

**UNITED STATES  
SECURITIES AND EXCHANGE COMMISSION**  
Washington, D.C. 20549

**Form 8-K**

**CURRENT REPORT**  
Pursuant to Section 13 or 15(d)  
of the Securities Exchange Act of 1934

**Date of Report (Date of earliest event reported): October 4, 2022**

**WAVE LIFE SCIENCES LTD.**

(Exact name of registrant as specified in its charter)

**Singapore**  
(State or other jurisdiction  
of incorporation)

**001-37627**  
(Commission  
File Number)

**00-0000000**  
(IRS Employer  
Identification No.)

**7 Straits View #12-00, Marina One  
East Tower  
Singapore**  
(Address of principal executive offices)

**018936**  
(Zip Code)

**Registrant's telephone number, including area code: +65 6236 3388**

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
- Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
- Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
- Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading symbol	Name of each exchange on which registered
<b>\$0 Par Value Ordinary Shares</b>	<b>WVE</b>	<b>The Nasdaq Global Market</b>

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

**Item 7.01 Regulation FD Disclosure.**

From time to time, Wave Life Sciences Ltd. (the “Company”) presents and/or distributes slides and presentations to the investment community to provide updates and summaries of its business. On October 4, 2022, the Company updated its corporate presentation, which is available on the “For Investors & Media” section of the Company’s website at <http://ir.wavelifesciences.com/>. This presentation is also furnished as Exhibit 99.1 to this Current Report on Form 8-K.

*The information in this Item 7.01 is being furnished and shall not be deemed “filed” for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the “Exchange Act”), or otherwise subject to the liabilities of that Section, nor shall it be deemed incorporated by reference into any registration statement or other filing under the Securities Act of 1933, as amended, or the Exchange Act, except as shall be expressly set forth by specific reference in such filing.*

**Item 9.01 Financial Statements and Exhibits.**

(d) Exhibits

The following exhibit relating to Item 7.01 is furnished and not filed:

<b>Exhibit No.</b>	<b>Description</b>
99.1	<a href="#">Corporate Presentation of Wave Life Sciences Ltd. dated October 4, 2022</a>
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

**SIGNATURES**

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

**WAVE LIFE SCIENCES LTD.**

By: /s/ Paul B. Bolno, M.D.  
Paul B. Bolno, M.D.  
President and Chief Executive Officer

Date: October 4, 2022



# Wave Life Sciences Corporate Presentation

October 4, 2022

**WAVE**  
LIFE SCIENCES

# 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.



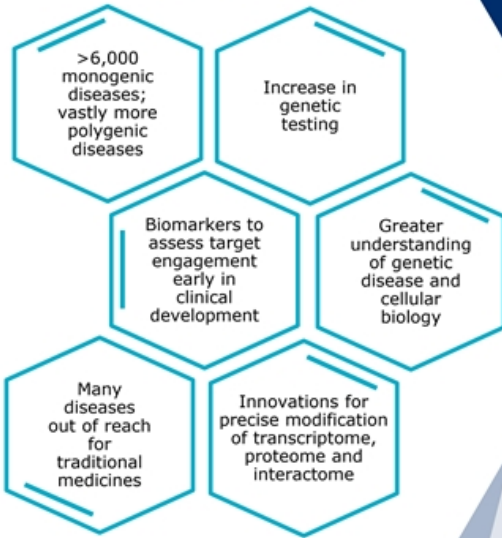


UNLOCKING THE BODY'S OWN ABILITY TO TREAT GENETIC DISEASE  
*realizing a brighter future for patients and families*

WAVE  
LIFE SCIENCES

# Building a leading genetic medicines company

## LEVERAGING THE ONGOING GENETIC REVOLUTION



**WAVE**  
LIFE SCIENCES

## TARGETING THE TRANSCRIPTOME TO UNLOCK THE BODY'S OWN ABILITY TO TREAT GENETIC DISEASE



### Innovative Platform

Stereopure oligonucleotides  
Novel backbone modifications (PN chemistry)  
Silencing, splicing, and editing modalities  
Strong and broad IP position<sup>1</sup>

### Clinical Expertise

Multiple global clinical trials  
Innovative trial designs

### Diversified Pipeline

CNS: ALS, FTD, HD  
Muscle: DMD  
Hepatic diseases: AATD

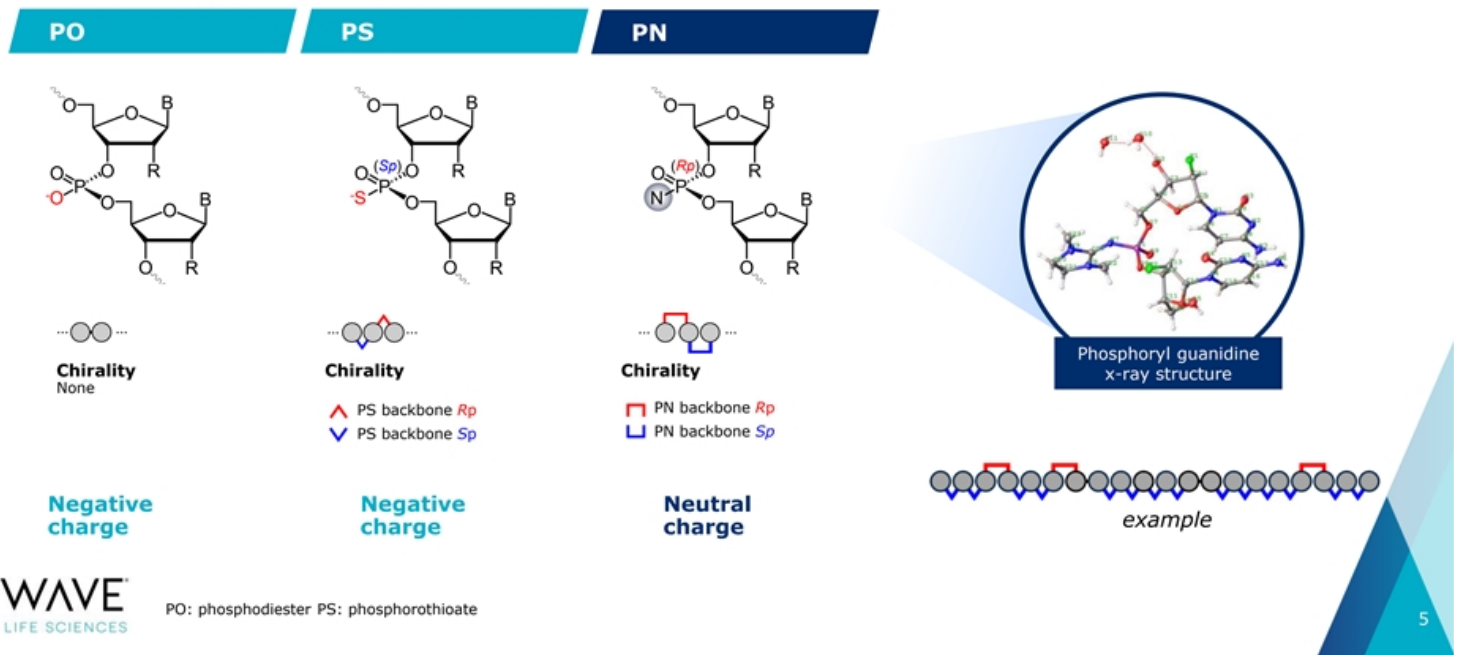
### GMP Manufacturing

Internal manufacturing capable of producing oligonucleotides at scale

ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; HD: Huntington's disease; DMD: Duchenne muscular dystrophy; AATD: Alpha-1 antitrypsin deficiency  
<sup>1</sup>stereopure oligonucleotides and novel backbone chemistry modifications

# Wave's ability to rationally design oligonucleotides enables access to unique disease targets

## PRISM backbone linkages



WAVE<sup>™</sup>  
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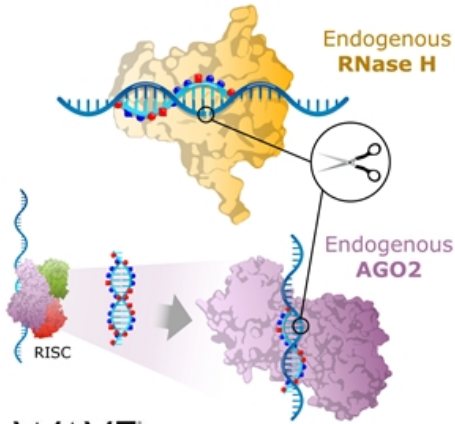
PO: phosphodiester PS: phosphorothioate



# Harnessing the biological machinery in our cells to treat genetic diseases

## Silencing

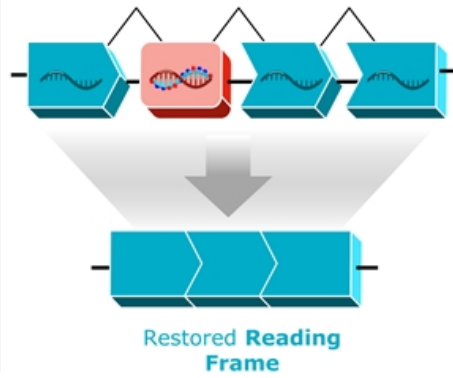
- Degradation of RNA transcripts to **turn off** protein production



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## Splicing

- Restore RNA transcripts and **turn on** protein production

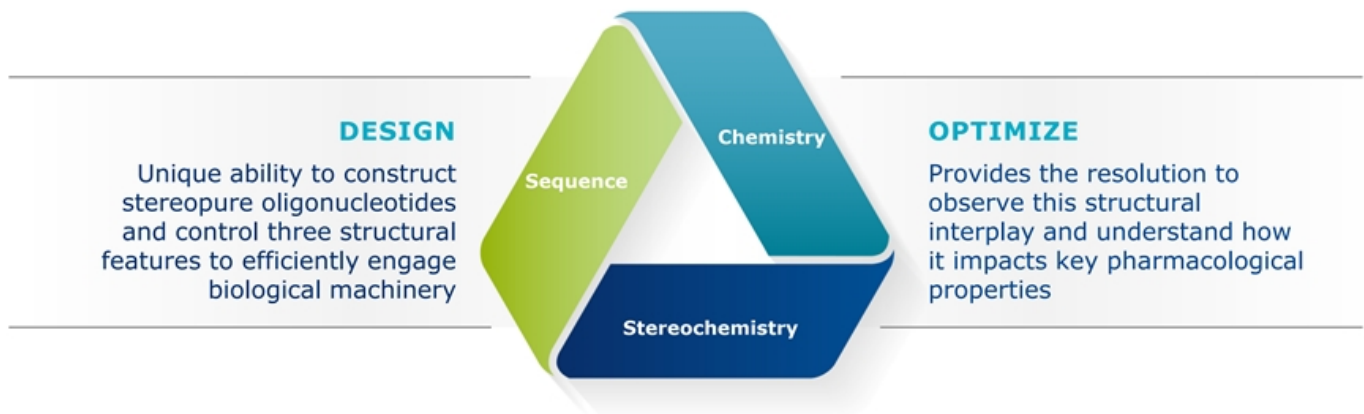


## RNA Base Editing

- Efficient editing of RNA bases to **restore** or **modulate** protein production



# PRISM. Unlocking the body's own ability to treat genetic disease



**Built-for-Purpose Candidates to Optimally Address Disease Biology**  
Silencing | Splicing | RNA Editing





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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<sub>4</sub>C<sub>2</sub>)- repeat expansions in C9orf72 gene are common autosomal dominant cause for ALS and FTD



*Different manifestations across a clinical spectrum*

## **Amyotrophic Lateral Sclerosis (ALS)**

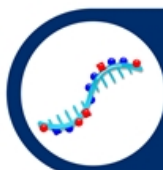
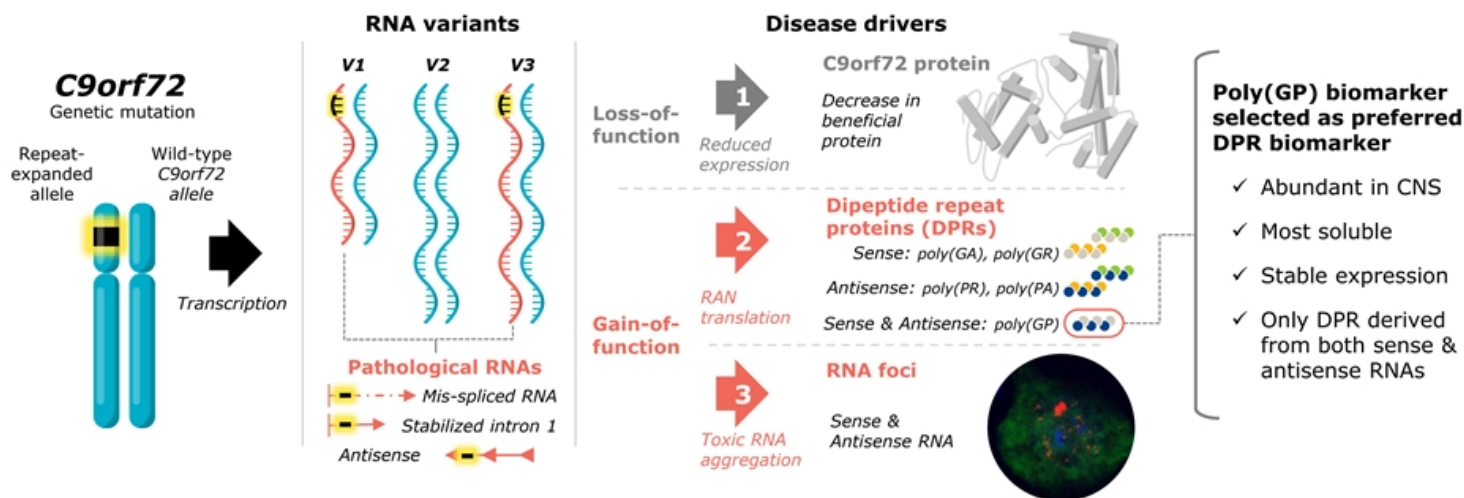
- Fatal neurodegenerative disease
- Progressive degeneration of motor neurons in brain and spinal cord
- C9-specific ALS: ~2,000 patients in US

## **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

**Including patients with C9-associated ALS, FTD or both**

# WVE-004 addresses each biological aspect of *C9orf72*-associated ALS and FTD



**WVE-004 is designed to affect multiple drivers of toxicity**

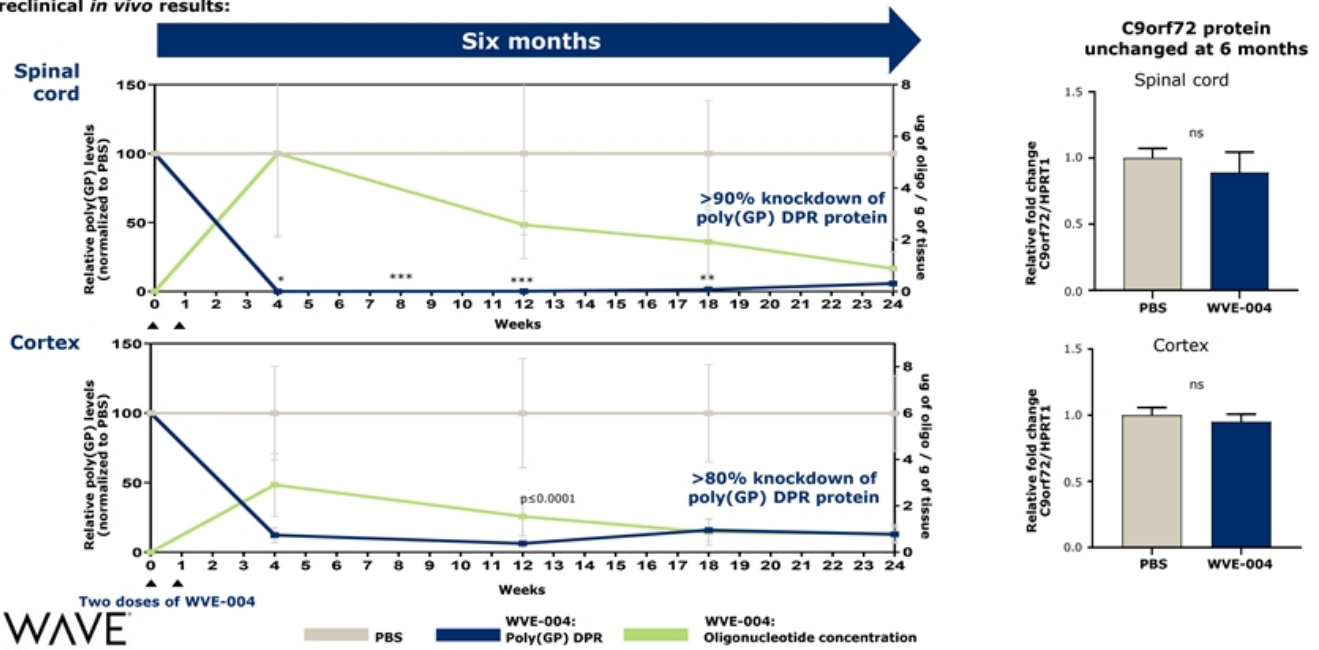
**Variant-selective** oligonucleotide, lowering V1 & V3 in preclinical studies<sup>1</sup>

**Preserves** *C9orf72* protein expression; does not exacerbate potential loss-of-function driver of disease

**Reduces** toxic gain-of-function drivers of disease (RNA foci, DPRs)

# Preclinical studies with WVE-004 demonstrated durable reduction of poly(GP) in spinal cord and cortex 6 months after two doses

Preclinical *in vivo* results:



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Liu et al., 2022 *Molecular Therapy Nucleic Acids* doi: 10.1016/j.omtn.2022.04.007; 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. DPR: Dipeptide repeat protein

# WVE-004 clinical data demonstrate successful translation of preclinical approach to clinic

PK/PD modeling using preclinical *in vivo* models predicted pharmacodynamically active starting dose

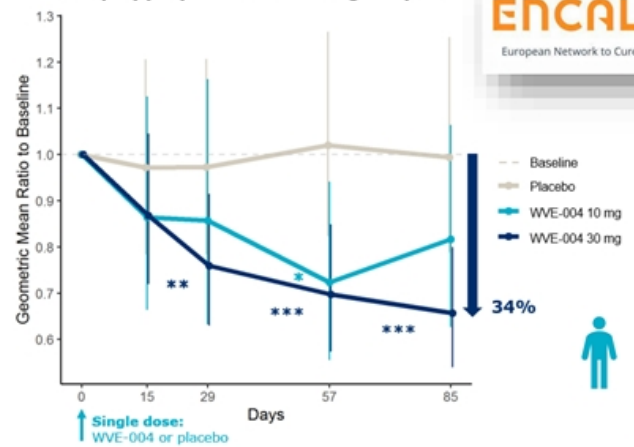


- ✓ Poly(GP) reduction in cortex and spinal cord in transgenic mice with WVE-004
- ✓ Sufficient concentrations of WVE-004 in cortex and spinal cord of NHP for target engagement



Target engagement confirmed in patients supports advancing FOCUS-C9 clinical study

CSF poly(GP) reduction through day 85

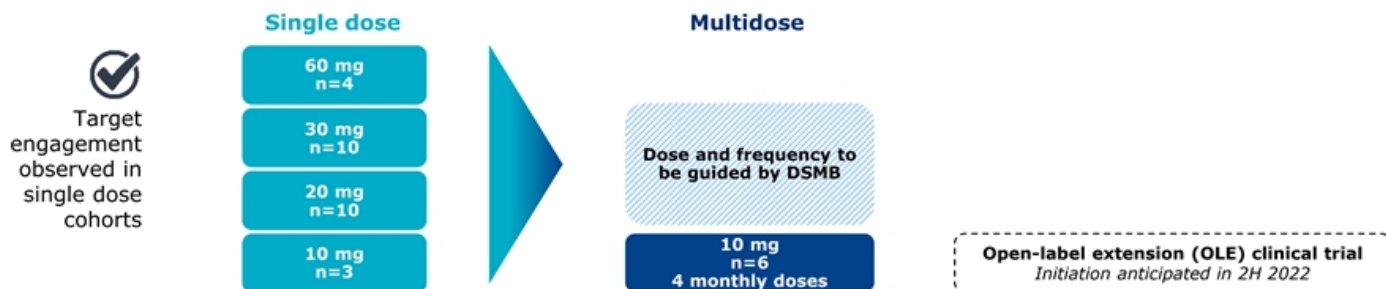


PK: pharmacokinetic PD: pharmacodynamic; Right: Mixed model for repeated measures used to estimate geometric mean ratio to baseline via least squares mean and to calculate p-values. P-values represented by asterisks are for within-dose group geometric mean ratios. \*p<0.05, \*\*p<0.01, \*\*\*p<0.001. Poly(GP) assay: Wilson et al., 2022 J Neurol Neurosurg Psychiatry doi:10.1136/jnnp-2021-328710. Data presented at ENCALS Meeting (June 1-3, 2022)



# FOCUS-C9 clinical trial underway

## FOCUS C9



Additional single and multidose clinical data for WVE-004 expected in 2H 2022

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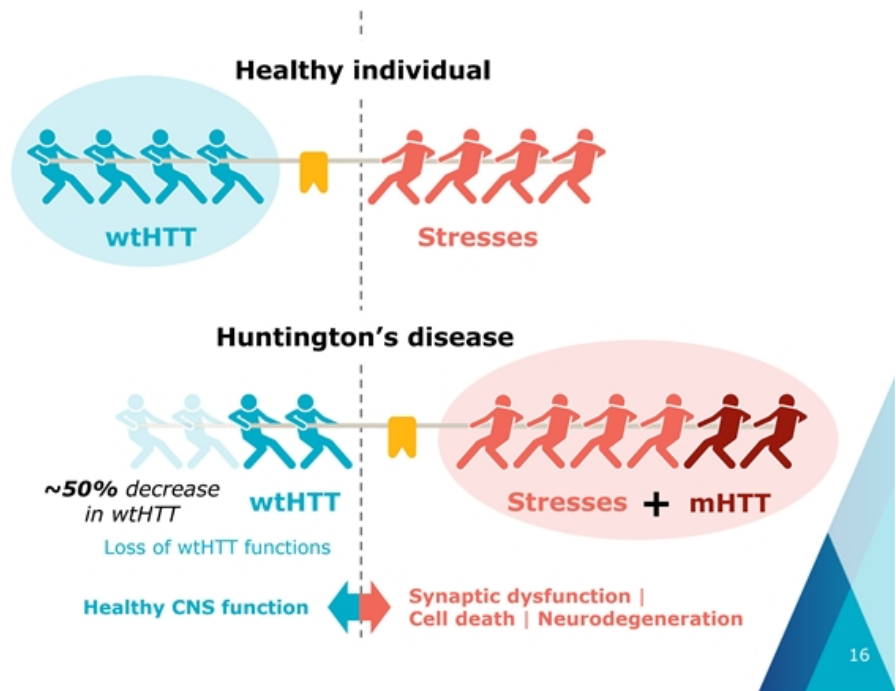
WVE-003

Huntington's Disease

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

## Huntington's disease (HD)

- Wild-type HTT (wtHTT) is critical for normal neuronal function\*
- Expanded CAG triplet repeat in HTT gene results in production of mutant huntingtin protein (mHTT)
- HD is a monogenic autosomal dominant genetic disease; fully penetrant and affects entire brain
- Fatal disease characterized by cognitive decline, psychiatric illness, and chorea
- 30,000 people with HD in the US and more than 200,000 at risk of developing HD



# WVE-003: Allele-selective oligonucleotide designed to lower mHTT while sparing wtHTT

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



Promotes neuronal survival



Supports synaptic protein transport



Regulates synaptic plasticity



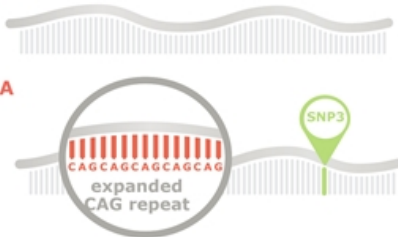
Supports cilia and CSF circulation

Only wtHTT-sparing oligonucleotide in clinical development

Contains Wave's novel PN chemistry

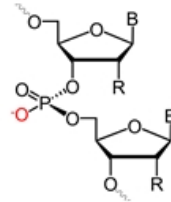
wtHTT RNA

mHTT RNA



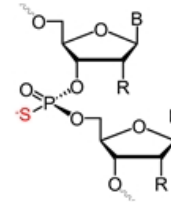
WVE-003 targets mHTT "SNP3"

PO



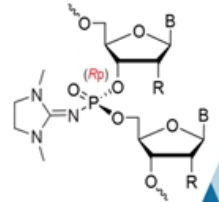
Negative

PS



Negative

PN



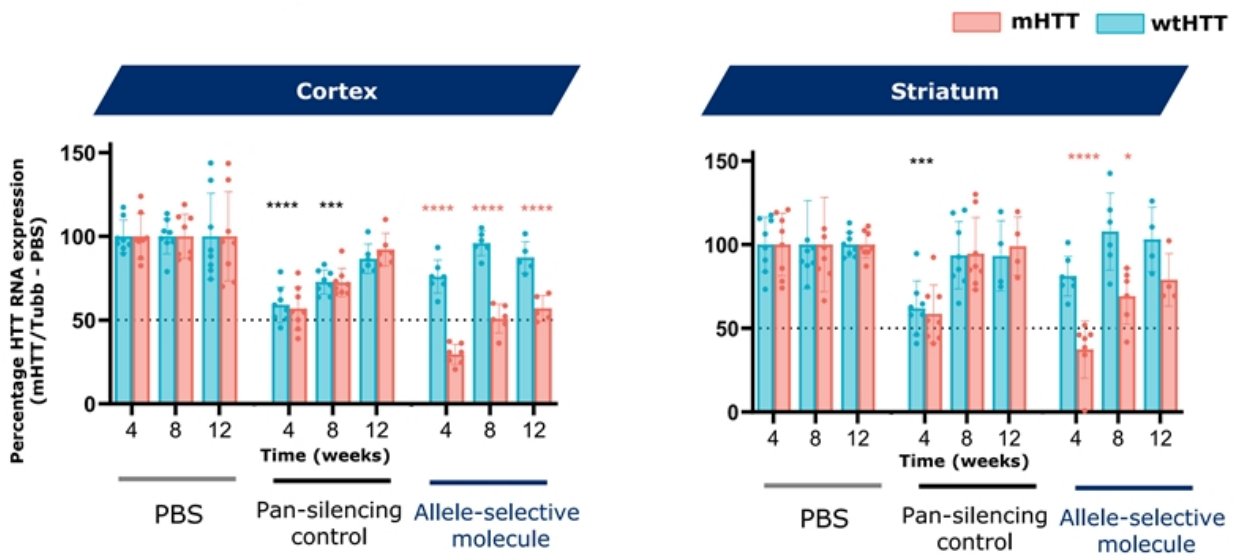
Neutral

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mHTT, mutant HTT; wtHTT, wild-type HTT; PO, phosphodiester; PS, phosphorothioate; PN, phosphoryl guanidine; wtHTT literature 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-Djajk 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

# Allele-selective molecule decreases mHTT, spares wtHTT; Pan-silencer uniformly decreases both

Allele-selective activity in CNS of Hu97/18 mice

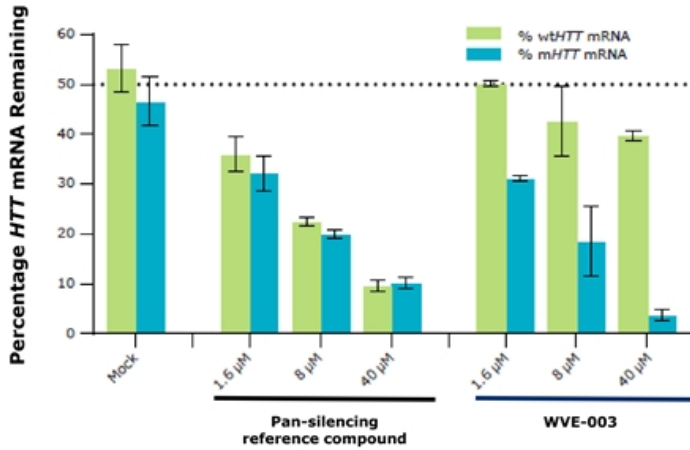


Hu97/18 mouse

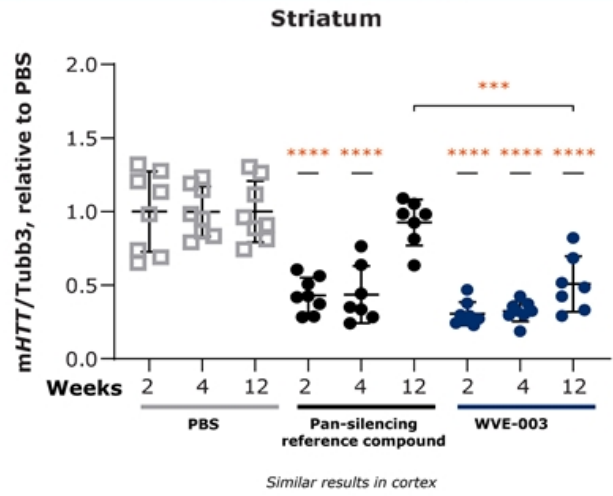
Hu97/18 mice administered 3x100  $\mu$ g intracerebroventricular doses PBS or oligonucleotide. Relative mHTT RNA in cortex (left) striatum (middle) or hippocampus (right) at 4, 8 and 12-weeks post-dosing. Data are mean  $\pm$  SD, n=8. Stats: ns non-significant, \*P<0.05, \*\*P<0.01, \*\*\*P<0.0001,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

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

Selectively reduces mHTT mRNA in HD iPSC neurons in vitro



Durable striatal mHTT knockdown for 12 weeks in BACHD mouse model



Results from NDS0036 iPSC-derived medium spiny neurons. Total *HTT* knockdown quantified by qPCR and normalized to *HPRT1*. Oligonucleotide or PBS [100 μg ICV injections through cannula on days 1, 3, 5] delivered to BACHD transgenic. Mean ± SD (n=8, \*P<0.0332, \*\*\*P<0.0002, \*\*\*\*P<0.0001 versus PBS unless otherwise noted). *HPRT1*, hypoxanthine-guanine phosphoribosyl transferase; iPSC, induced pluripotent stem cell; ICV, intracerebroventricular; PBS, phosphate-buffered saline

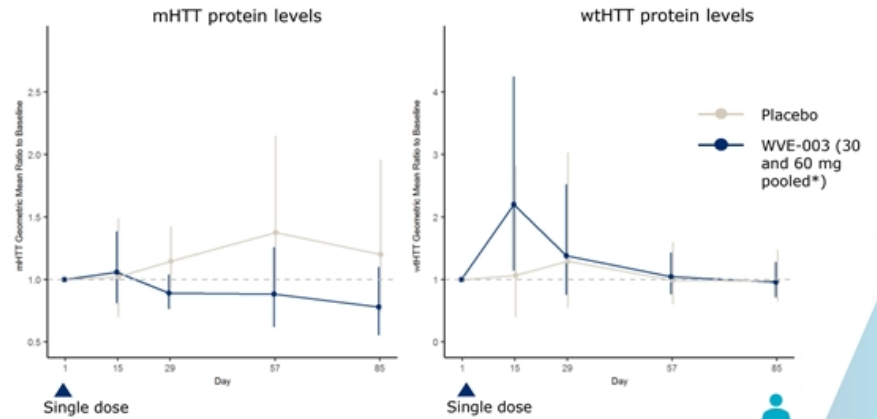
# Initial results indicating allele-selective target engagement with WVE-003 suggests translation of preclinical data

PK/PD modeling using preclinical *in vivo* models predicted pharmacodynamically active starting dose



- ✓ Demonstrated allele selectivity for mHTT in Hu97/18 mice
- ✓ mHTT reduction in cortex and striatum in transgenic mice with WVE-003
- ✓ Achieved sufficient concentrations of WVE-003 in NHP brain tissues for target engagement

## Reductions in mean CSF mHTT and preservation of wtHTT observed in pooled analysis of single dose cohorts in SELECT-HD clinical study



mHTT: mutant huntingtin protein

wtHTT: wild-type huntingtin protein

\*Pooled considering no apparent dose response between 2 cohorts



# Expanding single dose cohorts to optimize dose level based on initial results



**Additional single-dose biomarker and safety data are expected in 1H 2023**



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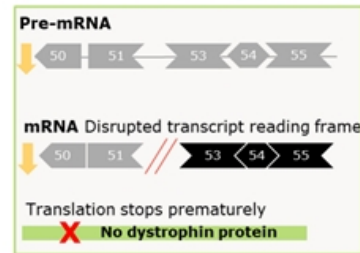
WVE-N531  
Duchenne muscular dystrophy

# Duchenne muscular dystrophy

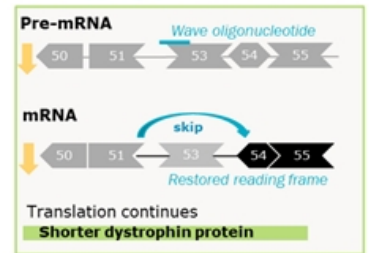
## Duchenne muscular dystrophy

- Genetic mutation in dystrophin gene prevents the production of dystrophin protein, a critical component of healthy muscle function.
- Dystrophin protein established by FDA as surrogate endpoint reasonably likely to predict benefit in patients<sup>1</sup> for accelerated approval in DMD
  - Confirmatory studies ongoing
  - Increasing amount of functional dystrophin expression over minimal amount shown with approved therapies is expected to result in greater benefit for patients
- Impacts 1 in every 5,000 newborn boys each year; 20,000 new cases annually worldwide.

### Dysfunctional splicing (Disease)

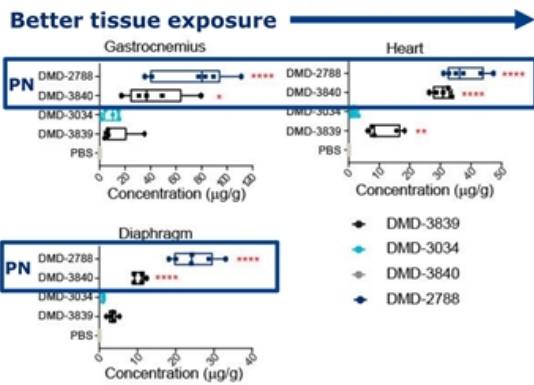


### Exon skipping (Partial Restoration)

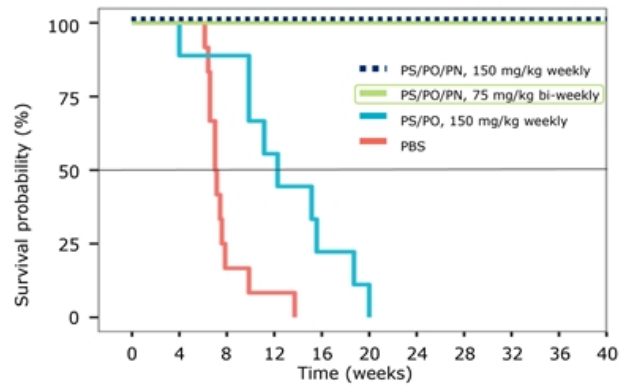


# PN chemistry improved muscle exposure and survival in preclinical mouse models

PN boosted muscle concentrations after single dose, which correlated with exon-skipping activity

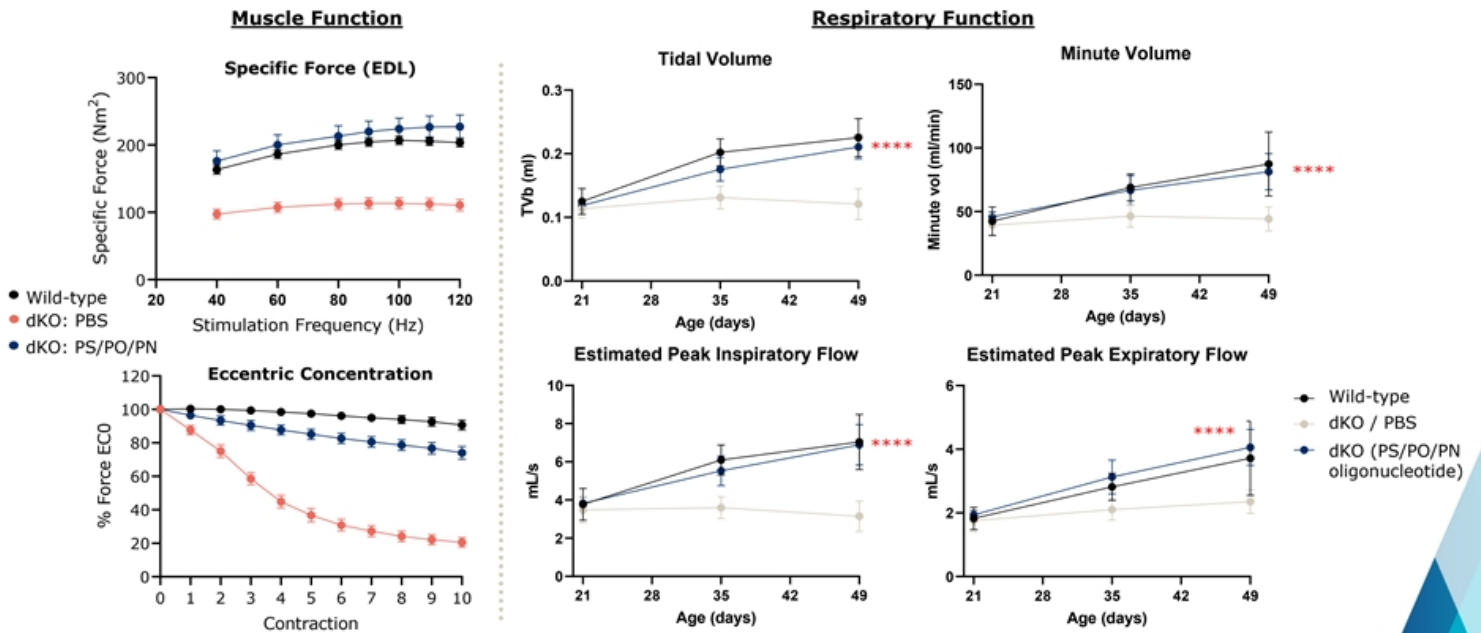


Treatment with PN-modified molecules led to 100% survival of dKO mice at time of study termination



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

# PS/PO/PN splicing compound restores muscle and respiratory function to wild-type levels in dKO mice

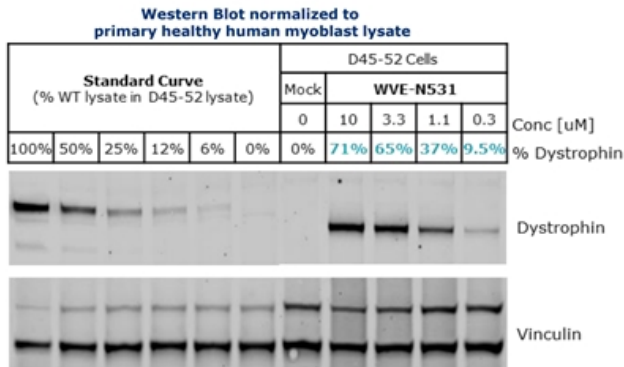


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Left: *Mdx/utr-/-* mice received weekly subQ 150 mg/kg dose of PS/PO/PN stereopure oligonucleotide (postnatal day 10). Age-matched *mdx/utr-/-* littermates treated with PBS, *wild-type C57BL10* mice not treated. Wild-type, dKO PBS mice: 6 wks old; dKO PS/PO/PN: 28 – 41 wks old; Electrophysiology performed at Oxford University based on Goyenvalle et al., 2010 Mol Therapy; Right: Kandasamy et al., 2022; doi: 10.1093/nar/gkac018

# WVE-N531: Dystrophin restoration *in vitro* and enhanced muscle distribution in NHPs

## Dystrophin protein restoration of up to 71% *in vitro*



## Enhanced muscle distribution in NHPs

**Plasma and tissue concentrations of WVE-N531 (PS/PO/PN) significantly higher than suvodirsen (1st-gen PS/PO) in multiple NHP studies**

- ✓ Substantially higher muscle concentrations (including heart and diaphragm) as compared to suvodirsen
- ✓ Higher plasma C<sub>max</sub>, AUC and C<sub>trough</sub>

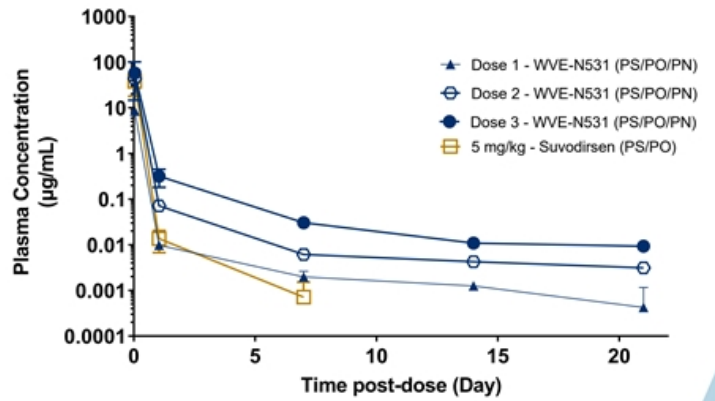
# Currently dosing at human equivalent doses in the range explored in preclinical dKO model

## dKO mouse model



- ✓ Treatment with PN-modified molecules led to 100% survival of dKO mice at time of study termination

## Plasma WVE-N531 concentrations compared to plasma suvodirsen concentrations



Dosing underway at Dose 4 of WVE-N531

# Dose escalation ongoing in clinical trial of WVE-N531

- Open-label clinical trial of boys with DMD amenable to exon 53 skipping
- Dose level and dosing frequency guided by tolerability and plasma PK

## *Initial cohort*

- Ascending intra-patient doses of WVE-N531
- Up to 4 dose levels (administered  $\geq 4$  weeks apart) evaluated to select dose level for multidose
- Up to 3 additional doses given every-other-week at selected dose level, followed by muscle biopsy

Cohort expansion to be guided by assessment of muscle biopsies: (drug distribution in muscle and biomarkers)

## *Possible cohort expansion (up to 15 boys)*

- Additional patients enrolled and dosed every other week at selected dose level
- Up to 7 total doses to be given followed by a minimum 8-week safety monitoring period
- Powered to evaluate change in dystrophin expression

**Clinical data, including muscle biopsies, expected in 4Q 2022**

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WVE-006

Alpha-1 antitrypsin  
deficiency (AATD)



# WVE-006: Designed to correct mutant SERPINA1 transcript to address both liver and lung manifestations of AATD

**WVE-006 designed to correct Z allele mRNA to enable M-AAT protein to be produced**



SERPINA1 Z allele mRNA encodes Z-AAT protein with E342K mutation

**WVE-006**  
(GalNAc-conjugated AIMer)



Edited SERPINA1 mRNA enables wild-type M-AAT protein production

**WVE-006 ADAR editing approach to address key goals of AATD treatment:**

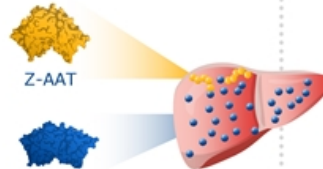
**1) Restore** circulating, functional wild-type M-AAT

**2) Reduce** Z-AAT protein aggregation in liver

**3) Retain** M-AAT physiological regulation



M-AAT reaches lungs to protect from proteases



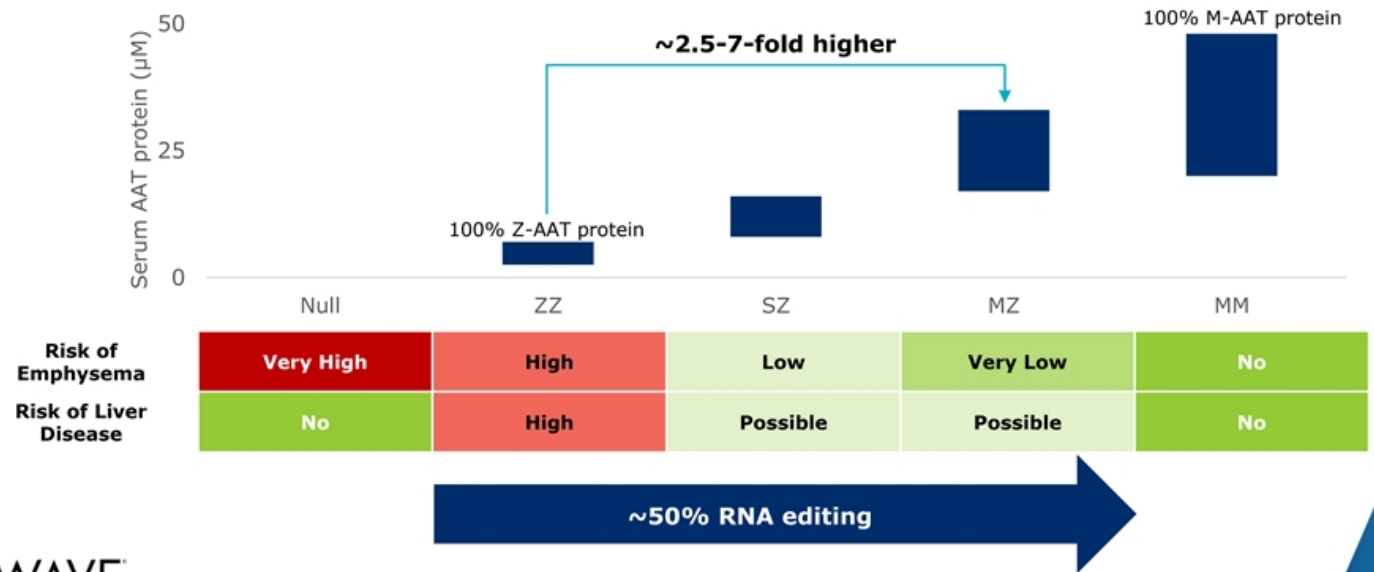
RNA correction replaces mutant Z-AAT protein with wild-type M-AAT protein



M-AAT secretion into bloodstream

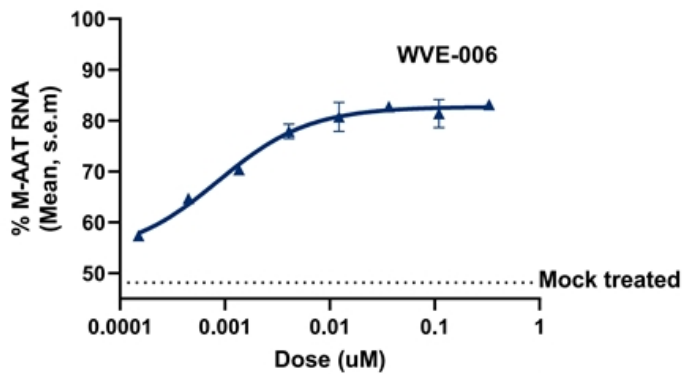
# ~50% RNA editing expected to increase PI\*ZZ patient serum AAT levels to PI\*MZ levels, with low risk of disease

Serum AAT Protein Levels and Risk of AATD by Genotype



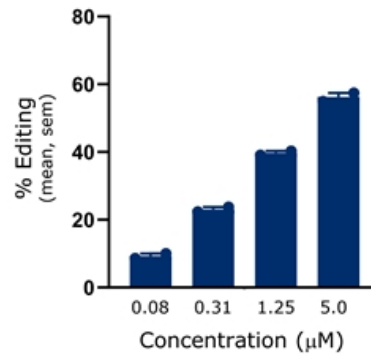
# WVE-006 supports dose-dependent RNA editing in human preclinical model systems

## Efficient SERPINA1 editing in donor-derived primary human hepatocytes with WVE-006 (MZ genotype)



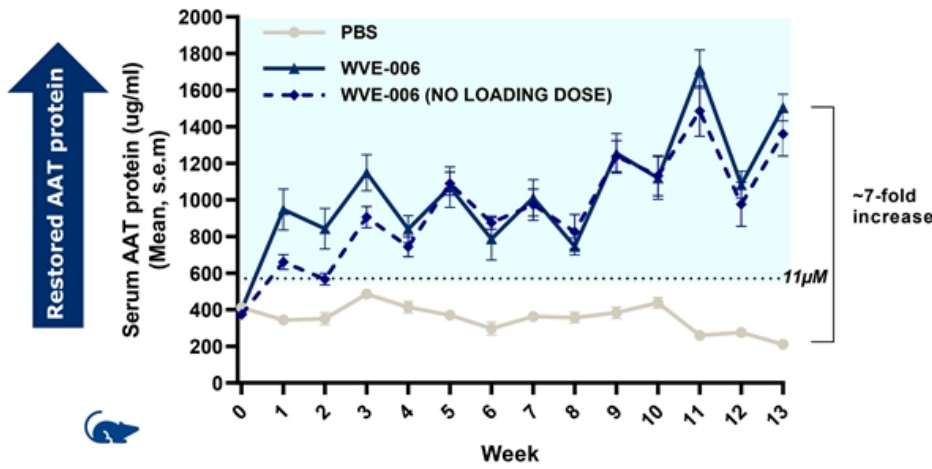
Note: Due to MZ genotype, Y-axis ranges from ~50-100%

## iPSC-derived human hepatocytes (ZZ genotype)

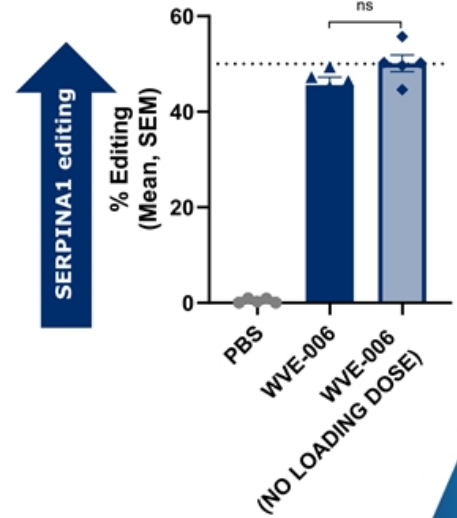


# WVE-006 results in circulating AAT protein levels 7-fold above PBS control, well above established 11 $\mu$ M threshold

**WVE-006 treatment results in serum AAT protein levels >11  $\mu$ M in AATD mouse model (NSG-PiZ mice)**



**SERPINA1 mRNA editing in liver of AATD mouse model (NSG-PiZ mice) (Week 13)**

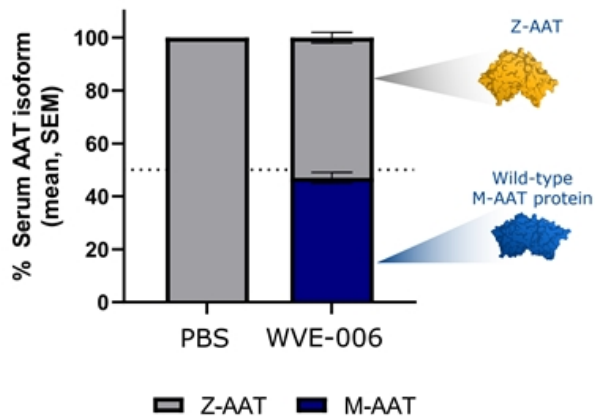


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WVE-006 administered subcutaneously (10 mg/kg bi-weekly) in 7-week old NSG-PiZ mice (n=5 per group); Loading dose: 3 x 10 mg/kg at Day 0. Left: Liver biopsies collected at week 13 (one week after last dose) and SERPINA1 editing was quantified by Sanger sequencing; Stats: One-way ANOVA with adjustment for multiple comparisons (Tukey); Right: Total serum AAT protein quantified by ELISA; Stats: Two-Way ANOVA with adjustment for multiple comparisons (Tukey)

# WVE-006 leads to restoration of confirmed, wild-type M-AAT protein in serum

**Overall percentages of serum AAT protein isoforms in NSG-PiZ mice (Week 13)**

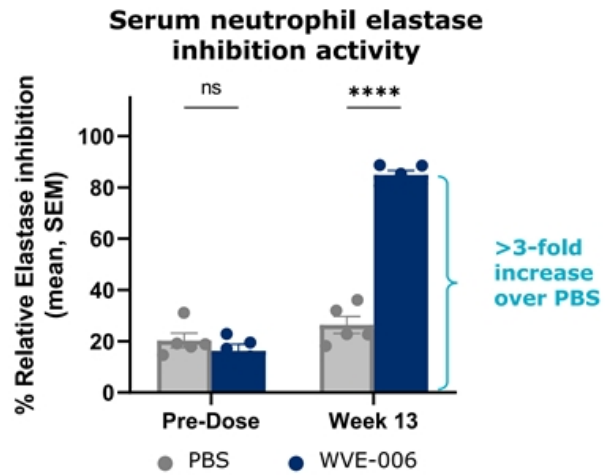


- Mass spectrometry confirms restoration of circulating healthy M-AAT protein *in vivo* after WVE-006 treatment
- Consistent with RNA editing of mutant transcript

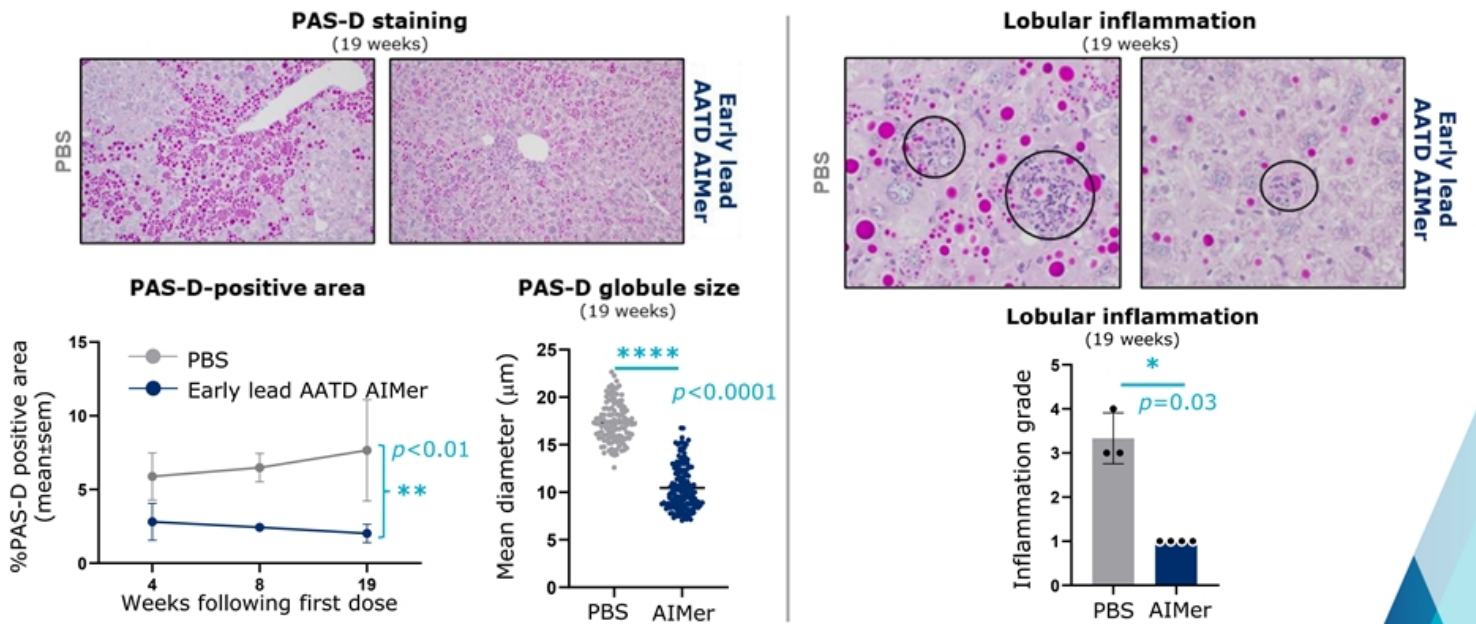
# Significant increase in neutrophil elastase inhibition activity indicates restored M-AAT protein is functional

## Increased neutrophil elastase inhibition activity demonstrates functionality of AAT protein

- Increases in neutrophil elastase, a proteolytic enzyme, may cause emphysema and damage the surrounding lung tissue
- Main function of AAT protein is to neutralize/control neutrophil elastase



# Early lead (pre-optimization) AATD AIMER reduces aggregation of Z-AAT and inflammation in mouse liver



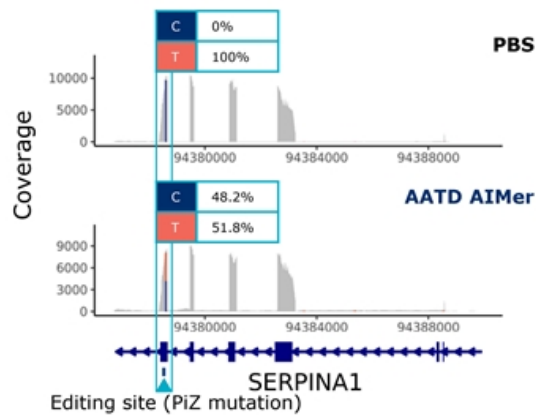
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Early lead pre-optimization AATD AIMER (SA1-5) administered in huADAR/SERPINA1 mice (8–10 wks old); lower left: 20x liver images PAS-D stained, 19 weeks; Quantification of PAS-D positive staining, Stats 2-way ANOVA; Right: Quantification lobular inflammation grade (Grade based on # of inflammatory foci in lobules: Grade 0: 0; G1 1-5; G2 6-10; G3 11-15; G4 ≥16) and mean globular diameter (40 largest globules/ animal) with HALO. Stats Wilcox rank-sum tests

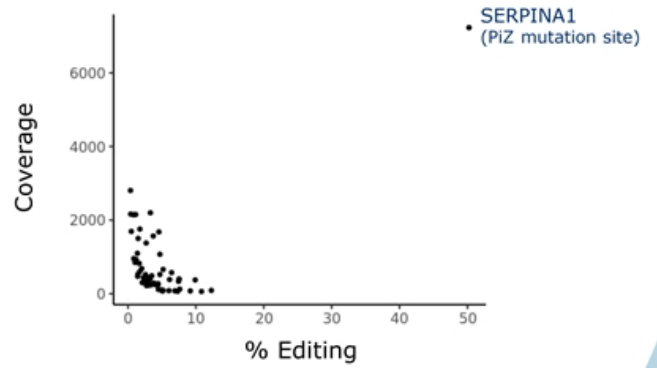
# AIMer-directed editing is highly specific in mice

No bystander editing observed on SERPINA1 transcript

**RNA editing only detected at PiZ mutation site in SERPINA1 transcript (mouse liver)**



**RNA editing across transcriptome (mouse liver)**



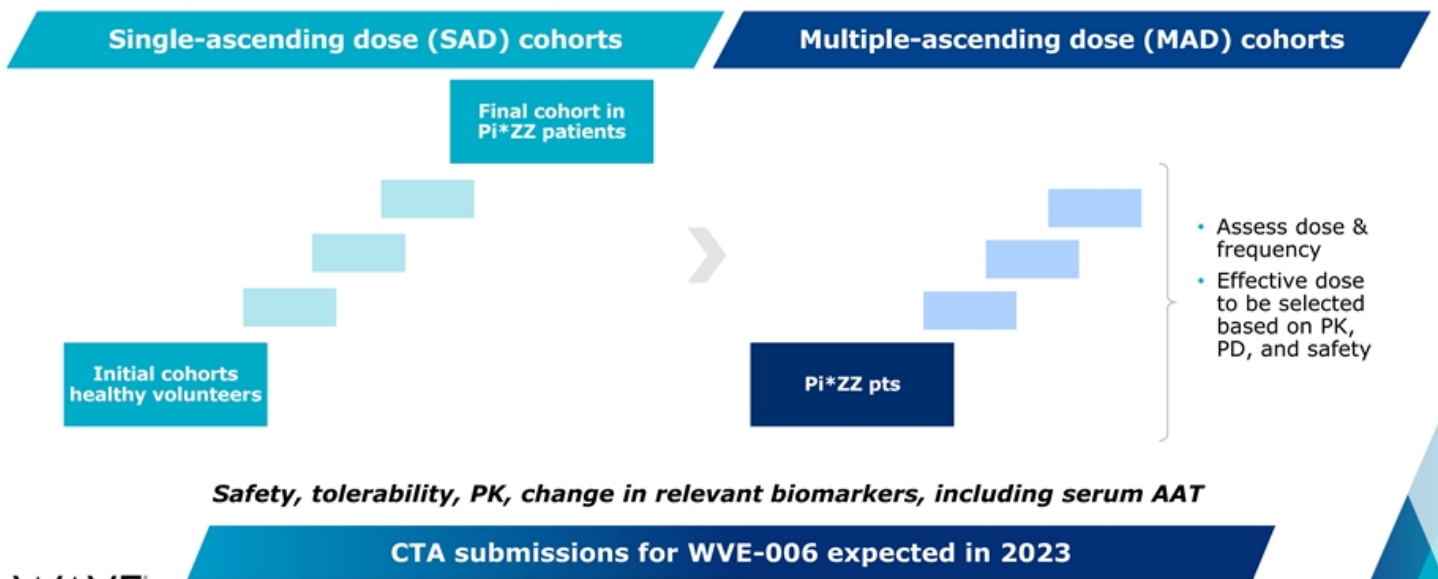


# WVE-006 is a potential first- and best-in-class candidate for AATD

- ▶ **Correct Z-allele mRNA to replace mutant Z-AAT protein with functional wild-type M-AAT protein**
  - RNA editing levels show potential to support conversion of a patient from ZZ to MZ mRNA expression
  - M-AAT protein can address lung disease
  - Reduction of Z-AAT protein enables clearance of protein aggregates in liver
- ▶ **M-AAT protein produced with WVE-006 would remain under physiological regulation**
- ▶ **mRNA editing is highly specific**
- ▶ **Potentially applicable across AATD patient subpopulations**
- ▶ **Convenience of subcutaneous administration**

# Planning for clinical development for WVE-006 underway

Phase 1/2 placebo-controlled study to establish dose and evaluate target engagement



The logo for WAVE LIFE SCIENCES is located in the top left corner. It features the word "WAVE" in a large, white, sans-serif font with a registered trademark symbol. Below it, the words "LIFE SCIENCES" are written in a smaller, white, sans-serif font. The background of the logo area is a dark blue triangle pointing downwards, which is part of a larger geometric design of overlapping triangles in various shades of blue and white.

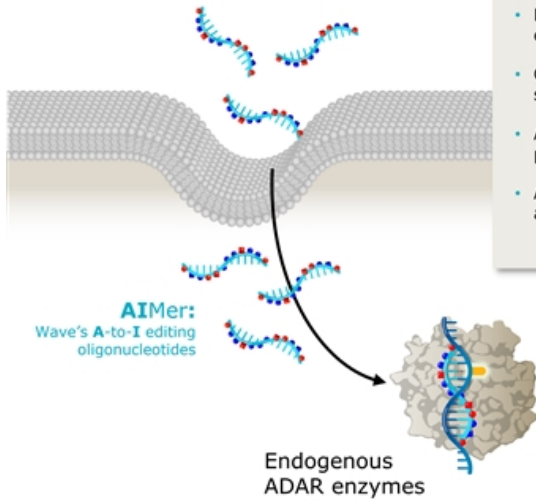
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AIMers

RNA base editing capability

# Unlocking RNA editing with PRISM platform to develop AIMers: A-to-I editing oligonucleotides

Free-uptake of chemically modified oligonucleotides  
(No need for LNPs or viral vectors)

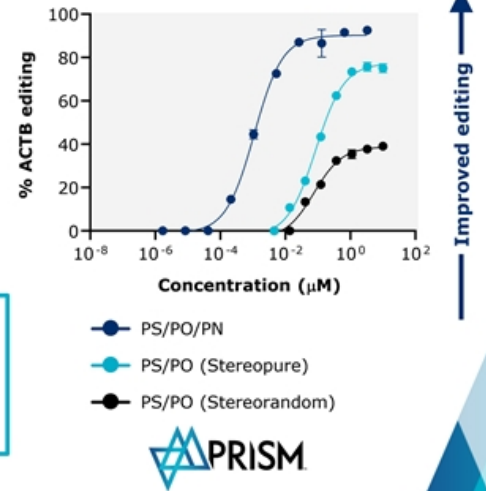


## ADAR enzymes

- First publication (1995) using oligonucleotide to edit RNA with endogenous ADAR<sup>1</sup>
- Catalyze conversion of A-to-I (G) in double-stranded RNA substrates
- A-to-I (G) edits are one of the most common post-transcriptional modifications
- ADAR1 is ubiquitously expressed across tissues, including liver and CNS

- ✓ Learnings from biological concepts
- ✓ Applied to ASO structural concepts
- ✓ Applied PRISM chemistry

## Stereochemistry and PN chemistry enhance potency and editing efficiency of GalNAc AIMers in primary human hepatocytes

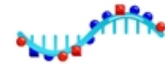
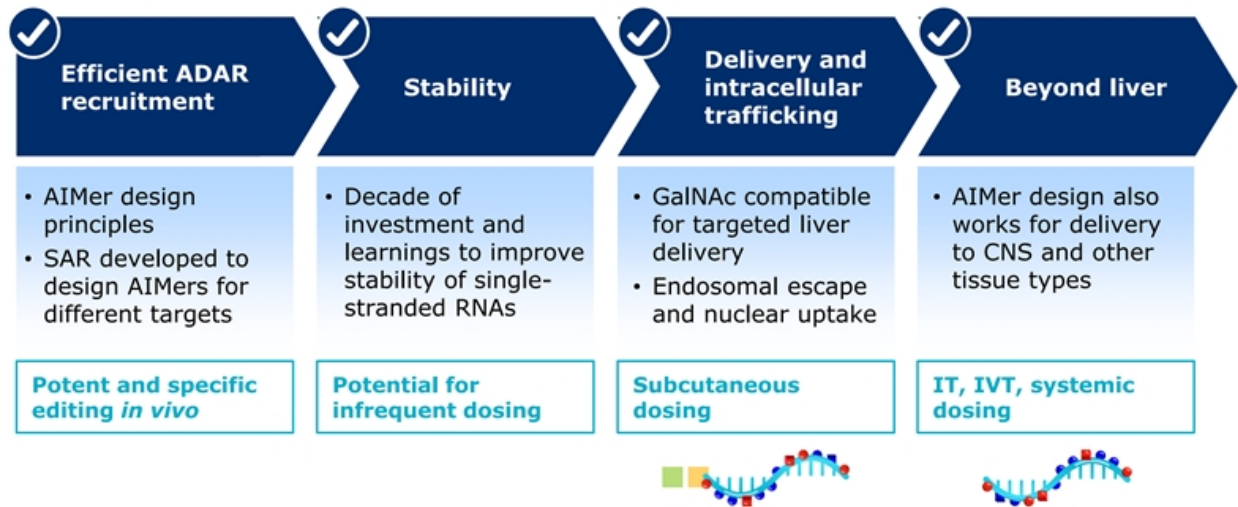


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<sup>1</sup>Woolf et al., PNAS Vol. 92, pp. 8298-8302, 1995; Right: Data from independent experiments; Total RNA was harvested, reverse transcribed to generate cDNA, and the editing target site was amplified by PCR and quantified by Sanger sequencing

# AIMers: Realizing potential of therapeutic RNA editing by harnessing endogenous ADAR

Solved for key therapeutic attributes for potential best-in-class RNA editing therapeutics



- Systematized AIMer design enables rapid advancement of new targets
- Strong and broad IP in chemical and backbone modifications, stereochemistry patterns, novel and proprietary nucleosides

# Proof-of-concept preclinical RNA editing data published in *Nature Biotechnology* (March 2022)

nature  
biotechnology

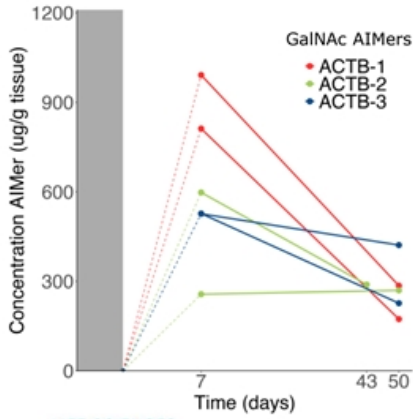
ARTICLES

<https://doi.org/10.1038/s41587-022-01225-1>

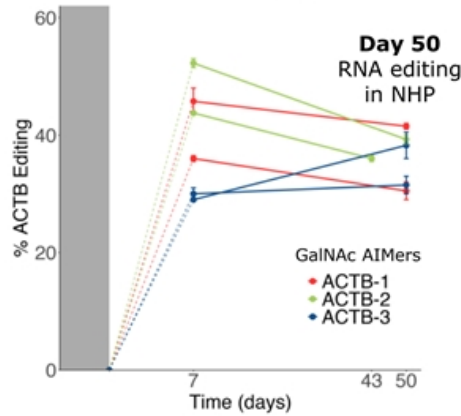
Endogenous ADAR-mediated RNA editing in non-human primates using stereopure chemically modified oligonucleotides

- Specificity *in vitro* & *in vivo* (NHPs)
- *In vitro-in vivo* translation (NHPs)
- GalNAc conjugation
- Foundational AIMer SAR

## AIMers detected in liver of NHP at Day 50 (PK)



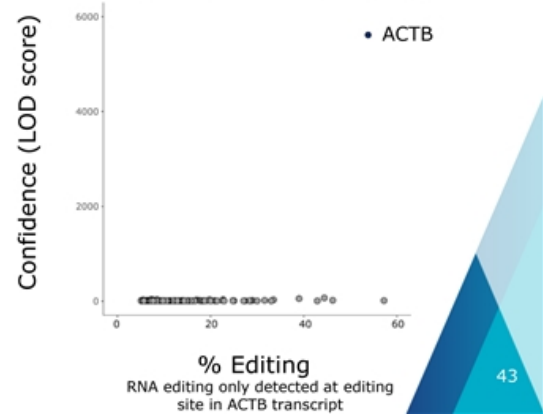
## Substantial and durable editing in NHP liver *in vivo* (PD)



LIFE SCIENCES Monian et al., 2022 published online Mar 7, 2022; doi: 10.1038.s41587-022-01225-1 SAR structure-activity relationship

## ADAR editing with ACTB AIMer is highly specific

RNA editing within full transcriptome (primary human hepatocytes)



# Systemic *in vivo* editing without delivery vehicles

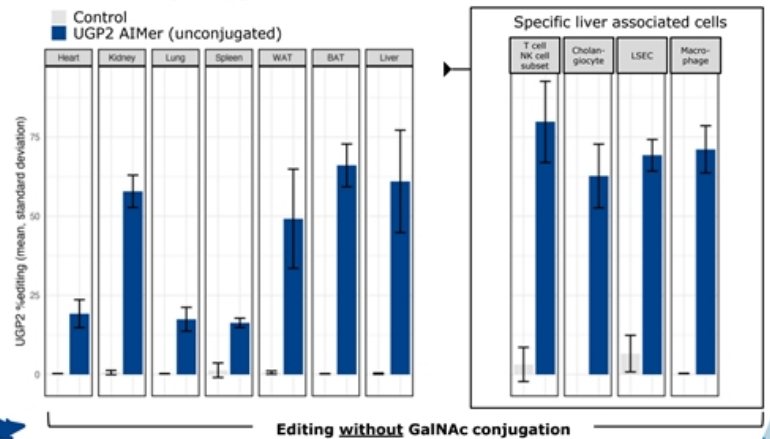


**Editing:** Potent, durable, specific A → I (G) RNA editing

**Delivery:** Efficient RNA editing in preclinical *in vivo* models:

- ✓ Targeted delivery (GalNAc)
- ✓ Systemic delivery
- ✓ Local delivery (IT, IVT, others)

## Substantial RNA editing across multiple tissues following single subcutaneous dose of UGP2 AIMer



**Potential to accelerate timelines to candidate with AIMer pipeline expansion**

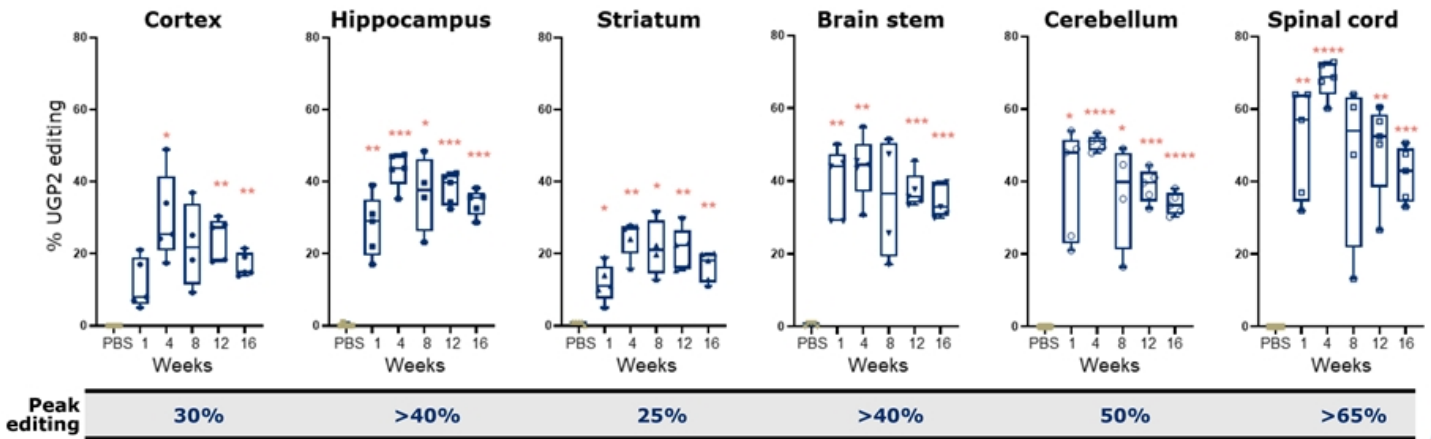


Right: Single dose of 100mg/kg unconjugated UGP2 AIMer, seven days post dose; WAT: White adipose tissue; BAT: Brown adipose tissue; CD3+: T-cells and subset of NK cells; EpCAM+(Epithelial cell adhesion molecule): mainly cholangiocytes within liver; LSEC cells (Liver Sinusoidal Endothelial Cells); M0 cells: macrophages

# Substantial *in vivo* editing without delivery vehicles in CNS tissues

Peak RNA editing observed one-month post-single dose across tissues

■ UGP2 AIMer-1  
■ PBS



**Potential CNS editing targets to benefit from learnings taken from clinical CNS silencing programs**

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Transgenic huADAR mice administered 100 µg AIMer or PBS on day 0 and evaluated for UGP2 editing across CNS tissues at 1, 4, 8, 12, and 16-weeks post dose. Percentage UGP2 editing determined by Sanger sequencing. Stats: 2-way ANOVA compared to PBS (n=5 per time point per treatment) \*P<0.05, \*\*P<0.01, \*\*\*P<0.001, \*\*\*\*P<0.0001. ICV intracerebroventricular; PBS phosphate buffered saline



# Expanding addressable disease target space using AIMers to activate pathways and upregulate expression

Correct G-to-A driver mutations with AIMers

Modulate protein interactions with AIMers

Restore or correct protein function

**WVE-006**  
(GalNAc AIMer)  
AATD



**Modulate protein-protein interaction**

**Upregulate expression**

Modify function

Post-translational modification

Alter folding or processing

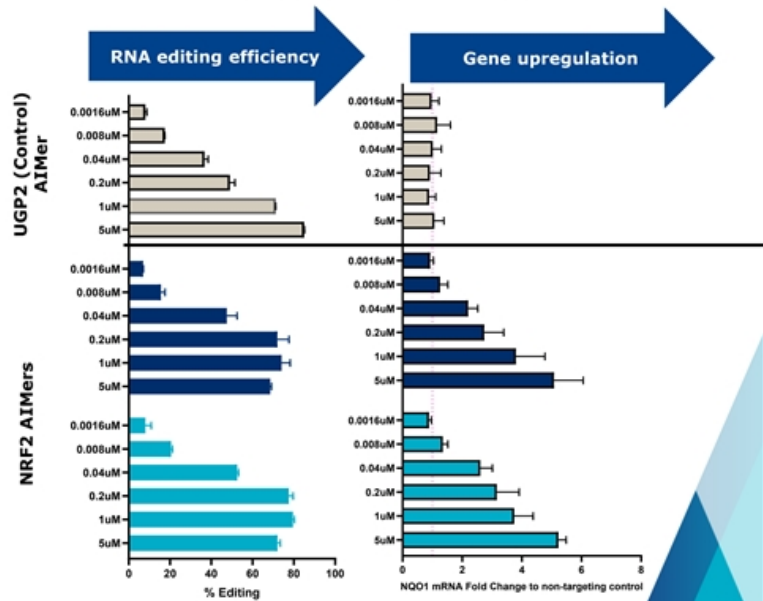
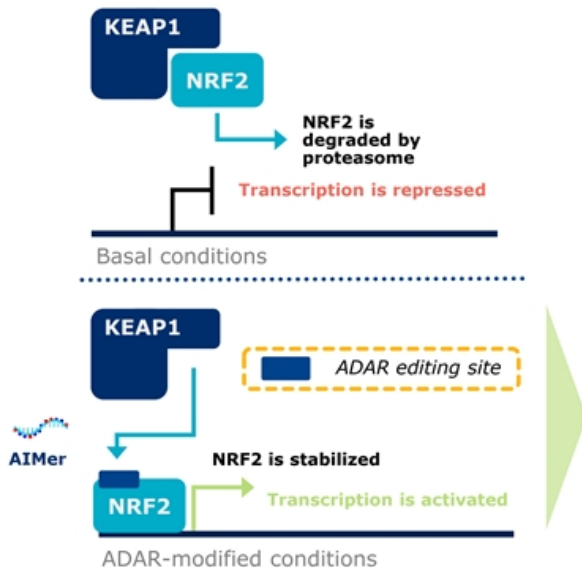
Achieved  
POC



AIMers provide dexterity, with applications beyond precise correction of genetic mutations, including upregulation of expression, modification of protein function, or alter protein stability

# Dose dependent modulation of protein/protein interactions

## Dose-dependent gene upregulation (NQO1) *in vitro* following Nrf2 editing to disrupt protein/protein interaction



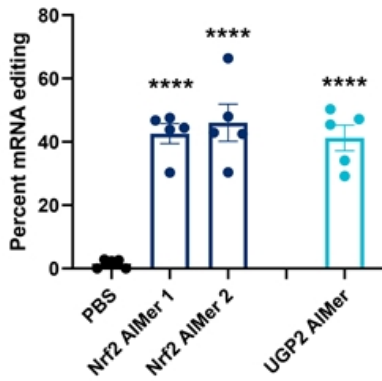
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n=2; Primary hepatocytes 48h of treatment with the indicated dose concentration of AIMers

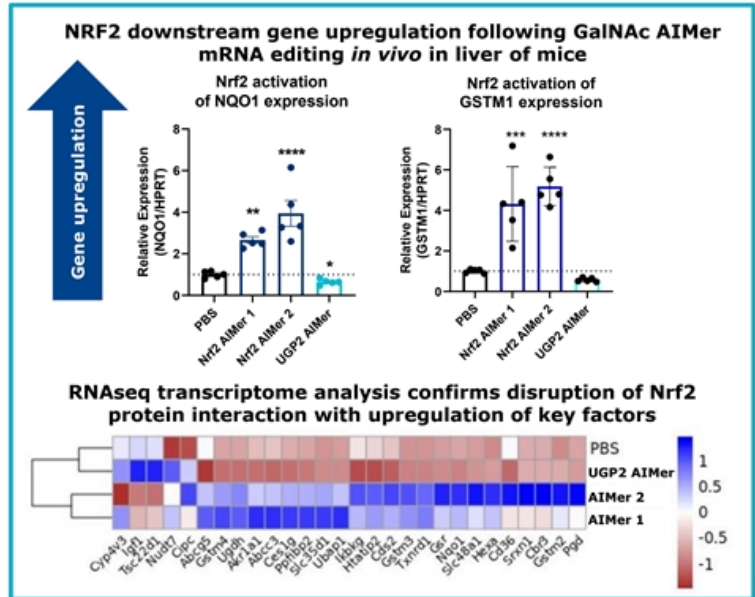
# AIMers enable activation of gene pathway *in vivo* with single edit



**Nrf2 mRNA editing *in vivo* in liver of mice with GalNac AIMers**



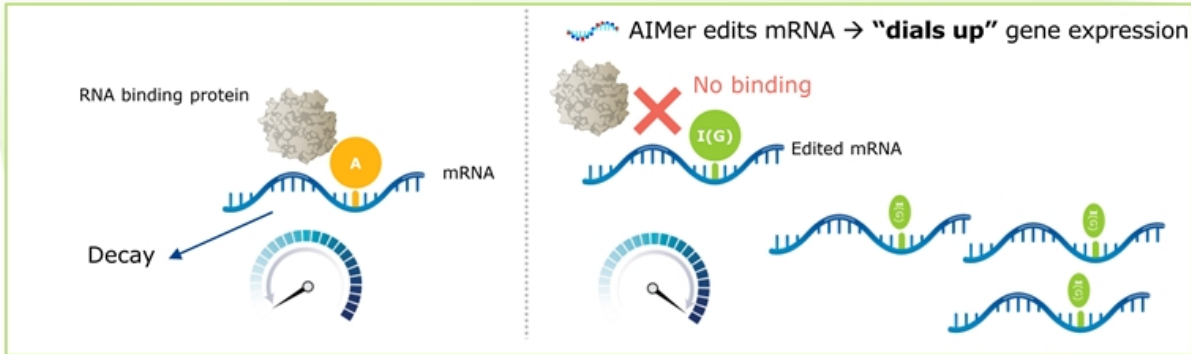
Note: Editing percentage for UGP2 control Aimer indicates editing of UGP2 mRNA



Methods: hADAR C57BL/6 mice dosed subQ (days 0, 2, 4) at 10mg/kg GalNac-conjugated AIMers. Livers harvested (day 7), analyzed for editing and NQO1 expression via Sanger sequencing or qPCR, respectively. Data analyzed via One-way ANOVA with Tukey's multiple comparison test. Asterisks indicate statistical significance to PBS-treated animals as follows: \* = p<0.05; \*\* = p<0.01; \*\*\* = p<0.001; \*\*\*\* = p<0.0001

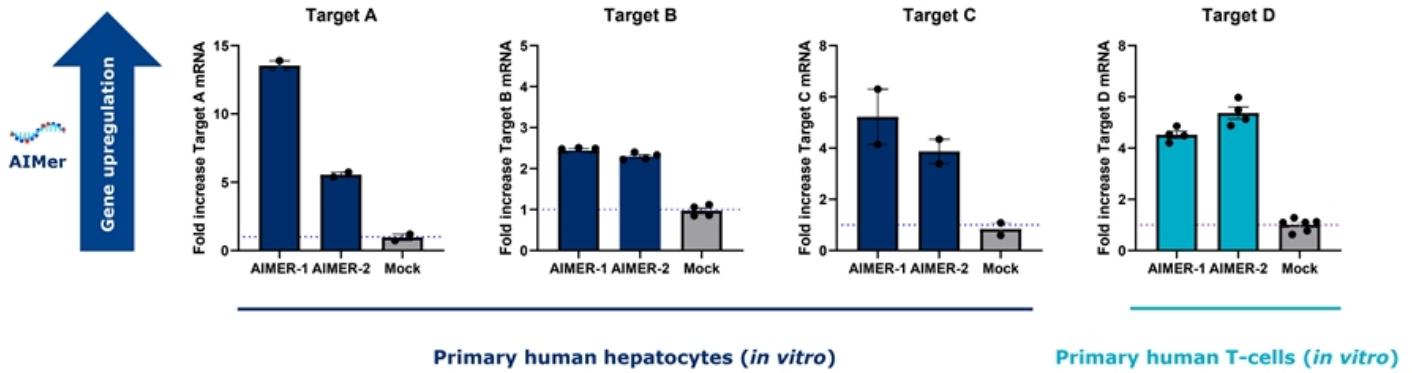
# Upregulation: AIMers can edit RNA motifs to restore or upregulate gene expression

RNA binding proteins recognize sequence motifs to regulate various mRNA properties



# AIMers can edit RNA motifs to upregulate gene expression in hepatocytes and T-cells *in vitro*

Editing RNA Motifs to regulate RNA half-life to upregulate RNA expression is possible for clinically-relevant targets, including both metabolic and immune targets

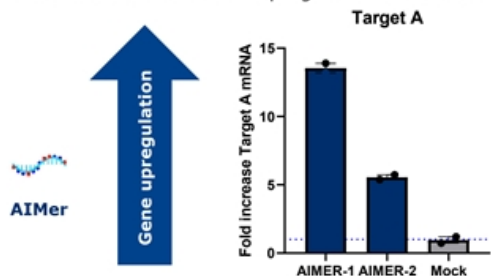


Achieving >2-fold mRNA upregulation *in vitro* across multiple different targets with AIMer editing

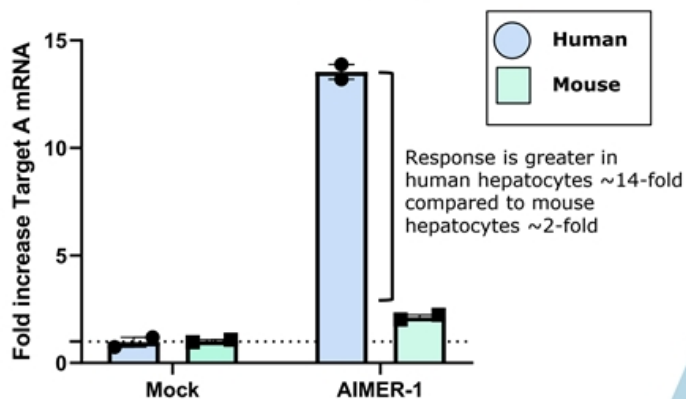
# Proof-of-concept: Considerations to translate Target A upregulation results *in vivo*

## Target A (undisclosed liver target)

- High unmet need with potential for multiple large indications
- Preserves endogenous protein function
- Serum protein with biomarkers of pathway activation
- Potential benefit 3-fold+ upregulation in mouse models



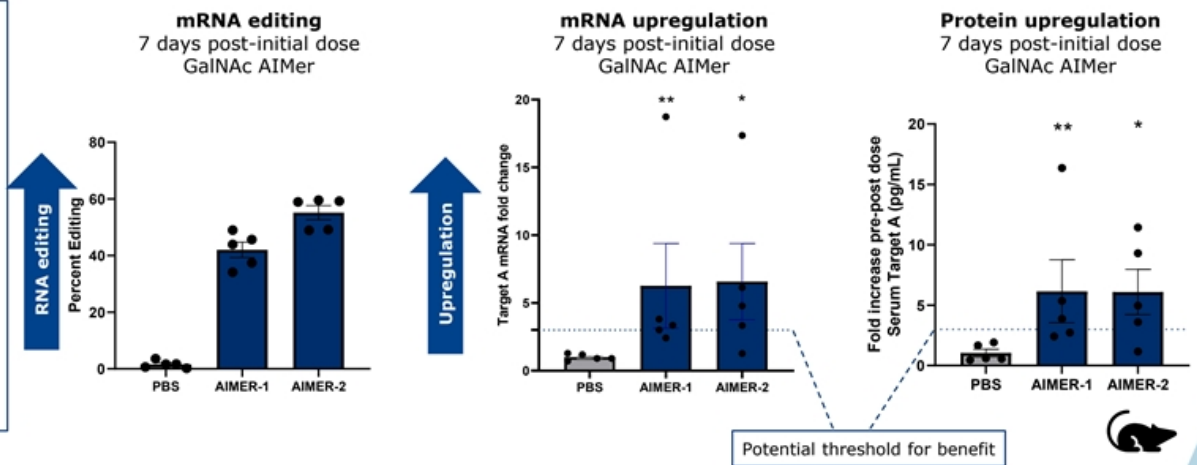
## Mouse model may underpredict potential translation of Target A upregulation



# AIMers upregulate mRNA and downstream serum protein *in vivo* above anticipated threshold

## Target A (undisclosed liver target)

- High unmet need with potential for multiple large indications
- Preserves endogenous protein function
- Serum protein with biomarkers of pathway activation
- Potential benefit 3-fold+ upregulation in mouse



- ✓ *In vitro* to *in vivo* translation of mouse Target A mRNA upregulation
- ✓ *In vivo* mRNA upregulation corresponds to an upregulation of Target A protein in serum at Day 7 demonstrating proof-of-concept



# RNA editing of nonsense mutation found in MECP2 (Rett Syndrome) restores functional protein

Normal: ... CGA... wild type protein  
 Rett Syndrome: ... TGA... premature stop codon  
 ADAR editing: ... TGG... restored protein

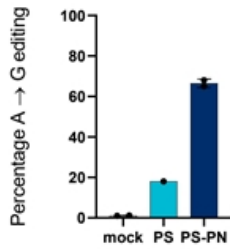
Variant base  
 ADAR editing site

Nonsense mutations found in Rett Syndrome can occur in multiple locations on RNA transcript:

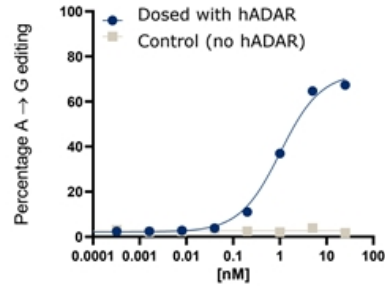


**in vitro ADAR editing of over 60% targeting MECP2 disease transcript**

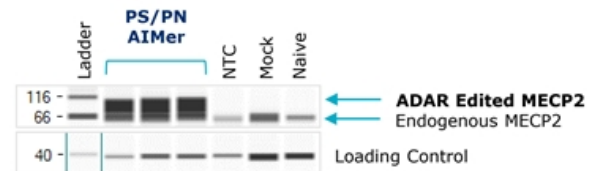
PN chemistry improved editing efficiency *in vitro*



Dose-dependent RNA editing of MECP2 mutation with PS/PN AIMer



**Full length MECP2 protein is expressed following ADAR editing**



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293T cells transfected with both nonsense mutation on MECP2 (GFP-fusion construct) and ADAR plasmids. AIMers transfected for 48h prior to RNA extraction and sequencing. Percentage editing determined by Sanger sequencing. Left: Single dose (25nM) treatment Middle: Full dose response curve (25nM, 5-fold dilution, 48h treatment) in presence or absence of hADAR Right: Western blot for MECP2 protein. Three biological replicates, NTC AIMer, mock and naive 293T cells probed for fusion protein.



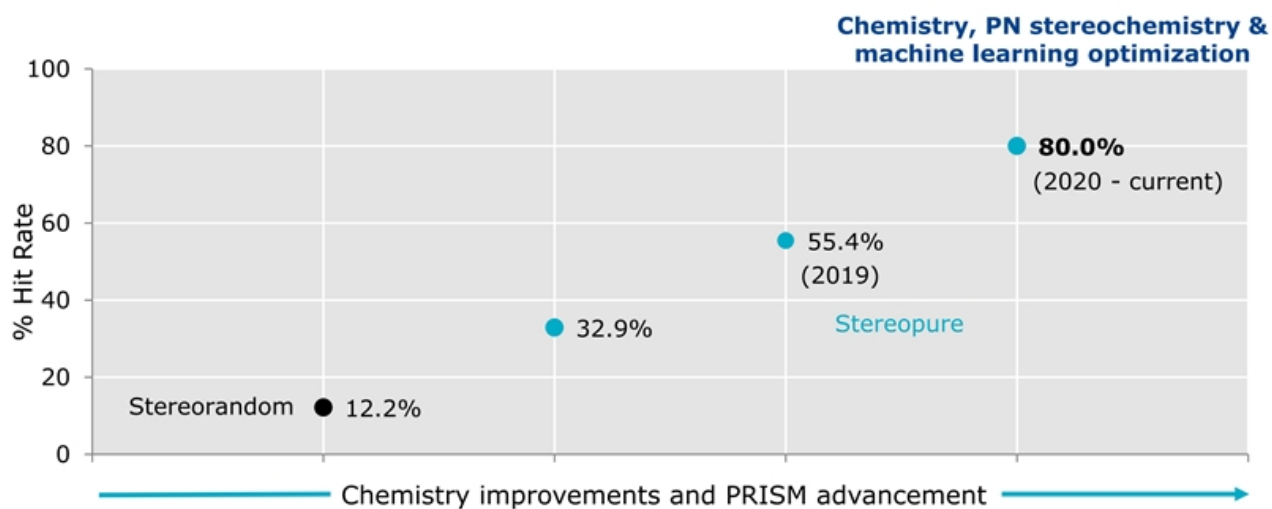
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Wave's discovery and drug  
development platform

# Improvements in PRISM primary screen hit rates accelerate drug discovery over time

Primary screen hit rates with silencing far above industry standard hit rates

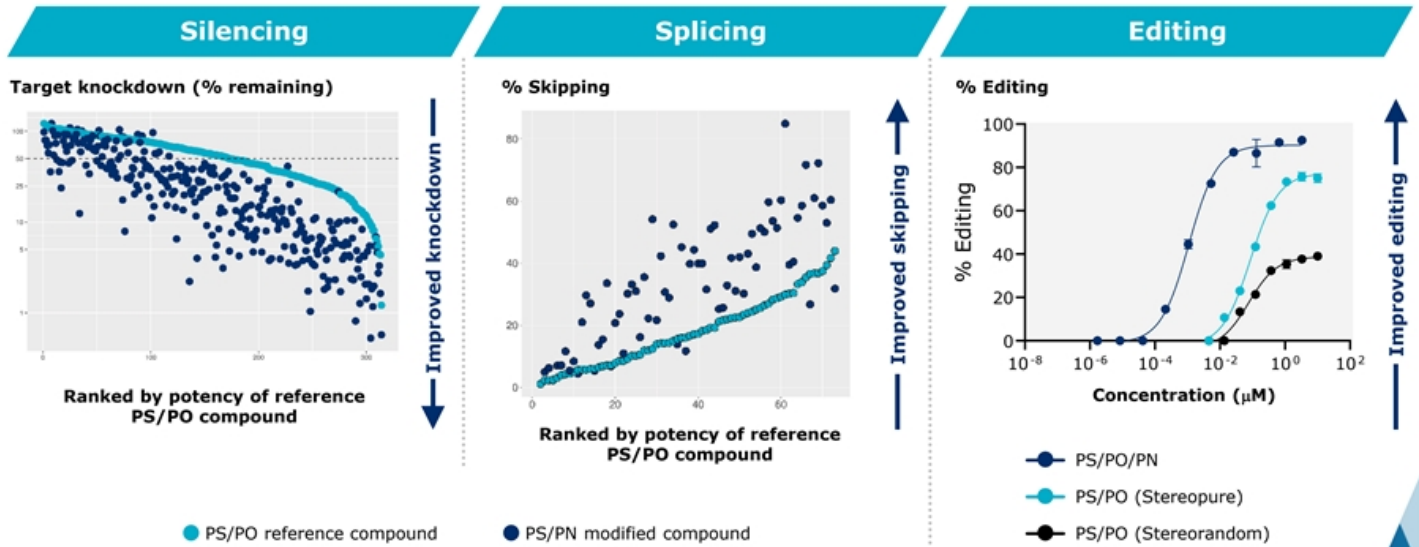


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All screens used iPSC-derived neurons; Data pipeline for improved standardization. Hit rate = % of oligonucleotides with target knockdown greater than 50%. Each screen contains >100 oligonucleotides. ML: machine learning



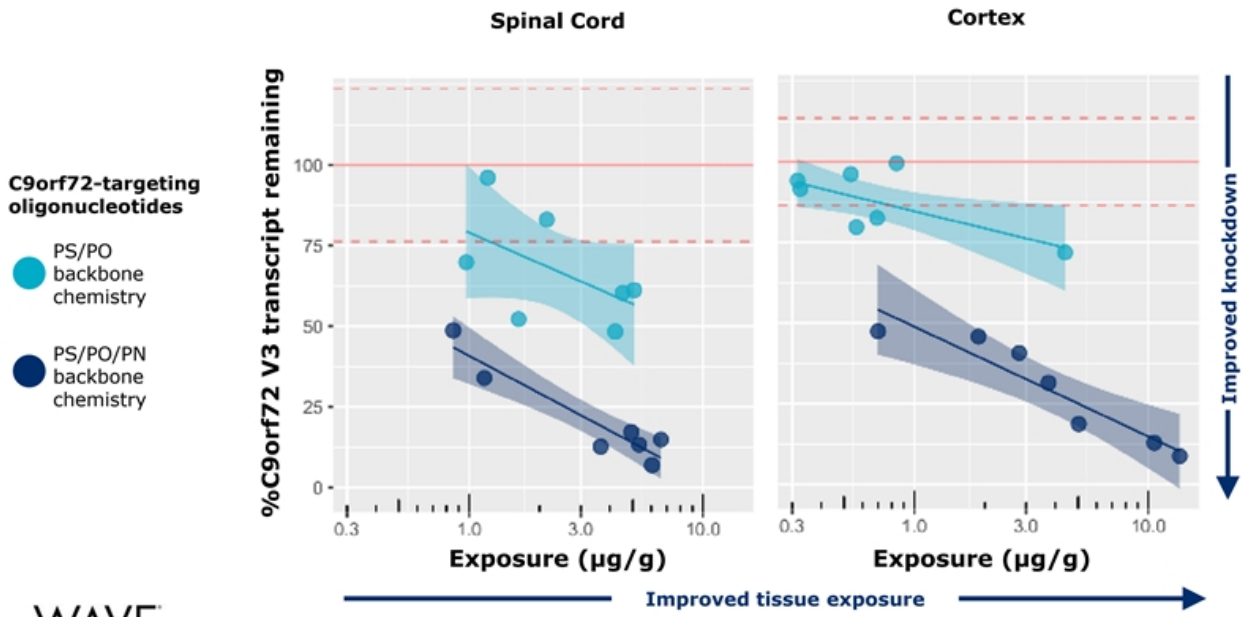
# Potency is enhanced with addition of PN modifications across modalities



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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  $\Delta\Delta\text{Ct}$  method; Middle: DMD patient-derived myoblasts treated with PS/PO or PS/PO/PN stereopure oligonucleotide under free-uptake conditions. Exon-skipping efficiency evaluated by qPCR. Right: Data from independent experiments

# Adding PN chemistry modifications to C9orf72-targeting oligonucleotides improved potency *in vivo*

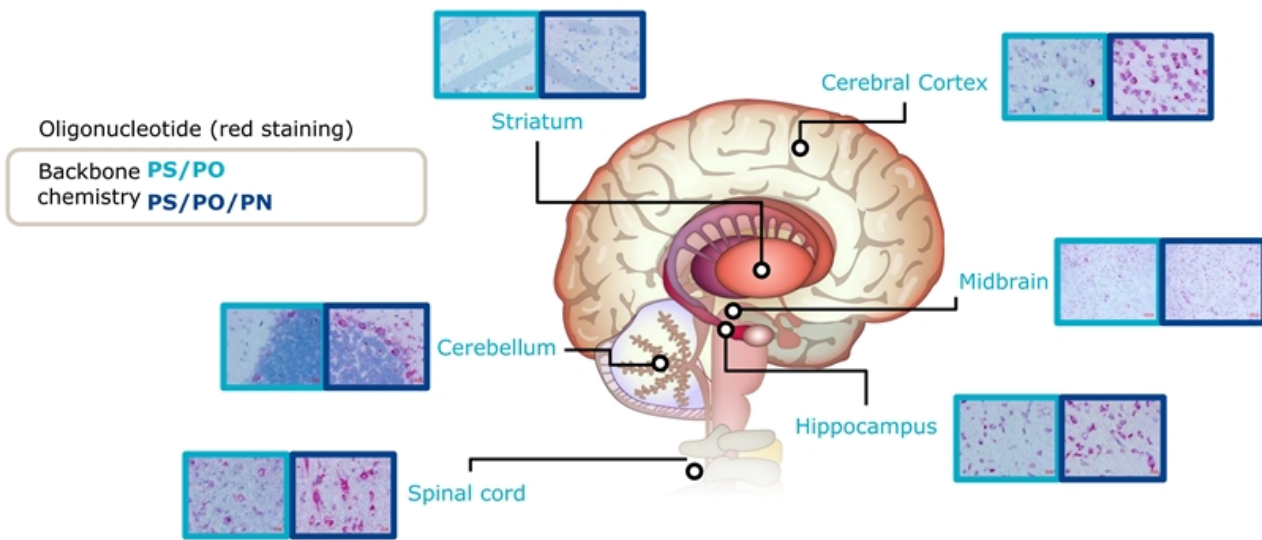


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Oligonucleotide concentrations quantified by hybridization ELISA. Graphs show robust best fit lines with 95% confidence intervals (shading) for PK-PD analysis; Liu et al. Molecular Therapy Nucleic Acids 2022; Kandasamy et al., Nucleic Acids Research, 2022, doi: 10.1093/nar/gkac037

# PN chemistry improves distribution to CNS

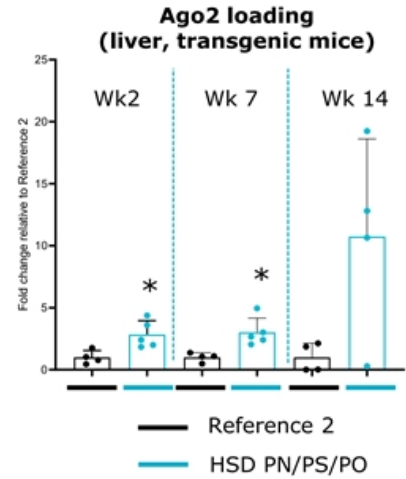
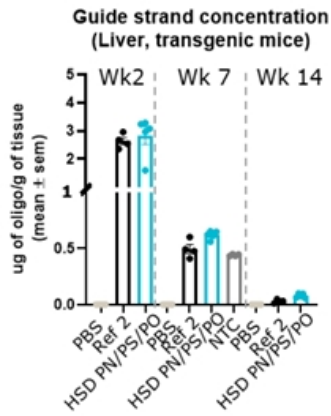
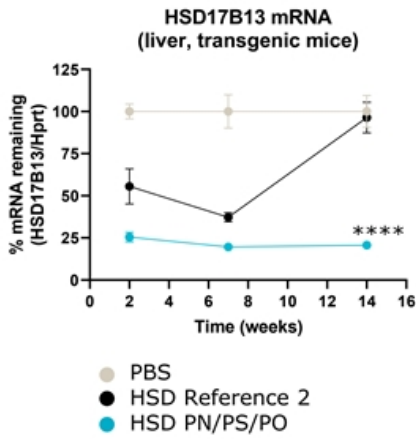
Distribution of oligonucleotides in non-human primate CNS 1-month post single IT dose



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NHPs administered 1x12 mg oligonucleotide or PBS by intrathecal injection/lumbar puncture (IT). CNS tissue evaluated 11 or 29 days after injection (n=6 per group). Oligonucleotide was visualized by ViewRNA (red), and nuclei are counterstained with hematoxylin. Images from day 29.

# PRISM PN siRNA led to unprecedented silencing >3 months after single dose



# Established internal GMP manufacturing for multiple oligonucleotide modalities

## Strong technical knowhow and operating expertise

- Experienced team led by Sridhar Vaddeboina, PhD (SVP Chemistry, Manufacturing, Controls)
- Experts in oligonucleotide synthesis (ASOs, DNAs, RNAs, siRNAs)
- Proven track record scaling complex chemistries; delivered clinical supply for six programs at Wave

## Established infrastructure

- State of the art facilities (90,000 sq ft) and expansion space
- Process and analytical development labs
- GMP oligonucleotide (API) manufacturing
- Established Quality and GMP systems (QA, supply chain, logistics, QC testing)



**Scalable to support Wave's GMP manufacturing needs, as well as potential new partners**

## Upcoming milestones



# Continued clinical validation of PRISM platform and PN stereochemistry

<b>WVE-004</b> C9orf72 ALS & FTD	<ul style="list-style-type: none"> <li>✓ Delivered clinical target engagement data with single doses</li> <li>• Additional single and multidose data in 2H 2022</li> <li>• Discussions with regulatory authorities regarding next phase of development later in 2022</li> <li>• Initiate an OLE clinical trial in 2H 2022</li> </ul>		<b>Silencing</b>	<b>CNS</b> <i>(Intrathecal)</i>
<b>WVE-003</b> HD SNP3	<ul style="list-style-type: none"> <li>✓ Delivered single-dose clinical data indicating reduction in mHTT with wtHTT preserved, appearing consistent with allele-selectivity</li> <li>• Additional single-dose biomarker and safety data in 1H 2023</li> </ul>		<b>Splicing</b>	<b>Muscle</b> <i>(IV)</i>
<b>WVE-N531</b> DMD Exon 53	<ul style="list-style-type: none"> <li>• Clinical data to enable decision making in 4Q 2022</li> </ul>		<b>ADAR editing</b>	<b>Targeted delivery liver</b> <i>(Subcutaneous)</i>
<b>WVE-006</b> AATD	<ul style="list-style-type: none"> <li>✓ Selected an AATD AIMer development candidate and initiated IND-enabling activities</li> <li>• Submit clinical trial applications in 2023</li> </ul>			

**Additional data generated in 2022 expected to further inform future opportunities and unlock value**



WVE-004 FOCUS-C9 clinical trial ([NCT04931862](https://clinicaltrials.gov/ct2/show/study/NCT04931862)); WVE-003 SELECT-HD clinical trial ([NCT05032196](https://clinicaltrials.gov/ct2/show/study/NCT05032196)); WVE-N531 open-label clinical trial ([NCT04906460](https://clinicaltrials.gov/ct2/show/study/NCT04906460))

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