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Wave Life Sciences

Corporate Presentation

October 1, 2020

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
- Ataxias
- Parkinson's disease
- Alzheimer's disease

PRISM™

Wave's drug discovery and 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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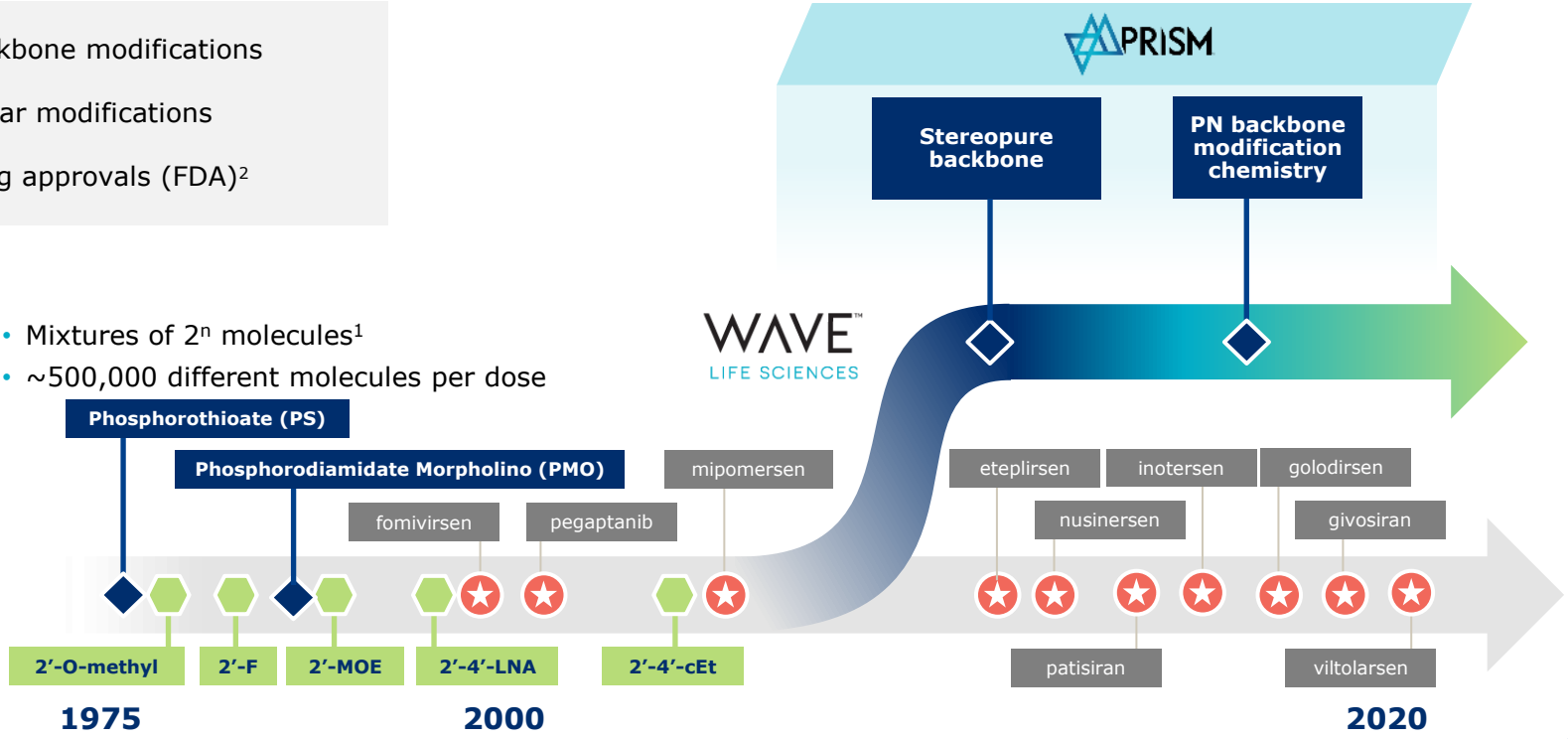
ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia

[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]

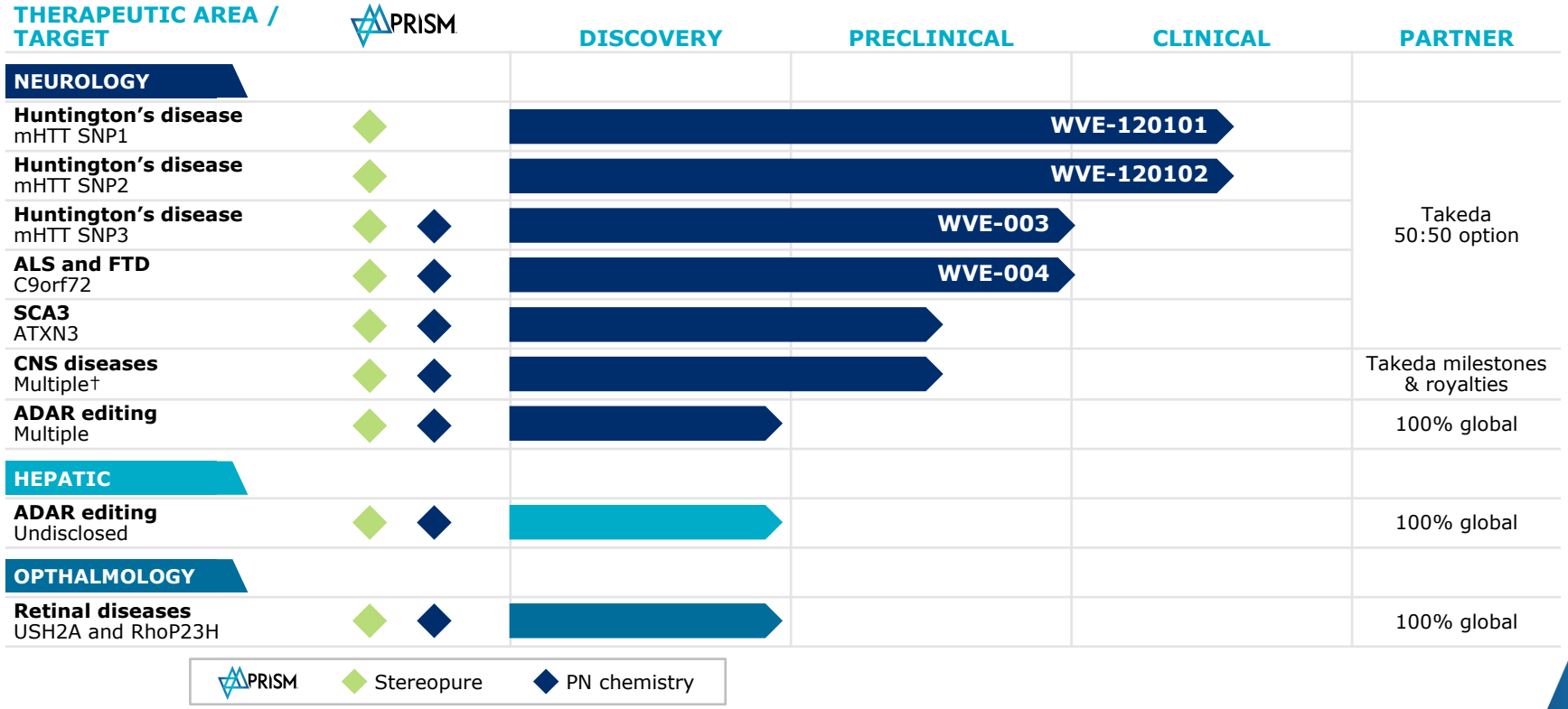
- Mixtures of 2^n molecules[1]
- ~500,000 different molecules per dose



[1]n=number of chiral centers

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

Innovative pipeline led by neurology programs



†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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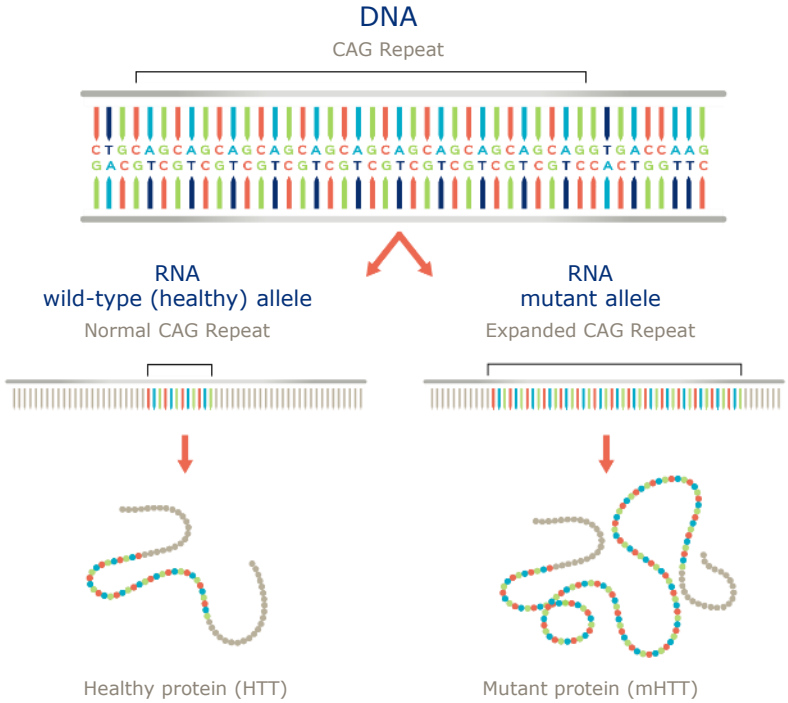
WVE-120101
WVE-120102
WVE-003

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
- 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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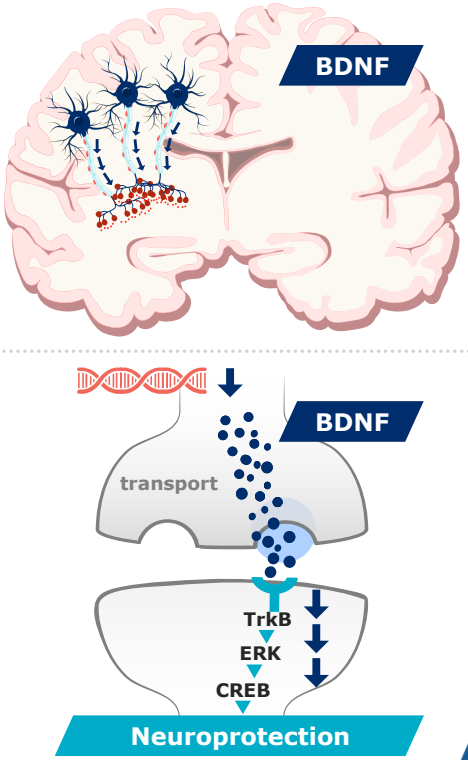
Importance of wild-type huntingtin (wtHTT) in HD

Huntington's disease (HD) may be caused by a dominant gain of function in mutant HTT *and* a loss of function of wtHTT protein

- Evidence suggests wild-type or healthy HTT is neuroprotective in an adult brain
  - Transport of key neurotrophic factors such as brain-derived neurotrophic factor (BDNF) are regulated by wtHTT levels
- Relative proportion of wild-type to mutant protein is critical
  - Increased amount of wild-type protein relative to mutant HTT may result in slower disease progression (measured by age-at-onset)
  - Patients with lack of wild-type have significantly more severe disease (measured by disease progression after symptom onset)



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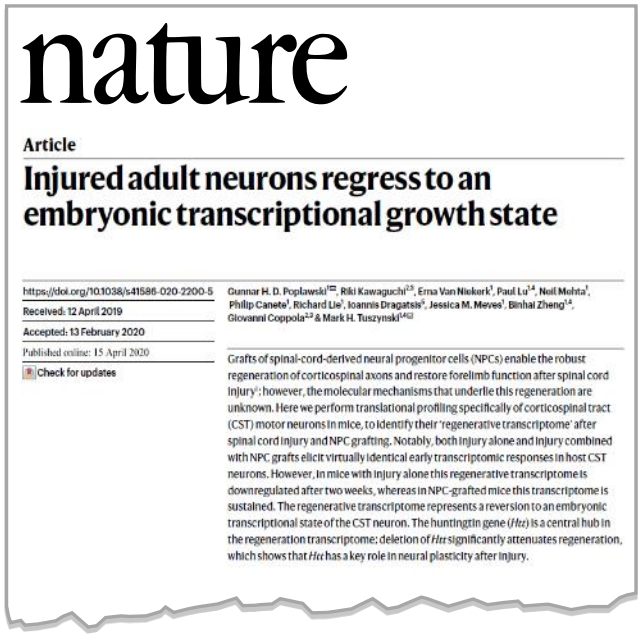
Sources: Van Raamsdonk, J.M., et al., Hum Mol Genet, 2005; Van Raamsdonk, J.M., et al., BMC Neurosci, 2006; Becanovic, K., et al., Nat Neurosci, 2015; Saudou, F. and S. Humbert, The Biology of Huntingtin. Neuron, 2016; Gauthier, L.R., et al., Cell, 2004; Caviston, J.P. and E.L. Holzbaur, Trends Cell Biol, 2009; Ho, L.W., et al., J Med Genet, 2001, Zuccato et al., Science 2001; Zuccato et al., Brain Pathol 2007; Marullo et al. Genome Biol 2010; Squitieri et. al, Brain 2003

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



nature

Article

Injured adult neurons regress to an embryonic transcriptional growth state

https://doi.org/10.1038/s41586-020-2200-5
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Check for updates

Gunnar H. D. Poplawski[1✉], Riki Kawaguchi[2,3], Erna Van Niekerk[1], Paul Lu[1,4], Neil Mehta[1], Philip Canete[1], Richard Lie[1], Ioannis Dragatsis[5], Jessica M. Meves[1], Binhai Zheng[1,4], Giovanni Coppola[2,3] & Mark H. Tuszynski[1,4✉]

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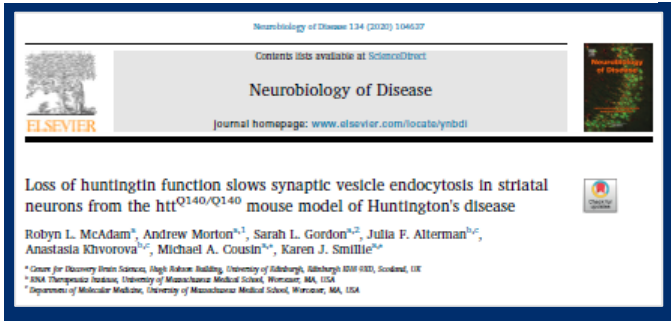
Source: Poplawski et al., *Nature*, April 2019
Htt: Huntingtin protein

Increasing evidence on the importance of wtHTT in HD pathogenesis, CNS and systemic health

Recent publications on wtHTT LoF as a likely driver of HD pathogenesis


Neurobiology of Disease 134 (2020) 104637

Contents lists available at ScienceDirect

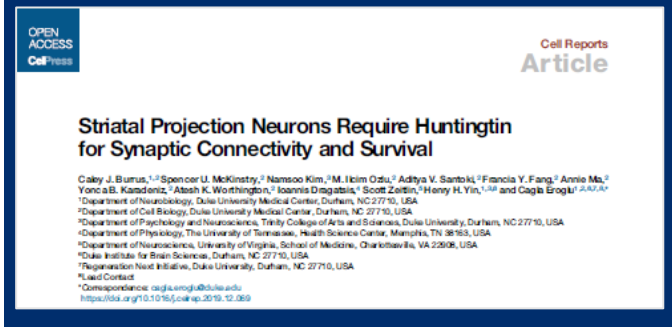
Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Loss of huntingtin function slows synaptic vesicle endocytosis in striatal neurons from the htt$^{Q140/Q140}$ mouse model of Huntington's disease

Robyn L. McAdam[a], Andrew Morton[a,1], Sarah L. Gordon[a,2], Julia F. Alterman[b,c], Anastasia Khvorova[b,c], Michael A. Cousin[a,*], Karen J. Smillie[a,*]

- Striatum-specific defect in synaptic vesicle endocytosis that was not corrected by total lowering of HTT
- Corrected by overexpression of wild-type protein


OPEN ACCESS CellPress

Cell Reports

Article

Striatal Projection Neurons Require Huntingtin for Synaptic Connectivity and Survival

Caley J. Burrus,[1,2] Spencer U. McKinstry,[2] Namsoo Kim,[3] M. Ilcim Ozlu,[2] Aditya V. Santoki,[2] Francia Y. Fang,[2] Annie Ma,[2] Yonca B. Karadeniz,[2] Atesh K. Worthington,[2] Ioannis Dragatsis,[4] Scott Zeitlin,[5] Henry H. Yin,[1,6,8] and Cagla Eroglu[1,2,6,7,9,*]

- Striatal projection neurons require HTT for motor regulation, synaptic development, cell health, and survival during aging
- Loss of HTT function could play a critical role in HD pathogenesis

wtHTT in HD highlighted at CHDI 15th Annual HD Therapeutics Conference:

HTT LOWERING: EXPLORING DISTRIBUTION, TIMING, AND SAFETY (LOSS OF FUNCTION)

Key points discussed at meeting:

- wtHTT has numerous critical functions throughout life (e.g., intracellular trafficking, cell-cell adhesion, BDNF transport)
- Near elimination of mouse wtHtt detrimental regardless of when suppression begins
- Specific brain regions, e.g., STN, may be particularly vulnerable to wtHTT lowering
- Mouse Htt lowering can lead to thalamic, hepatic, pancreatic toxicity
- HTT LoF mutations highly constrained in human population, suggesting selection against LoF mutations

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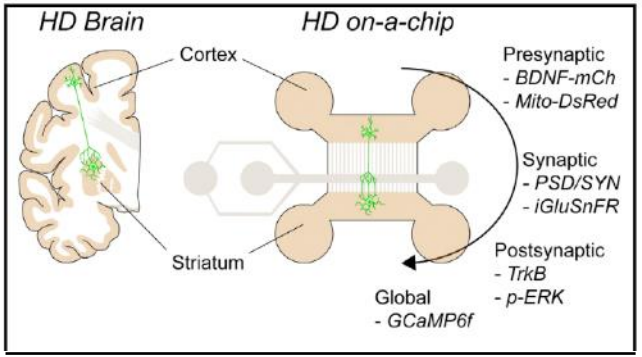
LoF: Loss of function; wtHTT: wild-type huntingtin; HD: Huntington's disease; STN: subthalamic nucleus

Wild-type HTT in the cortex appears critical for striatal health



Neuron Type	Genetic Status				Compartment
Cortical	WT	WT	HD	HD	Presynaptic
Striatal	WT	HD	HD	WT	Synaptic / Post-synaptic
Network Status	*Functional*		*Dysfunctional*		

Status of the presynaptic compartment determines the integrity of the network

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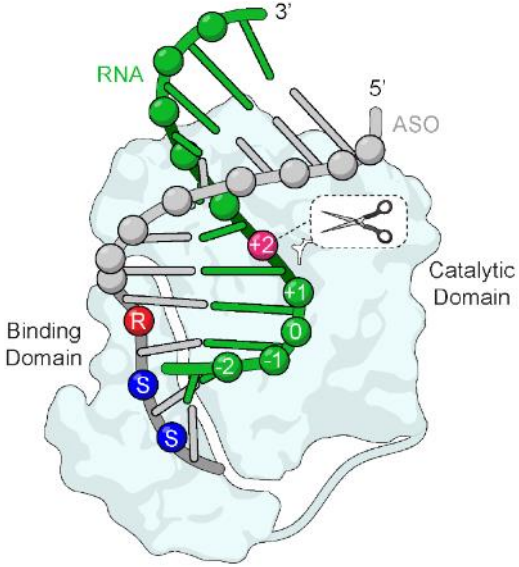
Presented by Dr. Frederic Saudou at Wave's Analyst and Investor Research Day on October 7, 2019
Virlogeux et al., Cell Reports 2018

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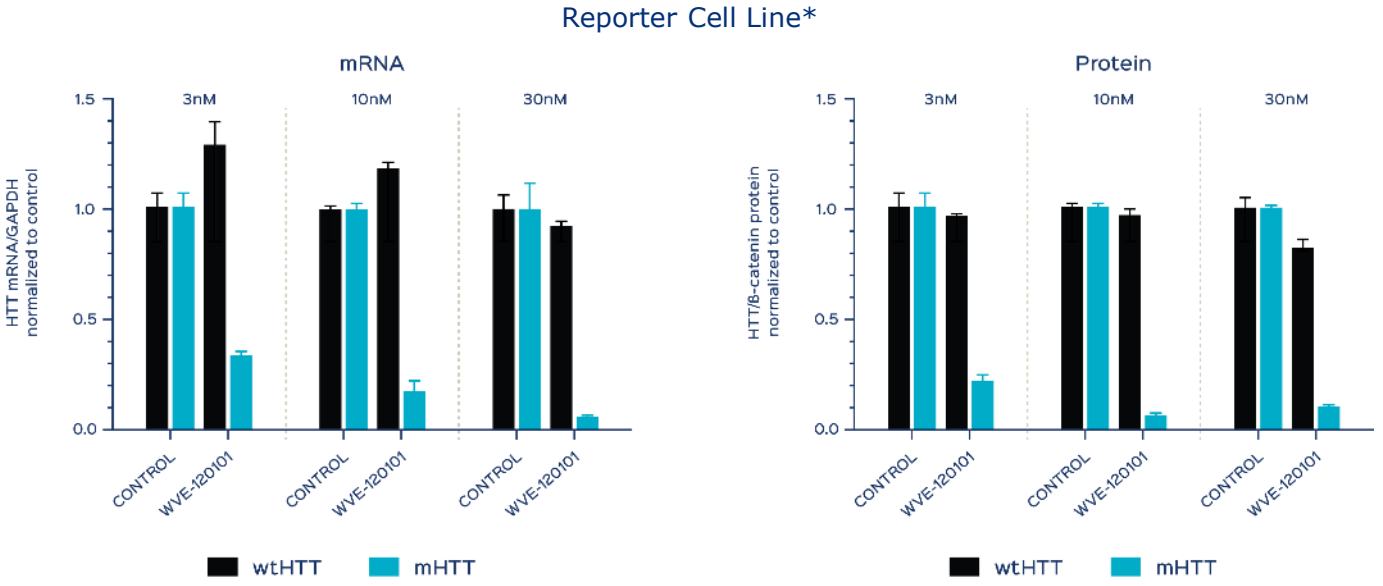
Source: Kay, et al. Personalized gene silencing therapeutics for Huntington disease. *Clin Genet.* 2014;86:29–36.

WVE-120101: Selective reduction of mHTT mRNA and protein

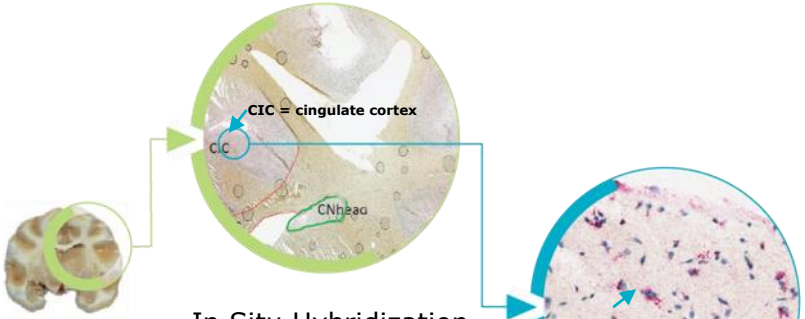


*These results were replicated in a patient-derived cell line

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

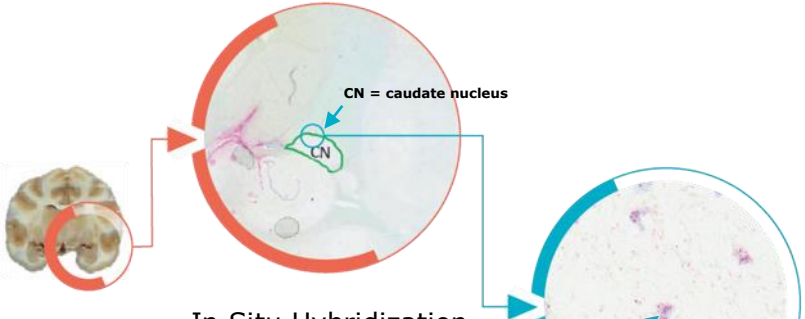
- WVE-120101 and WVE-120102 distribution in cynomolgus non-human primate brain following intrathecal bolus injection



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

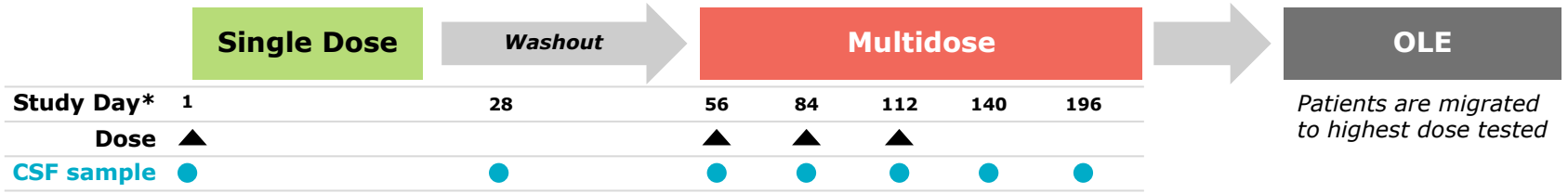
Red dots are WVE-120102 oligonucleotide

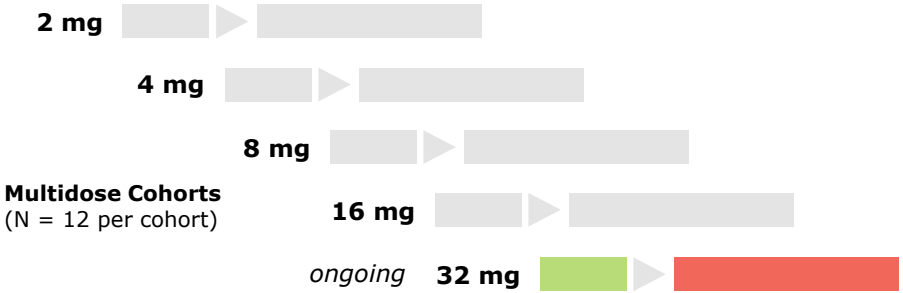
Arrow points to nuclear and perinuclear distribution of WVE-120102 in caudate nucleus

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





PRECISION-HD2 interim data
(2-16 mg cohorts pooled)

- **Safety profile** supported addition of higher dose cohorts

Biomarker Effects

- **Reduction in mHTT** (-12.4%[1]); Analysis across groups suggests dose response at highest doses[2]
- **No change in total HTT**
- Not all patients had reached Day 140 at interim analysis

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

OLE: Open label extension; CSF: cerebrospinal fluid; mHTT: mutant huntingtin; wtHTT: wild-type HTT; tHTT: total HTT
* Study day may vary depending on patient washout period [1]Hodges-Lehmann non-parametric shift estimates of the difference between treatment and placebo, p<0.05 (Wilcoxon-Mann-Whitney non-parametric significance test); [2]Multiple Contrast Test (MCT), p=0.03; Interim data announced December 2019

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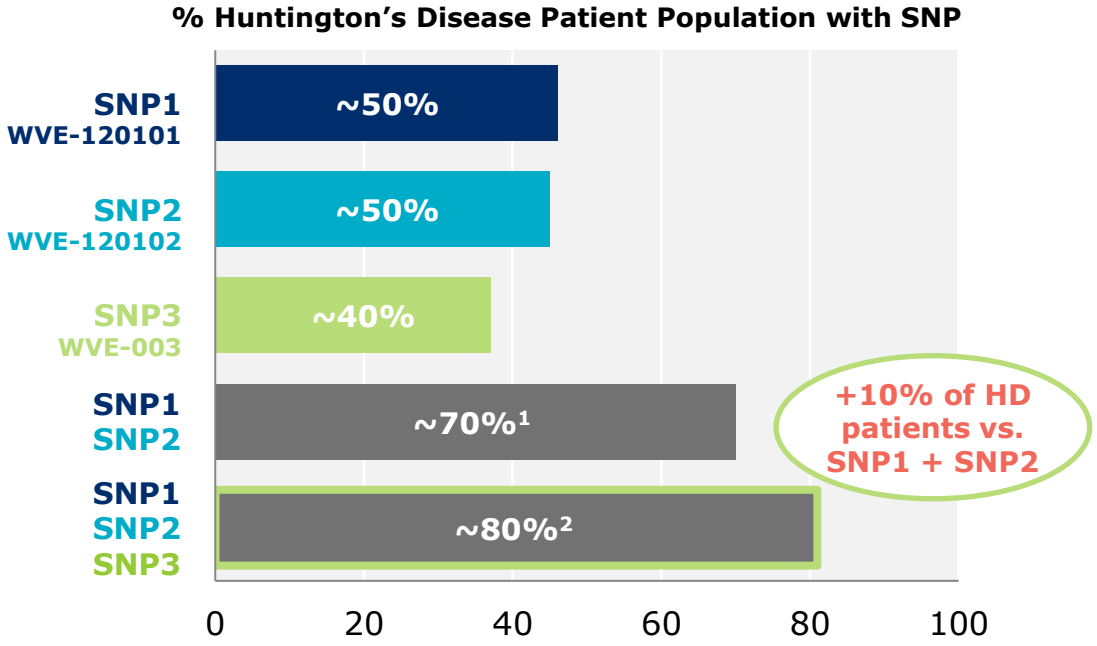
Three allele-selective HD programs

Potential to address ~80% of HD patient population



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

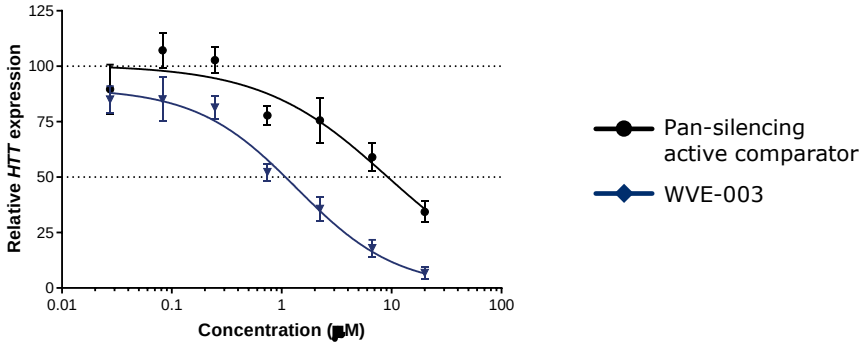
[1] Percentage of patient population with SNP1 and/or SNP2

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

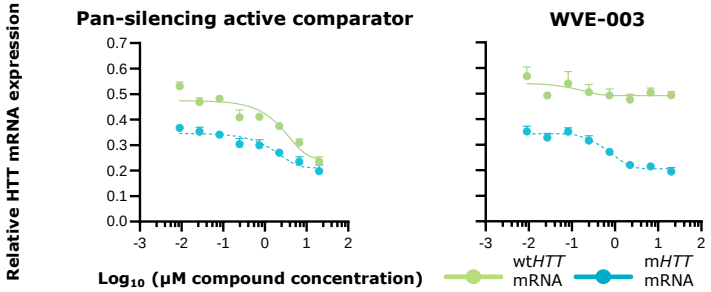
WVE-003 (SNP3) approaching clinical development

Incorporates PN modified backbone chemistry

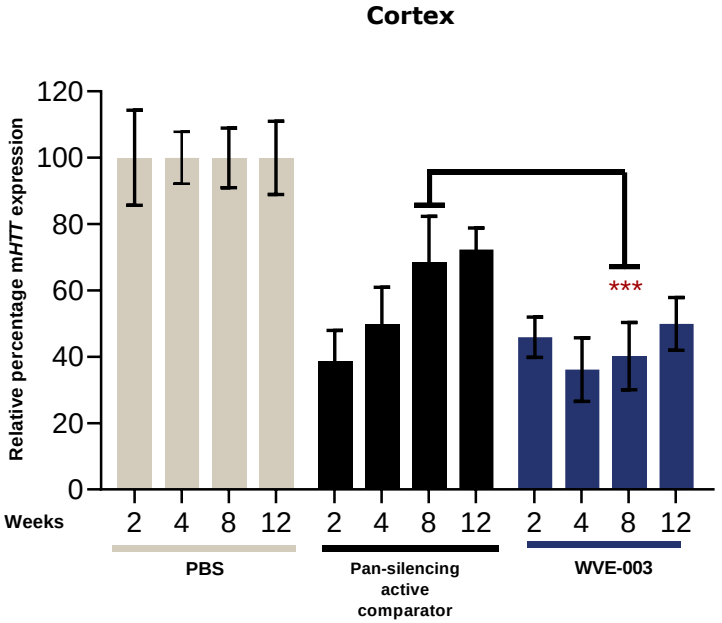
Potent mutant *HTT* knockdown activity in homozygous iCell neurons



No loss of selectivity with increasing concentrations



Knockdown persists for 12 weeks in BACHD mouse model



Similar knockdown achieved in striatum

Clinical development expected to initiate with CTA submission in 4Q 2020

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CTA: clinical trial application; wtHTT: wild-type huntingtin; mHTT: mutant huntingtin

[Figure on right] Statistics: All oligo treatment groups statistically significantly different from PBS; ***, P<0.005

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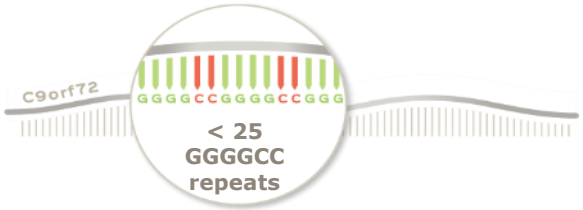
WVE-004

Amyotrophic Lateral Sclerosis (ALS)

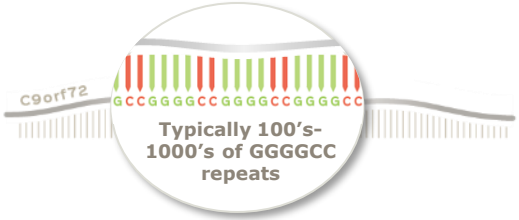
Frontotemporal Dementia (FTD)

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

Normal (non-expanded) Allele



Expanded Allele



- C9orf72 hexanucleotide repeat expansions (GGGGCC) are 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

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

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

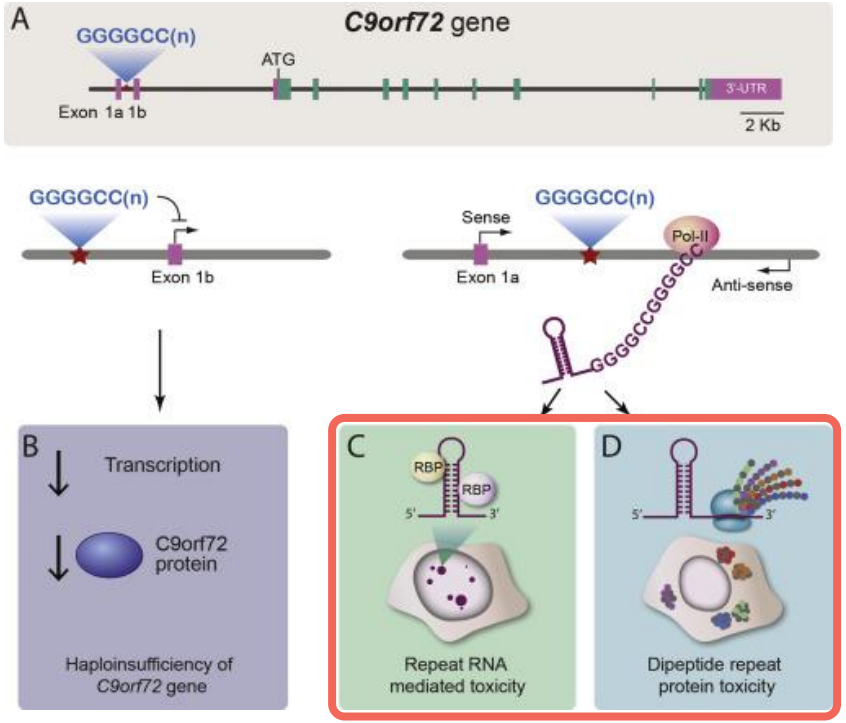
Two devastating diseases with a shared genetic basis

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

C9orf72 repeat expansions: Mechanisms of cellular toxicity

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

Variant-selective targeting could address multiple potential drivers of toxicity



Targeted by Wave ASOs

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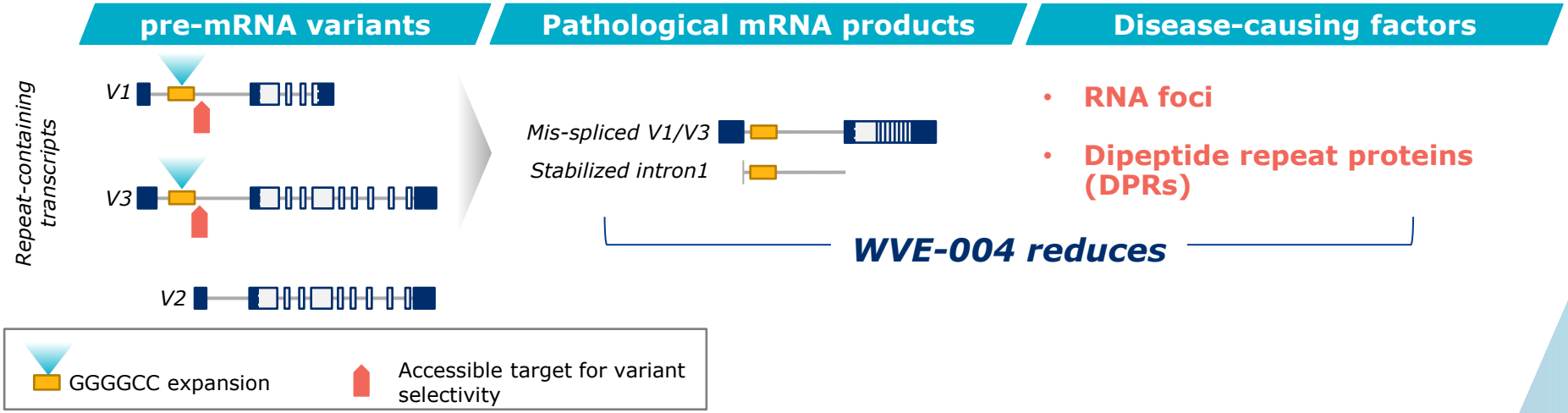
Sources: Gitler et al, Brain Research, September 2016. Zhu et al, Nature Neuroscience, May 2020

C9orf72 targeting strategy spares C9orf72 protein

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



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

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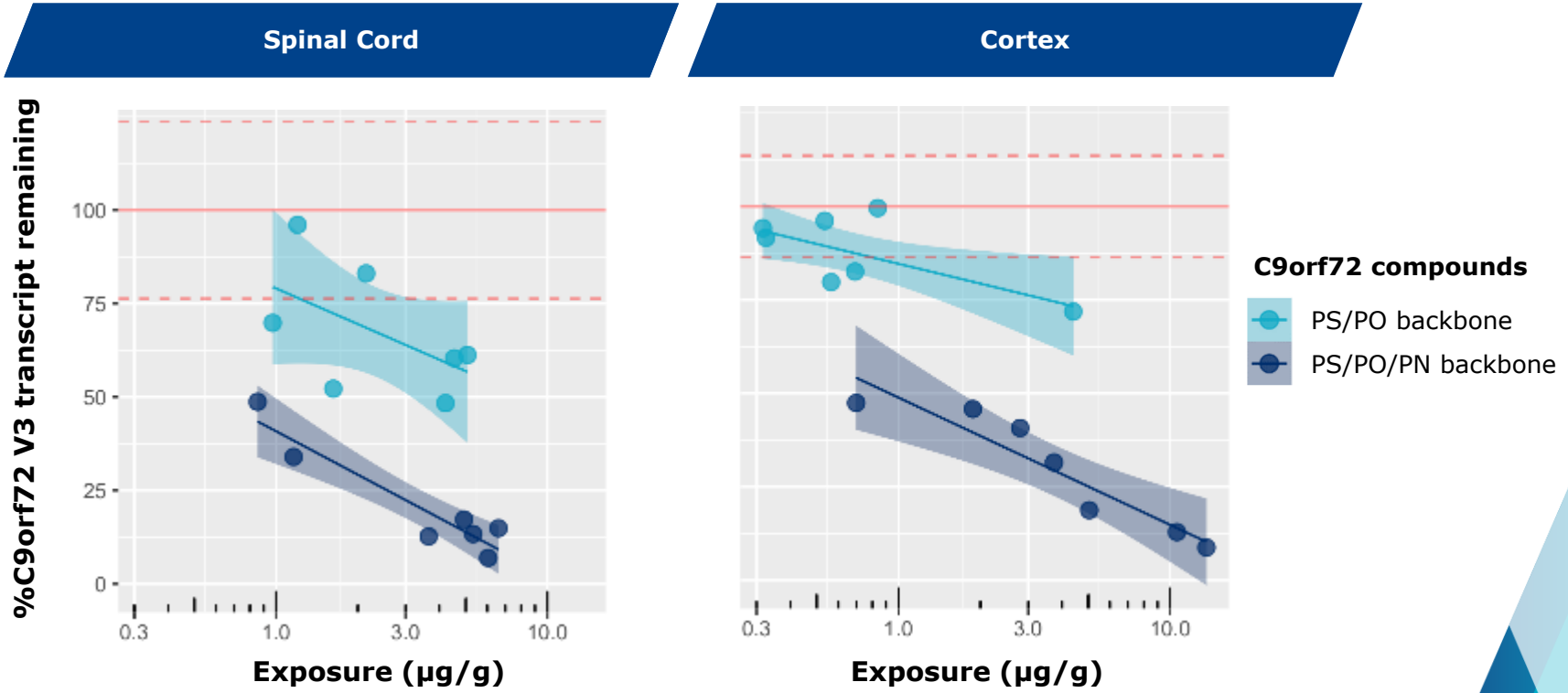
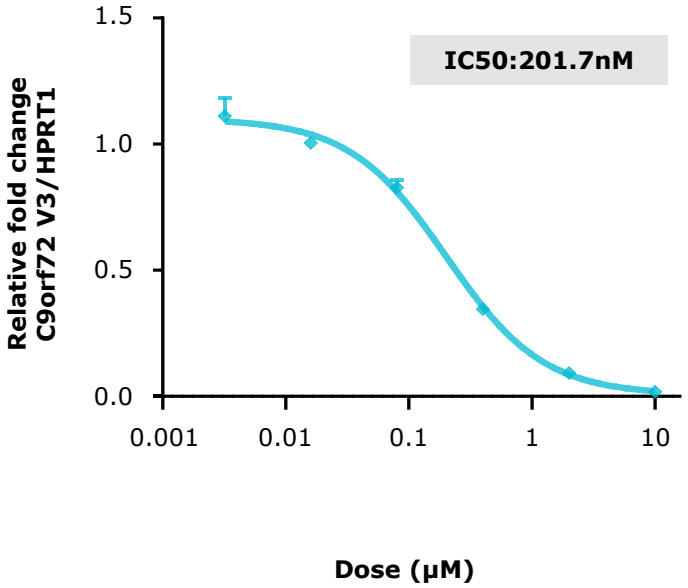
PN backbone chemistry: Improved potency among C9orf72-targeting oligonucleotides *in vivo*



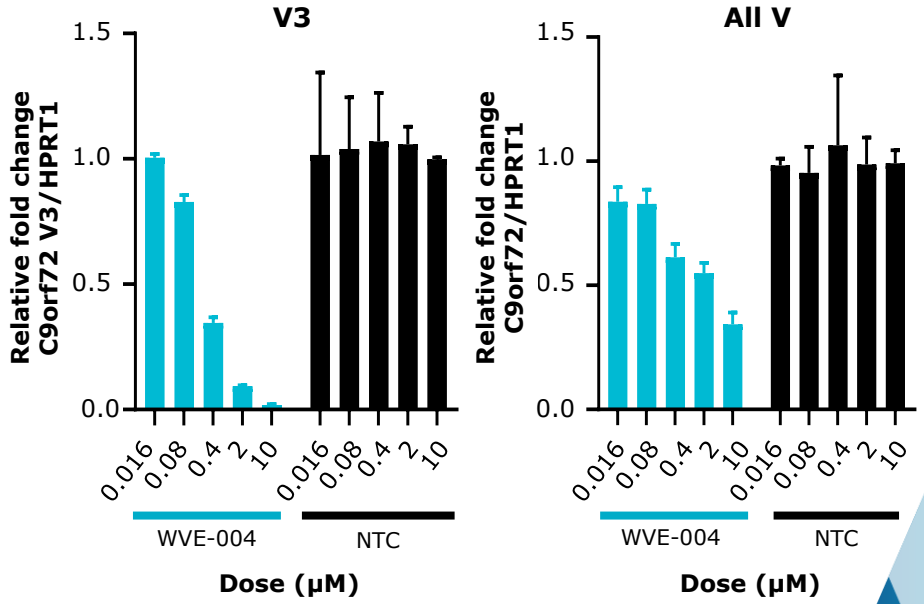
Mice received 2 x 50 ug ICV doses on days 0 & 7; mRNA from spinal cord and cortex quantified by PCR (Taqman assay) 8 weeks later. Oligonucleotide concentrations quantified by hybridization ELISA. Graphs show robust best fit lines with 95% confidence intervals (shading) for PK-PD analysis.

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.

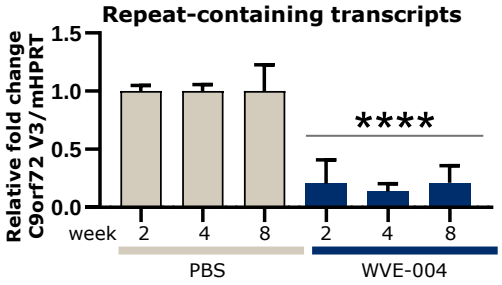
WVE-004: Potent and selective knockdown of repeat transcripts and DPRs *in vivo*

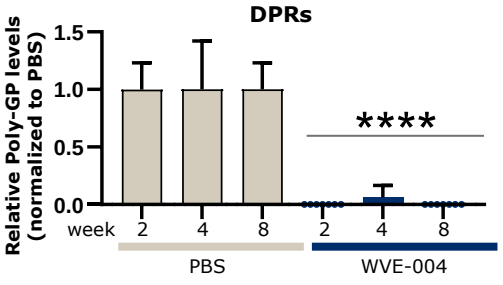
Incorporates PN modified backbone chemistry

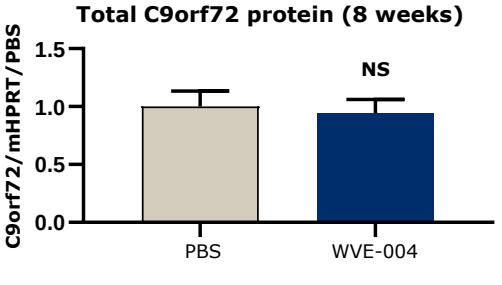
Potent *in vivo* knockdown of repeat containing transcripts and DPRs

Protein preservation

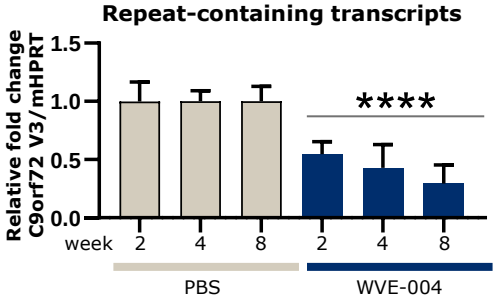
Spinal Cord

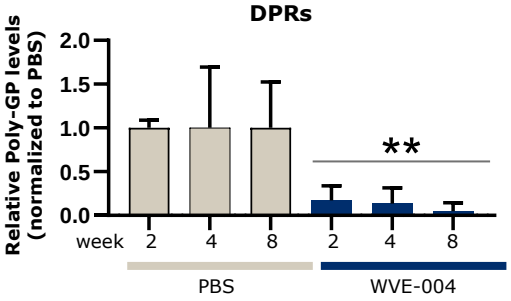


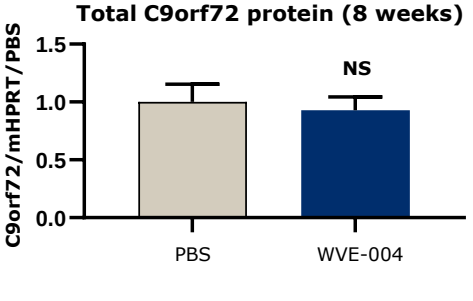




Cortex







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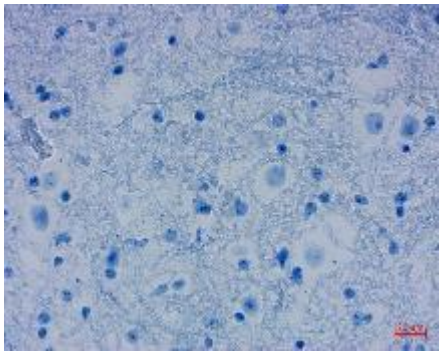
Experimental description: 2 x 50 ug on day 0 and day 7 dosed ICV; mRNA Samples were analyzed using quantitative PCR (Taqman assay), Dipeptide repeat proteins were measured by Poly-GP MSD assay. Protein samples were measured by Western Blot. NS: not significant

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

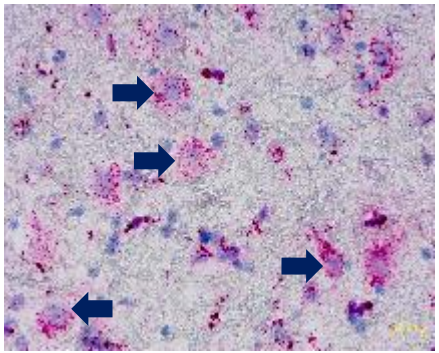
In situ hybridization of WVE-004 in spinal cord and cortex at 8 weeks

Spinal cord

PBS Control

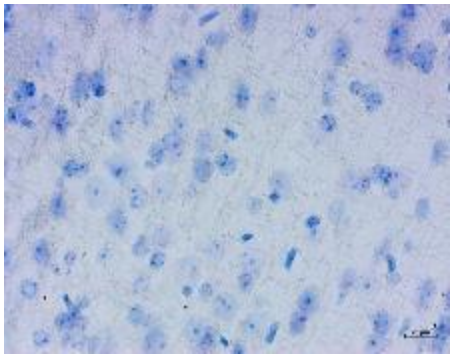


WVE-004

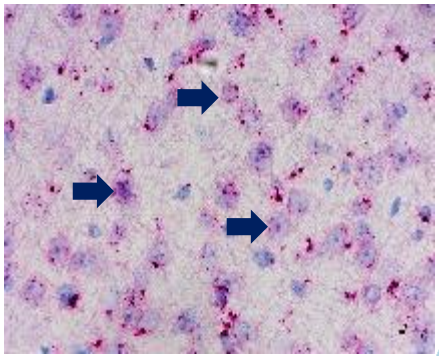


Cortex

PBS Control



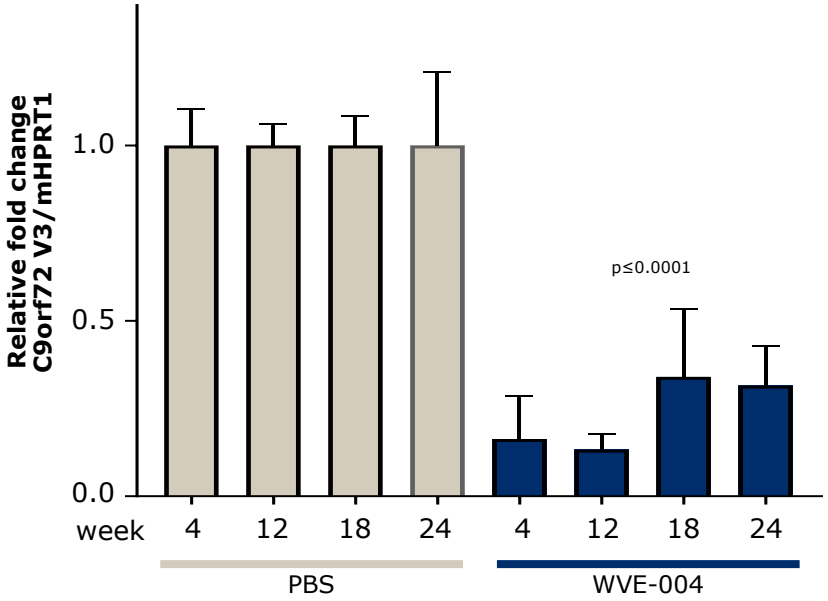
WVE-004



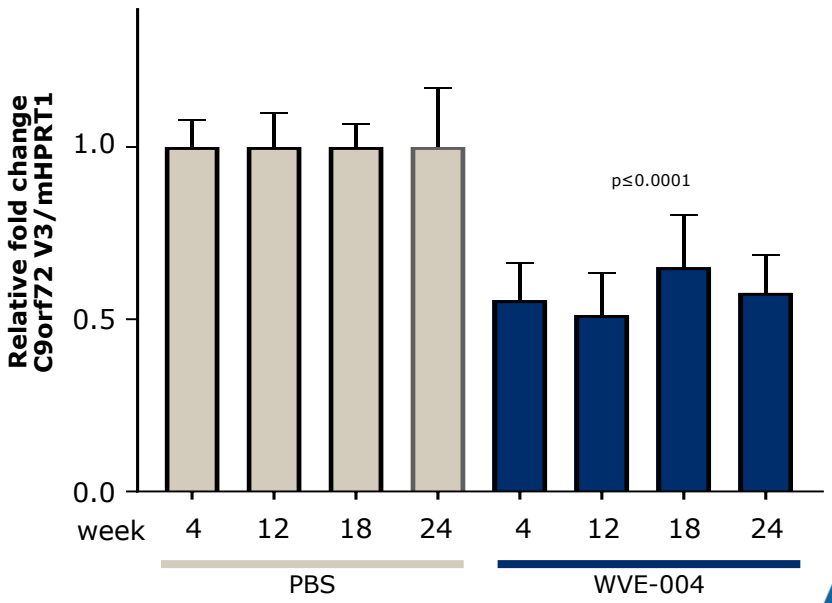
Red = viewRNA hybridization with WVE-004; blue = nucleus staining with Hematoxylin. 40X magnification.
C9 BAC transgenic mice were administered PBS or 50 ug of WVE-004, ICV, on day 0 and day 7. Mice were euthanized at 8 weeks after the first injection.

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

Spinal cord



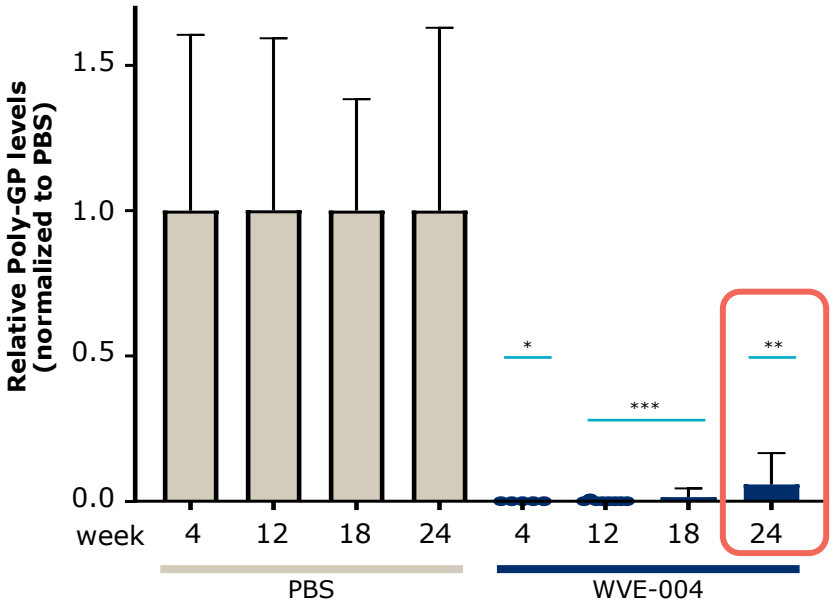
Cortex



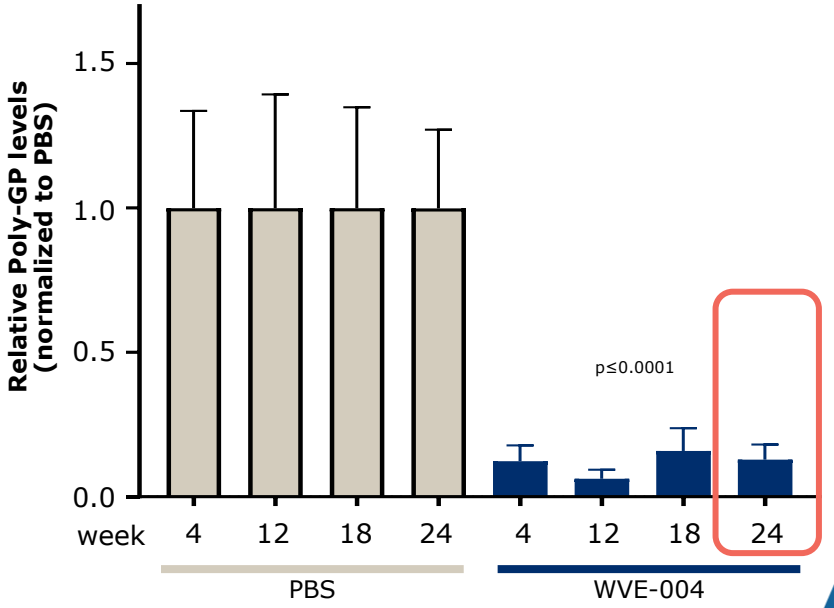
Experimental description: 2 x 50 ug on day 0 and day 7 dosed ICV; mRNA Samples were analyzed using quantitative PCR (Taqman assay)

WVE-004: Durable knockdown of DPRs *in vivo* after 6 months in spinal cord and cortex

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 study 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

Clinical trial application expected to be submitted in 4Q 2020

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NfL: neurofilament light chain; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale; CDRFTLD: Clinical Dementia Scale – frontotemporal lobar degeneration

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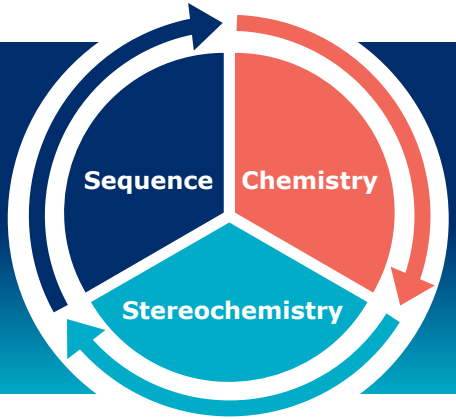
Wave's discovery and drug development platform

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 artificial intelligence-driven predictive modeling, Wave continues to define design principles that are deployed across programs to rapidly develop and manufacture clinical candidates that meet pre-defined product profiles

Multiple modalities
Silencing | Splicing | ADAR editing

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PRISM platform enables rational drug design

Sequence

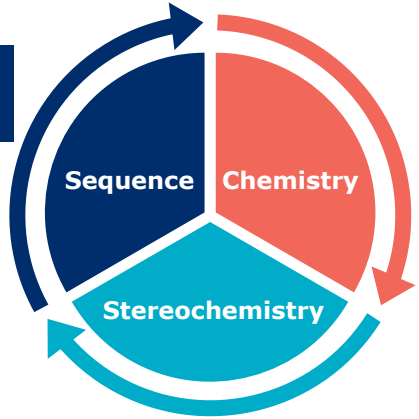
B: bases

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

Stereochemistry

Chiral control of
any stereocenter

5′ modifications,
backbone modifications



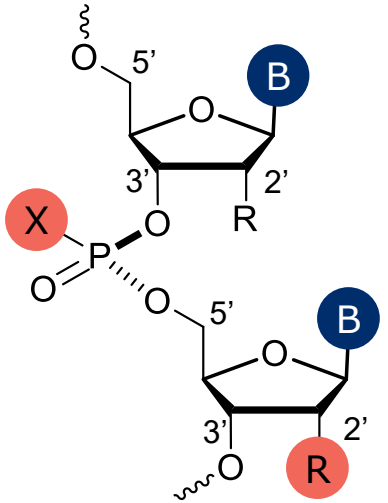
Chemistry

R: 2′ modifications

OMe, MOE, F,
other modifications

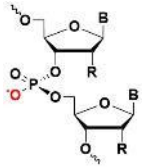
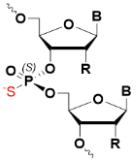
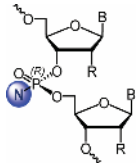
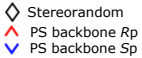
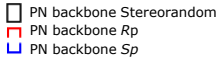
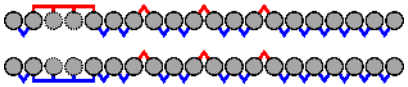
X: backbone chemistry

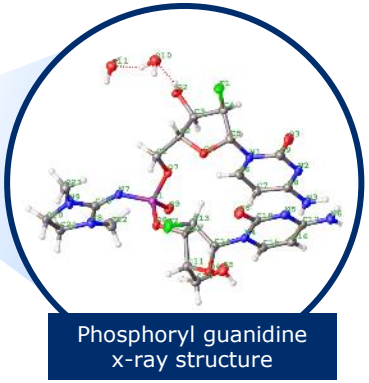
Phosphodiester (PO),
phosphorothioate (PS),
Phosphoramidate diester
(PN)



Expanding repertoire of backbone modifications with novel PN backbone chemistry

Backbone linkages

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



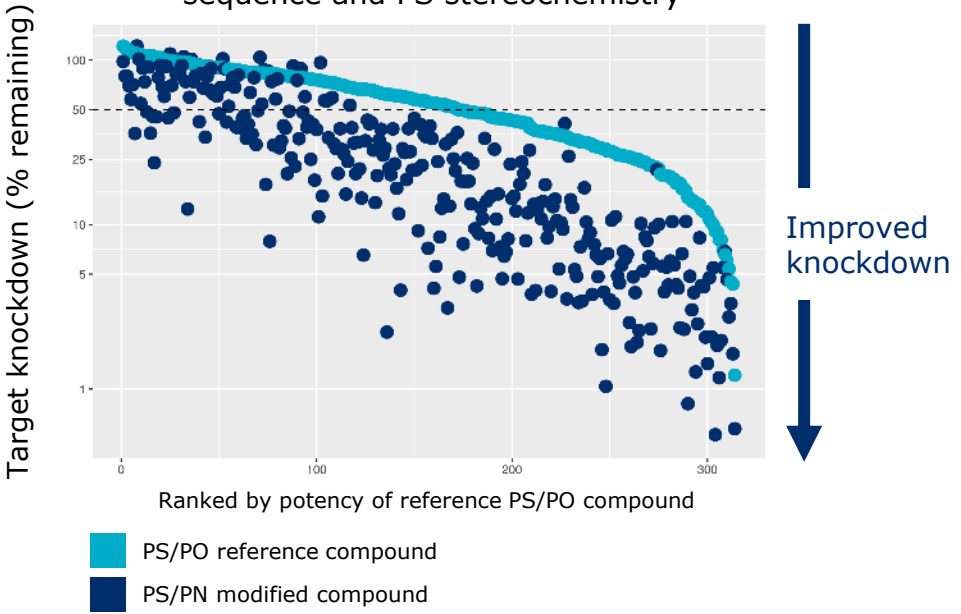
Phosphoryl guanidine x-ray structure

Molecule structure illustrative of backbone modification patterns

Rational design using PN chemistry backbone modification increases *in vitro* potency in most cases

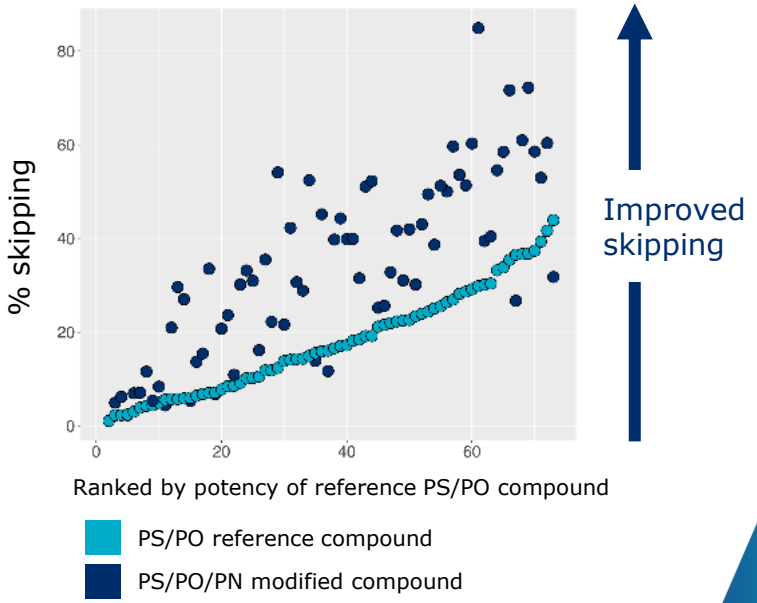
Silencing

In vitro knockdown of PS/PO containing compounds compared to PS/PN compounds with same sequence and PS stereochemistry



Splicing

In vitro skipping efficiency of PS/PO containing compounds compared to PS/PO/PN compounds with same sequence and PS stereochemistry



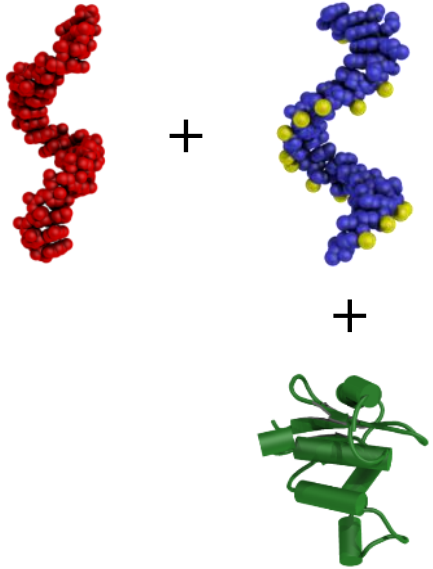
Presented at Analyst & Investor Research Webcast on August 25, 2020; Left: Experiment was performed in iPSC-derived neurons *in vitro*; target mRNA levels were monitored using qPCR against a control gene (HPRT1) using a linear model equivalent of the ΔΔCt method; Right: DMD patient-derived myoblasts treated with PS/PO or PS/PO/PN stereopure oligonucleotide under free-uptake conditions. Exon-skipping efficiency evaluated by qPCR. PS/PO compounds are rank-ordered on X-axis.

PRISM enables optimal placement of backbone stereochemistry

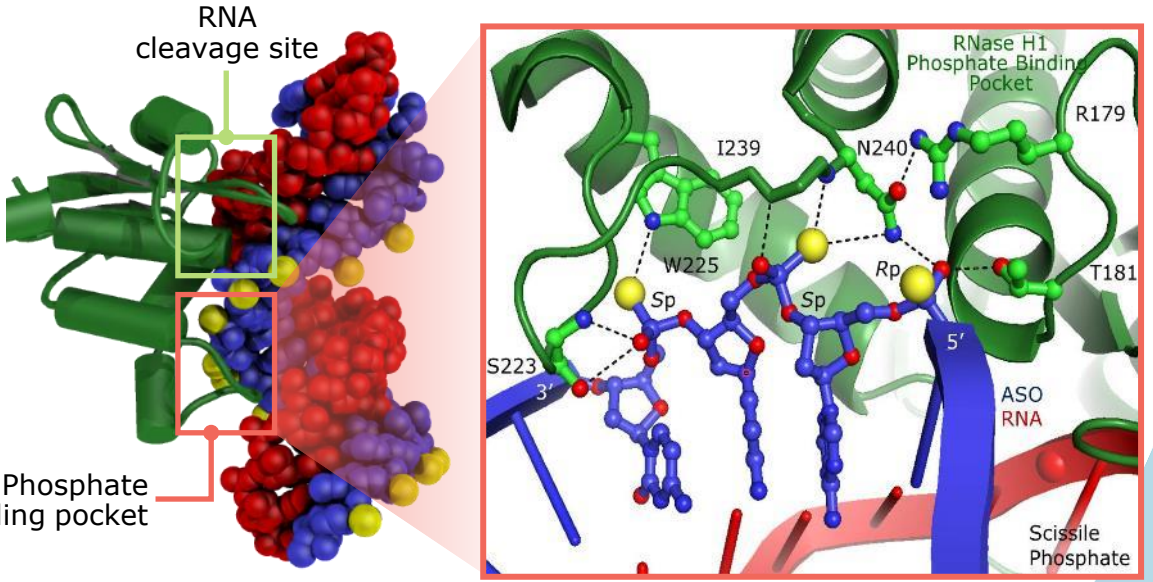
Crystal structure confirms phosphate-binding pocket of RNase H binds 3′-SSR-5′ motif in stereopure oligonucleotide – supports design strategy for Wave oligonucleotides

Target RNA

Stereopure Oligonucleotide (C9orf72 compound)



RNase H

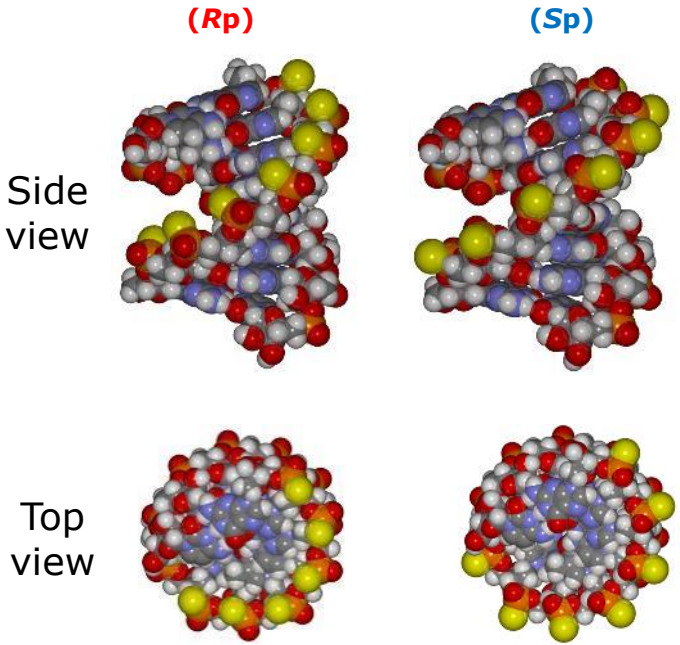


ASO/RNA duplex

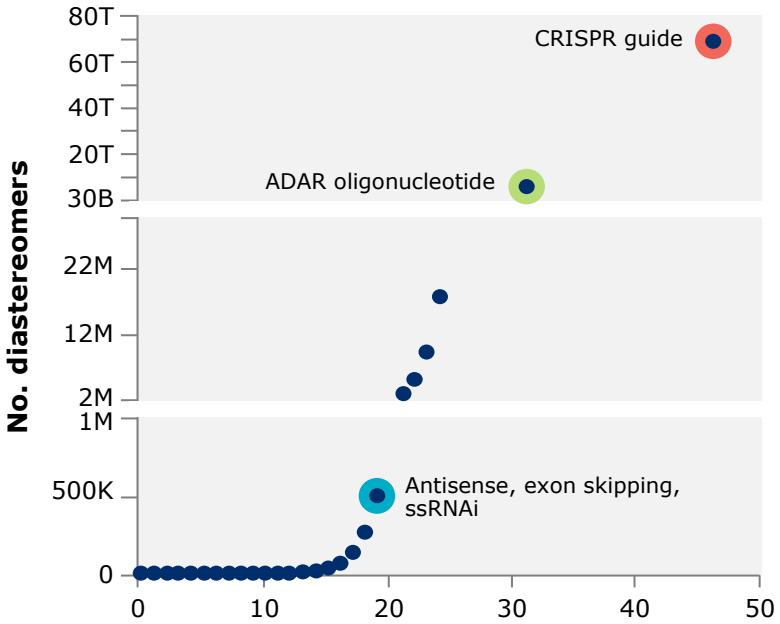
Yellow spheres represent ‘S’ atoms

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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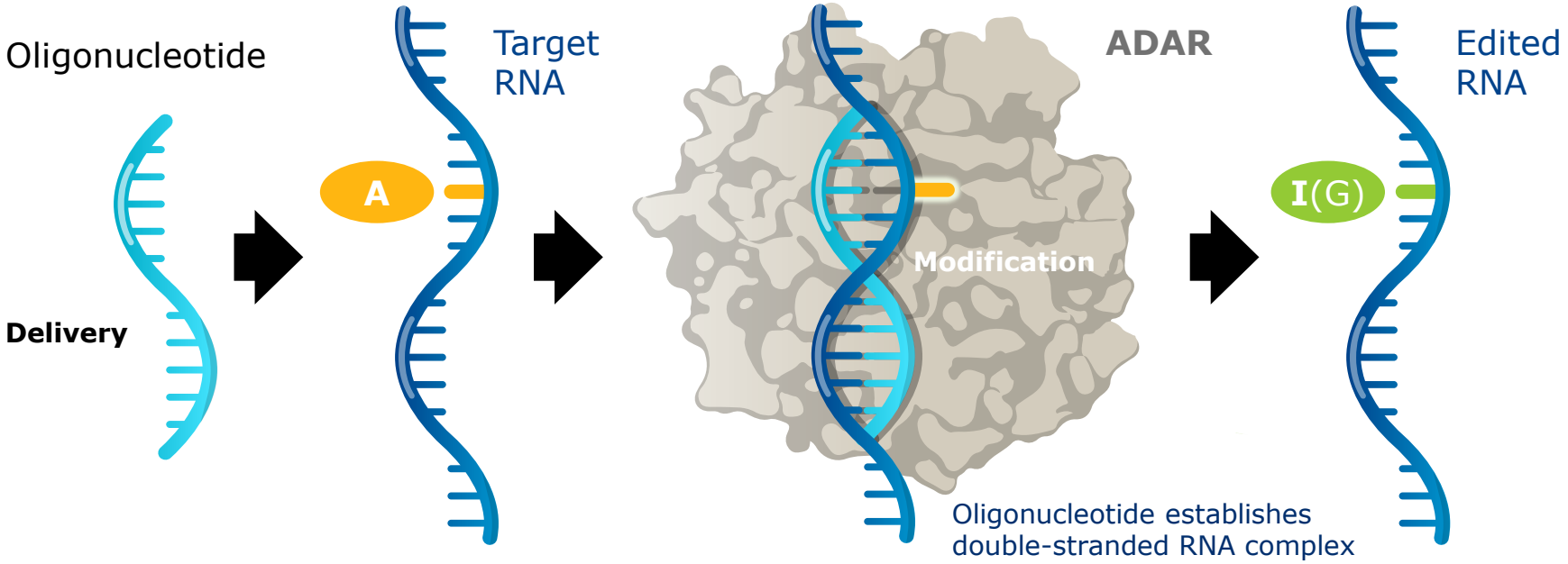
LIFE SCIENCES

ADAR editing

PRISM platform has unlocked ADAR editing

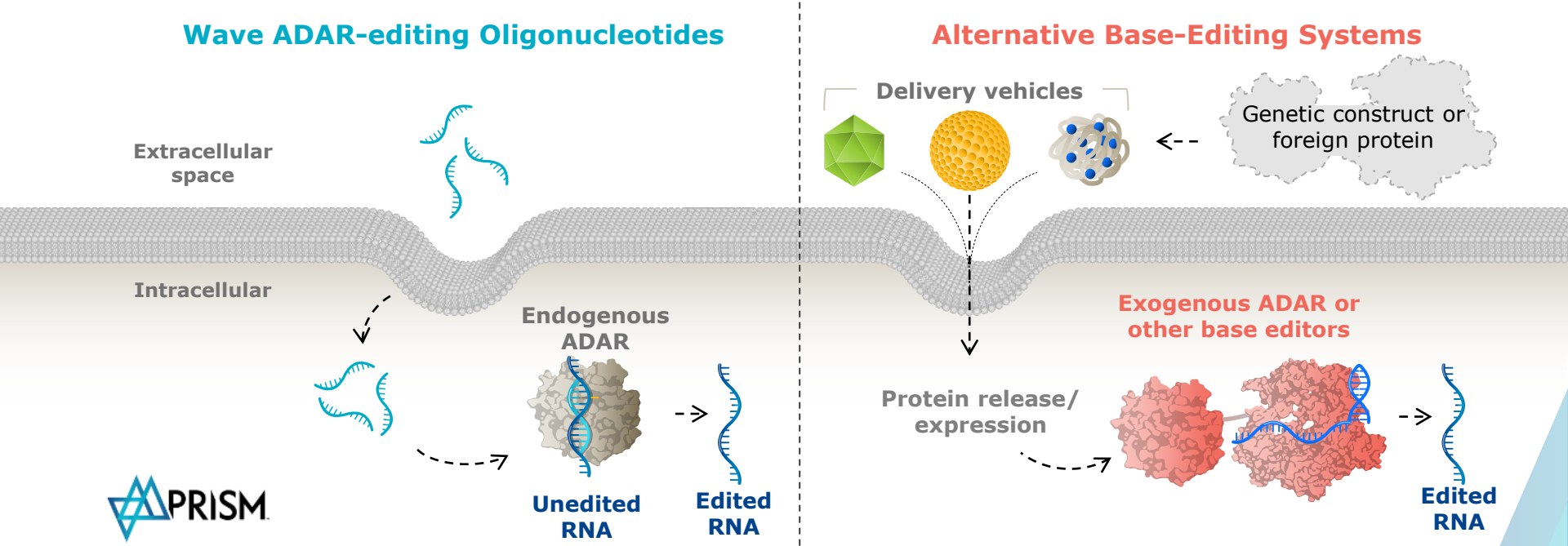


- **A**-to-**I** editing is one of most common post-transcriptional modifications
- ADAR is ubiquitously expressed across tissues, including liver and CNS

WAVE LIFE SCIENCES

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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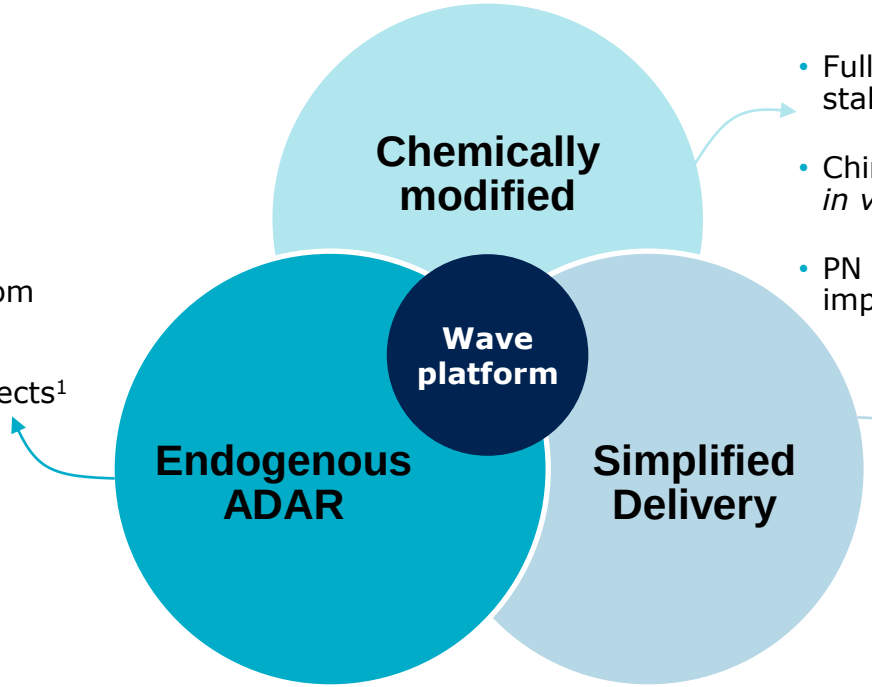
Advantages of Wave ADAR-mediated RNA editing platform



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

- No immunogenicity from exogenous proteins
- Reduced off-target effects[1]

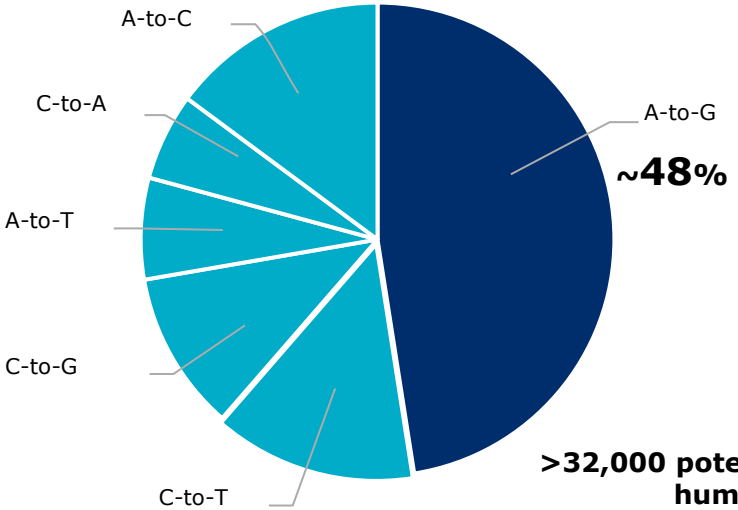
- GalNAc-conjugated for targeted delivery into liver
- No requirement for AAV / nanoparticles

Building RNA editing capability for PRISM platform

[1]Chen et al. 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
- Tens of thousands of potential disease variants A-to-I(G) editing could target[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

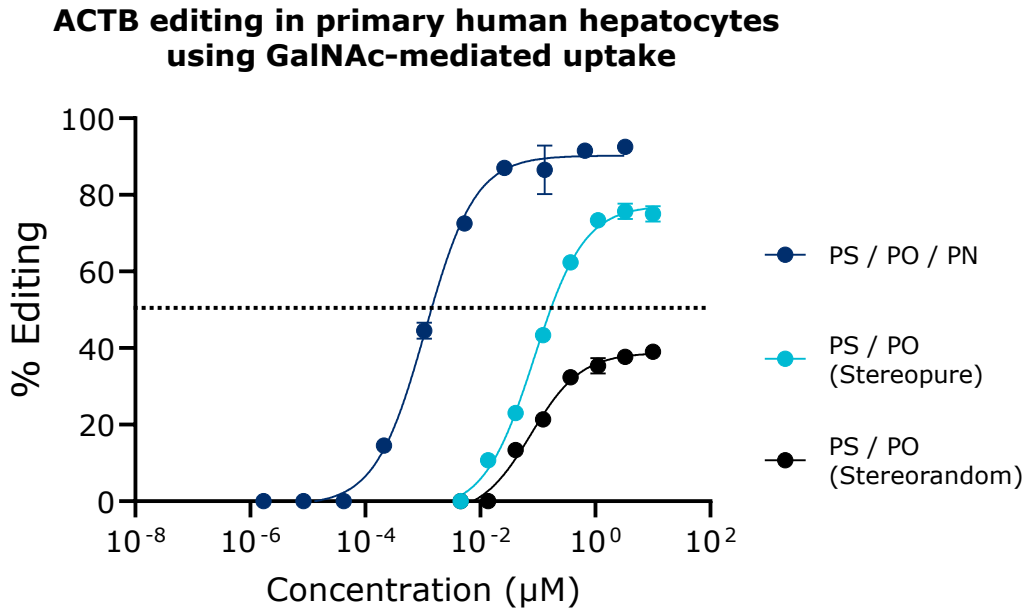
- miRNA target site modification
- Modifying upstream ORFs
- Modification of ubiquitination sites

Examples:

Haploinsufficient diseases

PN chemistry improves editing efficiency

PN backbone modification increased both potency and editing efficiency *in vitro*

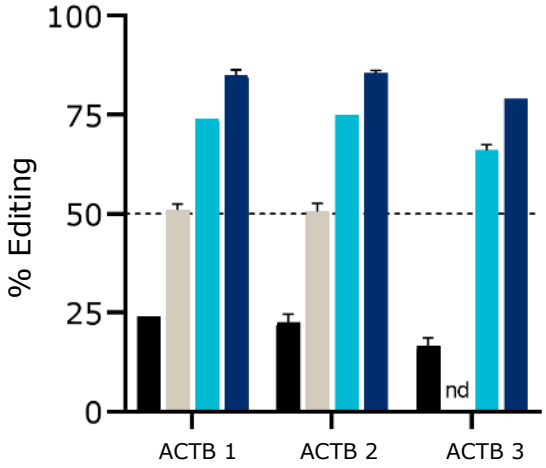


Data from independent experiments; Total RNA was harvested, reverse transcribed to generate cDNA, and the editing target site was amplified by PCR and quantified by Sanger sequencing

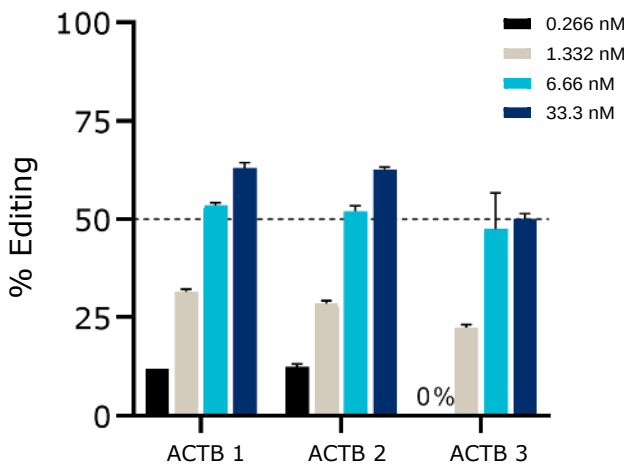
Significant ADAR editing demonstrated *in vitro* in NHP and primary human hepatocytes

ACTB GalNAc-conjugated oligonucleotides with stereopure PN chemistry modification

In vitro dose-response human hepatocytes



In vitro dose-response NHP hepatocytes

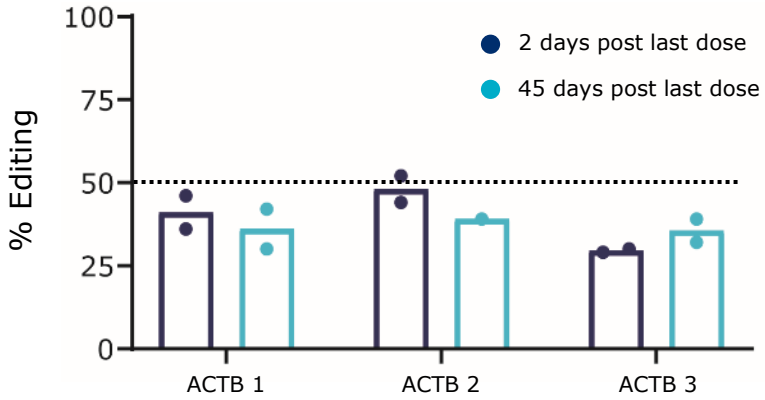


NHP: non-human primate; ACTB: Beta-actin; nd= not determined
Total RNA was harvested, reverse transcribed to generate cDNA, and the editing target site was amplified by PCR.

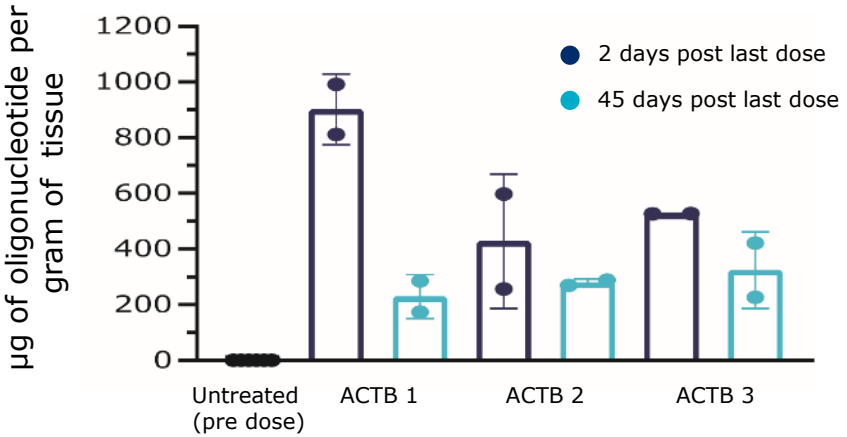
Efficient ADAR editing translated *in vivo* in non-human primate study

- 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



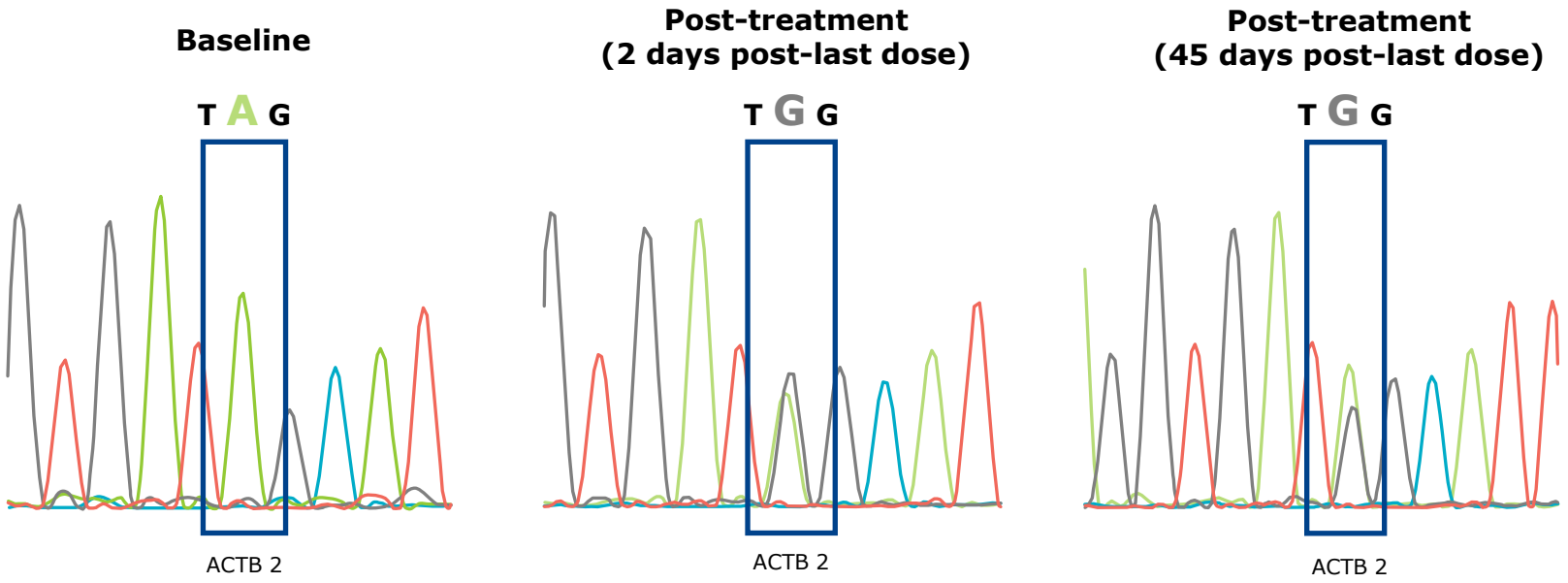
Oligonucleotide quantification in NHP following subcutaneous administration



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

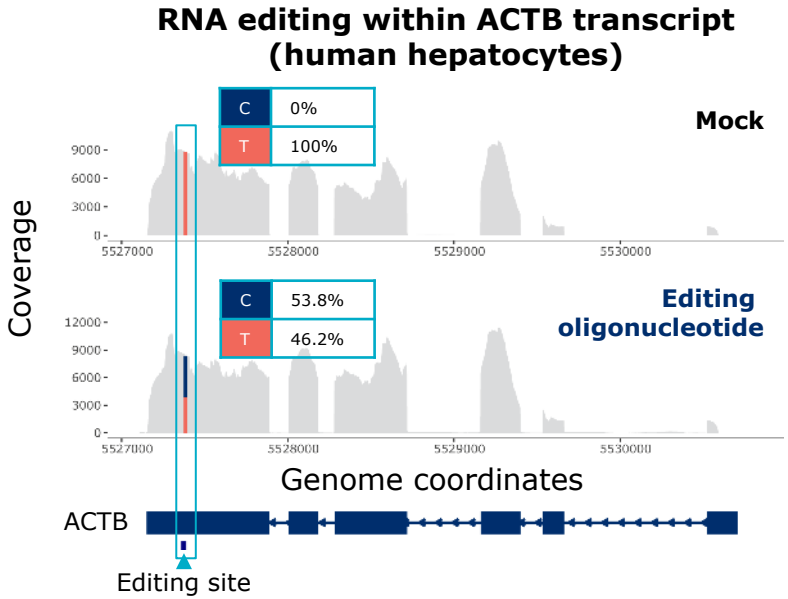
Sustained editing *in vivo* in non-human primates after 45 days

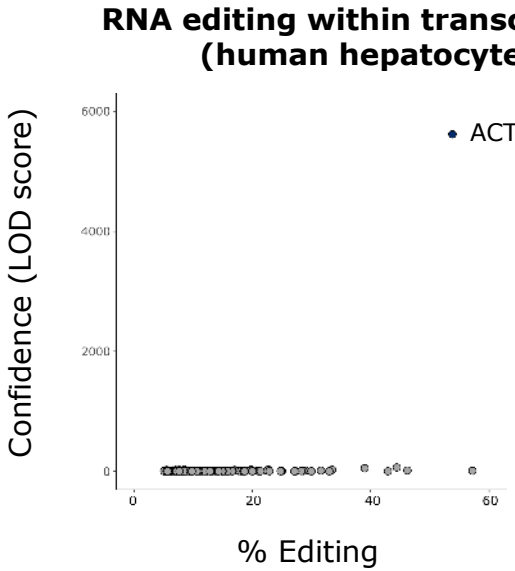
Efficient and potent editing of ACTB demonstrated with Sanger sequencing



% Editing quantified from Sanger sequencing using EditR program.

ADAR editing is highly specific

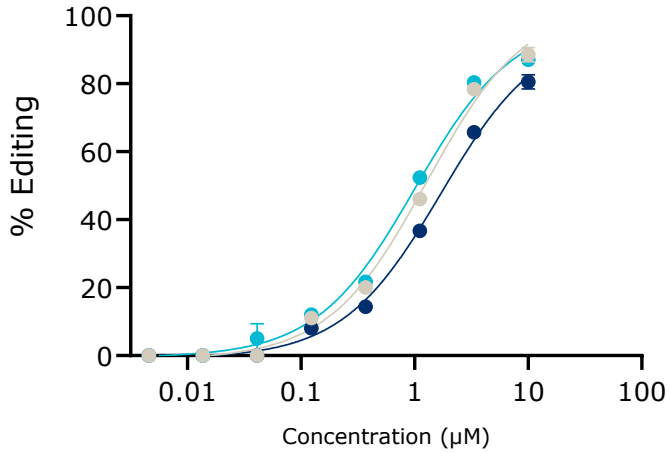




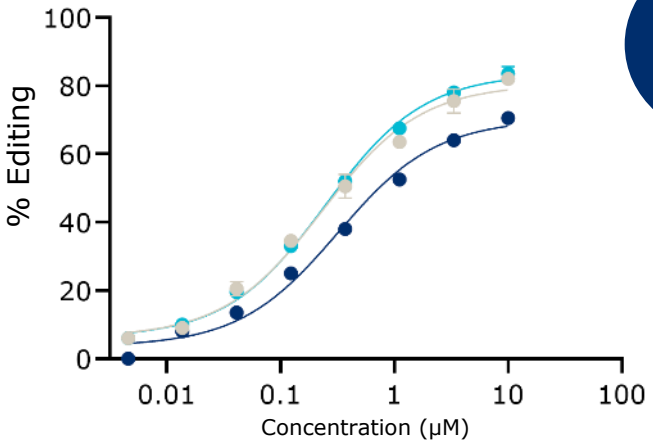
Human hepatocytes were dosed with 1um oligonucleotide, 48 hours later RNA was collected and sent for RNA sequencing. RNAseq conducted using strand-specific libraries to quantify on-target ACTB editing and off-target editing in primary human hepatocytes; plotted circles represent sites with LOD>3

Efficient and potent editing observed in neurons and astrocytes

ACTB editing in iCell Neurons



ACTB editing in human iCell Astrocytes



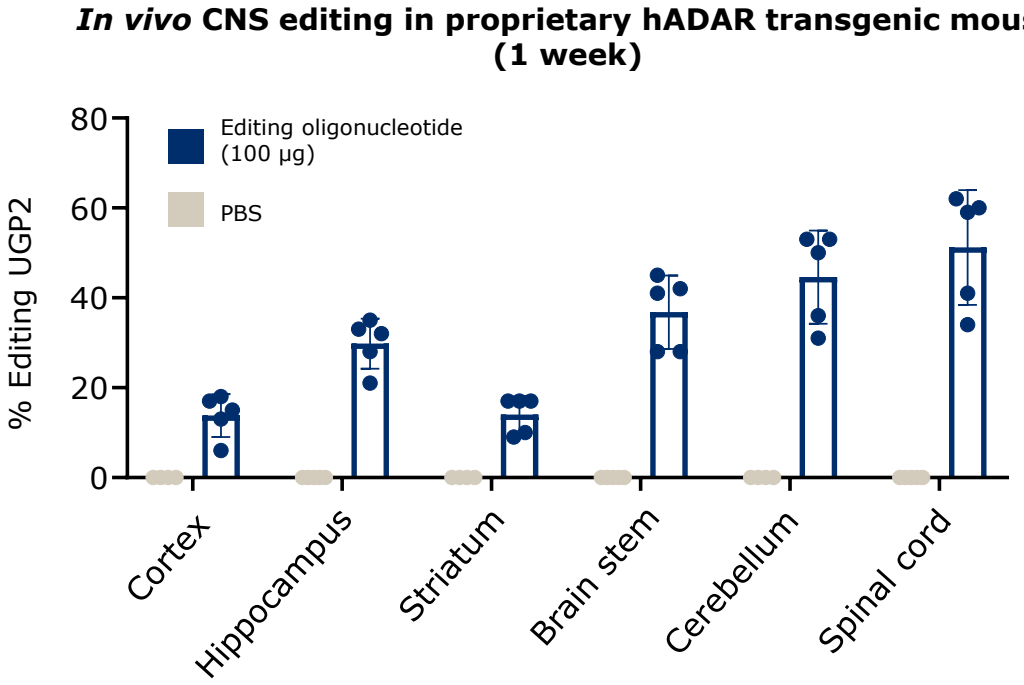
EC50: ~200-250nM

Compound 1 (PS / PN)
Compound 2 (PS / PN)
Compound 3 (PS / PN)

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

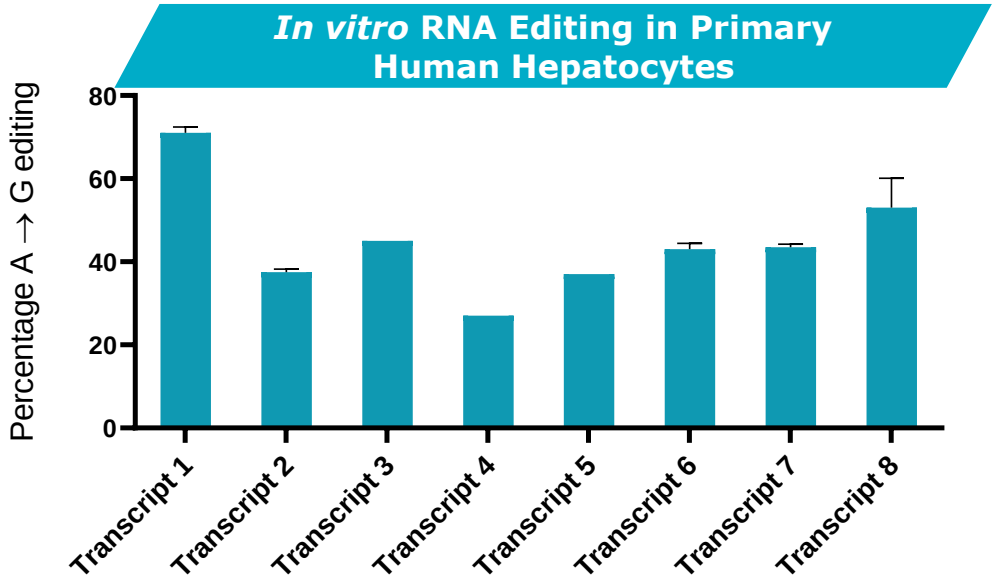
Opening the door to ADAR editing in CNS

First *in vivo* study in proprietary transgenic model yields efficient editing across all tissues



hADAR: human ADAR; UGP2: Glucose Pyrophosphorylase 2; CNS: central nervous system; Editing observed across all tested tissues of human-ADAR-transgenic mice by ICV injection. 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.

RNA editing design applicable across targets



- Editing achieved across several distinct RNA transcripts
- Supports potential for technology to be applied across variety of disease targets

First ADAR editing program in hepatic indication expected to be announced in 2020

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Data presented at 1st International Conference on Base Editing – Enzymes and Applications (Deaminet 2020); See poster for full dataset

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Ophthalmology

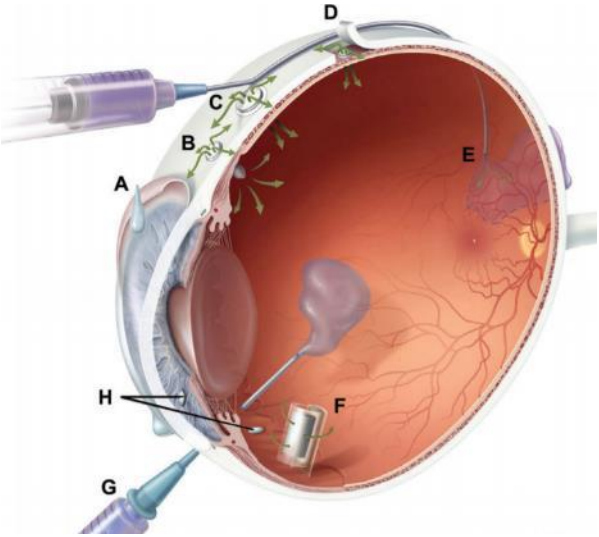
Stereopure oligonucleotides for inherited retinal diseases (IRDs)

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

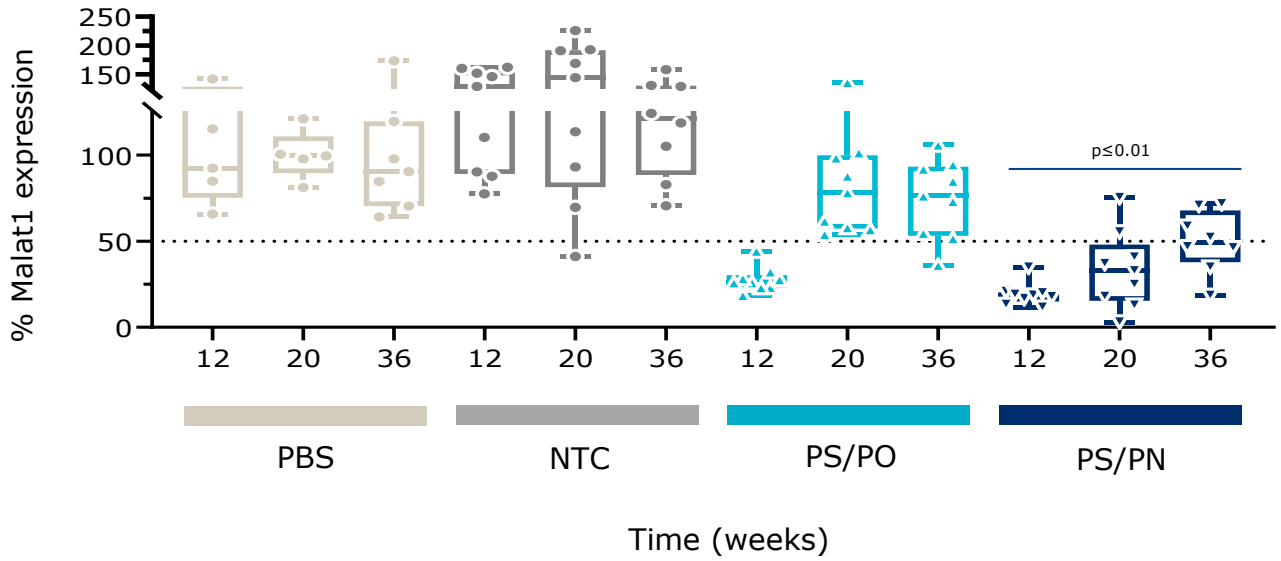


Intravitreal injection

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 chemistry

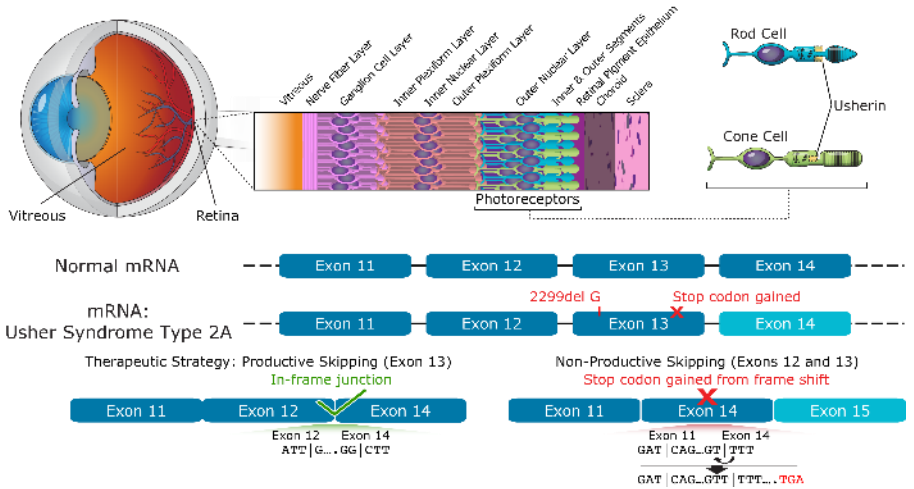
~50% Malat1 knockdown at 36 weeks in the posterior of the eye



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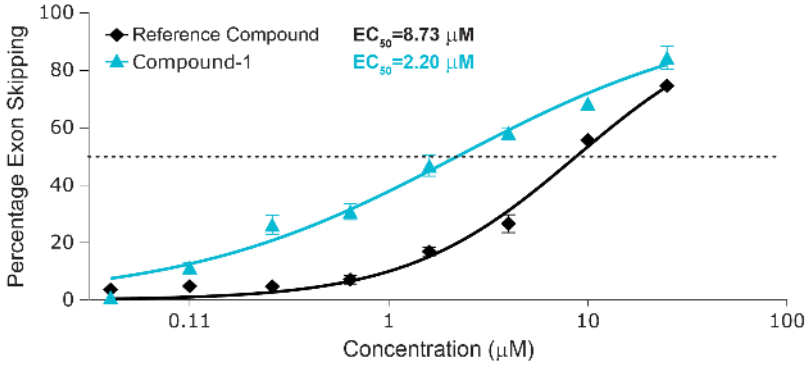
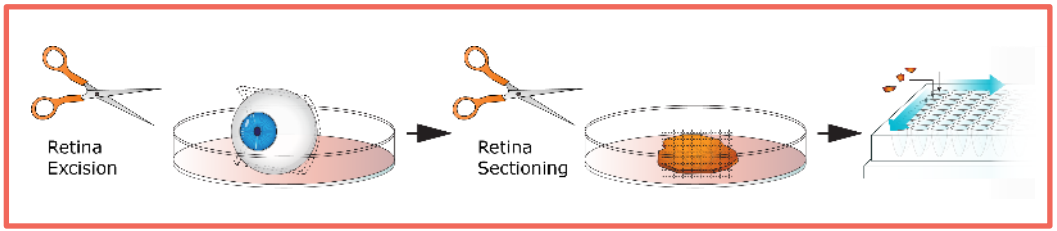
Sources: Boughman et al., 1983. *J Chron Dis*. 36:595-603; Seyedahmadi et al., 2004. *Exp Eye Res.* 79:167-173; Liu et al., 2007. *Proc Natl Acad Sci USA* 104:4413-4418.

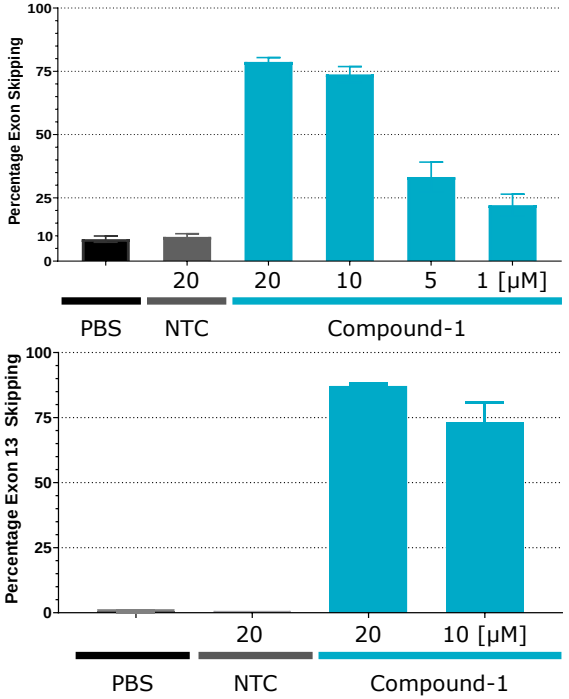
Potent USH2A exon 13 skipping with stereopure compound in *vitro* and *ex vivo*

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





Target engagement in NHP and human retinas (*ex vivo*)

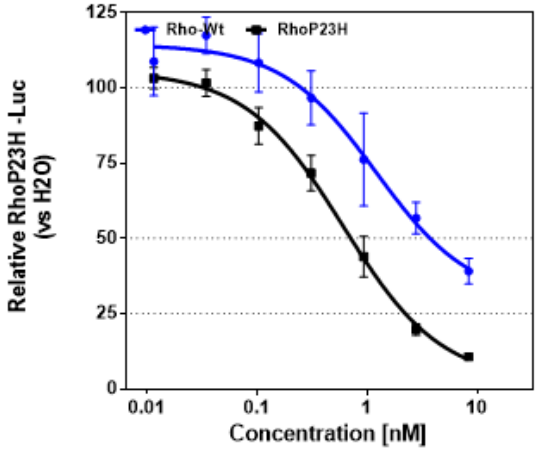


Left: Compounds were added to Y79 cells under free-uptake conditions. Exon skipping was evaluated by Taqman assays. *USH2A* transcripts were normalized to *SRSF9*. Data are mean±s.d., n=2. Reference Compound: van Diepen *et al.* 2018. Antisense oligonucleotides for the treatment of eye disease. W02018055134A1. Compound-1 is a stereopure antisense oligonucleotide. Right: Whole NHP and human eyes were enucleated (n=4 and n=2, respectively) and compounds (1–20 µM) were added to extracted retinas under free-uptake conditions. Exon skipping was evaluated by 48 hrs later by Taqman assays on RNA. USH2A transcript levels were normalized to SRSF9. Data presented are mean± s.e.m.

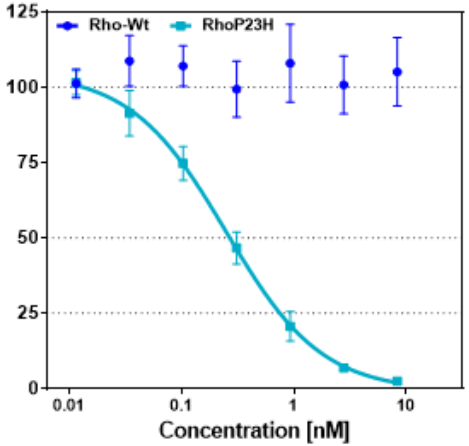
Allele-selective reduction of SNP-containing allele for adRP associated with Rhodopsin P23H mutation

- **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

Stereorandom



Stereopure



In vivo

Collaborations in place for evaluation in transgenic human Rho P23H pig model

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Ferrari et al., *Current Genomics.* 2011;12:238-249.; Reporter assays on a Wave stereopure sequence as well as a sequence described in WO2016138353A1: ASO and luciferase reporter plasmids (wild-type and mutant rhodopsin) are transfected into Cos7 cells. 48-hours later, cells are harvested, and relative luminescence is measured.

Anticipated upcoming Wave milestones

NEUROLOGY

Huntington's disease

- **4Q 2020**: Initiate clinical development with CTA filing of SNP3 program
- **1Q 2021**: PRECISION-HD2 data from 32 mg cohort and data from OLE trial
- **1Q 2021**: PRECISION-HD1 data, including 32 mg cohort, and data from OLE trial

ALS and FTD

- **4Q 2020**: Initiate clinical development with CTA filing of C9orf72 program in ALS and FTD

PRISM

ADAR editing

- ✓ *In vivo* ADAR-mediated RNA editing data
- ✓ **August 2020**: Additional *in vivo* ADAR editing data at Research webcast
  - **2020**: Announce first ADAR editing program in a hepatic indication

PRISM platform updates in 2020

- ✓ Research webcast held August 25 (introduced PN chemistry)

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ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; CTA: clinical trial application; OLE: open-label extension

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Realizing a brighter future for people affected by genetic diseases

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