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Wave Life Sciences

Corporate Presentation

April 1, 2021

Forward-looking statements

This document contains forward-looking statements. All statements other than statements of historical facts contained in this document, including statements regarding possible or assumed future results of operations, preclinical and clinical studies, business strategies, research and development plans, collaborations and partnerships, regulatory activities and timing thereof, competitive position, potential growth opportunities, use of proceeds and the effects of competition are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause the actual results, performance or achievements of Wave Life Sciences Ltd. (the "Company") to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "expect," "plan," "aim," "anticipate," "could," "intend," "target," "project," "contemplate," "believe," "estimate," "predict," "potential" or "continue" or the negative of these terms or other similar expressions. The forward-looking statements in this presentation are only predictions. The Company has based these forward-looking statements largely on its current expectations and projections about future events and financial trends that it believes may affect the Company's business, financial condition and results of operations. These forward-looking statements speak only as of the date of this presentation and are subject to a number of risks, uncertainties and assumptions, including those listed under Risk Factors in the Company's Form 10-K and other filings with the SEC, some of which cannot be predicted or quantified and some of which are beyond the Company's control. The events and circumstances reflected in the Company's forward-looking statements may not be achieved or occur, and actual results could differ materially from those projected in the forward-looking statements. Moreover, the Company operates in a dynamic industry and economy. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risk factors and uncertainties that the Company may face. Except as required by applicable law, the Company does not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

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Building a leading genetic medicines company

INNOVATIVE PLATFORM

- Stereopure oligonucleotides
- Novel backbone modifications (PN chemistry)
- Allele-selectivity
- Multiple modalities (silencing, splicing, ADAR editing)
- Strong IP position[1]

FOUNDATION OF NEUROLOGY PROGRAMS

- Huntington's disease
- ALS / FTD
- Neuromuscular diseases
- Ataxias
- Parkinson's disease
- Alzheimer's disease

PRISM

Wave's discovery and drug development platform

CLINICAL DEVELOPMENT EXPERTISE

- Multiple global clinical trials
- Innovative trial designs

MANUFACTURING

- Established internal manufacturing capabilities to produce oligonucleotides at scale

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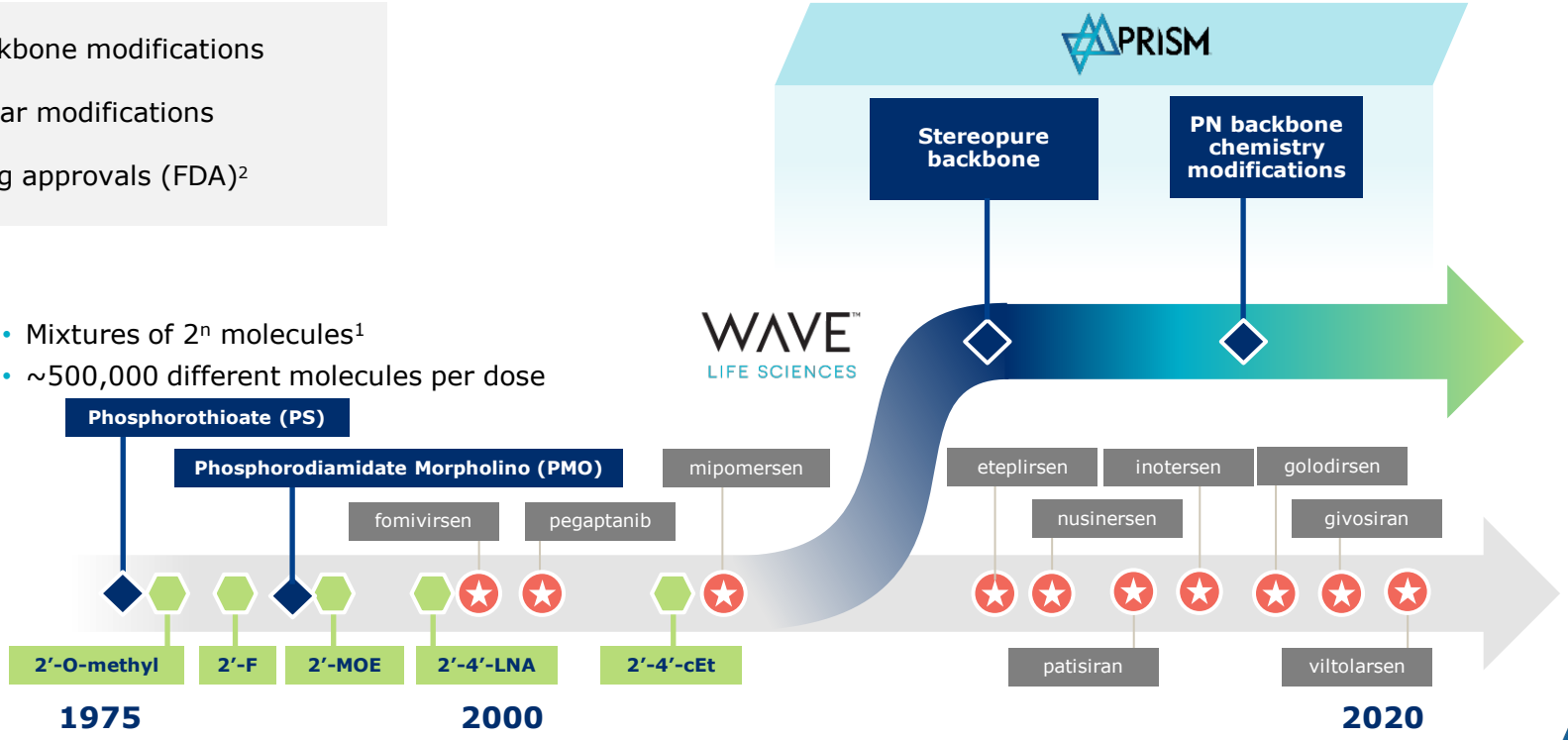
ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia
[1]stereopure oligonucleotides and novel backbone chemistry modifications

PRISM has unlocked novel and proprietary advances in oligonucleotide design

- Backbone modifications
- Sugar modifications
- Drug approvals (FDA)[2]

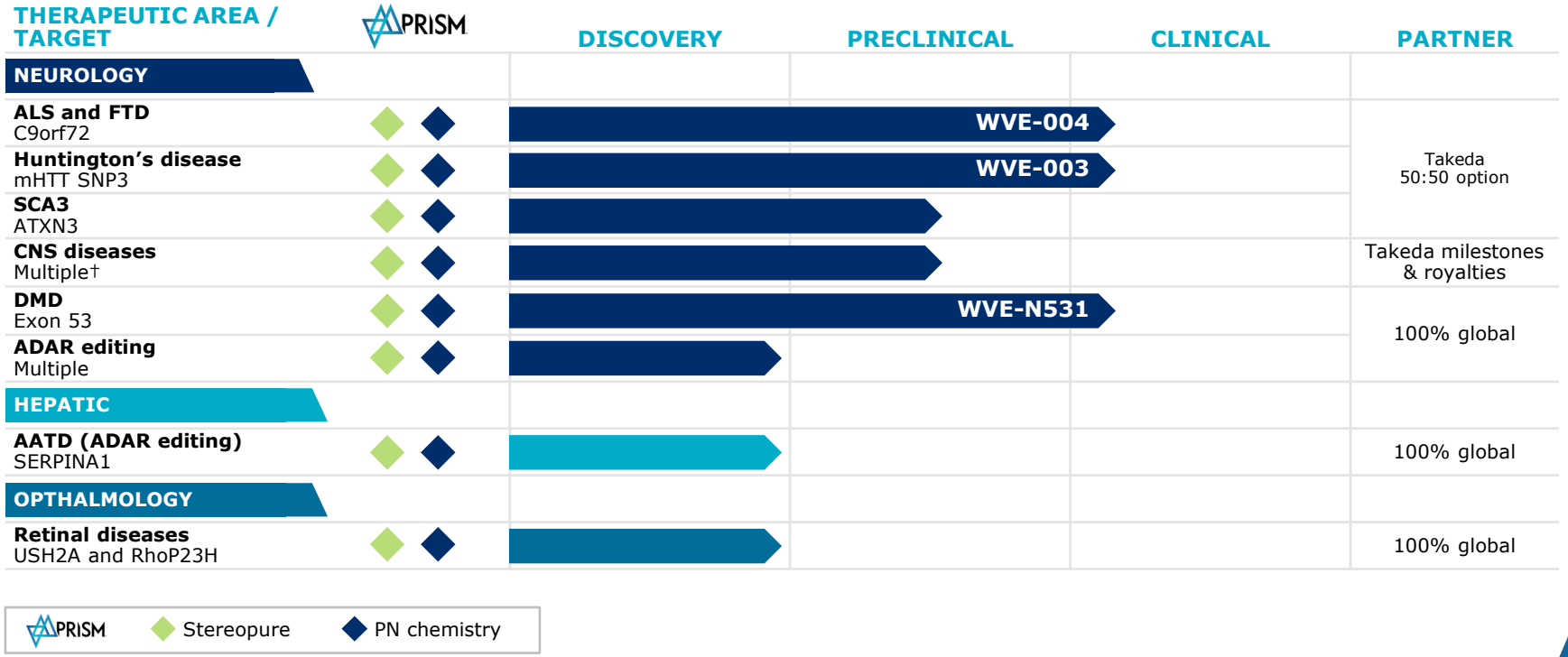
- Mixtures of 2^n molecules[1]
- ~500,000 different molecules per dose



[1]n=number of chiral centers

[2]oligonucleotide therapies approved by the FDA across the industry

Innovative pipeline led by neurology programs



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†During a four-year term, Wave and Takeda may collaborate on up to six preclinical targets at any one time.
ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; SCA3: Spinocerebellar ataxia 3; CNS: Central nervous system;
DMD: Duchenne muscular dystrophy; AATD: Alpha-1 antitrypsin deficiency

Platform evolution reflected in three upcoming clinical trials to start in 2021

Oligonucleotide innovation and optimization
- PN backbone chemistry modifications
- Interactions between sequence, chemistry and stereochemistry

***In vivo* models**
- Insight into PK / PD relationships
- Novel model generation

Leverage learnings of first generation programs
- Translational pharmacology
- Adaptive clinical trial design

C9orf72

WVE-004

Variant-selective silencing candidate in ALS and FTD

SNP3

WVE-003

Allele-selective silencing candidate in HD

Exon 53

WVE-N531

Exon skipping candidate in DMD

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HD: Huntington's disease ALS: amyotrophic lateral sclerosis FTD: frontotemporal dementia DMD: Duchenne muscular dystrophy

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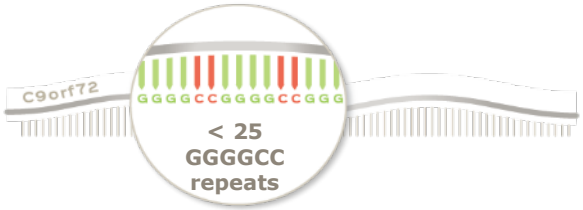
WVE-004

Amyotrophic Lateral Sclerosis (ALS)

Frontotemporal Dementia (FTD)

C9orf72 repeat expansions: A critical genetic driver of ALS and FTD

Normal (non-expanded) Allele



Expanded Allele

- C9orf72 hexanucleotide repeat expansions (GGGGCC) are one of the most common genetic causes of the sporadic and inherited forms of Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD)
- The C9orf72 repeat expansions also lead to accumulation of repeat-containing transcripts, nuclear sequestration of RNA binding proteins and synthesis of toxic dipeptide-repeat (DPR) proteins
- The C9orf72 repeat expansions lead to reduced expression of wild-type C9orf72 and to cellular changes that reduce neuronal viability

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Sources: DeJesus-Hernandez et al, Neuron, 2011. Renton et al, Neuron, 2011. Zhu et al, Nature Neuroscience, May 2020

C9-ALS and C9-FTD: Manifestations of a clinical spectrum

	Disease	C9 specific US population	Mean disease duration	Standard of care
C9-ALS	• Fatal neurodegenerative disease • Progressive degeneration of motor neurons in brain and spinal cord	~2,000	3.1 years	Significant unmet need despite two approved therapies in US
C9-FTD	• Progressive neuronal atrophy in frontal/temporal cortices • Personality and behavioral changes, gradual impairment of language skills	~10,000	6.4 years	No approved disease modifying therapies

Two devastating diseases with a shared genetic basis

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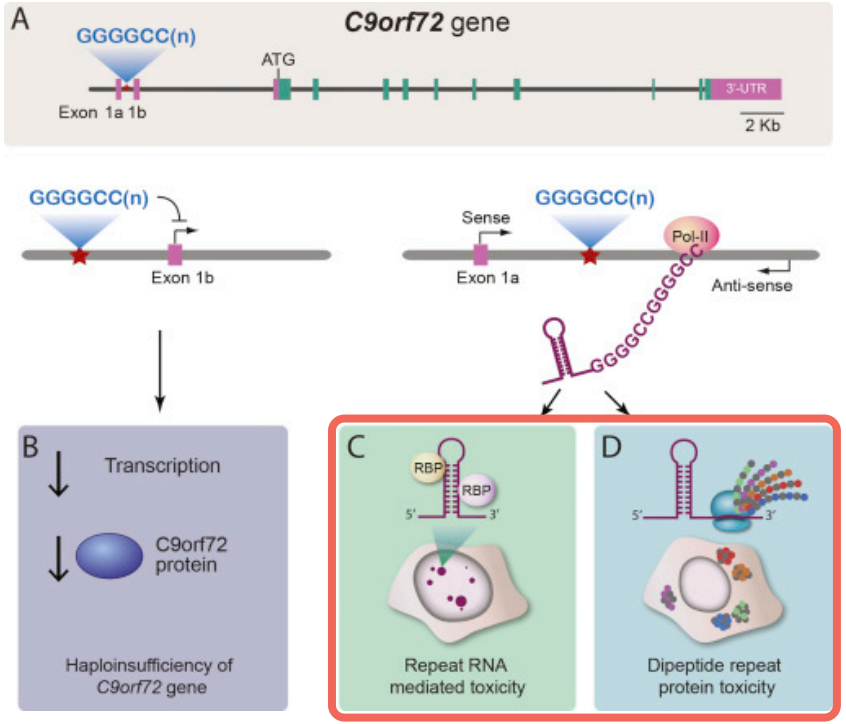
ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia
Sources: Cammack et al, Neurology, October 2019. Moore et al, Lancet Neurology, February 2020

C9orf72 repeat expansions: Mechanisms of cellular toxicity

- C9-ALS and C9-FTD may be caused by multiple factors:
  - Insufficient levels of C9orf72 protein
  - Accumulation of repeat-containing RNA transcripts
  - Accumulation of aberrantly translated DPR proteins
- Recent evidence suggests lowering C9orf72 protein exacerbates DPR-dependent toxicity

Variant-selective targeting could address multiple potential drivers of toxicity



Targeted by Wave ASOs

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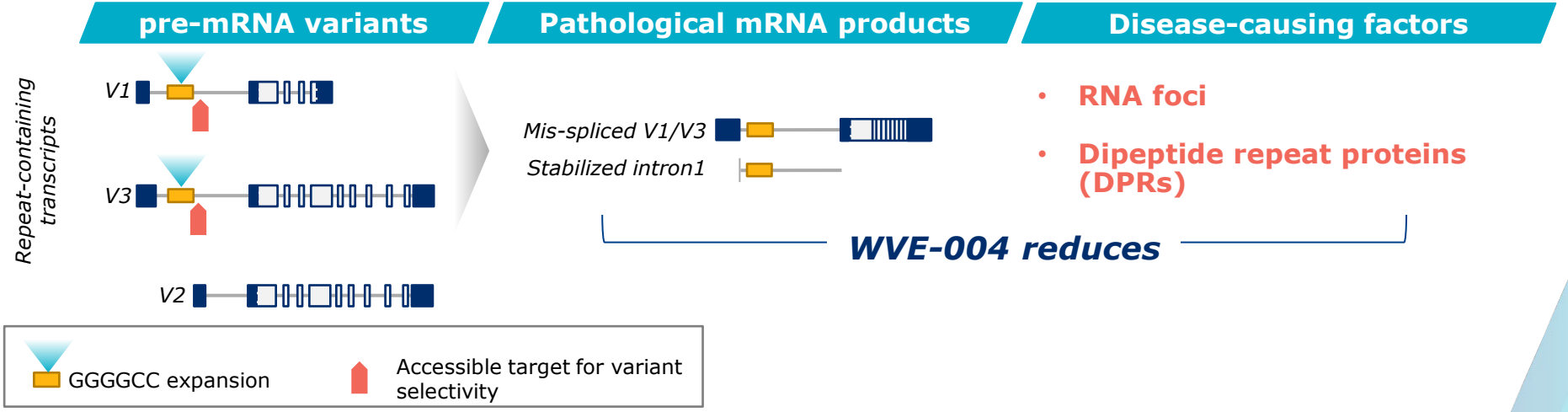
Sources: Gitler et al, Brain Research, September 2016. Zhu et al, Nature Neuroscience, May 2020

C9orf72 targeting strategy spares C9orf72 protein

- Normal C9orf72 allele produces three mRNA transcripts (~80% are V2, ~20% are V1 and V3)
- **Pathological allele** with expanded repeat leads to **healthy V2** and **pathological V1 and V3** transcript by-products



WVE-004 targets only V1 and V3 transcripts, sparing V2 transcripts and healthy C9orf72 protein

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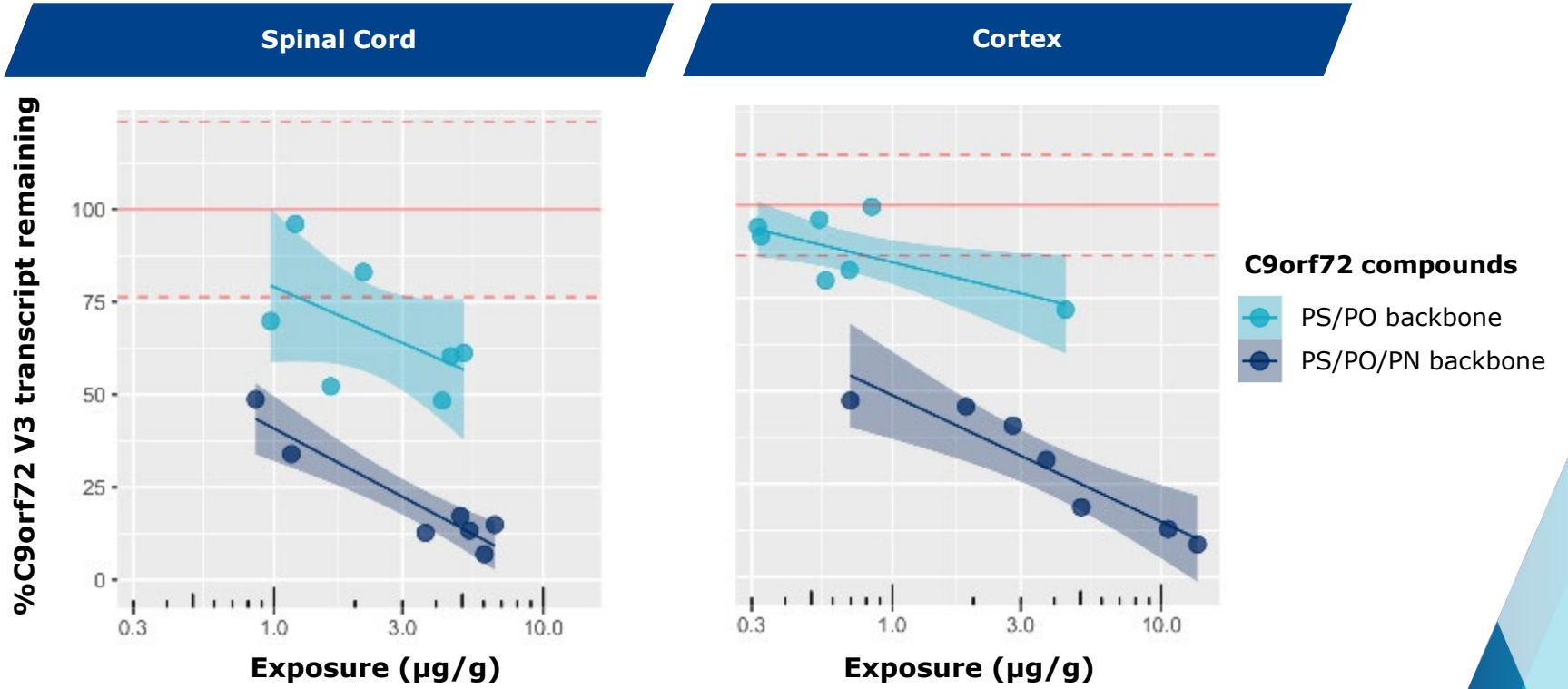
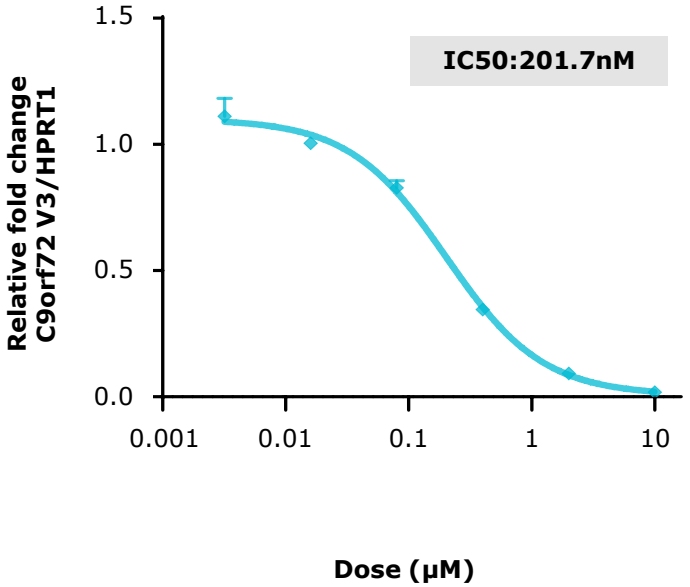
PN backbone chemistry modifications: Improved potency among C9orf72-targeting oligonucleotides *in vivo*



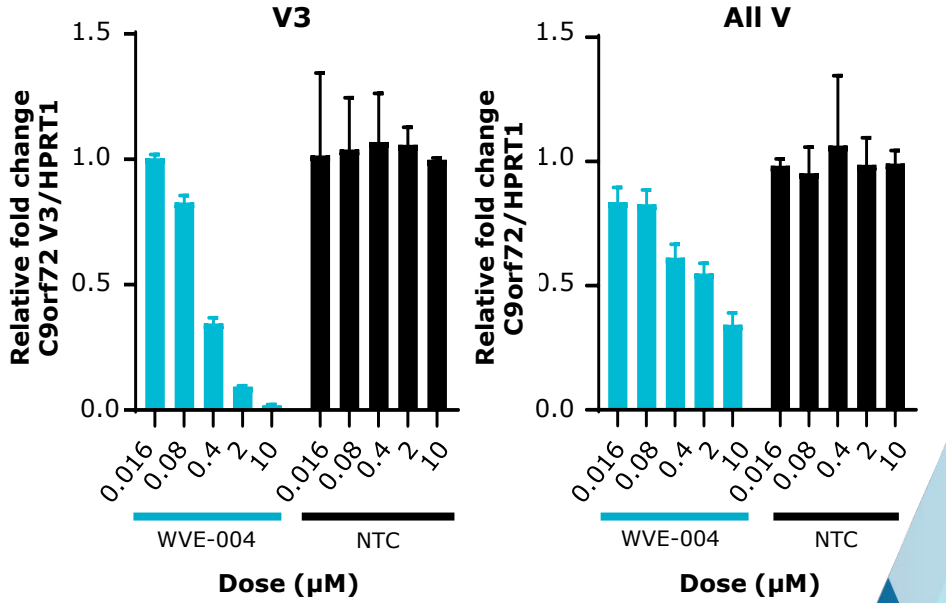
Mice received 2 x 50 ug ICV doses on days 0 & 7; mRNA from spinal cord and cortex quantified by PCR (Taqman assay) 8 weeks later. Oligonucleotide concentrations quantified by hybridization ELISA. Graphs show robust best fit lines with 95% confidence intervals (shading) for PK-PD analysis.

WVE-004: Potent and selective knockdown of repeat-containing transcripts *in vitro*

In vitro activity in C9 patient-derived neurons



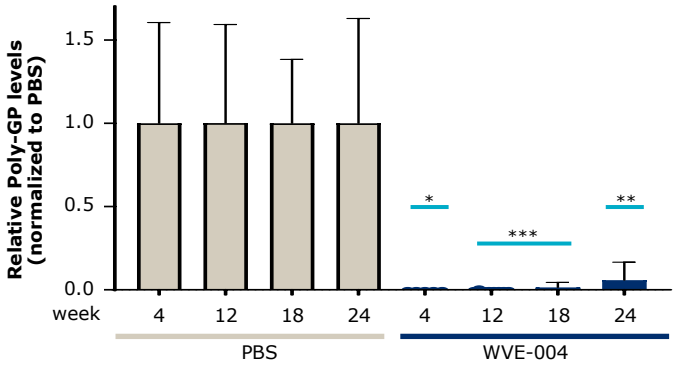
In vitro selectivity in C9 patient-derived neurons



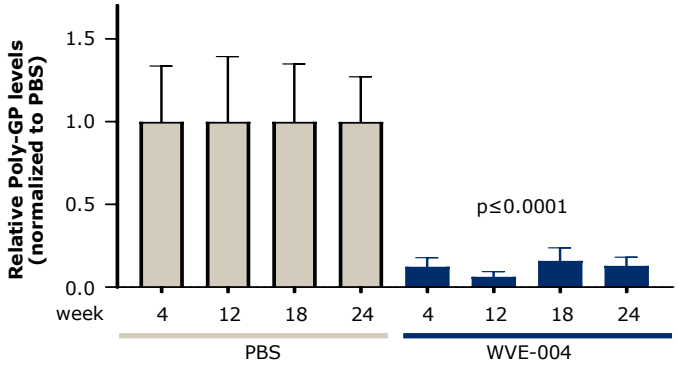
C9 patient-derived motor neurons were treated with C9orf72 candidate and NTC under gymnotic conditions up to 10uM. Taqman qPCR assays were used to evaluating V3 and all V transcripts. NTC- non-targeting control.

WVE-004 demonstrates durable reduction of DPRs in vivo after 6 months in spinal cord and cortex

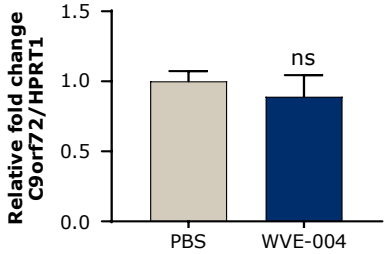
Spinal cord

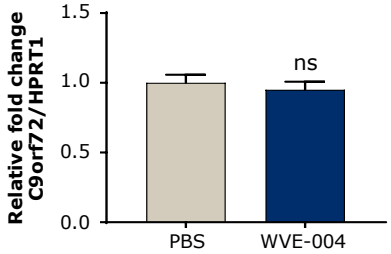


Cortex



Healthy C9orf72 protein relatively unchanged ~6 months after WVE-004 administration





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Full results presented at the 31st International Symposium on ALS/ MND (December 2020)
Top: 2 x 50 ug (day 0, day 7) dosed ICV; DPRs measured by Poly-GP MSD assay. *: p≤ 0.05 **: P ≤ 0.01, ***: P ≤ 0.001. ICV: intracerebroventricular; DPR: Dipeptide repeat protein; Bottom: C9 BAC transgenic mice administered PBS or 50 ug WVE-004, ICV, (day 0, day 7). ns: not significant; PBS: phosphate-buffered saline

WVE-004: Adaptive SAD/MAD design to optimize dose level and frequency

- Patients with documented C9orf72 expansion and confirmed ALS, FTD, or mixed phenotype (up to 50 patients planned)
- Starting dose informed by preclinical *in vivo* models
- Dose escalation and dosing interval guided by safety committee
- Key biomarkers of target engagement and neurodegeneration will be assessed
  - PolyGP
  - NfL
- Key exploratory clinical outcome measures
  - ALSFRS-R and CDR-FTLD
- Clinical trial site activation ongoing

Dosing in Phase 1b/2a trial expected to initiate in 2021

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CTA: clinical trial application; NfL: neurofilament light chain; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale; CDRFTLD: Clinical Dementia Scale – frontotemporal lobar degeneration; PolyG: poly glycine-proline; SAD: Single ascending dose; MAD: Multiple ascending dose

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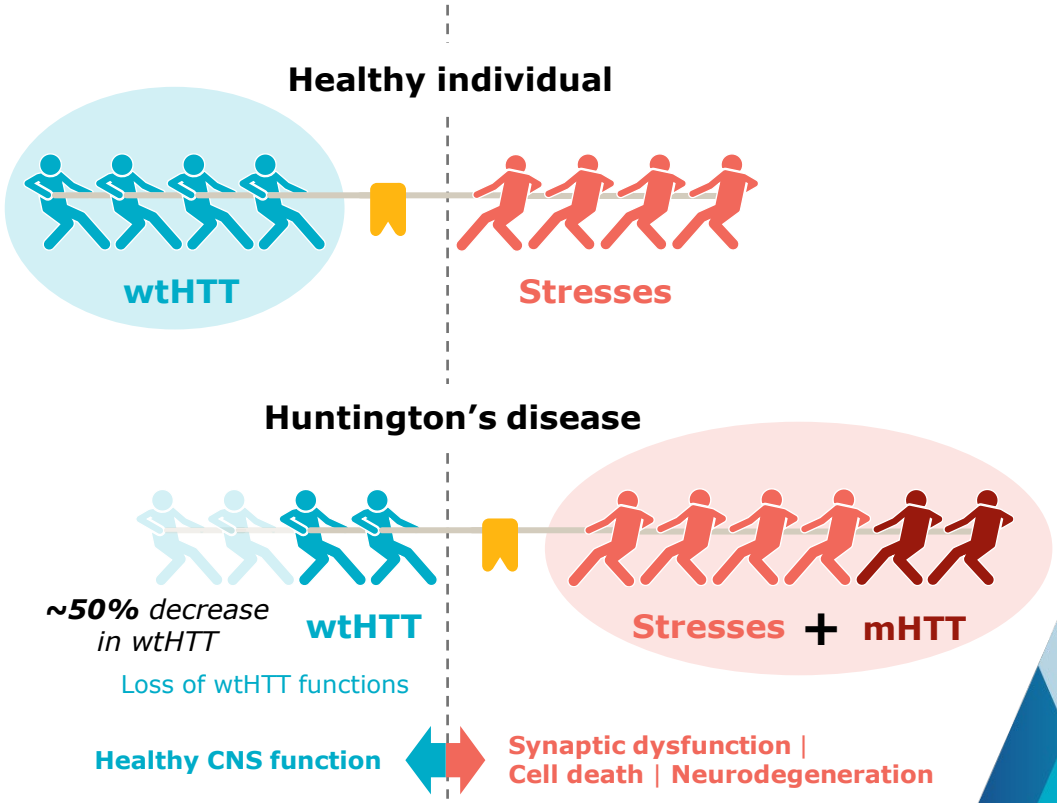
WVE-003

Huntington's Disease

mHTT toxic effects lead to neurodegeneration, loss of wtHTT functions may also contribute to HD

- Wild-type HTT is critical for normal neuronal function
- Expanded CAG triplet repeat in HTT gene results in production of mutant huntingtin protein
- Huntington's disease affects entire brain
- Monogenic autosomal dominant genetic disease; fully penetrant
- Characterized by cognitive decline, psychiatric illness, and chorea; fatal disease



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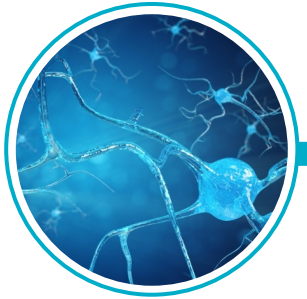
HD: Wild-type HTT is a critical protein for important functions in the central nervous system

NEURON



Promotes neuronal survival by protecting against stress (e.g., excitotoxicity, oxidative stress, toxic mHTT aggregates)[1-8]

SYNAPSE

Plays an essential role in the transport of synaptic proteins—including neurotransmitters and receptors—to their correct location at synapses[9-12]

BRAIN CIRCUITS

Supplies BDNF to the striatum to ensure neuronal survival[13-16]

Regulates synaptic plasticity, which underlies learning and memory[17-22]

CSF CIRCULATION

Plays a critical role in formation and function of cilia—sensory organelles that control the flow of CSF—which are needed to clear catabolites and maintain homeostasis[23]

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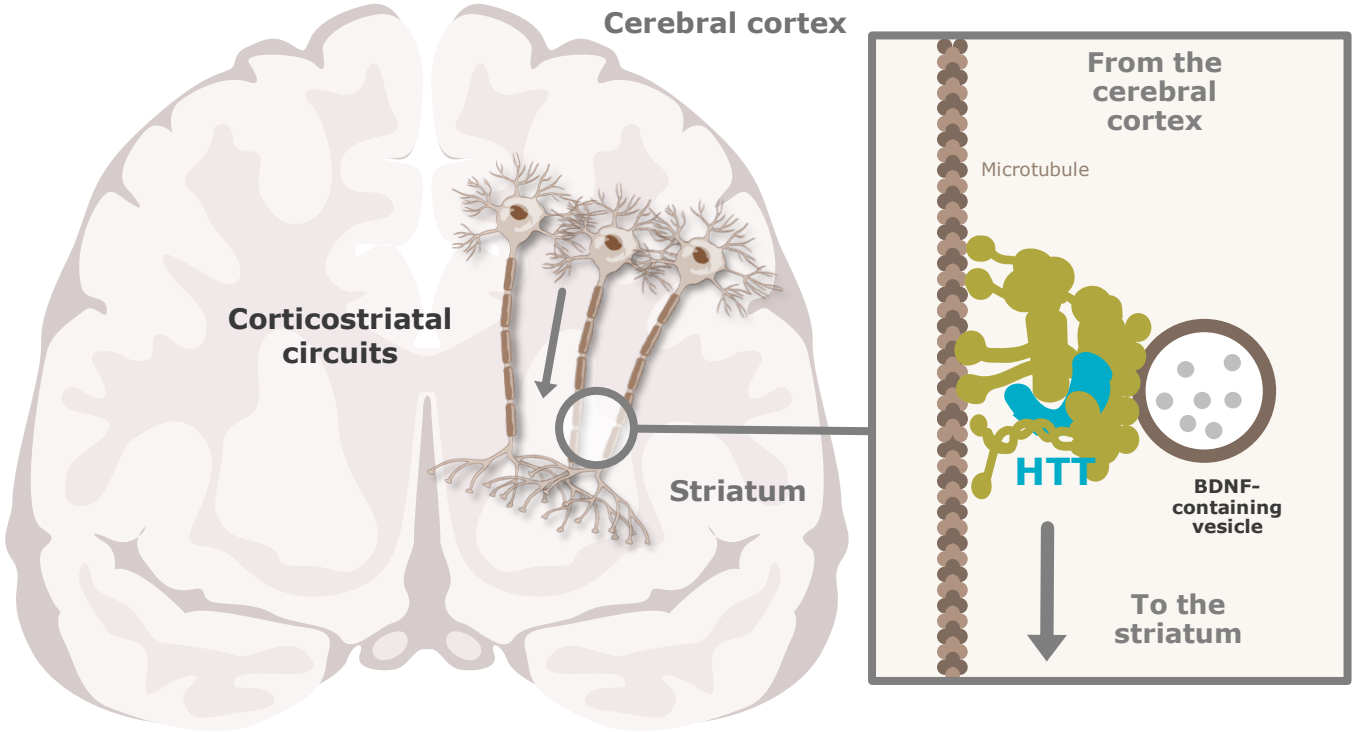
BDNF, brain-derived neurotrophic factor; CSF, cerebrospinal fluid; mHTT, mutant huntingtin protein. Sources: 1. Leavitt 2006 2. Cattaneo 2005 3. Kumar 2016 4. Franco-Iborra 2020 5. Hamilton 2015 6. Ochaba 2014 7. Wong 2014 8. Rui 2015 9. Caviston 2007 10. Twelvetrees 2010 11. Strehlow 2007 12. Milnerwood 2010 13. Smith-Dijak 2019 14. Tousley 2019 15. Zhang 2018 16. McAdam 2020 17. Altar 1997 18. Zuccato 2001 19. Gauthier 2004 20. Ferrer 2000 21. Baquet 2004 22. Liu 2011 23. Karam 2015

HTT provides BDNF, a growth factor critical for survival of striatal neurons



Striatal neurons do not produce BDNF, but they need it to survive[1]

HTT promotes the production of BDNF and transports BDNF from the **cortex** to the striatum[2,3]

In HD, decreased levels of BDNF contribute to degeneration of corticostriatal circuits[2,4,5]

Reduction of wtHTT may decrease the availability of BDNF and accelerate corticostriatal degeneration[6]

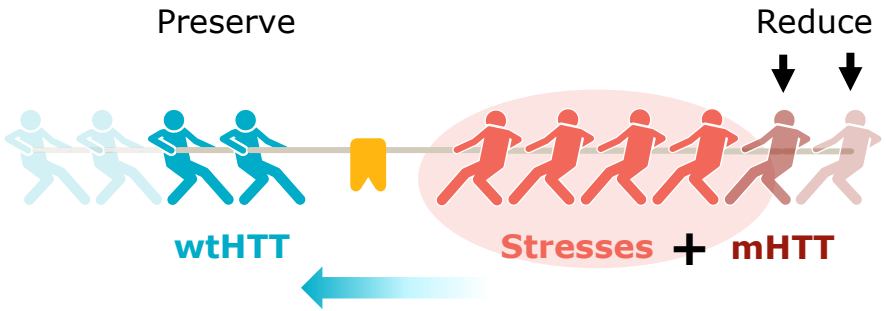
BDNF, brain-derived neurotrophic factor; HD, Huntington's disease; HTT, huntingtin protein.

1. Altar CA, Cai N, Bliven T, et al. *Nature*. 1997;389(6653):856-860. 2. Zuccato C, Ciammola A, Rigamonti D, et al. *Science*. 2001;293(5529):493-498. 3. Gauthier LR, Charrin BC, Borrell-Pagès M, et al. *Cell*. 2004;118(1):127-138. 4. Ferrer I, Goutan E, Marín C, et al. *Brain Res*. 2000;866(1-2):257-261. 5. Baquet ZC, Gorski JA, Jones KR. *J Neurosci*. 2004;24(17):4250-4258. 6. Cattaneo E, et al. *Nat Rev Neurosci*. 2005;6(12):919-930.

Allele-selective approach to treating HD

Wave has only allele-selective clinical program in Huntington's disease

- ✓ Target mutant mRNA HTT transcript to reduce mutant HTT protein
- ✓ Preserve wild-type HTT protein reservoir in brain



Only an allele-selective approach is designed to address <u>both</u> toxic gain of function and toxic loss of function drivers of HD

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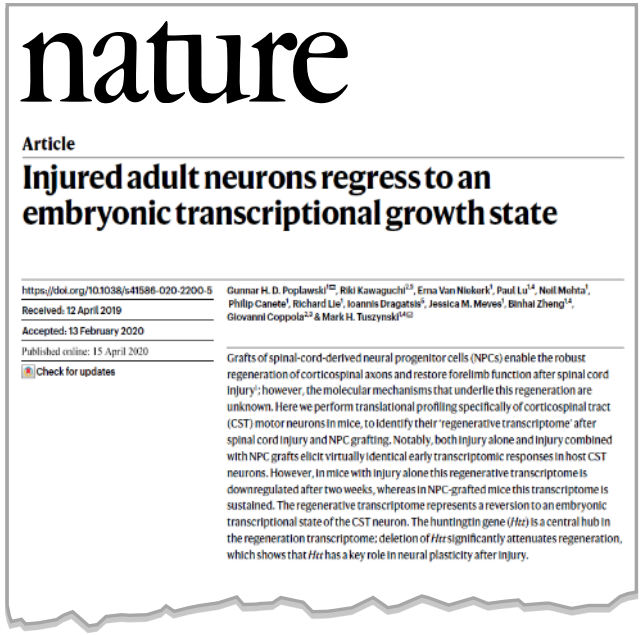
Nature publication contributes to weight of evidence on importance of wild-type huntingtin



nature

Article

Injured adult neurons regress to an embryonic transcriptional growth state

https://doi.org/10.1038/s41586-020-2200-5
Received: 12 April 2019
Accepted: 13 February 2020
Published online: 15 April 2020
Check for updates

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Grafts of spinal-cord-derived neural progenitor cells (NPCs) enable the robust regeneration of corticospinal axons and restore forelimb function after spinal cord injury[1]; however, the molecular mechanisms that underlie this regeneration are unknown. Here we perform translational profiling specifically of corticospinal tract (CST) motor neurons in mice, to identify their 'regenerative transcriptome' after spinal cord injury and NPC grafting. Notably, both injury alone and injury combined with NPC grafts elicit virtually identical early transcriptomic responses in host CST neurons. However, in mice with injury alone this regenerative transcriptome is downregulated after two weeks, whereas in NPC-grafted mice this transcriptome is sustained. The regenerative transcriptome represents a reversion to an embryonic transcriptional state of the CST neuron. The huntingtin gene (*Htt*) is a central hub in the regeneration transcriptome: deletion of *Htt* significantly attenuates regeneration, which shows that *Htt* has a key role in neural plasticity after injury.

- Conditional knock-out of Htt in 4-month old mice (post-neuronal development)
- Results suggest that:
  1) Htt plays a central role in the regenerating transcriptome (potentially influencing genes such as NFKB, STAT3, BDNF)
  2) Htt is essential for regeneration

> **"Indeed, conditional gene deletion showed that Htt is required for neuronal repair. Throughout life, neuronal maintenance and repair are essential to support adequate cellular functioning"**

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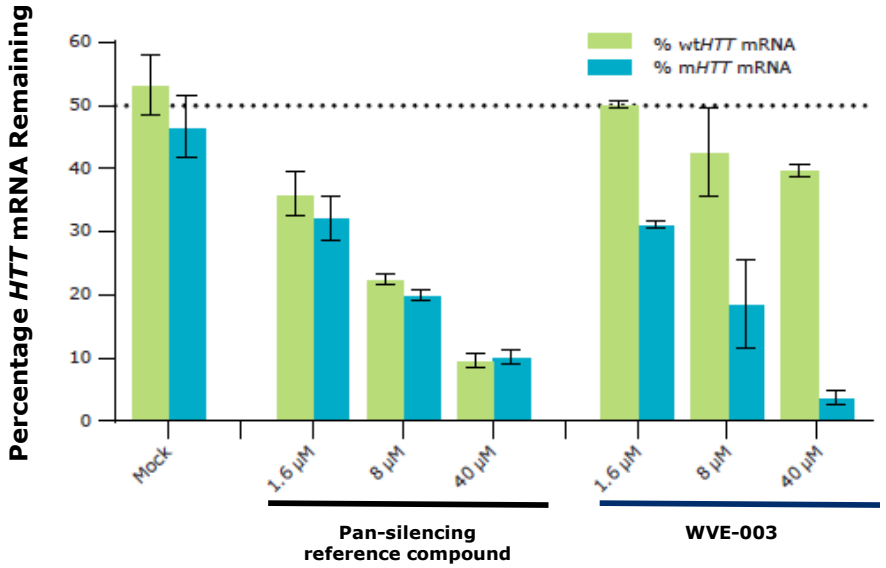
Source: Poplawski et al., *Nature*, April 2019
Htt: Huntingtin protein

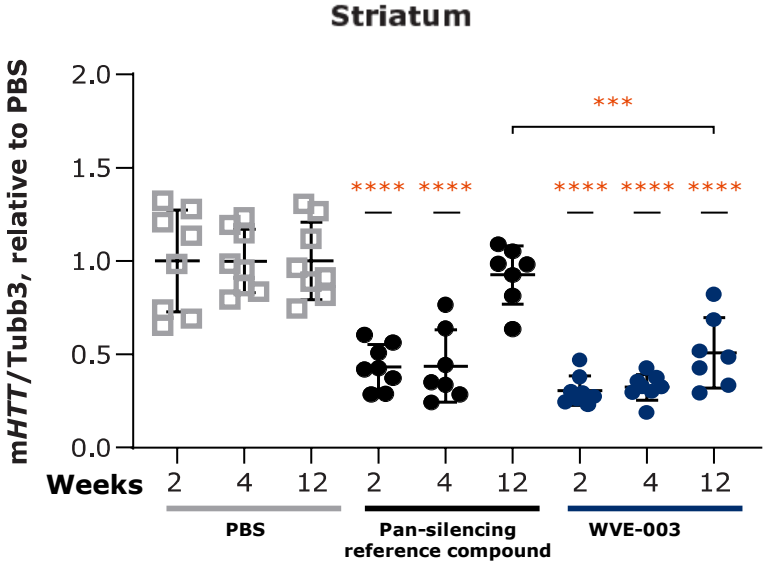
WVE-003 (SNP3) demonstrates selective, potent, and durable reduction of mHTT in preclinical models

Incorporates PN backbone chemistry modifications

Selectively reduces mHTT mRNA in HD iPSC neurons in vitro



Durable striatal mHTT knockdown for 12 weeks in BACHD mouse model



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Results from ND50036 iPSC-derived medium spiny neurons. Total *HTT* knockdown quantified by qPCR and normalized to HPRT1
Oligonucleotide or PBS [100 µg ICV injections through a cannula on days 1, 3, and 5] delivered to BACHD transgenic. Mean ± SD (n=8, **P*<0.0332, ****P*<0.0002, *****P*<0.0001 versus PBS unless otherwise noted).
HPRT1, hypoxanthine-guanine phosphoribosyl transferase; iPSC, induced pluripotent stem cell; ICV, intracerebroventricular; PBS, phosphate-buffered saline

PK-PD modeling to guide dosing in clinical trial

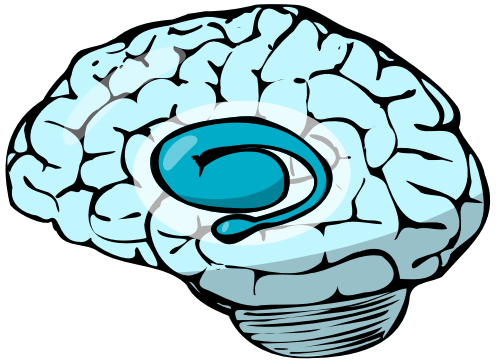
BACHD

Ascending dose studies
- PK & mHTT knockdown data
- IC_{50} determination

NHP

Concentrations in **cortex** and **striatum** sufficient for target engagement

Human
(cortex, striatum)



Anticipated mHTT knockdown in **cortex** and **striatum**

PK: pharmacokinetic PD: pharmacodynamic IC_{50}: the concentration of observed half of the maximal effect mHTT: mutant huntingtin protein

WVE-003: Clinical trial to leverage experience and learnings in HD

Leveraging learnings from PRECISION-HD

- Starting dose informed by preclinical *in vivo* models
- Asuragen assay to improve efficiency of patient identification
- Drawing from experience of sites from PRECISION-HD1 and PRECISION-HD2 trials

Adaptive SAD/MAD design

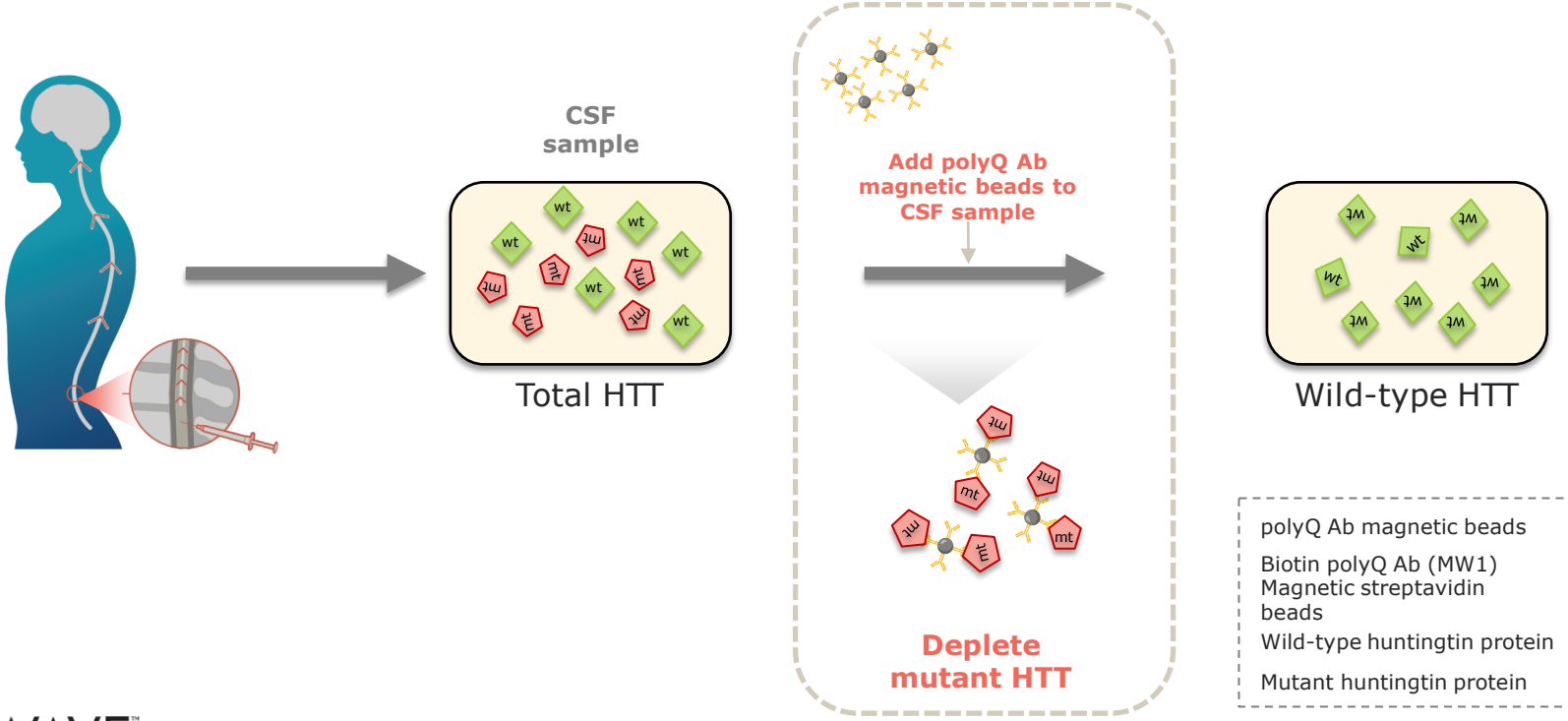
- Patients with confirmed manifest HD diagnosis with SNP3 mutation (up to 40 patients planned)
- Dose escalation and dosing interval guided by independent DSMB
- Safety and tolerability
- Biomarkers
  - mHTT
  - NfL
  - wtHTT
- Clinical trial site activation ongoing

Dosing in Phase 1b/2a trial expected to initiate in 2021

SAD: Single ascending dose MAD: Multiple ascending dose mHTT: mutant huntingtin NfL: neurofilament light chain wtHTT: wild-type huntingtin

Assessment of wild-type protein in CSF

Depletion of mutant HTT key to ability to measure wild-type HTT protein

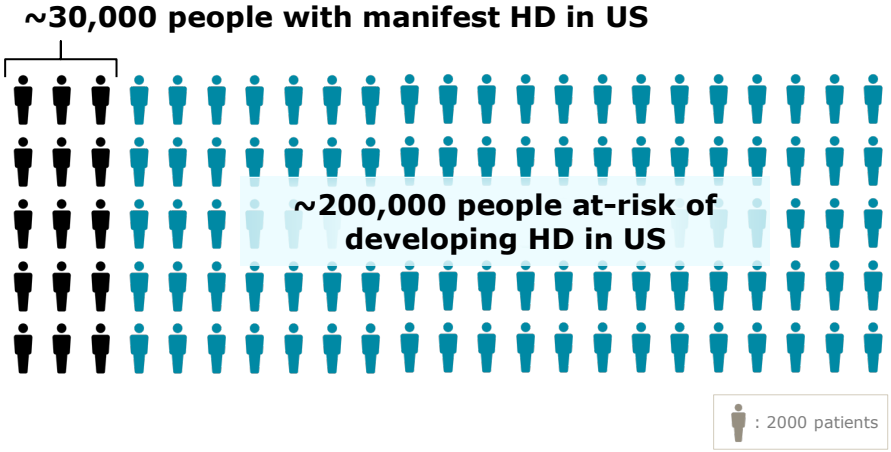


Ab: antibody CSF: cerebrospinal fluid HTT: huntingtin protein MW1: Wild et al. JCI 2015

Wave approach: novel, allele-selective silencing

~40% of HD Patients Carry SNP3

Allele-selective Treatments Have Potential to Benefit Many of Those At-risk of HD



Personalized approach to wtHTT sparing opens possibility of early treatment

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[1] Claassen et al. Neurol Genet Jun 2020; Carroll et al. Mol Ther. 2011 Dec; HDSA.org

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WVE-N531

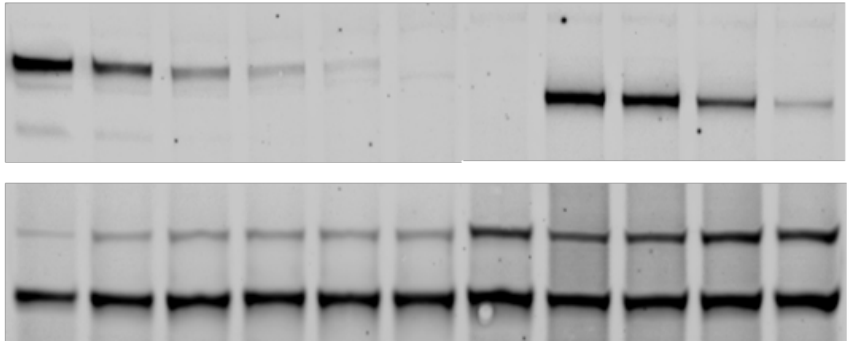
Duchenne muscular dystrophy

WVE-N531 *in vitro* dose-dependent dystrophin restoration

Dystrophin protein restoration of up to 71%

Western Blot normalized to primary healthy human myoblast lysate

Standard Curve (% WT lysate in D45-52 lysate)						D45-52 Cells				
						Mock	WVE-N531			
						0	10	3.3	1.1	0.3	Conc [uM]
100%	50%	25%	12%	6%	0%	0%	71%	65%	37%	9.5%	% Dystrophin

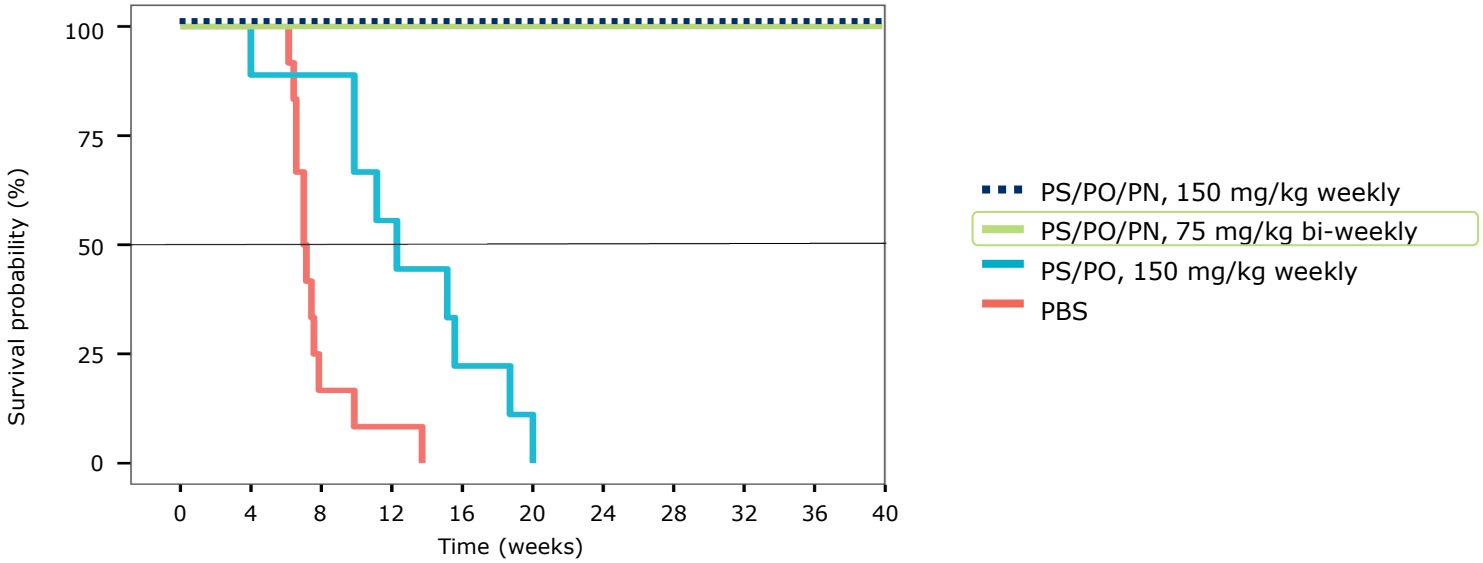


- WVE-N531 contains novel PN backbone chemistry modifications
- Free uptake for 6 days in differentiation media with no transfection agent and no peptide conjugated to the oligonucleotide
- Demonstrated a dose-dependent increase in dystrophin restoration in DMD patient-derived myoblasts

Experimental conditions: Δ45-52 (D45-52) patient myoblasts were treated with oligonucleotide for 6d under free-uptake conditions in differentiation media. Protein harvested in RIPA buffer and dystrophin restoration analyzed by Western Blot. Signal normalized to vinculin loading control and to primary healthy human myotube lysate (pooled from four donors) forming a standard curve in Δ45-52 cell lysate.

PN chemistry led to overall survival benefit in dKO model

PN-containing molecules led to 100% dKO survival at time of study termination



Note: Untreated, age-matched mdx mice had 100% survival at study termination [not shown]

dKO; double knockout mice lack dystrophin and utrophin protein. mdx mice lack dystrophin. Left: Mice with severe disease were euthanized. dKO: PS/PO/PN 150 mg/kg n= 8 (p=0.0018); PS/PO/PN 75 mg/kg n=9 (p=0.00005); PS/PO n=9 (p=0.0024), PBS n=12 Stats: Chi square analysis with pairwise comparisons to PBS using log-rank test

Clinical trial of WVE-N531

- Unmet need in DMD remains high
- Planned clinical trial designed to evaluate change in dystrophin production, drug concentration in muscle, and initial safety
  - Open-label study; targeting every-other-week administration in up to 15 boys with DMD
- Potential to apply PN chemistry to other exons if successful

Dosing in clinical trial expected to initiate in 2021

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PRISM™

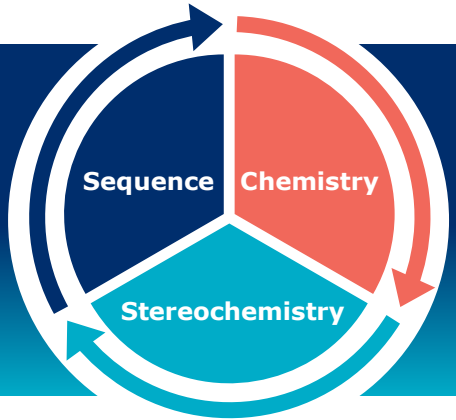
Wave's discovery and drug development platform

PRISM™

Enables Wave to target genetically defined diseases with stereopure oligonucleotides across multiple therapeutic modalities

DESIGN

Unique ability to construct stereopure oligonucleotides with one defined and consistent profile



OPTIMIZE

A deep understanding of how the interplay among oligonucleotide sequence, chemistry, and backbone stereochemistry impacts key pharmacological properties

Through iterative analysis of *in vitro* and *in vivo* outcomes and machine learning-driven predictive modeling, Wave continues to define design principles that are deployed across programs to rapidly develop and manufacture clinical candidates that meet pre-defined product profiles

Multiple modalities
Silencing | Splicing | ADAR editing

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PRISM platform enables rational drug design

Sequence

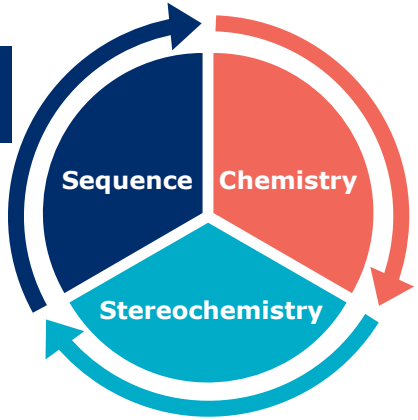
B: bases

A, T, C, mC, G, U,
other modified bases

Stereochemistry

Chiral control of
any stereocenter

5′ modifications,
backbone modifications



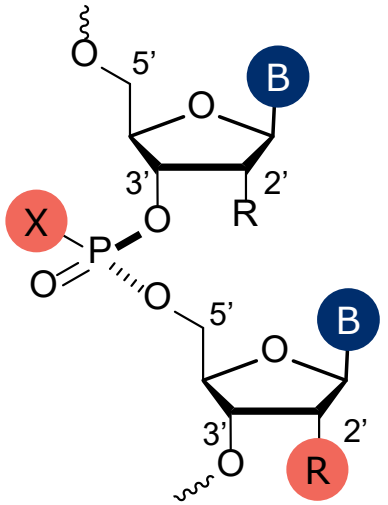
Chemistry

R: 2′ modifications

OMe, MOE, F,
other modifications

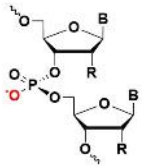
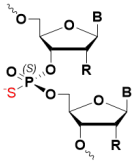
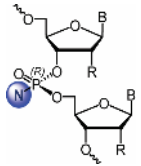
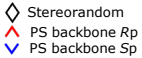
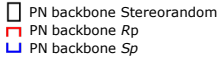
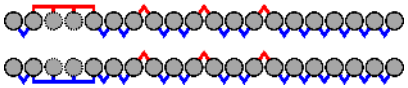
X: backbone chemistry

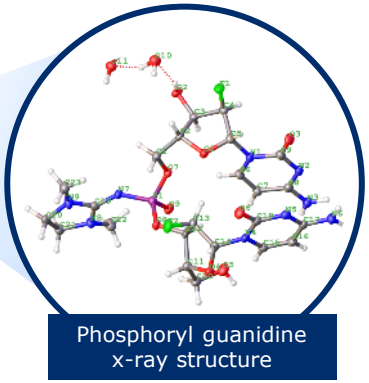
Phosphodiester (PO),
phosphorothioate (PS),
Phosphoramidate diester
(PN)



Expanding repertoire of backbone modifications with novel PN backbone chemistry

Backbone linkages

	PO	PS	PN
Backbone modification (X)	Phosphodiester 	Phosphorothioate 	Phosphoramidate diester 
Stereochemistry	Not chiral	Chiral 	Chiral 
Charge	Negative	Negative	Neutral
Depiction			
PRISM backbone modifications	PO/PS		
	PO/PS/PN		



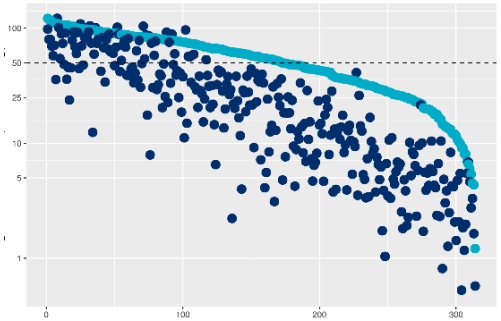
Phosphoryl guanidine x-ray structure

Molecule structure illustrative of backbone modification patterns

PN chemistry increases potency in silencing, splicing, and editing preclinical studies

Silencing

Target knockdown (% remaining)

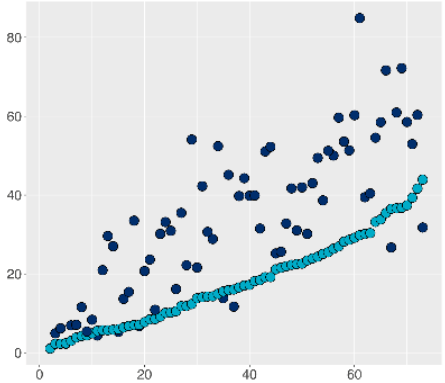


Ranked by potency of reference PS/PO compound

Improved knockdown

Splicing

% Skipping

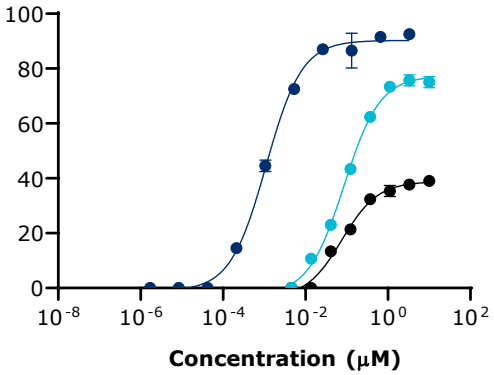


Ranked by potency of reference PS/PO compound

Improved skipping

Editing

% Editing



Improved editing

PS/PO/PN
PS/PO (Stereopure)
PS/PO (Stereorandom)

PS/PO reference compound

PS/PN modified compound

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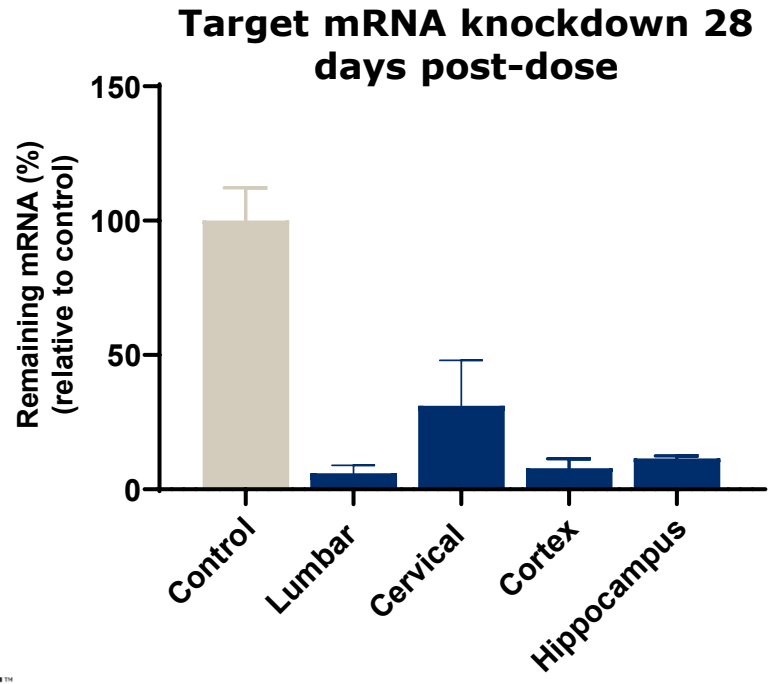
Presented at Analyst & Investor Research Webcast on August 25, 2020; Right: Data from independent experiments

Lead program in Takeda collaboration reinforces potential of PN chemistry in the CNS

Substantial and widespread target mRNA reduction following single intrathecal dose in NHPs



- Single IT dose of 12 mg (n=3)
- Therapeutic candidate widely distributed across brain and spinal cord
- ~90% mRNA knockdown one-month following single dose

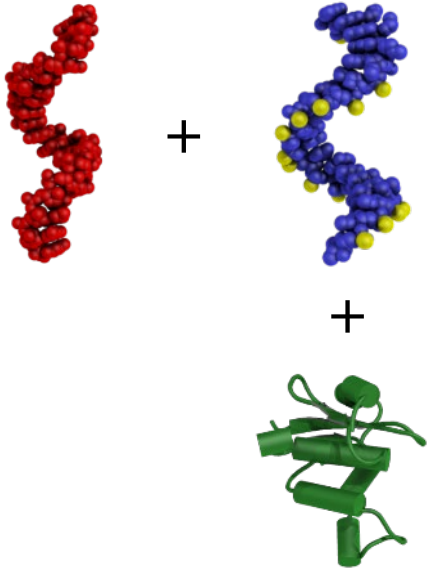
NHPs: Non-human primates; IT: intrathecal
NHPs were administered 12 mg on day 1 via IT bolus injection; tissue samples were collected from 3 NHPs at 28 days post-dose.

PRISM enables optimal placement of backbone stereochemistry

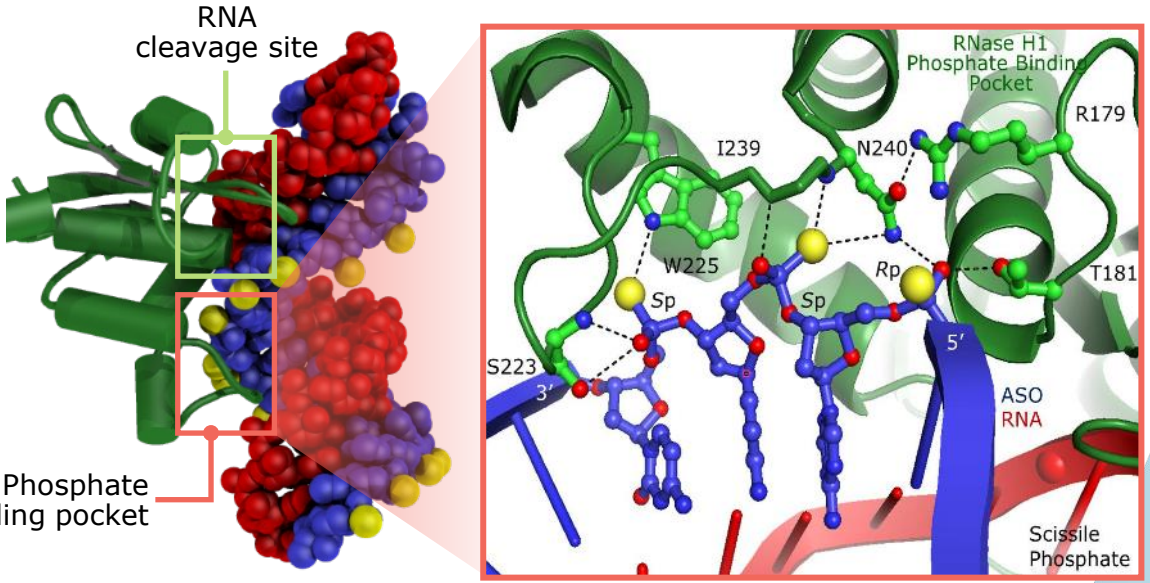
Crystal structure confirms phosphate-binding pocket of RNase H binds 3′-SSR-5′ motif in stereopure oligonucleotide – supports design strategy for Wave oligonucleotides

Target RNA

Stereopure Oligonucleotide (C9orf72 compound)



RNase H

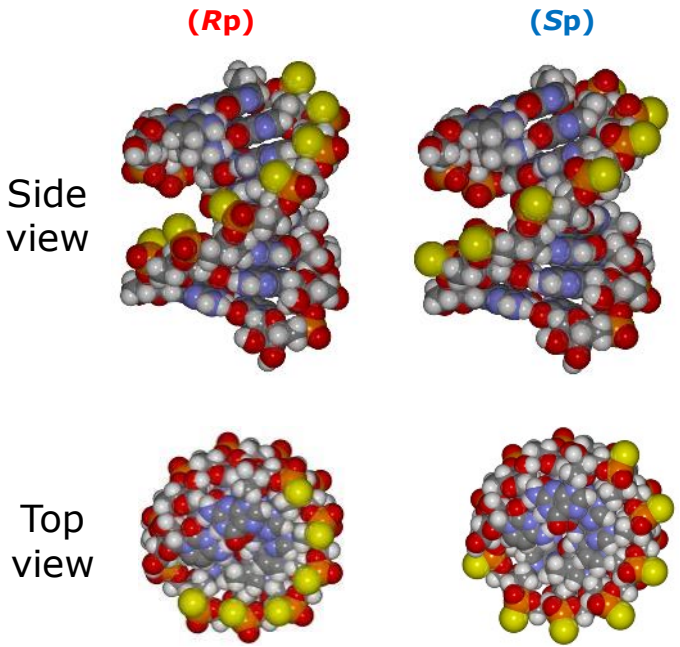


ASO/RNA duplex

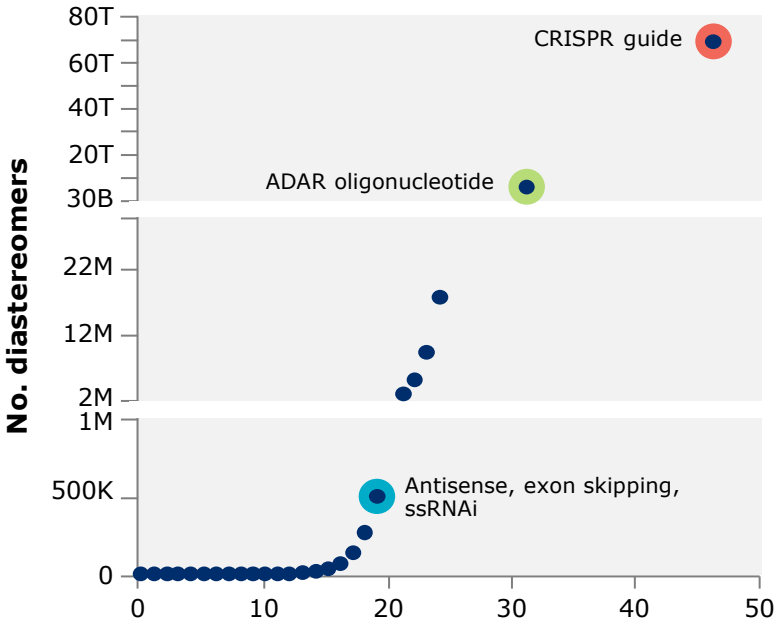
Yellow spheres represent ‘S’ atoms

Importance of controlling stereochemistry

Stereochemical diversity



Exponential diversity arises from uncontrolled stereochemistry



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Yellow spheres represent 'S' atoms

PS: Phosphorothioate

Number of PS linkages in oligonucleotide backbone

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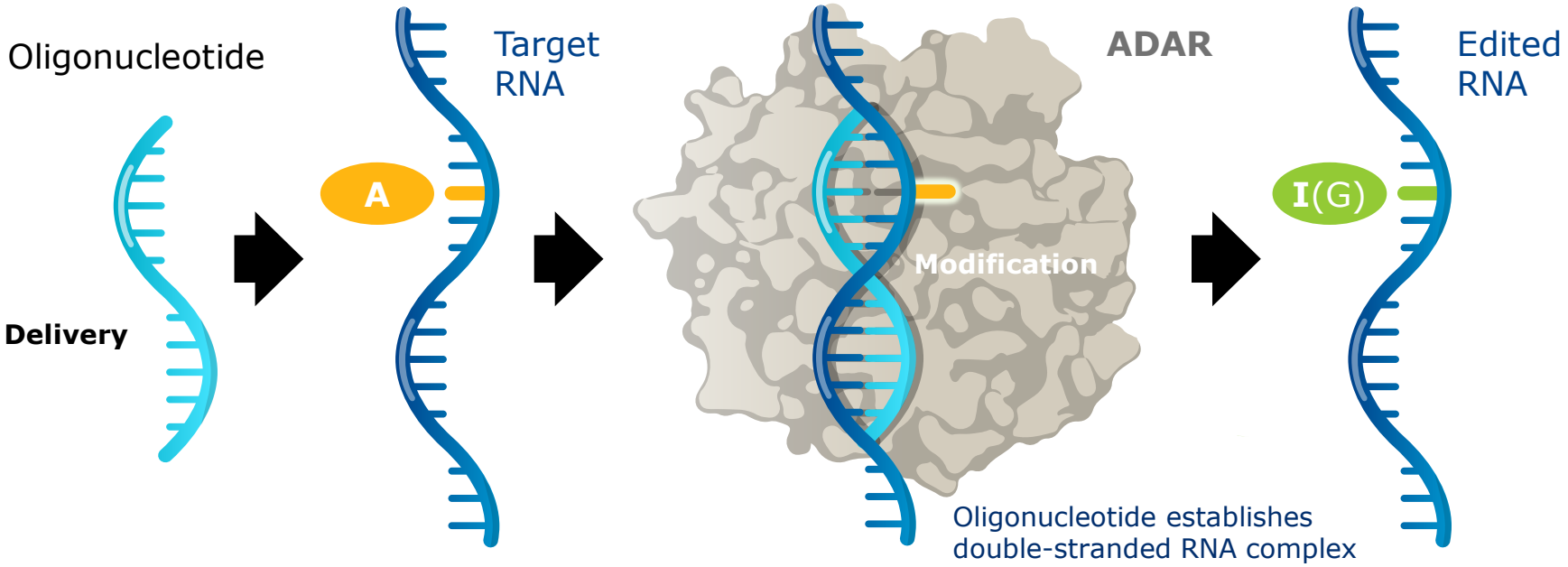
ADAR editing

Platform capability and Alpha-1 antitrypsin deficiency

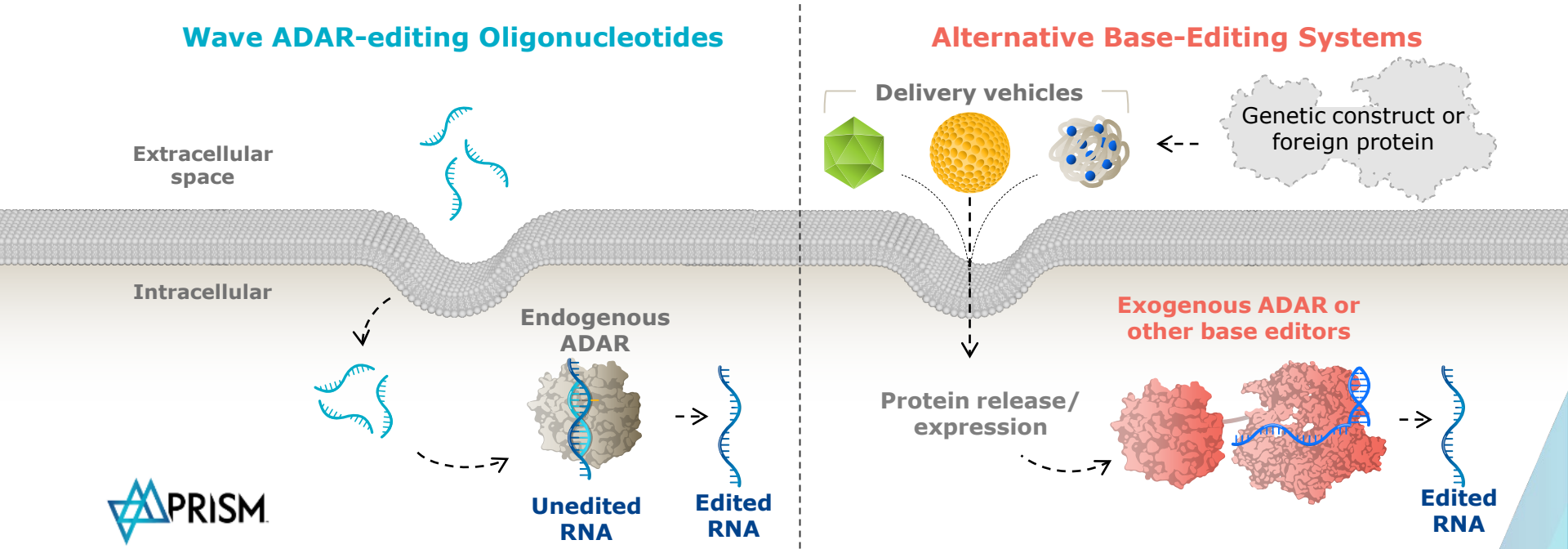
PRISM platform has unlocked ADAR editing



- **A**-to-**I** editing is one of most common post-transcriptional modifications
- ADAR is ubiquitously expressed across tissues, including liver and CNS

A: adenosine; I: inosine; G: guanosine; Nishikura, K. A-to-I editing of coding and non-coding RNAs by ADARs. Nat. Rev. Mol. Cell Biol. 2016; Picardi, E. *et al.* Profiling RNA editing in human tissues: towards the inosinome Atlas. *Scientific reports* **5**, 14941, doi:10.1038/srep14941 (2015).

PRISM enables practical approach to RNA editing without need for viruses or exogenous protein



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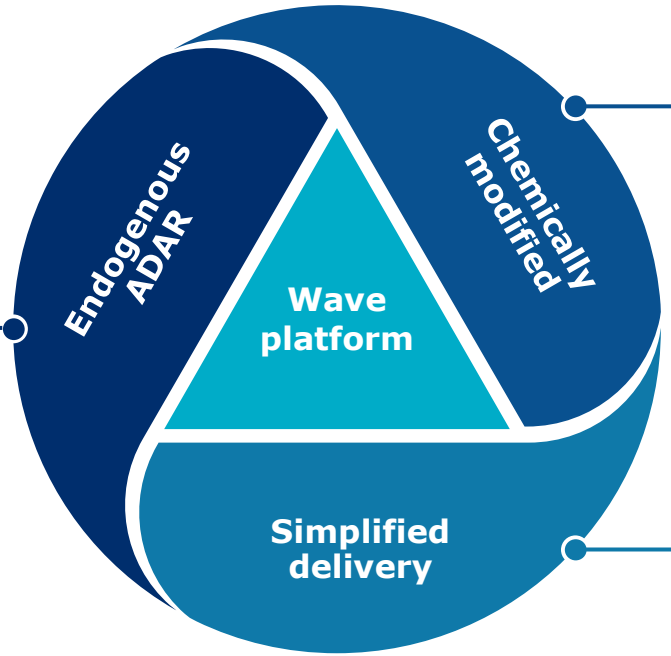
Advantages of Wave ADAR editing platform

- Avoids permanent off-target DNA edits
- No immunogenicity from exogenous proteins
- Reduced off-target effects



- Fully chemically modified to increase stability *in vivo*
- Chirally-controlled backbone to maximize *in vitro* activity
- PN backbone chemistry modification improves editing efficiency

- No requirement for AAV / nanoparticles
- GalNAc-conjugated for targeted delivery into liver

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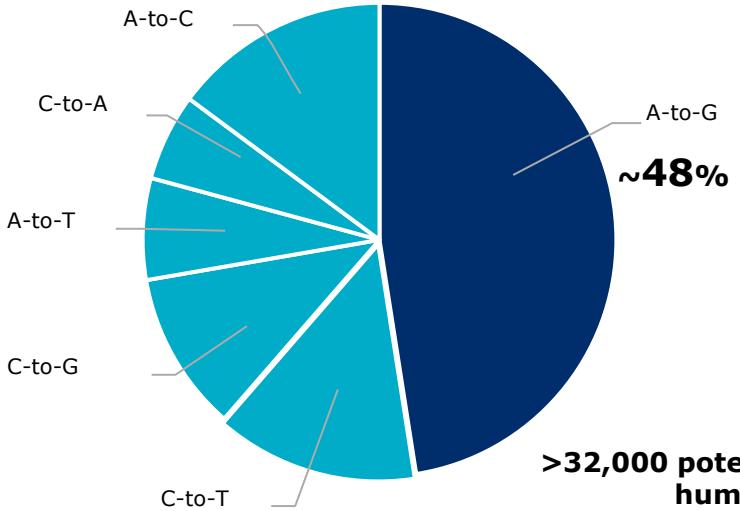
Sources: Chen Biochemistry 2019

ADAR amenable diseases represent a sizeable opportunity

Potentially pathogenic human SNPs by base pair corrections



>32,000 potentially pathogenic human SNPs[2]

- Nearly half of known human SNPs associated with disease are G-to-A mutations
- A-to-I(G) editing could target tens of thousands of potential disease variants[1]

SNP: single nucleotide polymorphism A: Adenosine I: Inosine G: Guanosine
[1]ClinVar database [2]Gaudeli NM et al. *Nature* (2017).

RNA editing opens many new therapeutic applications

Restore protein function

- Fix nonsense and missense mutations that cannot be splice-corrected
- Remove stop mutations
- Prevent protein misfolding and aggregation

Examples:

Recessive or dominant genetically defined diseases

Modify protein function

- Alter protein processing (e.g. protease cleavage sites)
- Protein-protein interactions domains
- Modulate signaling pathways

Examples:

Ion channel permeability

Protein upregulation

- miRNA target site modification
- Modifying upstream ORFs
- Modification of ubiquitination sites

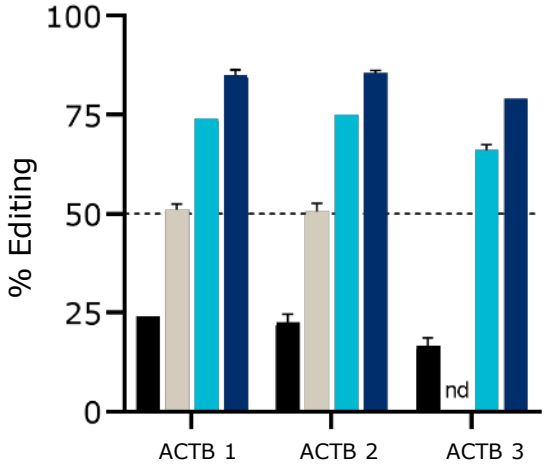
Examples:

Haploinsufficient diseases

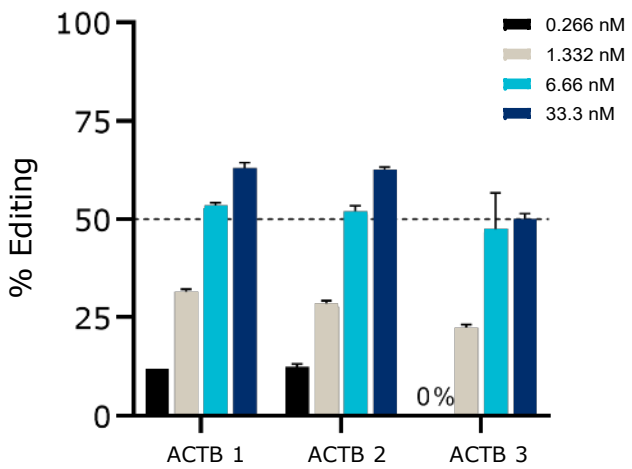
Significant ADAR editing demonstrated *in vitro* in NHP and primary human hepatocytes

ACTB GalNAc-conjugated oligonucleotides with stereopure PN backbone chemistry modifications

In vitro dose-response human hepatocytes



In vitro dose-response NHP hepatocytes

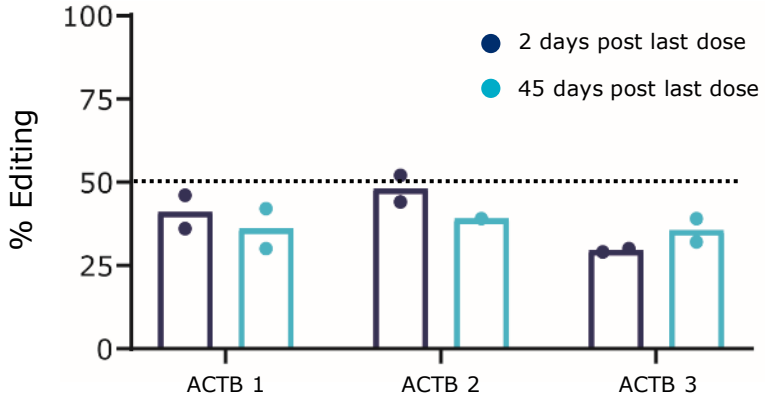


NHP: non-human primate; ACTB: Beta-actin; nd= not determined
Total RNA was harvested, reverse transcribed to generate cDNA, and the editing target site was amplified by PCR.

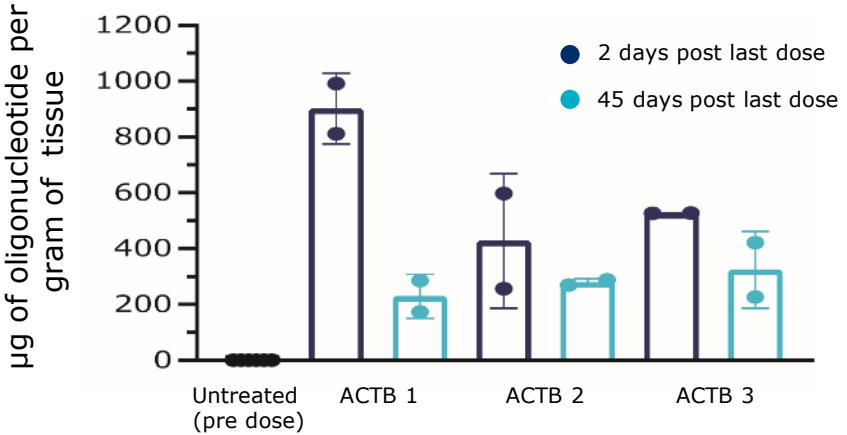
Efficient ADAR editing translated *in vivo* in non-human primate study

- Up to 50% editing efficiency observed at Day 7, 2 days post last dose
- Substantial and durable editing out to at least Day 50, 45 days post last dose

In vivo editing in NHP following subcutaneous administration

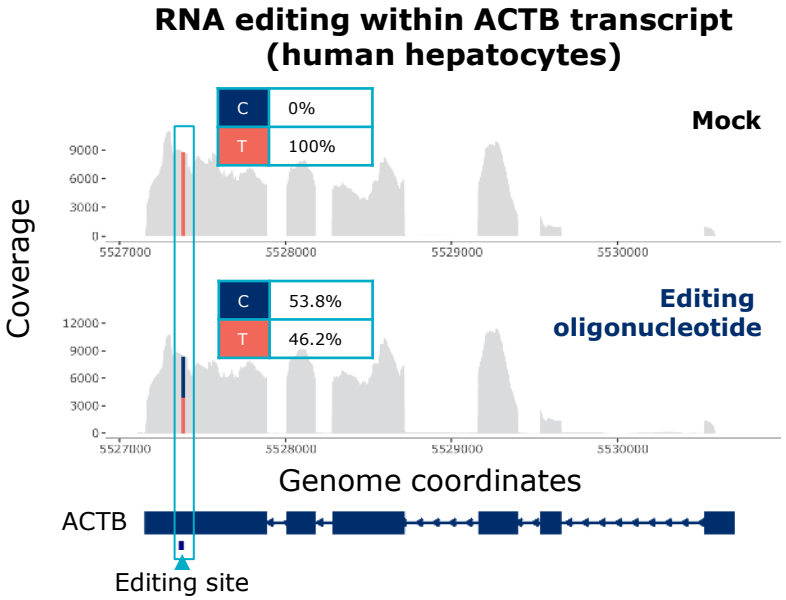


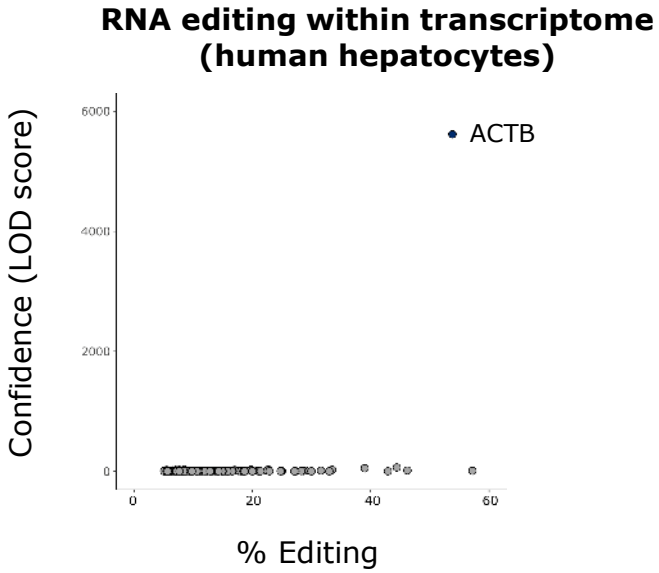
Oligonucleotide quantification in NHP following subcutaneous administration



NHP: non-human primate; ACTB: Beta-actin; Left: 5mg/kg SC: Day 1,2,3,4,5; Liver Biopsy for mRNA (ACTB Editing) & eASO Exposure: Day 7

Wave ADAR editing oligonucleotides are highly specific





Human hepatocytes were dosed with 1um oligonucleotide, 48 hours later RNA was collected and sent for RNA sequencing. RNAseq conducted using strand-specific libraries to quantify on-target ACTB editing and off-target editing in primary human hepatocytes; plotted circles represent sites with LOD>3

Advancing Wave's first ADAR editing program in alpha-1 antitrypsin deficiency (AATD)

- Most common cause is a single G-to-A point mutation on the "Z" allele
- **~200K people in US and EU** with homozygous ZZ genotype, most common form of severe AATD
- Approved therapies modestly increase circulating levels of wild-type AAT in those with lung pathology; no therapies address liver pathology

Wave's approach may simultaneously address lung and liver manifestations by using ADAR editing to correct mutation:

- Increase circulating levels of wild-type AAT protein
- Reduce aggregation of Z-AAT in liver
- Retain wild-type AAT physiological regulation

Dual pathologies in AATD

Loss of function in lung

Lack of functional AAT in serum:

- Insufficient levels to counteract protease levels, e.g., neutrophil elastase
- Lung damage due to unchecked proteolytic activity and inflammation
- Other tissues may be affected (e.g., skin)

Gain of function in liver

Misfolding of AAT in hepatocytes:

- Inability to secrete AAT
- AAT polymerizes in liver
- Liver damage/cirrhosis

Sources: Strnad 2020; Blanco 2017
AAT: Alpha-1 antitrypsin

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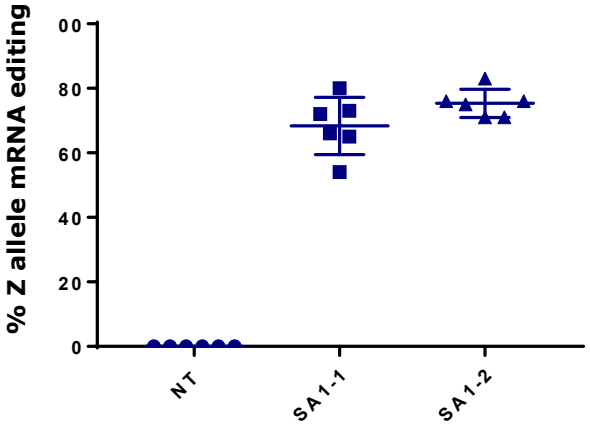
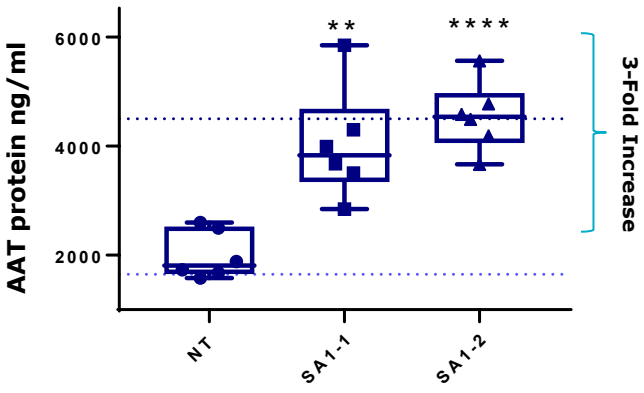
SERPINA1 Z allele mRNA editing increases edited AAT protein concentration *in vitro*

In primary hepatocyte *SERPINA1* Z cell model, editing the Z allele mRNA back to wild-type prevents protein misfolding and increases secretion of edited AAT protein from hepatocytes

SERPINA1 Z allele mRNA editing



AAT protein concentration in media



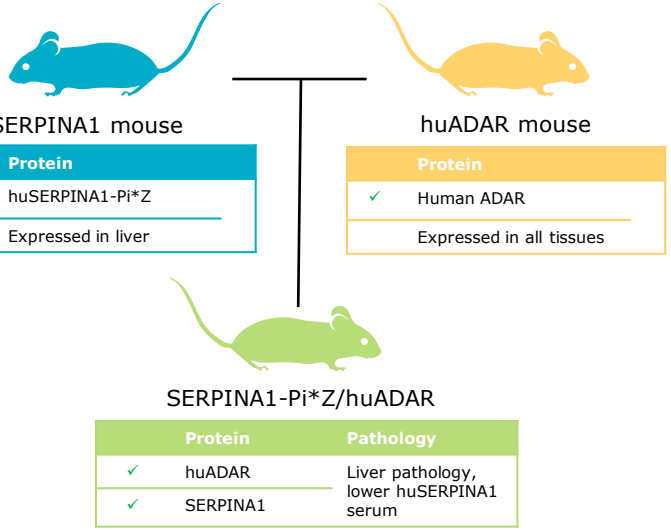
Edited AAT protein analysis

- Wild-type AAT protein confirmed by mass spectrometry
- Function of secreted, edited AAT protein confirmed by neutrophil elastase inhibition assay

Model validation and *in vivo* data expected 1H 2021

AAT (alpha-1 antitrypson); Mouse primary hepatocytes that express SERPINA1 Z allele mRNA were transfected with 25 nanomolar (nM) of SERPINA1 (SA1-1 and SA1-2) targeting antisense oligonucleotides (ASOs) and a control non-targeting (NT) ASO. Media and RNA was collected at 5 days post transfection. AAT protein in media was quantified by Elisa Assay, RNA editing was quantified by RT/PCR/Sanger sequencing.

Proprietary humanized mouse model developed to support ADAR platform



- Expression of huADAR in mouse is comparable to expression in human cells
- Expression of huADAR restores editing of endogenous targets in primary mouse cell types to levels seen in human primary cell types
- huADAR mouse model can be crossed with disease specific mouse models to provide model systems for use across Wave's ADAR editing programs

Model validation and *in vivo* data expected 1H 2021

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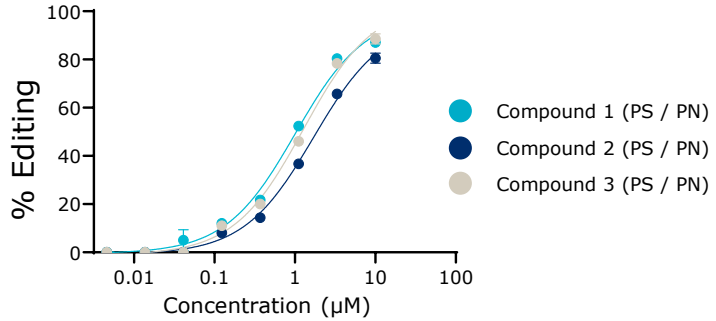
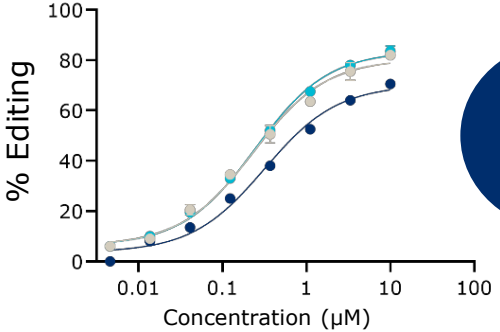
Multiple opportunities for ADAR editing in neurology

ACTB editing in iCell Neurons



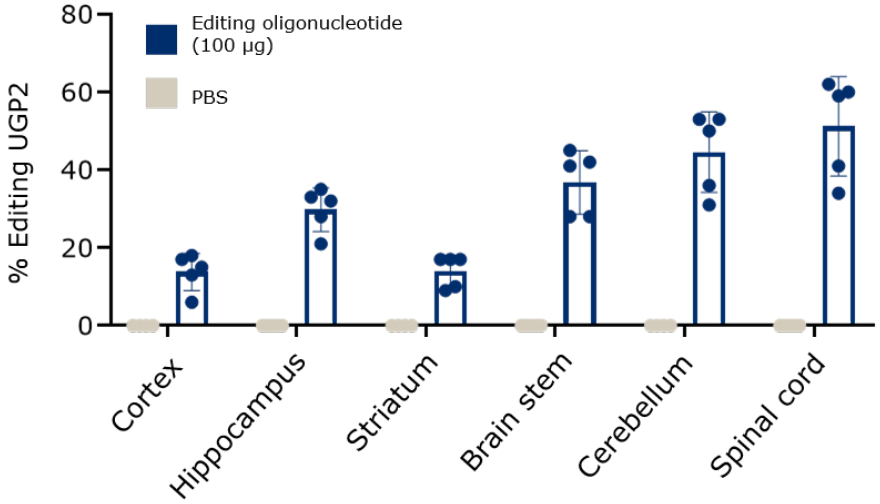
ACTB editing in human iCell Astrocytes



EC50: ~200-250nM

Gymnotic uptake; Total RNA was harvested, reverse transcribed to generate cDNA, and the editing target site was amplified by PCR and quantified by Sanger sequencing

In vivo CNS editing in proprietary hADAR transgenic mouse (1 week)



hADAR: human ADAR; UGP2: Glucose Pyrophosphorylase 2; 5 mice in each group were injected with PBS or a single 100uG dose on day 0. Animals were necropsied on day 7. RNA was harvested and editing measured by Sanger sequencing.

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Ophthalmology

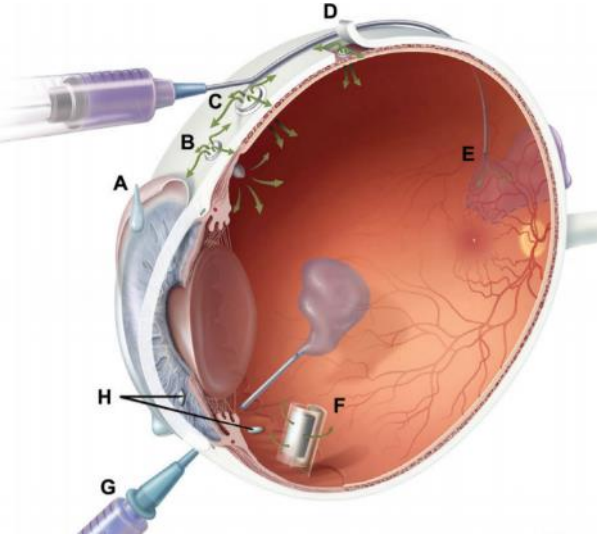
Stereopure oligonucleotides for inherited retinal diseases (IRDs)

Wave ophthalmology opportunity

- Oligonucleotides can be administered by intravitreal (IVT) injection; targeting twice per year dosing
- Stereopure oligonucleotides open novel strategies in both dominant and recessive IRDs; potential for potent and durable effect with low immune response

Successful targeting of *MALAT1* is a surrogate for an ASO mechanism of action

- Widely expressed in many different cell types
- Only expressed in the nucleus

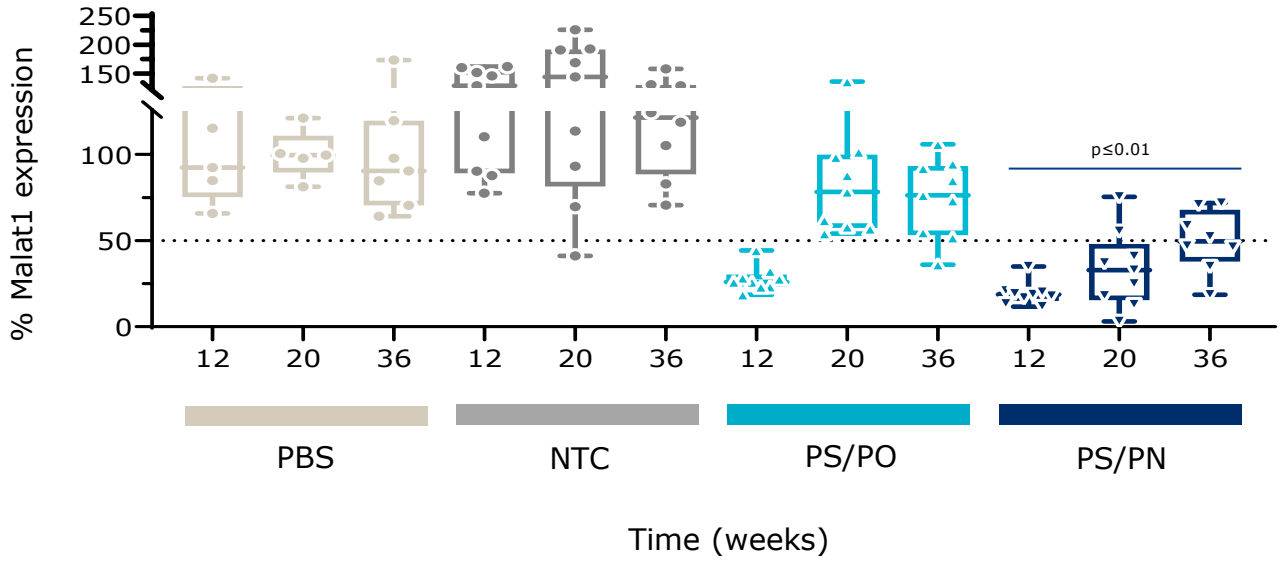


Intravitreal injection

Sources: Daiger S, et al. *Clin Genet*. 2013;84:132-141. Wong CH, et al. *Biostatistics*. 2018; DOI: 10.1093/biostatistics/kxx069. Athanasiou D, et al. *Prog Retin Eye Res*. 2018;62:1–23. Daiger S, et al. *Cold Spring Harb Perspect Med*. 2015;5:a017129. Verbakel S, et al. *Prog Retin Eye Res*. 2018:66:157-186.; Short, B.G.; *Toxicology Pathology*, Jan 2008.

Durable Malat1 knockdown through 9 months with PN backbone chemistry modifications

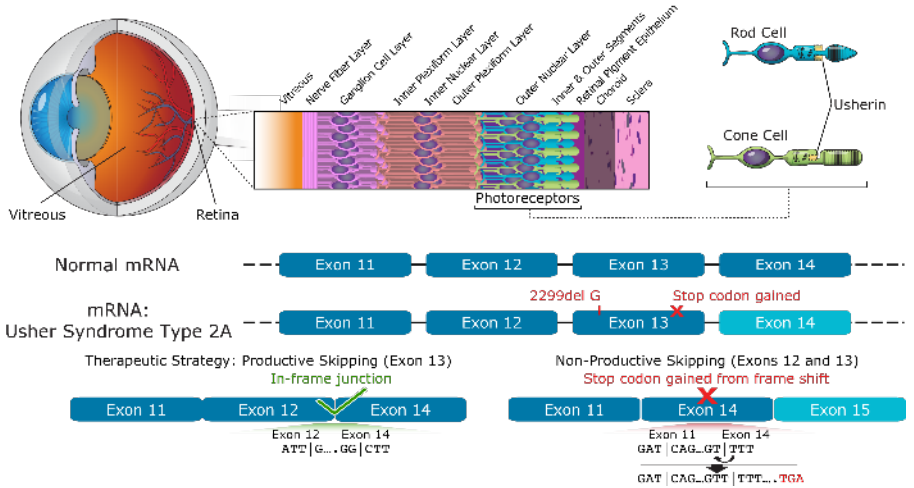
~50% Malat1 knockdown at 36 weeks in the posterior of the eye



Compound or PBS (1 x 50 ug IVT) was delivered to C57BL6 mice. Relative percentage of Malat1 RNA in the posterior of the eye (retina, choroid, sclera) to PBS-treated mice is shown at 12, 20 and 36 weeks post-single injection. PBS = phosphate buffered saline; NTC= chemistry matched non-targeting control

Usher Syndrome Type 2A: a progressive vision loss disorder

- Autosomal recessive disease characterized by hearing loss at birth and progressive vision loss beginning in adolescence or adulthood
- Caused by mutations in USH2A gene (72 exons) that disrupt production of usherin protein in retina, leading to degeneration of the photoreceptors
- No approved disease-modifying therapies
- **~5,000 addressable patients in US**



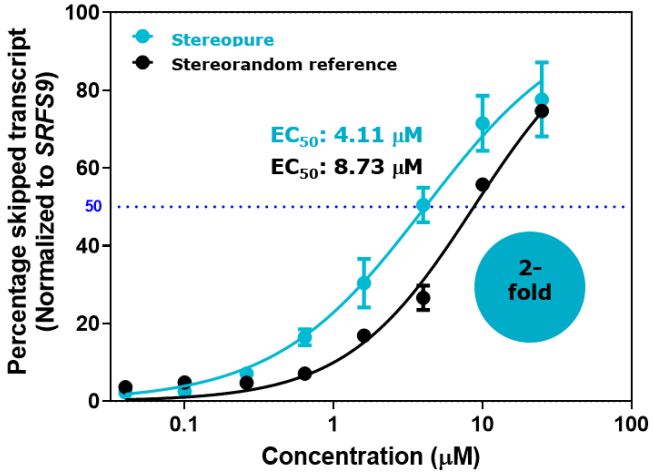
Oligonucleotides that promote USH2A exon 13 skipping may restore production of functional usherin protein

WAVE LIFE SCIENCES

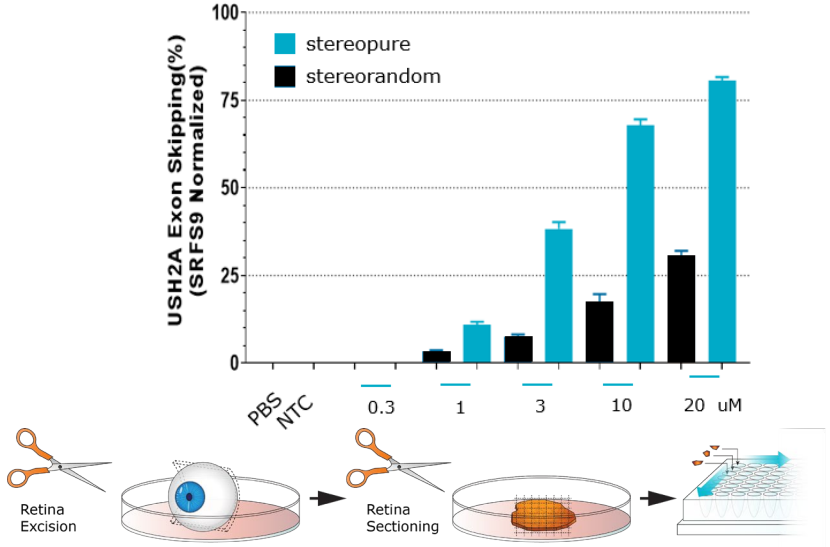
Sources: Boughman et al., 1983. *J Chron Dis*. 36:595-603; Seyedahmadi et al., 2004. *Exp Eye Res.* 79:167-173; Liu et al., 2007. *Proc Natl Acad Sci USA* 104:4413-4418.

Potent USH2A exon 13 skipping with stereopure compound in *vitro* and *ex vivo*

Enhanced potency over a stereorandom reference compound (*in vitro*)



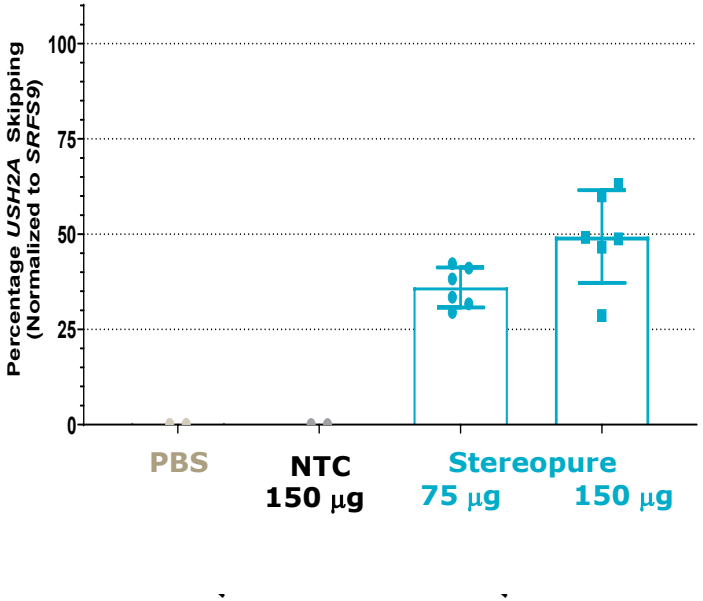
Target engagement in NHP retinas



Oligonucleotides were added to Y79 cells under free-uptake conditions. Exon skipping was evaluated by Taqman assays. USH2A transcripts were normalized to SRSF9. Data are mean±s.d., n=2. Stereorandom: Compound identified in van Diepen et al. 2018. Antisense oligonucleotides for the treatment of eye disease. W02018055134A1. Stereopure: is a stereopure antisense oligonucleotide. Right: Whole NHP were enucleated (n=4) and compounds (1–20 mM) were added to extracted retinas under free-uptake conditions. Exon skipping was evaluated by Taqman assays on RNA. USH2A transcript levels were normalized to SRSF9. Data presented are mean± s.e.m. stereorandom compound is from van Diepen et al. 2018. Antisense oligonucleotides for the treatment of eye disease. W02018055134A1. Compound-1 is a stereopure antisense oligonucleotide.

Stereopure oligonucleotide elicits dose-dependent exon skipping in NHP eye *in vivo*

Dose-dependent and specific exon skipping in NHP eye



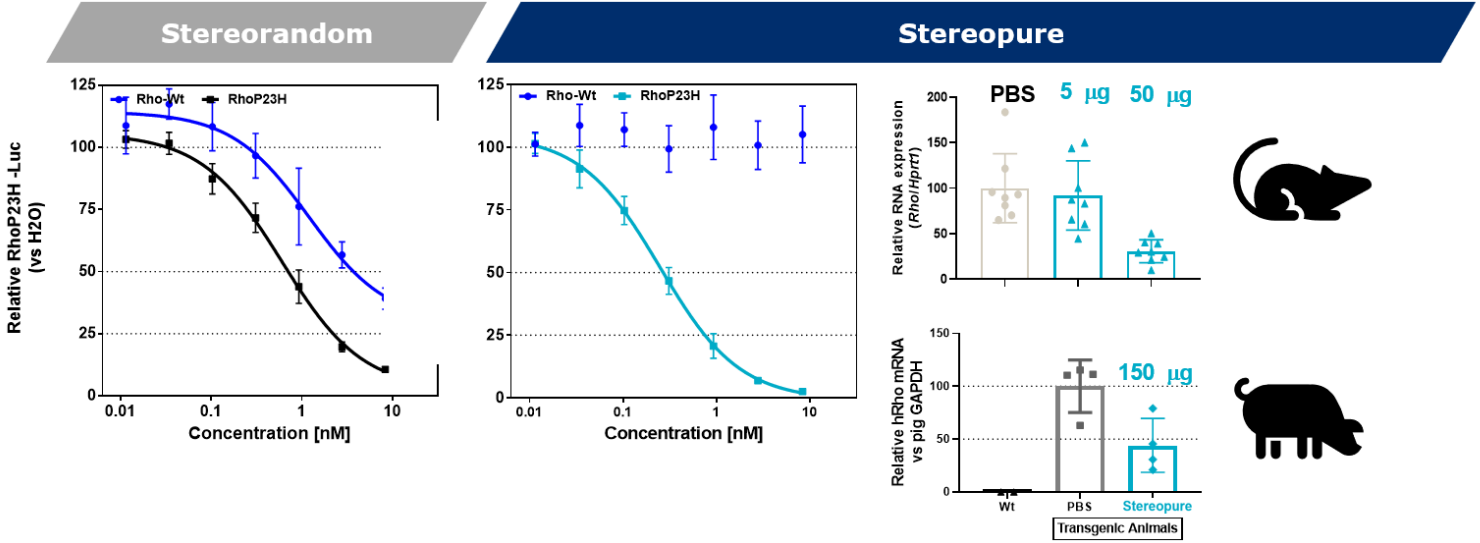
- Oligonucleotide is complementary to NHP *USH2A* exon 12*
- Evaluated 1-week post-single IVT injection
- Dose-dependent activity of **stereopure** oligonucleotides
- Substantial exposure in retina
- Exon-skipping integrity confirmed by RNA-seq at both doses

*NHP exon 12 = human exon 13

Stereopure *USH2A* skipping oligonucleotide, PBS or NTC antisense oligonucleotide was delivered to NHP by single IVT injection. One-week post-injection, retina was isolated and exon skipping was evaluated by Taqman assays. *USH2A* skipped transcript levels were normalized to *SRSF9*. Data are mean± s.e.m. Stereopure is an *USH2A* exon-13 skipping stereopure antisense oligonucleotide. PBS, phosphate buffered saline; NTC, non-targeting control; IVT, intravitreal

Allele-selective reduction of SNP-containing allele for adRP associated with Rhodopsin P23H mutation

- **Retinitis pigmentosa (RP)**: group of rare, genetic eye disorders resulting in progressive photoreceptor cell death and gradual functional loss; currently no cure
- ~10% of US autosomal dominant RP cases are caused by the P23H mutation in the rhodopsin gene (RHO)
- Mutant P23H rhodopsin protein is thought to misfold and co-aggregate with wild-type rhodopsin, resulting in a gain-of-function or dominant negative effect in rod photoreceptor cells



Left: Reporter assays on a sequence described in WO2016138353A1. Oligonucleotide and luciferase reporter plasmids (wild-type and mutant RHO) are transfected into Cos7 cells. Cells are harvested after 48 hrs, and relative luminescence is measured. Right: Single IVT injection (1 mL) in mouse Rho P23H mouse model or (150 mL) in human P23H pig model. Eyes collected 1-week post injection for mouse or 2-weeks post injection for pig; RNA isolated; Rho, Hprt1, and Gapdh levels determined by qPCR.

Expected upcoming milestones

THERAPEUTIC AREA / TARGET	PRISM	Milestone
NEUROLOGY		
Huntington's disease mHTT SNP3	◆ ◆	**2021:** Dosing of first patient in clinical trial of WVE-003
ALS and FTD C9orf72	◆ ◆	**2021:** Dosing of first patient in clinical trial of WVE-004
DMD Exon 53	◆ ◆	**2021:** Dosing of first patient in clinical trial of WVE-N531
ADAR editing Multiple	◆ ◆	**1H 2021**: Humanized mouse model validation
HEPATIC		
AATD (ADAR editing) SERPINA1	◆ ◆	**1H 2021:** *in vivo* AATD data

PRISM ◆ Stereopure ◆ PN chemistry

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ALS: Amyotrophic lateral sclerosis FTD: Frontotemporal dementia AATD: Alpha-1 antitrypsin deficiency

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