Enhancing the pharmacologic profiles of CNS targeting therapeutic oligonucleotides

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TIDES USA
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Forward-looking statements

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Overview

- PRISM™ Platform
- Wave Neurology Pipeline
- WVE-004 in ALS and FTD
- WVE-003 in Huntington’s disease
- RNA Editing as a New Therapeutic Modality

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PRISM

PRISM platform enables rational drug design

Sequence

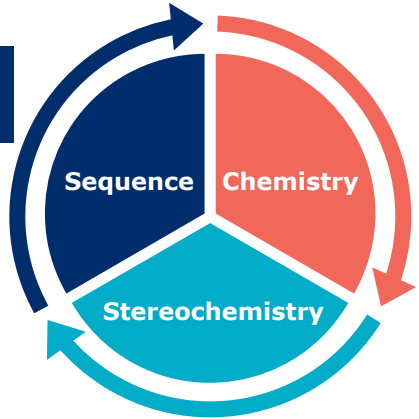
B: bases

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

Stereochemistry

Chiral control of
any stereocenter

5’ modifications,
backbone modifications



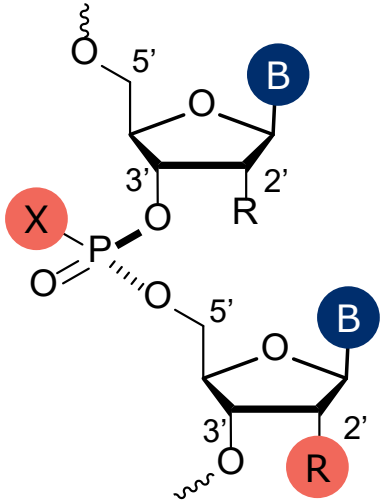
Chemistry

R: 2’ modifications

OMe, MOE, F,
other modifications

X: backbone chemistry

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



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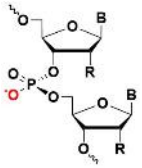
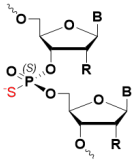
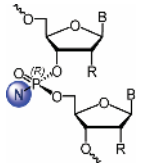
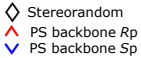
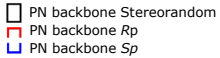
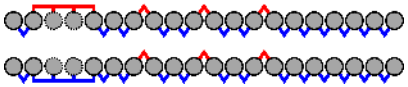
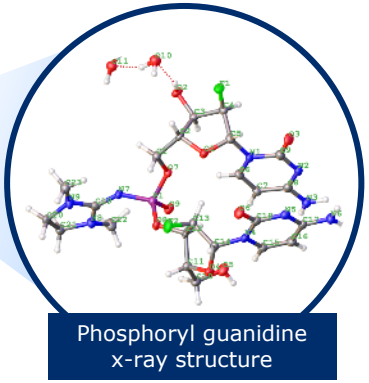
Expanding repertoire of backbone modifications with novel PN backbone chemistry

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		

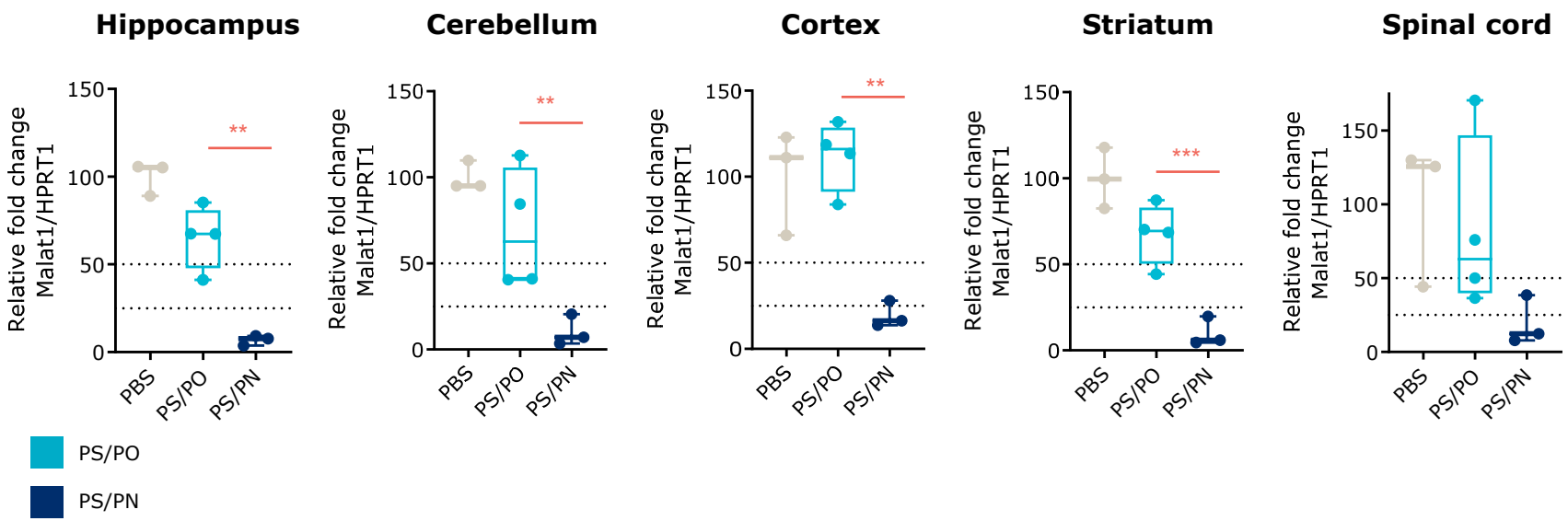


Phosphoryl guanidine x-ray structure

Molecule structure illustrative of backbone modification patterns

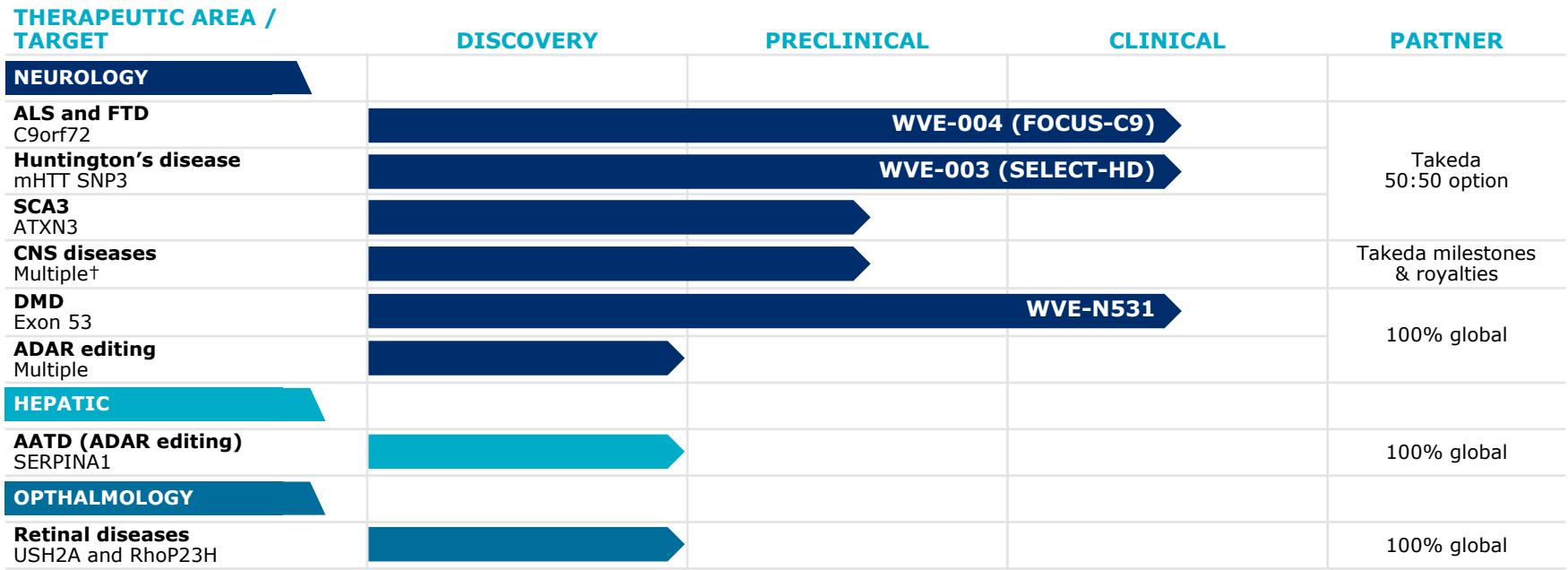
PN chemistry increases durability across CNS tissues

Malat1 knockdown at 10 weeks in mouse CNS (100 µg)



Mice received a single 100 ug ICV injection (n=3 per group). Relative fold-change in MALAT1 expression is shown for the indicated tissues 10-weeks post-dose. MALAT1 expression levels are normalized to Hprt1. PBS, phosphate buffered saline. ICV, intracerebroventricular. Stats: 1-way ANOVA ** P<0.01, *** P<0.001

Robust portfolio of stereopure, investigational PN-modified oligonucleotides



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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

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WVE-004

Amyotrophic Lateral Sclerosis (ALS)

Frontotemporal Dementia (FTD)

C9orf72 repeat expansions: One of the most common genetic causes of ALS and FTD

Hexanucleotide (G_4C_2)- repeat expansions in C9orf72 gene are common autosomal dominate cause for ALS and FTD

Different manifestations across a clinical spectrum

Amyotrophic Lateral Sclerosis (ALS)

- Fatal neurodegenerative disease
- Progressive degeneration of motor neurons in brain and spinal cord
- C9-specific ALS: ~2,000 patients in US

Frontotemporal Dementia (FTD)

- Progressive neuronal degeneration in frontal / temporal cortices
- Personality and behavioral changes, gradual impairment of language skills
- C9-specific FTD: ~10,000 patients in US

WVE-004 is the first investigational therapy in clinical development for both C9-ALS and C9-FTD

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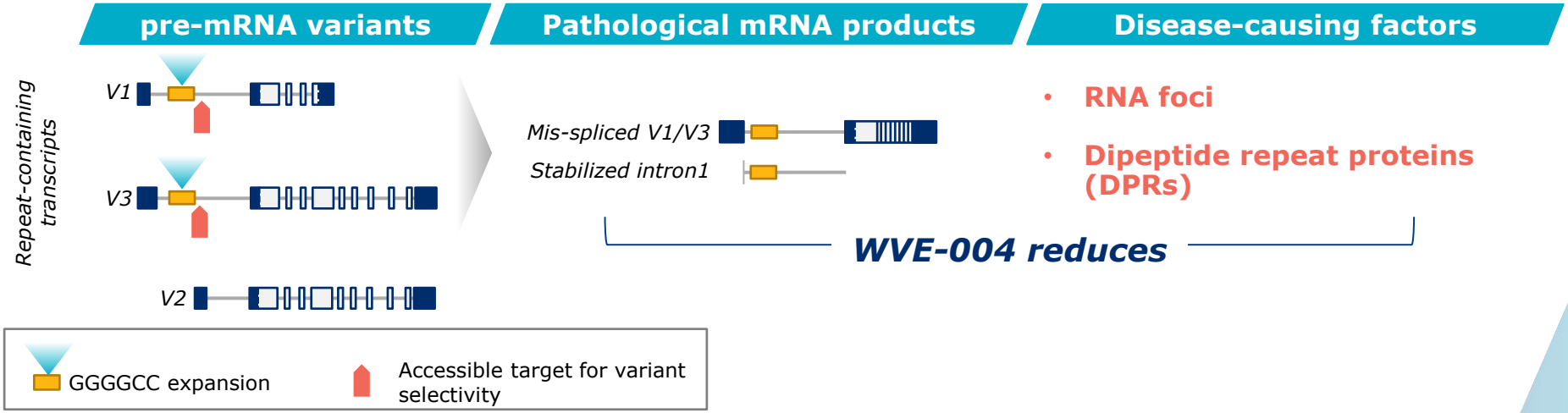
Sources: Balendra et al, EMBO Mol Med, 2017; Brown et al, NEJM, 2017, DeJesus-Hernandez et al, Neuron, 2011. Renton et al, Neuron, 2011. Zhu et al, Nature Neuroscience, May 2020, Stevens et al, Neurology 1998

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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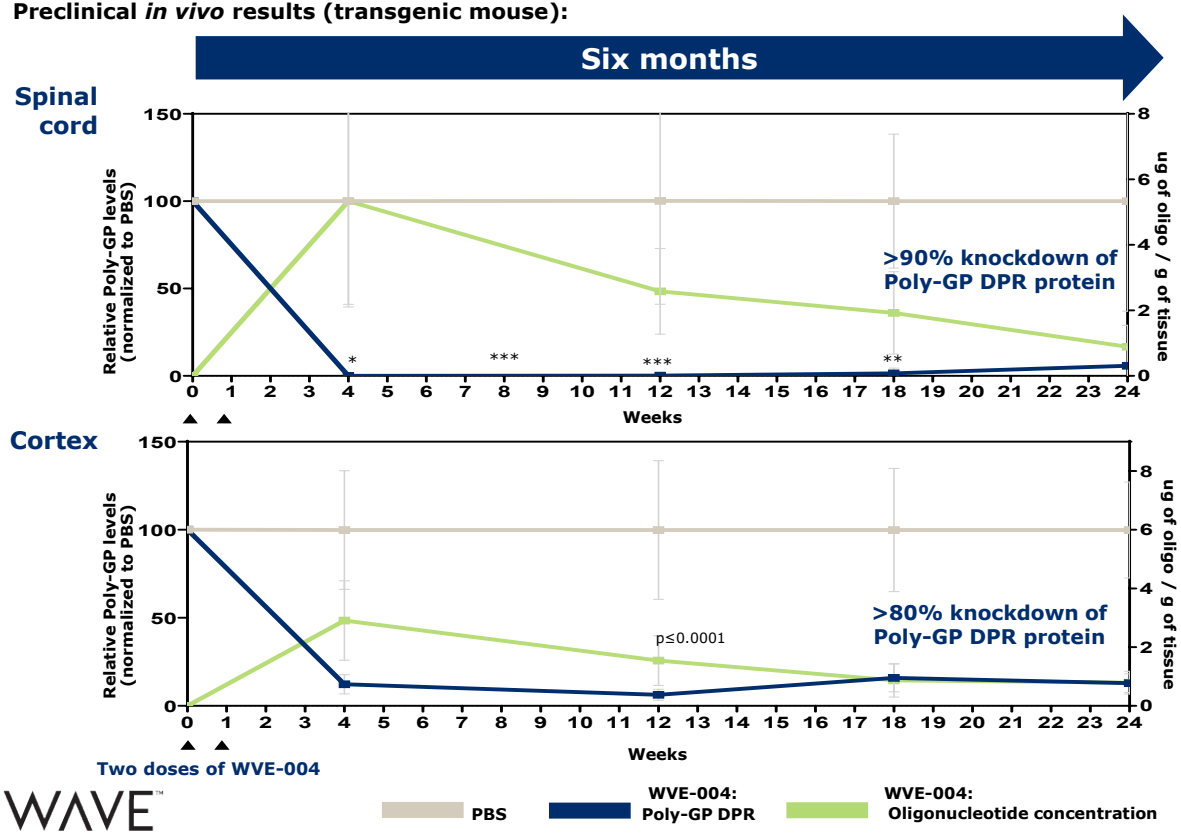
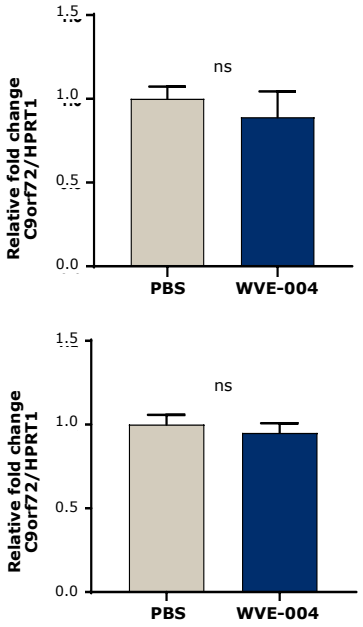
WVE-004: Durable reduction in vivo of poly-GP in spinal cord and cortex; Preservation of C9orf72 protein

Preclinical *in vivo* results (transgenic mouse):



C9orf72 protein unchanged at 6 months



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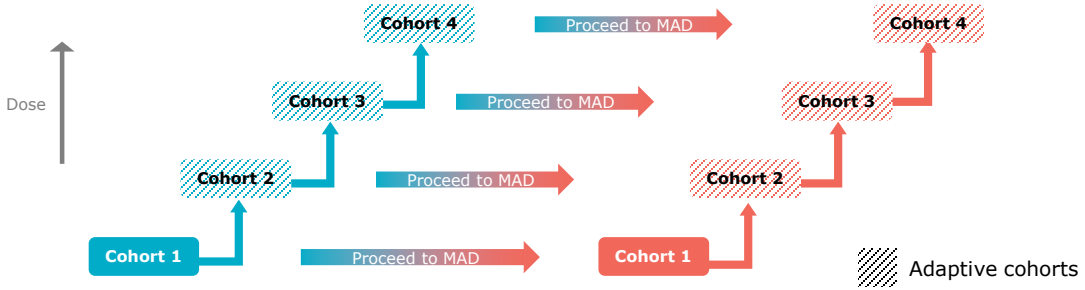
Full results presented at the 31st International Symposium on ALS/ MND (December 2020); 2 x 50 ug (day 0, day 7) dosed ICV; DPRs measured by Poly-GP MSD assay. *: p≤ 0.05 **: P ≤ 0.01, ***: P ≤ 0.001.

FOCUS-C9: Adaptive trial designed to enable rapid assessment of target engagement

Phase 1b/2a global, multicenter, randomized, double-blind, placebo-controlled trial

FOCUS C9

~50 patients with C9-ALS, C9-FTD or mixed phenotype



Single-ascending dose (SAD)

Day	1-3	15	29	57	85
Dose	▼				
Biomarker Samples	●	●	●	●	●
Clinical Evaluations	●		●	●	●

Multi-ascending dose (MAD)

Week	1	4	8	12	16	20	24
	▼	▼	▼	▼			
	●	●	●	●	●	●	●
	●	●	●	●	●	●	●

Primary objectives

- Safety and tolerability

Secondary objectives

- Plasma and CSF PK profile
- PolyGP in CSF

Exploratory objectives

Biomarkers:

- p75NTR^{ECD} in urine
- NfL in CSF

Clinical endpoints:

- ALSFRS-R
- CDR-FTDLD
- FVC
- HHD

Dose escalation and MAD dosing frequency guided by independent committee

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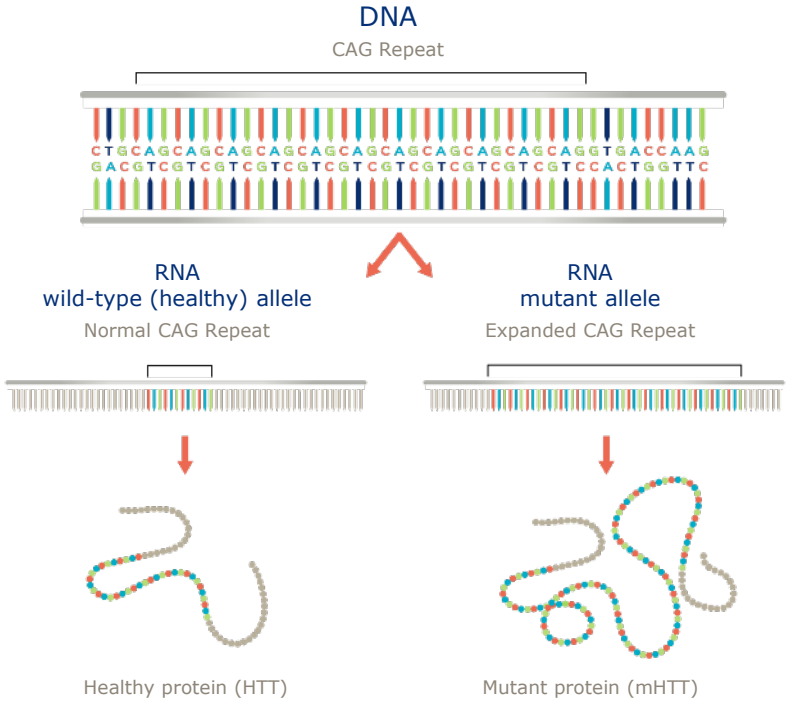
WVE-003

Huntington's Disease

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
- 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. HDSA 'What is Huntington's disease?' https://hdsa.org/what-is-hd/overview-of-huntingtons-disease/ Accessed: 11/2/18.; 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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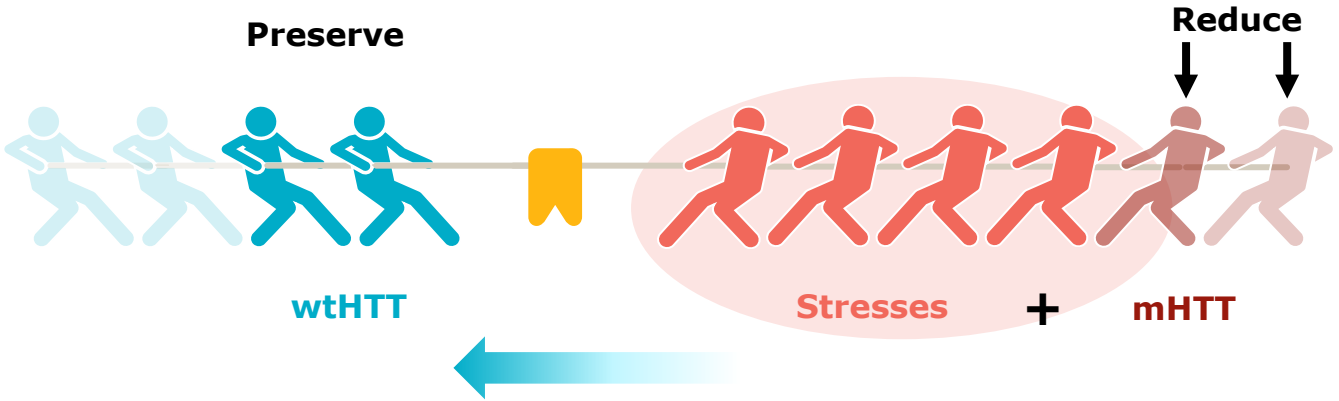
Allele-selective approach to treating HD

Preserve neuroprotective effects of wildtype HTT and reduce toxic mutant HTT



wtHTT supports healthy brain function, especially in the context of stress

Promotes neuronal survival

Essential role in synaptic protein transport

Supplies BDNF to striatum to regulate synaptic plasticity

Critical role in cilia function underlying CSF circulation needed to clear catabolites & maintain homeostasis

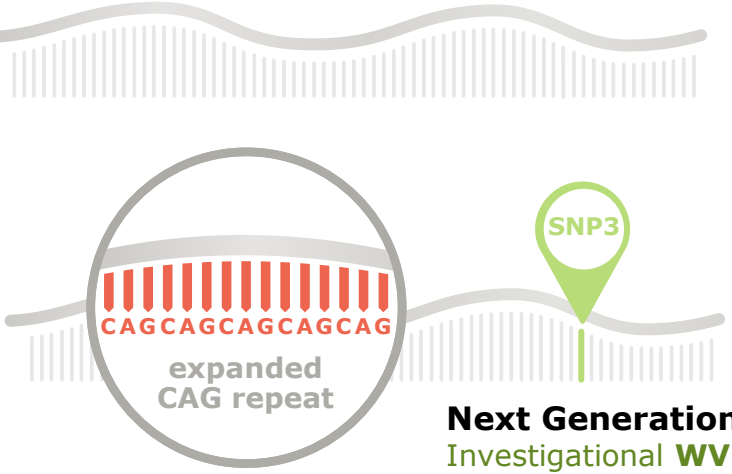
mHTT, mutant HTT; wtHTT, wild-type HTT; CSF: cerebrospinal fluid; BDNF, brain-derived neurotrophic factor Sources: 1. Leavitt 2006 2. Cattaneo 2005 3. Kumar 2016 4. Franco-Iborra 2020 5. Hamilton 2015 6. Ochaba 2014 7. Wong 2014 8. Rui 2015 9. Caviston 2007 10. Twelvetrees 2010 11. Strehlow 2007 12. 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, 24. Menalled et al., 2009

Allele-selectivity achieved by targeting downstream SNPs

Target mHTT transcript to selectively reduce mHTT protein with antisense oligonucleotides

Wildtype huntingtin RNA

Mutant huntingtin RNA



Next Generation Chemistry
Investigational **WVE-003** targets mHTT "SNP3"

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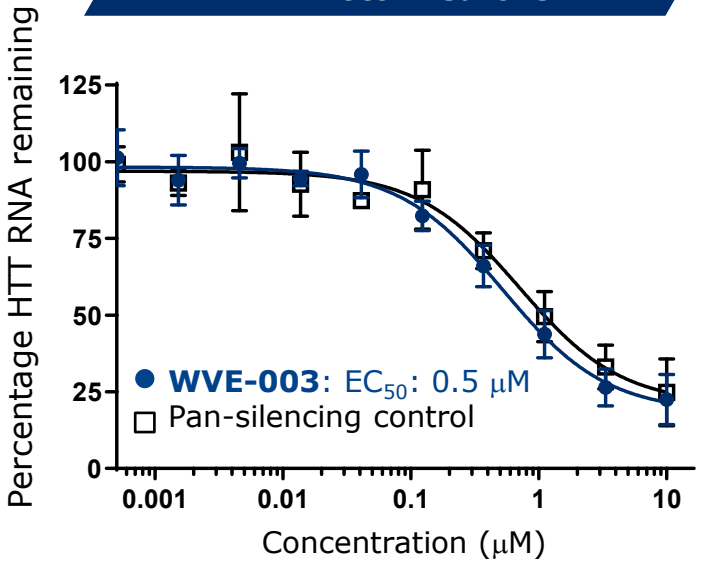
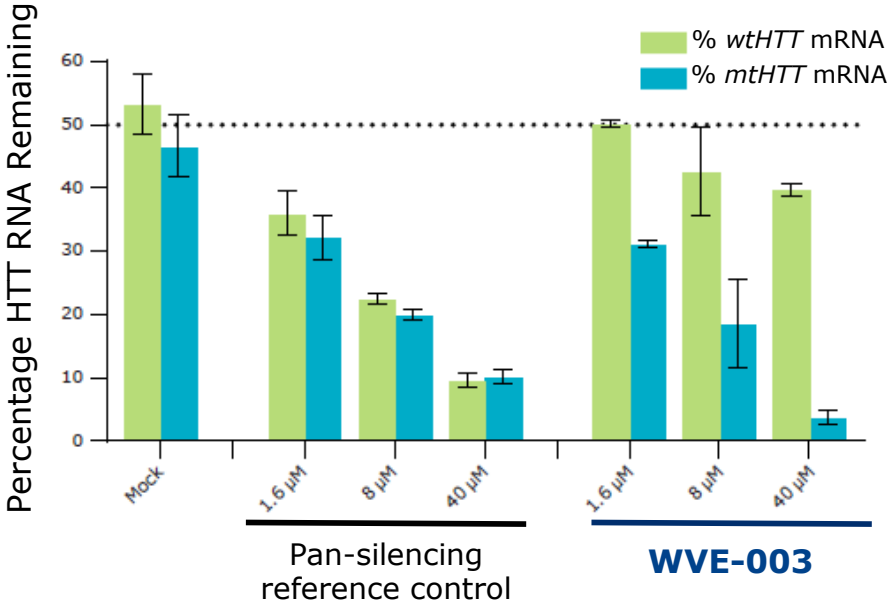
mHTT, mutant huntingtin; SNP, single nucleotide polymorphism

WVE-003 is potent and allele selective *in vitro*

Potently decreases HTT in HD motor neurons



Selectively reduces mHTT in HD motor neurons



Left: dose-response for HTT remaining in iPSC-derived motor neurons homozygous for SNP3, mean ± SD, n=4. Right: mHTT and wtHTT RNA expression in iPSC-derived motor neurons heterozygous for SNP3, mean ± sem, n=4
iPSCs (induced pluripotent stem cells) generated from HD patient cells
mHTT, mutant HTT; wtHTT, wild-type HTT

Mouse models

Evaluation of potency

BACHD Mouse[1]

HTT	Key characteristics
mHTT (human)	❖ 97 CAA-CAG repeats ❖ Multiple copies ❖ Subset of copies contain SNP3
wtHTT (mouse)	❖ Mouse genomic *Hdh* ❖ Lacks SNP3

Evaluation of selectivity

Hu97/18 Mouse[2]

HTT	Key characteristics
mHTT (human)	❖ 97 CAA-CAG repeats ❖ Multiple copies ❖ Subset of copies contain SNP3
wtHTT (human)	❖ 18 CAG repeats ❖ Lacks SNP3 ❖ Lacks mouse *Hdh*

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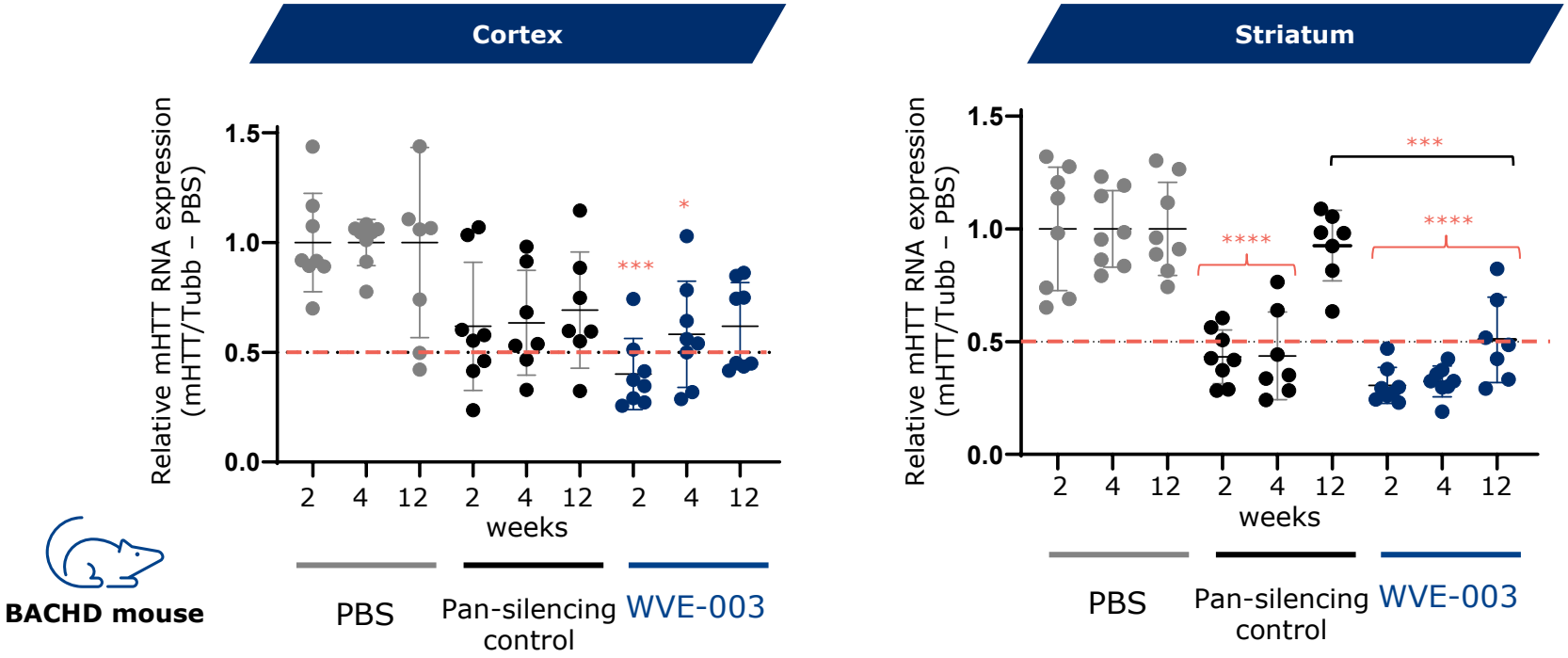
1. Gray et al., 2008 J Neurosci. 28:6182-95, 2. Southwell et al., 2013 Hum Mol Genet. 22:18-34.

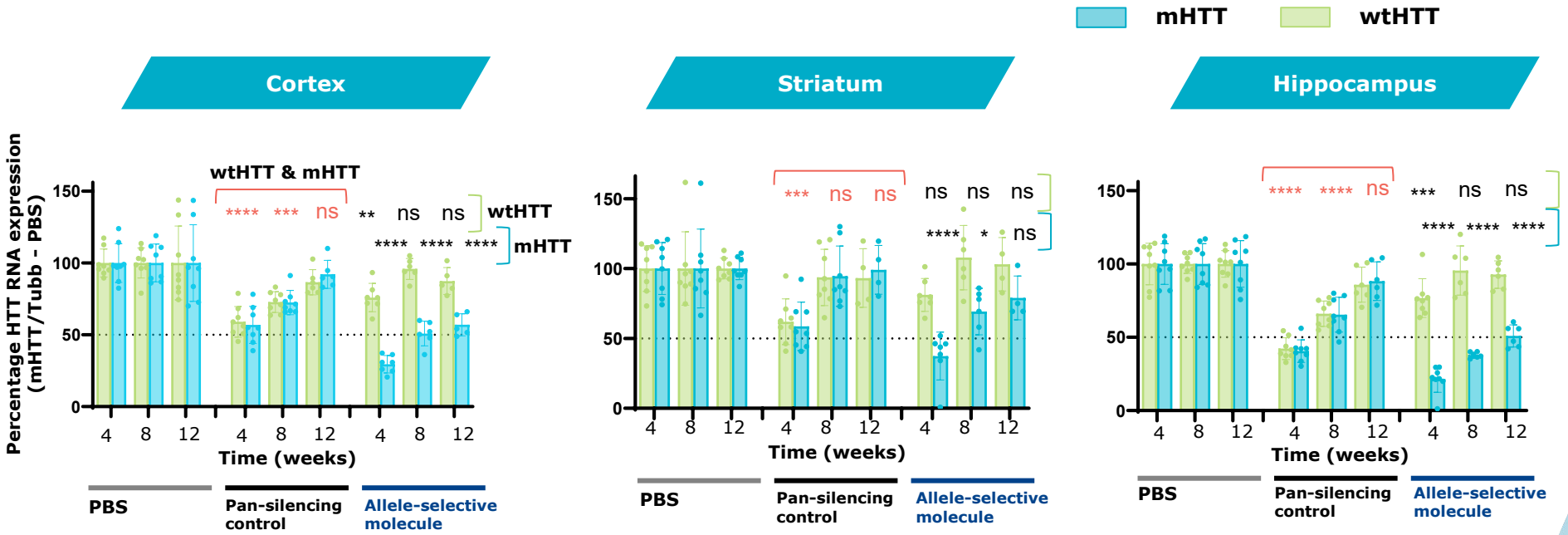
WVE-003 has potent and durable effects in cortex and striatum of BACHD mice

Maximum knockdown of 75% with ~50% knockdown persisting for at least 3 months



BACHD mice administered 3x100 μg intracerebroventricular doses PBS or oligonucleotide. (Left) Relative mHTT RNA in cortex at 2, 4 and 12-weeks post-dosing. (Right): Relative mHTT in striatum at same time points as cortex. BACHD contains SNP3 only in some mHTT transgenes. Data are mean ± SD, n=8. *P<0.0332, ***P<0.0002, ****P<0.0001 versus PBS unless otherwise noted). P values were calculated via 1-way analysis of variance. mHTT, mutant HTT; Tubb, tubulin

Allele-selective activity in CNS of Hu97/18 mice



Hu97/18 mouse

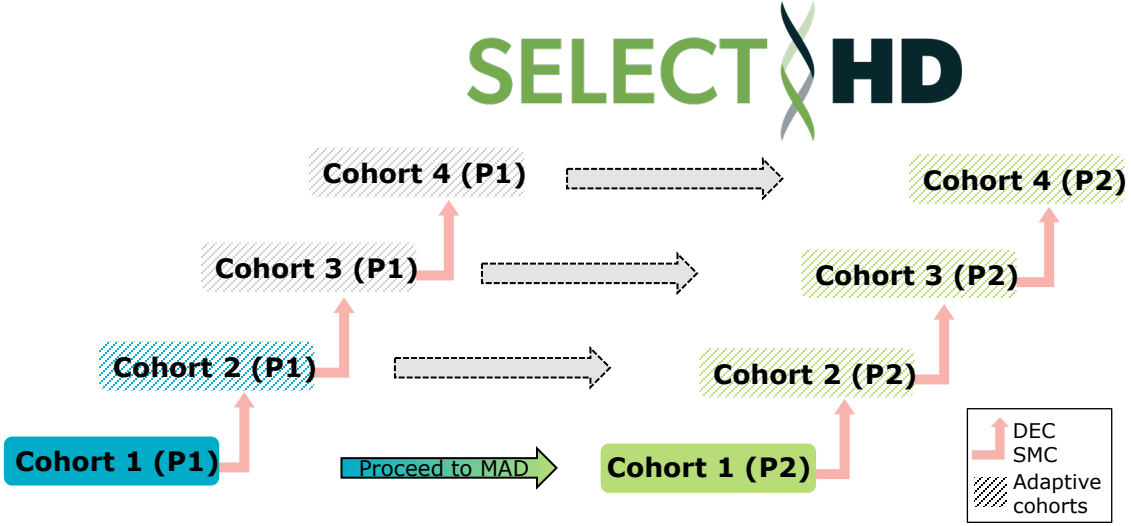
- Pan-acting molecule uniformly decreases **wtHTT** & **mHTT**
- Allele-selective molecule decreases **mHTT**, spares **wtHTT**

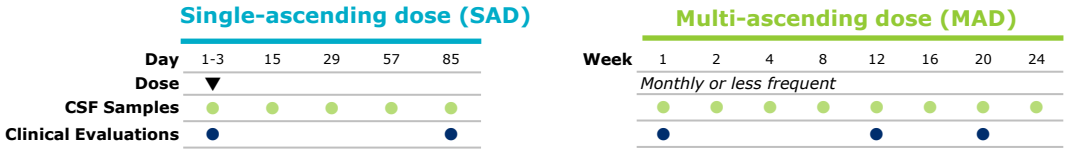
Hu97/18 mice administered 3x100 μg intracerebroventricular doses PBS or oligonucleotide. Relative mHTT RNA in cortex (left) striatum (middle) or hippocampus (right) at 4, 8 and 12-weeks post-dosing. Data are mean ± SD, n=8. Stats: ns non-significant, *P<0.05, **P<0.01, ***P<0.0001, ****P<0.0001 versus PBS by 1-way ANOVA. mHTT, mutant HTT; Tubb, tubulin

SELECT-HD: Adaptive first-in-human study for investigational WVE-003

Ph 1b/2a global, multicenter, randomized, double-blind placebo-controlled trial

Eligible PRECISION-HD participants can transition to this study after wash out





Patients

- Targeting 36 patients
- ≥18 and ≤60 years of age
- Confirmed early manifest HD diagnosis with SNP3 variant

Primary Objectives

- Safety and Tolerability

Secondary Objectives

- Plasma PK profile
- CSF exposure

Exploratory Objectives

Biomarkers

- mHTT
- NfL
- wtHTT
- MRI

Clinical Endpoints

- UHDRS

Adaptive cohorts: dose escalation and dosing interval guided by independent safety monitoring committee.
wtHTT, wild-type HTT; mHTT, mutant HTT; Nfl, neurofilament light chain; SNP, single nucleotide polymorphism; UHDRS, United Huntington's Disease Rating Scale; MRI, Magnetic Resonance Imaging; PK, pharmacokinetic; PD, pharmacodynamic; CSF, cerebrospinal fluid; SNP, single nucleotide polymorphism; DEC, Dose Escalation Committee; SMC, Safety Monitoring Committee

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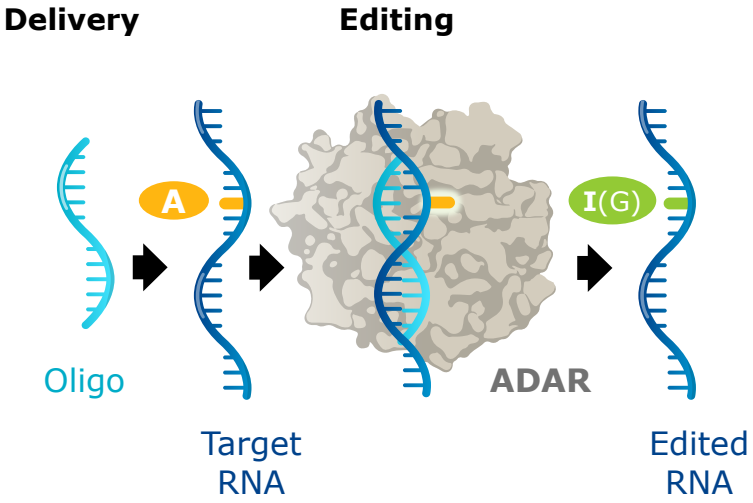
ADAR Editing

RNA editing opens many new therapeutic applications

AIMers direct RNA editing with endogenous ADAR enzymes



- **A**-to-**I** editing is one of most common post-transcriptional modifications

Nearly half of known human genetic pathogenic SNPs are G-to-A mutations

Restore protein function

- Recessive or dominant genetically defined diseases

Modify protein function

- Post-translational modifications

Upregulate protein expression

- Haploinsufficiency

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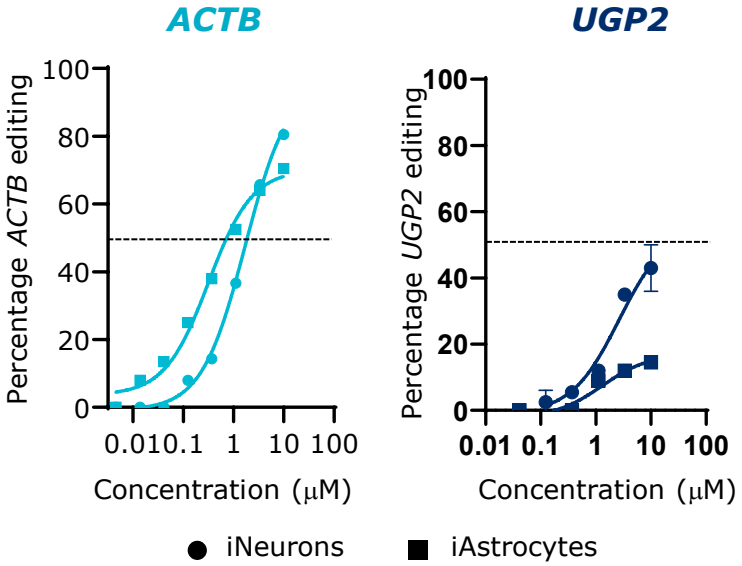
Nishikura, K. A-to-I editing of coding and non-coding RNAs by ADARs. *Nat. Rev. Mol. Cell Biol.* 2016; ClinVar database; Gaudeli NM et al. *Nature* (2017).

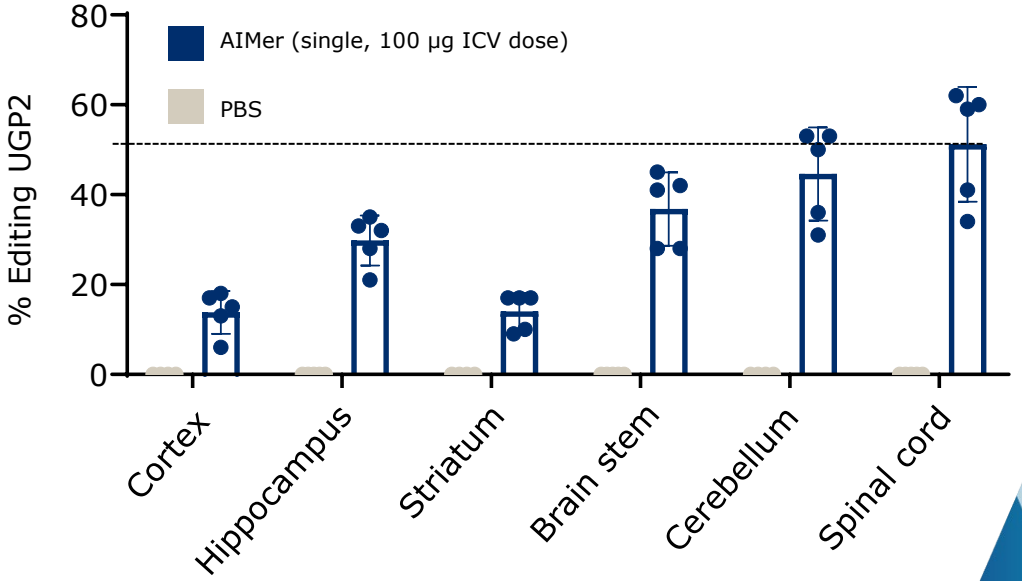
AIMers direct editing throughout CNS of hADAR mouse

PN-containing AIMers direct editing of *UGP2 in vivo*

In vitro dose-response curves



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



HADAR, human ADAR; UGP2, Glucose Pyrophosphorylase 2; CNS, central nervous system; Editing observed across all tested tissues of human-ADAR-transgenic mice by intracerebroventricular (ICV) injection. 5 mice in each group were injected with PBS or a single 100 μg dose on day 0. Animals were necropsied on day 7. RNA was harvested and editing measured by Sanger sequencing. UGP2, UDP-glucose pyrophosphorylase 2; ACTB, β-actin, AIMer, A-to-I editing oligonucleotide

Summary

- PRISM creates new therapeutic opportunities across a range of CNS diseases
- New backbone modifications, including PN chemistry, improve potency and durability for oligonucleotides in the CNS
- WVE-004, a variant-selective oligonucleotide targeting C9orf72, is the first molecule in clinical development for both C9-ALS and C9-FTD
- WVE-003 achieved potent, durable and selective target engagement in two mouse models and is currently in clinical development for HD
- AIMers enable reversible RNA editing with endogenous ADAR enzymes, enabling a new therapeutic modality for CNS diseases

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