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# Wave Life Sciences

## Corporate Presentation

March 4, 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 ongoing across eight countries
- Innovative trial designs

## MANUFACTURING

- Established internal manufacturing capabilities to produce oligonucleotides at scale

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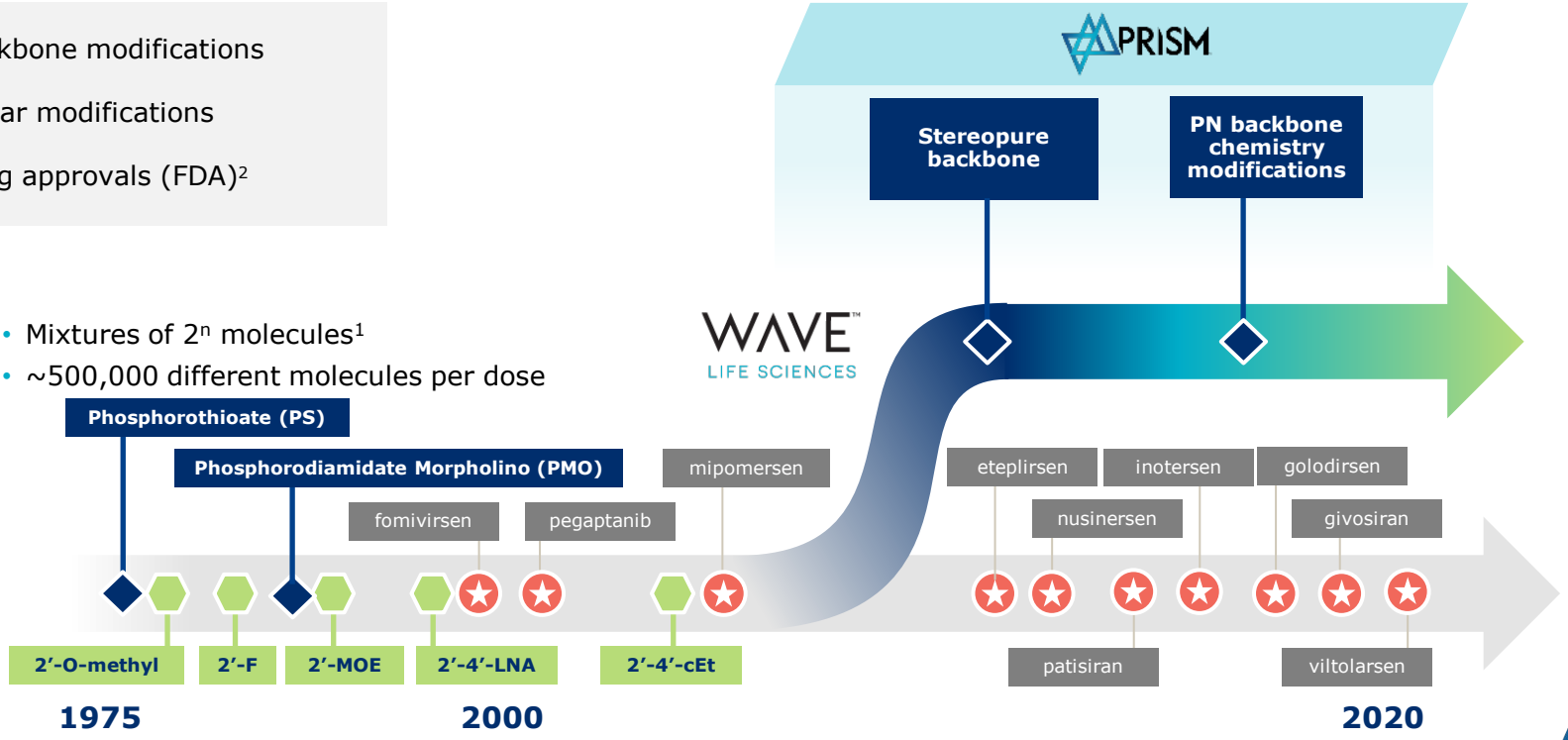
ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia
[1]stereopure oligonucleotides and novel backbone chemistry modifications

# PRISM has unlocked novel and proprietary advances in oligonucleotide design

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

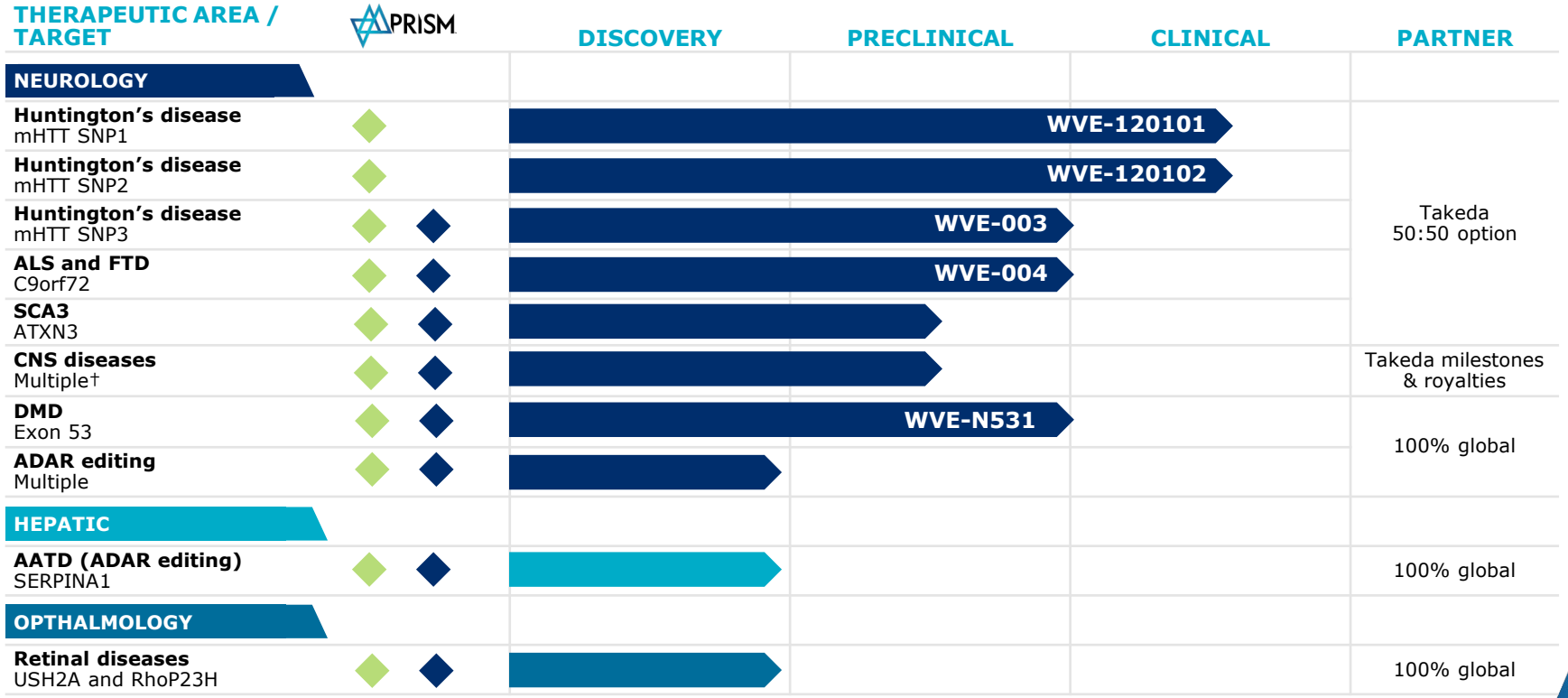
- Mixtures of $2^n$ molecules[1]
- ~500,000 different molecules per dose




[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

PRISM

**Oligonucleotide optimization**
- Stereopure backbone
- PN backbone chemistry modifications

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

**Leverage learnings of first generation programs**
- Translational pharmacology
- Clinical trial design

SNP3

**WVE-003**

Allele-selective silencing candidate in HD

C9orf72

**WVE-004**

Variant-selective silencing candidate in ALS and FTD

Exon 53

**WVE-N531**

Exon skipping candidate for DMD

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

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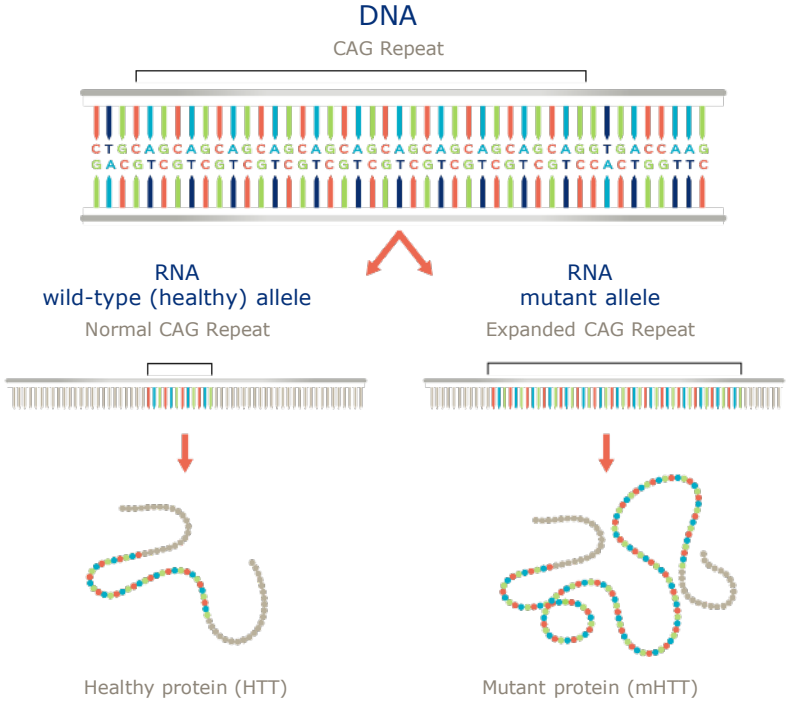
# WVE-120101
# WVE-120102
# WVE-003

## Huntington's Disease Portfolio

# Huntington's disease: a hereditary, fatal disorder

- Autosomal dominant disease, characterized by cognitive decline, psychiatric illness and chorea; fatal
- No approved disease-modifying therapies
- Expanded CAG triplet repeat in HTT gene results in production of mutant huntingtin protein (mHTT); accumulation of mHTT causes progressive loss of neurons in the brain
- Wild-type (healthy) HTT protein critical for neuronal function; evidence suggests wild-type HTT loss of function plays a role in Huntington's disease (HD)
- 30,000 people with HD in the US and more than 200,000 at risk of developing HD




Sources: Auerbach W, et al. *Hum Mol Genet.* 2001;10:2515-2523. Dragatsis I, et al. *Nat Genet.* 2000;26:300-306. Leavitt BR, et al. *J Neurochem*. 2006;96:1121-1129. Nasir J, et al. *Cell*. 1995;81:811-823. Reiner A, et al. *J Neurosci.* 2001;21:7608-7619. White JK, et al. *Nat Genet*. 1997;17:404-410. Zeitlin S, et al. *Nat Genet*. 1995;11:155-163. Carroll JB, et al. *Mol Ther.* 2011;19:2178-2185. HDSA 'What is Huntington's disease?' https://hdsa.org/what-is-hd/overview-of-huntingtons-disease/ Accessed: 3/3/21. HDSA 'Who is at Risk' https://hdsa.org/what-is-hd/history-and-genetics-of-huntingtons-disease/who-is-at-risk/ Accessed: 3/3/21. Becanovic, K., et al., Nat Neurosci, 2015. 18(6): p. 807-16. Van Raamsdonk, J.M., et al., Hum Mol Genet, 2005. 14(10): p. 1379-92.; Van Raamsdonk, J.M., et al., BMC Neurosci, 2006. 7: p. 80.

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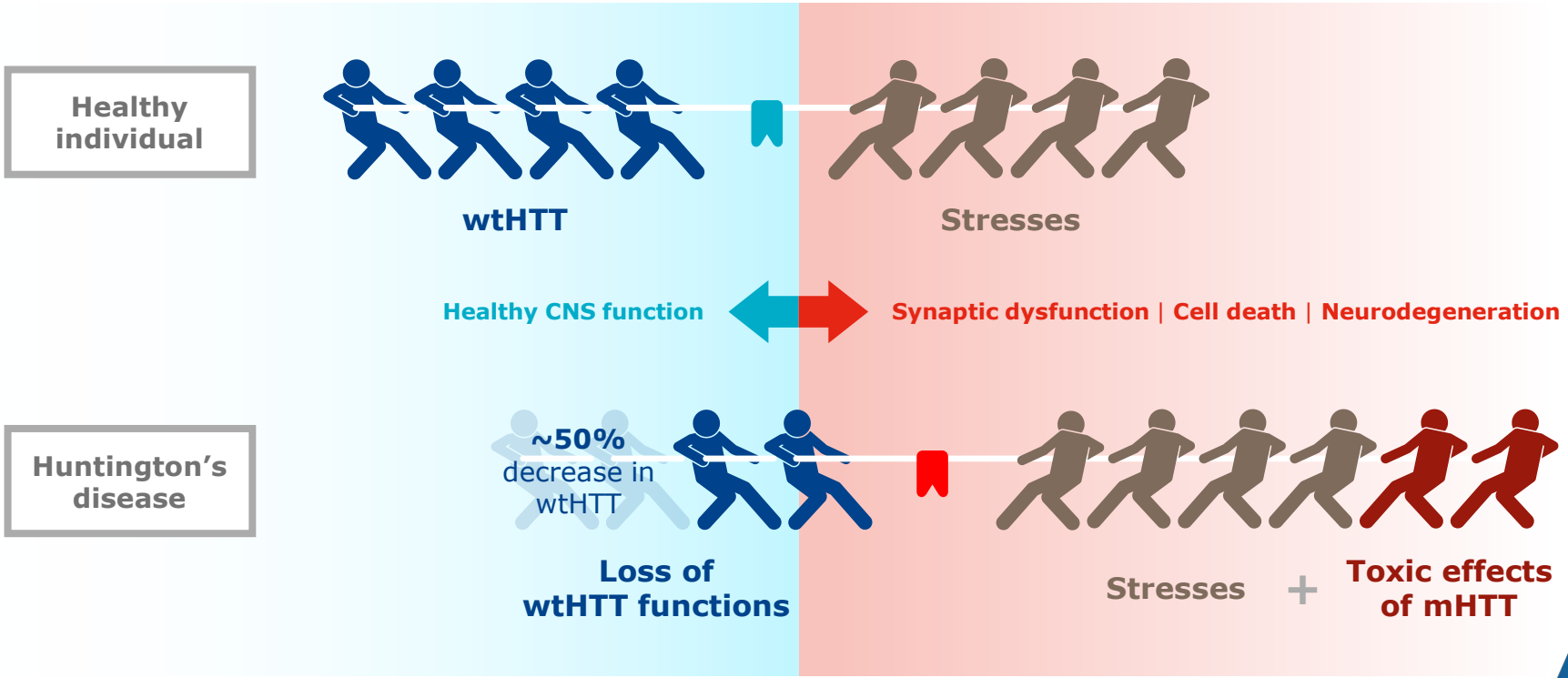
# mHTT toxic effects lead to neurodegeneration, loss of wtHTT functions may also contribute to HD




CNS, central nervous system; HD, Huntington's disease; HTT, huntingtin protein; mHTT, mutant huntingtin protein; wtHTT, wild-type huntingtin protein.

1. Ross CA, Tabrizi SJ. *Lancet Neurol*. 2011;10(1):83-98. 2. Saudou F, Humbert S. *Neuron*. 2016;89(5):910-926. 3. Cattaneo E, et al. *Nat Rev Neurosci*. 2005;6(12):919-930. 4. Milnerwood AJ, Raymond LA. *Trends Neurosci*. 2010;33(11):513-523.

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


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

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

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

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

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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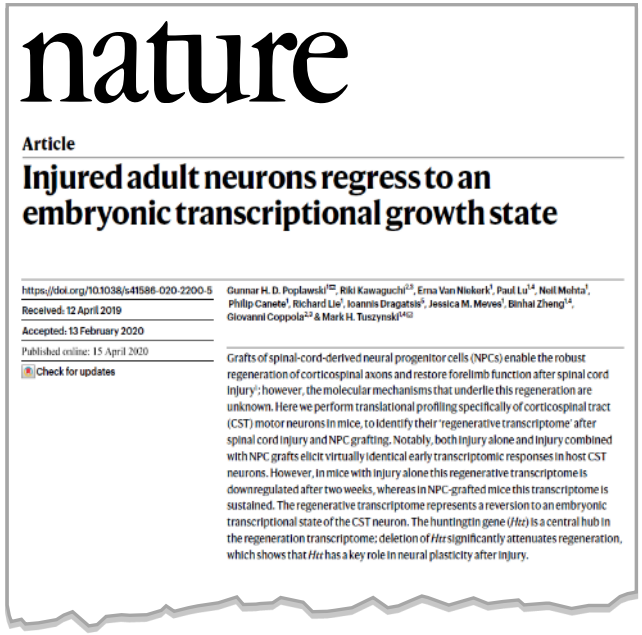
BDNF, brain-derived neurotrophic factor; CSF, cerebrospinal fluid; mHTT, mutant huntingtin protein. Sources: 1. Leavitt 2006 2. Cattaneo 2005 3. Kumar 2016 4. Franco-Iborra 2020 5. Hamilton 2015 6. Ochaba 2014 7. Wong 2014 8. Rui 2015 9. Caviston 2007 10. Twelvetrees 2010 11. Strehlow 2007 12. Milnerwood 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

# *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**

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Received: 12 April 2019
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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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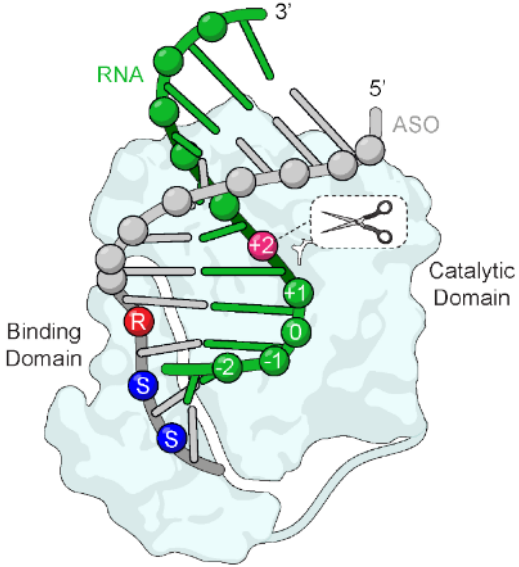
Source: Poplawski et al., *Nature*, April 2019
Htt: Huntingtin protein

# Wave approach: novel, allele-selective silencing

## Aims to lower mHTT transcript while leaving healthy wild-type HTT relatively intact

- Utilize association between single nucleotide polymorphisms (SNPs) and genetic mutations to specifically target errors in genetic disorders, including Huntington's disease (HD)
- Potential to provide treatment for up to 80% of HD population


**RNase H and ASO:RNA**

**Allele-selectivity possible by targeting SNPs associated with expanded long CAG repeat in HTT gene**

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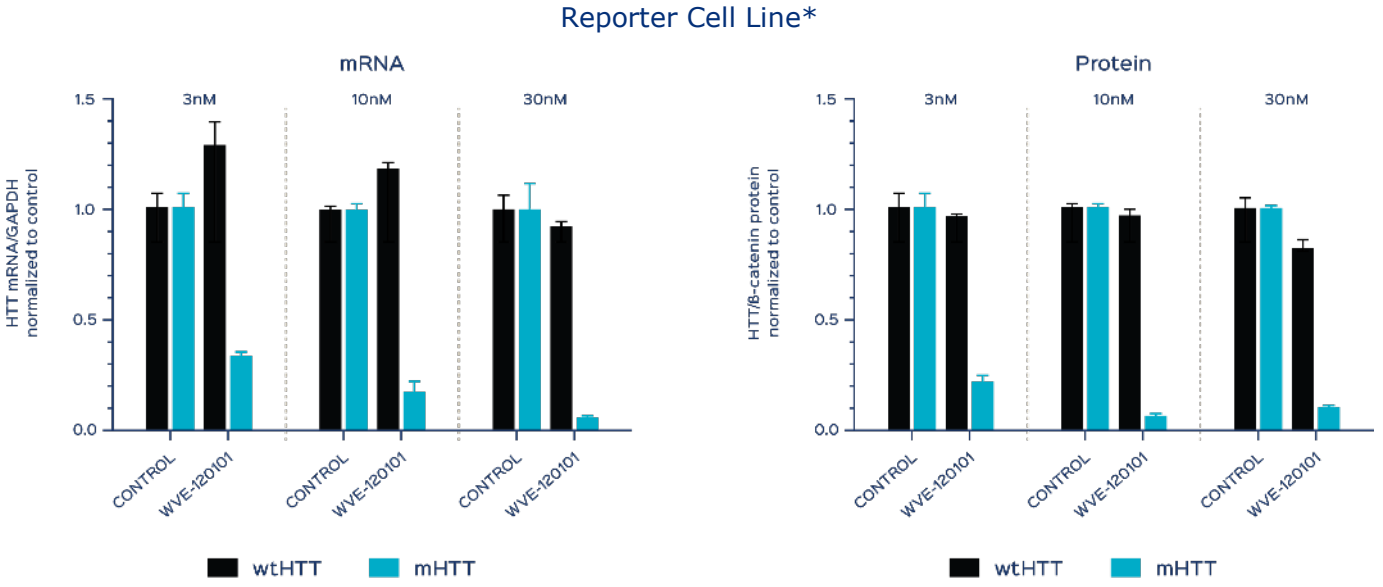
Source: Kay, et al. Personalized gene silencing therapeutics for Huntington disease. *Clin Genet.* 2014;86:29–36.

# WVE-120101: Selective reduction of mHTT mRNA and protein




*These results were replicated in a patient-derived cell line

Source: Meena, Zboray L, Svrzikapa N, et al. Selectivity and biodistribution of WVE-120101, a potential antisense oligonucleotide therapy for the treatment of Huntington's disease. Paper presented at: 69th Annual Meeting of the American Academy of Neurology; April 28, 2017; Boston, MA.

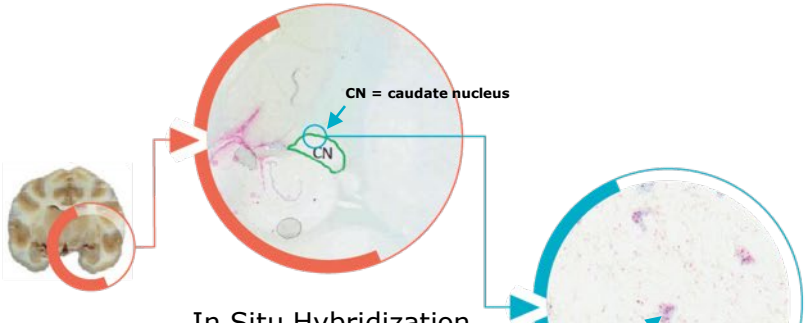
# Demonstrated delivery to brain tissue

- WVE-120101 and WVE-120102 distribution in cynomolgus non-human primate brain following intrathecal bolus injection


In Situ Hybridization ViewRNA stained tissue

Red dots are WVE-120101 oligonucleotide

Arrow points to nuclear and perinuclear distribution of WVE- 120101 in cingulate cortex




In Situ Hybridization ViewRNA stained tissue

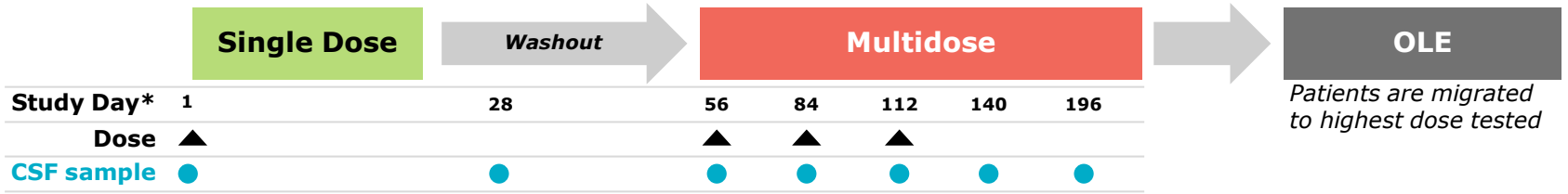
Red dots are WVE-120102 oligonucleotide

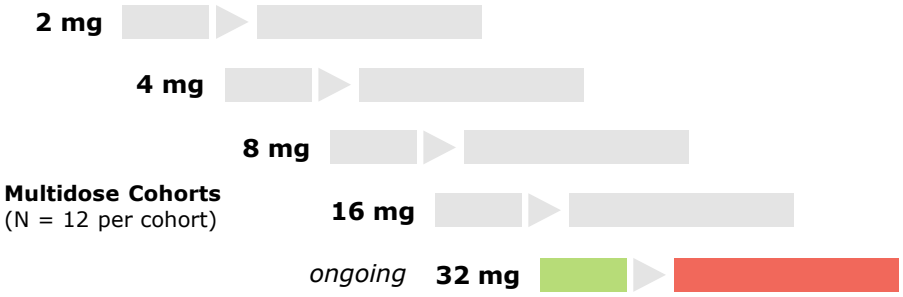
Arrow points to nuclear and perinuclear distribution of WVE-120102 in caudate nucleus

Source: Meena, Zboray L, Svrzikapa N, et al. Selectivity and biodistribution of WVE-120101, a potential antisense oligonucleotide therapy for the treatment of Huntington's disease. Paper presented at: 69th Annual Meeting of the American Academy of Neurology; April 28, 2017; Boston, MA.

# PRECISION-HD clinical trials

## Two Phase 1b/2a clinical trials for WVE-120101 and WVE-120102




### Trial results expected end of 1Q 2021

- **PRECISION-HD1 and OLE** (including complete 16 mg cohort)
- **PRECISION-HD2 and OLE** (including complete 32 mg cohort)

***Results***

- **Safety and tolerability**
- **Biomarkers**
  - mHTT
  - NfL
  - wtHTT

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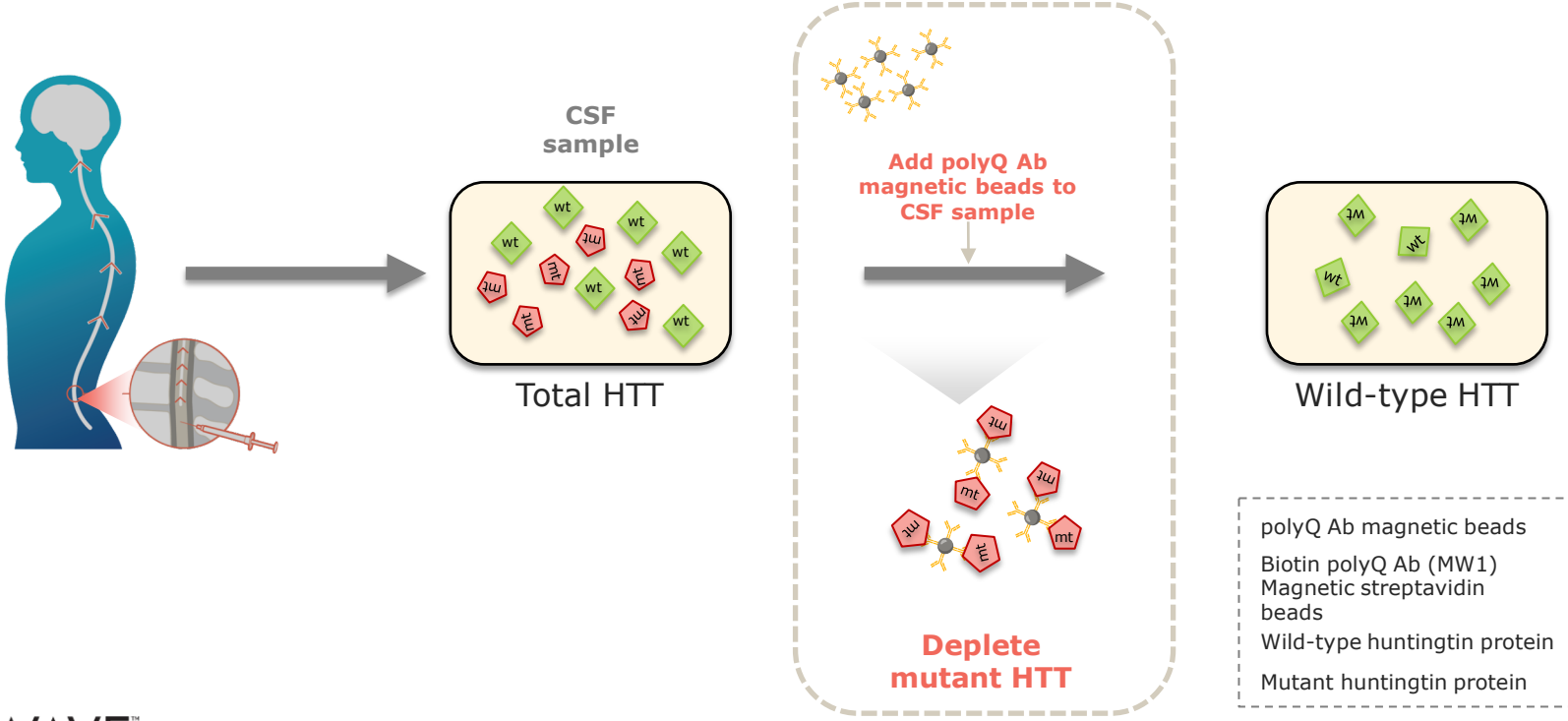
OLE: Open label extension; CSF: cerebrospinal fluid; mHTT: mutant huntingtin; NfL: neurofilament light chain; wtHTT: wild-type HTT
*Study day may vary depending on patient washout period

# Assessment of wild-type protein in CSF

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

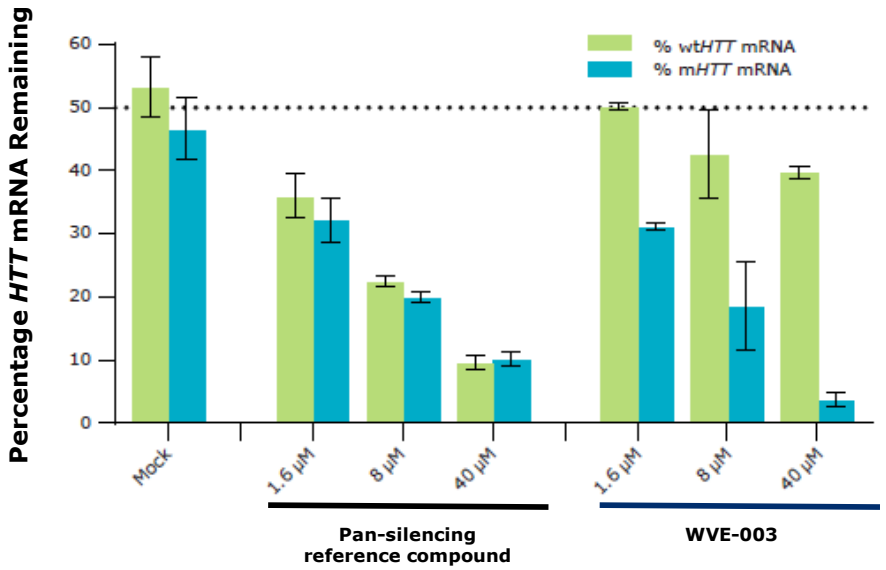



Ab: antibody CSF: cerebrospinal fluid HTT: huntingtin protein MW1: Wild et al. JCI 2015

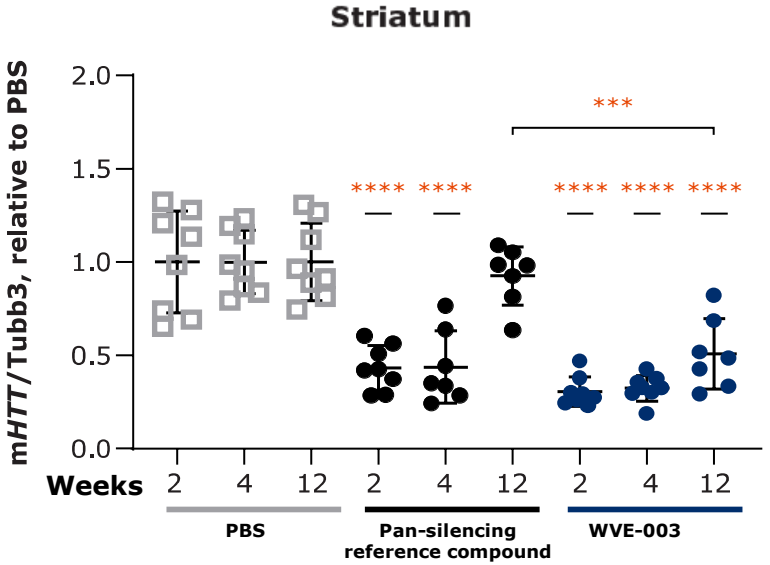
# WVE-003 (SNP3) demonstrates selective, potent, and durable reduction of mHTT in preclinical models

## 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

# 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**

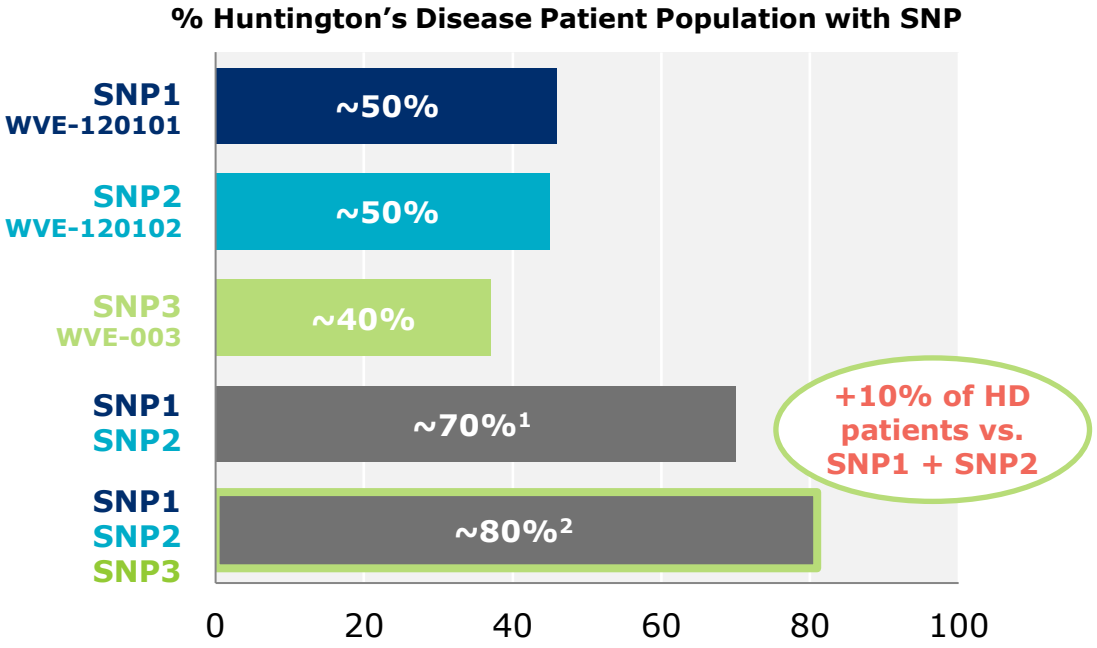
- Patients with confirmed manifest HD diagnosis with SNP3 mutation (up to 40 patients planned)
- Dose escalation and dosing interval guided by independent DSMB
- Safety and tolerability
- Biomarkers
  - mHTT
  - NfL
  - wtHTT
- Clinical trial site activation ongoing

**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

# Three allele-selective HD programs

## Potential to address ~80% of HD patient population




**Intend to explore efficacy in early manifest and pre-manifest HD patient populations**

[1] Percentage of patient population with SNP1 and/or SNP2

[2] Percentage of patient population with SNP1, SNP2 and/or SNP3

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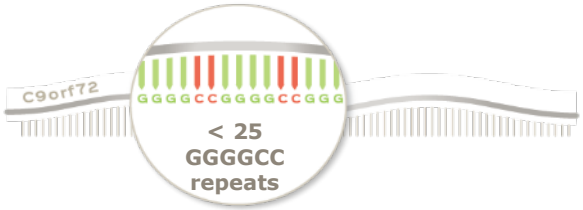
# WVE-004

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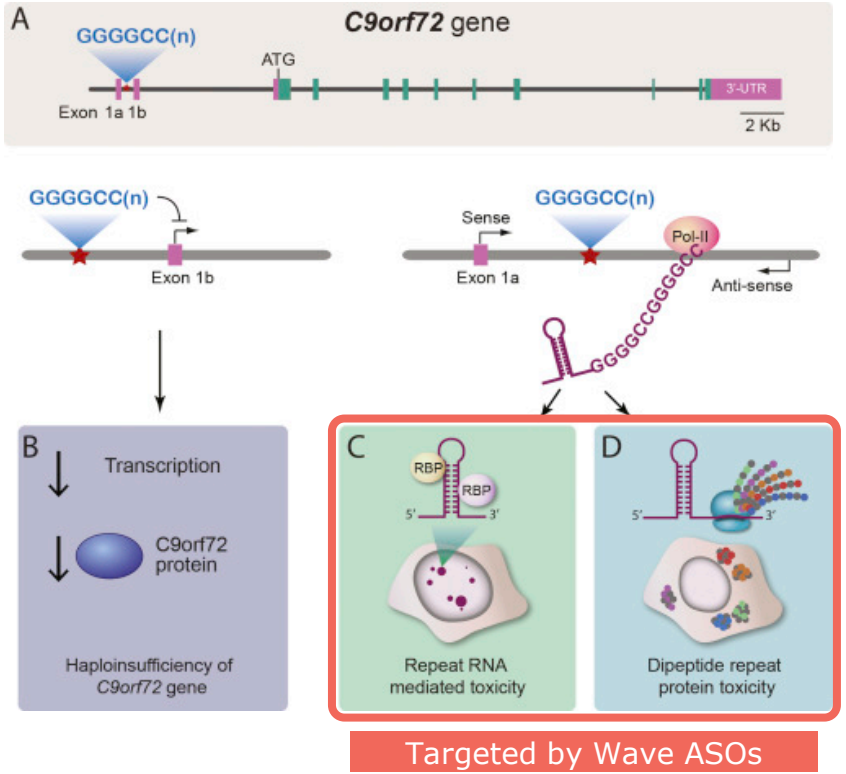
ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia
Sources: Cammack et al, Neurology, October 2019. Moore et al, Lancet Neurology, February 2020

# 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**

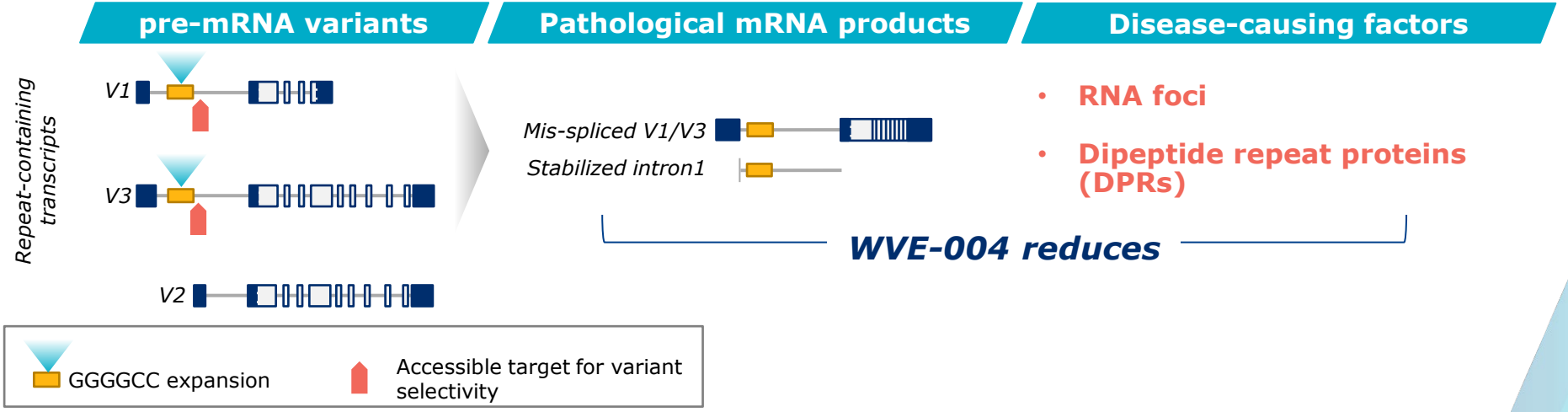



Targeted by Wave ASOs

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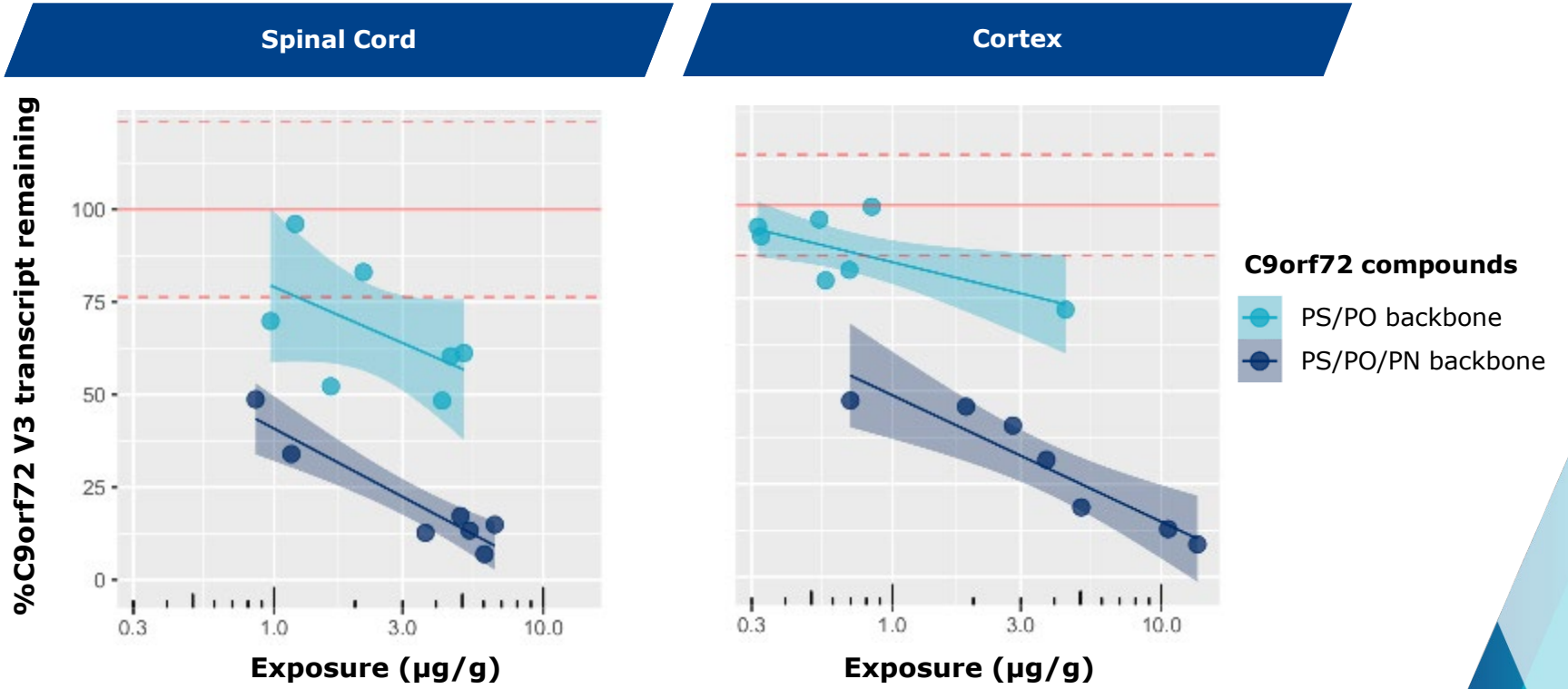
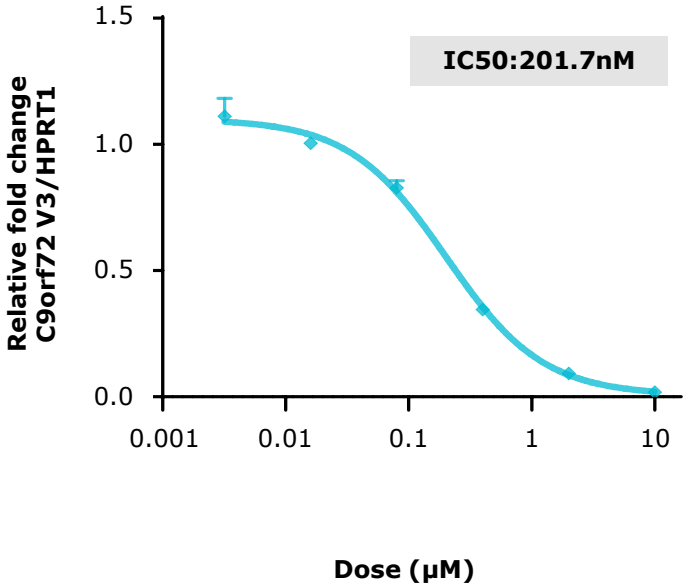
# PN backbone chemistry modifications: Improved potency among C9orf72-targeting oligonucleotides *in vivo*



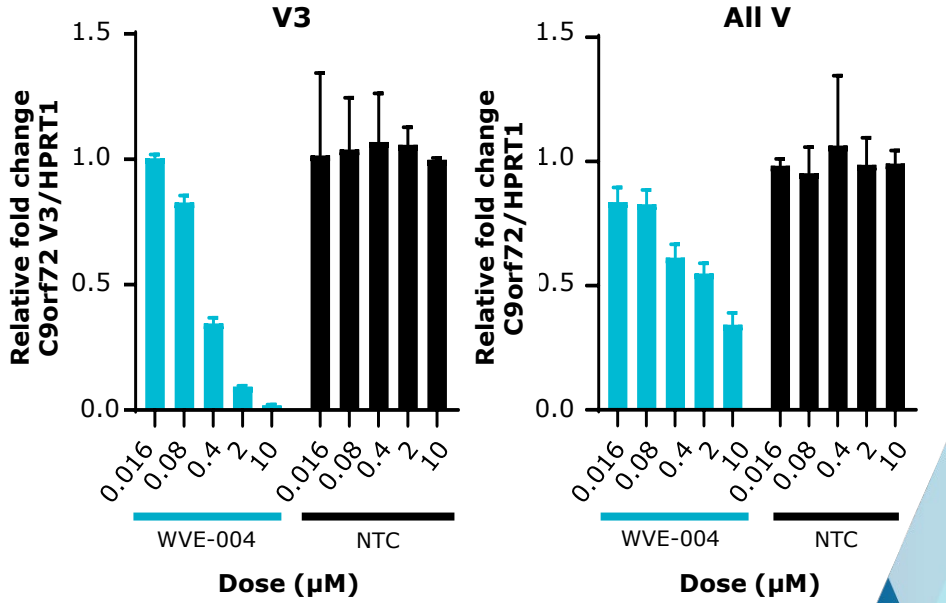

Mice received 2 x 50 ug ICV doses on days 0 & 7; mRNA from spinal cord and cortex quantified by PCR (Taqman assay) 8 weeks later. Oligonucleotide concentrations quantified by hybridization ELISA. Graphs show robust best fit lines with 95% confidence intervals (shading) for PK-PD analysis.

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

## *In vitro* activity in C9 patient-derived neurons



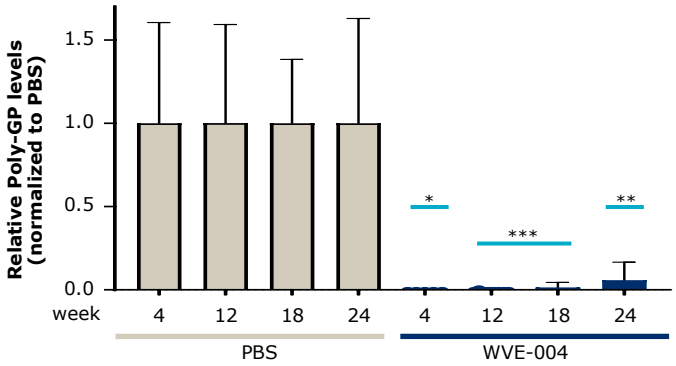

## *In vitro* selectivity in C9 patient-derived neurons



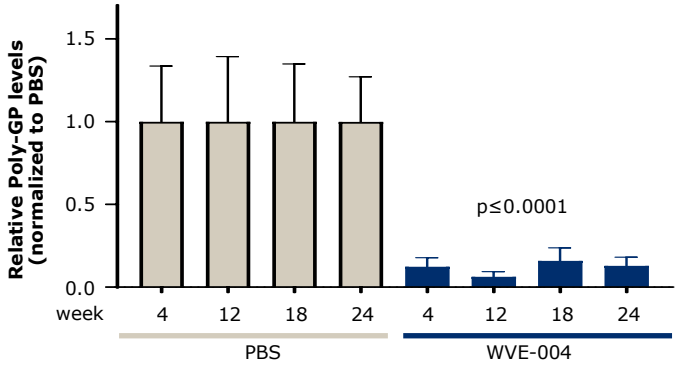

C9 patient-derived motor neurons were treated with C9orf72 candidate and NTC under gymnotic conditions up to 10uM. Taqman qPCR assays were used to evaluating V3 and all V transcripts. NTC- non-targeting control.

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

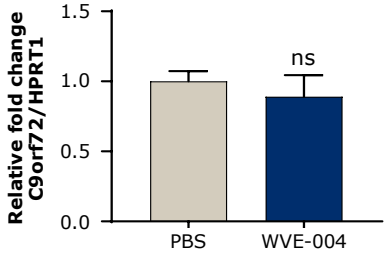
## Spinal cord

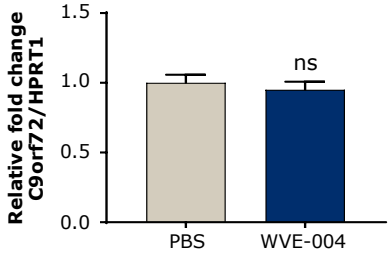



## Cortex




## 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 independent DSMB
- 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-N531

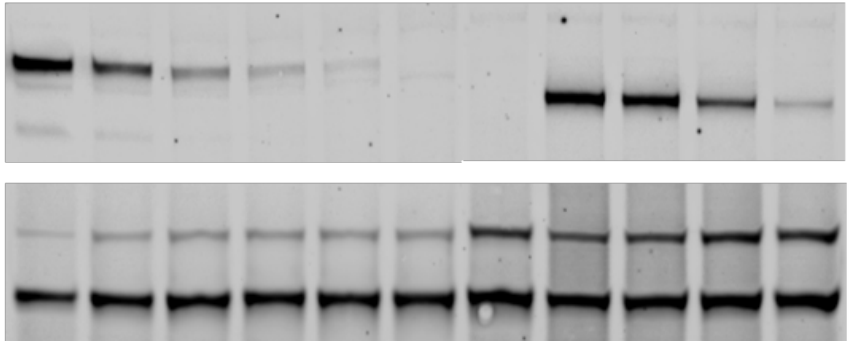
## Duchenne muscular dystrophy

# 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 |

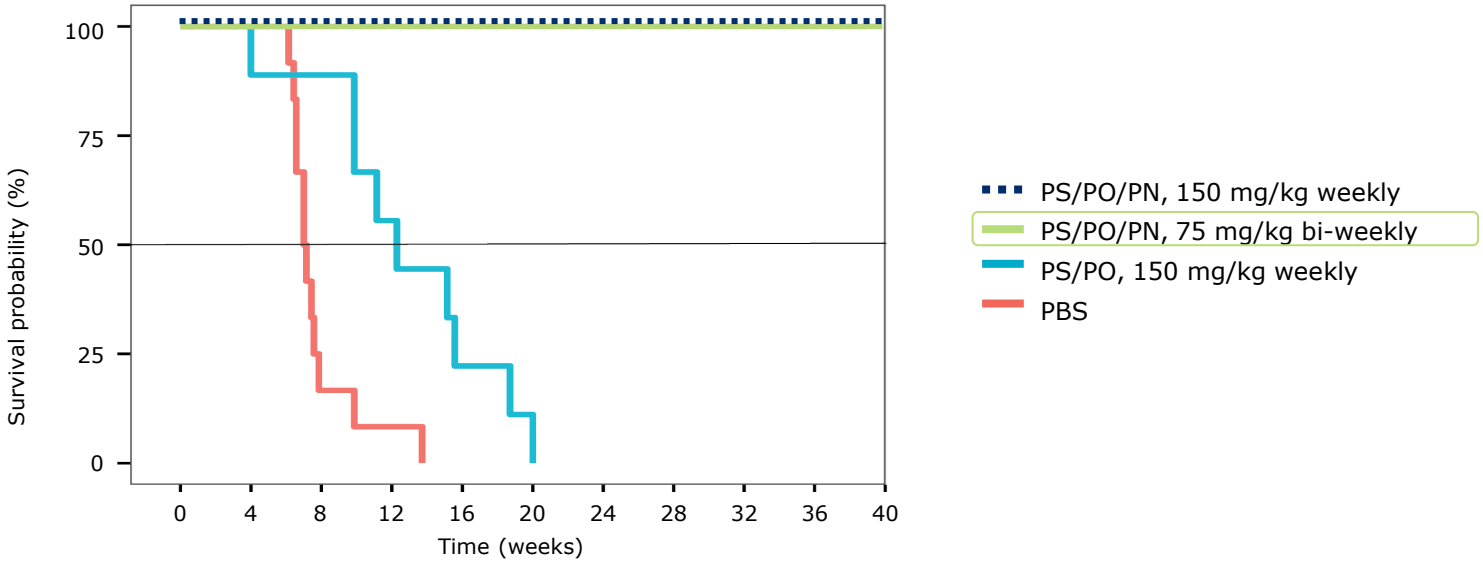



- WVE-N531 contains novel PN backbone chemistry modifications
- Free uptake for 6 days in differentiation media with no transfection agent and no peptide conjugated to the oligonucleotide
- Demonstrated a dose-dependent increase in dystrophin restoration in DMD patient-derived myoblasts

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 to initiate in 2021

- 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

**CTA submission expected in 1Q 2021**

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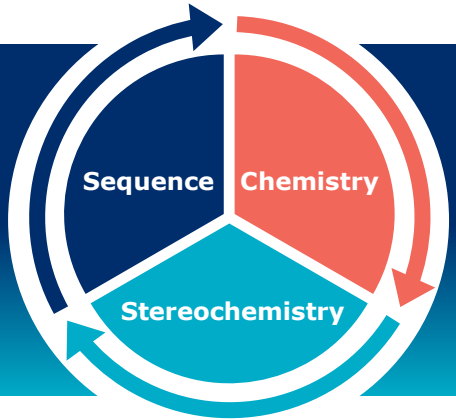
# Wave's discovery and drug development platform

# 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

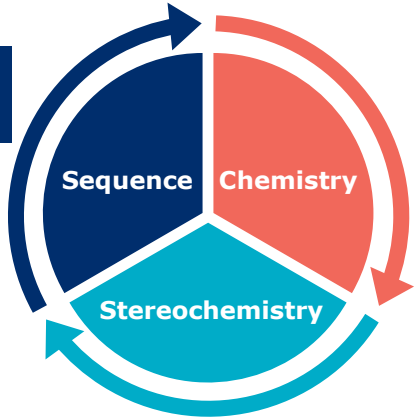
**B**: bases

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

## Stereochemistry

Chiral control of
any stereocenter

5′ modifications,
backbone modifications



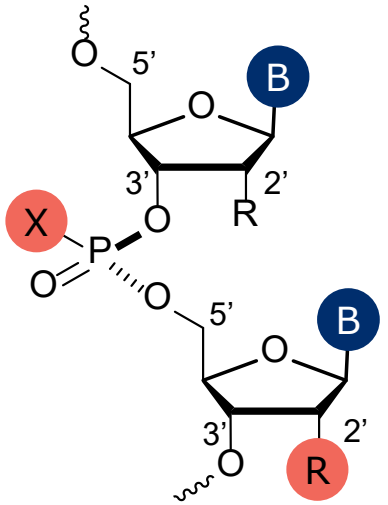

## Chemistry

**R**: 2′ modifications

OMe, MOE, F,
other modifications

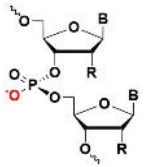
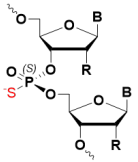
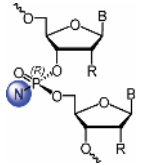
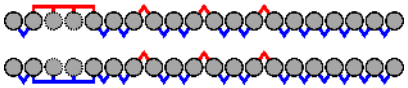
**X:** backbone chemistry

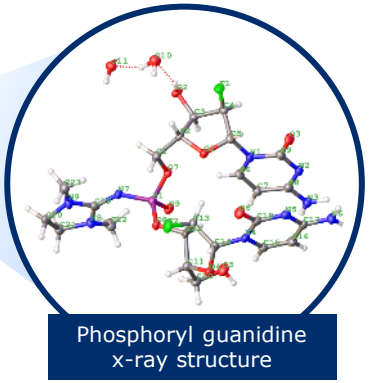
Phosphodiester (PO),
phosphorothioate (PS),
Phosphoramidate diester
(PN)



# 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 ◇ Stereorandom ⩓ PS backbone *Rp* ⩔ PS backbone *Sp* | Chiral ▯ PN backbone Stereorandom ⊓ PN backbone *Rp* ⊔ PN backbone *Sp* |
| **Charge** | Negative | Negative | Neutral |
| **Depiction** | |  |  |
| **PRISM backbone modifications** | PO/PS | | |
| | PO/PS/PN | | |



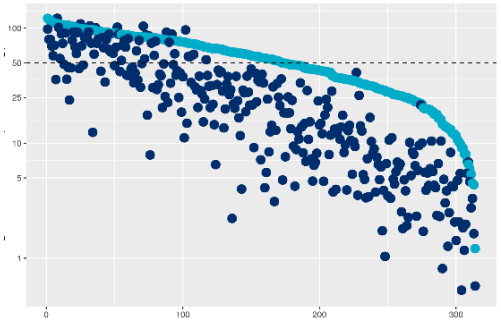
Phosphoryl guanidine x-ray structure

Molecule structure illustrative of backbone modification patterns

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

## Silencing

**Target knockdown (% remaining)**

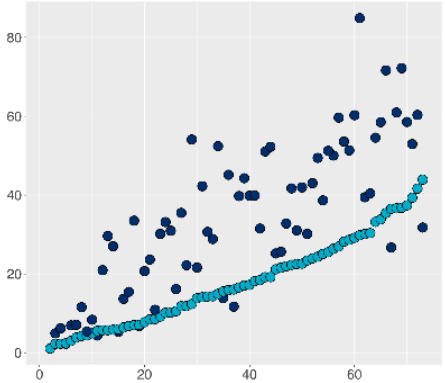


**Ranked by potency of reference PS/PO compound**

**Improved knockdown**

## Splicing

**% Skipping**

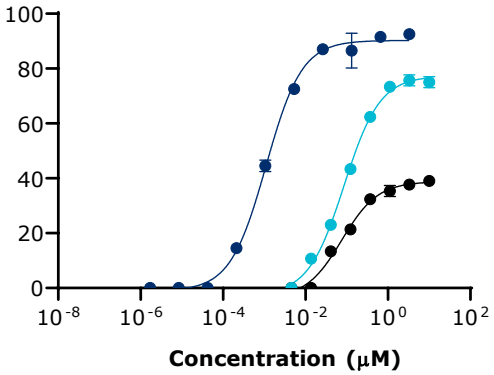


**Ranked by potency of reference PS/PO compound**

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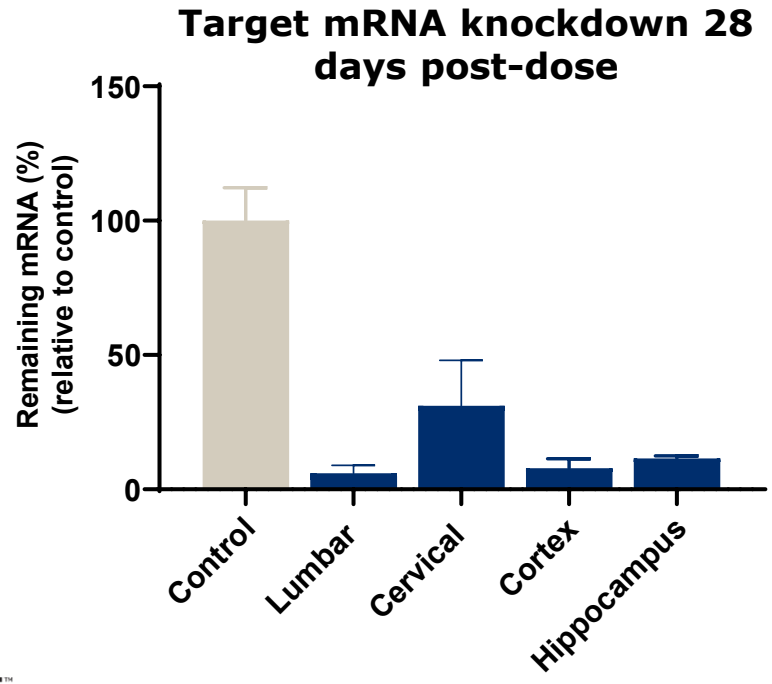
Presented at Analyst & Investor Research Webcast on August 25, 2020; Right: Data from independent experiments

# 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

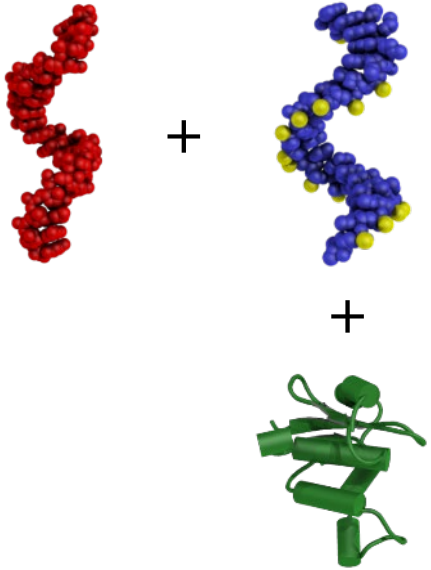
NHPs: Non-human primates; IT: intrathecal
NHPs were administered 12 mg on day 1 via IT bolus injection; tissue samples were collected from 3 NHPs at 28 days post-dose.

# PRISM enables optimal placement of backbone stereochemistry

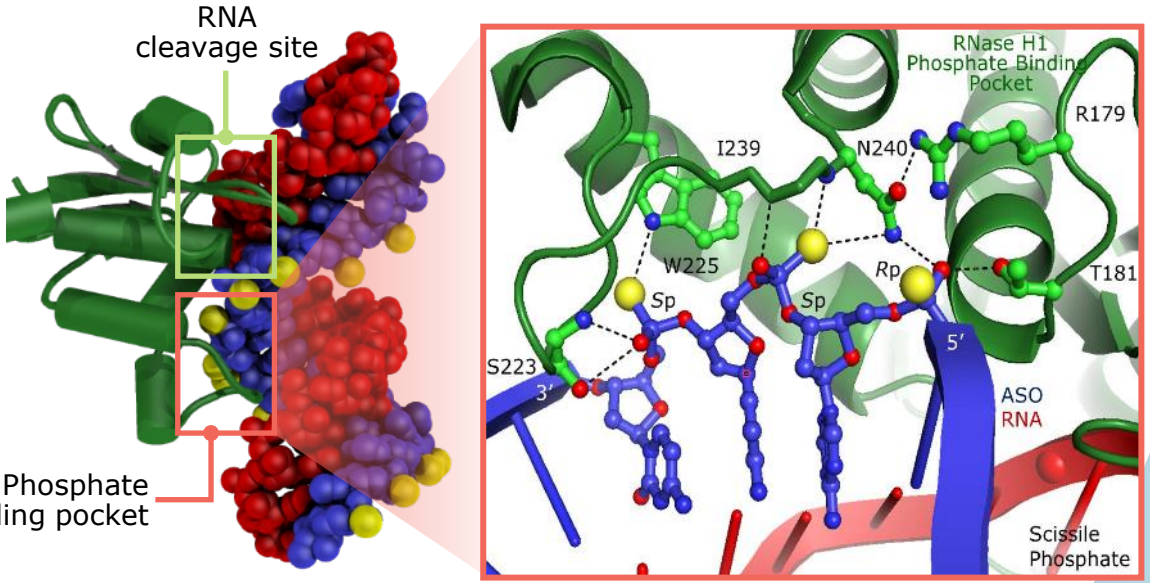
## Crystal structure confirms phosphate-binding pocket of RNase H binds 3′-SSR-5′ motif in stereopure oligonucleotide – supports design strategy for Wave oligonucleotides

Target RNA

Stereopure Oligonucleotide (C9orf72 compound)



RNase H

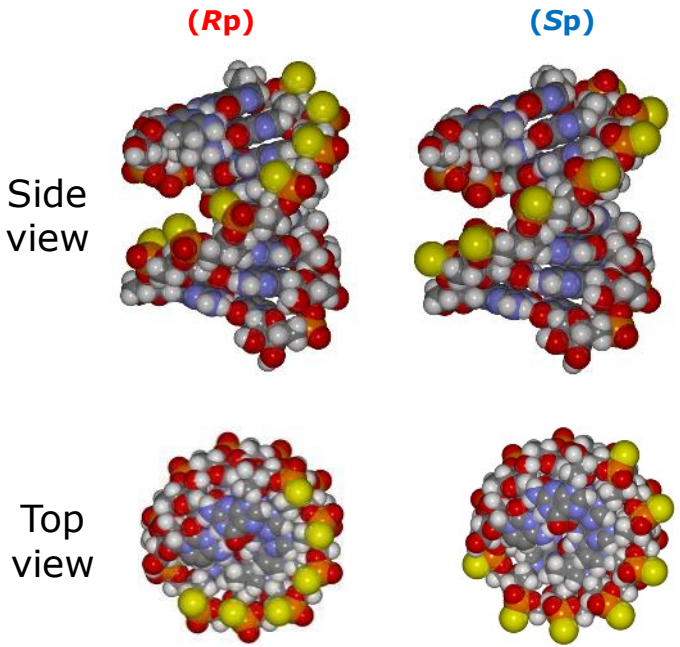



ASO/RNA duplex

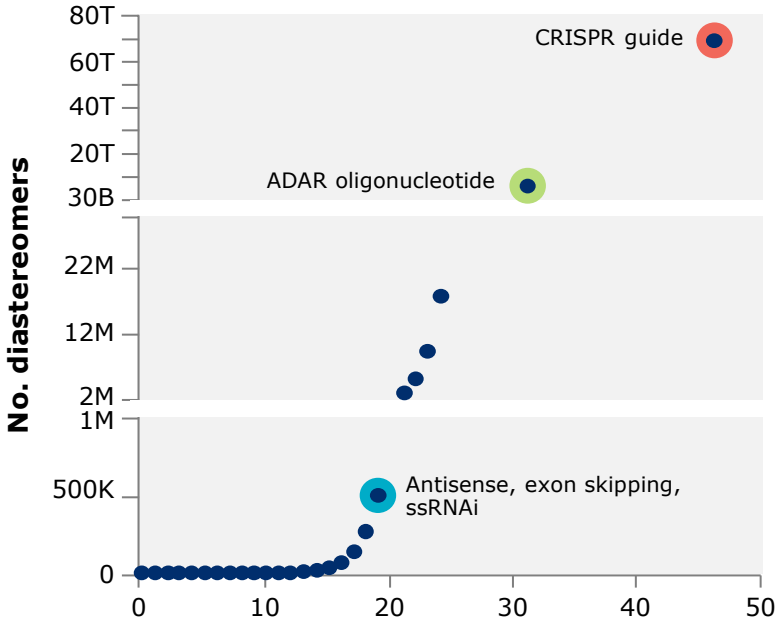
Yellow spheres represent ‘S’ atoms

# 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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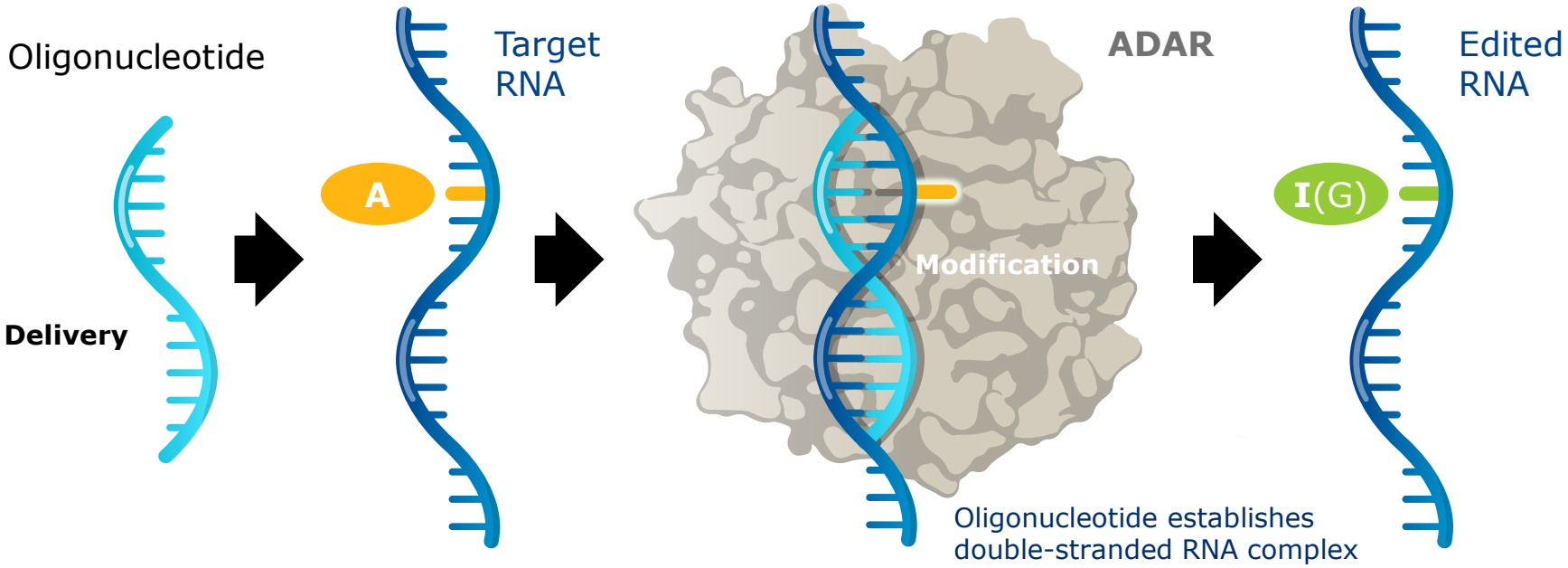
# ADAR editing

## 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

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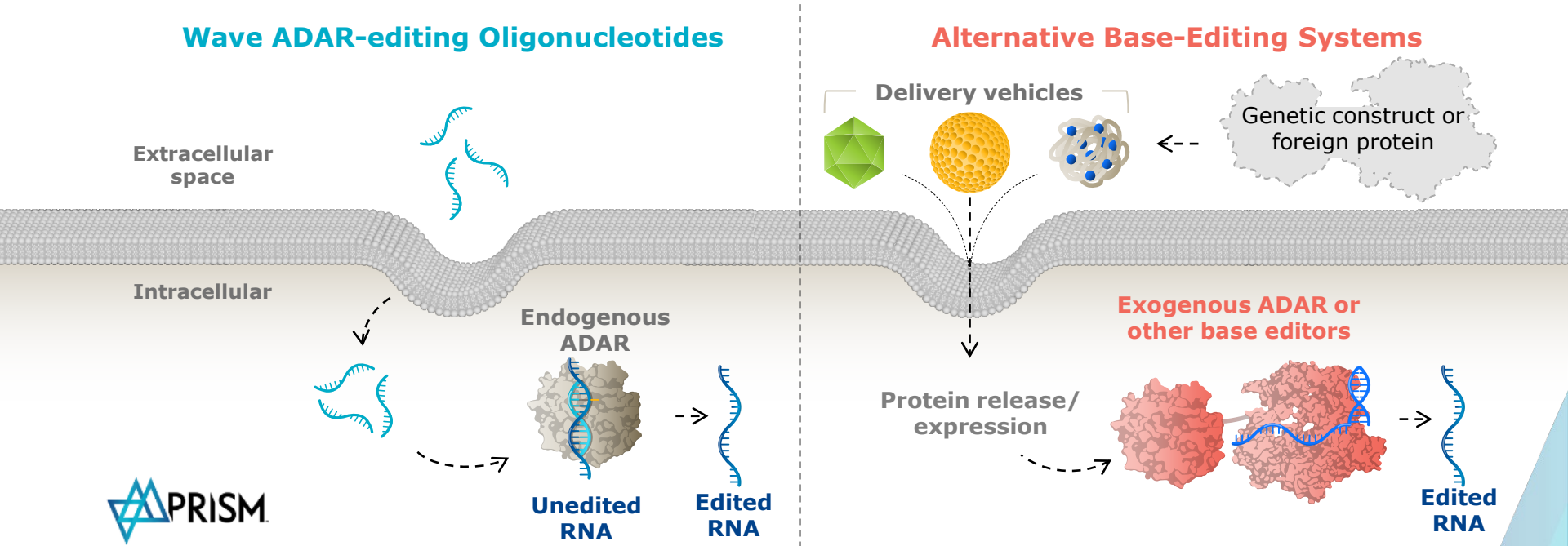
A: adenosine; I: inosine; G: guanosine; Nishikura, K. A-to-I editing of coding and non-coding RNAs by ADARs. Nat. Rev. Mol. Cell Biol. 2016; Picardi, E. *et al.* Profiling RNA editing in human tissues: towards the inosinome Atlas. *Scientific reports* **5**, 14941, doi:10.1038/srep14941 (2015).

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

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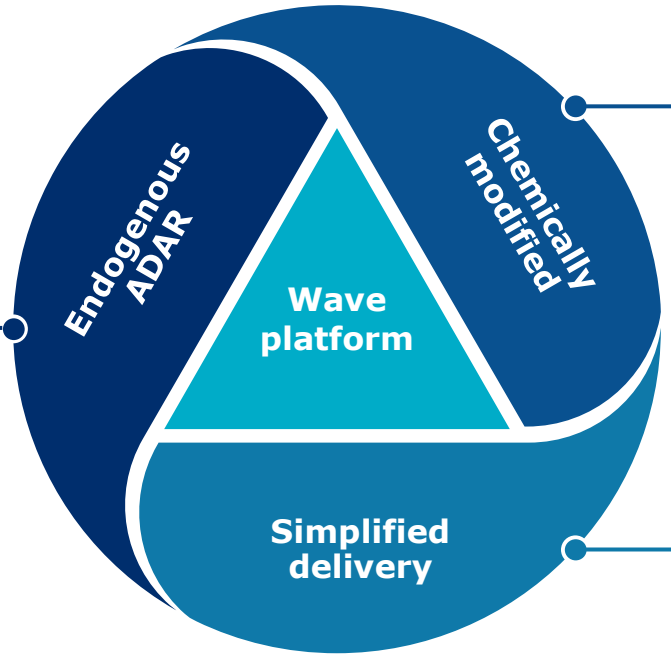
# Advantages of Wave ADAR editing platform

- 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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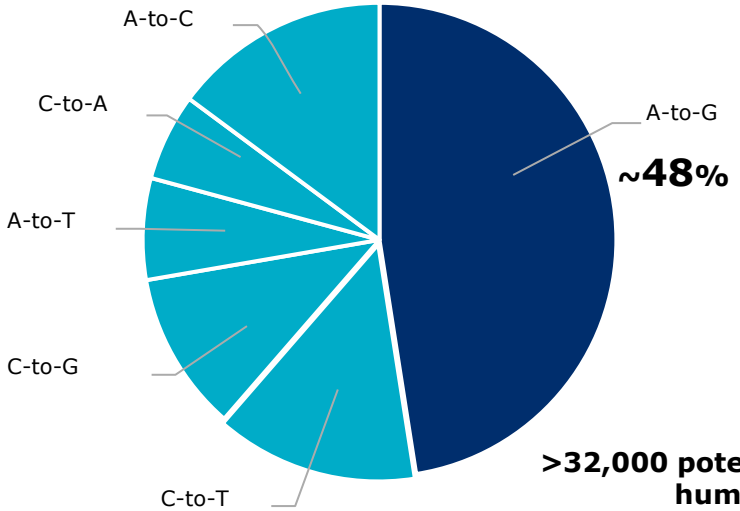
Sources: Chen Biochemistry 2019

# 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

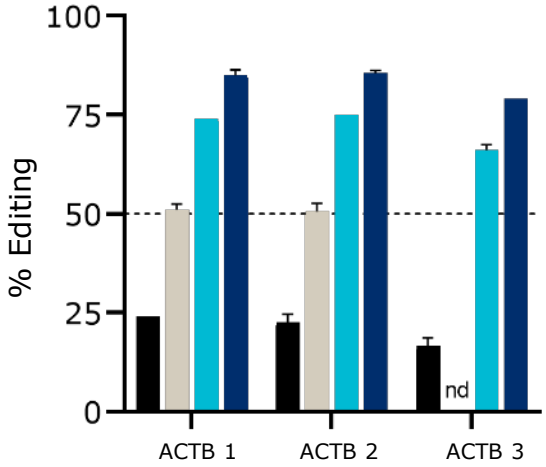
*Examples:*

**Haploinsufficient diseases**

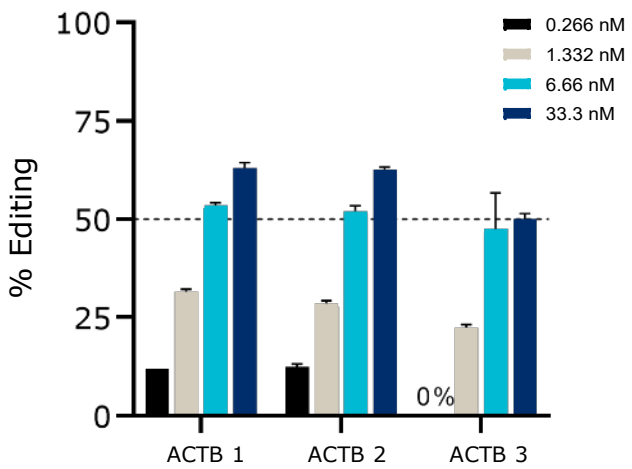
# Significant ADAR editing demonstrated *in vitro* in NHP and primary human hepatocytes

## ACTB GalNAc-conjugated oligonucleotides with stereopure PN backbone chemistry modifications

**_In vitro_ dose-response human hepatocytes**




**_In vitro_ dose-response NHP hepatocytes**

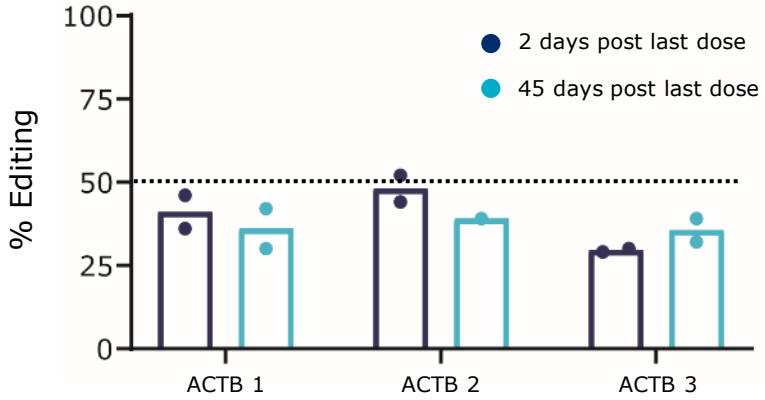



NHP: non-human primate; ACTB: Beta-actin; nd= not determined
Total RNA was harvested, reverse transcribed to generate cDNA, and the editing target site was amplified by PCR.

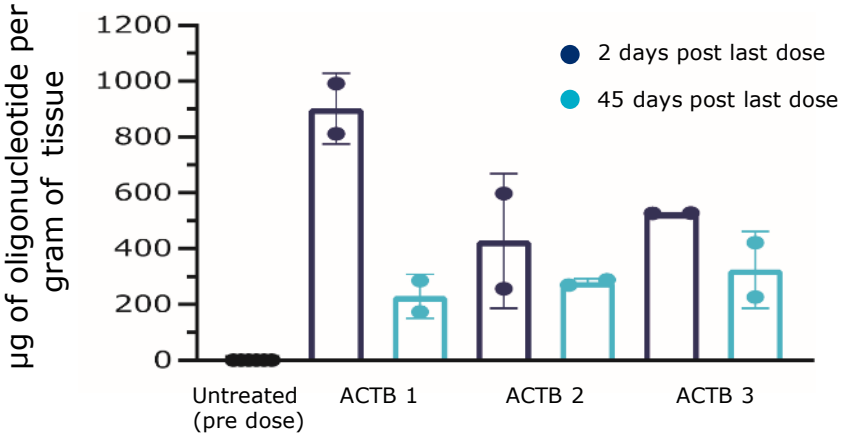
# Efficient ADAR editing translated *in vivo* in non-human primate study

- 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**

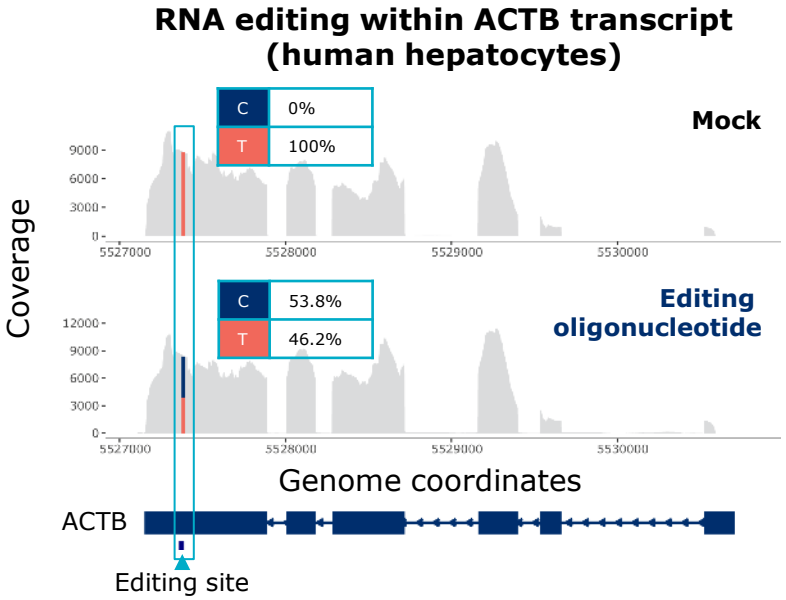


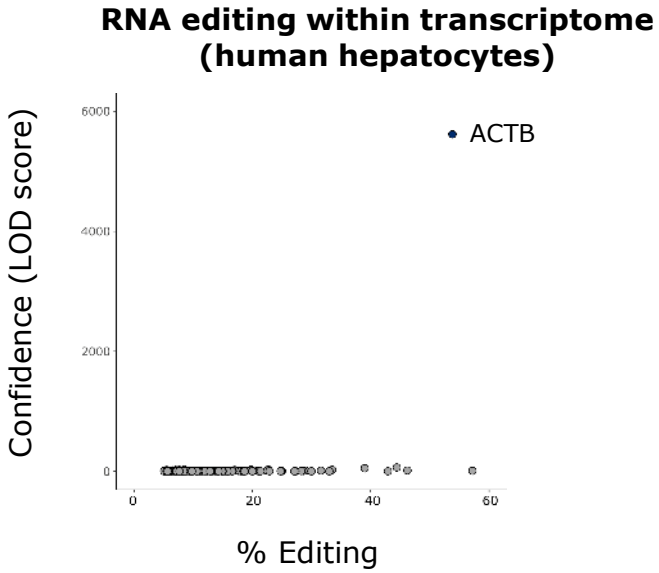

**Oligonucleotide quantification in NHP following subcutaneous administration**




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:**

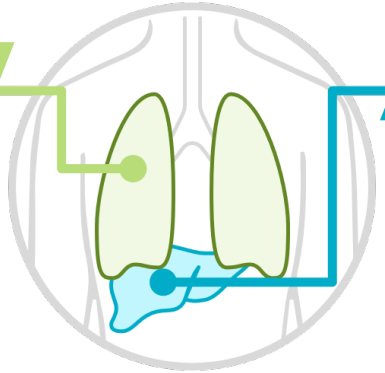
- Increase circulating levels of wild-type AAT protein
- Reduce aggregation of Z-AAT in liver
- Retain wild-type AAT physiological regulation

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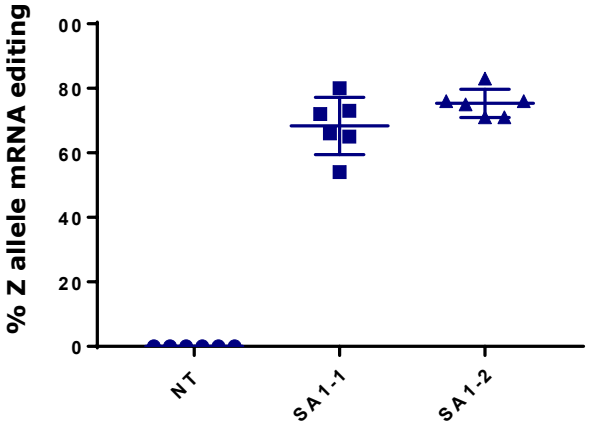
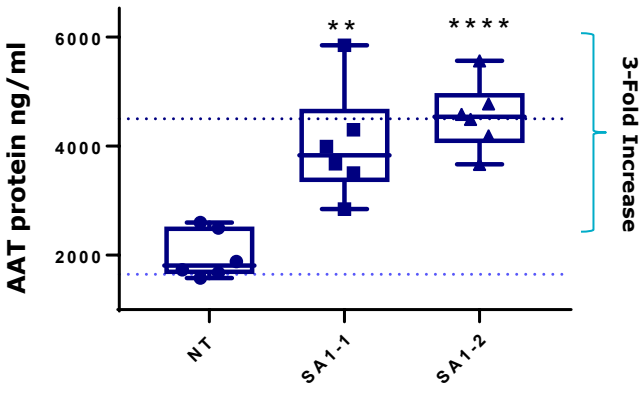
# *SERPINA1* Z allele mRNA editing increases edited AAT protein concentration *in vitro*

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**



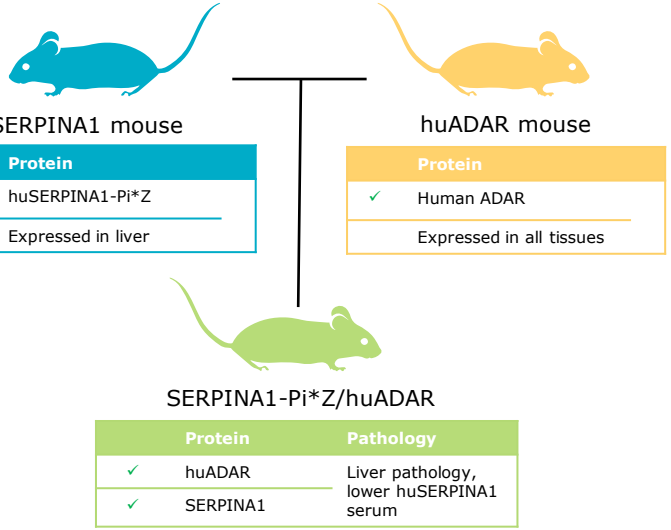

**Edited AAT protein analysis**

- 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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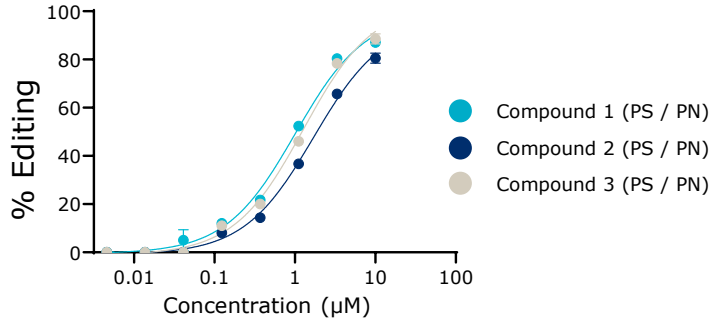
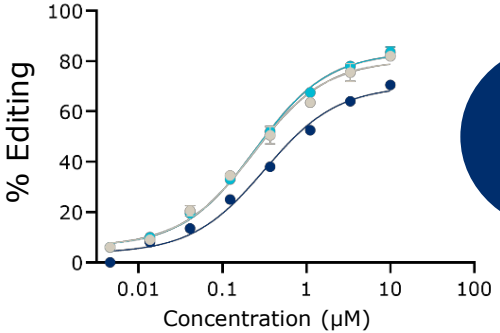
# Multiple opportunities for ADAR editing in neurology

**ACTB editing in iCell Neurons**



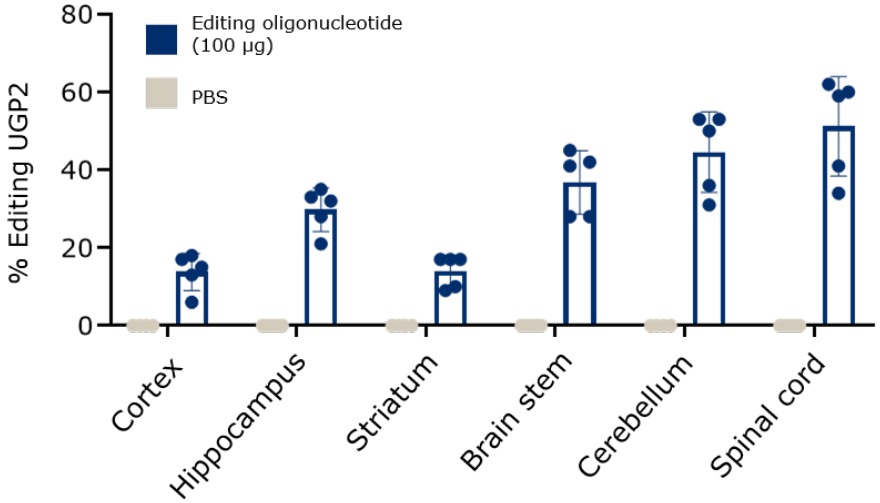

**ACTB editing in human iCell Astrocytes**




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

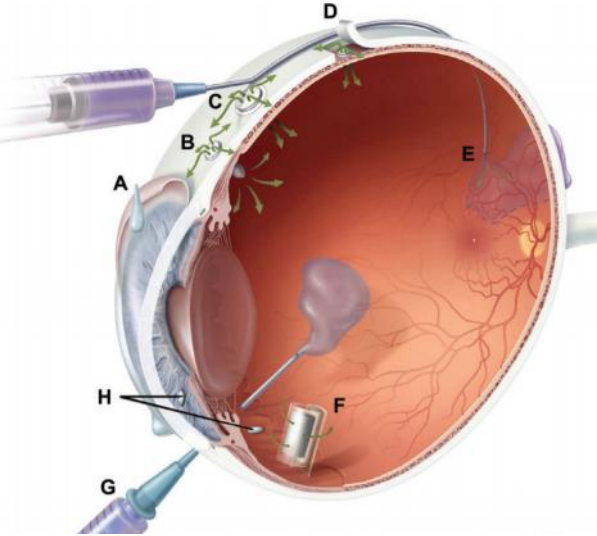
# Stereopure oligonucleotides for inherited retinal diseases (IRDs)

## 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

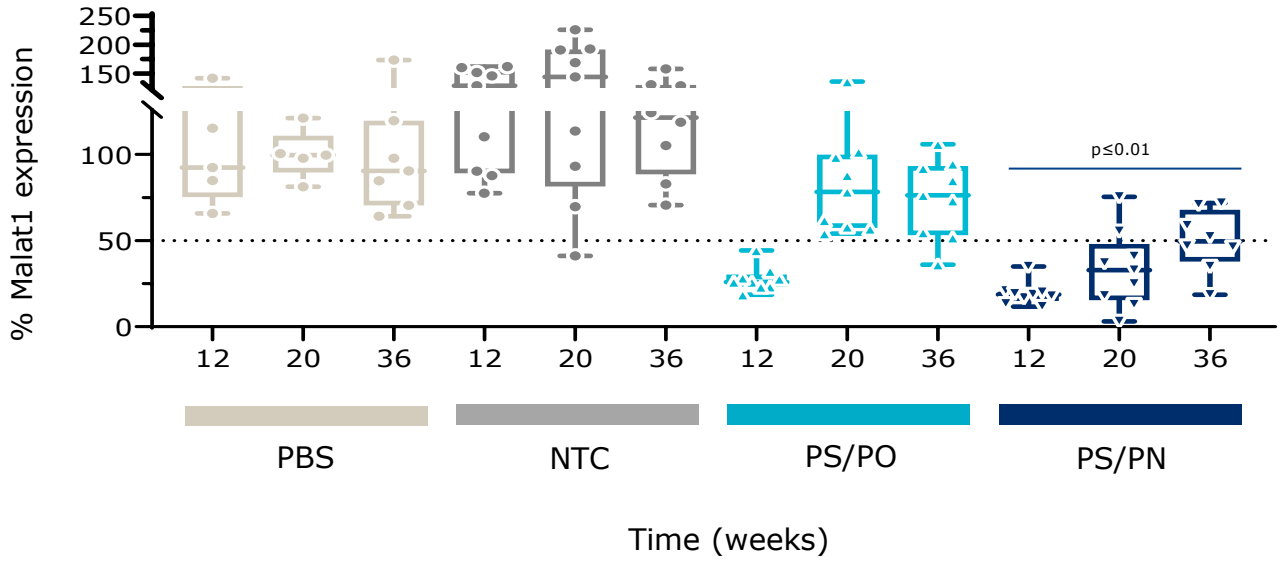



Intravitreal injection

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

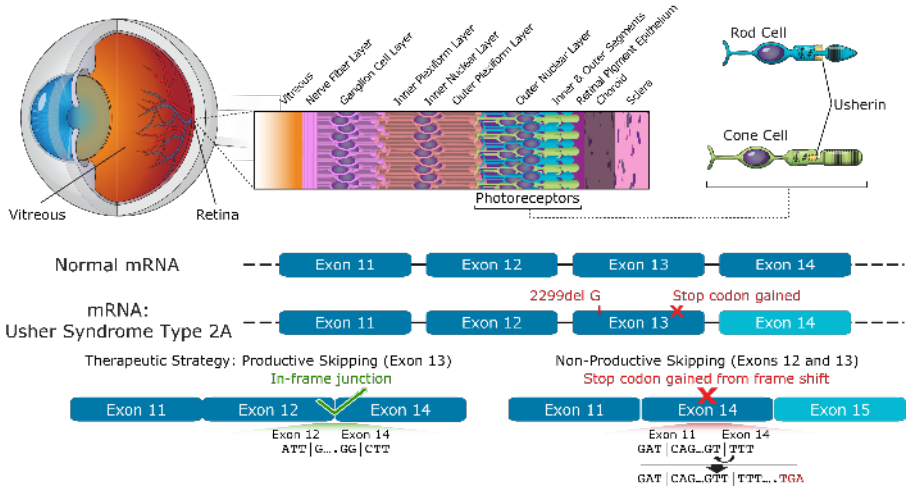
## ~50% Malat1 knockdown at 36 weeks in the posterior of the eye




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**

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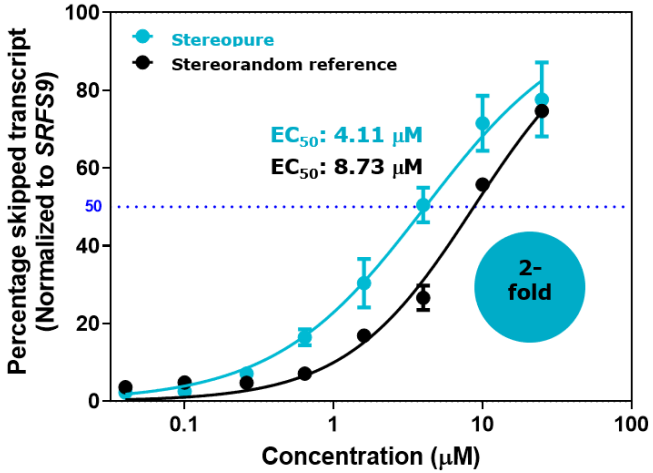
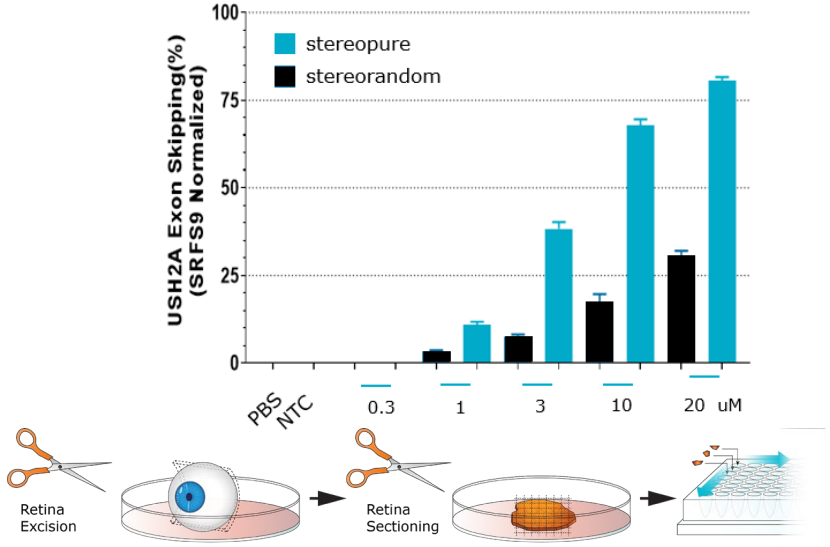
Sources: Boughman et al., 1983. *J Chron Dis*. 36:595-603; Seyedahmadi et al., 2004. *Exp Eye Res.* 79:167-173; Liu et al., 2007. *Proc Natl Acad Sci USA* 104:4413-4418.

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

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



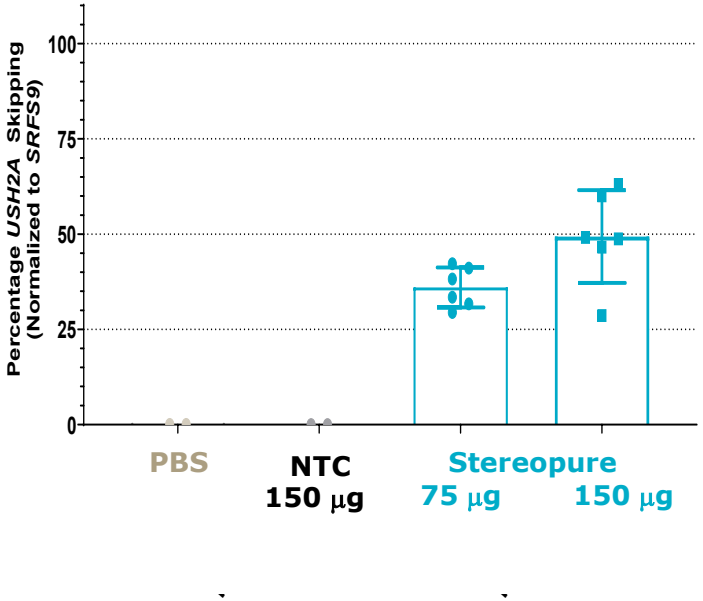

## Target engagement in NHP retinas




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



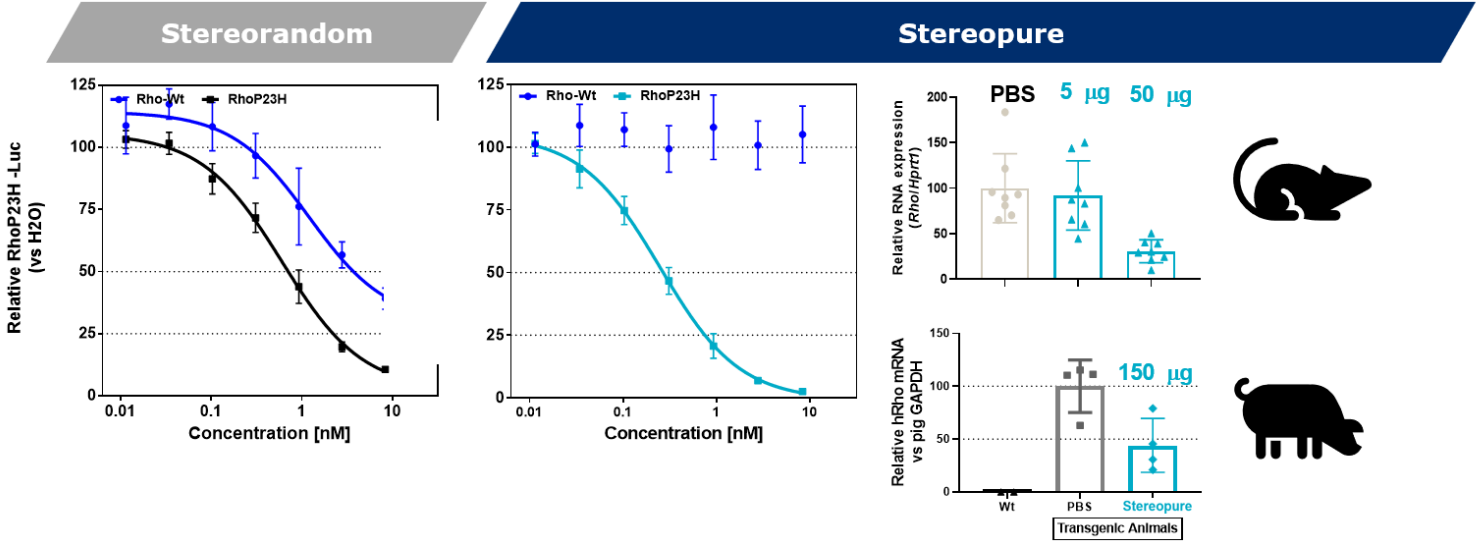

- Oligonucleotide is complementary to NHP *USH2A* exon 12*
- Evaluated 1-week post-single IVT injection
- Dose-dependent activity of **stereopure** oligonucleotides
- Substantial exposure in retina
- Exon-skipping integrity confirmed by RNA-seq at both doses

*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 SNP2 | ◆ | **End of 1Q 2021:** PRECISION-HD2 data, including complete 32 milligram cohort, and initial data from OLE trial |
| **Huntington's disease** mHTT SNP1 | ◆ | **End of 1Q 2021**: PRECISION-HD1 data, including complete 16 milligram cohort, and initial data from OLE trial |
| **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 |
| **Duchenne muscular dystrophy** Exon 53 | ◆ | ◆ **End of 1Q 2021:** CTA submission |
| **ADAR editing** Multiple | ◆ | ◆ **1H 2021**: Humanized mouse model validation |
| **HEPATIC** | | |
| **AATD (ADAR editing)** SERPINA1 | ◆ | ◆ **1H 2021:** *in vivo* AATD data |

First clinical compounds with PN chemistry to begin dosing in 2021

PRISM ◆ Stereopure ◆ PN chemistry

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

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# Realizing a brighter future for people affected by genetic diseases


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