



Brezosiran (ALN-HTT02)

An Investigational RNAi Therapeutic Targeting Exon 1 of the Huntingtin Gene to Slow Progression of Huntington's Disease

October 26, 2026



Agenda

01 Introduction

Pushkal Garg, M.D.
Chief Research & Development Officer

02 About Brezosiran (ALN-HTT02)

Kevin Sloan, Ph.D.
*Vice President, Development Programs,
ALN-HTT02 Program Lead*

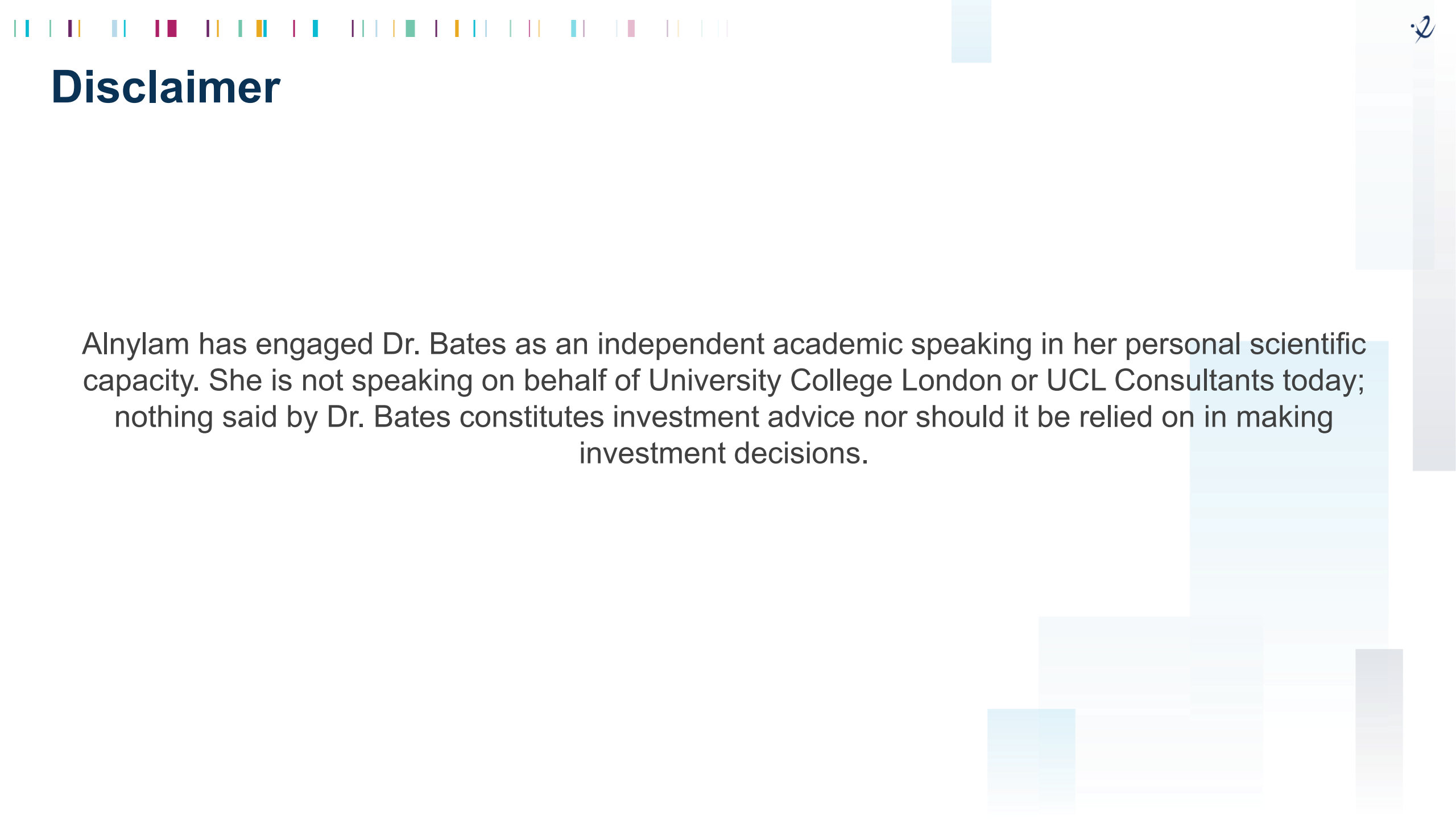
03 Targeting HTT1a in HTT Lowering Strategies

Gill Bates, Ph.D.
*Professor of Molecular Neuroscience, Co-Director of the
Huntington's Disease Centre, University College London*

04 Clinical Data and Progress

Toby Ferguson, M.D., Ph.D.
*Senior Vice President,
Neuroscience Therapeutic Area Head*

05 Q&A Session



Disclaimer

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This presentation contains forward-looking statements. Forward-looking statements include statements regarding Alnylam's expectations, beliefs, goals, plans or prospects, including, without limitation, statements regarding: the potential safety or efficacy of brezosiran as a treatment for Huntington's disease, including through the potential lowering of all HTT isoforms; the potential size of the patient population with Huntington's disease and the potential market opportunity for an effective treatment for Huntington's disease; the potential for Alnylam to initiate a pivotal, placebo-controlled efficacy study of brezosiran in adults with Huntington's disease in 2027; the potential for Alnylam to build a portfolio of RNAi therapeutics with transformational patient impact; the transformative potential of RNAi; and the timing of key data readouts from Alnylam's clinical trials, the number of pivotal studies Alnylam will have ongoing at any time, the number of new IND/CTA filings Alnylam will make in any calendar year, and the potential for Alnylam to launch additional products and the timing of any such product launches.

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, risks and uncertainties relating to: Alnylam's ability to successfully execute on its *Alnylam 2030* strategy; Alnylam's ability to successfully launch, market and sell Alnylam's approved products globally; Alnylam's ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of its product candidates; the pre-clinical and clinical results for Alnylam's product candidates; actions or advice of regulatory agencies and Alnylam's ability to obtain and maintain regulatory approval for its product candidates, as well as favorable pricing and reimbursement; delays, interruptions or failures in the manufacture and supply of Alnylam's marketed products or its product candidates; obtaining, maintaining and protecting intellectual property; Alnylam's ability to manage its growth and operating expenses through disciplined investment in operations; Alnylam's ability to maintain strategic business collaborations; Alnylam's dependence on third parties for the development and commercialization of certain products; the outcome of litigation and government investigations; the risk of future litigation and government investigations; and unexpected expenditures; as well as those risks and uncertainties more fully discussed in the "Risk Factors" filed with Alnylam's most recent periodic report (Quarterly Report on Form 10-Q or Annual Report on Form 10-K) filed with the SEC and in its other SEC filings. Alnylam explicitly disclaims any obligation, except to the extent required by law, to update any forward-looking statements.



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Pioneering a Generational Class of RNAi Medicines

Silence any gene in genome

Upstream of today's medicines

Catalytic mechanism

Highly potent

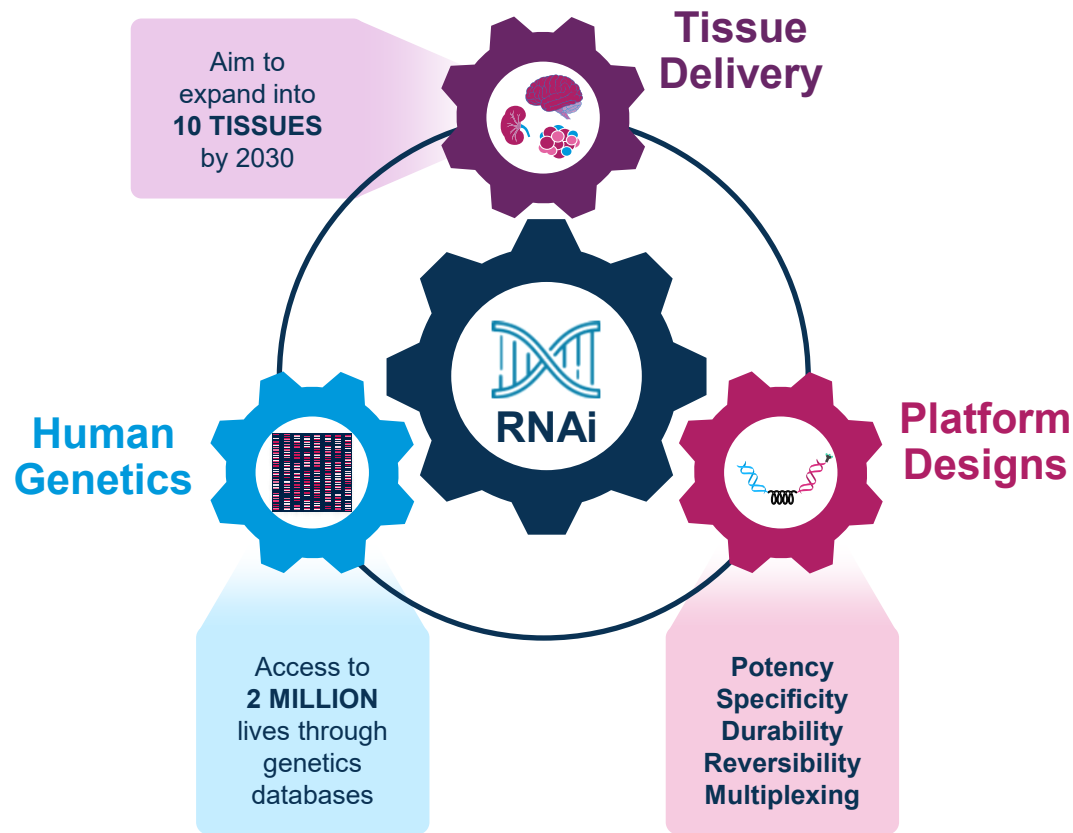
Highly specific and reversible

Infrequent administration

Building a Portfolio of RNAi Therapeutics with Transformational Patient Impact

Disciplined R&D Maximizes the Transformative Potential of RNAi

SUSTAINABLE INNOVATION ENGINE



STRATEGIC PRINCIPLES

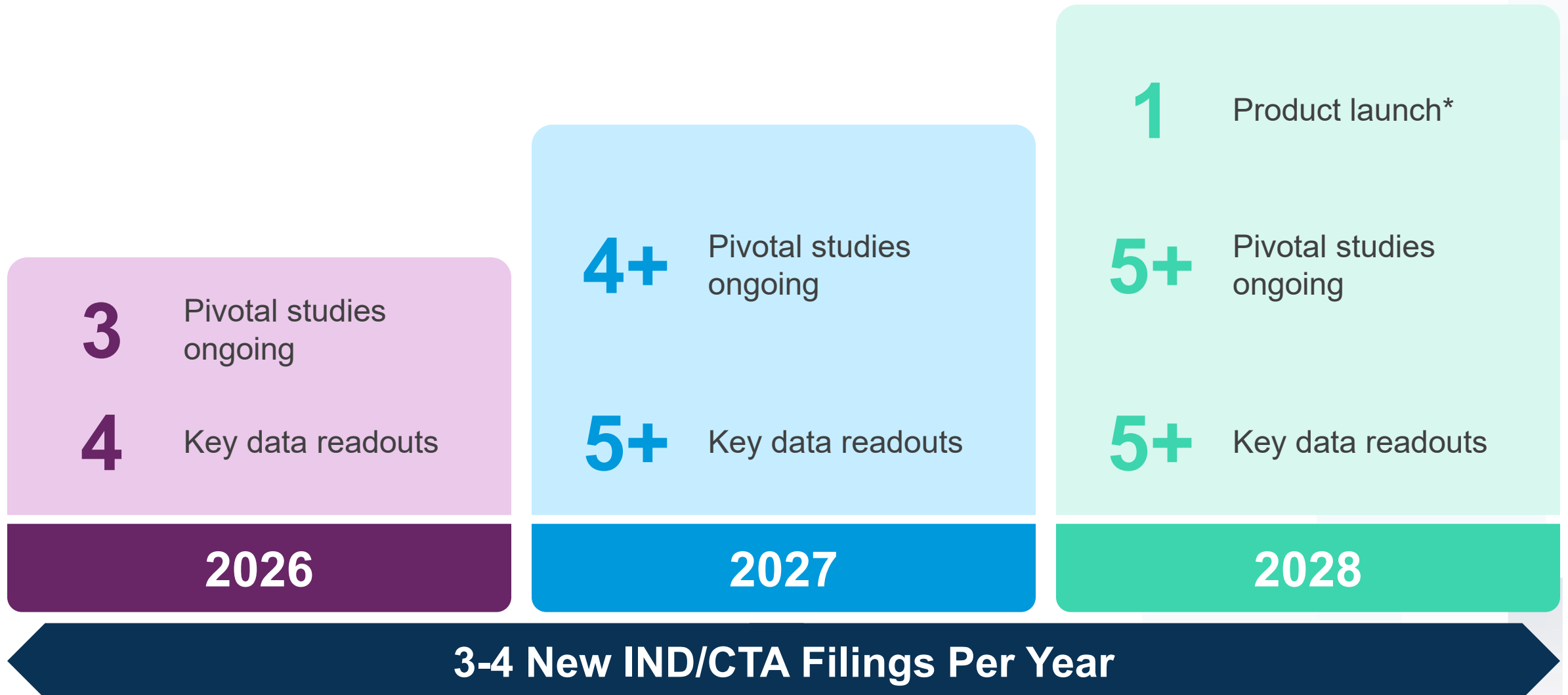
-  **Address diseases with high morbidity & mortality**
-  **Pursue high conviction targets**
Strong biologic rationale, informed by human genetics
-  **Potential to halt or reverse disease, & be best-in-class**
-  **Drive to clear clinical proof-of-concept**
-  **Encouraging market opportunity & access dynamics**

Industry Leading Pipeline of RNAi Therapeutics

			PHASE 1	PHASE 2	PHASE 3
TTR	Nucresiran	↺	ATTR Amyloidosis with Cardiomyopathy		
	Nucresiran	↺	hATTR Amyloidosis with Polyneuropathy		
CARDIOVASCULAR	Zilebesiran ²	↺	Hypertension		
	Zilebesiran REVERSIR ²	↺	Hypertension		
METABOLIC	Rapirosiran (ALN-HSD) ¹		Metabolic Dysfunction-Associated Steatohepatitis (MASH)		
	ALN-ANG3 ¹		Diabetic Kidney Disease		
	ALN-4324 (GRB14)	↺	Type 2 Diabetes Mellitus		
	ALN-PNP ¹		Metabolic Dysfunction-Associated Steatohepatitis (MASH)		
	ALN-CIDEB ¹		MASH		
	ALN-2232 (ACVR1C)	↺	Obesity & Weight Management		
	ALN-6222 (INHBE)	↺	Obesity & Weight Management		
	ALN-APOC3 ¹		Dyslipidemia		
NEUROSCIENCE	Cemdisiran ¹		Myasthenia Gravis		
	Mivelsiran	↺	Cerebral Amyloid Angiopathy		
	Mivelsiran	↺	Alzheimer's Disease		
	ALN-SOD ³	↺	SOD1 Amyotrophic Lateral Sclerosis		
	Brezosiran (ALN-HTT02) ⁴	↺	Huntington's Disease		
	ALN-5288 (MAPT) ⁴	↺	Alzheimer's Disease		
	ALN-SNCA ¹		Parkinson's Disease		
HEMATOLOGY	Cemdisiran ¹		Paroxysmal Nocturnal Hemoglobinuria		
	ALN-6400 (PLG)	↺	Hereditary Hemorrhagic Telangiectasia		
	ALN-6400 (PLG)	↺	Von Willebrand Disease		
	AG-236 (ALN-TMP) ¹		Polycythemia Vera		
	ALN-CFB ¹		Paroxysmal Nocturnal Hemoglobinuria		
OTHER	Cemdisiran ¹		Geographic Atrophy		
	Elebsiran ¹		Hepatitis D Virus Infection		
	ALN-BCAT	↺	Hepatocellular Carcinoma		
	ALN-4285	↺	Healthy Volunteers		
	ALN-4915	↺	Healthy Volunteers		
	ALN-F1202 ¹		Healthy Volunteers		

¹ Out-licensed with milestones and/or royalties; ² Partnered, Alnylam-led development with U.S. profit split and milestones/royalties ex-U.S.; ³ Partner-led with profit split; ⁴ Partnered, Alnylam-led with profit split; ↺ Alnylam-owned, -led, or -co-developed

Expect Significant Clinical Milestones Over Next Two Years

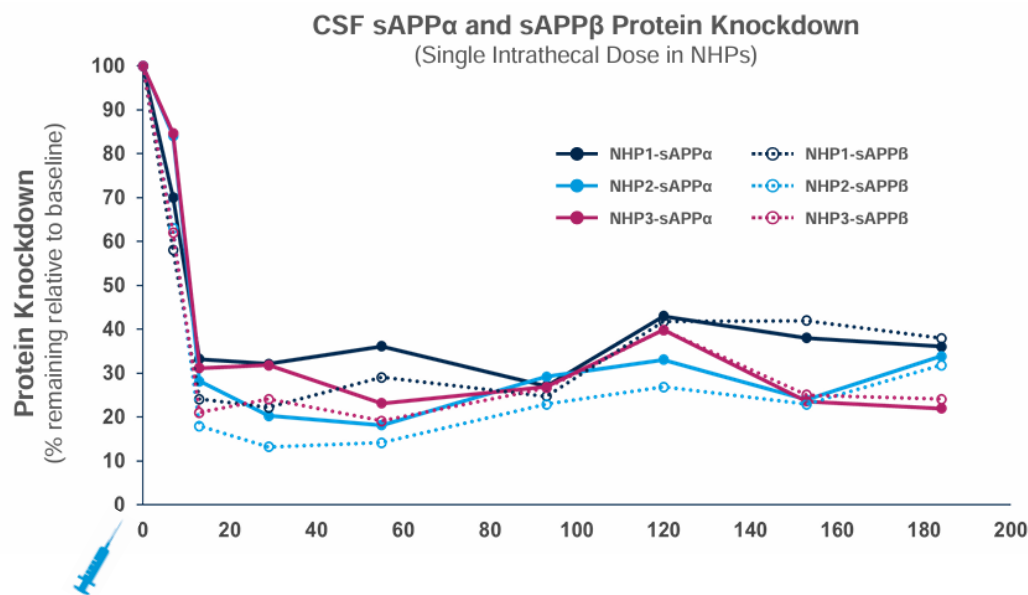


* Assuming positive phase 3 data and regulatory approval

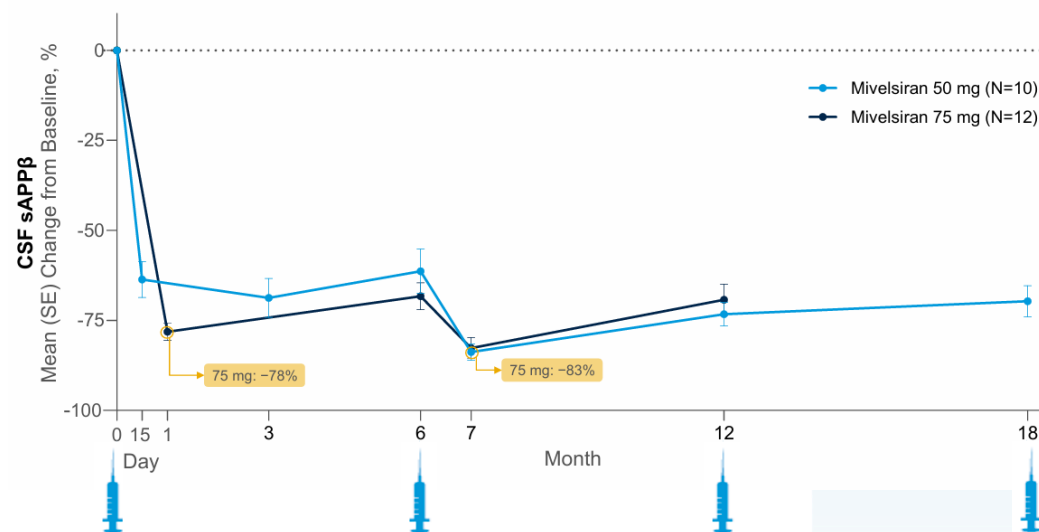
C16 Conjugates Unlocked the CNS for RNAi Therapeutics

Advancing a growing pipeline of investigational CNS-targeted RNAi therapeutics in collaboration with Regeneron

Preclinical Results of mivelsiran in NHPs



Phase 1 Multiple-Dose Results of Mivelsiran in Early-Onset AD



PHASE 1

Brezosiran (ALN-HTT02) | Huntington's Disease³
ALN-5222 (MAPT) | Alzheimer's Disease³
ALN-SNCA | Parkinson's Disease¹

PHASE 2

Mivelsiran | Cerebral Amyloid Angiopathy (CAA)
Mivelsiran | Down Syndrome-Associated Alzheimer's Disease (DS-AD)
ALN-SOD | SOD1 Amyotrophic Lateral Sclerosis (ALS)²



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Huntington's Disease (HD) Robs Generations of Patients of Body and Mind

Progressive, fatal monogenic neurodegenerative disease

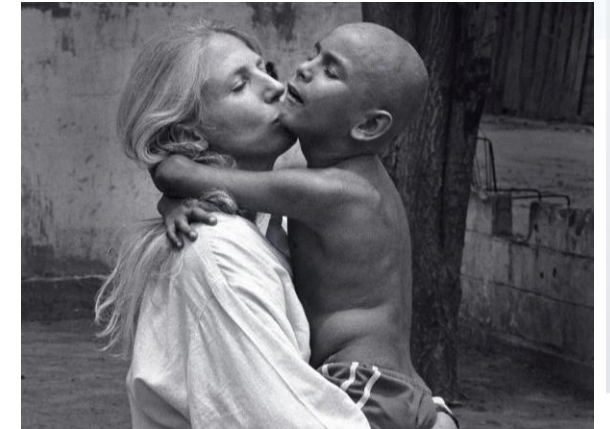
Movement: chorea, incoordination, falls

Thinking: executive dysfunction, memory loss

Mood: depression, apathy, personality change, suicidality



Woody Guthrie
PATIENT



Nancy Wexler & patient
PATIENT & HD RESEARCH PIONEER

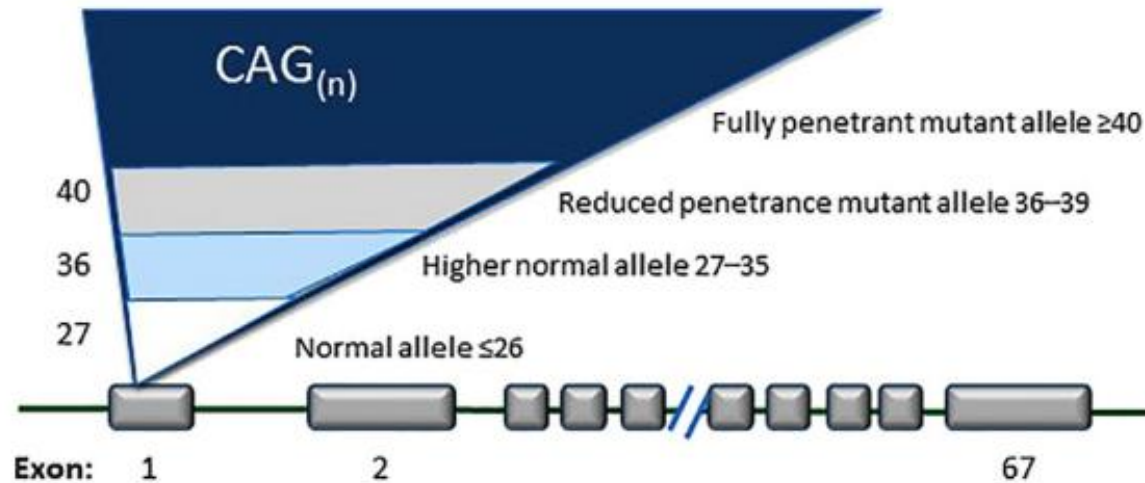
Average lifespan shortened to
~10–30y¹
from diagnosis

Mid-40s
typical symptom onset,
during prime working years

50%
chance each child of an
affected parent inherits HD

>100K
symptomatic patients globally²

HD is Caused by a CAG Repeat Expansion in the Huntingtin (HTT) Gene



Gato et al., 2020

Inherited CAG repeats ≥ 40
Expect to develop HD with lifetime

CAG repeat further expands over time
Somatic instability

mHTT accumulation
Full-length and HTT1a

Neuronal toxicity

HD-ISS STAGING

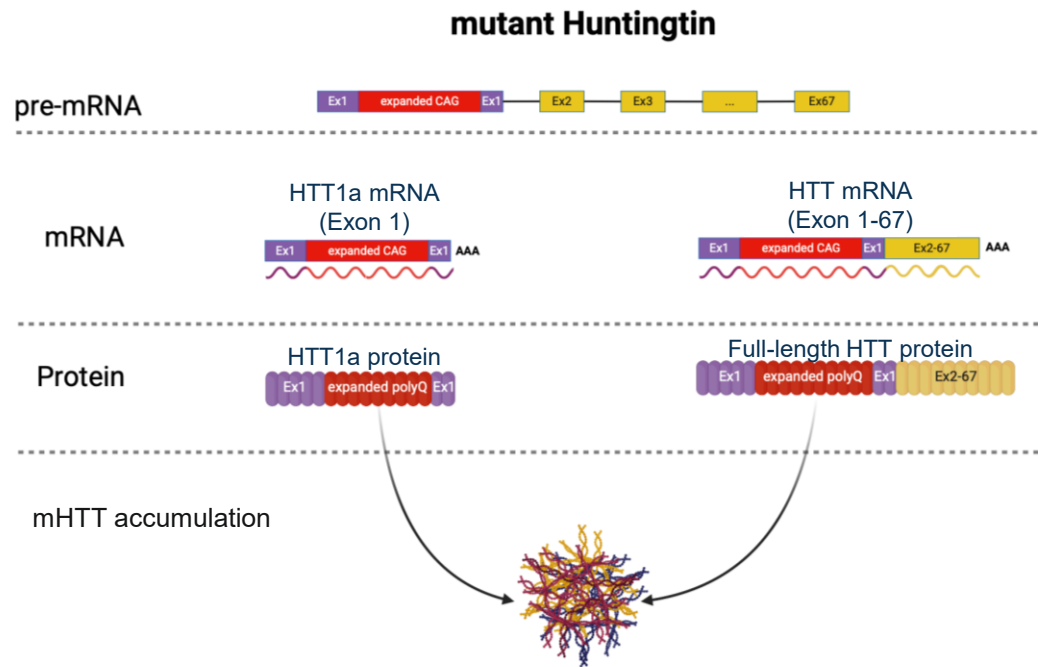
Stage 0
CAG repeats ≥ 40

Stage 1
Biomarker changes
(imaging, CSF)

Stage 2
Clinical signs and symptoms

Stage 3
Functional decline

One Gene, Two Potential Culprits



One gene, two proteins

The mutant gene gives rise to full-length mutant HTT (67 exons) and a shorter, toxic isoform, HTT1a (exon 1 only)²

Both likely contribute to disease

Full-length mutant HTT and the shorter HTT1a isoform implicated as toxicity drivers^{2,4-6}

Many approaches miss HTT1a

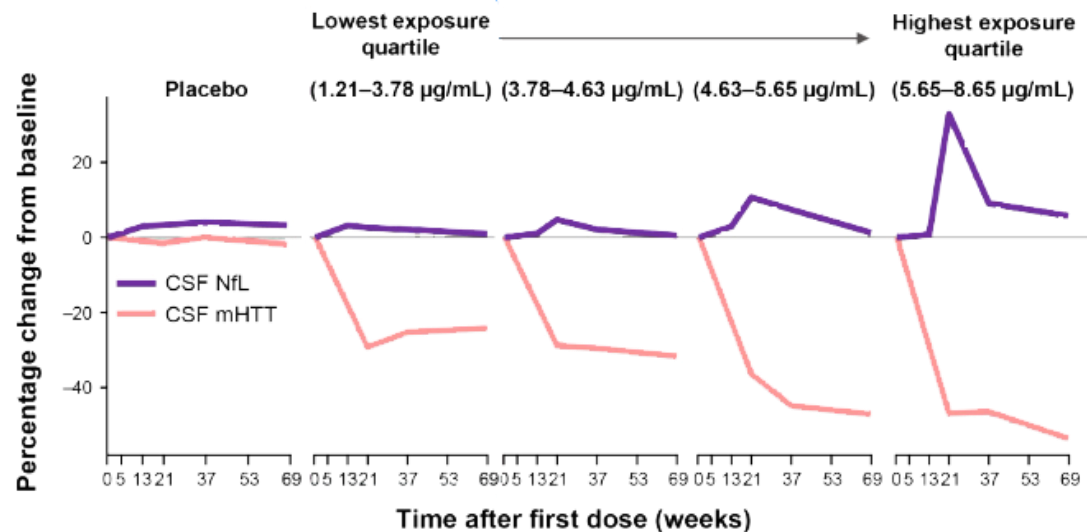
Not all HTT-lowering strategies in development effectively address the shorter isoform^{1,7}

Technical Challenges Have Slowed Progress in the Field

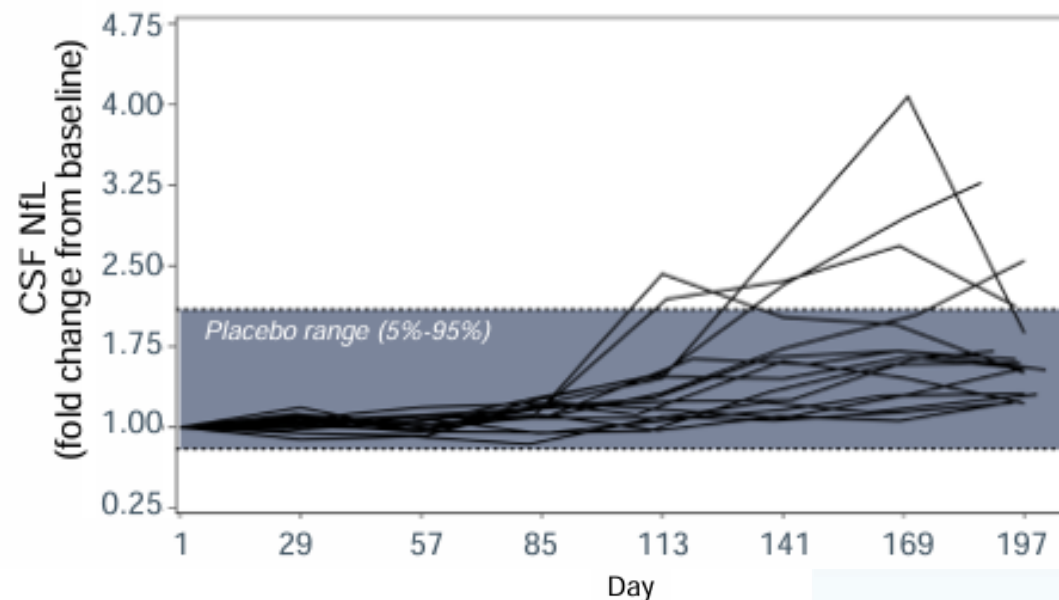
Exposure-related tolerability issues have prevented exploration of deep HTT lowering

Dose-dependent NfL increases observed with tominersen ASO

Data pooled across 120 mg Q8W and Q16W dosing regimens with loading dose (n=791)



NfL increases observed with WVE-003 allele-selective ASO



Our approach is poised to answer a key question in the field:
Can HTT-lowering provide safe and effective therapeutic benefit?

Brezosiran Targets Exon 1 of HTT

Intrathecally administered investigational
C16-RNAi therapeutic



Targets HTT exon 1

Binds a conserved mRNA sequence within exon 1



Designed to lower all HTT species in CNS

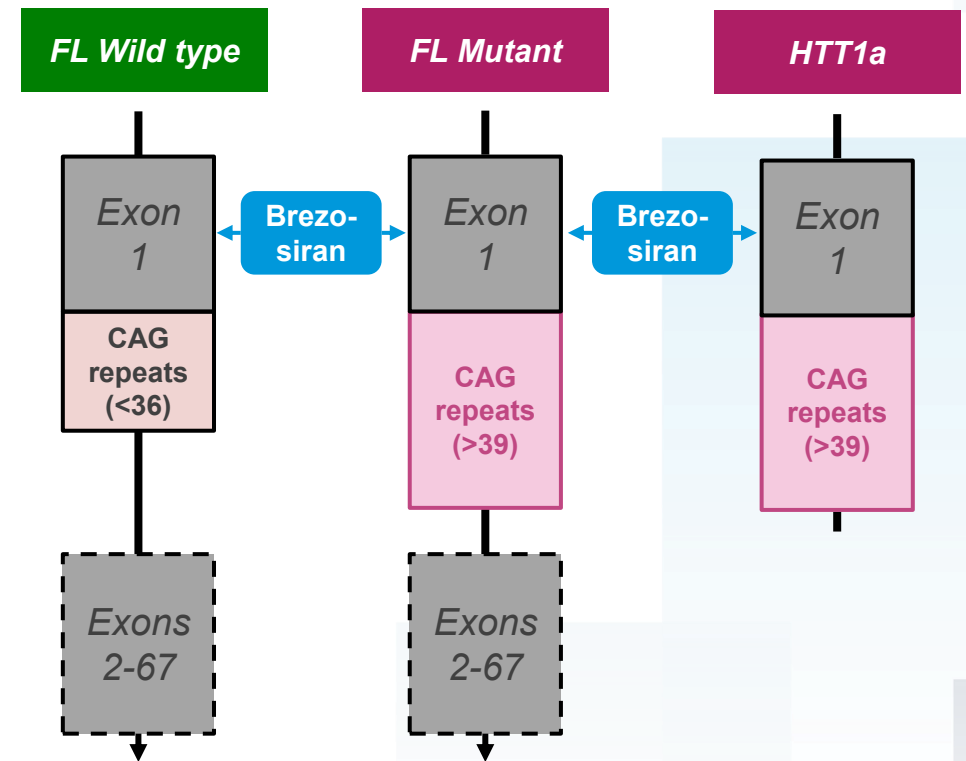
Includes full-length mHTT, HTT1a and wtHTT



Fully reversible

No permanent changes

HTT Alleles in HD



Therapeutic Hypothesis

Brezosiran Durably Lowered HTT Throughout the Brain with an Encouraging Safety Profile in Non-Human Primates¹



Deep and dose-dependent

HTT protein lowering sustained for months after a single intrathecal dose



Widespread across the CNS

HTT lowering in cortex and striatum

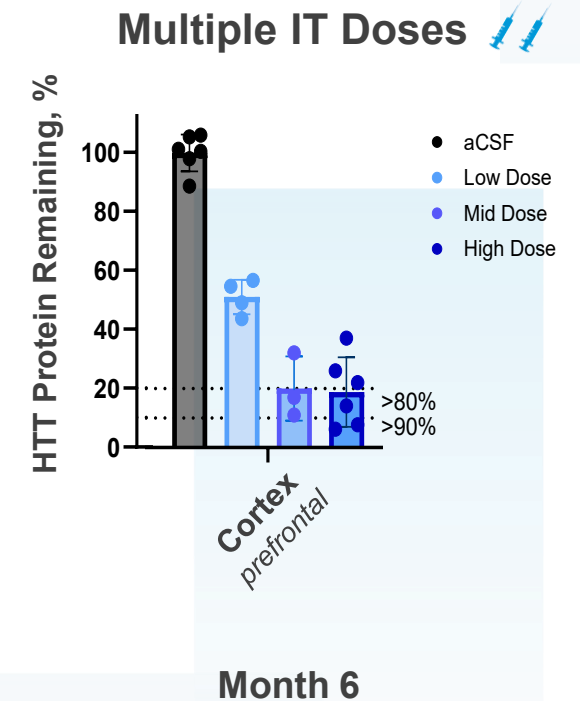
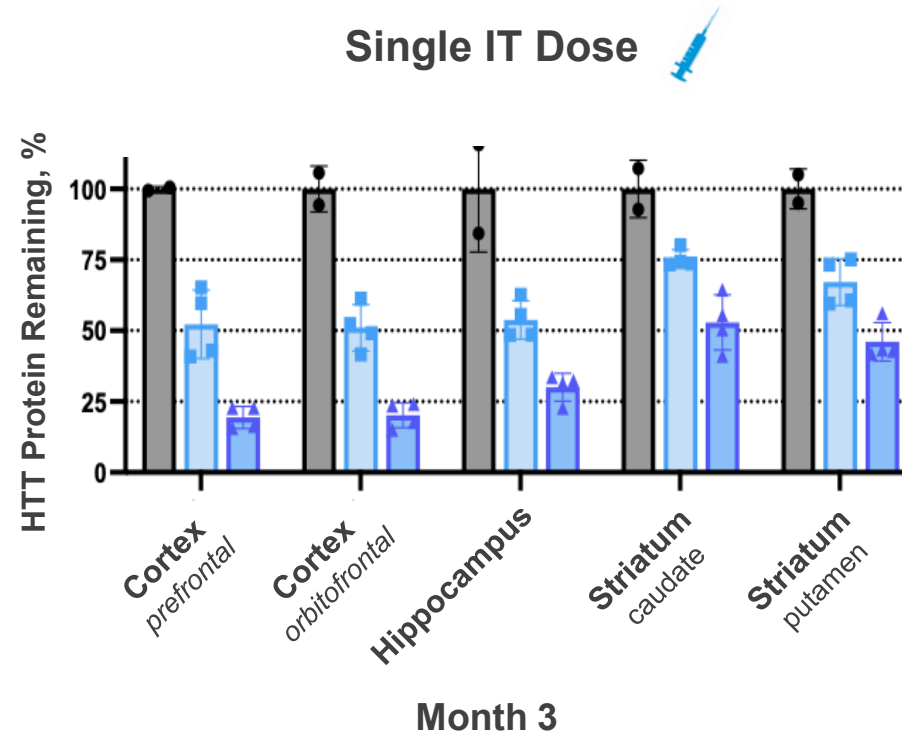


Encouraging safety

Across multiple NHP studies up to 12 months in duration:

- No neurological abnormalities
- No changes in CSF inflammatory markers or neurofilament light chain (NfL)
- No histological changes

No adverse findings, even after deep wtHTT-lowering >90%



Brezosiran Offers Three Key Reasons for Hope

THERAPEUTIC APPROACH:

Brezosiran is designed to reduce the production of all huntingtin protein (HTT) species in the CNS

DESIGN ELEMENTS:

- 1 Safety & durability of C16-siRNA delivery platform
- 2 Potential to fully explore deep & widespread HTT-lowering throughout the brain
- 3 Inclusive targeting strategy to lower all HTT isoforms, including HTT1a



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Targeting *HTT1a* in HTT lowering strategies

Professor Gillian Bates

Huntington's disease

Autosomal dominant

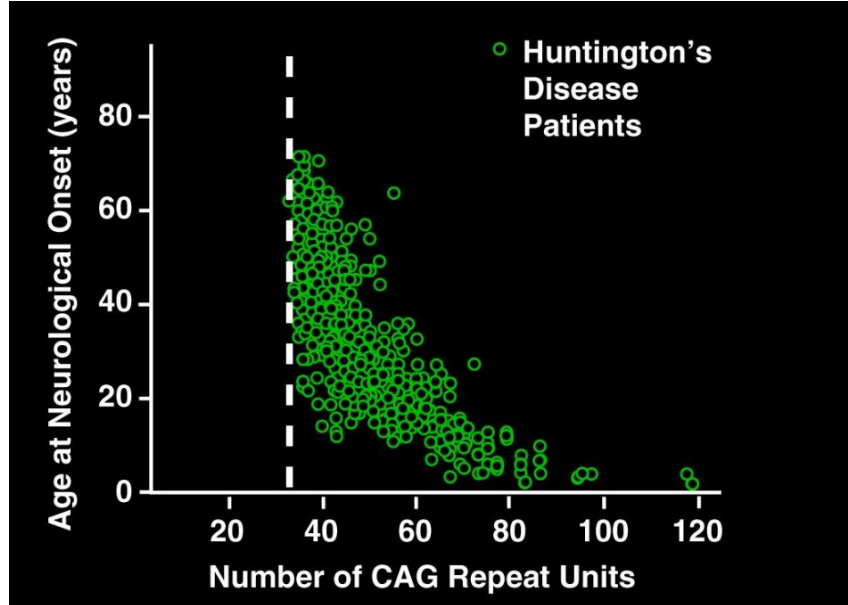
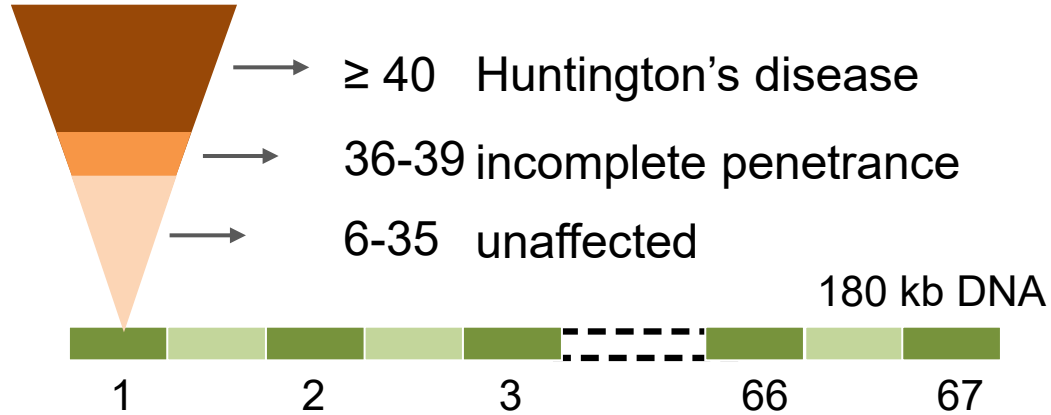
- midlife to late age onset
- movement disorder
- psychiatric disturbances
- cognitive decline
- systemic features

Video: Adult-onset Huntington's disease

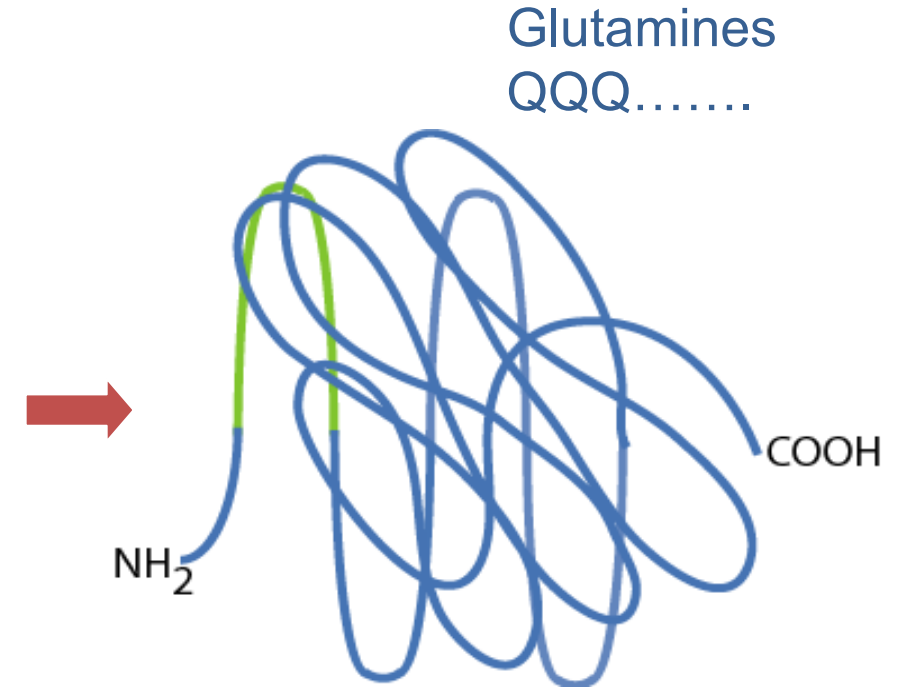
Sarah Tabrizi

The *HTT* gene and huntingtin (HTT) protein

CAG CAG CAG....

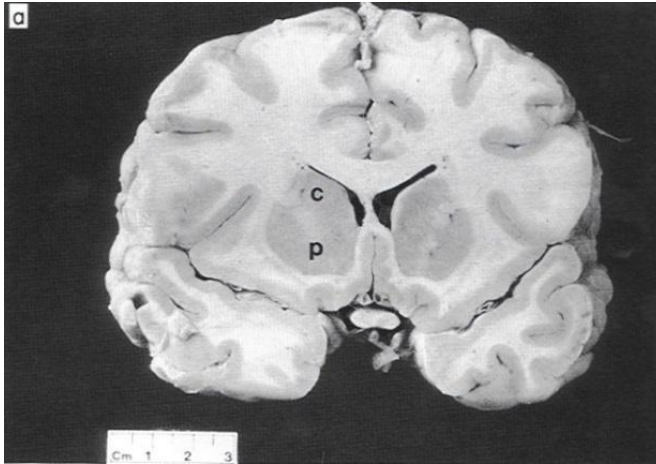


MacDonald 1998

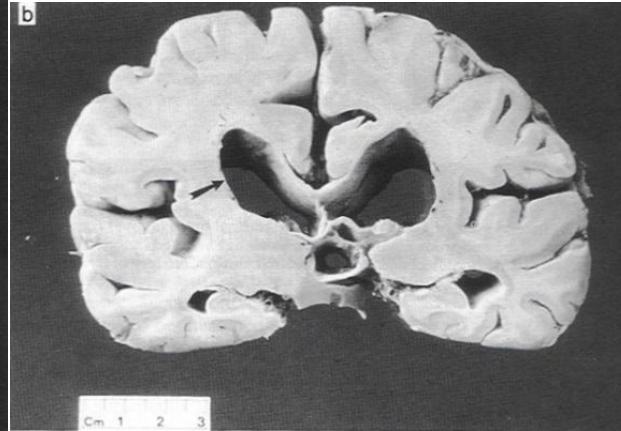


Mutation imparts a gain of function

The neuropathology of Huntington's disease

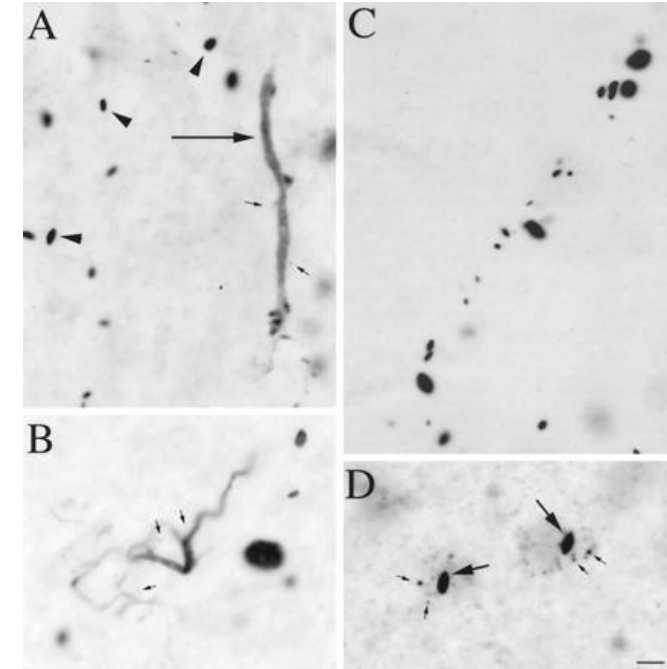


Unaffected



Huntington's disease

- generalized atrophy
- selective neuronal cell death
- aggregate pathology



HD Brain Cerebral Cortex

- nuclear and cytoplasmic inclusions
- anti-HTT antibodies to N-terminus
- presymptomatic

**Somatic CAG repeat expansion:
the driver of HD phenotypes**

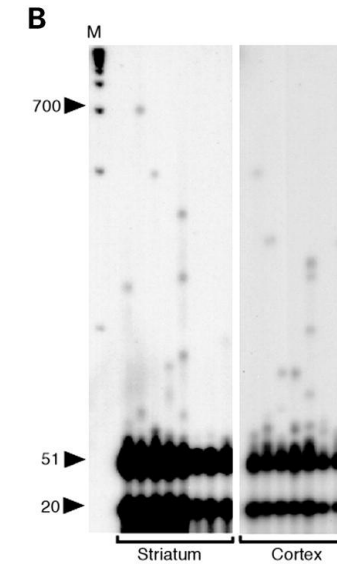
The molecular basis of Huntington's disease



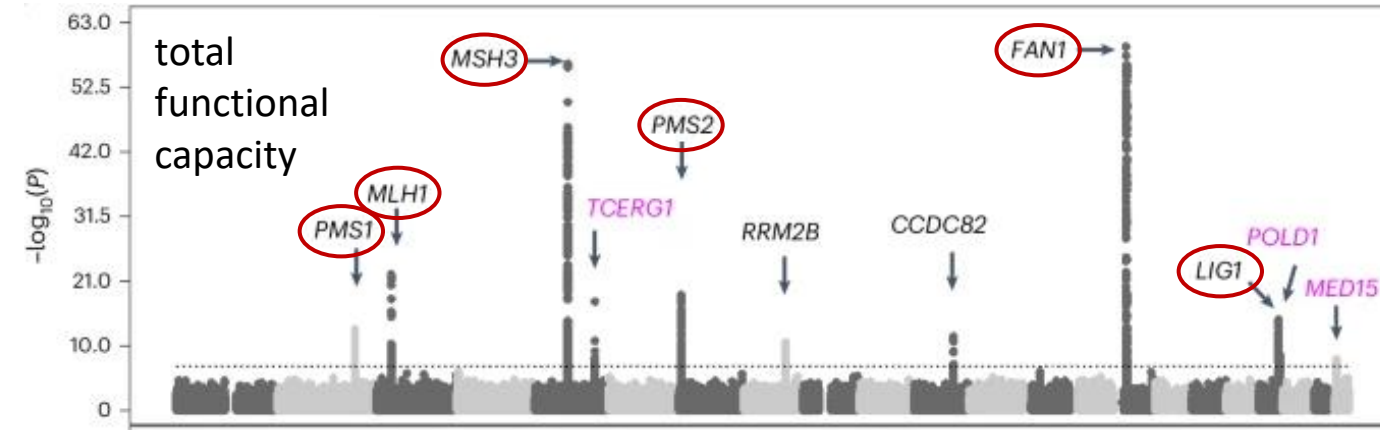
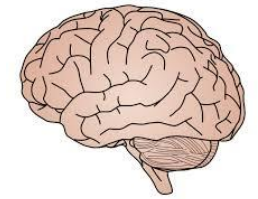
≥ 40 CAGs =
fully penetrant mutation



Somatic CAG
repeat expansion



Repeats of several
100 CAGs in brain
regions



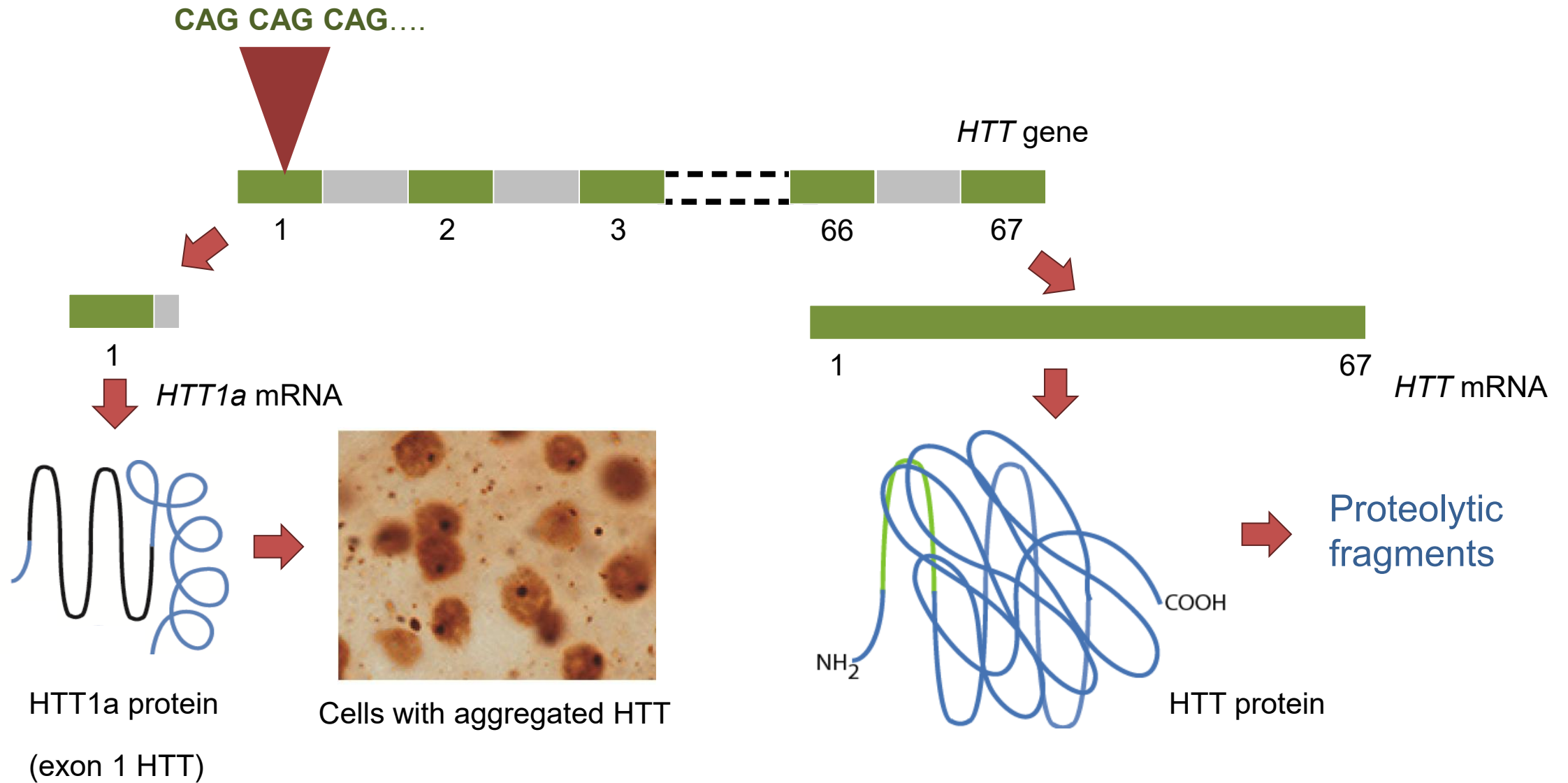
Genetic modifiers in DNA damage repair pathways

Absence of specific mismatch repair proteins
prevents somatic CAG expansion in mice

- Somatic CAG repeat expansion in brain drives the age at onset and rate of disease progression

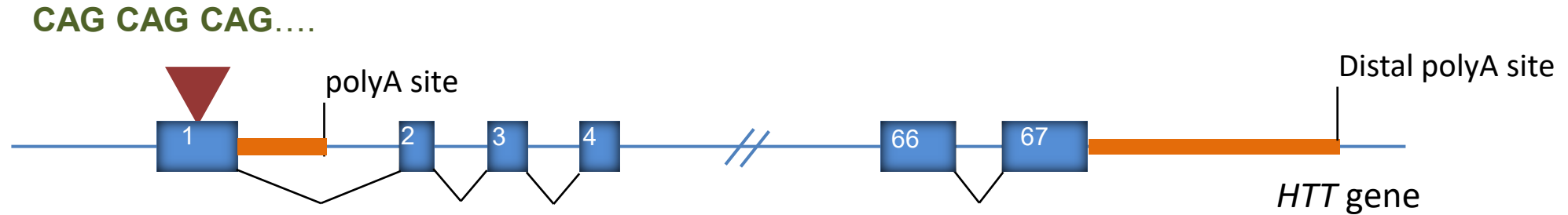
Step 2: the alternative processing of the *HTT* transcript

The molecular basis of Huntington's disease



Is *HTT1a* the effector through which CAG repeat expansion exerts its pathogenic consequences?

Alternative processing of huntingtin pre-mRNA



	Human <i>HTT</i>	Mouse <i>Htt</i>
Intron 1	~12 kb	~20 kb
Position of cryptic polyA sites	2710 + 7327 bp	680 + 1145 bp
Name of small transcript	<i>HTT1a</i>	<i>Htt1a</i>

Sathasivam et al. 2013 PNAS 110: 2366-2370; Neueder et al. 2017 Scientific Reports 7: 1307

The allelic series of knock-in mice as a model of CAG expansion

Knock-in mouse lines



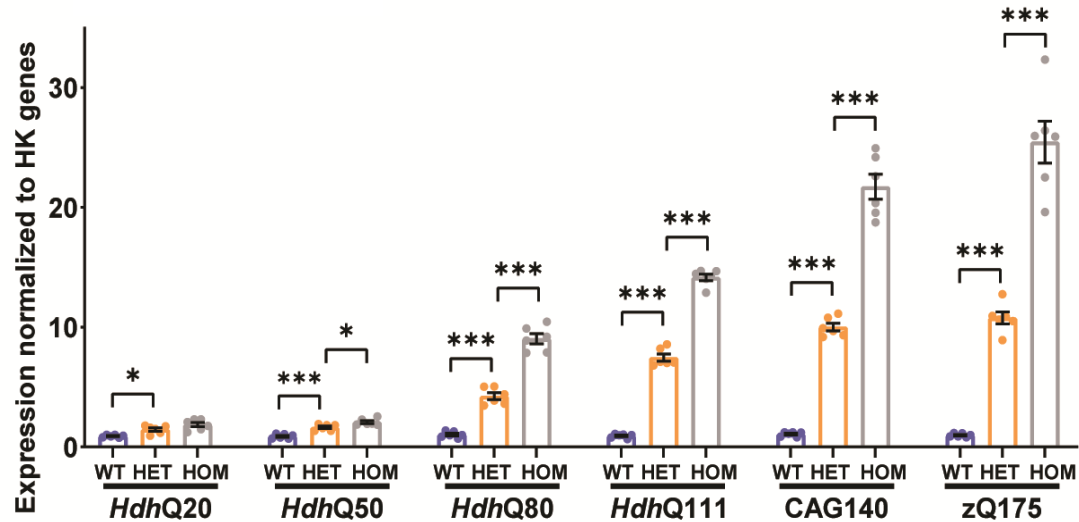
CAG repeat series

Knock-in mouse line	CAG repeat size
<i>Hdh</i> Q20	20
<i>Hdh</i> Q50	50
<i>Hdh</i> Q80	80
<i>Hdh</i> Q111	111
CAG140	140
zQ175	190

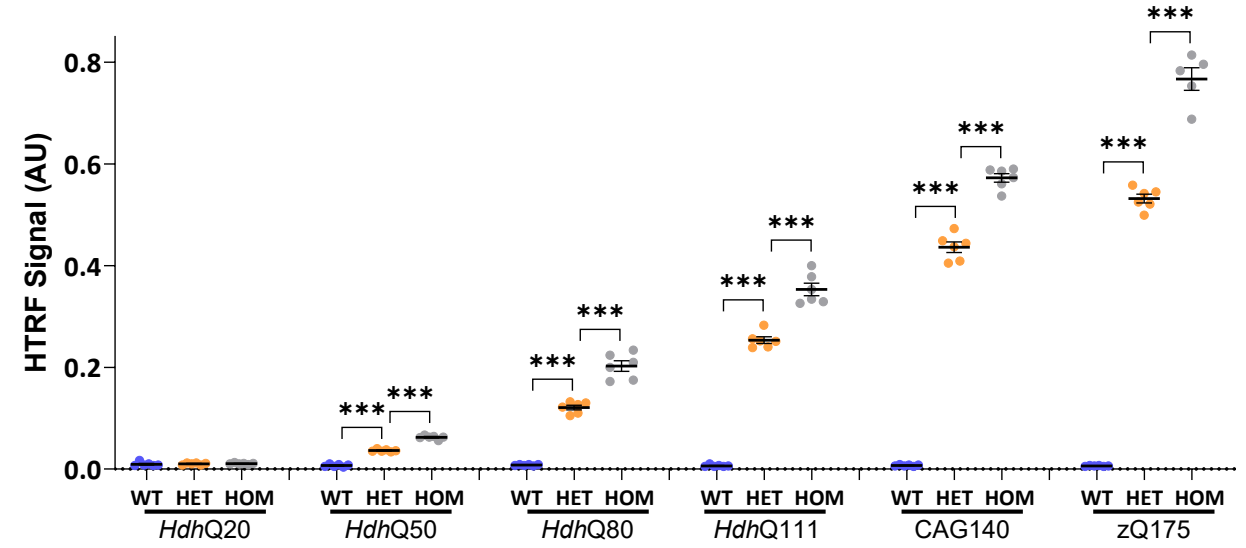
- *HTT1a* transcript and HTT1a protein levels

HTT1a levels increase with expanded CAG repeats

HTT1a transcripts



Soluble *HTT1a* levels

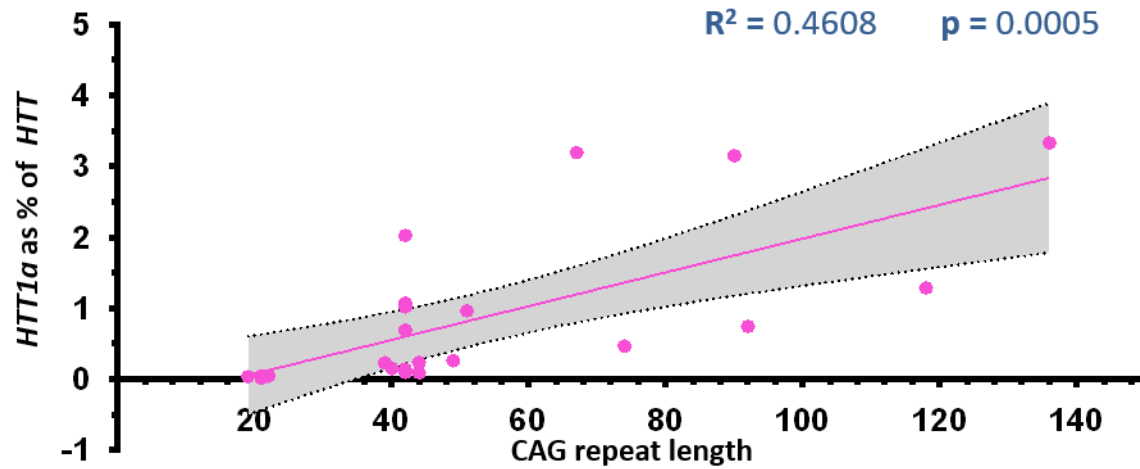


HTT1a transcript and *HTT1a* protein levels increase with increasing CAG repeat length.

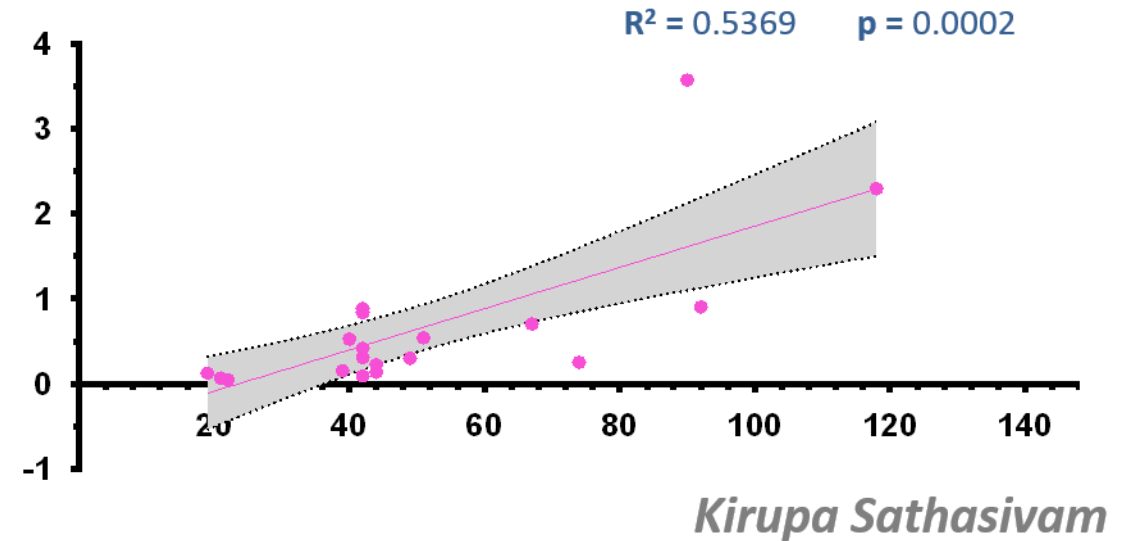
Can *HTT1a* be detected in human cells / tissues?

HTT1a mRNA in *postmortem* brain

Sensory Motor Cortex

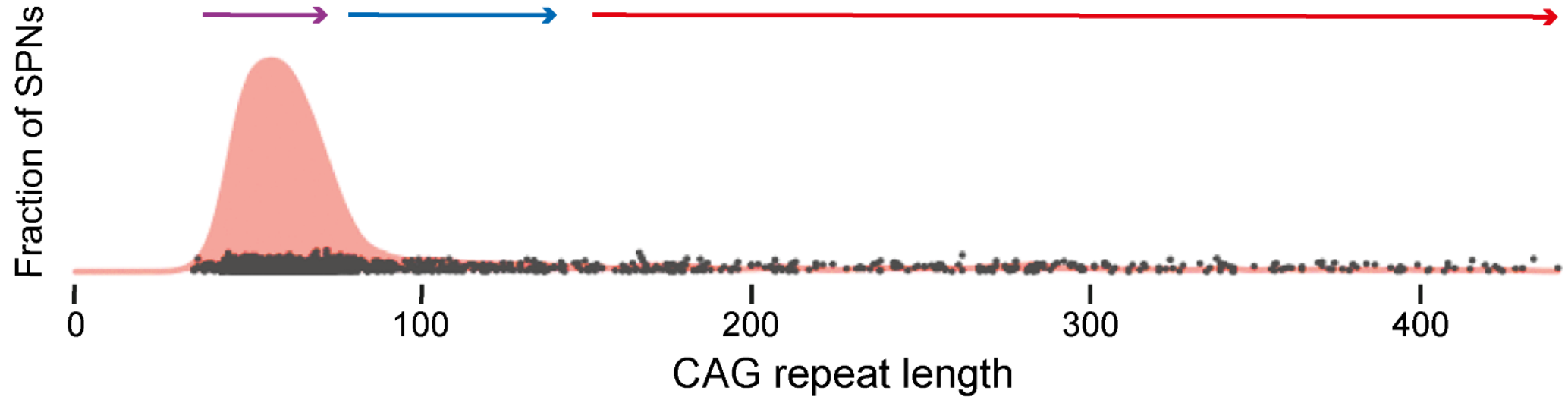


Hippocampus



- *HTT1a* levels increase with increasing CAG repeat length
- *HTT1a* most apparent in juvenile onset brains with longer CAG repeats.

CAG expansion in individual SPNs in HD *post-mortem* brain



- Expansions occur in specific sets of neurons
- In MSNs in the striatum, 95 – 98% expansions in the range up to 100 CAGs
- Higher proportion of cells with long CAG expansions in brains from juvenile HD

HTT1a inclusions in *postmortem* brain

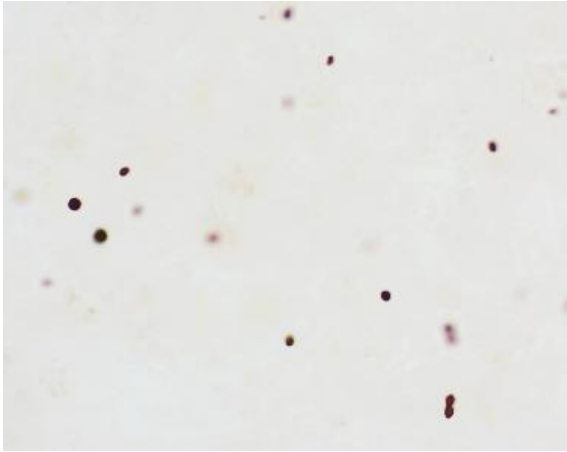
Age:89+ - HD

Huntington's disease, Vonsattel grade 3/4

Age:70 - control

Age related changes, LOW burden of AD pathology

S830

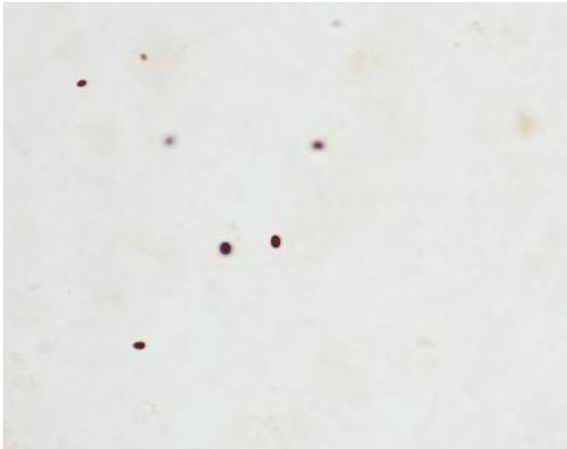


S830



N-terminus of
HTT

1B12



1B12



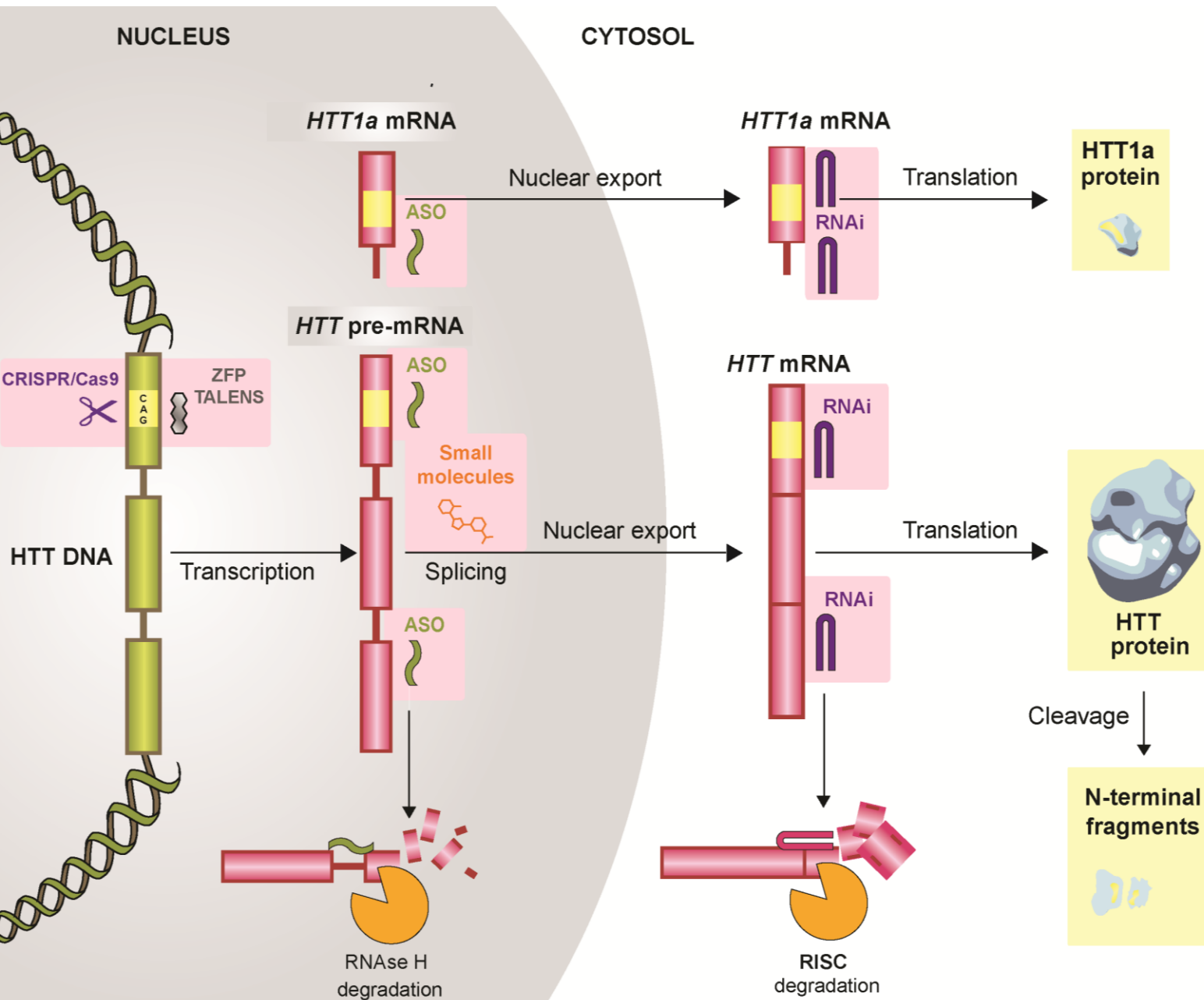
1B12 = HTT1a
specific

x40

x10

HTT Lowering

Strategies for targeting huntingtin transcripts



Full-length *HTT* alone

- *Agents that target HTT downstream of exon 1*

Full-length *HTT* and *HTT1a*

- *Agents that target exon 1 HTT*

HTT1a alone

- *Agents that target intron 1 HTT in the cytoplasm*

HTT lowering

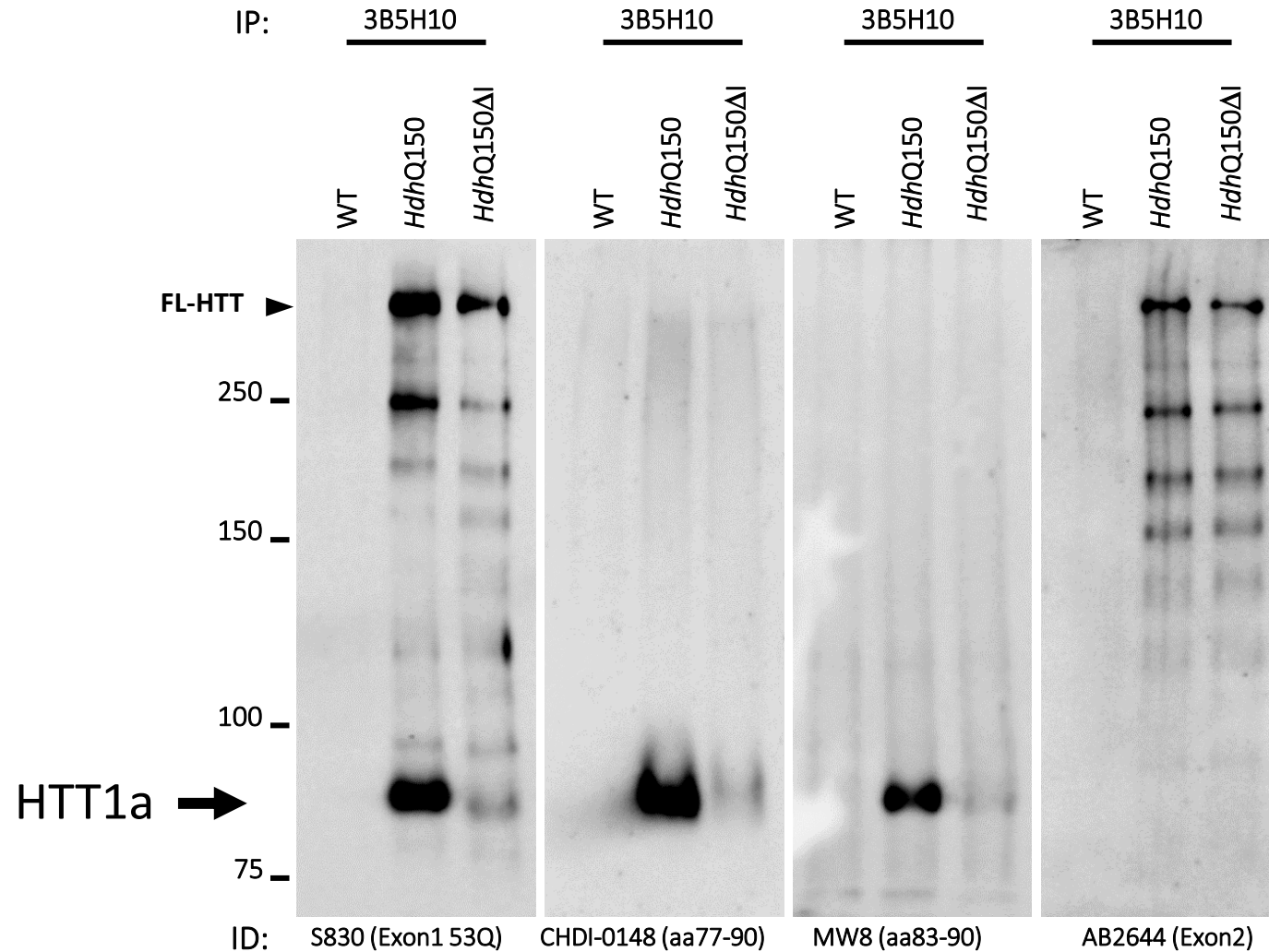
- What is the relative pathogenesis of HTT1a and full length mutant HTT?
- Should we target:
 - full-length *HTT* alone?
 - *HTT1a* alone?
 - full-length *HTT* and *HTT1a*?

Genetic approach to decrease HTT1a protein levels in a mouse model of HD

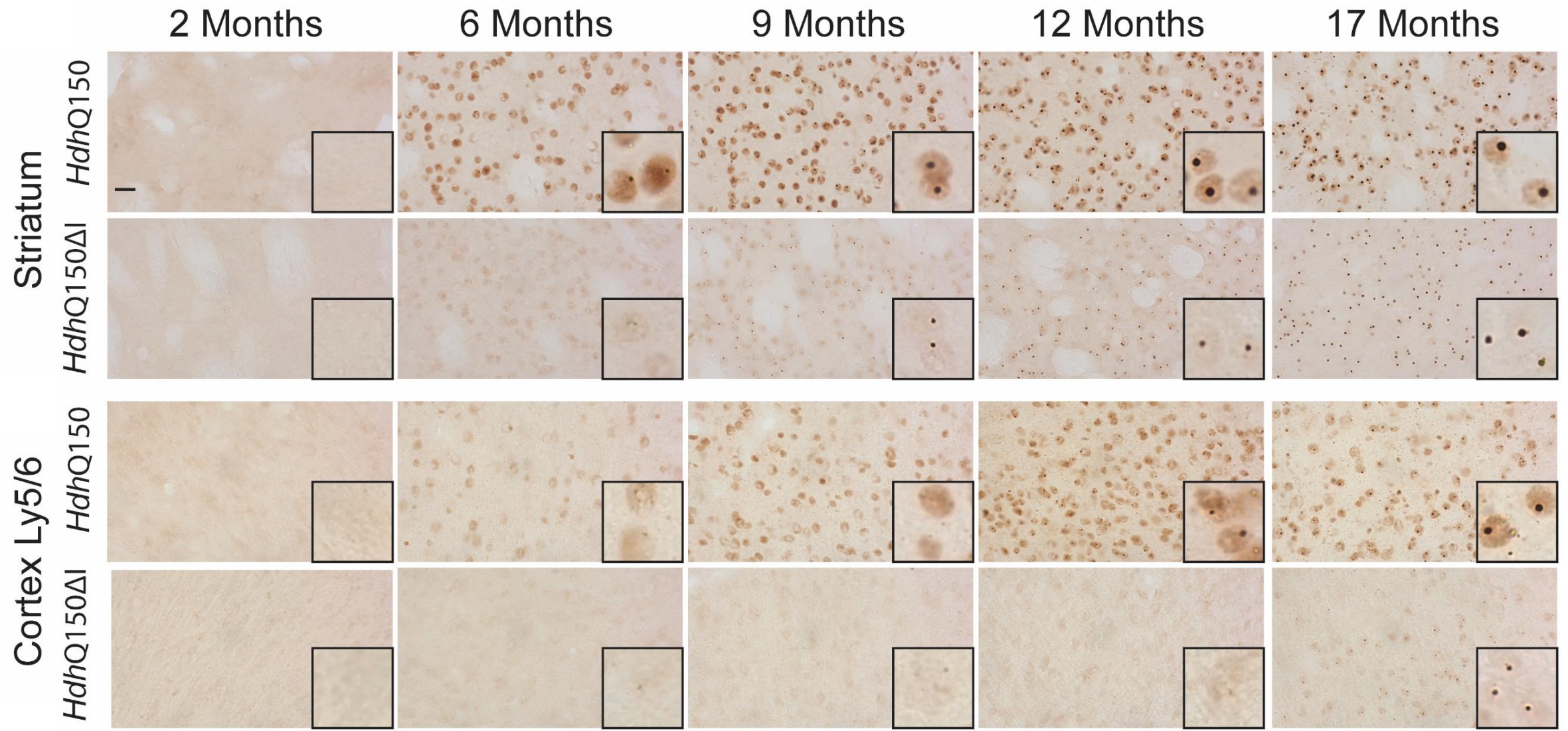
- Remove the cryptic polyA sites from intron 1 of *Hdh*Q150 knock in mice
- Prevent generation of HTT1a protein: *Hdh*Q150 Δ I

Analysis of soluble mutant HTT in *HdhQ150ΔI* mice

IP and western analysis (whole brain 2 months of age)



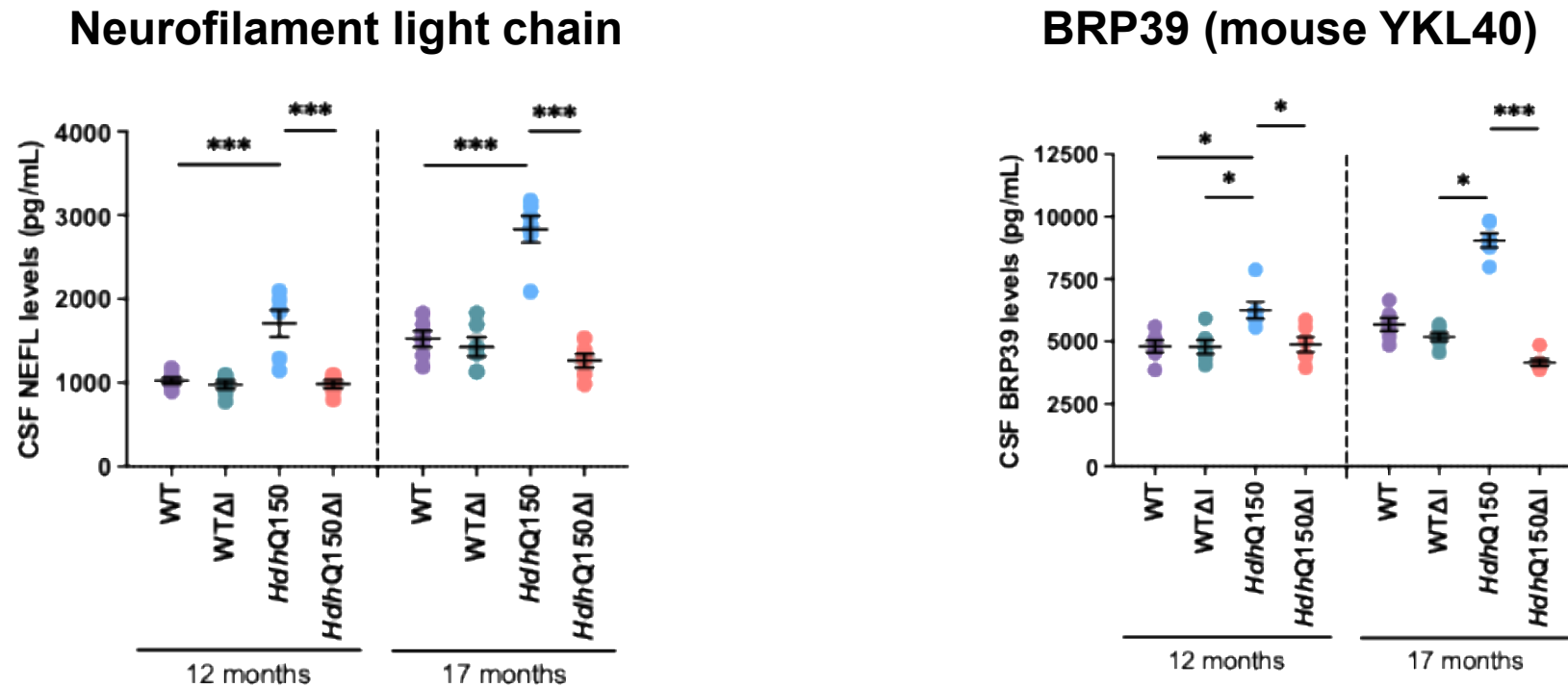
HTT aggregation delayed in *Hdh*Q150ΔI mice



1B12 – HTT1a specific antibody

CSF biomarkers at wild-type levels in *HdhQ150ΔI* mice

CSF



Reduction of HTT1a:

- Delays HTT aggregation
- rescues levels of NEFL and BRP39 – translatable biomarkers

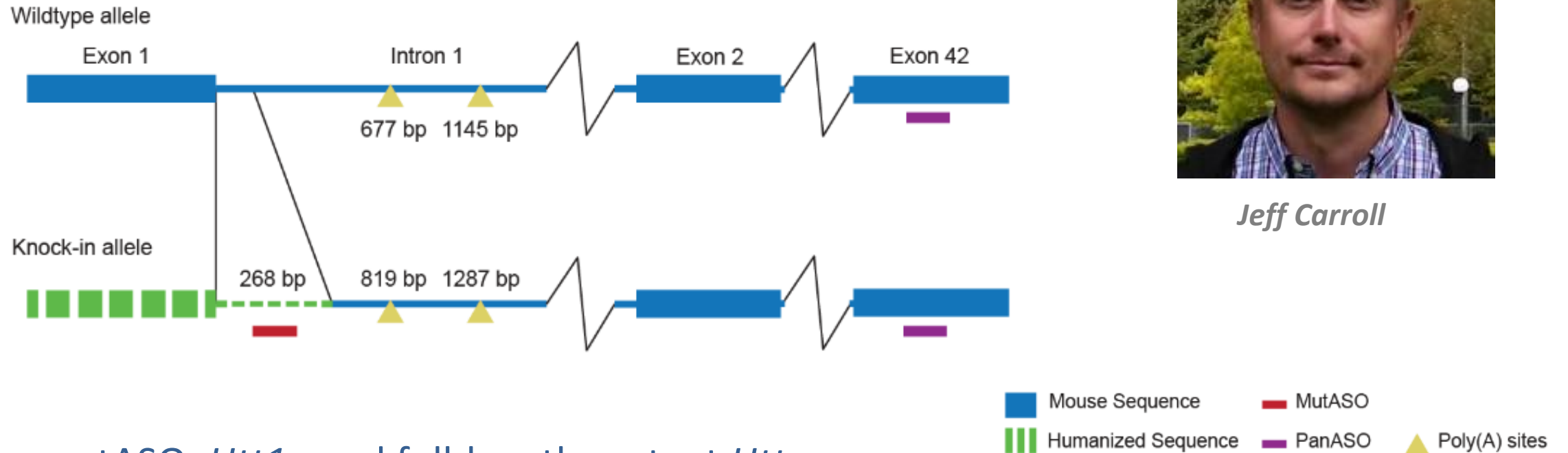
HdhQ111



Comparison of ASOs targeting:

- Mutant and wild type full-length *Htt*
- *Htt1a* and full-length mutant *Htt*

ASOs targeting *Htt* transcripts

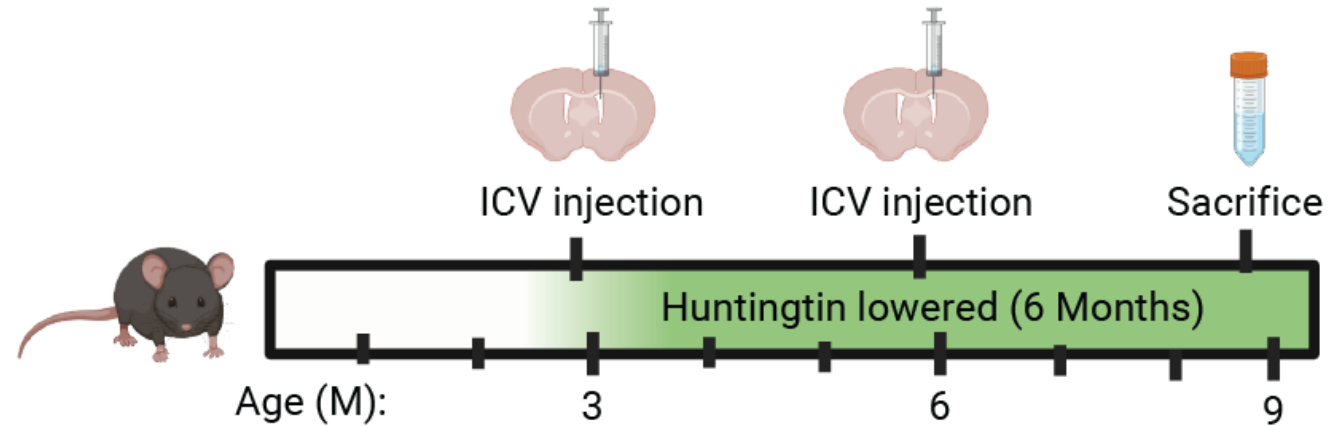


Jeff Carroll

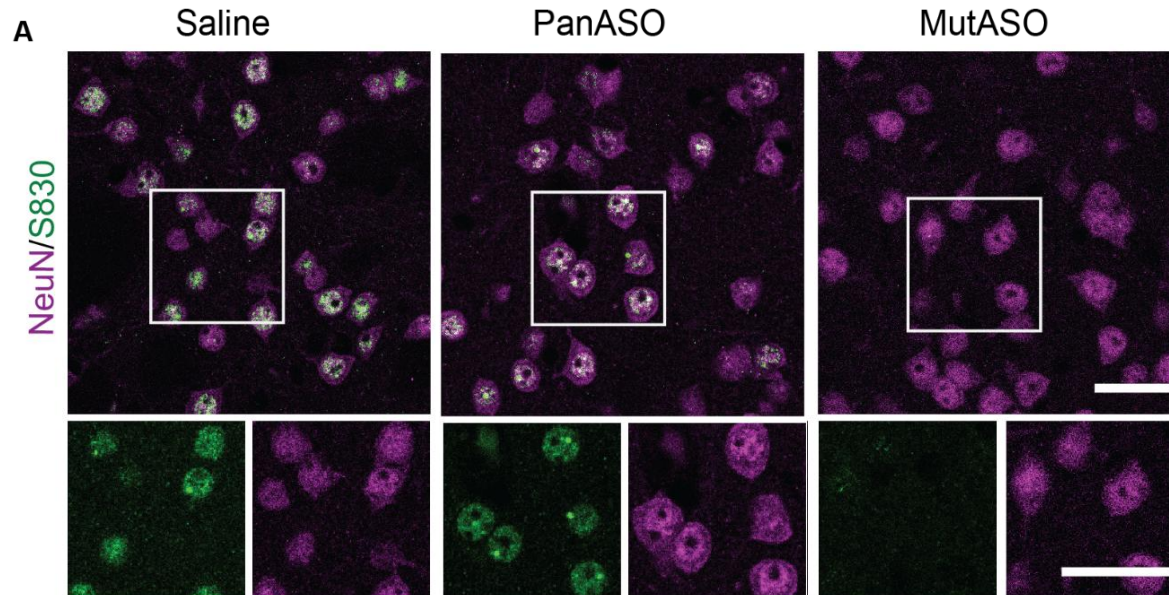
- mutASO: *Htt1a* and full-length mutant *Htt*
- panASO: full-length WT and full-length mutant *Htt*

mutASO targeting *Htt* and *HTT1a* delays molecular phenotypes

*Hdh*Q111 mice

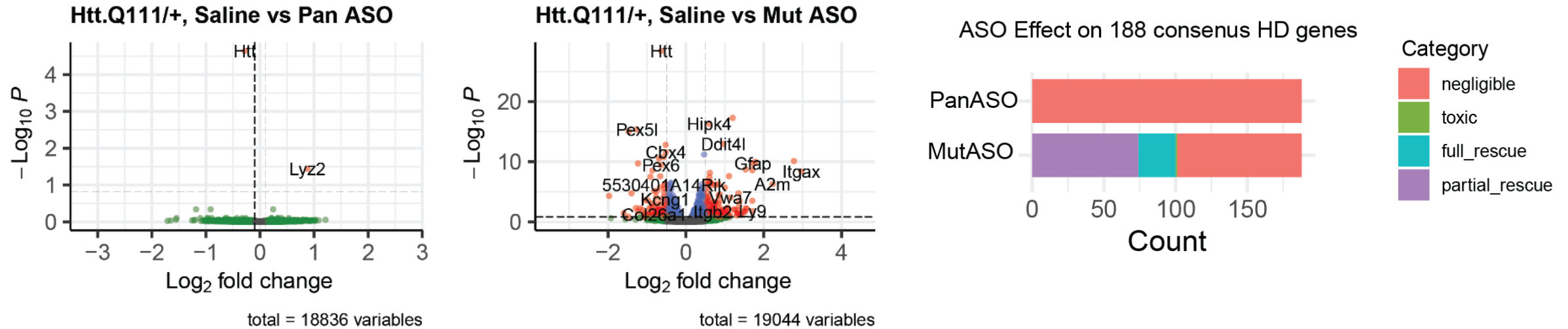


Aggregation in the striatum



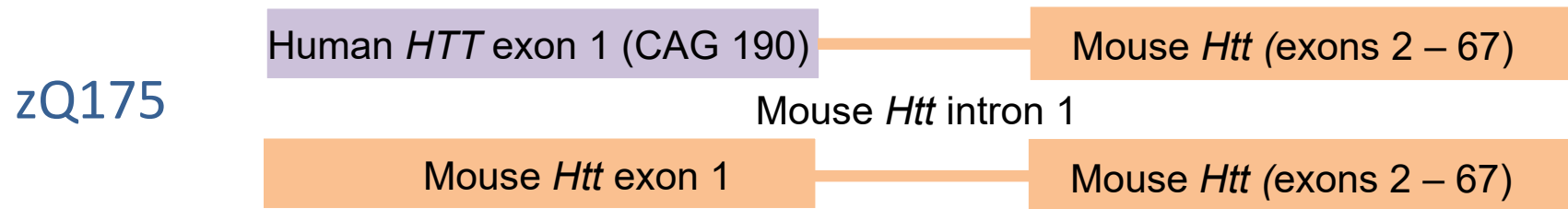
Aggregation delayed by lowering HTT1a and not full-length HTT

mutASO targeting *Htt* and *Htt1a* delays molecular phenotypes



PanASO: full-length wildtype and mutant *Htt* had negligible effect

MutASO: full length mutant *Htt* and *Htt1a* had profound effects



Comparison siRNAs targeting:

- Mutant and wild type full-length *Htt*
- *Htt1a* alone

siRNAs targeting *Htt* transcripts

siRNAs against full length *Htt*



HTT-10150 (3'-UTR)

siRNAs against intron1



I-486 and I-634



Anastasia Khvorova

1 month post administration *in vivo*:

- 10150: specific to full-length *Htt*: decreases WT and mutant *Htt* by ~80%
- 486/634: specific to *Htt1a*: decrease *Htt1a* by ~50%

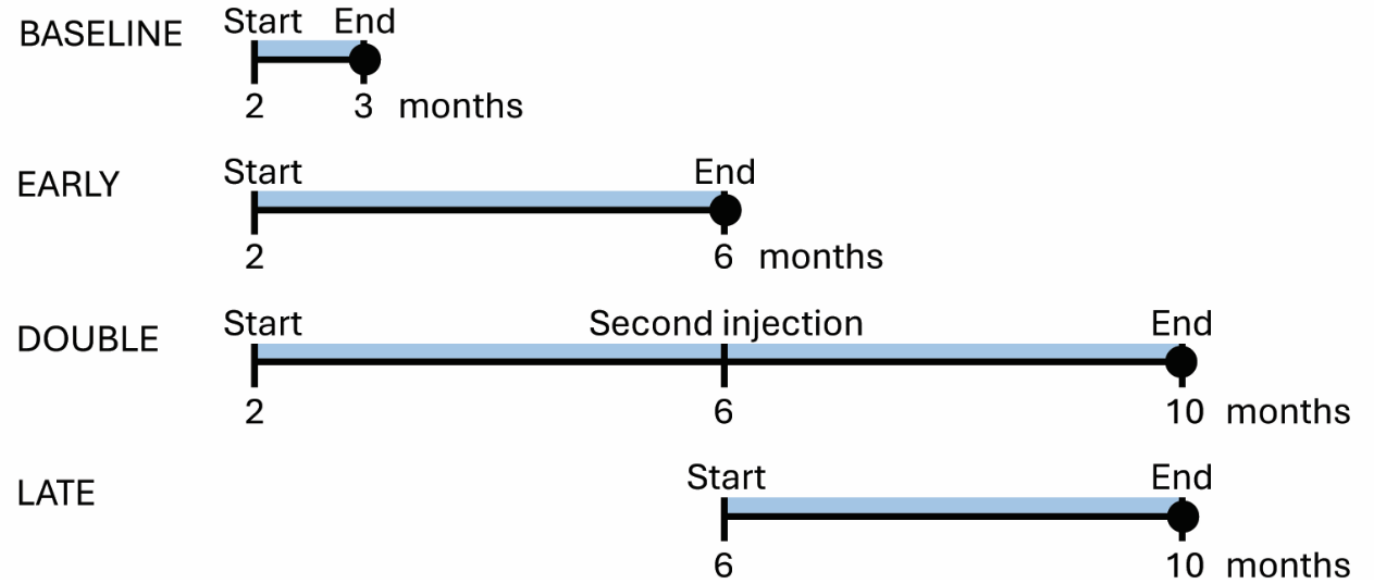
Preclinical trial to lower *Htt* or *Htt1a* levels with siRNAs

Mice: zQ175 and WT

Bilateral ICV injection

10 nmol / ventricle

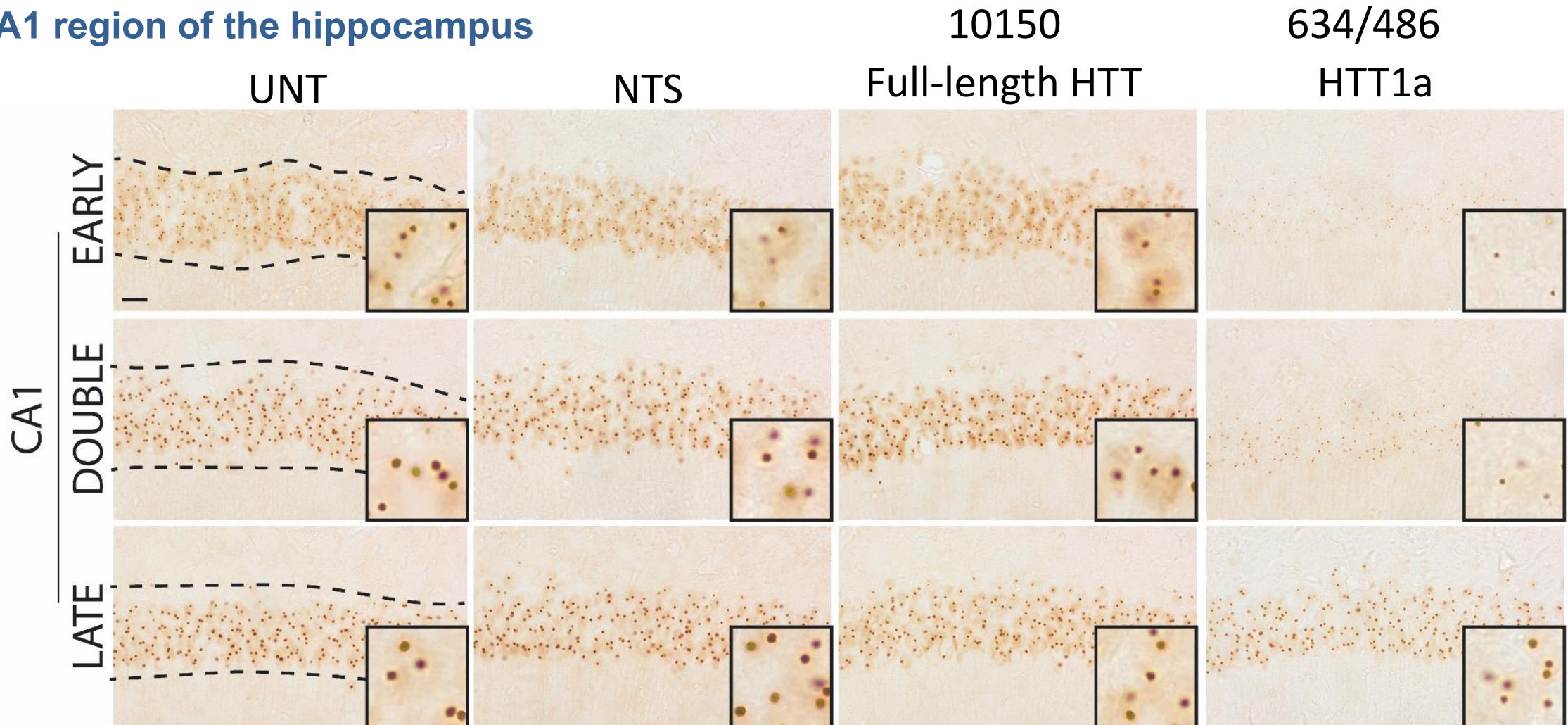
- Untreated
- NTS = non-targeting siRNA
- 10150 = siRNA to full-length *Htt*
- 634/486 = siRNA to *Htt1a*



4 months post administration: potency and durability were greatest in the hippocampus

Effect of lowering HTT or HTT1a on hippocampal HTT aggregation

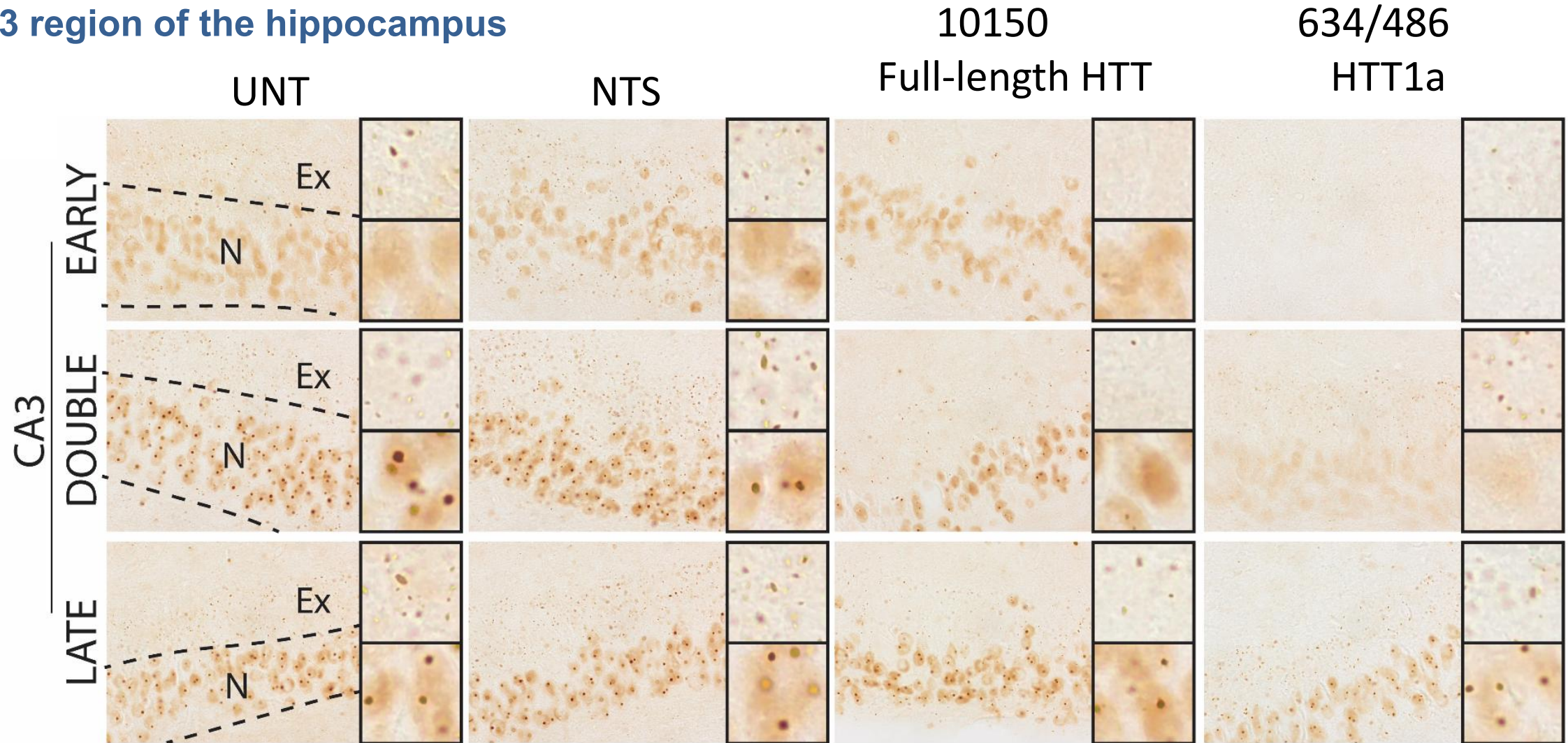
CA1 region of the hippocampus



Decrease in HTT1a but not HTT has profound effect on nuclear aggregation in the CA1

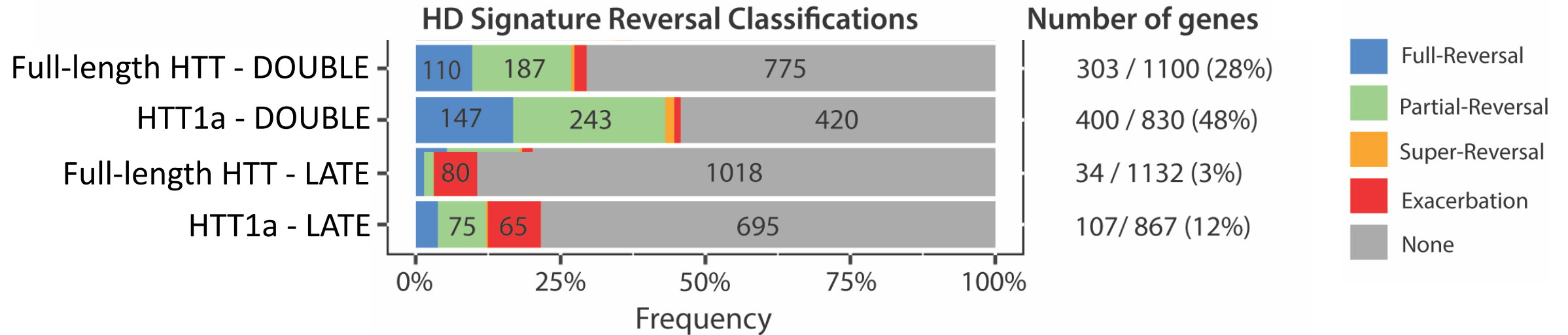
Effect of lowering HTT or HTT1a on hippocampal HTT aggregation

CA3 region of the hippocampus



Decrease in HTT1a more effective than decreasing full-length HTT in the CA3

Effect of lowering HTT or HTT1a on hippocampal transcriptome



Lowering HTT1a by ~50%:

- profound improvements in molecular phenotypes

Lowering full-length HTT by ~80%:

- some improvements in molecular phenotypes

Implications from preclinical research

- Targeting strategy should include *HTT1a*
- Targeting *HTT1a* + full-length mutant *HTT* together may have added benefit

Bates Lab, UCL

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Marie Bondulich
Maria Canibano-Pico
Sandra Fienko
Rachel Flomen
Casandra Gomez-Paredes
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Tom Vogt

Jackson Laboratory

Britt Callaghan





Agenda

01 Introduction

Pushkal Garg, M.D.
Chief Research & Development Officer

02 About Brezosiran (ALN-HTT02)

Kevin Sloan, Ph.D.
*Vice President, Development Programs,
ALN-HTT02 Program Lead*

03 Targeting HTT1a in HTT Lowering Strategies

Gill Bates, Ph.D.
*Professor of Molecular Neuroscience, Co-Director of the
Huntington's Disease Centre, University College London*

04 Clinical Data and Progress

Toby Ferguson, M.D., Ph.D.
*Senior Vice President,
Neuroscience Therapeutic Area Head*

05 Q&A Session



Phase 1b Study of Brezosiran Ongoing in Adults with HD

Study Designed in Partnership with the HD Community

Phase 1b, Randomized, Double-blind, Placebo-Controlled Trial

STUDY OBJECTIVE

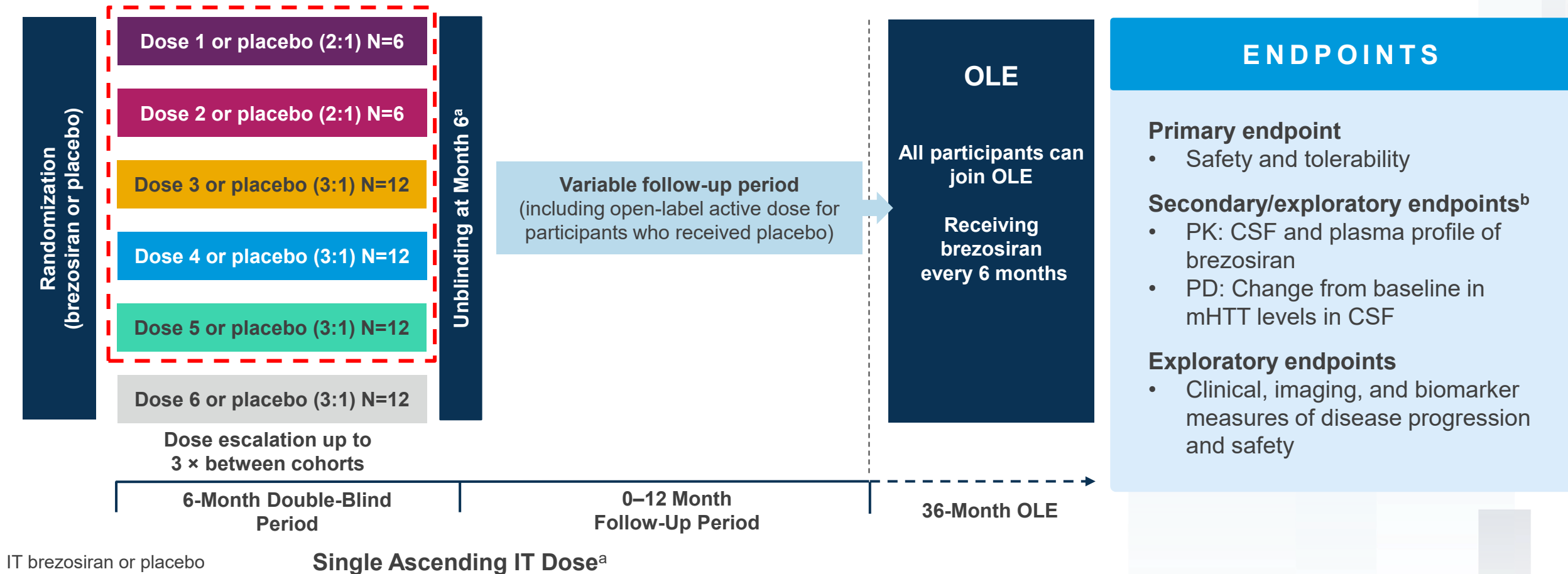
- Evaluate the safety, tolerability, and PK/PD effects of single IT doses of brezosiran

KEY INCLUSION CRITERIA

- Aged 25–70 years
- Genetically confirmed HD with >39 CAG repeats
- HD-ISS Stage 2 or early Stage 3

Phase 1b Study of Brezosiran Underway in Adults with HD

Study Designed in Partnership with the HD Community



^aThe decision to proceed to the next dosing cohort is determined by the Safety Review Committee. Each cohort is unblinded after all participants in a cohort have reached Month 6. ^bPK and PD are secondary endpoints for single-ascending doses and exploratory for repeat doses. CSF, cerebrospinal fluid; HD, Huntington's disease; IT, intrathecal; mHTT, mutant huntingtin; OLE, open-label extension; PD, pharmacodynamic; PK, pharmacokinetic.

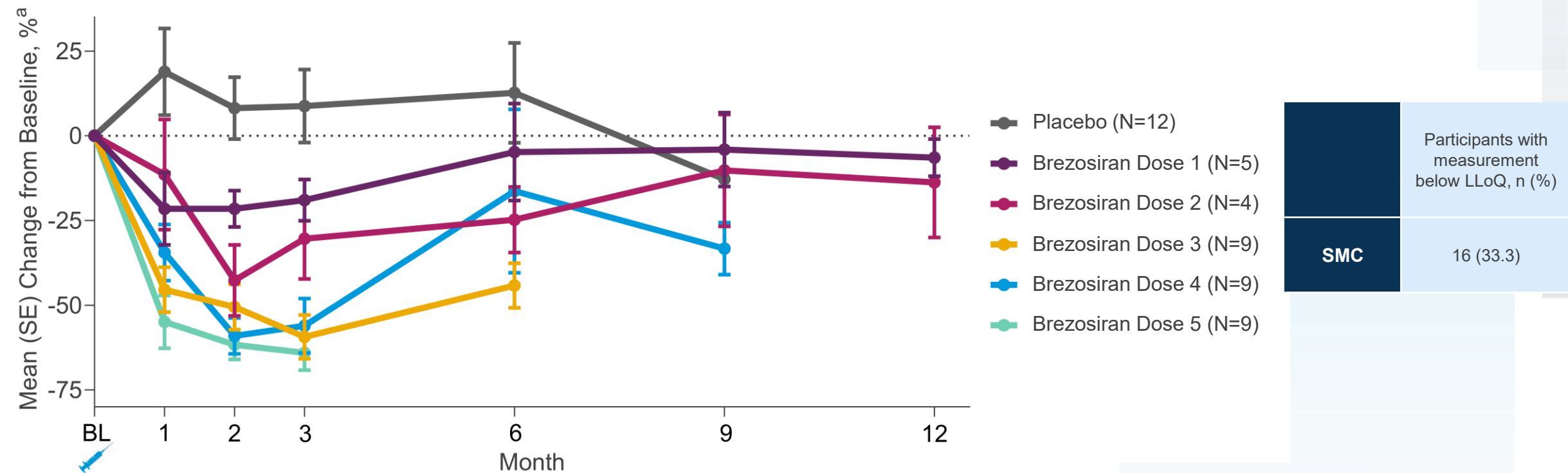
Baseline Patient Characteristics were Similar Across Cohorts

Demographic/Characteristic	Brezosiran dose 1 or placebo (N=6)	Brezosiran dose 2 or placebo (N=6)	Brezosiran dose 3 or placebo (N=12)	Brezosiran dose 4 or placebo (N=12)	Brezosiran dose 5 or placebo (N=12)
Age, years, mean (SD)	52.2 (8.8)	54.7 (9.0)	45.4 (11.0)	51.3 (8.8)	49.9 (8.7)
Female, n (%)	1 (16.7)	2 (33.3)	8 (66.7)	5 (41.7)	6 (50.0)
White, n (%)	5 (83.3)	6 (100.0)	12 (100.0)	10 (83.3)	11 (91.7)
BMI, kg/m ² , mean (SD)	25.8 (4.4)	30.4 (4.3)	28.2 (6.2)	26.1 (4.6)	27.1 (4.9)
HD-ISS stage, n (%)					
2	1 (16.7)	4 (66.7)	7 (58.3)	4 (33.3)	6 (50.0)
3	5 (83.3)	2 (33.3)	5 (41.7)	8 (66.7)	6 (50.0)
Number of CAG repeats, mean (SD)	43.8 (1.6)	42.5 (2.0)	44.8 (4.0)	43.3 (2.1)	43.0 (1.8)
CAP100, mean (SD)	111.0 (23.0)	103.1 (4.5)	98.4 (14.0)	102.5 (8.2)	98.4 (11.8)
Total Functional Capacity, mean (SD)	12.2 (0.8)	12.0 (1.3)	12.5 (0.7)	11.8 (1.1)	12.2 (1.0)

BMI, body mass index; CAP100, CAG Age Product 100 score; HD-ISS, Huntington's Disease Integrated Staging System; SD, standard deviation.

Robust, Dose-Dependent CSF mHTT Reduction Demonstrated with SMC Assay

Up to 64% Mean Reduction at Month 3 and up to 80% Individual Reduction in CSF mHTT After a Single IT Dose of Brezosiran

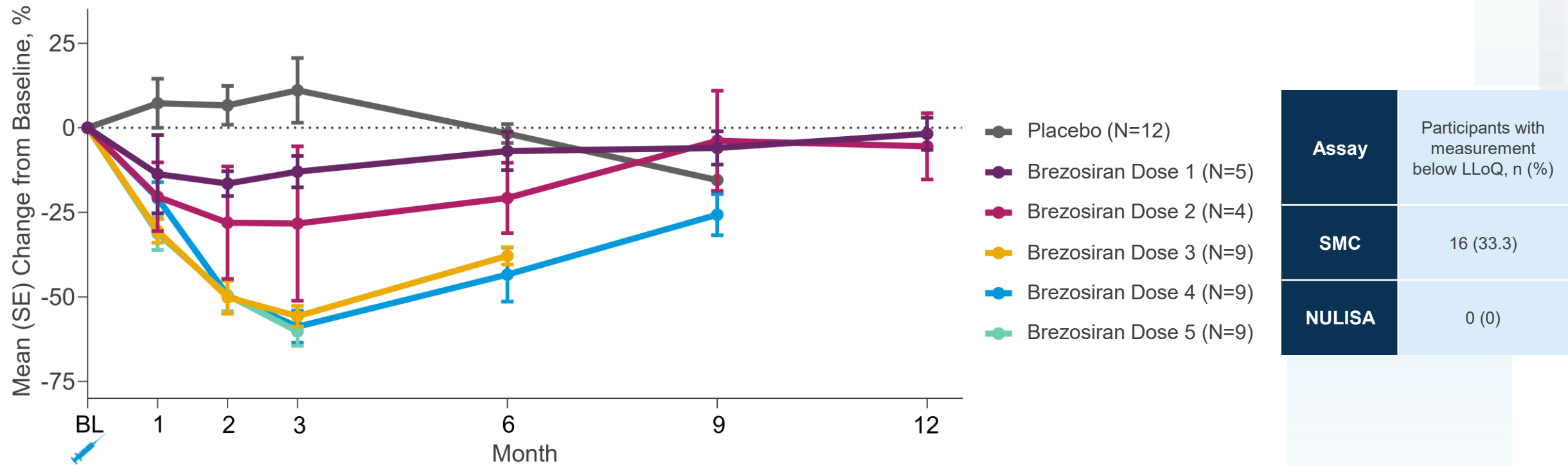


mHTT reduction	Placebo (N=12)	Brezosiran				
		Dose 1 (N=5)	Dose 2 (N=4)	Dose 3 (N=9)	Dose 4 (N=9)	Dose 5 (N=9)
Mean maximum observed, % (SD) ^b	2.9 (25.5)	35.6 (18.0)	45.5 (15.7)	52.9 (22.5)	65.7 (11.8)	64.8 (10.2)
Minimum individual, % ^b	-36.8	19.0	23.5	6.7	49.3	52.0
Maximum individual, % ^b	60.8	63.2	59.7	79.6	80.7	77.2

^{a,b}Post-baseline values reported as less than the LLoQ are set to LLoQ/2, which is the case for 16 participants in figure^a and 12 in table^b. LLoQ = 26.5 fM. BL, baseline; CSF, cerebrospinal fluid; IT, intrathecal; LLoQ, lower limit of quantification; mHTT, mutant huntingtin; SD, standard deviation; SE, standard error; SMC, single molecule counting immunoassay.

Deep, Durable HTT-Lowering Confirmed with NULISA Assay

Up to 60% Mean Reduction at Month 3 and up to 83% Individual Reduction in CSF mHTT After a Single IT Dose of Brezosiran



mHTT reduction	Placebo (N=12)	Brezosiran				
		Dose 1 (N=5)	Dose 2 (N=4)	Dose 3 (N=9)	Dose 4 (N=9)	Dose 5 (N=9)
Mean maximum observed, % (SD) ^b	4.9 (13.2)	28.4 (15.0)	32.2 (26.2)	52.7 (16.2)	57.3 (13.5)	59.2 (12.5)
Minimum individual, % ^b	-16.4	14.1	0.9	14.9	37.0	38.1
Maximum individual, % ^b	21.1	53.7	57.2	66.8	76.6	83.0

We gratefully acknowledge the CHDI Foundation and Alamar Biosciences for establishing the NULISA assay, the Alnylam BioA team, Evotec, and Alamar Biosciences for enabling clinical sample testing. BL, baseline; LLoQ, lower limit of quantification; mHTT, mutant huntingtin; NULISA, NUCleic acid Linked Immuno-Sandwich Assay; SD, standard deviation; SE, standard error; SMC, single molecule counting immunoassay.

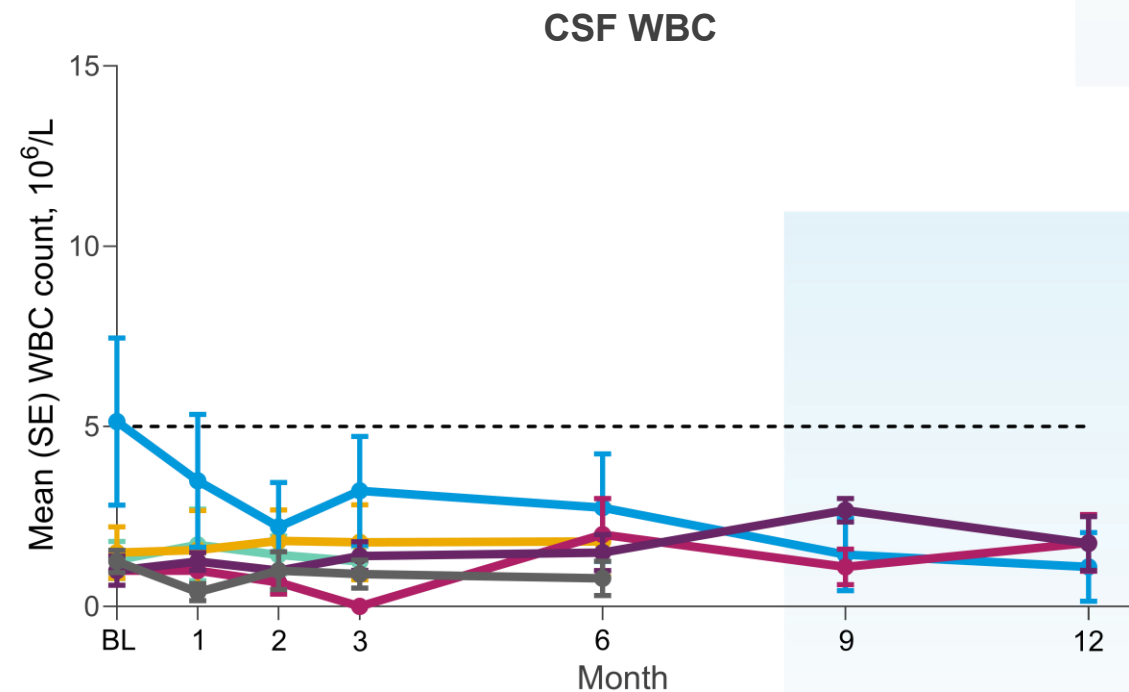
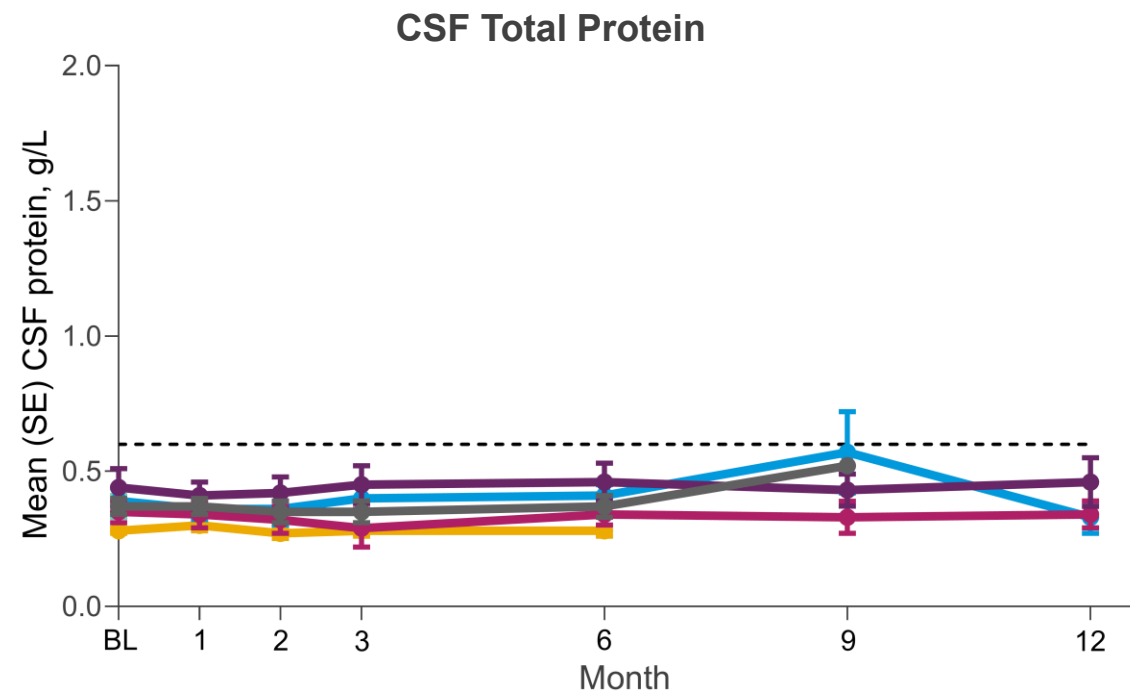
Blinded Safety Summary Supports Encouraging Safety Profile

Active and Placebo Participants Pooled Within Cohort Owing to Ongoing Blinded Study

Category	Brezosiran dose 1 or placebo (N=6)	Brezosiran dose 2 or placebo (N=6)	Brezosiran dose 3 or placebo (N=12)	Brezosiran dose 4 or placebo (N=12)	Brezosiran dose 5 or placebo (N=12)
Duration of study drug exposure, months, mean (SD)	18.7 (2.3)	12.5 (3.7)	6.9 (0.9)	11.4 (0.3)	4.7 (0.5)
At least one AE, n (%)	6 (100.0)	6 (100.0)	10 (83.3)	11 (91.7)	12 (100.0)
At least one severe AE, n (%)	0	1 (16.7)	0	2 (16.7) ^a	0
Related to study drug	0	1 (16.7) ^b	0	0	0
Related to lumbar puncture	0	1 (16.7)	0	1 (8.3)	0
At least one serious AE, n (%)	0	0	0	4 (33.3) ^c	0
Related to study drug	0	0	0	0	0
Related to lumbar puncture	0	0	0	2 (16.7)	0
Death, n (%)	0	0	0	0	0
At least one AE of clinical interest, n (%)	1 (16.7) ^d	0	0	1 (8.3) ^e	0

Data shown for double-blind period as of September 10, 2026. ^aTwo severe AEs were reported: radius fracture and likely bacterial meningitis; both were also reported as serious AEs. ^bOne participant experienced headache; assessed as severe, non-serious; the event was resolved. ^cFour serious AEs were reported: acute myocardial infarction (resolved with sequelae), radius fracture (resolved), post-lumbar puncture syndrome (resolved), and likely bacterial meningitis (resolving). None was assessed as related to study drug. ^dOne patient had one mild event of asthenia assessed as mild, unrelated to study drug or lumbar puncture; the event was resolved. ^eOne patient had one mild event of feeling of imbalance not related to study drug or lumbar puncture; the event was resolved. AE, adverse event; SD, standard deviation.

No Increase in CSF Inflammatory Markers

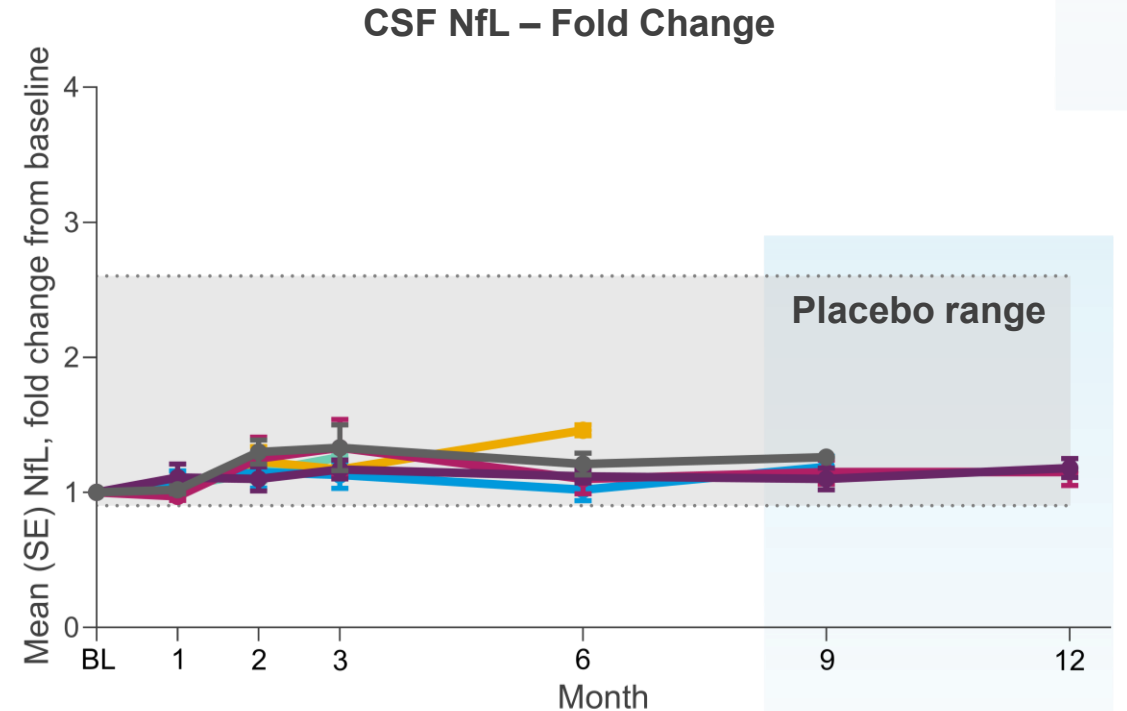
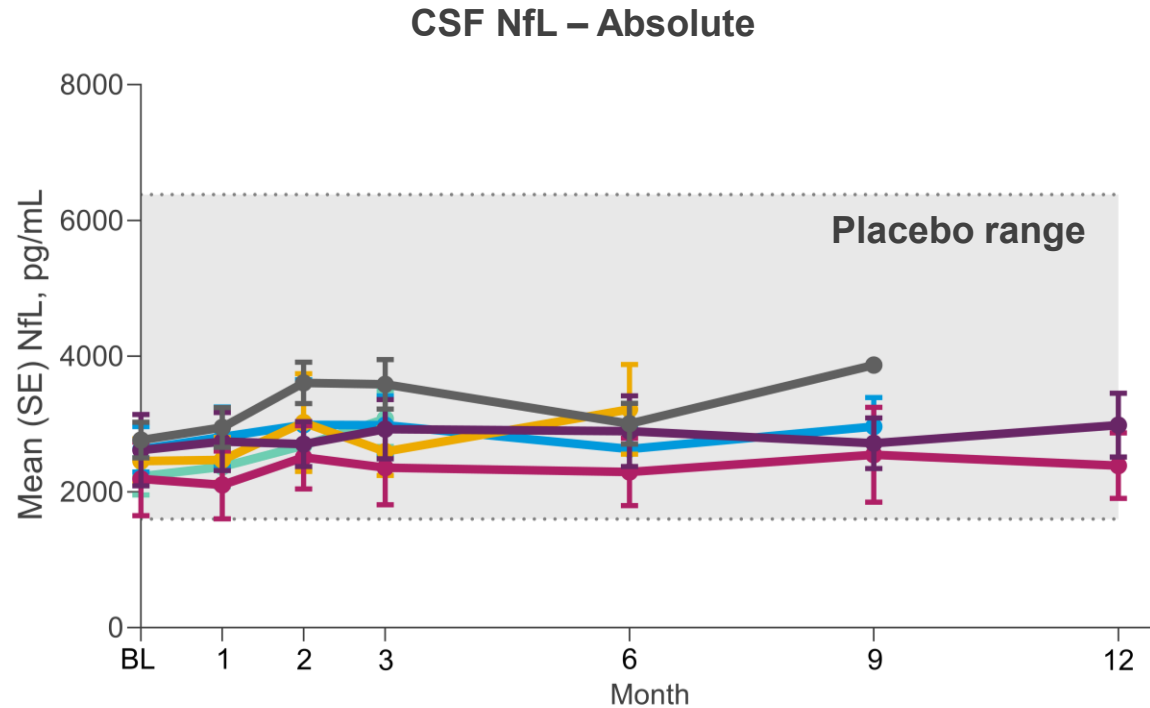


- Placebo (N=12)
- Brezosiran Dose 1 (N=5)
- Brezosiran Dose 2 (N=4)
- Brezosiran Dose 3 (N=9)
- Brezosiran Dose 4 (N=9)
- Brezosiran Dose 5 (N=9)

CSF total protein data from one participant in each of the dose 3 and dose 4 groups, and the 12-month data point from one participant in the dose 1 group, were excluded owing to suspected site input error. Dashed lines denote typical reference values. BL, baseline; CSF, cerebrospinal fluid; SE, standard error; WBC, white blood cell.

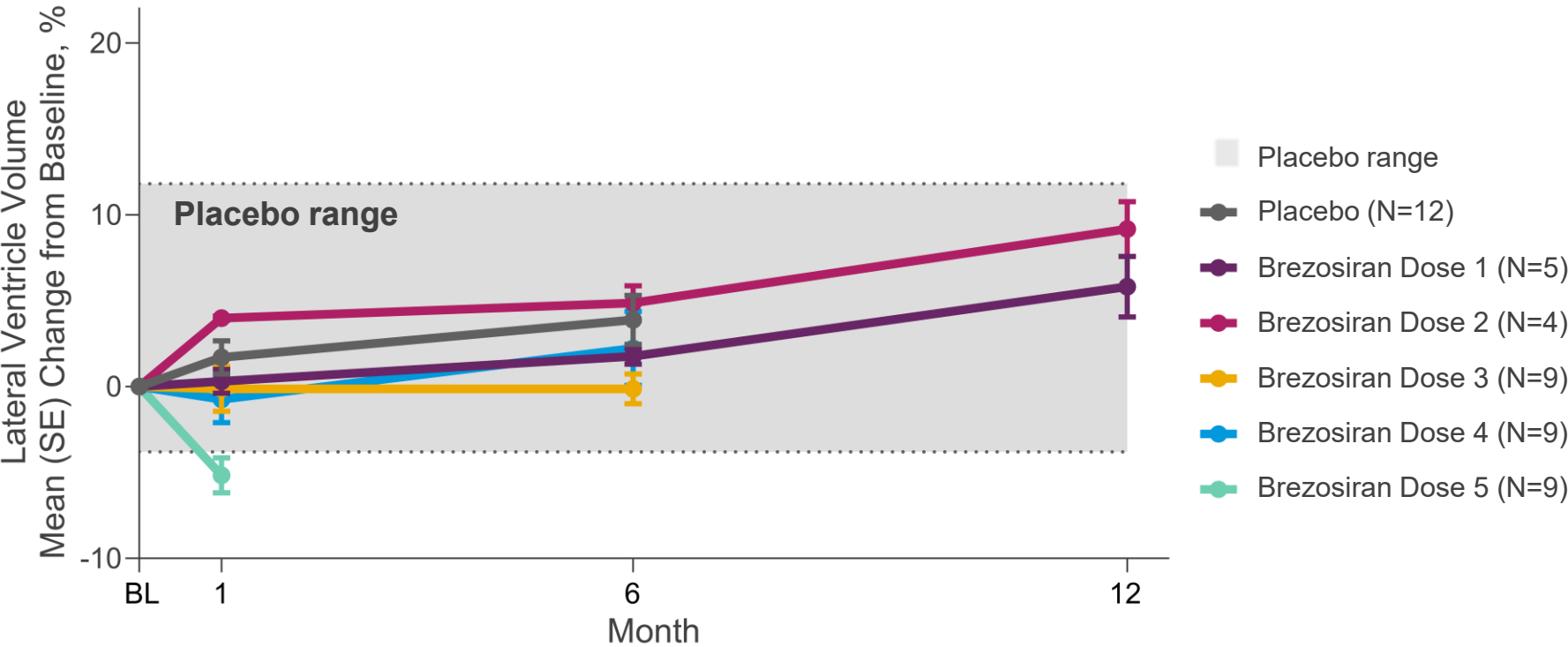
No Dose-Dependent Increases in CSF NfL

NfL is a biomarker of neuroaxonal injury



No Dose-Dependent Increases in Ventricle Size

No Increases Beyond Placebo Range Despite Robust mHTT-Lowering



NULISA assay	Placebo (N=12)	Brezosiran dose 1 (N=5)	Brezosiran dose 2 (N=4)	Brezosiran dose 3 (N=9)	Brezosiran dose 4 (N=9)	Brezosiran dose 5 (N=9)
Mean maximum observed mHTT reduction, % (SD)	4.9 (13.2)	28.4 (15.0)	32.2 (26.2)	52.7 (16.2)	57.3 (13.5)	59.2 (12.5)

Shaded placebo range indicates maximum and minimum observed individual placebo values. BL, baseline; mHTT, mutant huntingtin; NULISA, NUCleic acid Linked Immuno-Sandwich Assay; SD, standard deviation; SE, standard error.



Advancing Parallel Studies as Part of Commitment to HD Community

Investing in a large, placebo-controlled pivotal study, pending regulatory alignment

ONGOING

Phase 1b study (adults with HD)

Single ascending dose study to characterize target engagement and safety of brezosiran

ONGOING

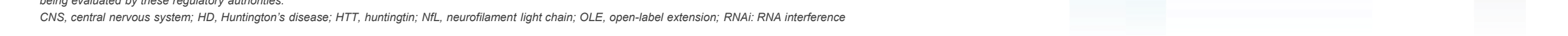
Phase 1b open-label extension study (adults with HD)

All participants eligible; repeat dosing every 6 months
Further characterizing safety of sustained HTT lowering and potential efficacy trends over time

PLAN TO INITIATE IN 2027

Pivotal, placebo-controlled efficacy study (adults with HD)

Definitive efficacy study to test whether brezosiran can slow HD progression



Brezosiran's Potential: Differentiated Approach to Lower All Forms of HTT with Encouraging Safety To Date

INCLUSIVE EXON-1 TARGETING STRATEGY

Approach designed to lower all
HTT isoforms, including HTT1a

DEEP, DURABLE HTT-LOWERING

Initial Phase 1b results show a
60%-64% mean reduction in CSF
mHTT at month 3 and up to 83%
individual reduction from baseline

ENCOURAGING SAFETY PROFILE

No evidence to date of:

- CNS inflammation (CSF protein, WBC)
- NfL increases
- Ventricular enlargement

Brezosiran is an investigational therapeutic in development for Huntington's Disease. The safety and efficacy of brezosiran have not been established or approved by the FDA, EMA or any other health authority. Safety and efficacy brezosiran are currently being evaluated by these regulatory authorities.

CNS, central nervous system; HD, Huntington's disease; HTT, huntingtin; NfL, neurofilament light chain; OLE, open-label extension; RNAi: RNA interference

Opportunity to Impact a Sizeable, High Unmet Need Population

Efficient Commercialization Path for an Effective HD Therapeutic

Genetically identifiable patient population

Established Huntington Disease Center
of Excellence network

Growing provider familiarity with
intrathecal injection

Strong patient advocacy groups



POTENTIAL MULTI-BILLION DOLLAR OPPORTUNITY



**Diagnosed Symptomatic
Patients**

~100K Global¹

~33K US¹



Alyssa

Living with the Huntington's disease gene

 Alnylam



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04 Clinical Data and Progress

Toby Ferguson, M.D., Ph.D.
*Senior Vice President,
Neuroscience Therapeutic Area Head*

05 Q&A Session

A photograph of two women sitting at a table in a dimly lit room, possibly a kitchen or dining area. The woman on the left is older with short grey hair, wearing a white and red patterned cardigan over a blue top. The woman on the right is younger with dark hair, wearing a green and white patterned cardigan over a blue top. They are both laughing heartily, looking towards the right. The background is dark with some kitchen items visible on a counter. A warm light source is visible behind them, creating a soft glow.

Silence disease

Amplify life™

 Alnylam®