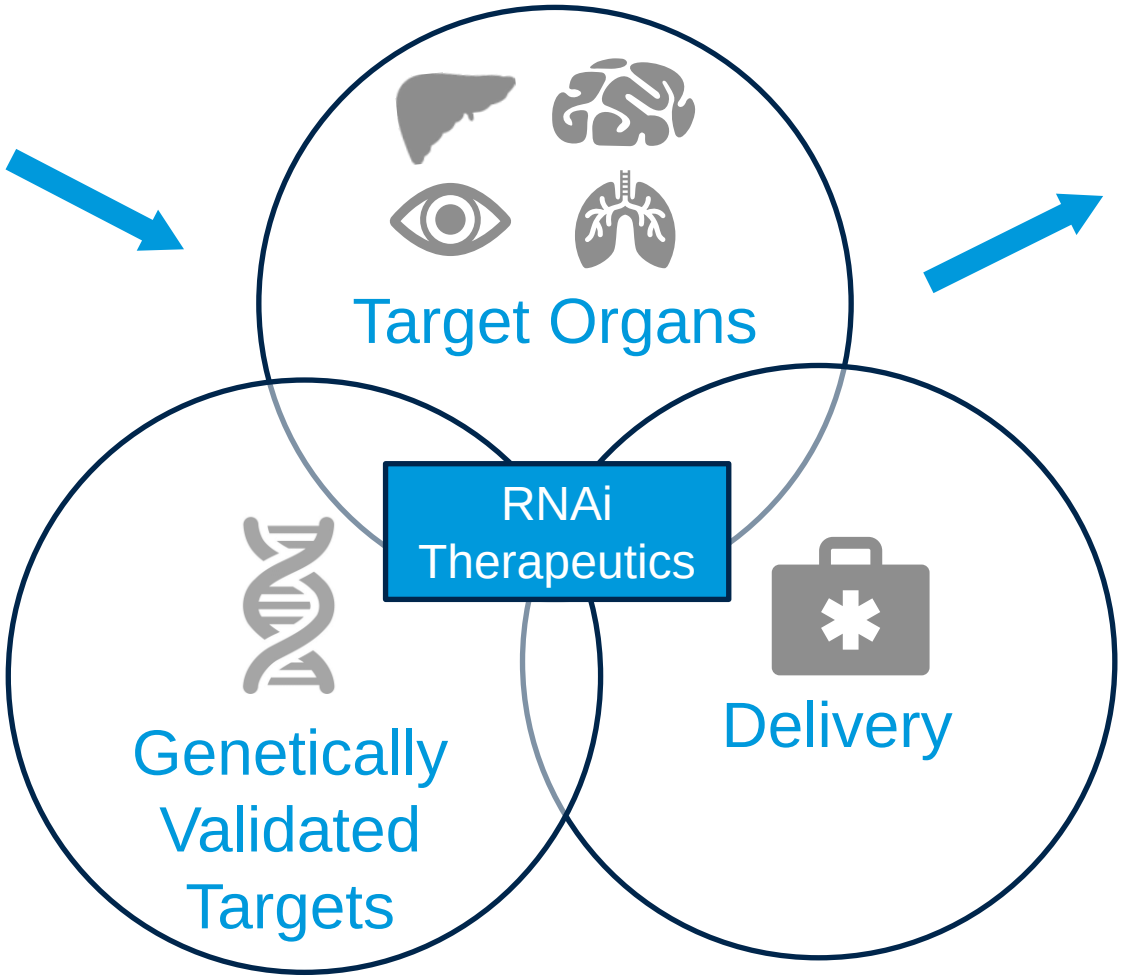


- **Nobel Prize-winning science**
- **Silence any gene in genome with siRNAs**
- **Potent and durable mechanism of action**
- **Product engine for sustainable innovation**
- **Multiple products impacting patients globally**

Focused R&D Strategy

Turning an *In Vitro* Observation into a New Class of Medicines

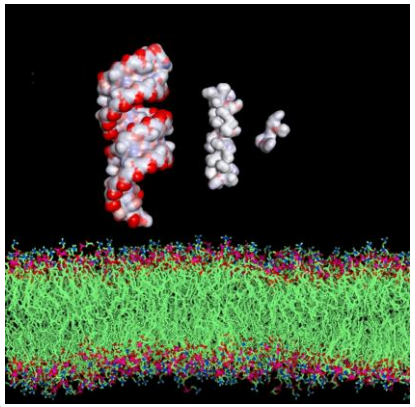




Addressing Delivery Challenges in Liver

siRNA Characteristics

- Large molecules (~14,000 Da)
- Highly negatively charged
- Hydrophilic

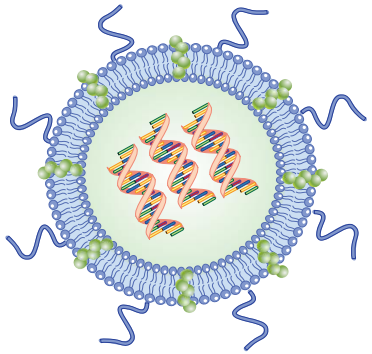


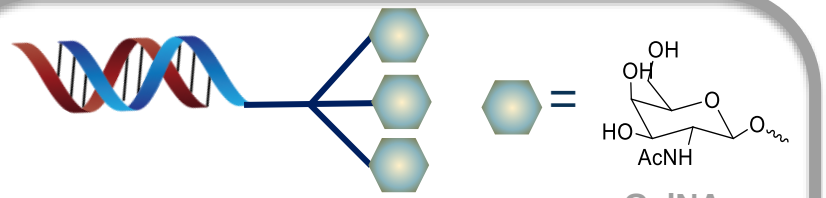
Challenges with natural, unmodified siRNAs

- Unstable in biological matrices
- Nuclease susceptibility and lack of passive uptake across cell membranes
- Immunostimulatory

Lipid Nanoparticles (LNPs)

- Multi-component lipid formulation
- Encapsulated siRNA
- Highly efficient for targeted delivery to liver
- Administered intravenously
- 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 (all current DCs in clinical development other than patisiran)

Without these lipid shells, there would be no mRNA vaccines for COVID-19

Fragile mRNA molecules used in COVID-19 vaccines can't get into cells on their own. They owe their success to lipid nanoparticles that took decades to refine

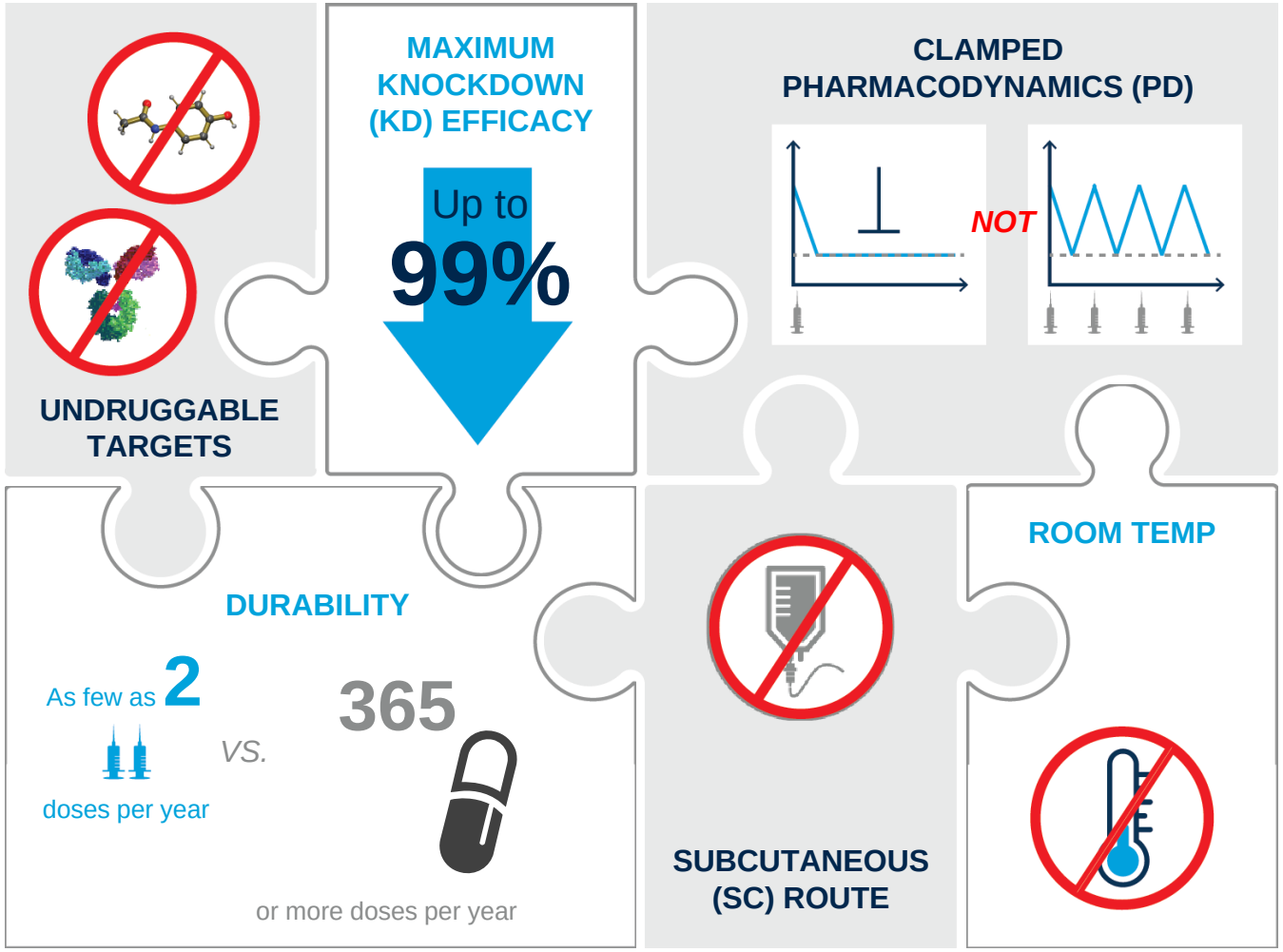
C&EN, March 2021

Continuous innovation

- STC → ESC → ESC+ → IKARIA

Key Features of Alnylam RNAi Therapeutics in Liver

Platform Profile Well-Suited for Large Indications

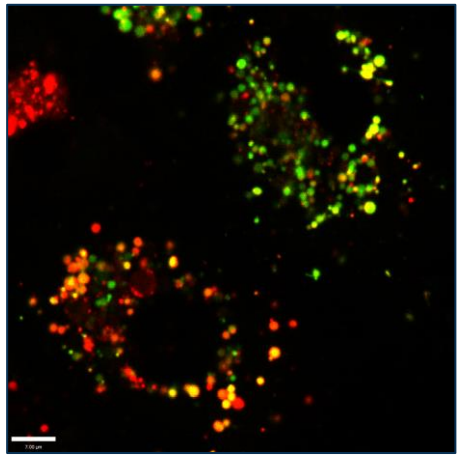


Alnylam RNAi Platform

- Infrequent, subcutaneous administration creates dosing flexibility for patients and eases treatment burden
  - Potential for quarterly and biannual dosing
- Wide therapeutic index with potential for transformative outcomes
- Extensive human safety experience across multiple indications, including large market indications such as hypercholesterolemia

RNAi is Durable AND Reversible

Intracellular Depot For the Durability of Conjugates



siRNA
Lysopainter

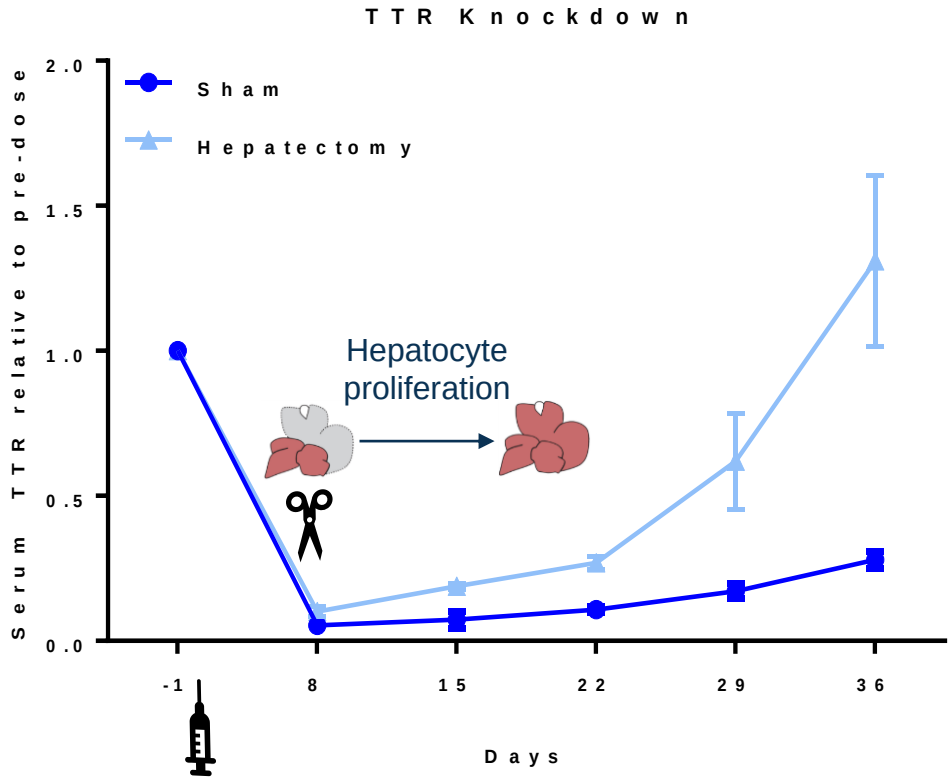
OTS Paper of the Year 2021

NAR Breakthrough Article

Investigating the pharmacodynamic durability of GalNAc–siRNA conjugates

Christopher R. Brown[1], Swati Gupta[1], June Qin[1], Timothy Racie[1], Guo He[1], Scott Lentini[1], Ryan Malone[1], Mikyung Yu[1], Shigeo Matsuda[1], Svetlana Shulga-Morskaya[1], Anil V. Nair[2], Christopher S. Theile[1], Karyn Schmidt[1], Azar Shahraz[1], Varun Goel[1], Rubina G. Parmar[1], Ivan Zlatev[1], Mark K. Schlegel[1], Jayaprakash K. Nair[1], Muthusamy Jayaraman[1], Muthiah Manoharan[1], Dennis Brown[2], Martin A. Maier[1] and Vasant Jadhav[1,*]

Activity in Proliferating Mouse Liver after Partial Hepatectomy (Two Thirds)



1 mg/kg siRNA by SC in mice

Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STARs):

- Genetic Medicines
- Cardio-Metabolic Diseases
- Infectious Diseases
- CNS/Ocular Diseases

		EARLY/MID-STAGE *(IND/CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION/ COMMERCIAL[1] (OLE/Phase 4/IIS/registries)	COMMERCIAL RIGHTS
onpattro (patisiran)	*hATTR Amyloidosis-PN*[2]			●	Global
GIVLAARI (givosiran)	*Acute Hepatic Porphyria*[3]			●	Global
OXLUMO (lumasiran)	*Primary Hyperoxaluria Type 1*[4]			●	Global
Leqvio® (inclisiran)	*Hypercholesterolemia*			●	Milestones & up to 20% Royalties[5]
Vutrisiran*	*hATTR Amyloidosis-PN*			●	Global
Patisiran	*ATTR Amyloidosis*		●		Global
Vutrisiran*	*ATTR Amyloidosis*		●		Global
Fitusiran*	*Hemophilia*		●		15-30% Royalties
Lumasiran	*Severe PH1* *Recurrent Kidney Stones*	●	●		Global
Cemdisiran*	*Complement-Mediated Diseases*	●			50-50
Cemdisiran/Pozelimab Combo[6]*	*Complement-Mediated Diseases*	●			Milestone/Royalty
Belcesiran[7]*	*Alpha-1 Liver Disease*	●			Ex-U.S. option post-Phase 3
ALN-HBV02 (VIR-2218)[8]*	*Hepatitis B Virus Infection*	●			50-50 option post-Phase 2
Zilebesiran (ALN-AGT)*	*Hypertension*	●			Global
ALN-HSD*	*NASH*	●			50-50

[1] Includes marketing application submissions; [2] Approved in the U.S. and Canada for the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy; [3] Approved in the U.S., Brazil and Canada for the treatment of adults with acute hepatic porphyria (AHP), and in the EU and Japan for the treatment of AHP in adults and adolescents aged 12 years and older; [4] Approved in the U.S., EU and Brazil for the treatment of primary hyperoxaluria type 1 in all age groups; [5] Novartis has obtained global rights to develop, manufacture and commercialize inclisiran; 50% of inclisiran royalty revenue from Novartis will be payable to Blackstone by Alnylam; [6] Cemdisiran and pozelimab are each currently in Phase 2 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics; [7] Dicerna is leading and funding development of Belcesiran; [8] Vir is leading and funding development of ALN-HBV02; * Not approved for any indication and conclusions regarding the safety or efficacy of the drug have not been established.

As of August 2021

Alnylam Advancements in Conjugate-Based Delivery of siRNAs

siRNA Designs with Enhanced Potency and Stability May Extend to Extrahepatic Tissues

articles

Therapeutic silencing of an endogenous gene by systemic administration of modified

J|A|C|S

Communication

Multivalent *N*-Acetylgalactosamine-Conjugated siRNA Localizes in Hepatocytes and Elicits Robust RNAi-Mediated Gene Silencing

Molecular Therapy

Original Article

Advanced siRNA Designs Further Improve *In Vivo* Per

nature COMMUNICATIONS

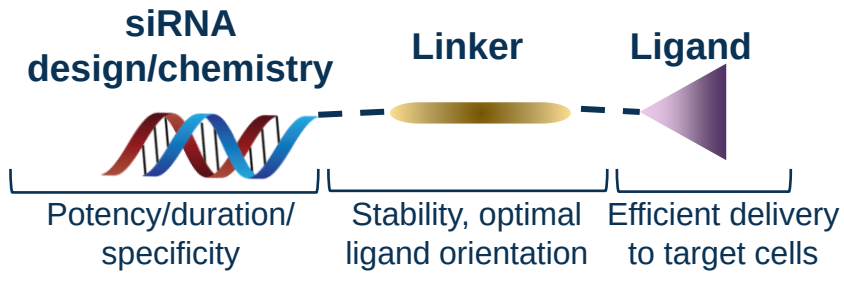
ARTICLE

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

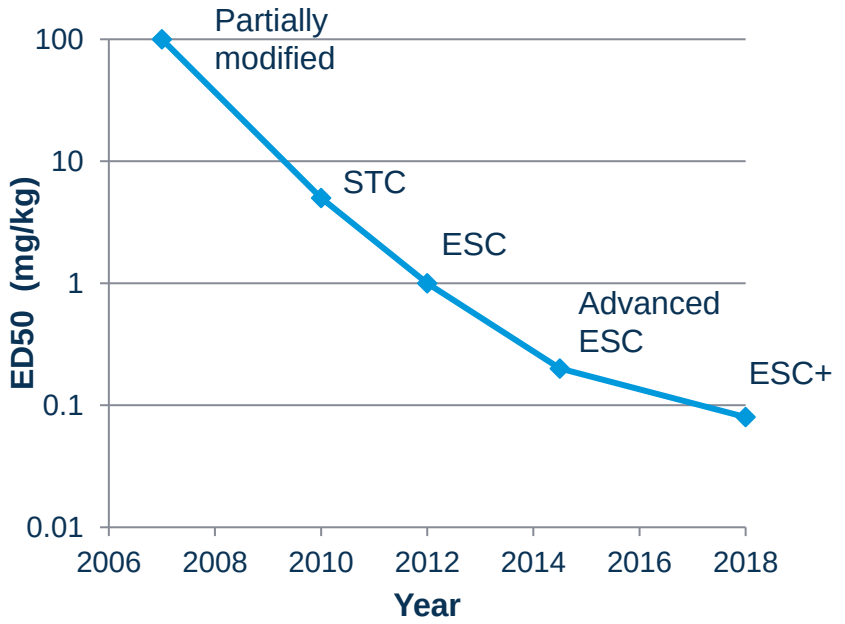
2004

2014

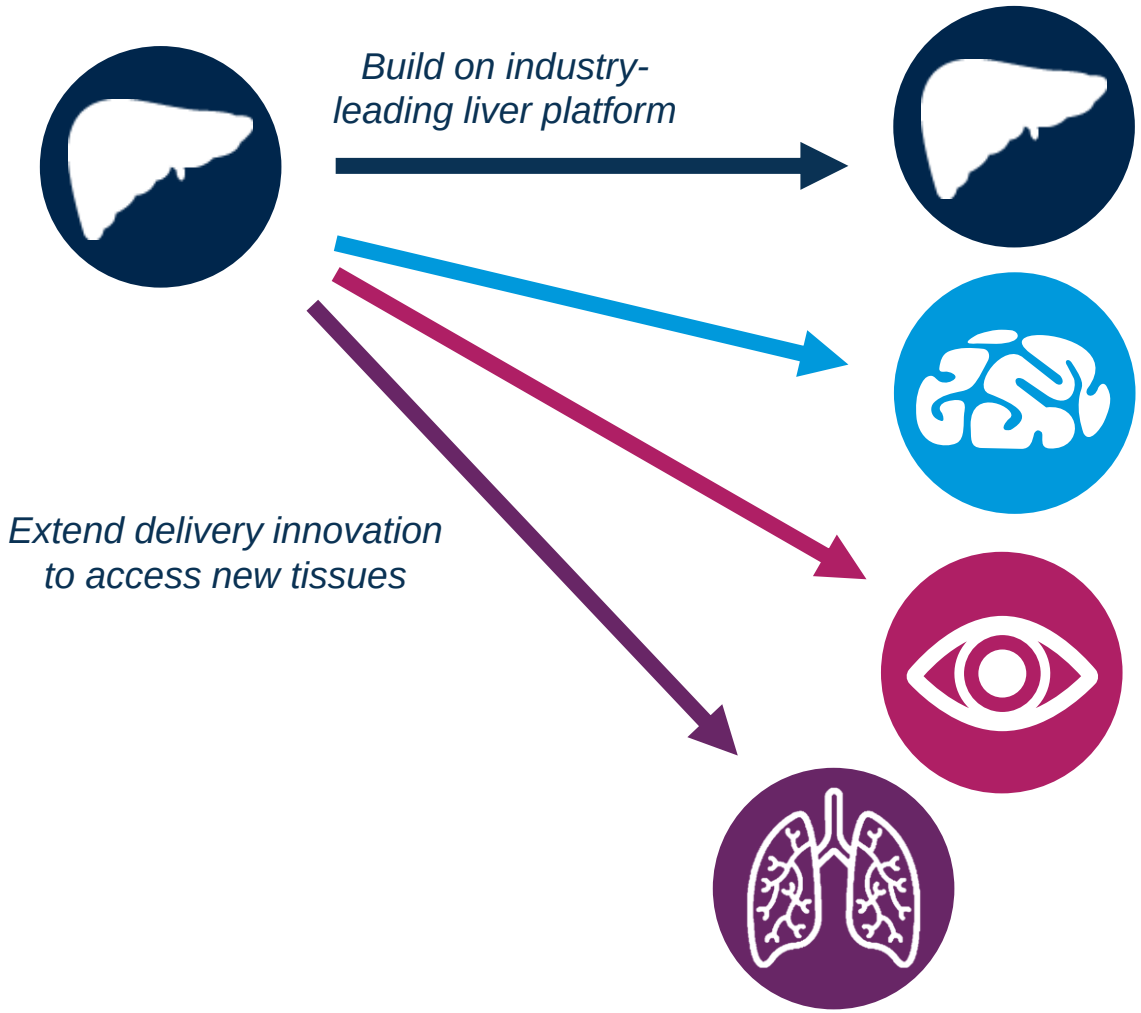
2018



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



Expanding Areas of Therapeutic Focus



Tissues for Extrahepatic Delivery

- Multiple disease areas with high unmet medical need
- Genetically validated targets for disease with established biomarkers
- Leveraging siRNA-conjugate approach for delivery of RNAi therapeutics across multiple organs

Alliances in Extrahepatic Discovery and Development

REGENERON

- Landmark alliance with Regeneron focused on CNS & ocular RNAi therapeutics
  - Leverages Alnylam R&D expertise and scientific excellence in RNAi therapeutics, in combination with Regeneron's world-leading capabilities in human genetics
  - 50-50 structure in CNS, with Regeneron leading development and commercialization of all programs targeting eye diseases.

PeptiDream

- Collaboration to discover and develop peptide-siRNA conjugates for targeted delivery of RNAi therapeutics to a broad range of extrahepatic tissues
  - PeptiDream to select, optimize, and synthesize peptides for Alnylam-selected receptors utilizing its peptide discovery platform
  - Final peptide selection to be supported by *in vitro* and *in vivo* studies evaluating novel peptide-siRNA conjugates

Over 25 Preclinical Programs in Four Tissues Feeding Pipeline

LIVER

Alnylam
- ALN-XDH
- ALN-KHK
- ALN-LEC
- ALN-CC3
- ALN-F12
- Many others

Alnylam/Regeneron
- ALN-PNP
- ALN-REGN-L2
- ALN-REGN-L4
- ALN-REGN-L5

CNS

Alnylam/Regeneron
- ALN-APP
- ALN-HTT
- ALN-REGN-C3
- ALN-REGN-C4
- ALN-REGN-C5
- ALN-REGN-C6
- ALN-REGN-C7
- ALN-REGN-C8
- ALN-REGN-C9

EYE

Alnylam
- ALN-TTRoc

Alnylam/Regeneron
- ALN-REGN-E1
- ALN-REGN-E2
- ALN-REGN-E3
- ALN-REGN-E4

LUNG

Alnylam/Vir
- ALN-VIR2 (ACE2)
- ALN-VIR3 (TMPRSS2)

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Q&A Session

RNAi Therapeutics for CNS Diseases

No Current Therapies to Prevent or Restore Neurodegenerative Disease

Very high unmet need for new treatments for CNS Diseases

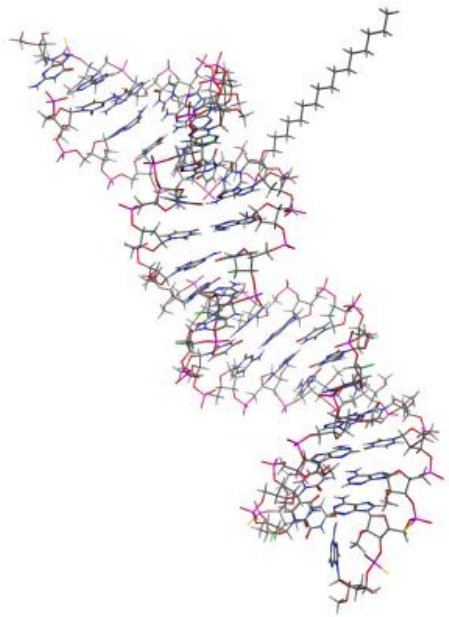
- Genetically defined neurodegenerative diseases include
  - Alzheimer's disease
  - Amyotrophic lateral sclerosis (ALS)
  - Frontotemporal dementia
  - Huntington's disease
  - Parkinson's disease
  - Prion disease
  - Spinocerebellar ataxia
  - Many other orphan genetic diseases with CNS component

- Number of genetically validated targets known but no current disease modifying therapies for these devastating, life-threatening disorders
- Significant opportunity for RNAi therapeutics directed to disease-causing, CNS-expressed genes
- Based on pre-clinical studies, expect superior potency, duration and systemic safety profile vs. ASOs

CNS Platform Objectives

Potential for Best-in-Class CNS Oligonucleotide Delivery Platform

- **High potency**
- **Wide biodistribution in CNS**
- **Long duration of action**
- **Favorable risk / benefit profile**



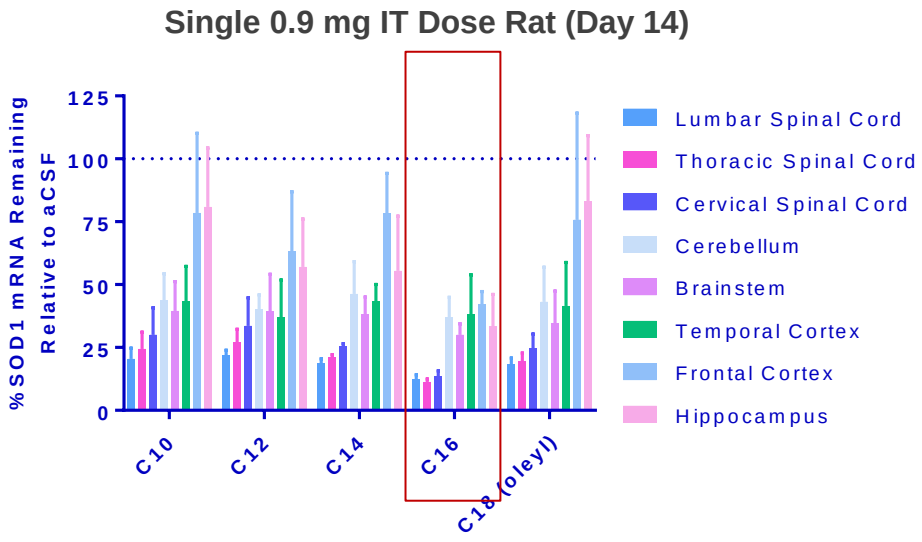
C16 Conjugate

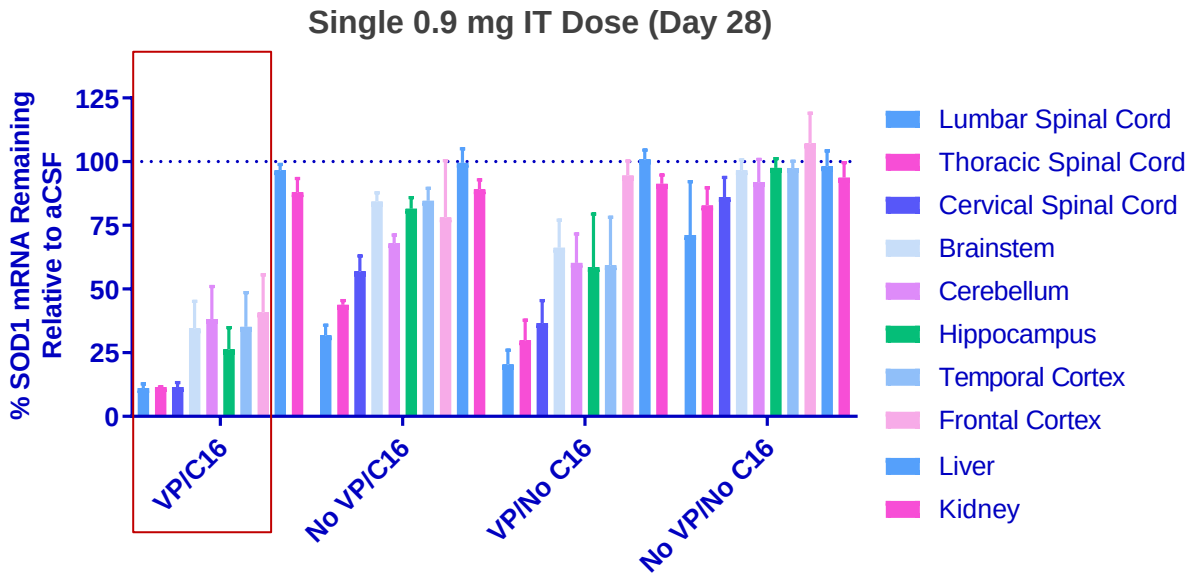
C16 Conjugate Platform

Optimized for CNS Delivery of RNAi Therapeutics

C16 conjugate platform designed to optimize potency, durability, and safety

- Exhaustive optimization of siRNA lipophilic moiety, position, and design chemistry
- Backbone modifications to enable similar metabolic stability to liver platform (e.g., ESC+)
- Vinylphosphonate (VP) modification improves potency through enhanced RISC-binding

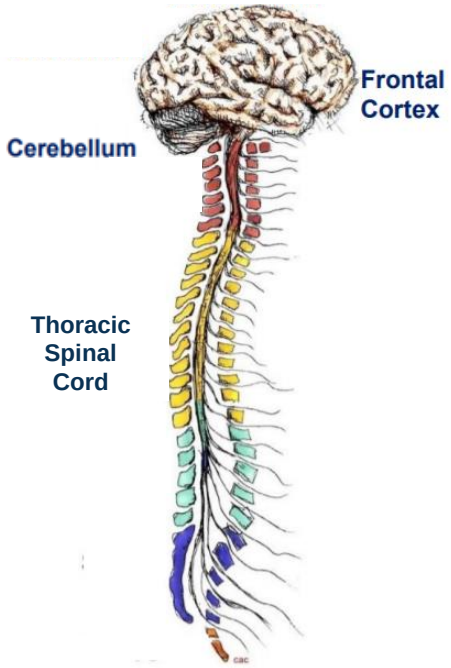


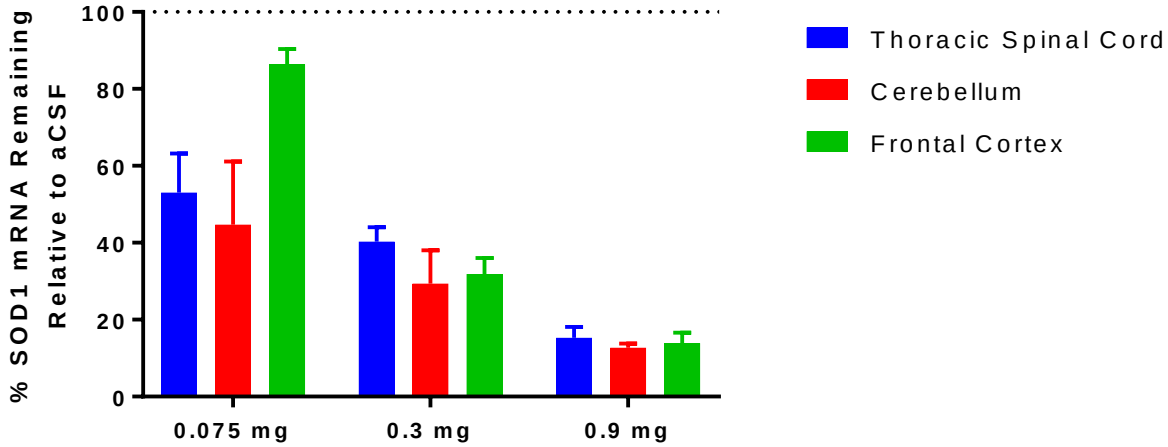


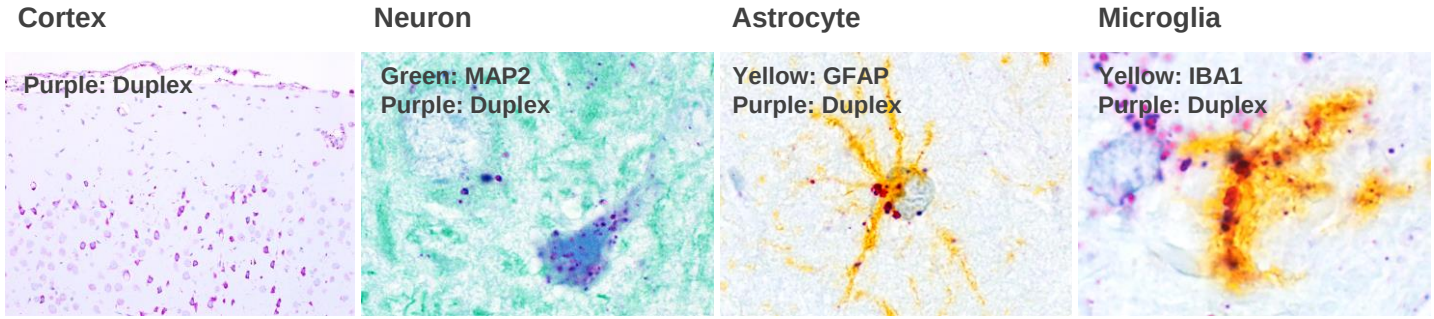
Robust Silencing Throughout Brain

Intrathecal Delivery of siRNA to Cell Types and Tissues Throughout CNS

Potent, dose dependent knockdown in cell types and tissues of rat spinal cord and brain

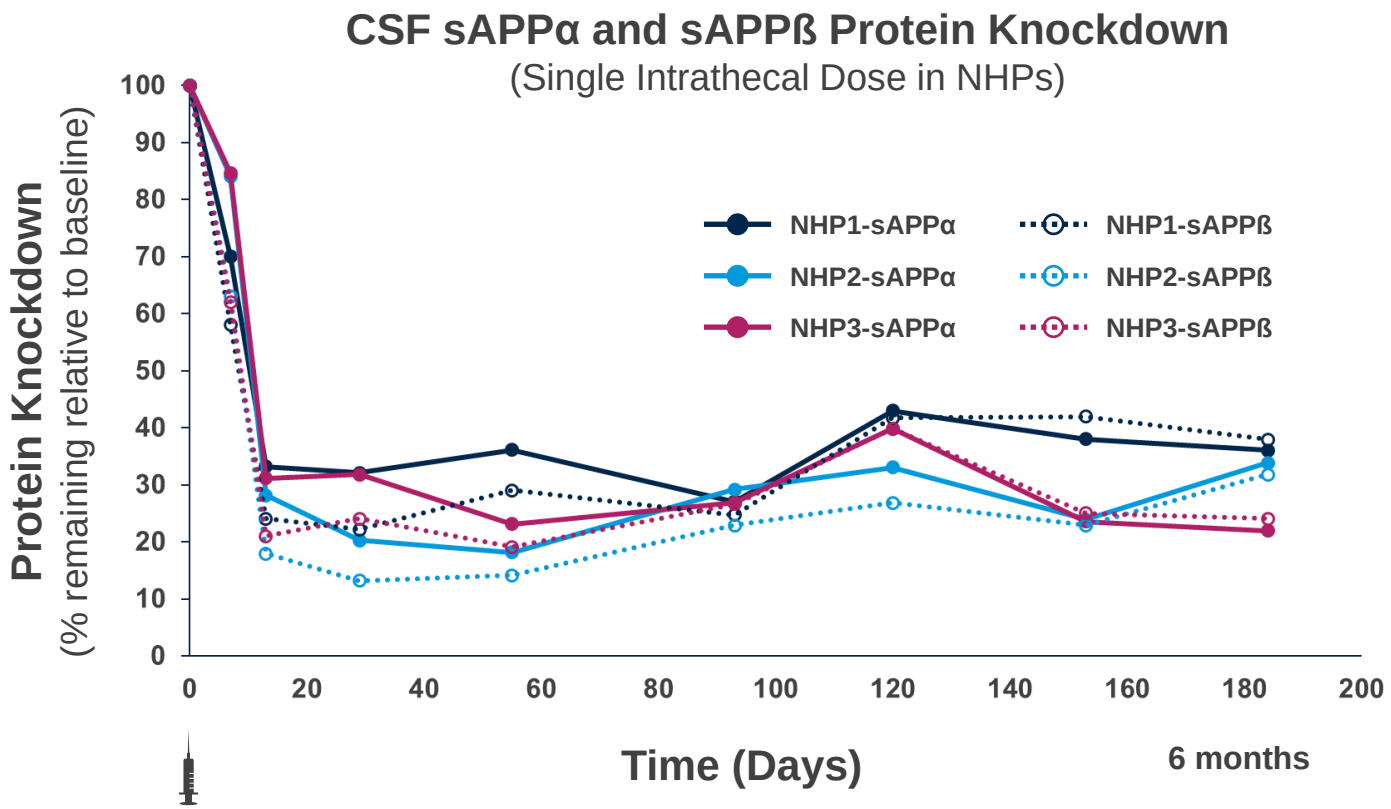






Long Duration of Action in CNS in Individual Subjects

Target Knockdown with Single Dose siRNA in NHP



Safety Summary for CNS siRNA Conjugates

No Test Article Related Changes in Rat and NHP Safety Assessments

6-month Platform PD Study in Rat

Single IT LP dose and Multi-IT LP dose

- No TA-related findings in spinal cord, brain, liver, kidney, lung, diaphragm, pituitary, sciatic nerve, skeletal muscle, spleen or thymus
- No TA-related findings on clinical signs, body weight or body weight gain

Platform non-GLP Tox Studies in Rat

15-day systemic tox

- No changes observed in serum chemistry, hematology or histopath

15-day IT LP tox

- No test article findings across all parameters examined: clinical observations, body weight, functional observational battery, clinical pathology parameters, macroscopic findings, and microscopic examinations including expanded neurological assessment with Fluoro-Jade

Platform non-GLP Tox Study in NHP

15-day IT LP tox

- No test article related findings across all parameters examined: clinical observations, body weight, neurological exams, macroscopic findings, and microscopic examinations including neurological assessment including Fluoro-Jade

GLP Tox Studies in rat and NHP

Completed for ALN-APP

CNS RNAi Platform Preclinical Summary

Expected to Enter Phase 1 Studies in Early 2022

C16 conjugates provide potent, durable silencing with distribution throughout the CNS

- C16 conjugate designed to optimize potency, durability, and safety of CNS platform
  - Lipophilic moiety provides for robust cellular uptake
  - VP modification enhances potency through enhanced engagement of RISC
  - “Walks” conducted to optimize potency and durability of construct design

- Robust silencing achieved throughout the brain and spinal cord at low doses

- Extended pharmacodynamic profile suggests possibility for infrequent dosing; single IT dose provides robust knockdown for 6+ months in NHP

- Platform and ALN-APP CTA-enabling toxicology studies support further development of C16 conjugates

Alnylam CNS Pipeline Strategy

Expanding a Pipeline of Potentially Transformative Medicines

Genetically validated target gene

Biomarker for POC in Phase 1

Definable path to approval and patient access

Over 25 Preclinical Programs in Four Tissues Feeding Pipeline

LIVER

Alnylam
- ALN-XDH
- ALN-KHK
- ALN-LEC
- ALN-CC3
- ALN-F12
- Many others

Alnylam/Regeneron
- ALN-PNP
- ALN-REGN-L2
- ALN-REGN-L4
- ALN-REGN-L5

CNS

Alnylam/Regeneron
- ALN-APP
- ALN-HTT
- ALN-REGN-C3
- ALN-REGN-C4
- ALN-REGN-C5
- ALN-REGN-C6
- ALN-REGN-C7
- ALN-REGN-C8
- ALN-REGN-C9

EYE

Alnylam
- ALN-TTRoc

Alnylam/Regeneron
- ALN-REGN-E1
- ALN-REGN-E2
- ALN-REGN-E3
- ALN-REGN-E4

LUNG

Alnylam/Vir
- ALN-VIR2 (ACE2)
- ALN-VIR3 (TMPRSS2)

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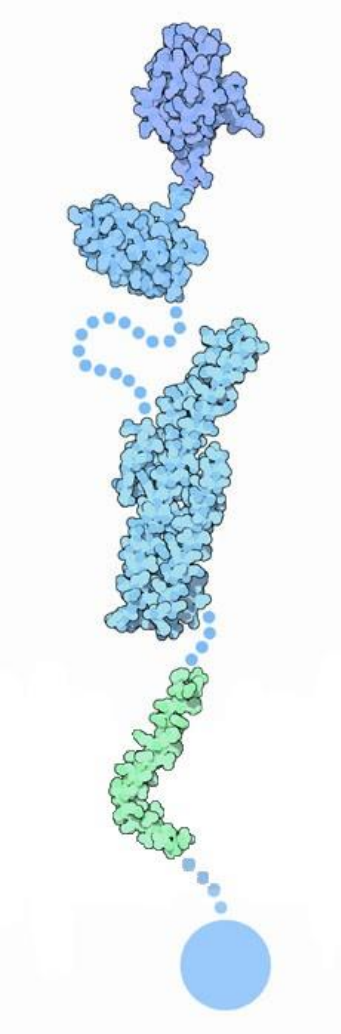
Q&A Session

Amyloid Precursor Protein (APP)

Alzheimer's Disease and Cerebral Amyloid Angiopathy



One target, two distinct pathological processes

- APP is an 87 kDA membrane-associated protein produced in many tissues, but with the highest expression in the nervous system
- APP is processed via serial cleavage by various enzymes include (α-, β-, and γ-secretase) to produce a variety of peptides, including Aβ
- APP is a genetically validated target for both Alzheimer's Disease and Cerebral Amyloid Angiopathy

Alzheimer's Disease (AD)

- APP mutations and duplications cause Early Onset AD
- Amyloid deposits in brain tissue, tau tangles in neurons, neurodegeneration

Cerebral Amyloid Angiopathy (CAA)

- APP mutations cause hereditary CAA
- Amyloid deposits in the walls of the arteries in the brain and causes cerebral hemorrhages and dementia

APP Protein Structure courtesy of David S. Goodsell and the RCSB Protein Data Bank

APP as a Target for Alzheimer's Disease (AD)

Alzheimer's Disease is Most Common Cause of Dementia Worldwide

High prevalence and high unmet need for new therapies

- Over 5M people affected by AD in the US (over 30M worldwide); population continues to grow as the population ages
- Life expectancy for those diagnosed after age 65 is 4-8 years
- Early-onset and genetic forms impact cognition earlier in life
- Limited progress in development of disease modifying therapies

Genetically Validated Target	✓	• Mutations that increase APP production or alter APP processing cause early-onset AD • Mutations decreasing APP processing to Aβ are protective
Biomarker In Phase 1	✓	• Target engagement: sAPPα, sAPPβ in CSF • Disease progression: Fluid biomarkers (Aβ, tTau, pTau, NfL, etc.), neuroimaging
Definable Path to Approval	✓	• Multiple populations for potential development • High unmet need for disease modifying therapy

Multiple Development Opportunities

- **Early Onset AD (<65 yo) (EOAD)**
  - Autosomal Dominant AD (ADAD)
  - Non-familial early onset AD (nf-EoAD)
  - Down Syndrome AD
- **Late Onset AD (>65 yo) (LOAD)**
- **Sporadic AD (All non-familial AD)**

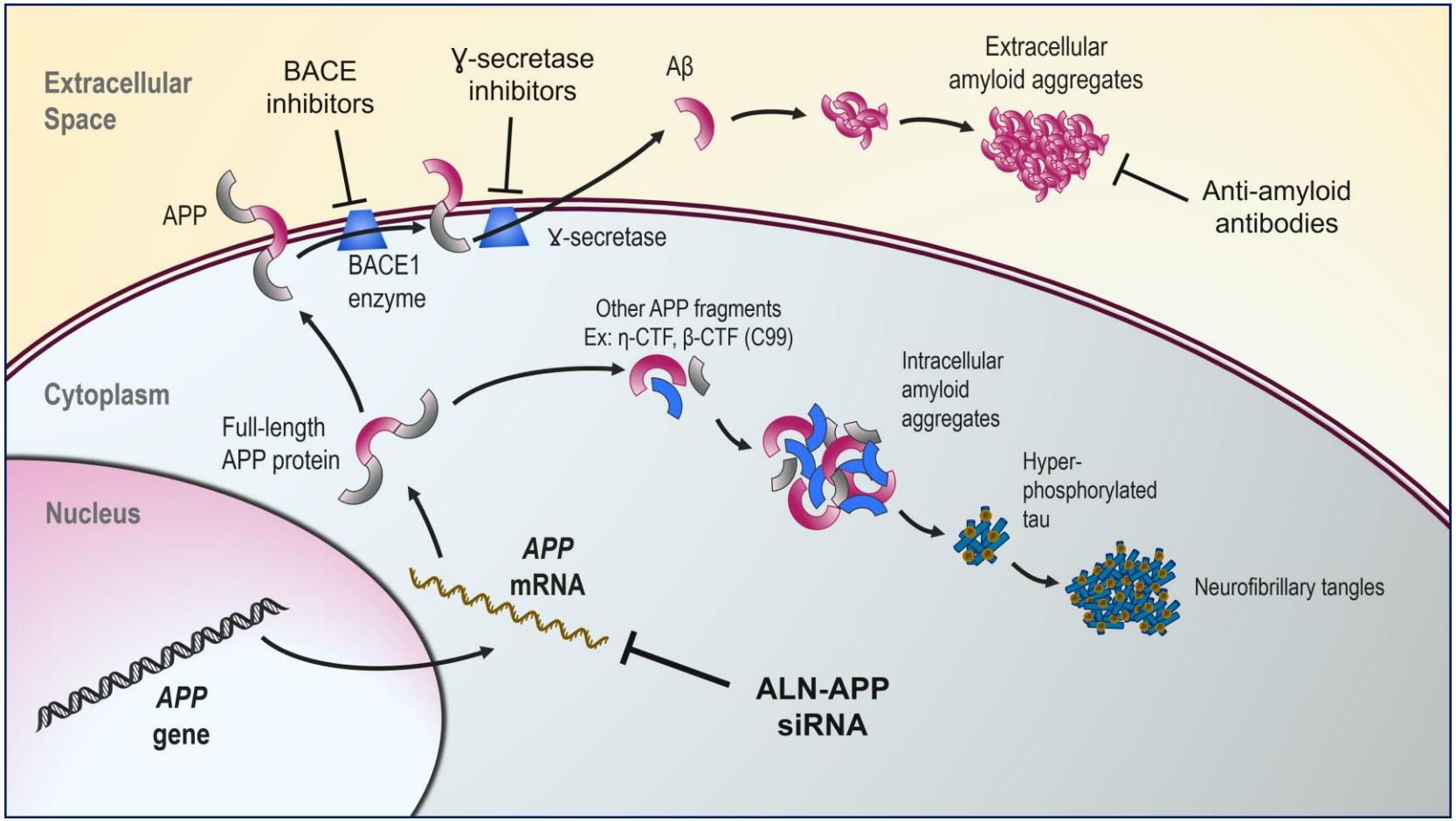
2020 AD Facts and Figures, *Alzheimer's Dementia* (2020); WHO Dementia Fact Sheet (2021); Tom SE, et al., Am J Public Health (2015)

Therapeutic Hypothesis: Alzheimer's Disease

A New Approach: Targeting the APP Protein

Lower APP production *at its source*, upstream of the pathogenic process

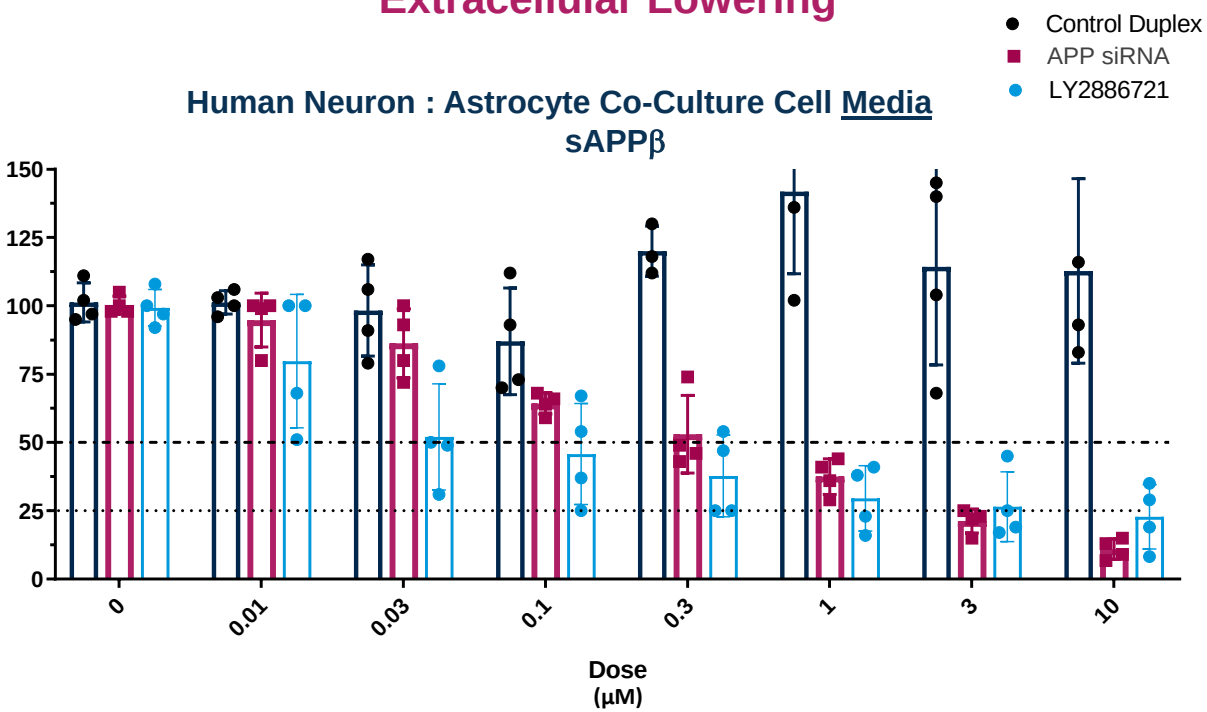
- Reduce ***both intracellular and extracellular*** drivers of disease pathology
- ***Reduce all APP cleavage products*** including all species of Aβ
- Removing substrate for amyloid deposit formation and ***enable natural clearance***



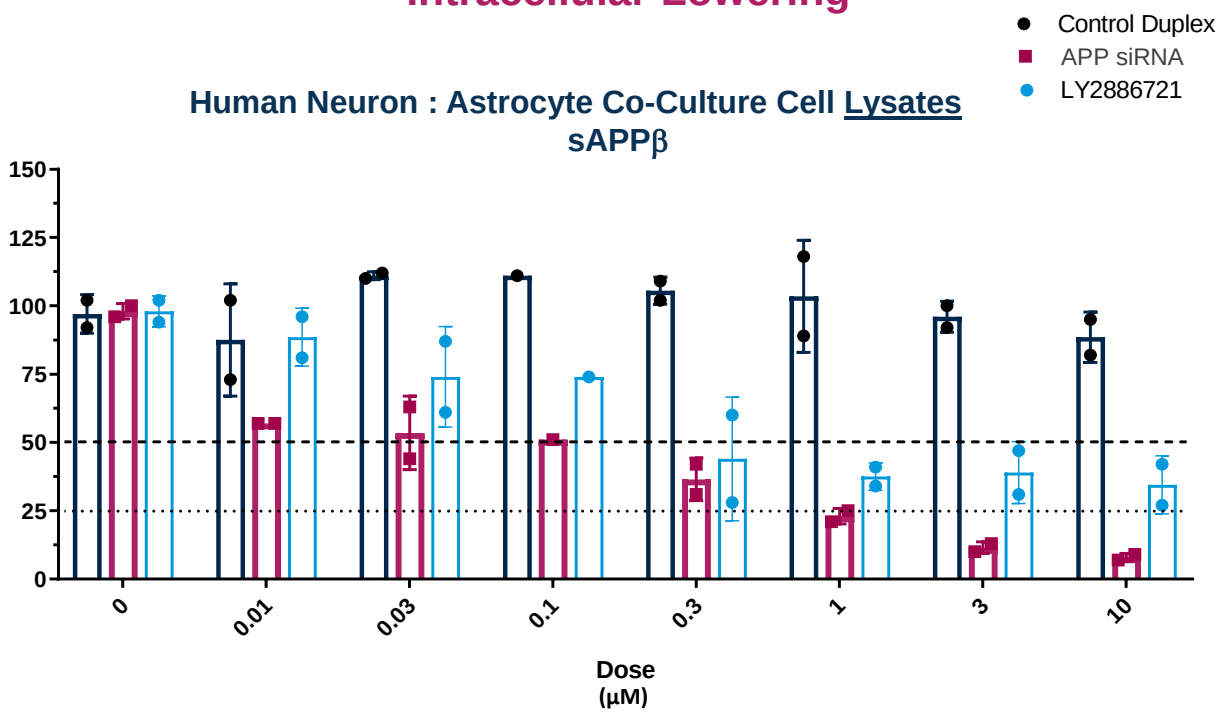
Intracellular and Extracellular sAPPβ Lowering

APP siRNA Lowers sAPPβ in Both Media and Lysates in Co-Culture System of Human Neurons and Astrocytes

Extracellular Lowering

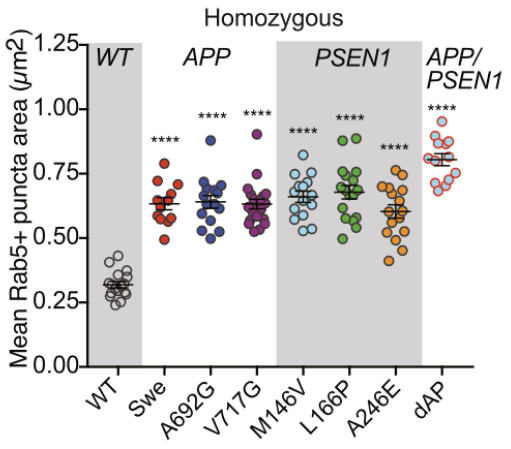


Intracellular Lowering



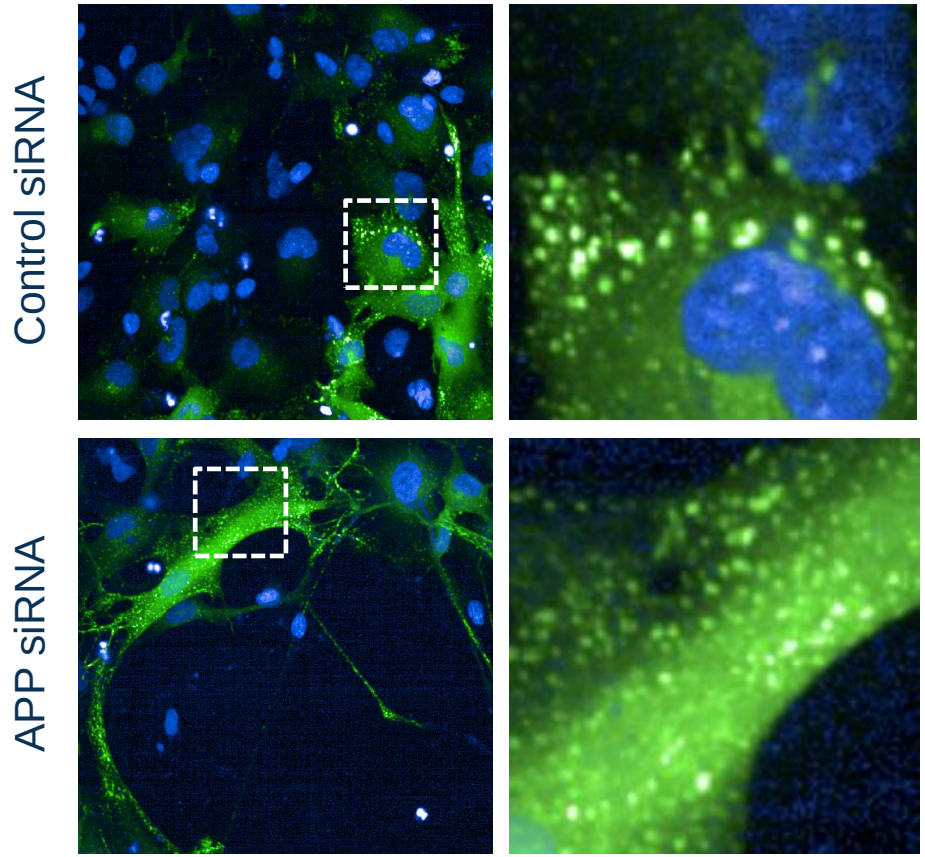
siRNA Targeting APP Shows Greater Intracellular Reductions in sAPPβ Compared to BACE Inhibition

PSEN1 ^{A246E} Patient iPSC-Derived Neurons Treated with APP siRNA Show Reduction in Rab5+ Early Endosome Size

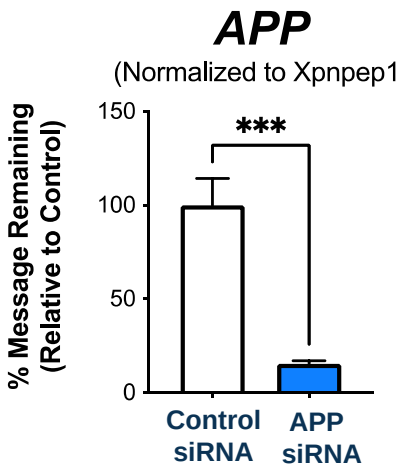


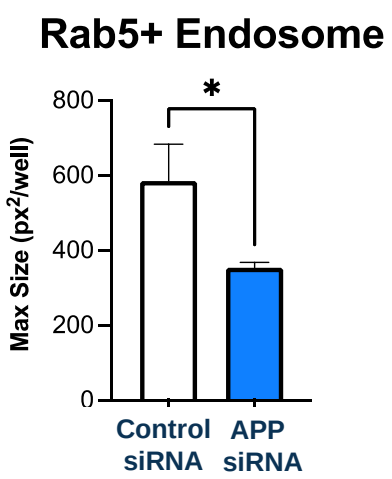
Mutations in APP and PSEN1 cause enlargement of Rab5+ Early Endosomes in human iPSC derived Neurons

Kwart et al., Neuron 2019



Phenix High Content Imaging, 63X, analysis on Harmony



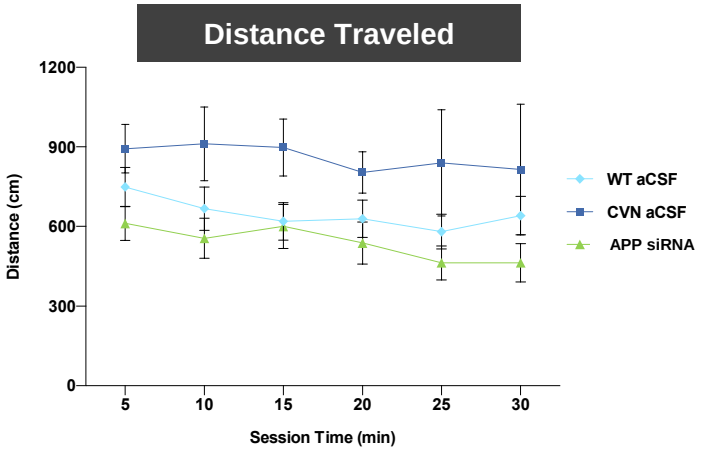


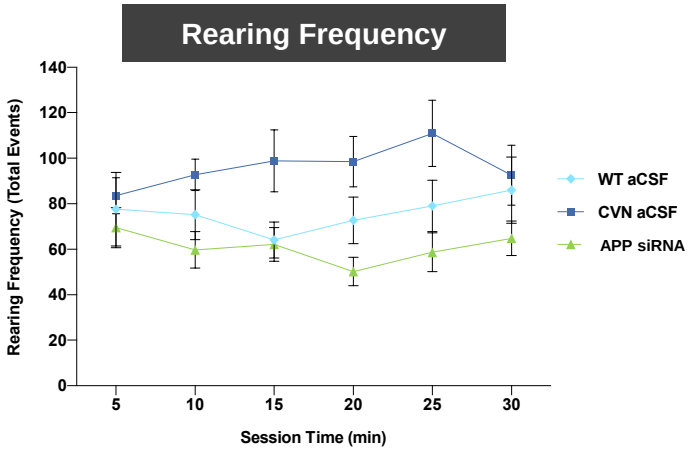
Phenotypic Improvement in CVN-AD Mice by Silencing Human APP with siRNA

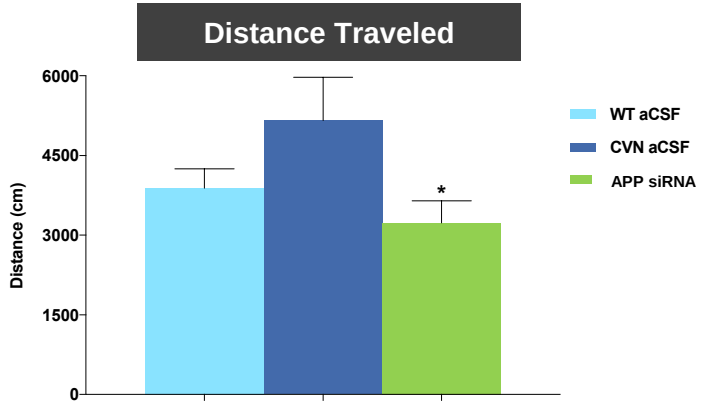
CVN-AD Mice: Transgenic mouse model of Alzheimer's Disease

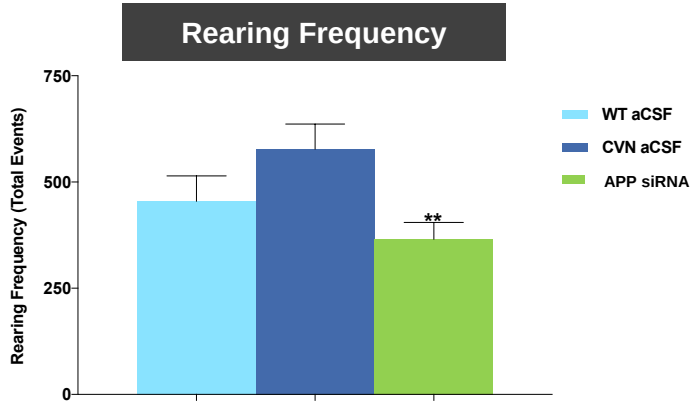
- Transgenic mice with three APP mutations associated with AD
- Disease onset occurs at 4 months of age
- Single ICV treatment with APP siRNA at 6 months
- Phenotypic observations at 9 months of age

CVN-AD mice treated with APP siRNA had reduced rearing frequency and distance traveled in open field test









ALN-APP Phase 1 Overview

CTA Filing by Year-End; Phase 1 Expected to Begin in Early 2022

Part A: Single Ascending Dose → **Part B**: Multiple Dose

- **Population**: Patients with Early Onset Alzheimer's Disease
- **Primary Objective**: Safety and tolerability of ALN-APP
- **Secondary Objective**: Pharmacology of ALN-APP
- **Exploratory Objective**: Impact of ALN-APP on disease
  - Fluid biomarkers for amyloid, tau, and neurodegeneration
  - Measures of synaptic health
  - Neuroimaging
  - Exploratory cognitive and functional clinical measures

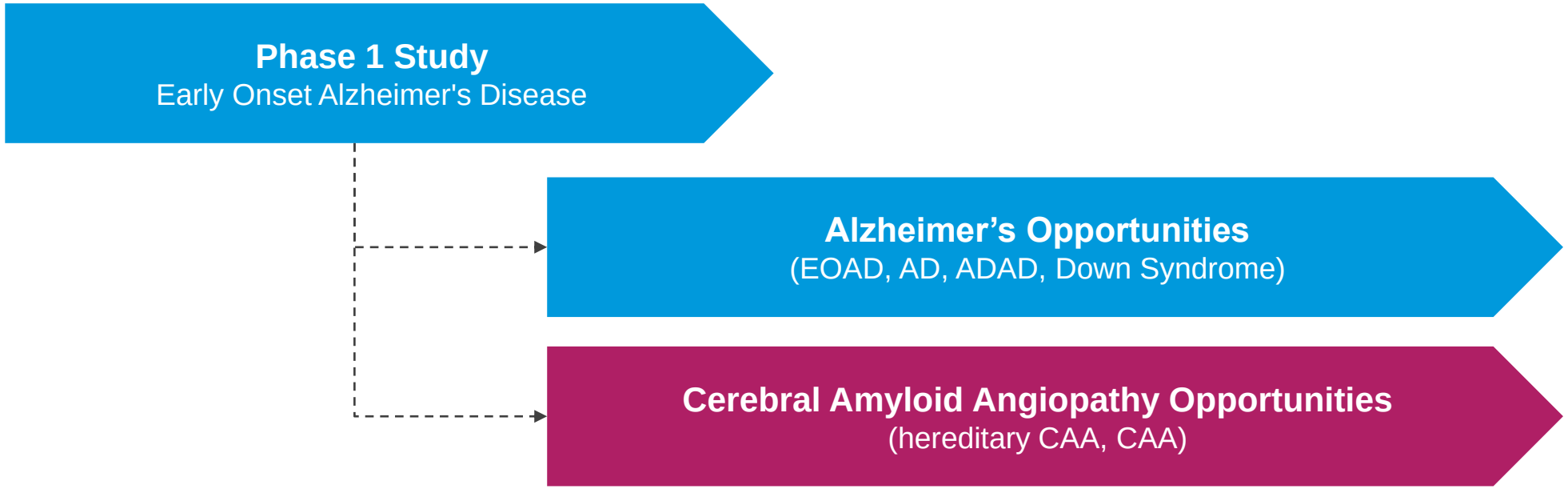
Early Onset Alzheimer's Disease

- ~5% of total Alzheimer's Disease population
- Age of onset < 65 years old
- More homogeneous population with fewer comorbidities
- Increased role of Aβ production in AD patients at earlier age

Mendes MF, Neurol Clin (2017), Patterson BW et al., Ann Neurol (2015)

Multiple Opportunities for Expansion

Phase 1 to Inform Late-Stage Development Plan



Significant opportunity for both Alzheimer's Disease and Cerebral Amyloid Angiopathy

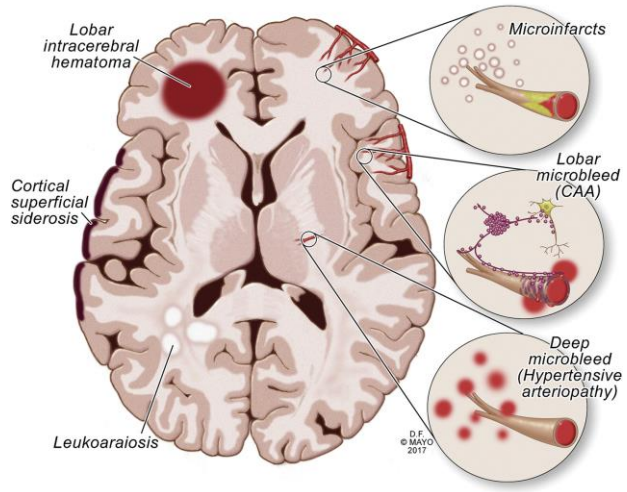
- Multiple disease area opportunities with the same target; Different disease processes, development strategies, competitive environment enable strategic options for future development

APP as a Target for Cerebral Amyloid Angiopathy (CAA)

Cerebral Amyloid Angiopathy is an Underdiagnosed Cause of Stroke and Dementia

Increasing awareness and diagnosis, but no targeted therapies

- >20% of the general elderly population have moderate-to-severe CAA pathology and higher risk of stroke and dementia
- CAA is the second most common risk factor for intracerebral hemorrhage (ICH) after hypertension
- Diagnosis increasing with increased neuroimaging
- No targeted therapies have been developed for CAA



Genetically Validated Target	✓	• Mutations that alter APP cleavage and Aβ aggregation cause hereditary CAA
Biomarker In Phase 1	✓	• Target engagement: sAPPα, sAPPβ • Disease progression: Measures of vascular reactivity (BOLD fMRI)
Definable Path to Approval	✓	• High unmet need for disease modifying therapy • Biomarkers for vascular reactivity • Orphan population with hereditary CAA

Multiple Development Opportunities

Hereditary CAA: Ultra-orphan genetically defined population found primarily in the Netherlands and Australia; onset in 40s/50s

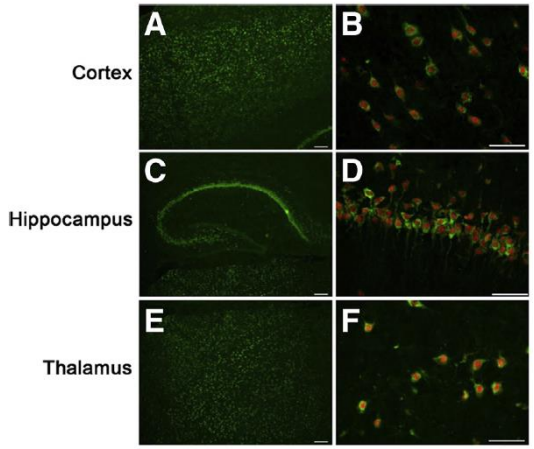
Sporadic CAA: Common cause of ICH that increases with age. Onset typically after age 60

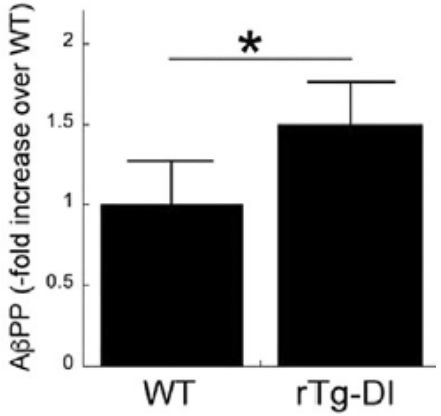
Jäkel L, et al., Alzheimer's Dement (2021); Aguilar MI, et al., Neurohospitalist (2012); Kozberg MG et al., Int J Stroke (2020).
Figure republished with permission of the American College of Cardiology from DeSimone CV, et al., J Am Coll Cardiol (2017)

Model for Cerebral Amyloid Angiopathy (CAA)

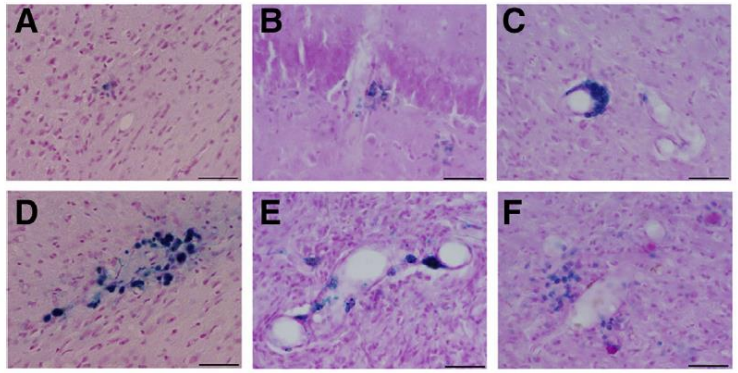
rTg-DI Rat Model – APP[1]

Human APP Expression

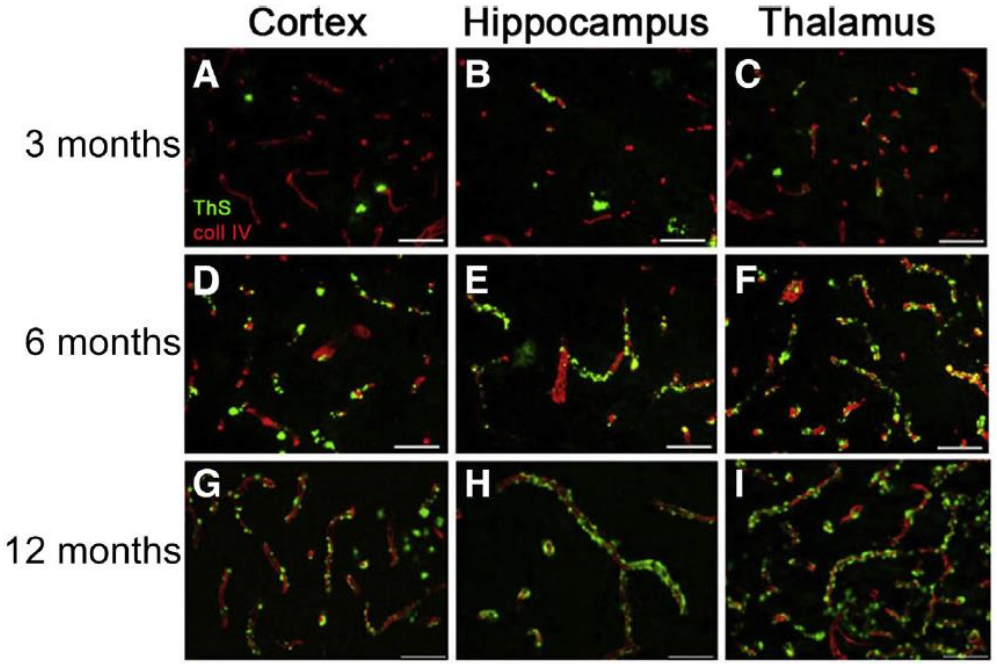




Microhemorrhages in Cortex, Hippocampus and Thalamus



Progressive Accumulation of Microvascular Amyloid[2]



Davis et al (2018) The American Journal of Pathology, Vol. 188, No. 12

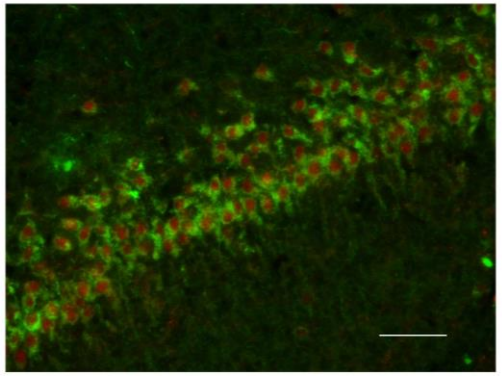
[1] Swedish K670N/M671L, Dutch E693Q, and Iowa D694N

[2] Van Nostrand lab, URI

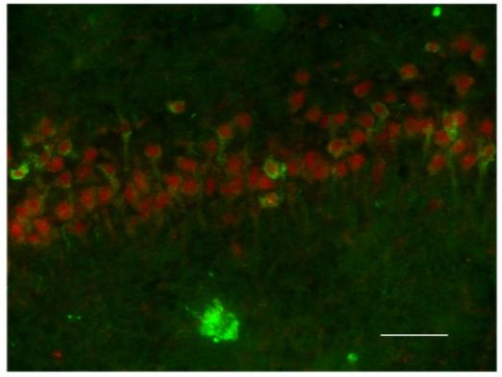
Robust Elimination of Human APP Protein in Rat hCAA Model

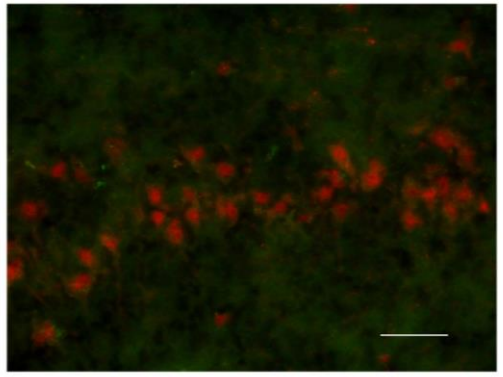
Single IT Dose of 0.9 mg in rTg-DI Rat – Day 28 in Hippocampus

ACSF-CTRL



siRNA Treatment





Detection Antibodies

- NeuN (red)
- hAPP (green)

Van Nostrand lab, URI

Potential to Make History with ALN-APP

Anticipating Many Future Firsts for Investigational RNAi Therapeutic

- ***First siRNA delivered to the human brain***
- First therapeutic **targeting *APP* mRNA**, the sole precursor of all APP cleavage products, including Aβ
- First therapeutic preventing synthesis of other potential **non-Aβ drivers of Alzheimer's Disease**: β-CTF (C99), η-CTF
- First therapeutic to comprehensively lower ***intracellular and extracellular*** amyloid proteins

Agenda

Welcome
- Joshua Brodsky – Senior Director, Investor Relations & Corporate Communications

Introduction & Extrahepatic Platform Overview
- Vasant Jadhav, Ph.D. – SVP, Research

RNAi Therapeutics for CNS Disorders
- CNS Delivery
  - Kirk Brown, Ph.D. – Senior Director, CNS Program
- CNS Pipeline
  - Bret Bostwick, M.D. – Director, Clinical Research

Advancing RNAi Therapeutics into Ocular and Lung Disorders
- Vasant Jadhav, Ph.D. – SVP, Research

Q&A Session

Over 25 Preclinical Programs in Four Tissues Feeding Pipeline

LIVER

Alnylam
- ALN-XDH
- ALN-KHK
- ALN-LEC
- ALN-CC3
- ALN-F12
- Many others

Alnylam/Regeneron
- ALN-PNP
- ALN-REGN-L2
- ALN-REGN-L4
- ALN-REGN-L5

CNS

Alnylam/Regeneron
- ALN-APP
- ALN-HTT
- ALN-REGN-C3
- ALN-REGN-C4
- ALN-REGN-C5
- ALN-REGN-C6
- ALN-REGN-C7
- ALN-REGN-C8
- ALN-REGN-C9

EYE

Alnylam
- ALN-TTRoc

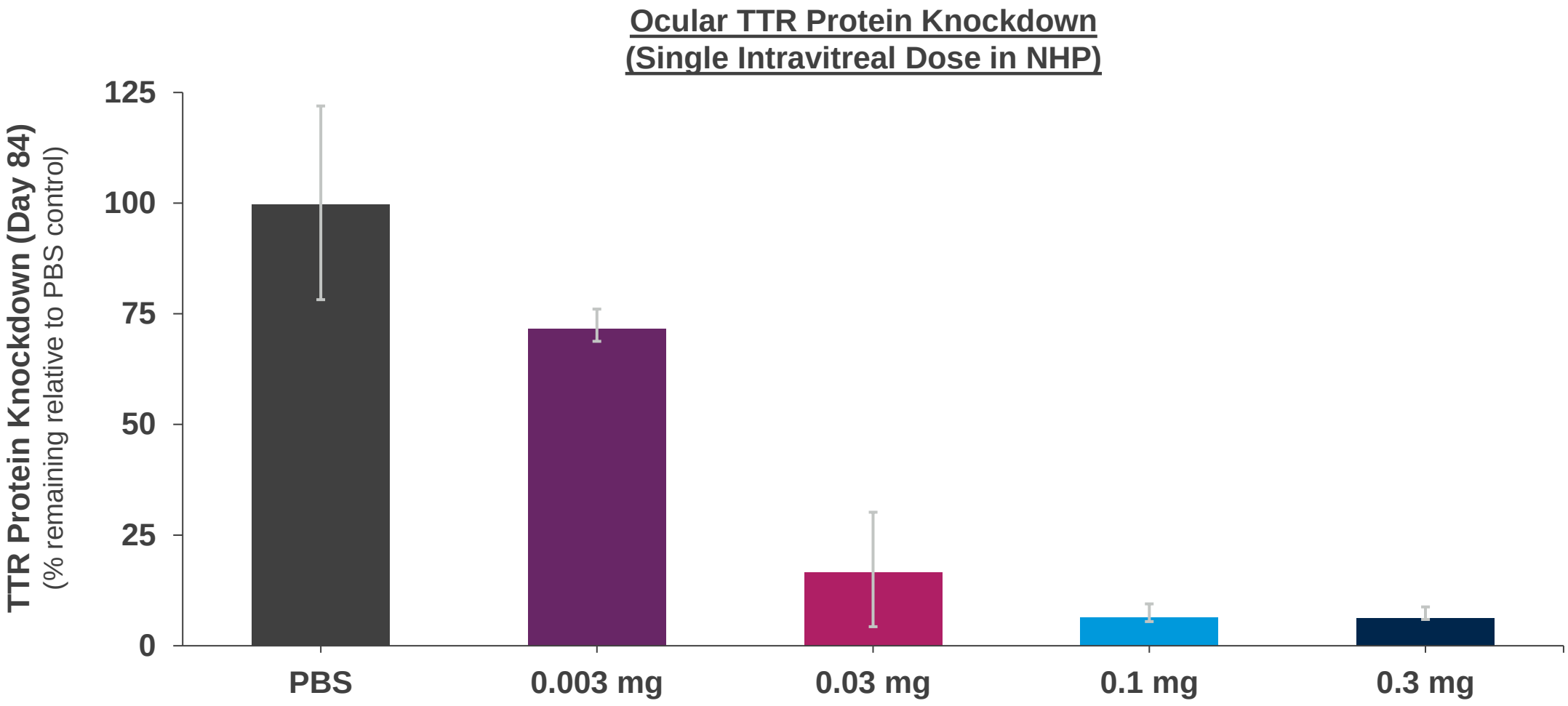
Alnylam/Regeneron
- ALN-REGN-E1
- ALN-REGN-E2
- ALN-REGN-E3
- ALN-REGN-E4

LUNG

Alnylam/Vir
- ALN-VIR2 (ACE2)
- ALN-VIR3 (TMPRSS2)

Ocular Program Update

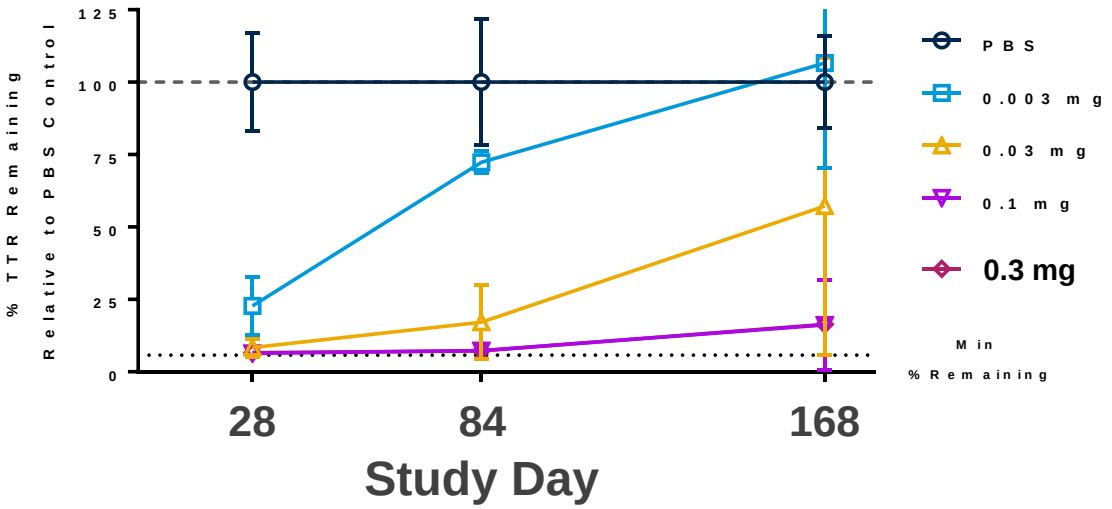
NHP Potency with Potential for Infrequent Dosing with Low ug Doses per Eye



Potent, Dose Dependent, Durable Activity After Single IVT Dosing in NHP Eye

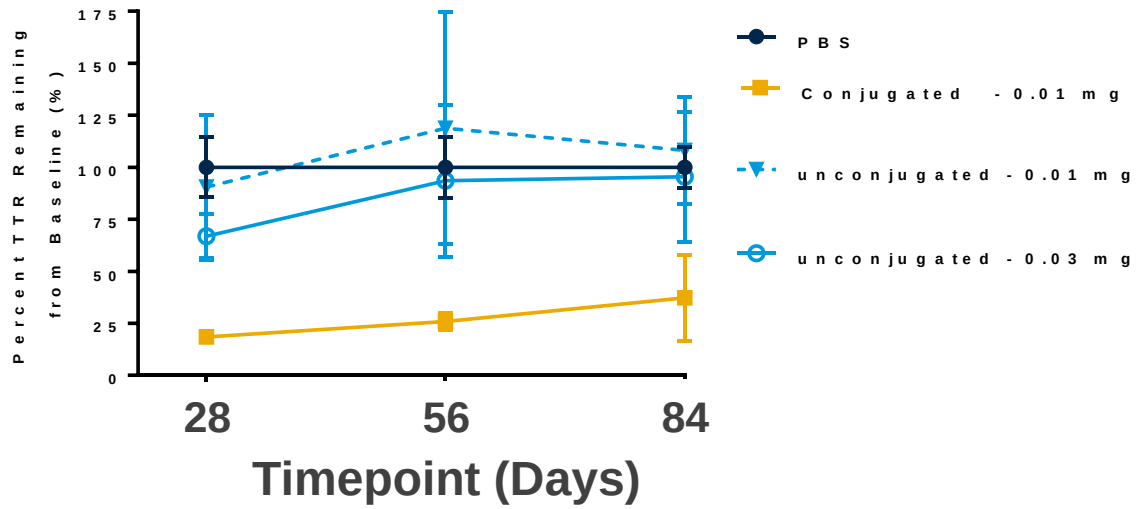
Durability Data Support q6M Dose Regimens

TTR Protein in Aqueous Humor



- Dose-dependent efficacy and duration up to 0.003 mg
- Persistent low siRNA levels in aqueous humor in line with observed duration

Conjugated vs. Unconjugated



- Unconjugated siRNA showed reduced potency; also reflected in reduced exposure in vitreous (~10-fold lower)

Over 25 Preclinical Programs in Four Tissues Feeding Pipeline

LIVER

Alnylam
- ALN-XDH
- ALN-KHK
- ALN-LEC
- ALN-CC3
- ALN-F12
- Many others

Alnylam/Regeneron
- ALN-PNP
- ALN-REGN-L2
- ALN-REGN-L4
- ALN-REGN-L5

CNS

Alnylam/Regeneron
- ALN-APP
- ALN-HTT
- ALN-REGN-C3
- ALN-REGN-C4
- ALN-REGN-C5
- ALN-REGN-C6
- ALN-REGN-C7
- ALN-REGN-C8
- ALN-REGN-C9

EYE

Alnylam
- ALN-TTRoc

Alnylam/Regeneron
- ALN-REGN-E1
- ALN-REGN-E2
- ALN-REGN-E3
- ALN-REGN-E4

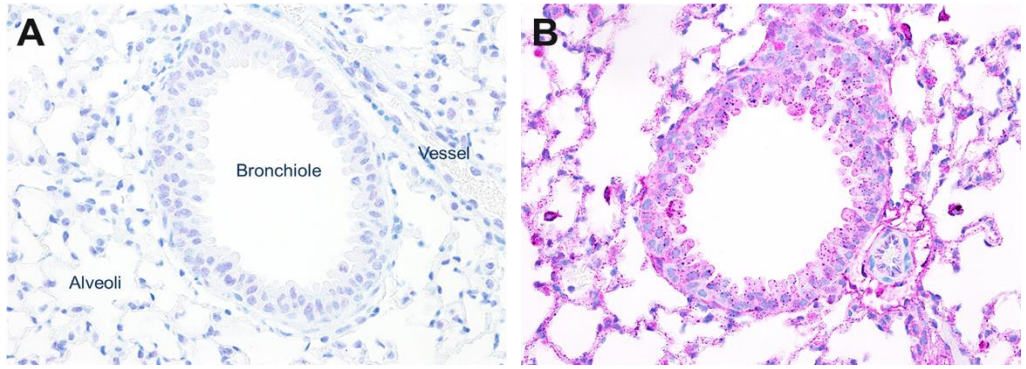
LUNG

Alnylam/Vir
- ALN-VIR2 (ACE2)
- ALN-VIR3 (TMPRSS2)

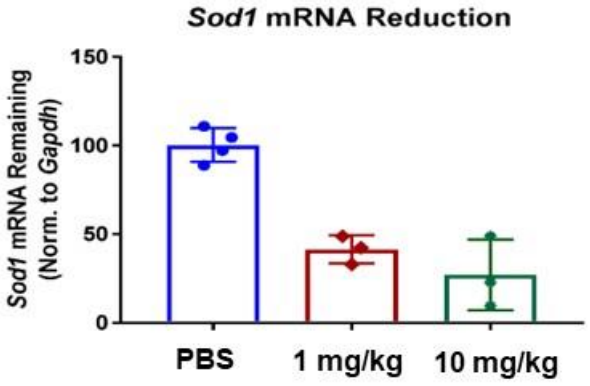
Chemistry Advances Enable Robust Tissue Distribution with Potent and Durable Gene Knockdown in Lung

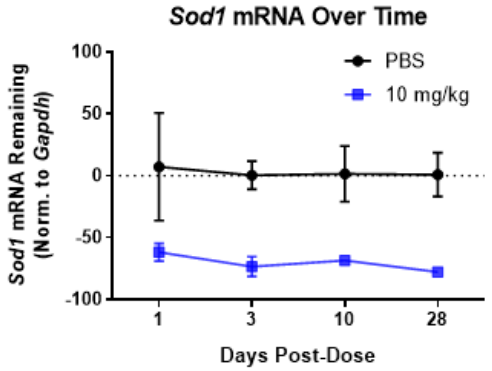
Surrogate siRNA Targeting Endogenous Target (Sod1) and Ectopic Target (ACE2)

Sod1 siRNA Distribution in the Mouse Lung Measured by IHC

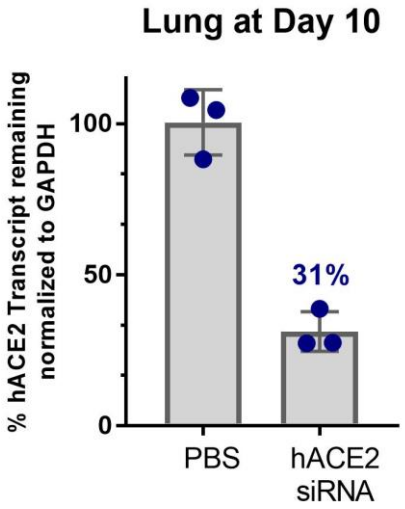


(**A**) PBS-treated animal on Day 10 post dose. (**B**) 10 mg/kg *Sod1* siRNA on Day 10 post dose. siRNA is magenta. Blue is hematoxylin counterstain.





hACE2 mRNA Reduction in Lung Following a Single 10mg/kg Dose



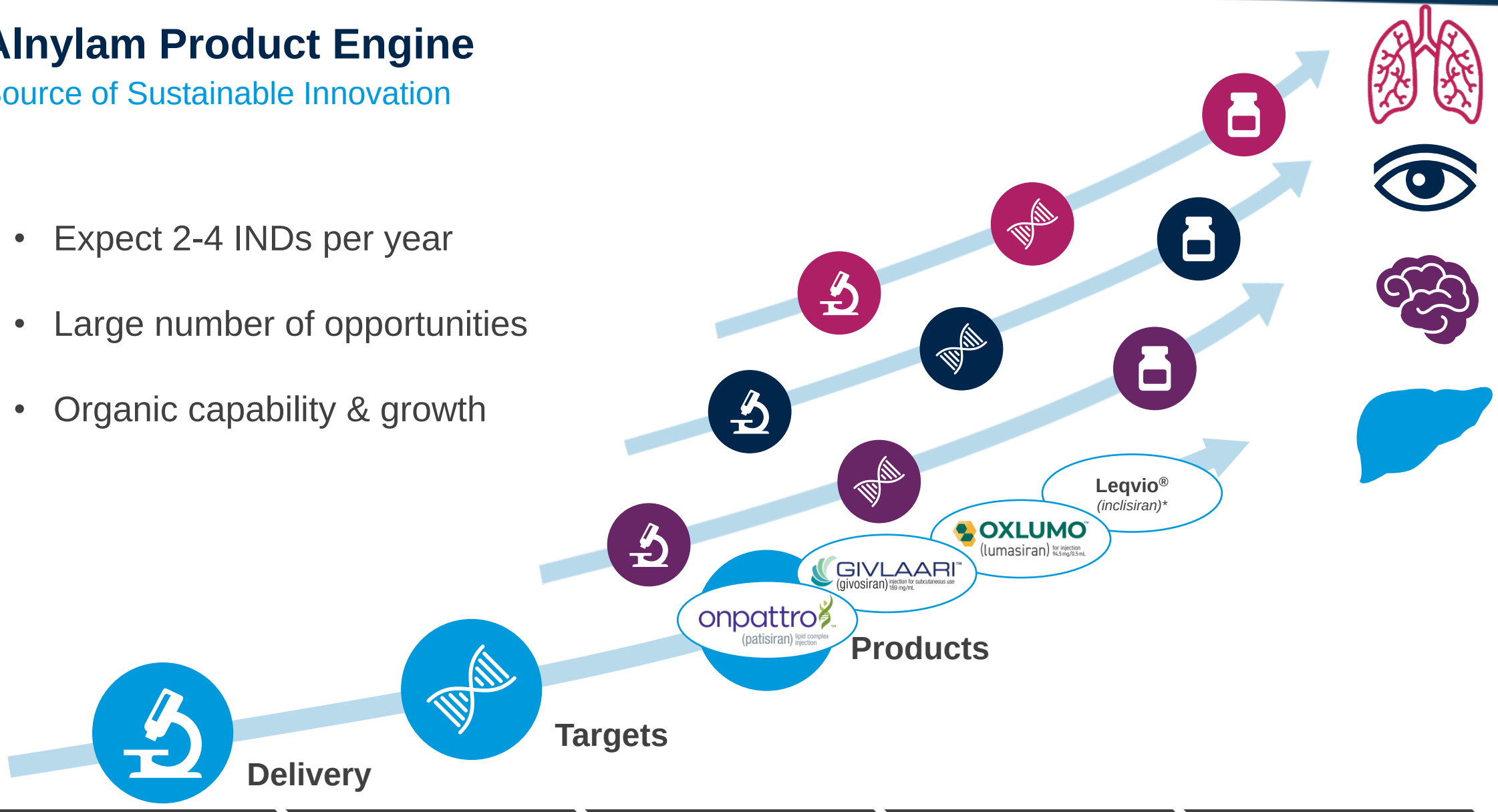
Lung Targets from Human Genetics

Gene	Indication	Human Genetics Support	Location and Cell Type
Target 1	Asthma	✓	Epithelium
Target 2	Asthma	✓	Epithelium
Target 3	Idiopathic pulmonary fibrosis	✓	Epithelium
Target 4	Nasal polyps	✓	Epithelium, immune cells
Target 5	COPD	Preliminary	Epithelium

Alnylam Product Engine

Source of Sustainable Innovation

- Expect 2-4 INDs per year
- Large number of opportunities
- Organic capability & growth



* Novartis has obtained global rights to develop, manufacture and commercialize inclisiran under a license and collaboration agreement with Alnylam Pharmaceuticals, a leader in RNAi therapeutics

Summary

- Platform advances leveraging conjugate-based approach extends delivery beyond liver
- RNAi therapeutics well-suited to address CNS disorders with high unmet need
  - ALN-APP presents opportunities in Alzheimer's Disease and Cerebral Amyloid Angiopathy, with potential for differentiated profile; initial CTA submission expected by YE'21
- Organic product engine to deliver long-term, sustainable innovation across multiple disease areas and organs
  - Ocular and lung disorders provide new frontier for RNAi therapeutics

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2021 RNAi Roundtables

Zilebesiran, in Development for the Treatment of Hypertension

Patisiran and Vutrisiran, in Development for the Treatment of ATTR Amyloidosis

Givosiran, for the Treatment of Acute Hepatic Porphyria

Lumasiran, for the Treatment of Primary Hyperoxaluria Type 1

Liver-Directed RNAi Pipeline Programs

CNS & Extrahepatic RNAi Pipeline Programs

Slides and transcripts from 2021 RNAi Roundtables can be found on the Capella section of the Company's website, www.alnylam.com/capella

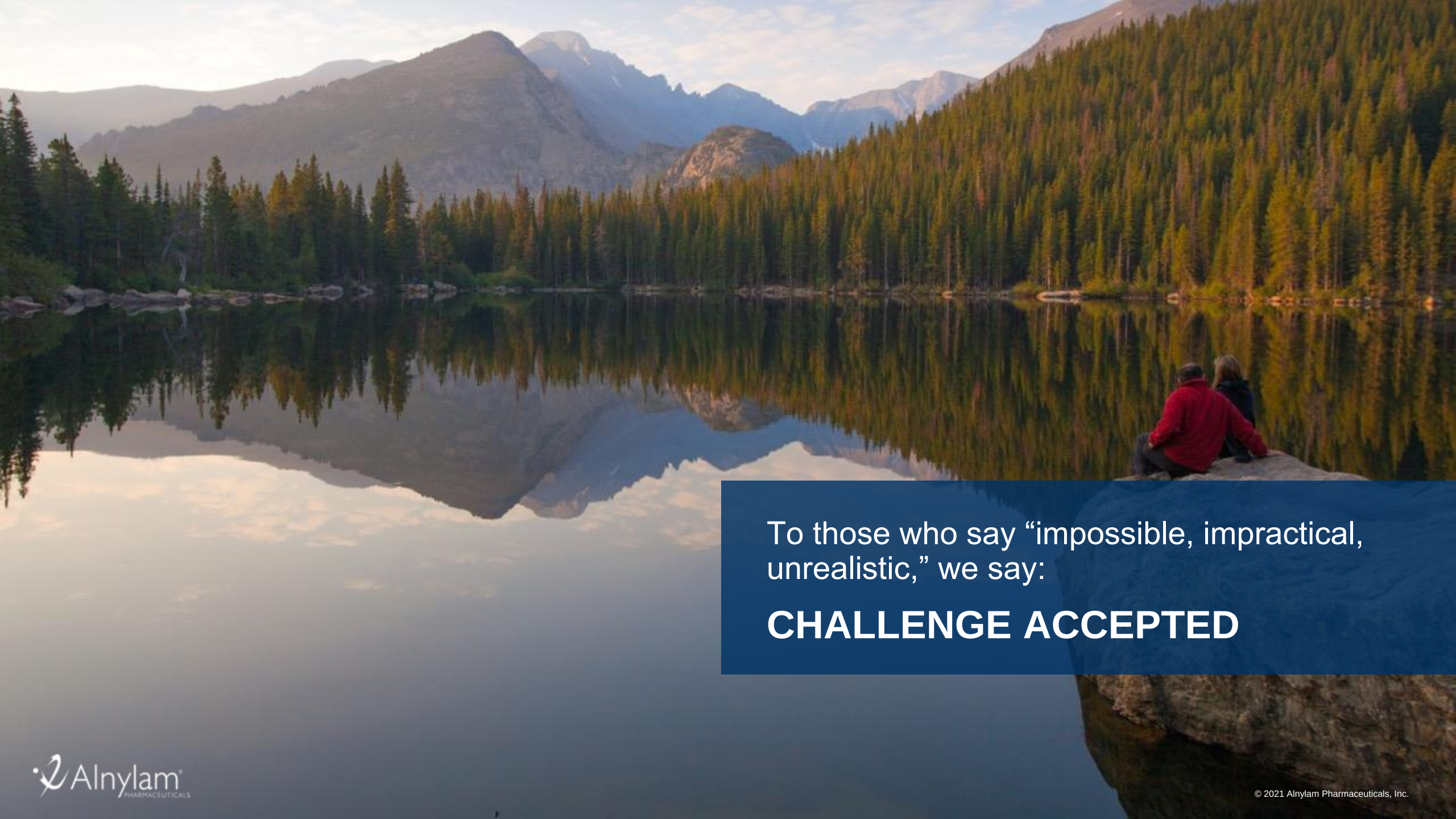
Save the date!

Alnylam® R&D Day

November 19, 2021

A VIRTUAL EVENT

Registration information coming soon.



Alnylam PHARMACEUTICALS