Stereopure Oligonucleotides in Development for the Treatment of Genetically Defined Diseases

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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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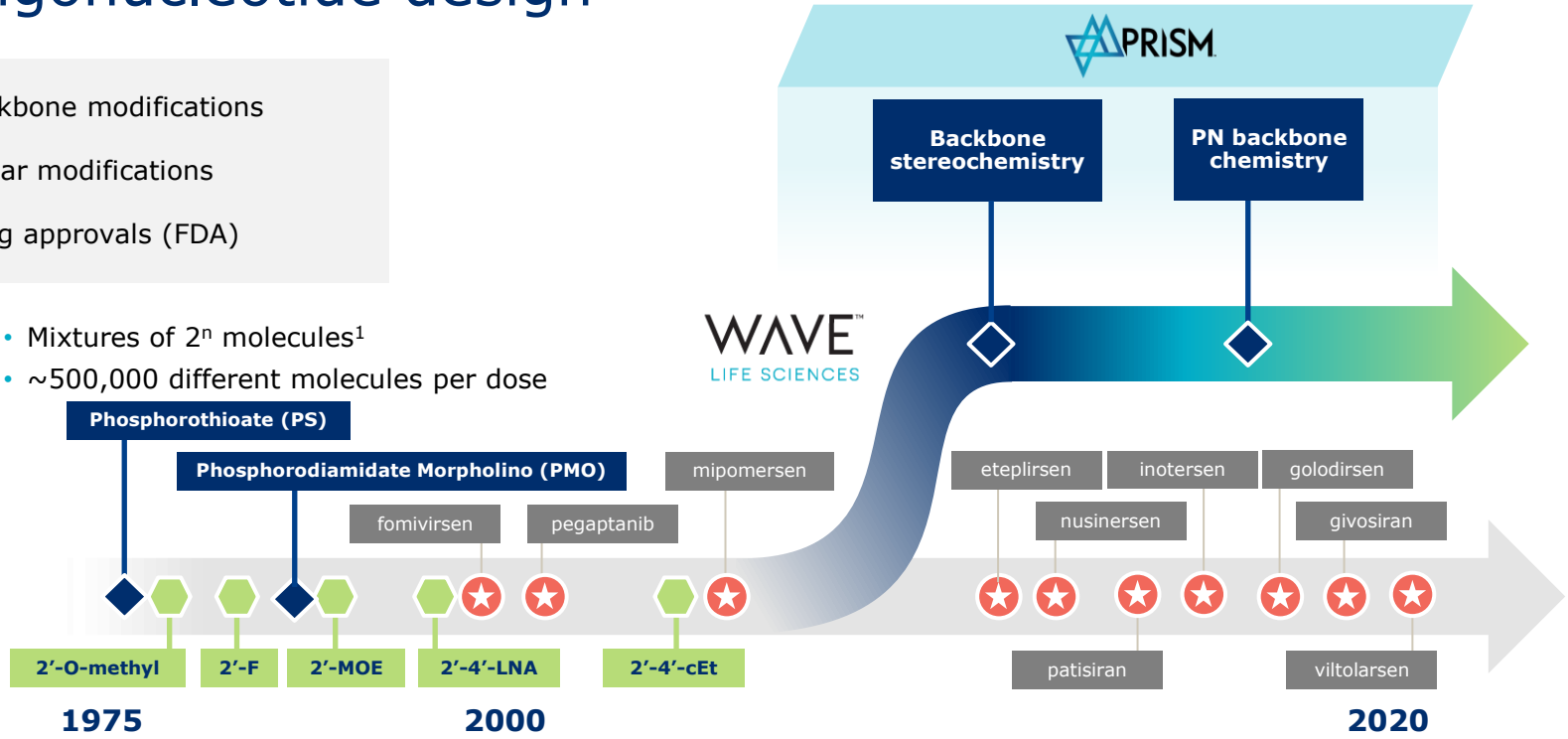
PRISM has unlocked novel and proprietary advances in oligonucleotide design

- Backbone modifications
- Sugar modifications
- Drug approvals (FDA)

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



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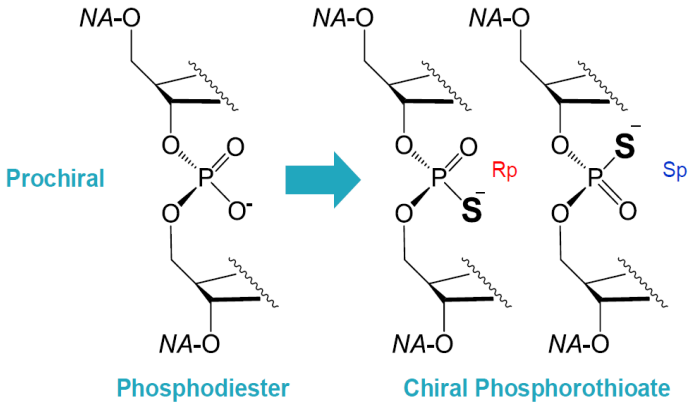
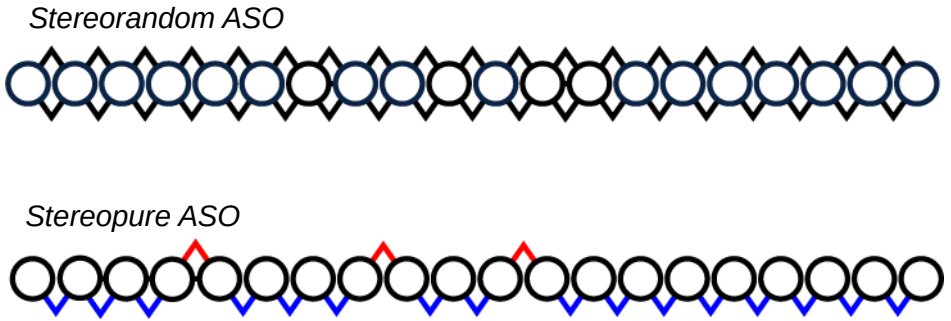
[1]n=number of chiral centers

Stereopure oligonucleotides

Phosphorothioate (PS) modifications introduce chiral centers

An enormous number of permutations exist (2^n), often resulting in over 500,000 different molecules in every dose





Nucleotide

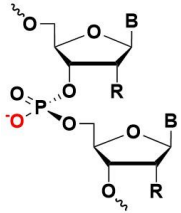
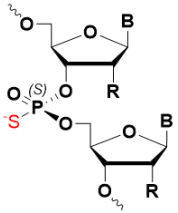
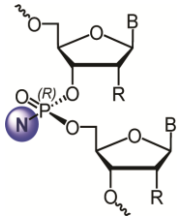
Stereorandom

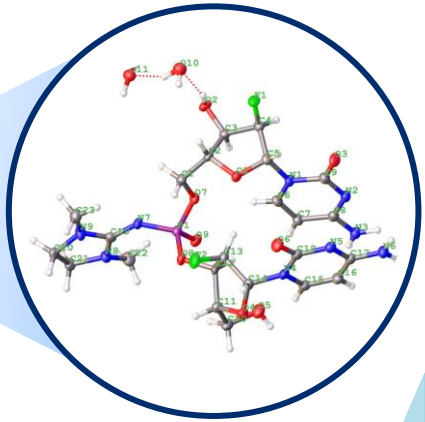
*R*p

*S*p

New backbone chemistry: PN modification

Extending backbone pharmacology

Backbone linkage	PO	PS	PN
	Phosphodiester	Phosphorothioate	Phosphoramidate diester
			
Charge	Negative	Negative	Neutral



Phosphoryl guanidine
x-ray structure

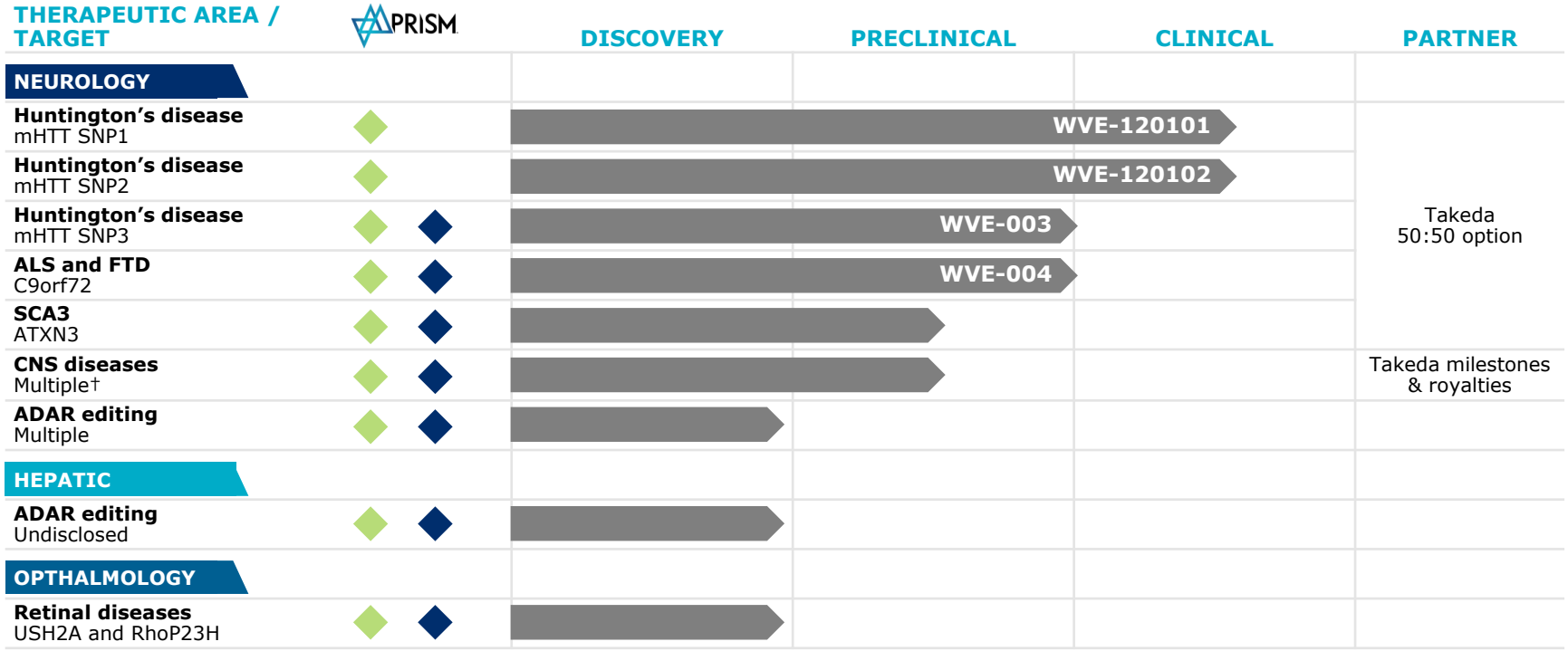
PRISM stereopure backbones

PS/PO chemistry

PS/PO/PN chemistry

Wave continues to innovate on new 2’ and backbone chemistries

Innovative pipeline led by neurology programs



†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

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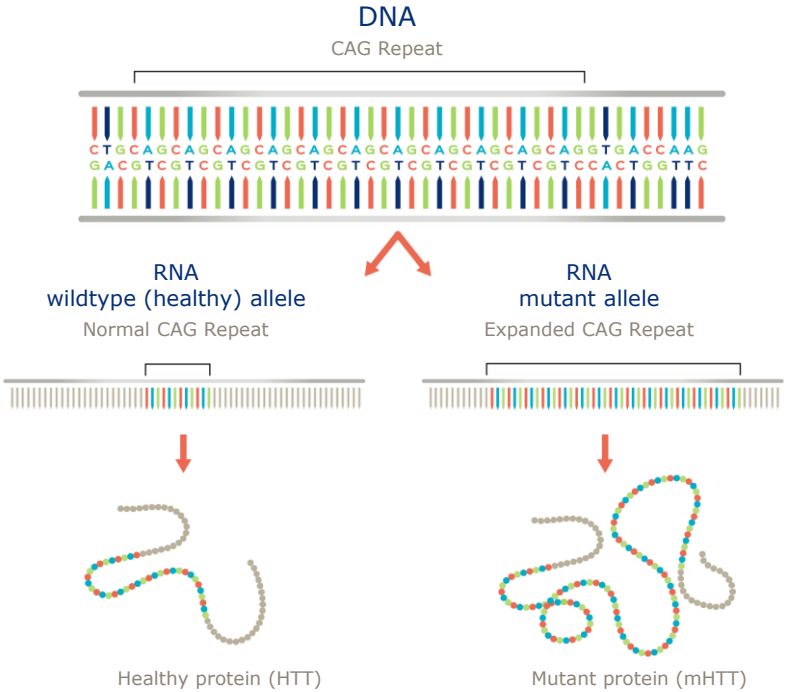
Our Approach to HD:

Selective Targeting of Mutant Huntingtin (mHTT) Protein

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
- Wildtype (healthy) HTT protein critical for neuronal function; suppression may have detrimental long-term consequences
- 30,000 people with Huntington's disease in the US; another 200,000 at risk of developing the condition



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. Huntington Disease Society of America (HDSA). What is Huntington's disease? Available at: http://hdsa.org/what-is-hd/. Accessed: November 2, 2018.

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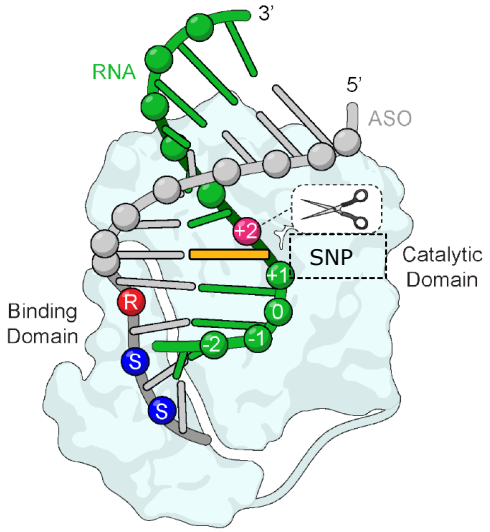
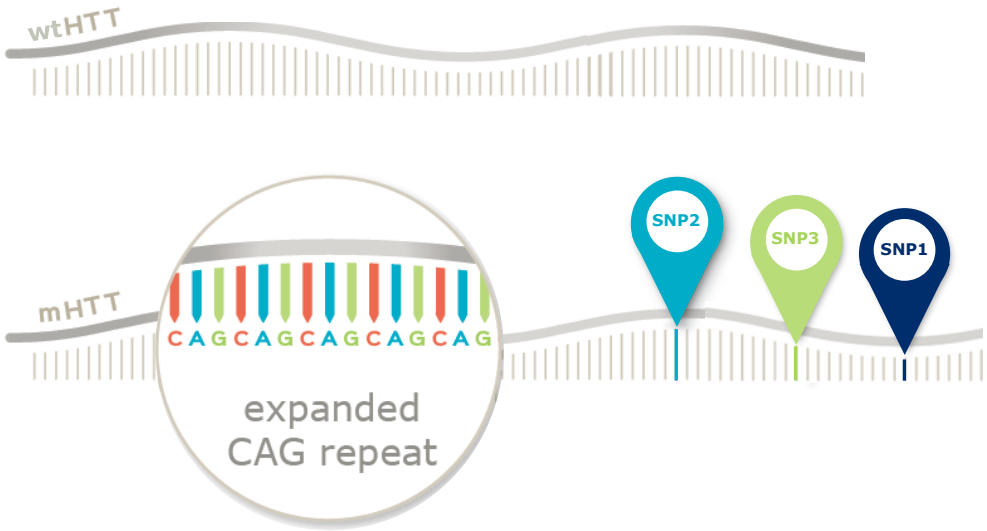
Wave approach: allele-selective silencing

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



RNase H and ASO:RNA



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

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SNP detection in *HTT* gene opens door to allele-selective treatment for Huntington's disease

Prospective Observational Study

202 patients with HD

Blood samples

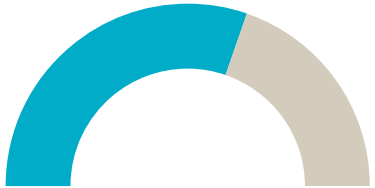
Long-range sequencing and phasing

CAG repeats
- Number and size

SNPs
- Frequency
- Heterozygosity
- Presence on m*HTT* allele

The most frequently occurring genotype in the study: wt*HTT* with **18** CAG repeats and m*HTT* with **43** CAG repeats

Heterozygosity of SNP1 and/or SNP2 identified in **72%** individuals



SNP1 and SNP2 associated with m*HTT* in **61%** individuals

HTT SNPs can be a candidate target for personalized HD treatment

Claassen DO, et al. Genotyping single nucleotide polymorphisms for allele-selective therapy in Huntington disease. *Neurol Genet.* 2020;6:e430. doi:10.1212/NXG.0000000000000430

PRECISION HD1 & PRECISION HD2

Primary endpoint

- Safety and tolerability of treatment, compared with placebo, as assessed by
  - Number (%) of patients with AEs
  - Severity of AEs
  - Number (%) of patients with SAEs
  - Number (%) of patients who withdrew due to AEs

Secondary endpoints

- Pharmacokinetics, pharmacodynamics, Total Functional Capacity

Exploratory endpoints

- UHDRS, behavior assessment, MRI

PRECISION-HD2 and PRECISION-HD1 data, including 32 mg cohorts and OLE data, expected in 1Q 2021

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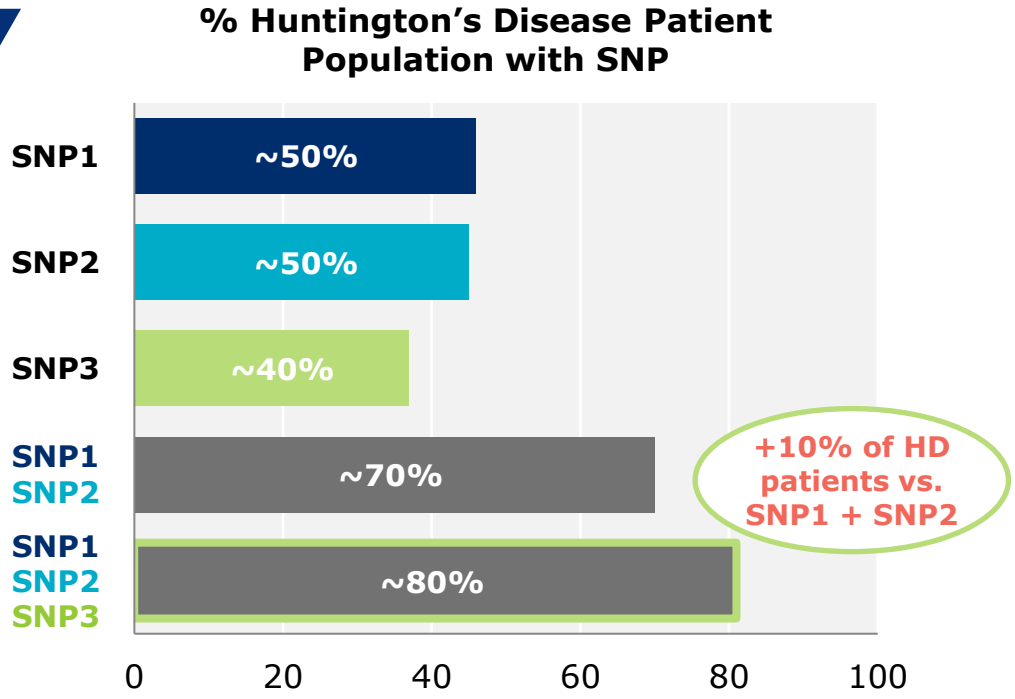
AE=adverse event; PK=pharmacokinetic; SAE=serious AE; UHDRS=unified Huntington's disease rating scale; MRI=magnetic resonance imaging

Broadening reach in Huntington's disease with SNP3

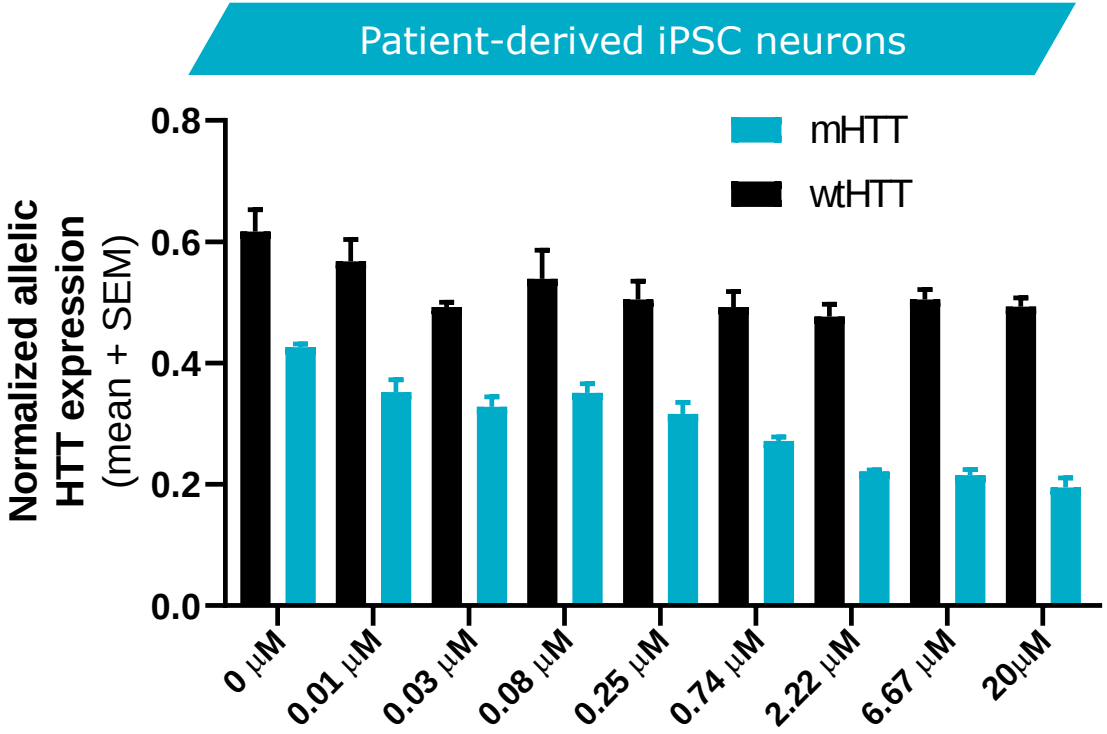
SNP3

- Due to overlap, ~80% of the total HD patient population carry SNP1 and/or SNP2 and/or SNP3
- *In vivo* models for SNP3 available for preclinical development



Predicted patient coverage calculated from published phasing data from Canadian HD patients (Carroll et al., 2011)

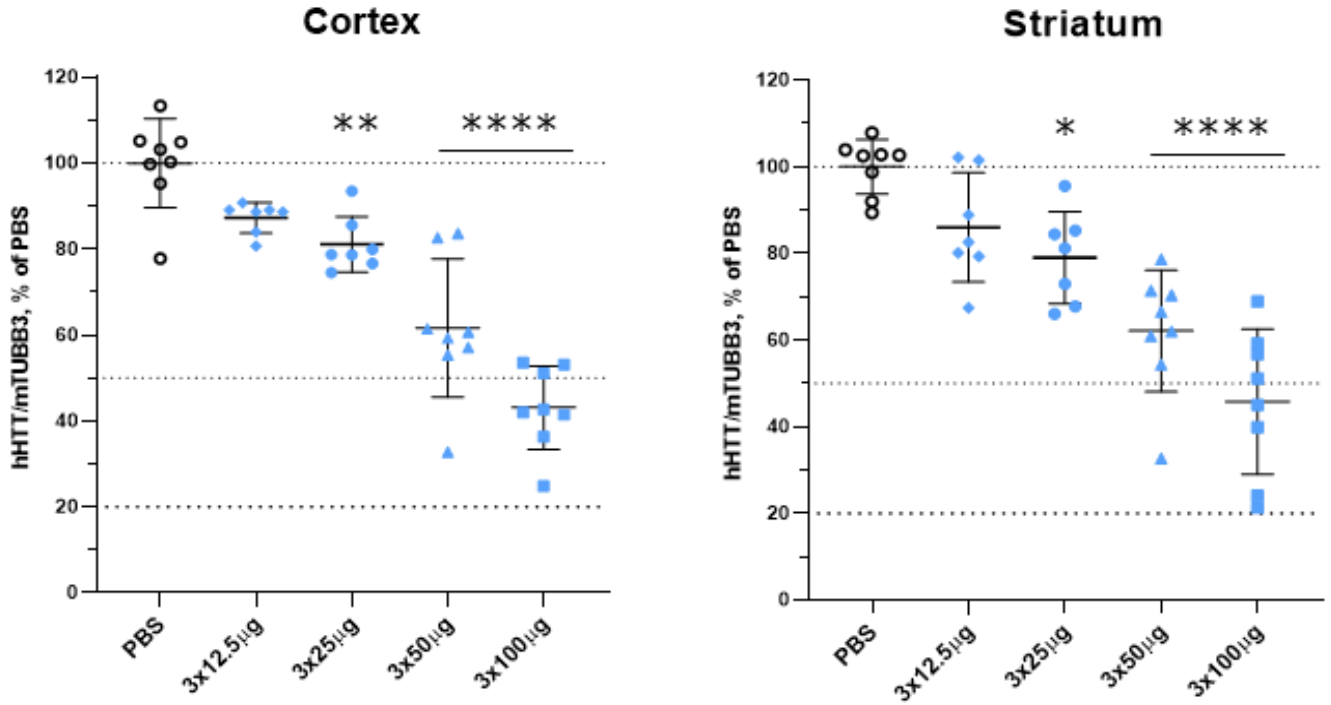
SNP3: Selective reduction of mHTT mRNA *in vitro*



iPSC = induced pluripotent stem cell
The neurons were treated with WVE-003 at concentrations up to 20 µM under free uptake conditions for seven days. The ratio of remaining mRNA associated with the A allele vs. G allele was indicated by a SNP3 allele specific genotyping PCR.

SNP3: Dose-dependent reduction of mHTT mRNA *in vivo*

BACHD mice homozygous for *mHTT* with SNP3



mHTT = mutant huntingtin; PBS = phosphate-buffered saline; TUBB3 = Tubulin Beta 3 Class III BACHD mice received 3 injections through an ICV cannula of PBS and WVE-003 (12.5 µg, 25 µg, 50 µg, or 100 µg) on Day 1, Day 3 and Day 5. Mice were euthanized on Day 15 (2 weeks after the first injection). *: p≤ 0.05, **: p ≤ 0.01, ****: p ≤ 0.0001

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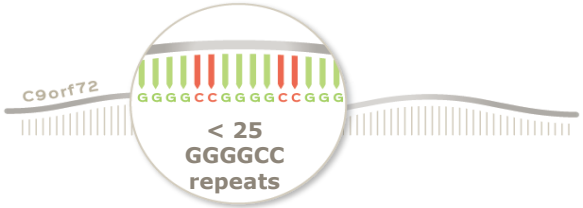
C9orf72 program

Amyotrophic Lateral Sclerosis (ALS)

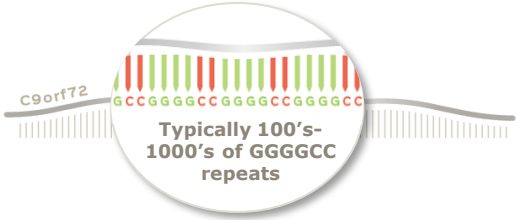
Frontotemporal Dementia (FTD)

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

Normal (non-expanded) Allele



Expanded Allele



- C9orf72 hexanucleotide repeat expansions (GGGGCC) are the strongest known risk factor for 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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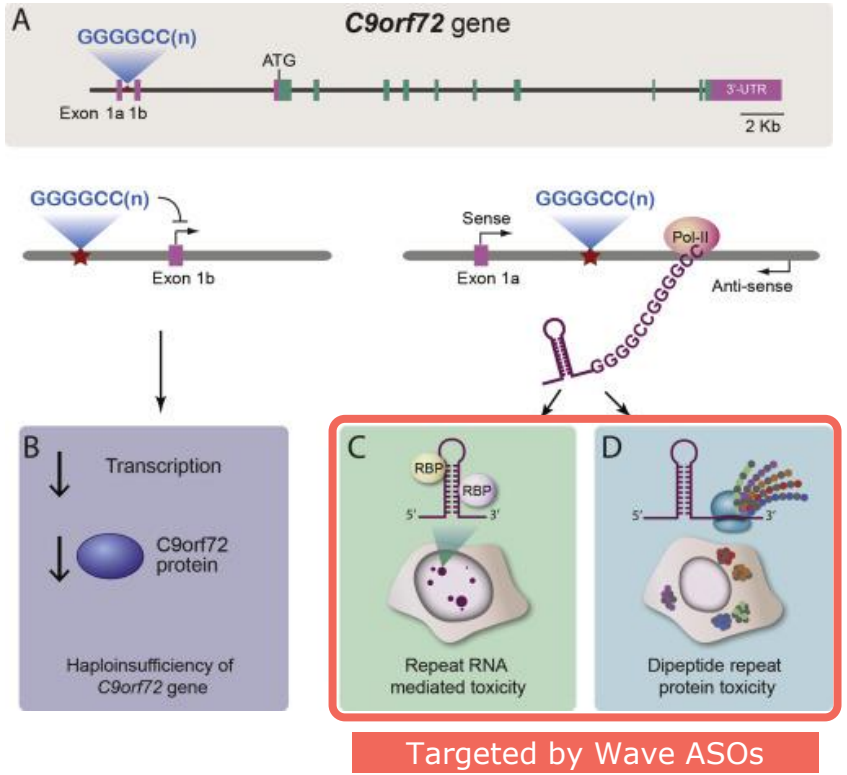
Sources: DeJesus-Hernandez et al, Neuron, 2011. Renton et al, Neuron, 2011. Zhu et al, Nature Neuroscience, May 2020

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

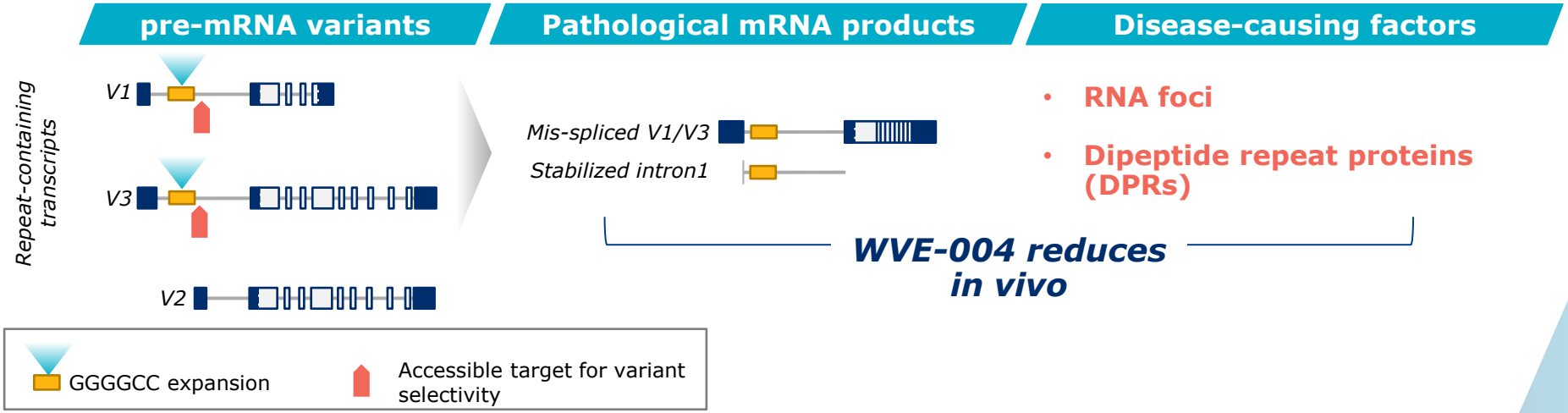


Targeted by Wave ASOs

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



Wave C9orf72 candidate targets only V1 and V3 transcripts, sparing V2 transcripts and healthy C9orf72 protein

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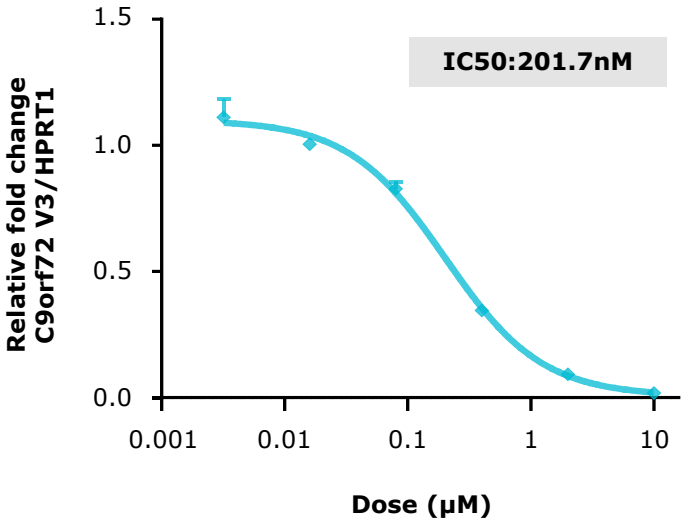
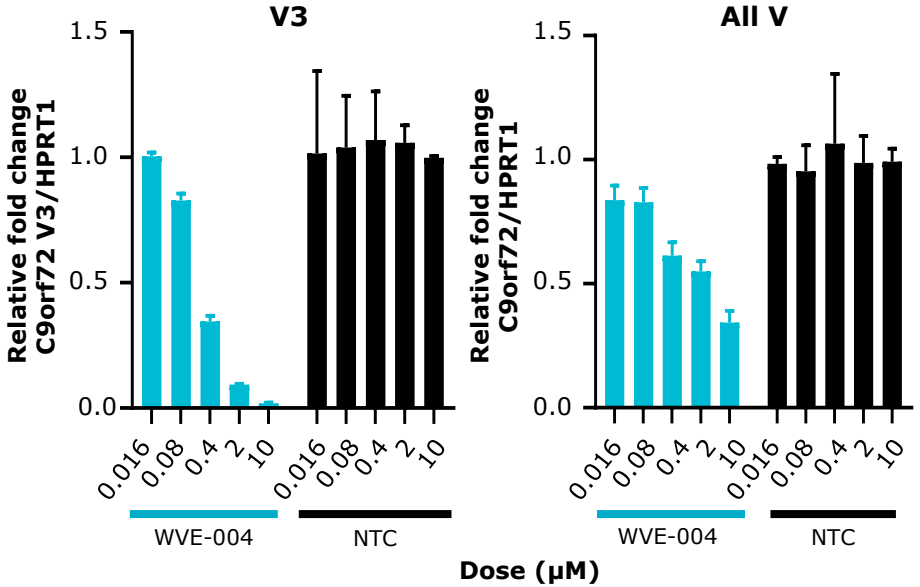
WVE-004: Potent and selective knockdown of repeat-containing transcripts *in vitro*

In vitro activity in C9 patient-derived neurons



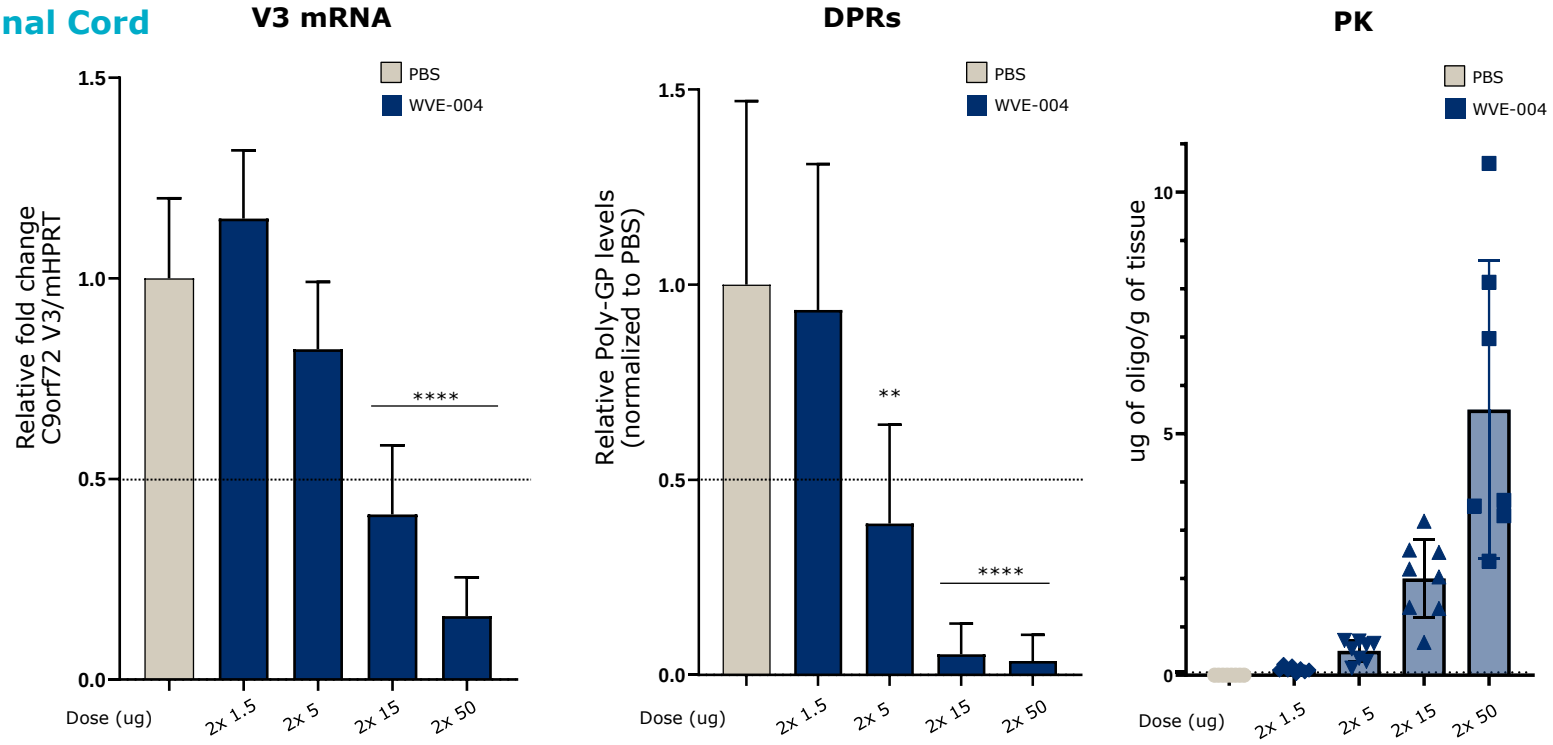
In vitro selectivity in C9 patient-derived neurons



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.

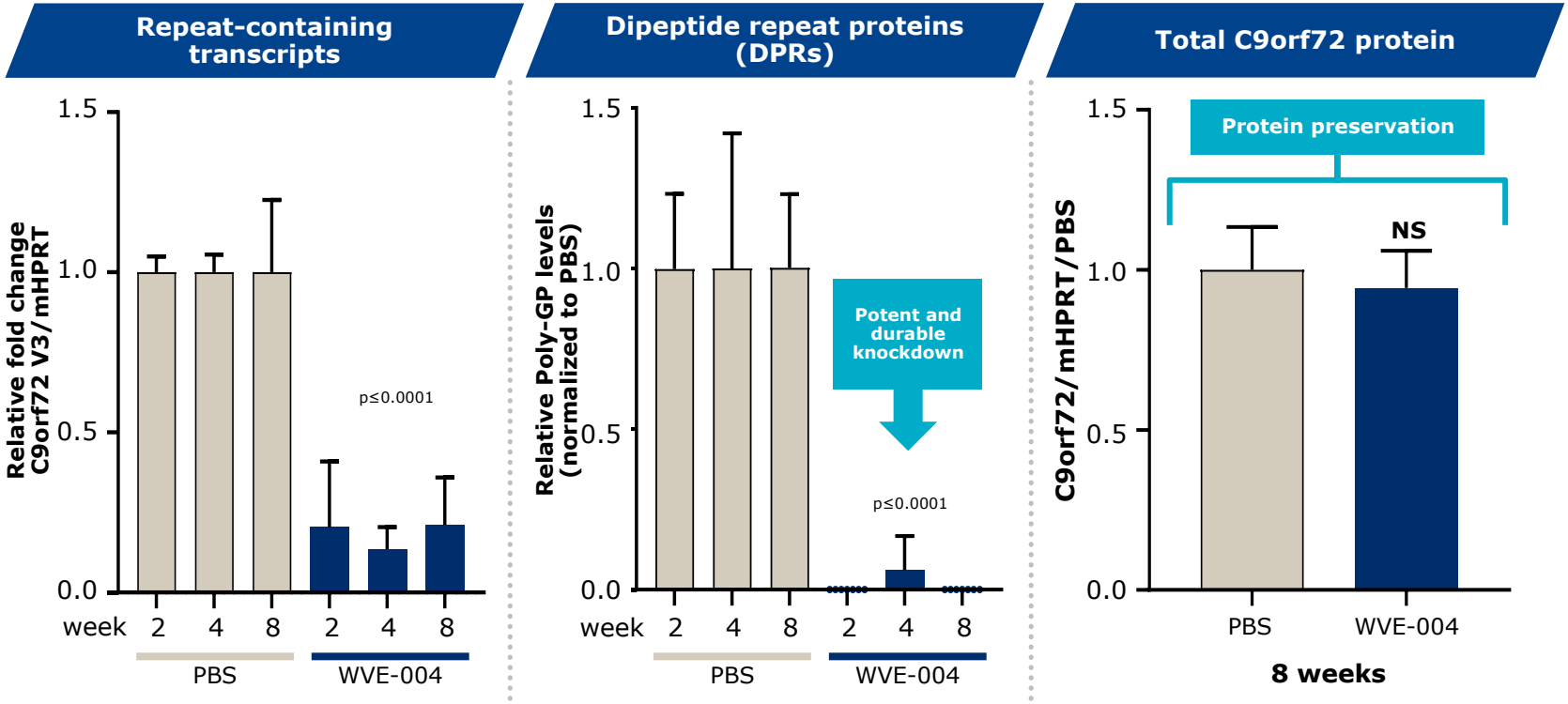
WVE-004 shows dose dependent knockdown of V3 mRNA and DPRs in C9 transgenic mouse model

Spinal Cord



C9 BAC transgenic mice were administered two times with PBS, 1.5ug, 5ug, 15ug or 50ug of WVE-004 on day 0 and day 7. Mice were euthanized 6 weeks after first injection. Taqman qPCR assay used to evaluate V3 transcripts. MSD assay used to detect ploy-GP protein. Hybridization Elisa used to detect ASO exposure.
**: $p \leq 0.01$, ***: $p \leq 0.001$, ****: $p \leq 0.0001$; DPR: dipeptide repeat protein; PK: pharmacokinetics

WVE-004: Potent and selective knockdown of repeat transcripts and DPRs in spinal cord of mice



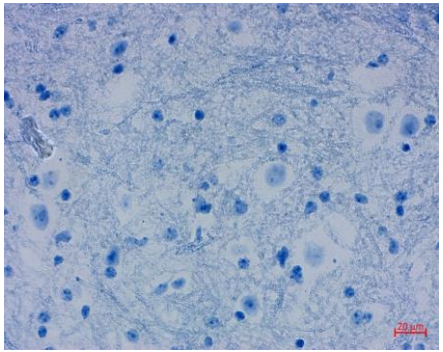
Experimental description: 2 x 50 ug on day 0 and day 7 dosed ICV; mRNA Samples were analyzed using quantitative PCR (Taqman assay), Dipeptide repeat proteins were measured by Poly-GP MSD assay. Protein samples were measured by Western Blot. NS: not significant

WVE-004 reaches target brain regions and cell types *in vivo*

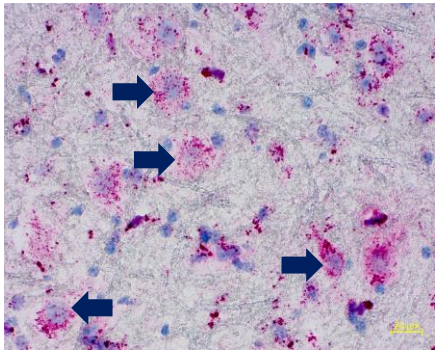
In situ hybridization of WVE-004 in spinal cord and cortex at 8 weeks

Spinal cord

PBS Control

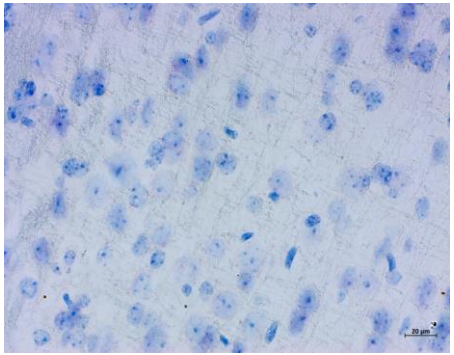


WVE-004

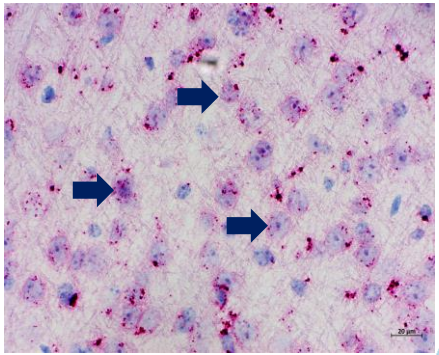


Cortex

PBS Control



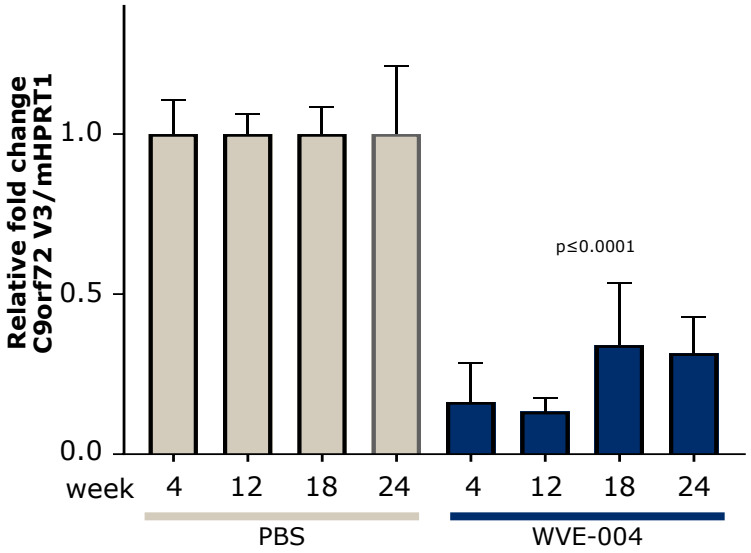
WVE-004



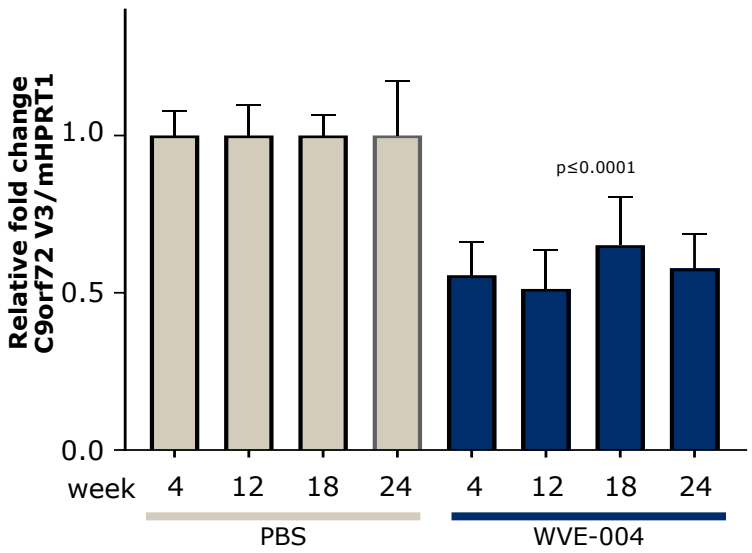
In situ hybridization: Red - ViewRNA for WVE-004; Blue – Hematoxylin. 40X magnification.
C9 BAC transgenic mice were administered PBS or 50 ug of WVE-004, ICV, on day 0 and day 7. Mice were euthanized at 8 weeks after the first injection.

Durable knockdown of repeat transcripts *in vivo* after 6 months in spinal cord and cortex of mice

Spinal cord



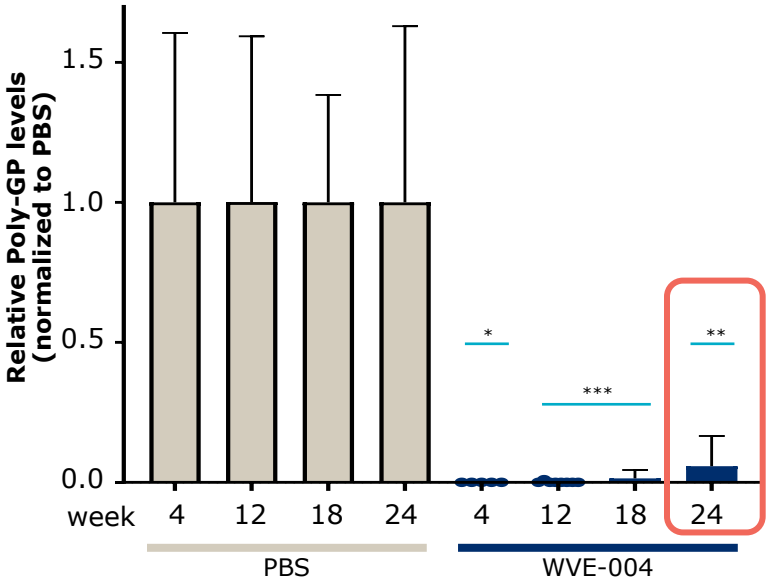
Cortex



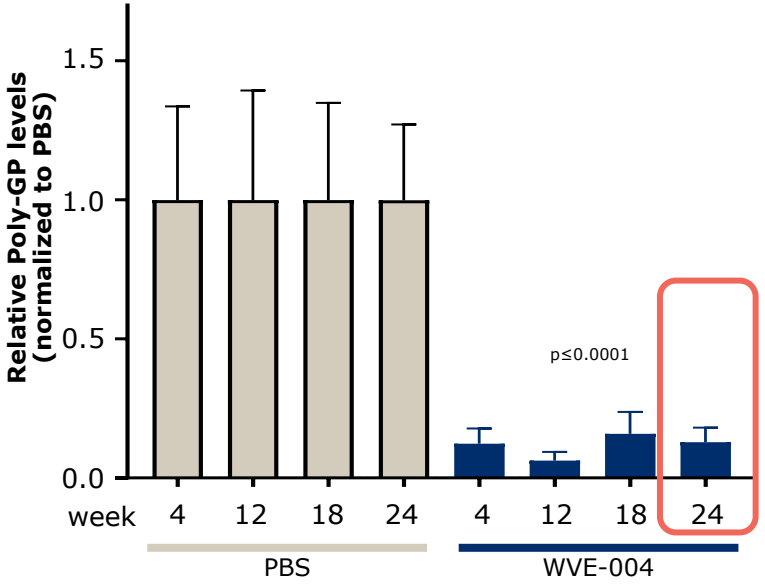
Experimental description: 2 x 50 ug on day 0 and day 7 dosed ICV; mRNA Samples were analyzed using quantitative PCR (Taqman assay)

Durable knockdown of DPRs *in vivo* after 6 months in spinal cord and cortex of mice

Spinal cord



Cortex



Experimental description: 2 x 50 ug on day 0 and day 7 dosed ICV; Dipeptide repeat proteins were measured by Poly-GP MSD assay.
*: p≤ 0.05 **: p ≤ 0.01, ***: p ≤ 0.001

WVE-004 proof-of-concept clinical trial to include both ALS and FTD patients

- Patients with documented C9orf72 expansion and confirmed ALS or FTD diagnosis
- Single and multiple ascending doses to be explored
- Safety and tolerability
- Pharmacodynamic effects on key biomarkers while on treatment
  - PolyGP
  - NfL
- Key exploratory clinical outcome measures
  - ALSFRS-R and CDR-FTLD

CTA submission expected in 4Q 2020

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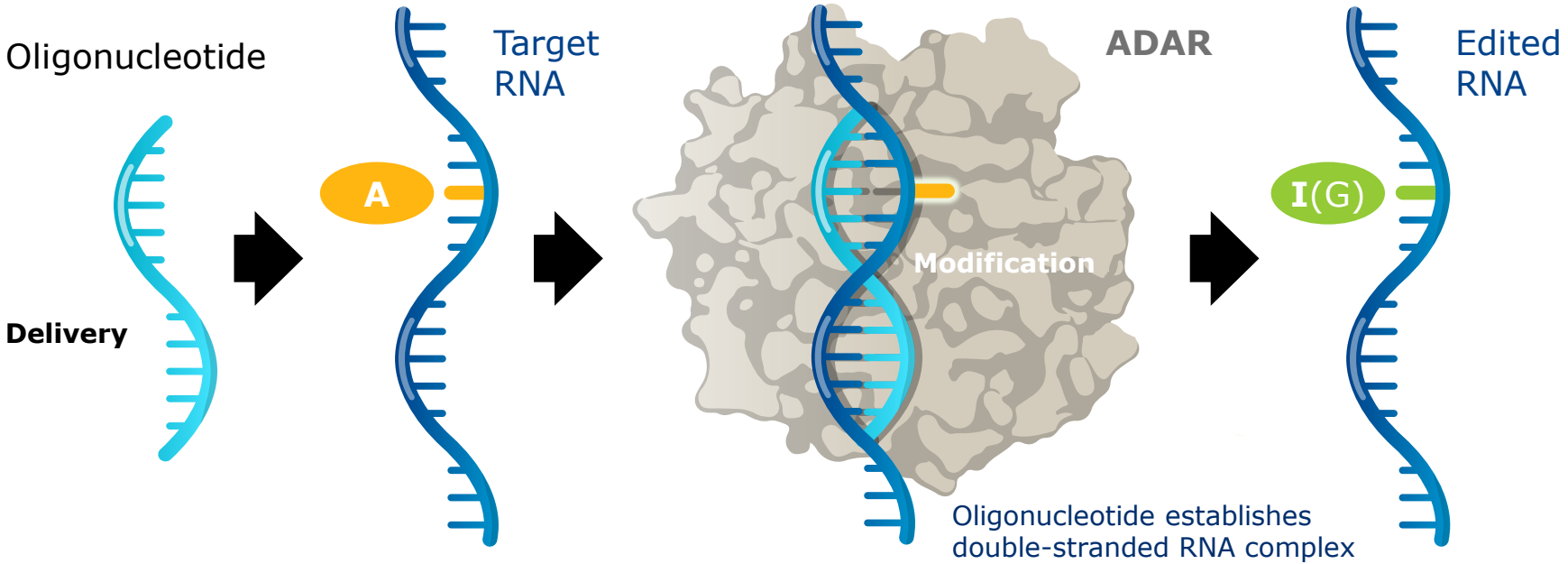
CTA: clinical trial application; NfL: neurofilament light chain; ALSFRS: Amyotrophic Lateral Sclerosis Functional Rating Scale; CDRFTLD: Clinical Dementia Scale – frontotemporal lobar degeneration

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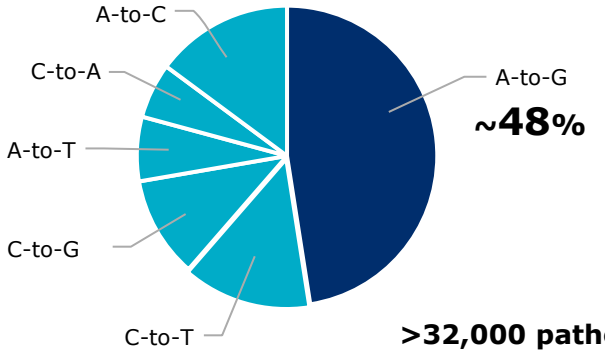
Nishikura, K. A-to-I editing of coding and non-coding RNAs by ADARs. Nat. Rev. Mol. Cell Biol. 2016; Picardi, E. *et al.* Profiling RNA editing in human tissues: towards the inosinome Atlas. *Scientific reports* **5**, 14941, doi:10.1038/srep14941 (2015).

RNA editing: A promising new therapeutic modality for treatment of genetic diseases

Disease associated mutations are frequently ADAR amenable

- Nearly half of known human genetic pathogenic SNPs are G-to-A mutations
- Tens of thousands of potential disease variants A-to-I(G) editing could target

Pathogenic human SNPs by base pair corrections



>32,000 pathogenic human SNPs[2]

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

Wave's Mission: Apply innovative nucleic acid chemistry and deep biological insights to develop transformative medicines for people living with devastating conditions

HD	Wave is developing investigational stereopure oligonucleotides designed to selectively target the mutant allele of the huntingtin (mHTT) gene, while leaving the wild-type (wtHTT) protein relatively intact We expect to report data from the PRECISION-HD1 and PRECISION-HD2 trials, evaluating investigational WVE-120101 and WVE-120102, in the first quarter of 2021
ALS and FTD	Wave's C9orf72 program is designed to selectively target the transcripts containing the hexanucleotide repeat expansion in the C9orf72 gene We are advancing our C9orf72 preclinical program to potentially treat ALS and FTD and expect to initiate clinical development with the submission of a CTA in the fourth quarter of 2020
ADAR	Wave has leveraged platform learnings to develop new RNA-editing modality for new therapeutic applications

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