Oligonucleotides: important therapeutic agents

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Conflict of Interest

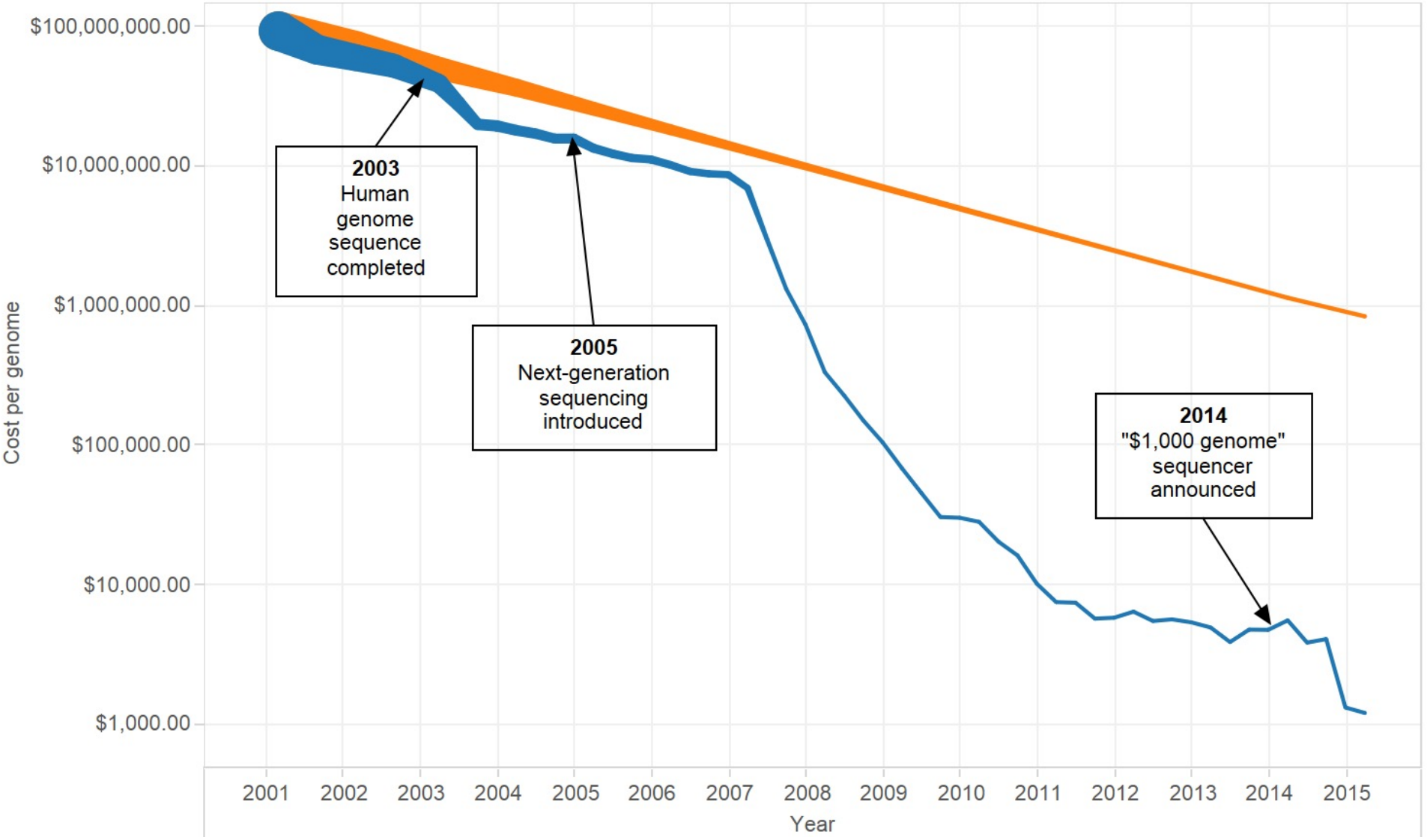
Alnylam Pharmaceuticals—co-Founder, Stock holder, Member of Board of Directors, and Chair of Scientific Advisory Board

Biotechnology—new therapeutic modalities

1980–1990	Interferons, protein hormones
1990–2000	Monoclonal antibodies
2000–2010	Oligonucleotides, siRNA
2010–2020	CRISPR, cell therapy

Gene Therapy (1980–2020)

DNA sequencing costs over time



Information science for medical care- Kendall Square

Courtesy of MIT Tech Review

Human genetic- disease genes

1. ~3,000 Mendelian disease genes known

2. ~8% of live births- genetic disorder by early adulthood

3. Estimated- each child with genetic disorder ~costs $5,000,000

4. Diagnostic rate of genetic disorders:
   children ~11%, adults ~34%

Chong et al. (2015) Am. J. Hum. Gent. 97, 1999.

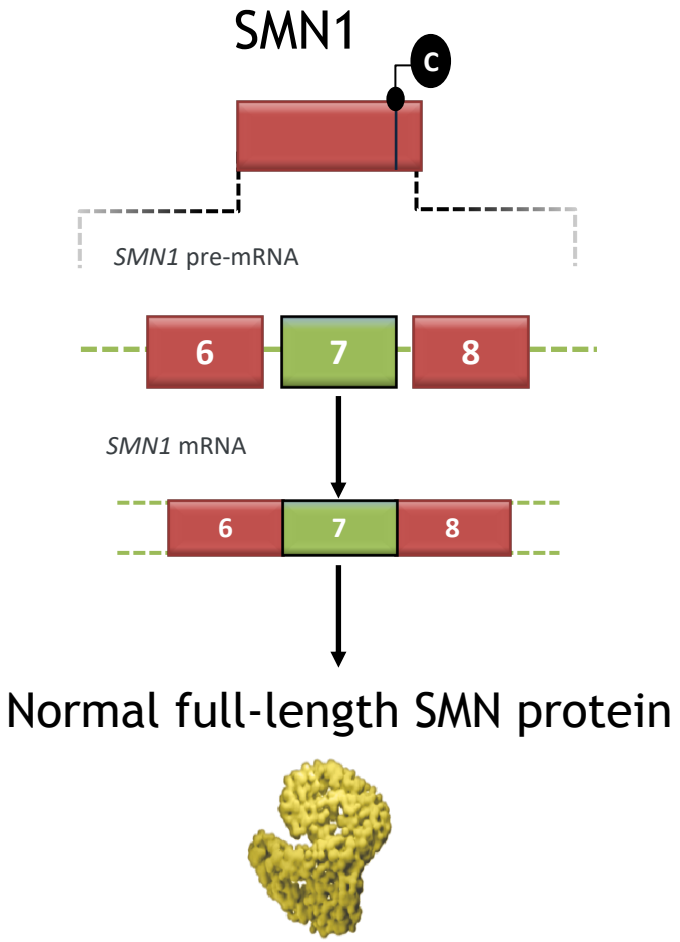
Recent advances in Spinal Muscular Atrophy (SMA)

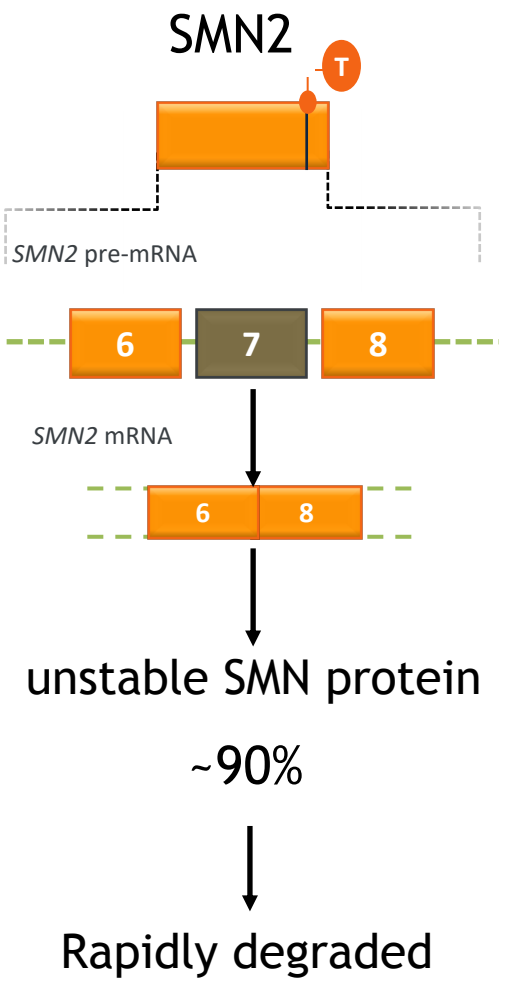
Emma walks!

Harbor Transcript
Vol. 36, Issue 2, 2016
Cold Spring Harbor

Summary of the genetics of SMA

- SMN1 gene- survival motor neuron
- SMA patients- mutation in SMN1 gene
- SMN2 gene or genes- poorly expressed
  - Defect in RNA splicing





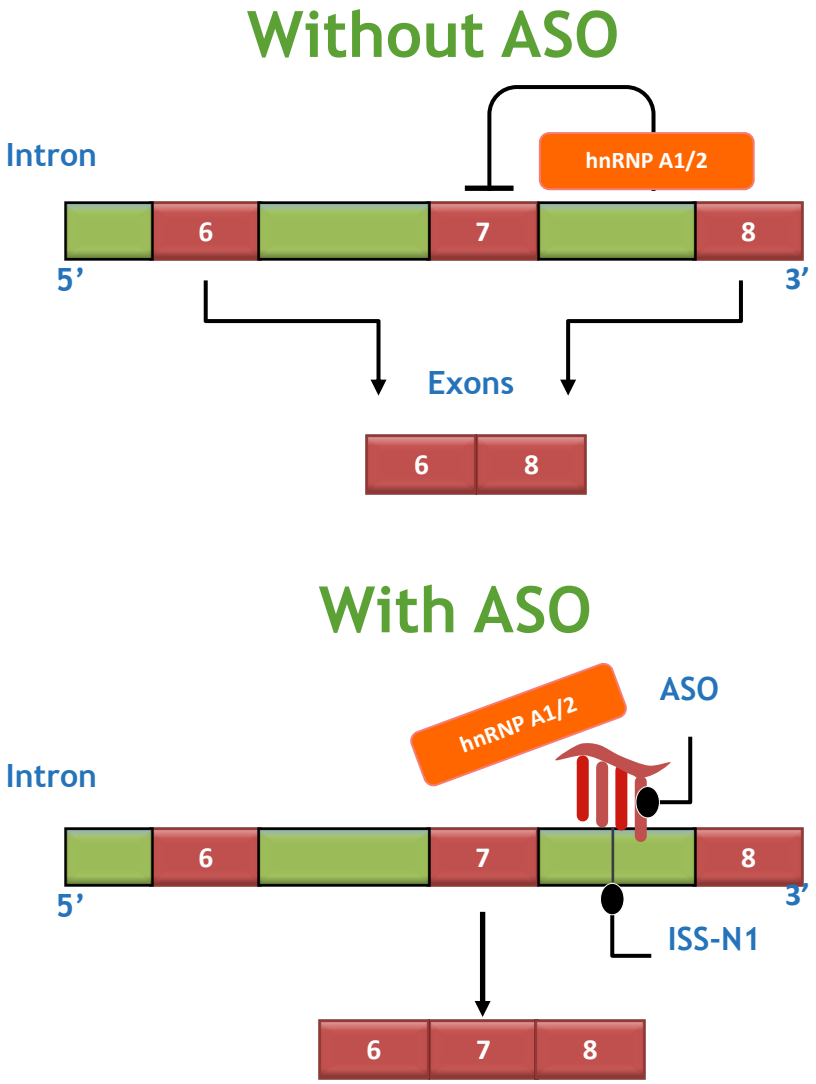
C, centromeric; gDNA, genomic deoxyribonucleic acid; mRNA, messenger RNA; pre-mRNA, precursor messenger RNA; SMA, spinal muscular atrophy; SMN, survival motor neuron; T, telomeric. 1. d'Ydewalle C & Sumner CJ. Neurotherapeutics. 2015;12:303-316; 2. Prior TW & Russman BS. GeneReviews®. http://www.ncbi.nlm.nih.gov/books/NBK1352/. Accessed Mar 2016; 3. Lunn MR & Wang CH. Lancet. 2008;371:2120-2133

Released May 2016

ASOs can modify splicing of SMN2

- Antisense Oligonucleotide (ASO) to intron 7- inclusion of exon 7

- Inclusion of exon7- functional SMN protein



ASO, antisense oligonucleotide; hnRNP, heterogeneous nuclear ribonucleoprotein; ISS-N1, intronic splicing silencer N1; mRNA, messenger RNA; SMN, survival motor neuron. Rigo F, et al. J Cell Biol. 2012;199:21-25

Development of (the anti-sense oligonucleotide) Spinraza for treatment of SMA

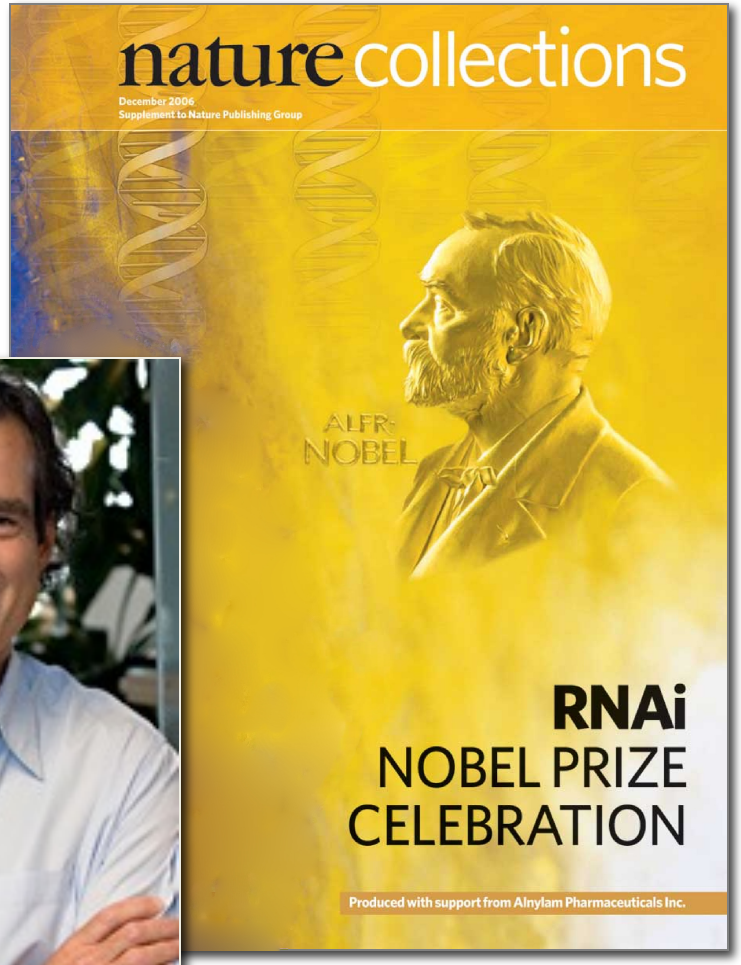
1. Adrian Krainer (CSHL) collaborated with Frank Bennett of Ionis (2008)

2. Ionis Pharmaceutical developed the anti-sense oligonucleotide, founded by Stanley Crooke in 1989

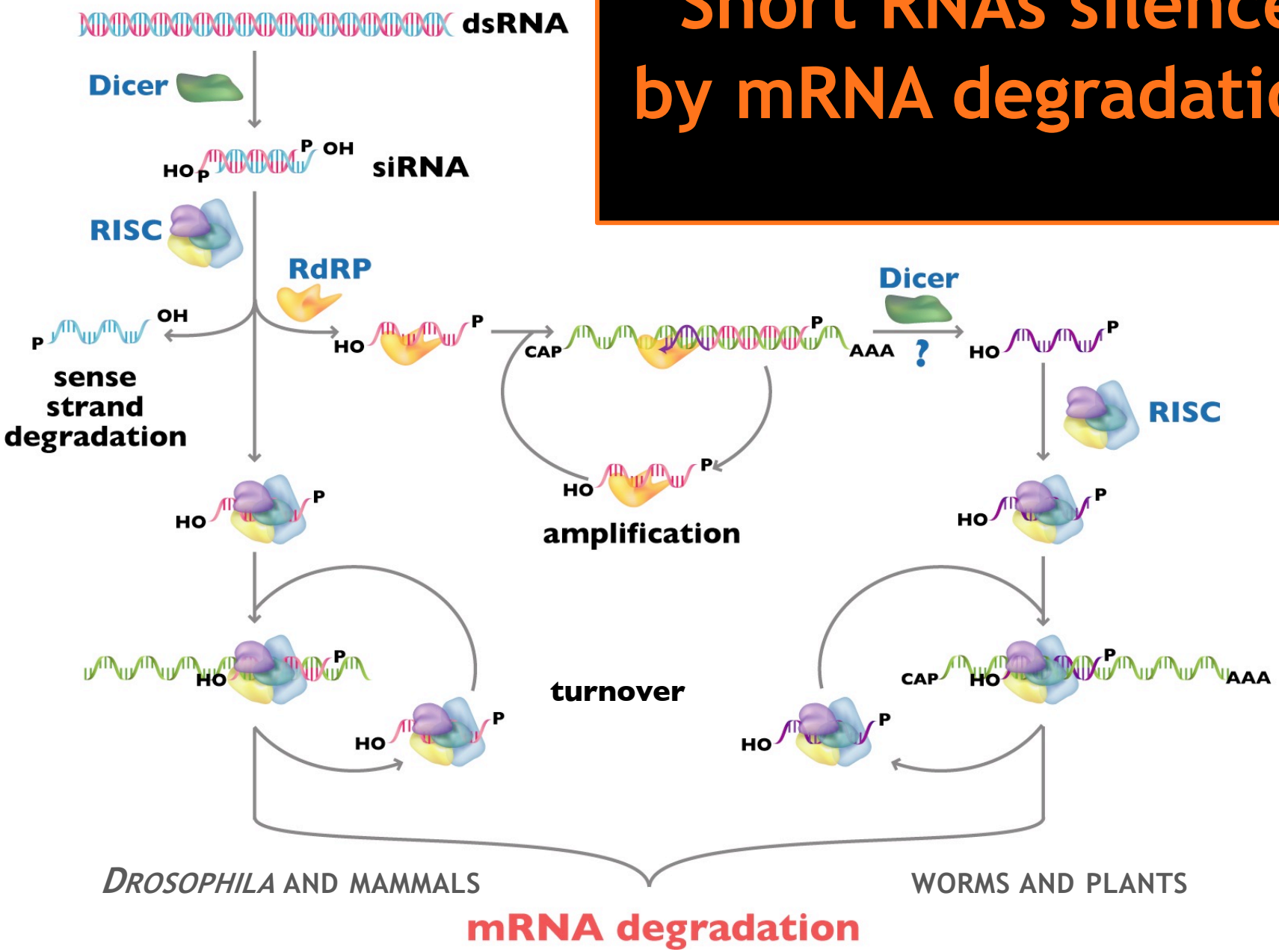
3. Biogen licensed technology (2012) clinical trials (FDA approved 2016)

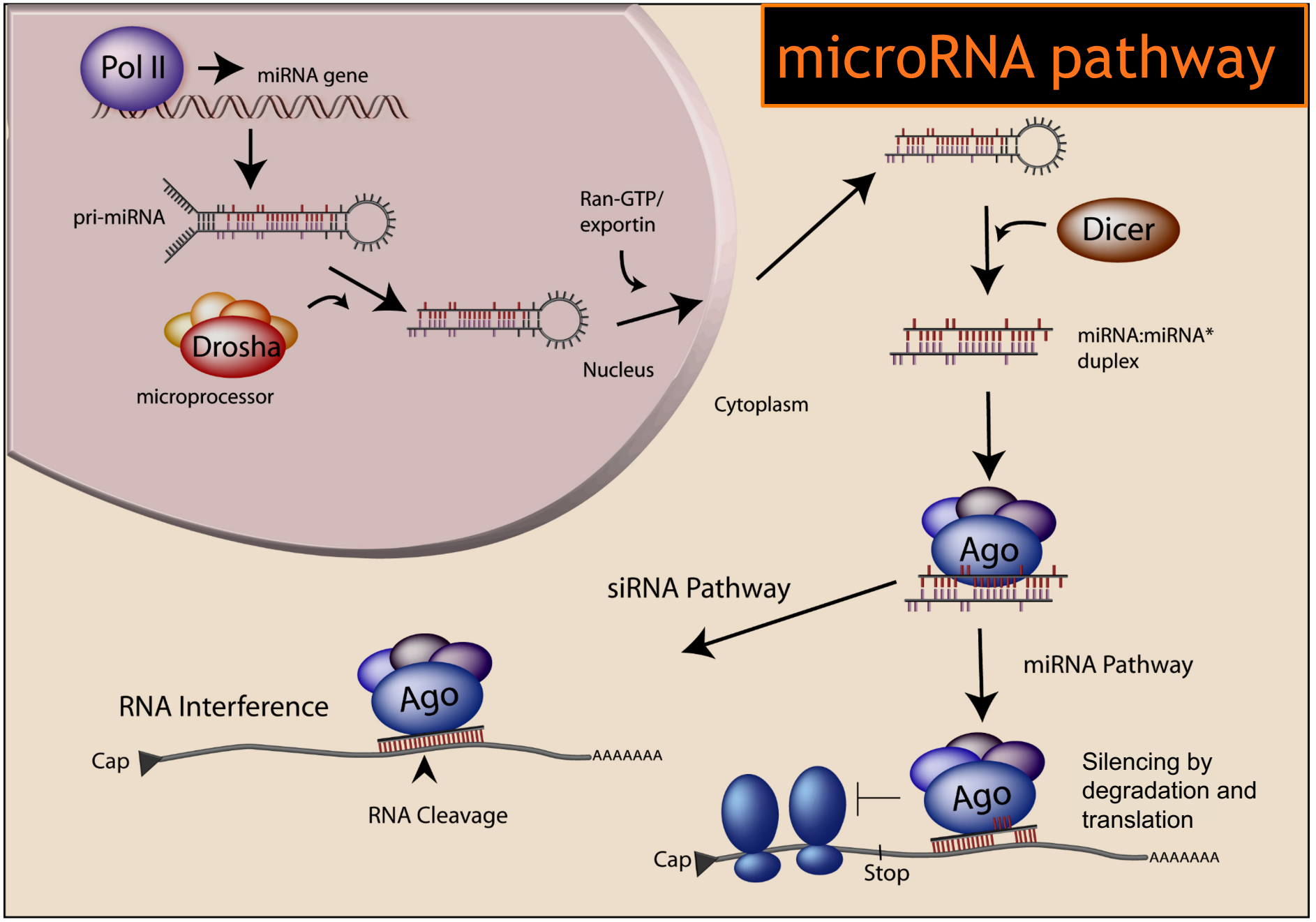
Celebrating the Nobel Prize for RNAi

Drs. Andrew Fire and Craig Mello



Short RNAs silence by mRNA degradation




microRNA pathway
Pol II
miRNA gene
pri-miRNA
Drosha
microprocessor
Ran-GTP/
exportin
Nucleus
Cytoplasm
Dicer
miRNA:miRNA*
duplex
Ago
siRNA Pathway
miRNA Pathway
RNA Interference
Ago
Cap
AAAAAAA
RNA Cleavage
Ago
Cap
Stop
AAAAAAA
Silencing by
degradation and
translation

Investigational RNAi Therapeutics
A New Class of Innovative Medicines

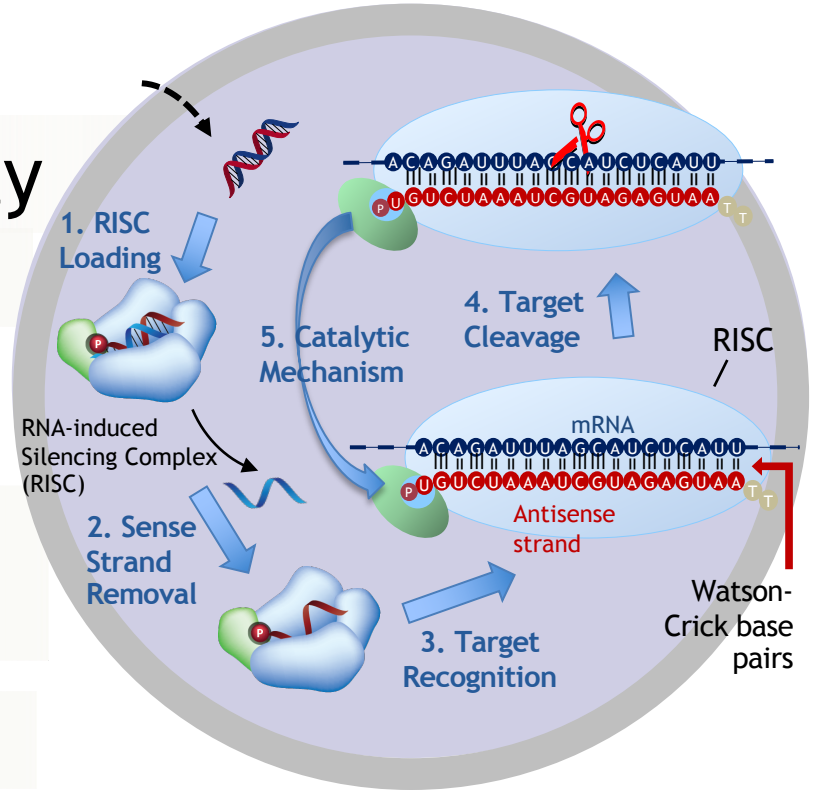
Harness natural pathway

Catalytic mechanism

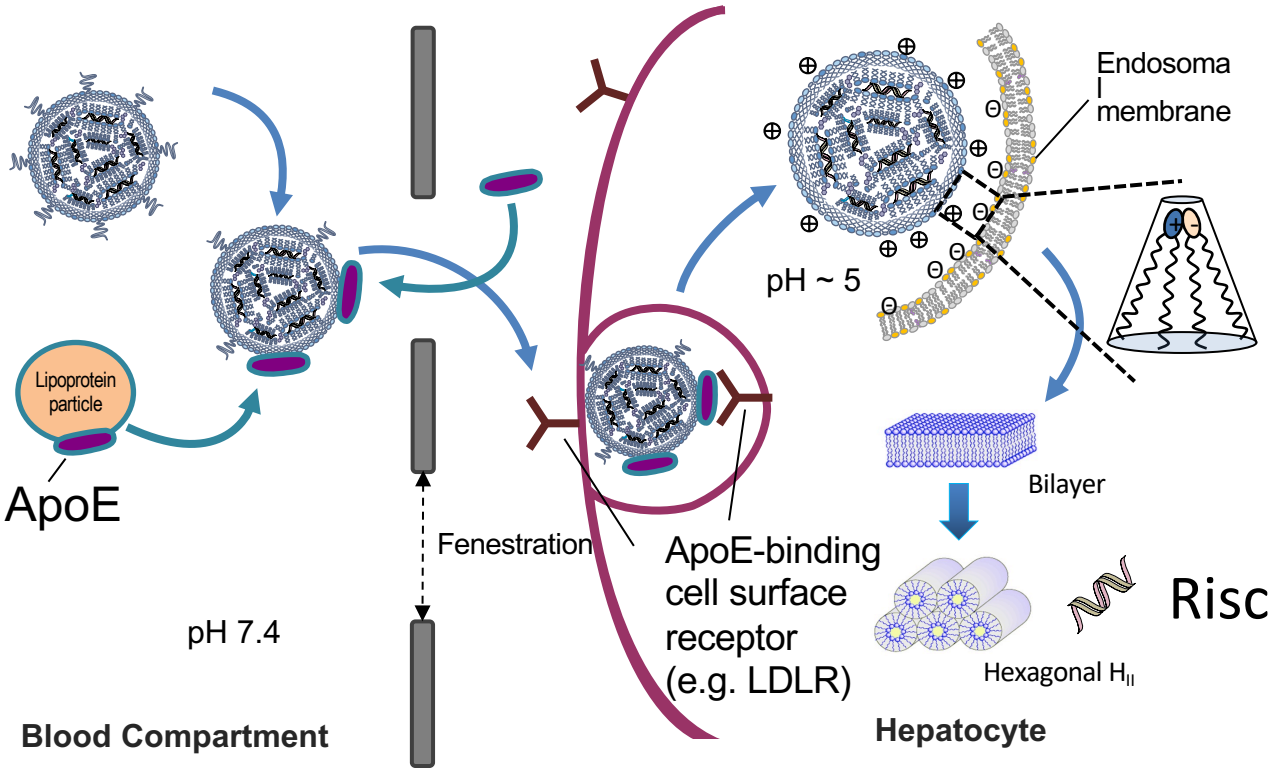
Silence any gene in genome

Upstream of today's medicines

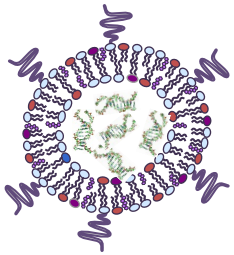
Clinically proven approach

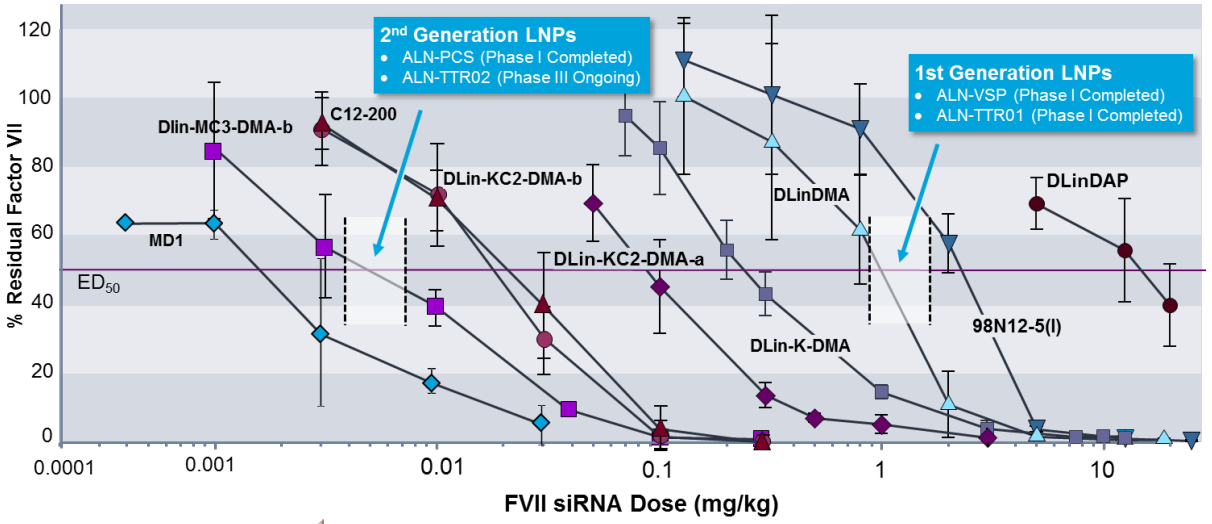


Proposed mechanism of iLNP-mediated siRNA delivery



Innovating LNP Delivery: Highlights 2006-2013





>100 fold potency improvement

MC3/Patisiran ← 500X less drug needed/TI increased

TTR02 PCS02 TTR01 VSP

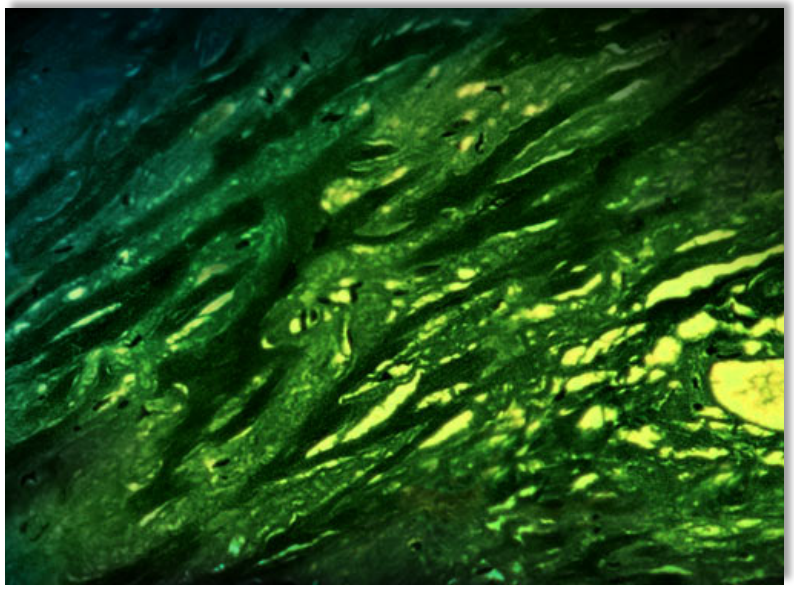
2011 2006

Alnylam data on file

Transthyretin (TTR)-mediated amyloidosis (ATTR) program

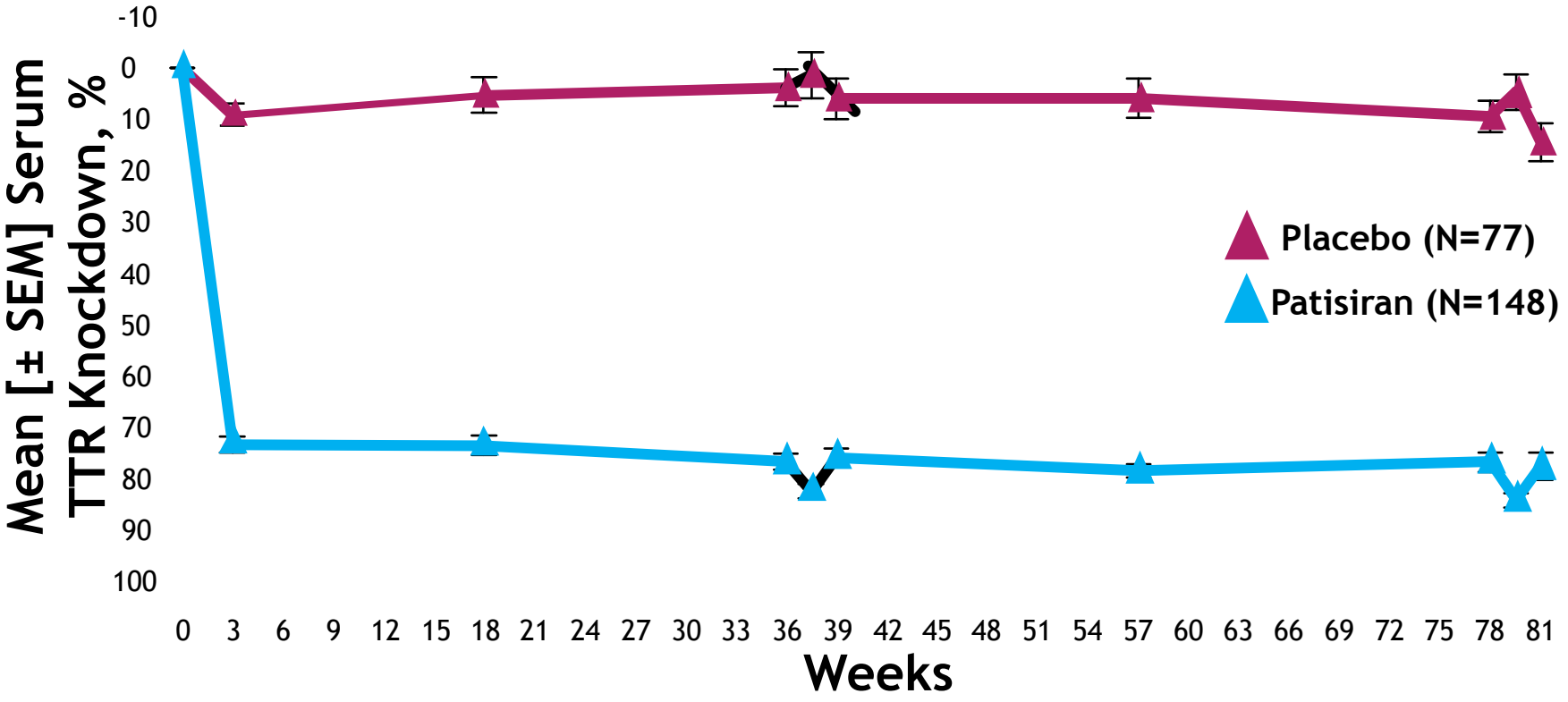
Unmet Need and Product Opportunity

- ATTR is significant orphan disease
  - ~50,000 Patients worldwide
- Clinical pathology
  - Onset ~40 to >60 yr
  - Peripheral sensorimotor neuropathy, autonomic neuropathy, and/or cardiomyopathy
  - Fatal within 5-15 years

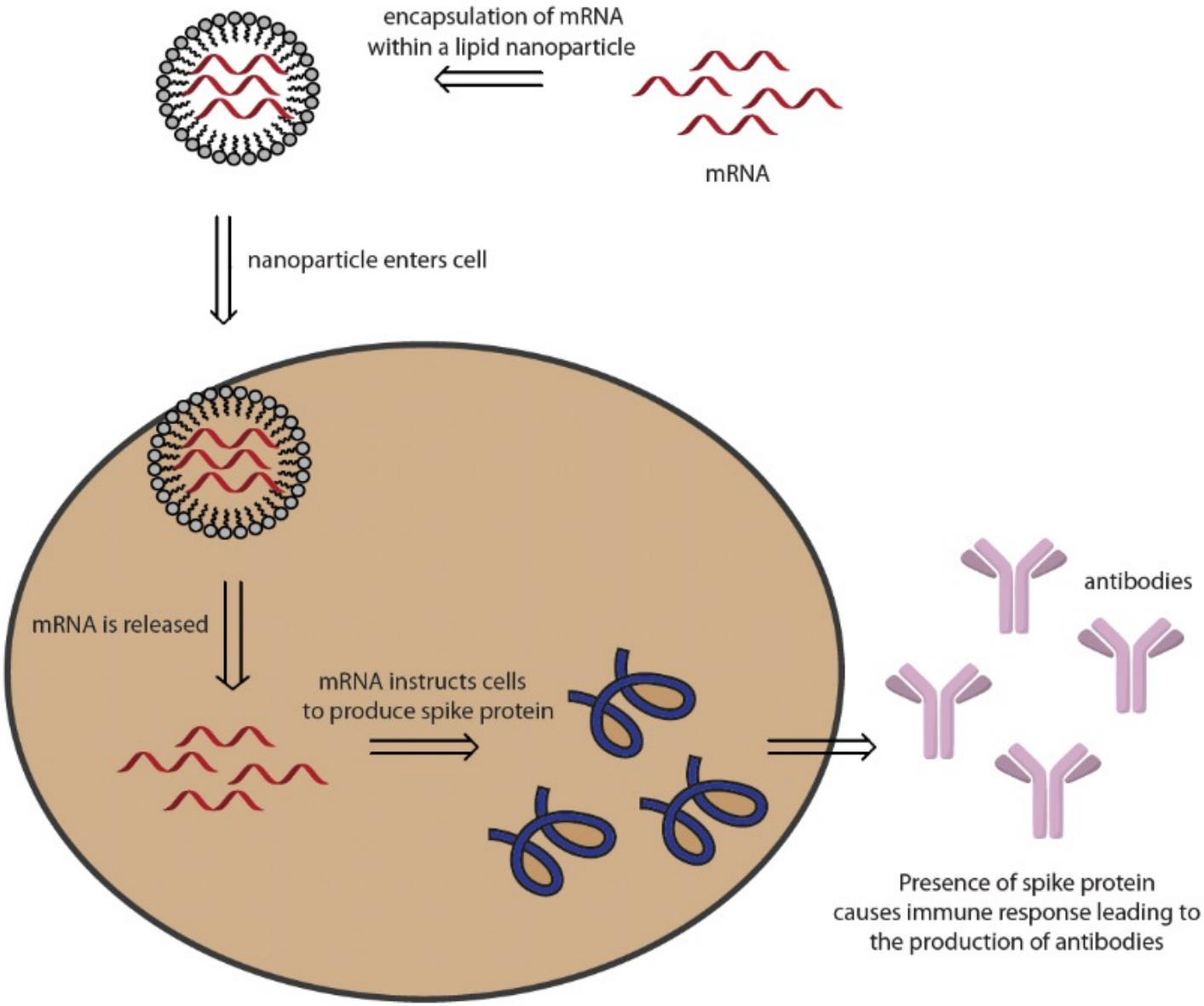


Patisiran Phase 3 APOLLO Study Results
Serum TTR Reduction

87.8% mean max serum TTR reduction from baseline for patisiran over 18 months



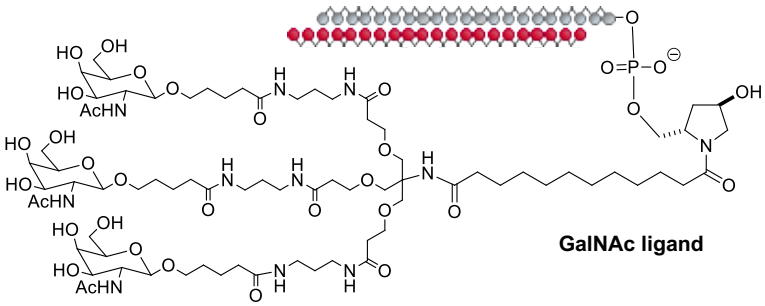
Lipid nanoparticle delivery of mRNA

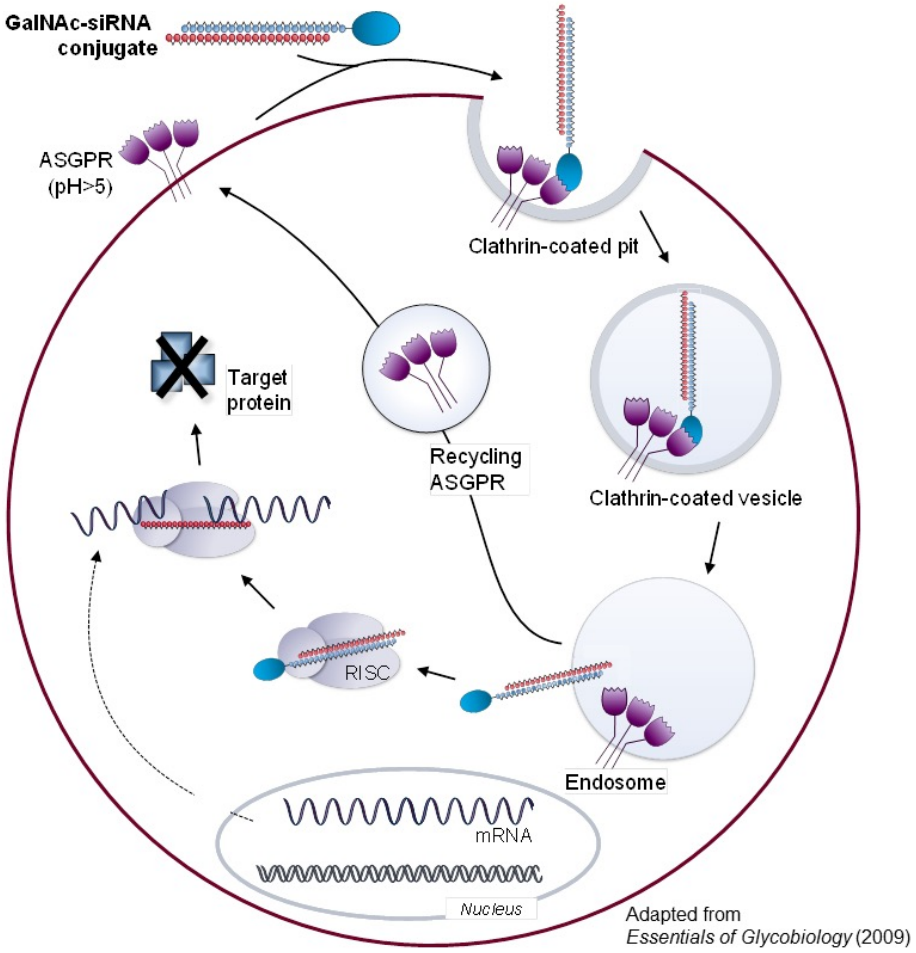


Tissue and Cellular Uptake

Targeting the liver: ASGPR and GalNAc

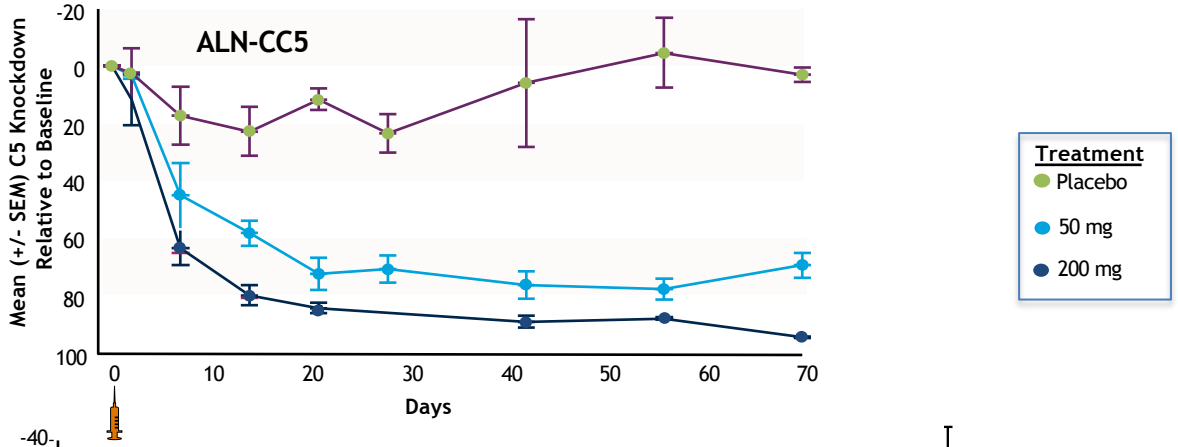
- GalNAc-siRNA Conjugate
  - GalNAc ligand conjugated to chemically modified siRNA to mediate targeted delivery
  - Trivalent GalNAc carbohydrate cluster has nM affinity for ASGPR
  - Administered subcutaneously (SC)



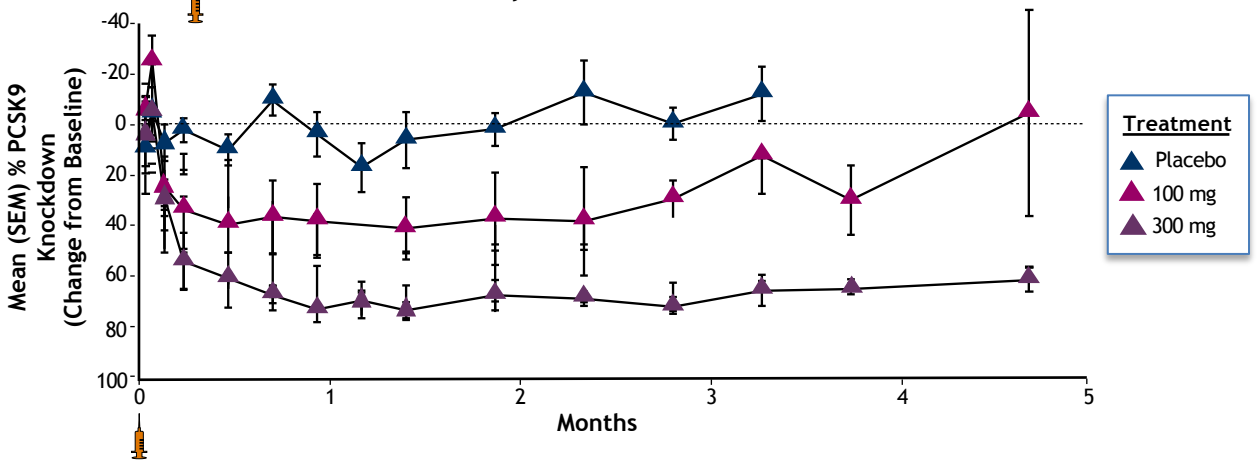


Potent and Durable Silencing Supports Quarterly Dosing in Humans

ALN-CC5



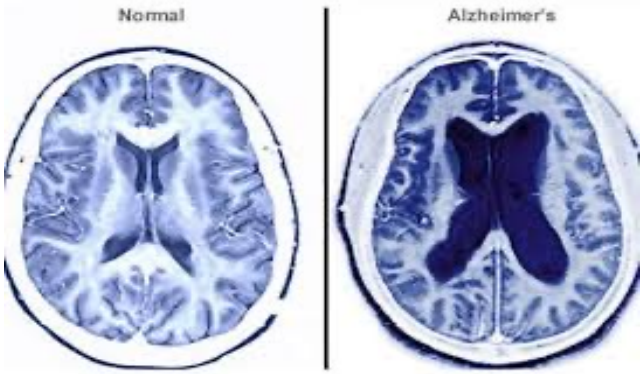
ALN-PCS



RNAi Therapeutics for CNS Diseases

No current therapies to prevent or reverse neurodegenerative disease

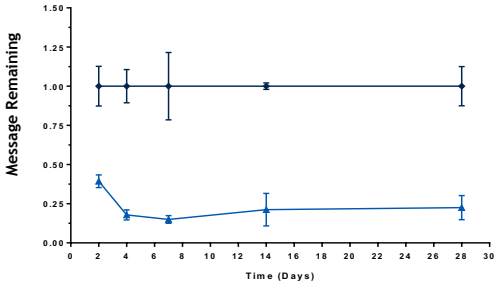
- Dominantly inherited neurodegeneration
  - Alzheimer's disease
  - Parkinson's disease
  - Frontotemporal dementia
  - Huntington's disease
  - Amyotrophic lateral sclerosis (ALS)
  - Spinocerebellar ataxia
  - Many others



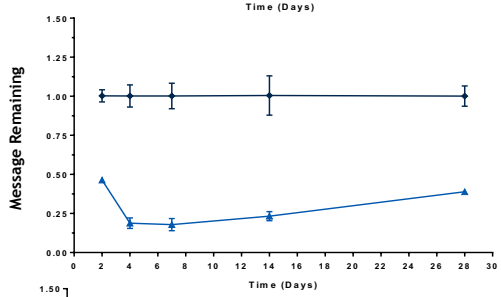
IT Dosing of SOD1 siRNA Conjugate to Evaluate CNS RNAi activity

Spinal cord regions

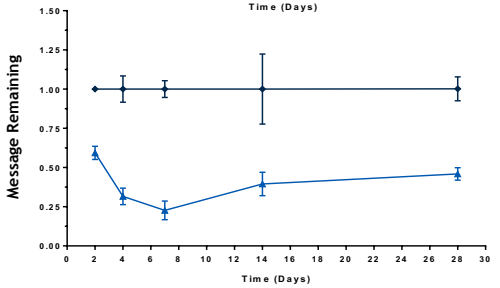
Lumbar

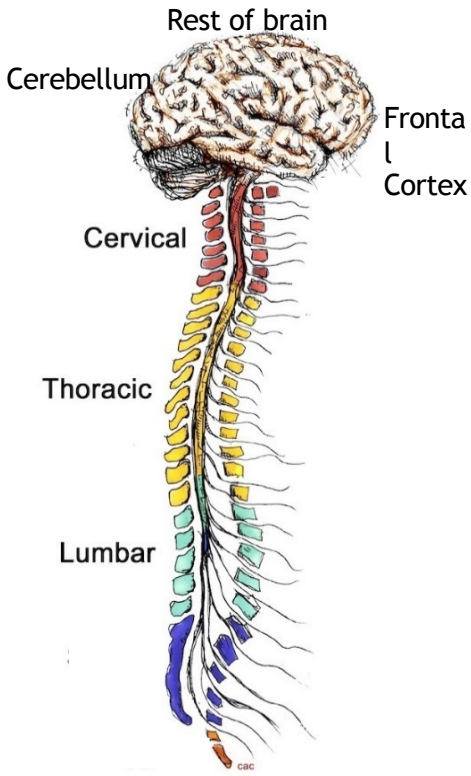


Thoracic

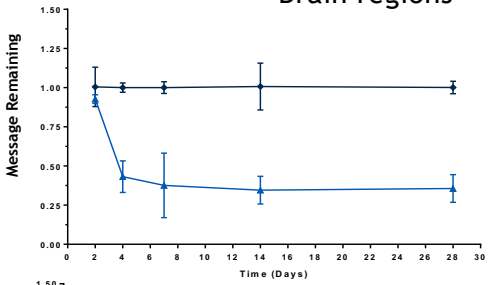


Cervical

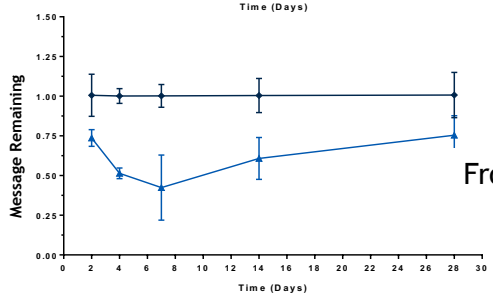




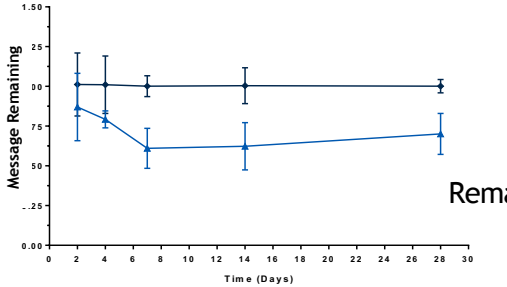
Brain regions



Cerebellum



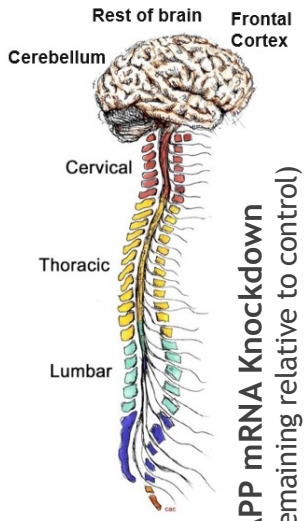
Frontal Cortex

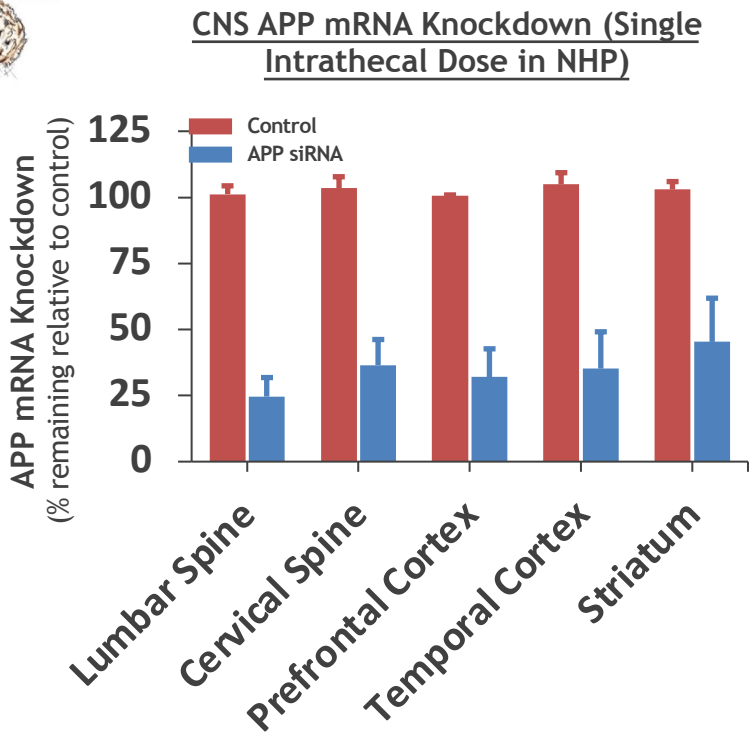


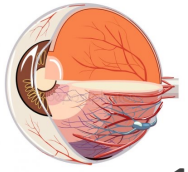
Remaining Brain

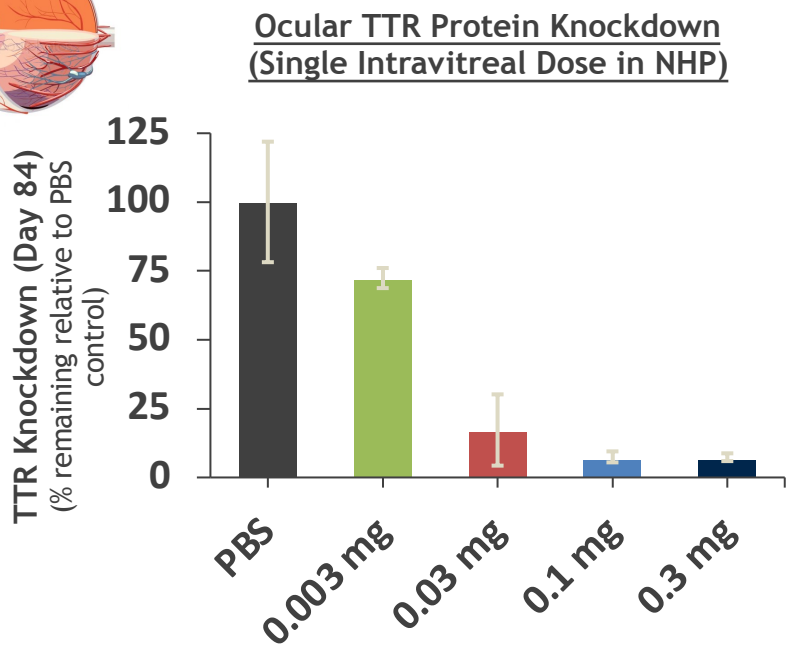
Durable SOD1 mRNA silencing is seen in all regions of the brain and spinal card tested

Robust Silencing of CNS and Ocular Targets









Thank you for the opportunity to present this lecture.

- Phil Sharp