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): August 17, 2022

WAVE LIFE SCIENCES LTD.
(Exact name of registrant as specified in its charter)

Singapore	**001-37627**	**00-0000000**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

7 Straits View #12-00, Marina One East Tower
Singapore **018936**
(Address of principal executive offices) **(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
$0 Par Value Ordinary Shares	**WVE**	**The Nasdaq Global Market**

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 August 17, 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:

Exhibit No.	Description
99.1	Corporate Presentation of Wave Life Sciences Ltd. dated August 17, 2022
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: August 17, 2022

Exhibit 99.1

Wave Life Sciences
Corporate Presentation

August 17, 2022

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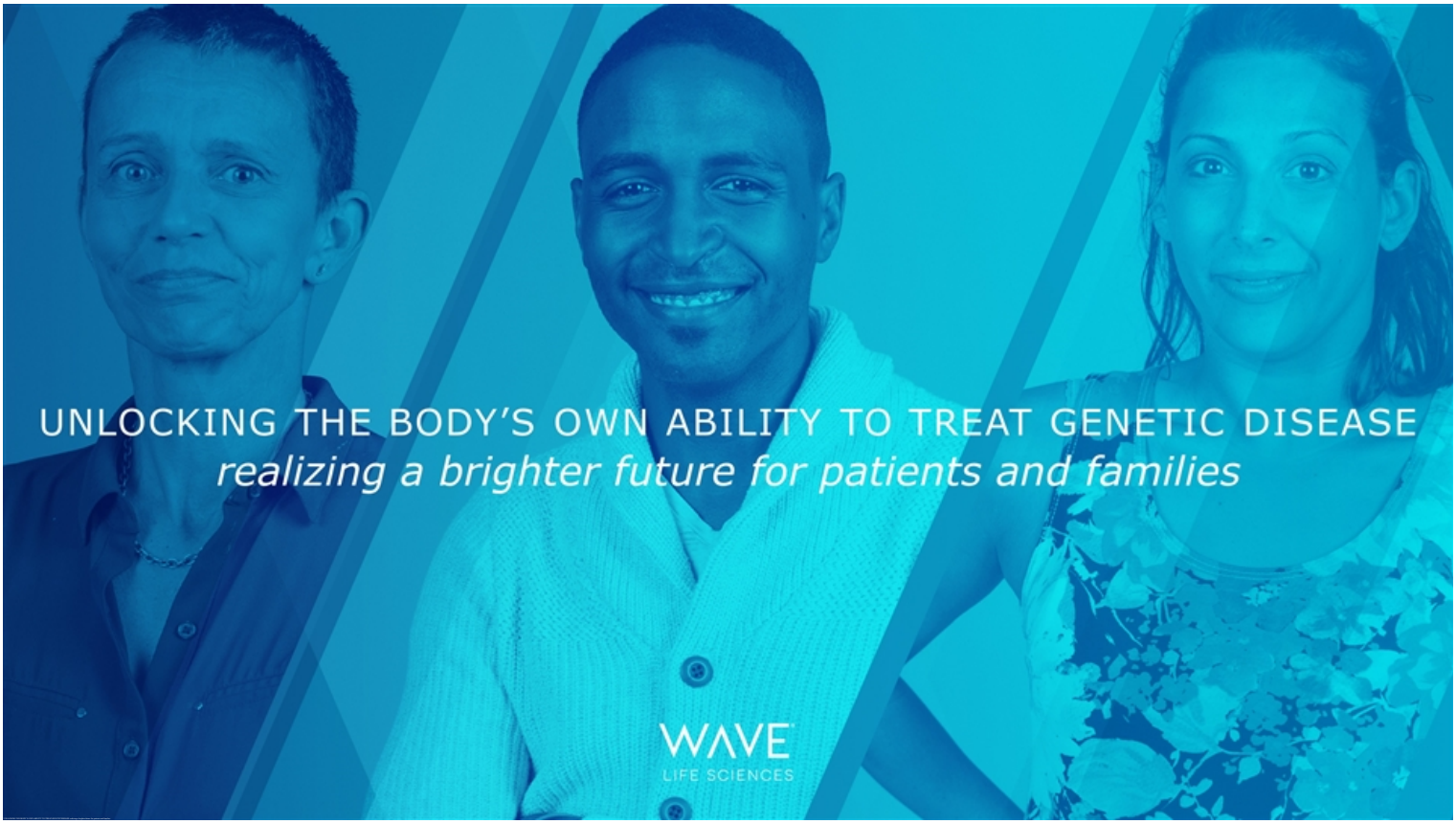
Forward-looking statements

This document contains forward-looking statements. All statements other than statements of historical facts contained in this document, including statements regarding possible or assumed future results of operations, preclinical and clinical studies, business strategies, research and development plans, collaborations and partnerships, regulatory activities and timing thereof, competitive position, potential growth opportunities, use of proceeds and the effects of competition are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause the actual results, performance or achievements of Wave Life Sciences Ltd. (the "Company") to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "expect," "plan," "aim," "anticipate," "could," "intend," "target," "project," "contemplate," "believe," "estimate," "predict," "potential" or "continue" or the negative of these terms or other similar expressions. The forward-looking statements in this presentation are only predictions. The Company has based these forward-looking statements largely on its current expectations and projections about future events and financial trends that it believes may affect the Company's business, financial condition and results of operations. These forward-looking statements speak only as of the date of this presentation and are subject to a number of risks, uncertainties and assumptions, including those listed under Risk Factors in the Company's Form 10-K and other filings with the SEC, some of which cannot be predicted or quantified and some of which are beyond the Company's control. The events and circumstances reflected in the Company's forward-looking statements may not be achieved or occur, and actual results could differ materially from those projected in the forward-looking statements. Moreover, the Company operates in a dynamic industry and economy. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risk factors and uncertainties that the Company may face. Except as required by applicable law, the Company does not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.


UNLOCKING THE BODY'S OWN ABILITY TO TREAT GENETIC DISEASE
realizing a brighter future for patients and families
WAVE
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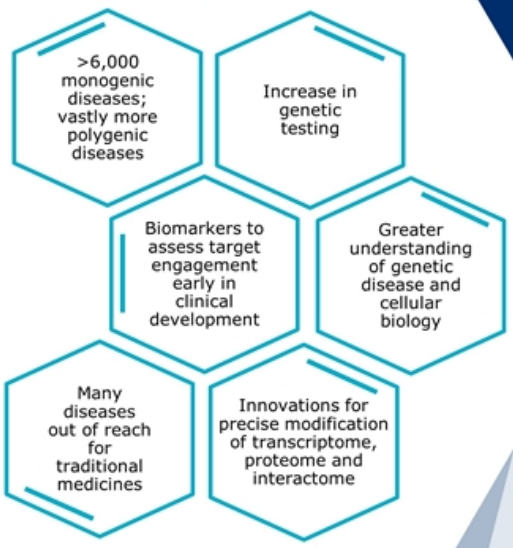
Building a leading genetic medicines company

LEVERAGING THE ONGOING GENETIC REVOLUTION



WAVE LIFE SCIENCES

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

PRISM

Innovative Platform

Stereopure oligonucleotides

Novel backbone modifications (PN chemistry)

Silencing, splicing, and editing modalities

Strong and broad IP position[1]

Diversified Pipeline

CNS: ALS, FTD, HD

Muscle: DMD

Hepatic diseases: AATD

Clinical Expertise

Multiple global clinical trials

Innovative trial designs

GMP Manufacturing

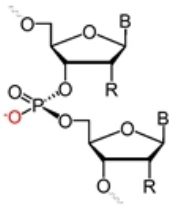
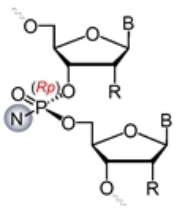
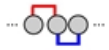
Internal manufacturing capable of producing oligonucleotides at scale

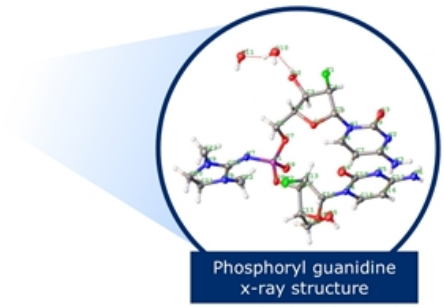
ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; HD: Huntington's disease; DMD: Duchenne muscular dystrophy; AATD: Alpha-1 antitrypsin deficiency

[1]stereopure oligonucleotides and novel backbone chemistry modifications

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

PRISM backbone linkages

PO	PS	PN
		
		
Chirality None	**Chirality** PS backbone *Rp* PS backbone *Sp*	**Chirality** PN backbone *Rp* PN backbone *Sp*
Negative charge	**Negative charge**	**Neutral charge**



example

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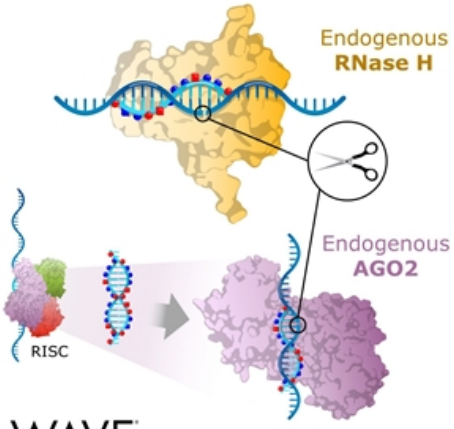
PO: phosphodiester PS: phosphorothioate

Harnessing the biological machinery in our cells to treat genetic diseases

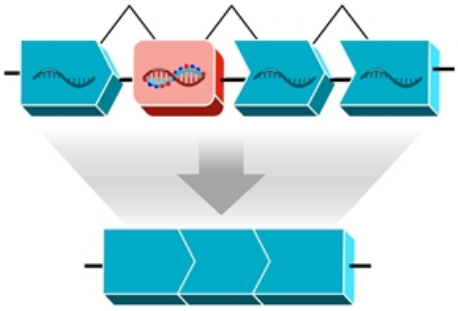
Silencing

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



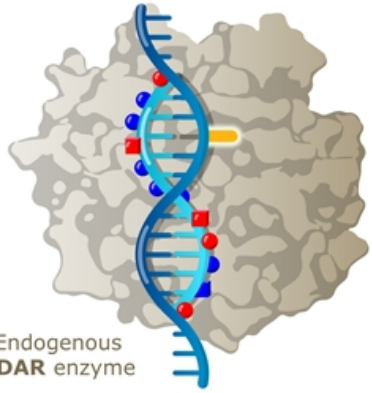
Splicing

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



RNA Base Editing

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



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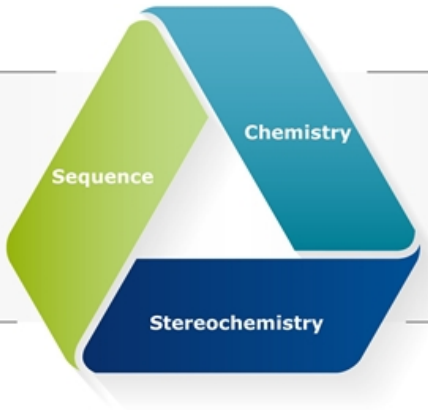
PRISM Unlocking the body's own ability to treat genetic disease

DESIGN

Unique ability to construct stereopure oligonucleotides and control three structural features to efficiently engage biological machinery



OPTIMIZE

Provides the resolution to observe this structural interplay and understand how it impacts key pharmacological properties

Built-for-Purpose Candidates to Optimally Address Disease Biology

Silencing | Splicing | RNA Editing

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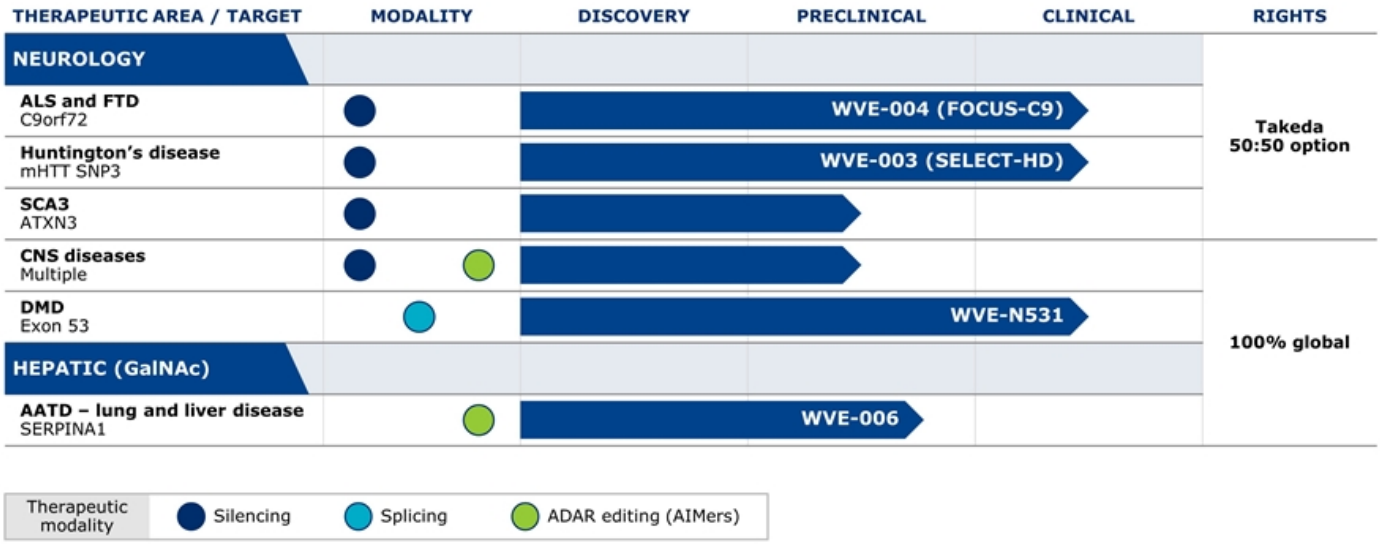
Robust portfolio of stereopure, PN-modified oligonucleotides



ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; SCA3: Spinocerebellar ataxia 3; CNS: Central nervous system; DMD: Duchenne muscular dystrophy; AATD: Alpha-1 antitrypsin deficiency

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WVE-004

Amyotrophic Lateral Sclerosis (ALS)

Frontotemporal Dementia (FTD)

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

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

Different manifestations across a clinical spectrum

Amyotrophic Lateral Sclerosis (ALS)	Frontotemporal Dementia (FTD)
• Fatal neurodegenerative disease	• Progressive neuronal degeneration in frontal / temporal cortices
• Progressive degeneration of motor neurons in brain and spinal cord	• Personality and behavioral changes, gradual impairment of language skills
• C9-specific ALS: ~2,000 patients in US	• C9-specific FTD: ~10,000 patients in US

Including patients with C9-associated ALS, FTD or both

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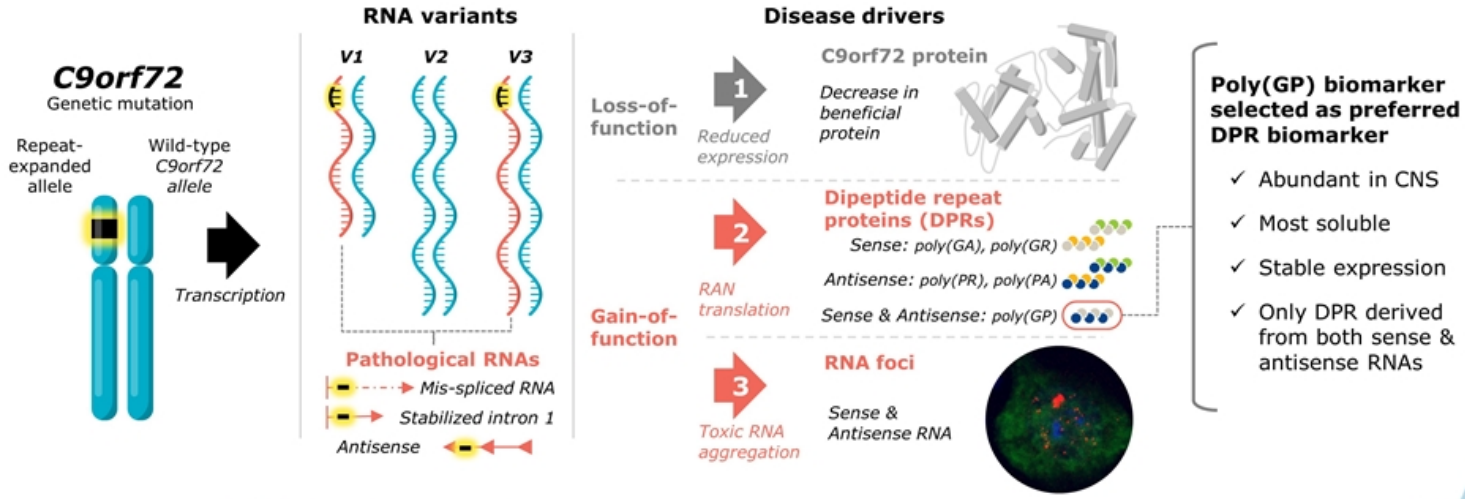
Sources: Balendra et al, EMBO Mol Med, 2017; Brown et al, NEJM, 2017, DeJesus-Hernandez et al, Neuron, 2011. Renton et al, Neuron, 2011. Zhu et al, Nature Neuroscience, May 2020, Stevens et al, Neurology 1998

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[1]

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

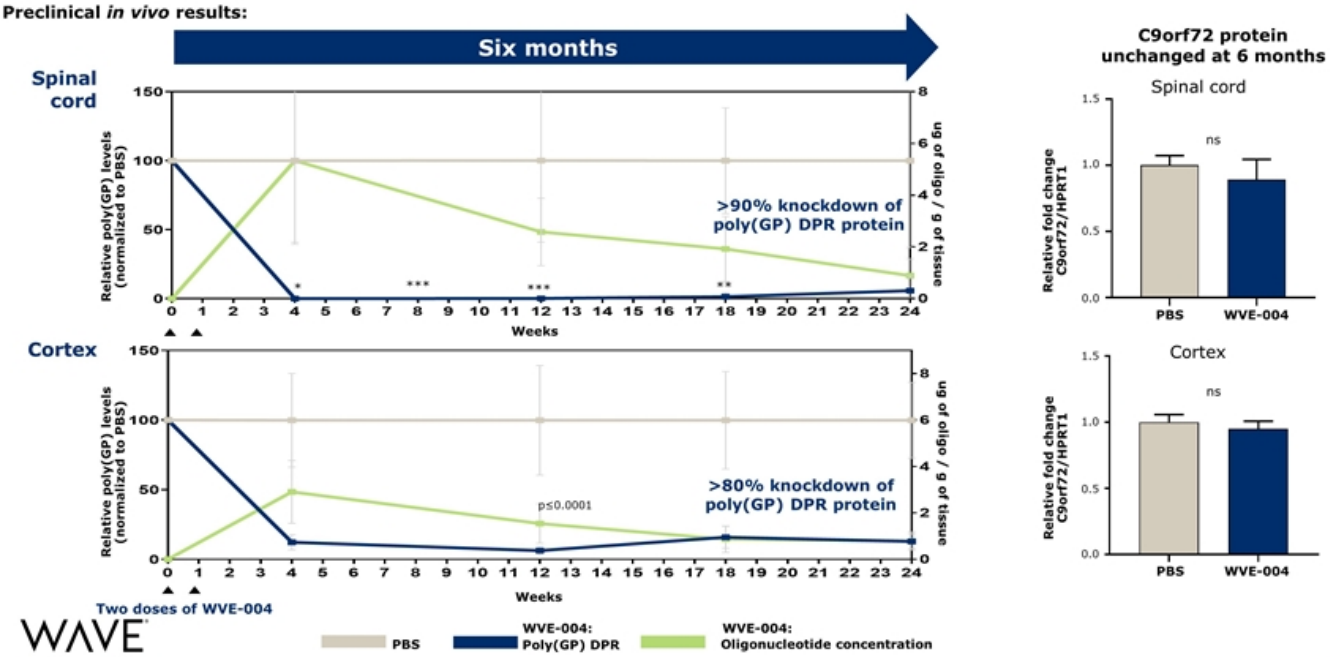
Reduces toxic gain-of-function drivers of disease (RNA foci, DPRs)

FOCUS ON C9 WAVE LIFE SCIENCES

[1]**Liu et al., 2022** *Mol Ther Nuc Acids* doi: 10.1016/j.omtn.2022.04.007

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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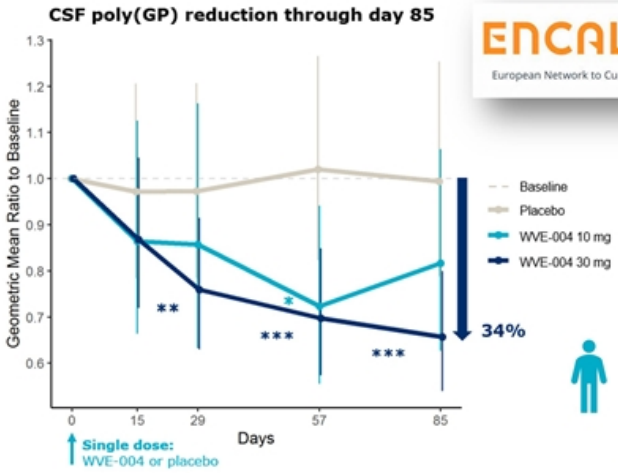
Liu *et al., 2022 Molecular Therapy Nucleic Acids* doi: 10.1016/j.omtn.2022.04.007; 2 x 50 ug (day 0, day 7) dosed ICV; DPRs measured by poly(GP) MSD assay.
*: p≤ 0.05 **: P ≤ 0.01, ***: P ≤ 0.001. DPR: Dipeptide repeat protein

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



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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

Target engagement observed in single dose cohorts

Single dose

- 60 mg n=4
- 30 mg n=10
- 20 mg n=10
- 10 mg n=3

Multidose

Dose and frequency to be guided by DSMB

10 mg n=6 4 monthly doses

Open-label extension (OLE) clinical trial
Initiation anticipated in 2H 2022

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

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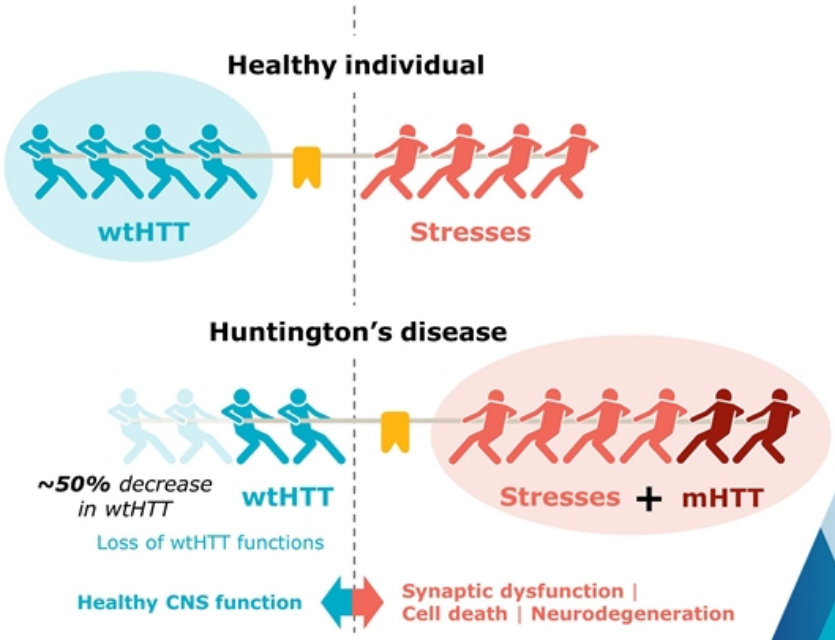
WVE-003

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



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

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

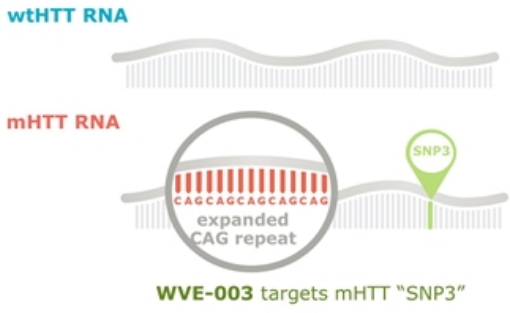

Promotes neuronal survival


Supports synaptic protein transport


Regulates synaptic plasticity

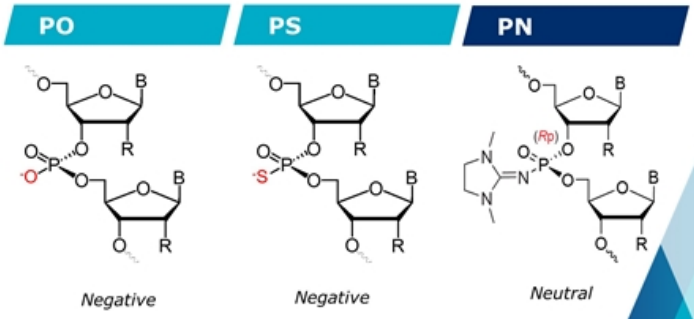

Supports cilia and CSF circulation

Only wtHTT-sparing oligonucleotide in clinical development



WVE-003 targets mHTT "SNP3"

Contains Wave's novel PN chemistry



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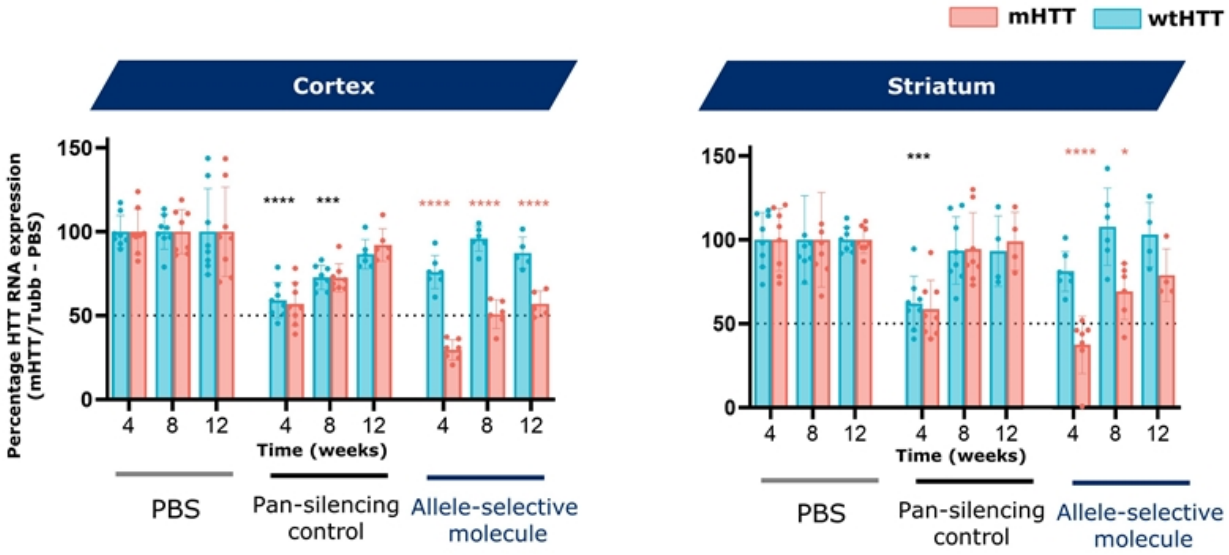
mHTT, mutant HTT; wtHTT, wild-type HTT; PO, phosphodiester; PS, phosphorothioate; PN, phosphoryl guanidine; wtHTT literature sources: 1. Leavitt 2006 2. Cattaneo 2005 3. Kumar 2016 4. Franco-Iborra 2020 5. Hamilton 2015 6. Ochaba 2014 7. Wong 2014 8. Rui 2015 9. Caviston 2007 10. Twelvetrees 2010 11. Strehlow 2007 12. Milnerwood 2010 13. Smith-Dijak 2019 14. Tousley 2019 15. Zhang 2018 16. McAdam 2020 17. Altar 1997 18. Zuccato 2001 19. Gauthier 2004 20. Ferrer 2000 21. Baquet 2004 22. Liu 2011 23. Karam 2015

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

Allele-selective activity in CNS of Hu97/18 mice

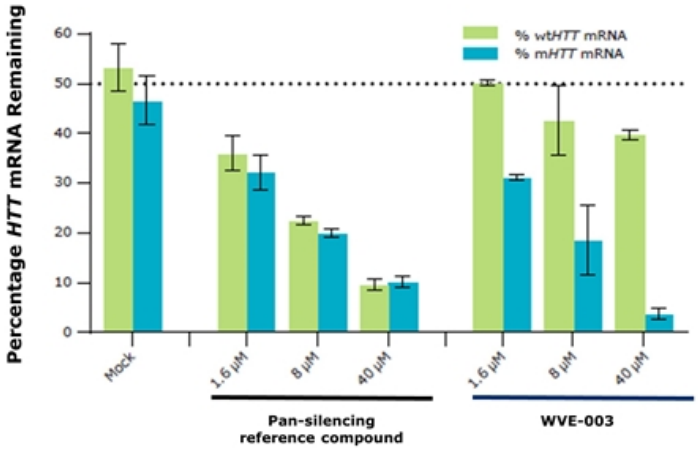


Hu97/18 mouse

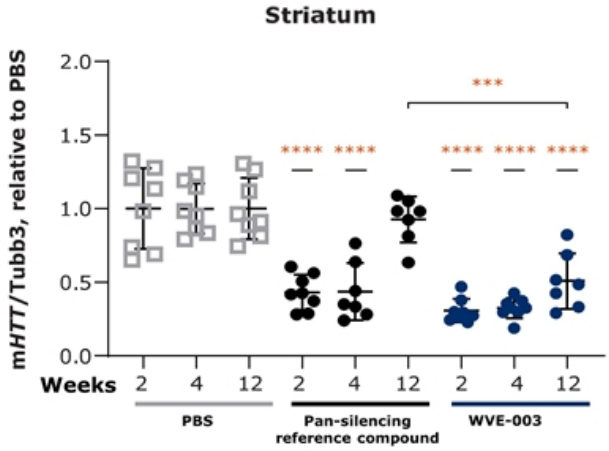
Hu97/18 mice administered 3x100 mg intracerebroventricular doses PBS or oligonucleotide. Relative mHTT RNA in cortex (left) striatum (middle) or hippocampus (right) at 4, 8 and 12-weeks post-dosing. Data are mean ± SD, n=8. Stats: ns non-significant, *P<0.05, **P<0.01, ***P<0.0001, ****P<0.0001 versus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



Similar results in cortex

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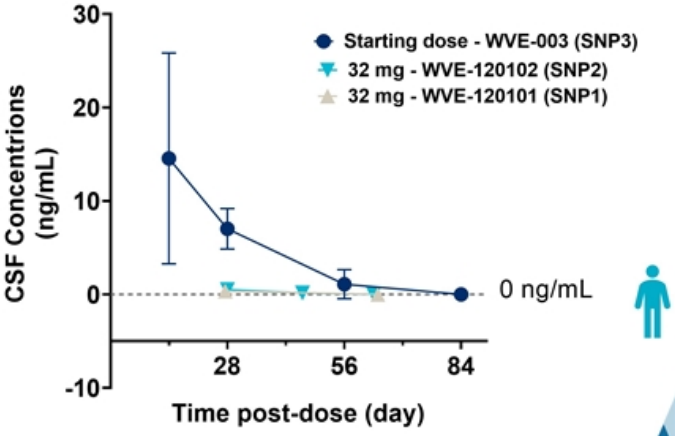
Results from ND50036 iPSC-derived medium spiny neurons. Total *HTT* knockdown quantified by qPCR and normalized to HPRT1. Oligonucleotide or PBS [100 µg ICV injections through cannula on days 1, 3, 5] delivered to BACHD transgenic. Mean ± SD (n=8, **P*<0.0332, ****P*<0.0002, *****P*<0.0001 versus PBS unless otherwise noted). HPRT1, hypoxanthine-guanine phosphoribosyl transferase; iPSC, induced pluripotent stem cell; ICV, intracerebroventricular; PBS, phosphate-buffered saline

WVE-003 (allele-selective compound in HD) achieves concentrations in patient CSF expected to engage target

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

- ✓ Demonstrated allele selectivity for mHTT
- ✓ 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

Blinded CSF WVE-003 concentrations compared to CSF WVE-120102/WVE-120101 concentrations



Dose escalation continues in ongoing SELECT-HD clinical trial

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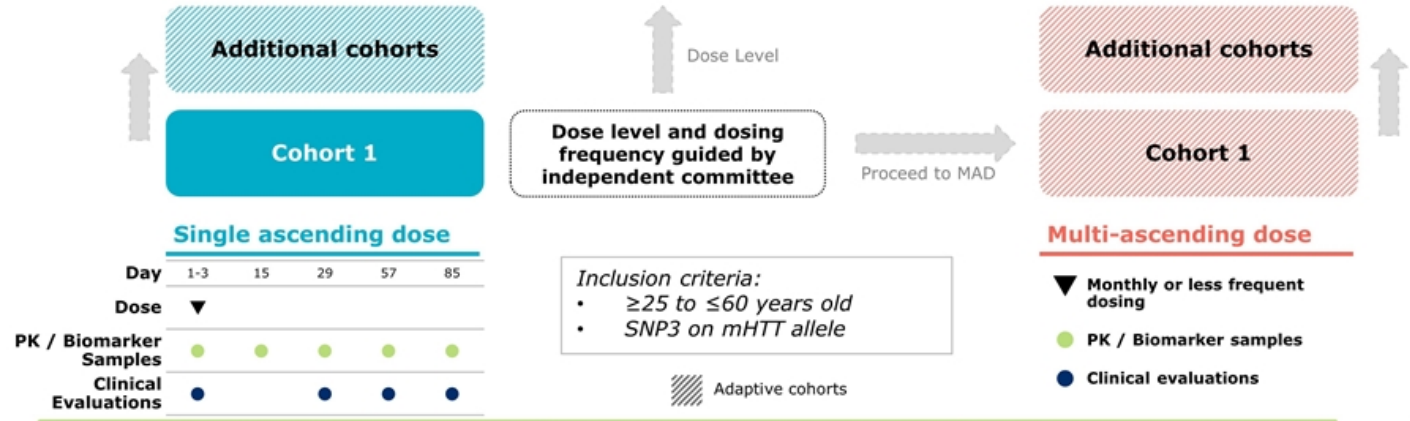
WVE-120101 (SNP1) and WVE-120102 (SNP2): First-generation PS/PO compounds for HD

SELECT-HD clinical trial: Dose level and dosing frequency guided by independent committee



SELECT HD

Clinical evaluations
- Safety and tolerability
- UHDRS

Key biomarkers:
- mHTT
- wtHTT
- NfL

Clinical data expected in 2H 2022

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PK: pharmacokinetic mHTT: mutant HTT wtHTT: wild-type HTT NfL: neurofilament light chain

WVE-N531

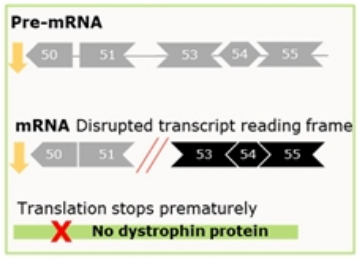
Duchenne muscular dystrophy

Duchenne muscular dystrophy

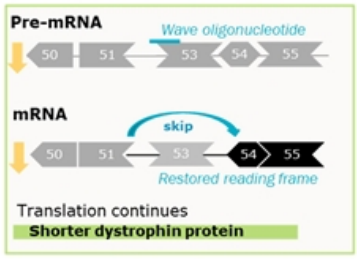
Duchenne muscular dystrophy

- 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[1] 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)



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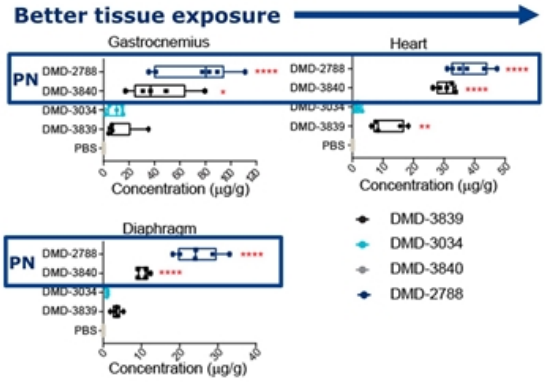
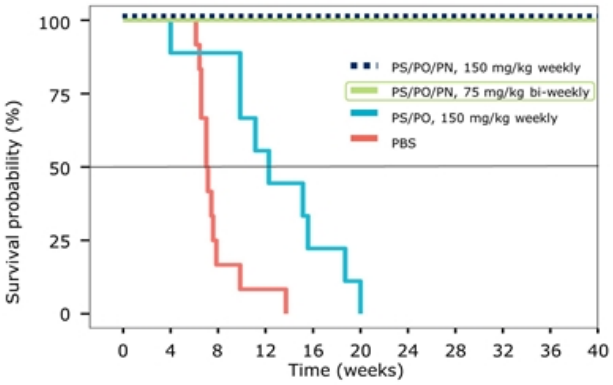
[1]Vyondys: www.fda.gov; viltepso; www.fda.gov; Exondys; www.fda.gov; Amondys: www.fda.gov

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]

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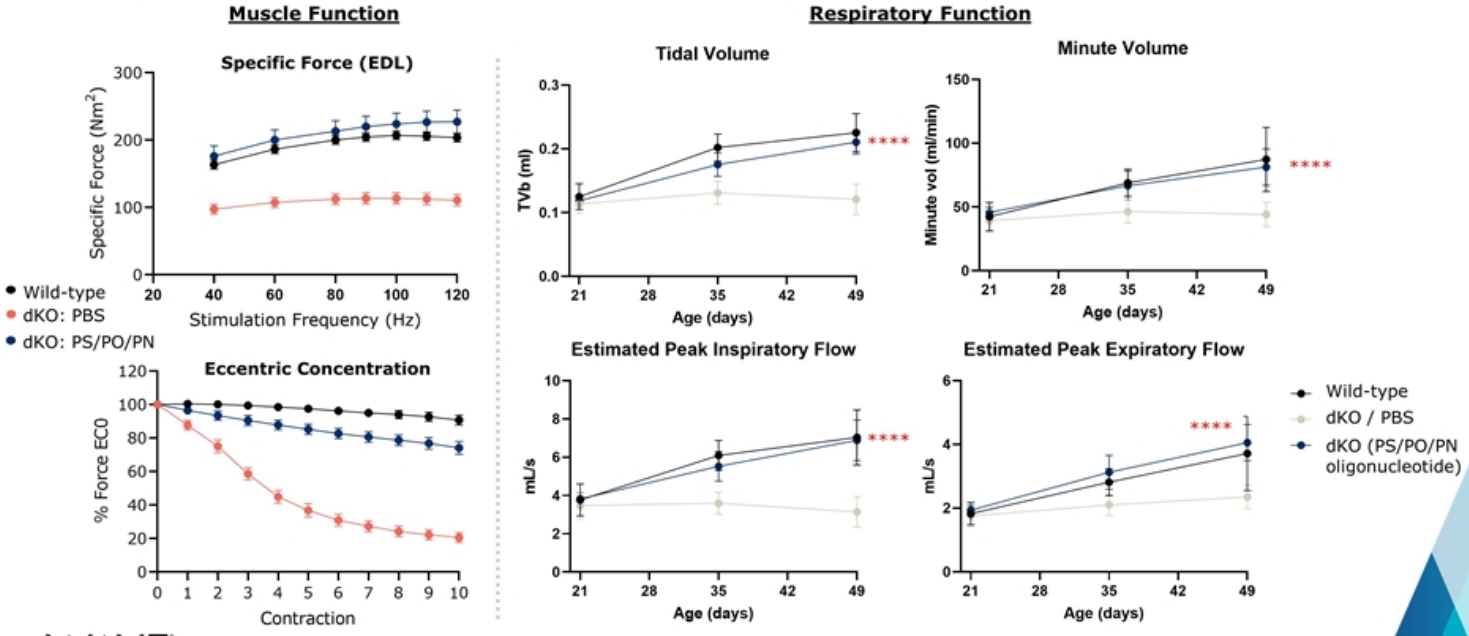
Kandasamy et al., 2022; doi: 10.1093/nar/gkac018

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



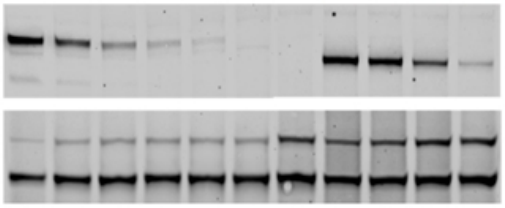
Left: *Mdx/utr-/-* mice received weekly subQ 150 mg/kg dose of PS/PO/PN stereopure oligonucleotide (postnatal day 10). Age-matched *mdx/utr-/-* littermates treated with PBS, *wild-type C57BL10* mice not treated. Wild-type, dKO PBS mice: 6 wks old; dKO PS/PO/PN: 28 – 41 wks old; Electrophysiology performed 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*

Western Blot normalized to primary healthy human myoblast lysate

Standard Curve (% WT lysate in D45-52 lysate)						D45-52 Cells					
						Mock	WVE-N531				
						0	10	3.3	1.1	0.3	Conc [uM]
100%	50%	25%	12%	6%	0%	0%	71%	65%	37%	9.5%	% Dystrophin



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 Cmax, AUC and Ctrough

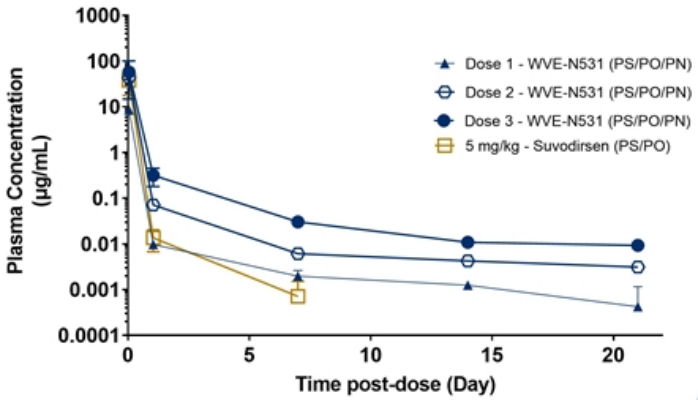
WAVE LIFE SCIENCES

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

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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 ≥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

WAVE LIFE SCIENCES

DMD: Duchenne muscular dystrophy

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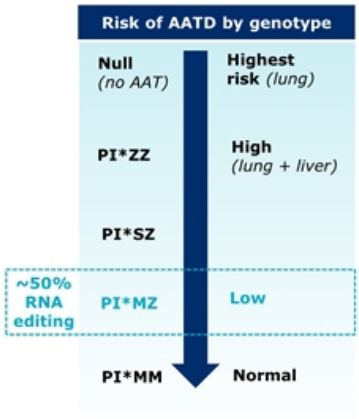
WVE-006

Alpha-1 antitrypsin deficiency (AATD)

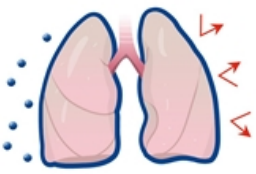
WVE-006: designed to correct mutant AATD transcript to address both liver and lung manifestations of AATD

AATD is an inherited genetic disorder that is commonly caused by a G-to-A point mutation ("Z allele") in the *SERPINA1* gene, which leads to lung disease due to lack of wild-type alpha1-antitrypsin (M-AAT) in lungs and liver disease due to aggregation of misfolded Z-AAT protein in hepatocytes



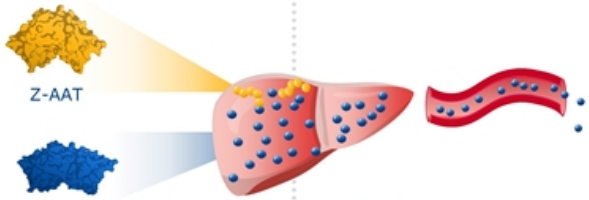
WVE-006 ADAR editing approach to address key goals of AATD treatment:

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



M-AAT reaches lungs to protect from proteases

2) Reduce Z-AAT protein aggregation in liver



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

3) Retain M-AAT physiological regulation

M-AAT secretion into bloodstream

~200K people in US and EU with mutation in *SERPINA1* Z allele (PI*ZZ)

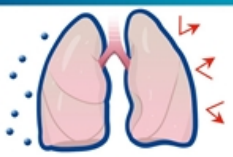
WAVE LIFE SCIENCES

AAT: Alpha-1 antitrypsin Strnad *et al.*, 2020 *N Engl J Med* 382:1443-55; Blanco *et al.*, 2017 *Int J Chron Obstruct Pulmon Dis* 12:561-69; Remih *et al.*, 2021 *Curr Opin Pharmacol* 59:149-56.

AATD AIMer restores functional M-AAT protein and alleviates liver aggregation in preclinical model

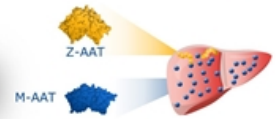
Correction of loss-of-function phenotypes

Restored M-AAT reaches lungs to protect from proteases



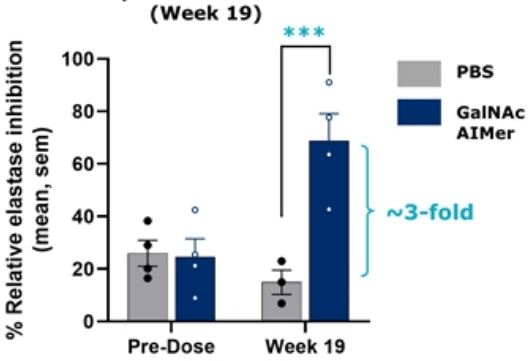
HYBRID EVENT TIDES USA | Oligonucleotide & Peptide Therapeutics

Correction of gain-of-function phenotypes

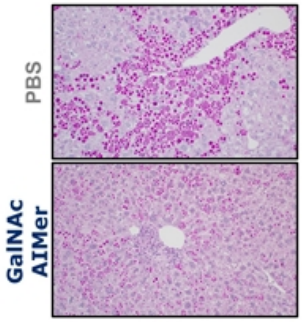


Wild-type M-AAT protein replaces Z-AAT with RNA correction

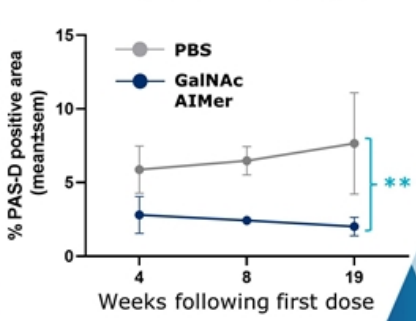
Neutrophil elastase inhibition (Week 19)



PAS-D staining (19 weeks)



PAS-D-positive area declines with AIMer treatment



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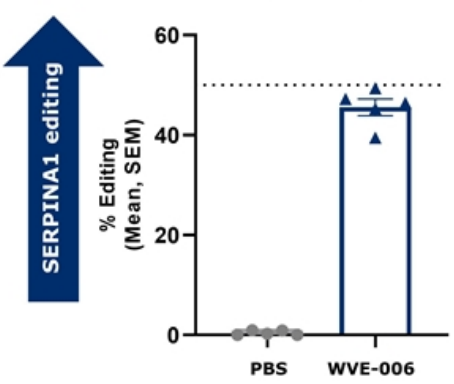
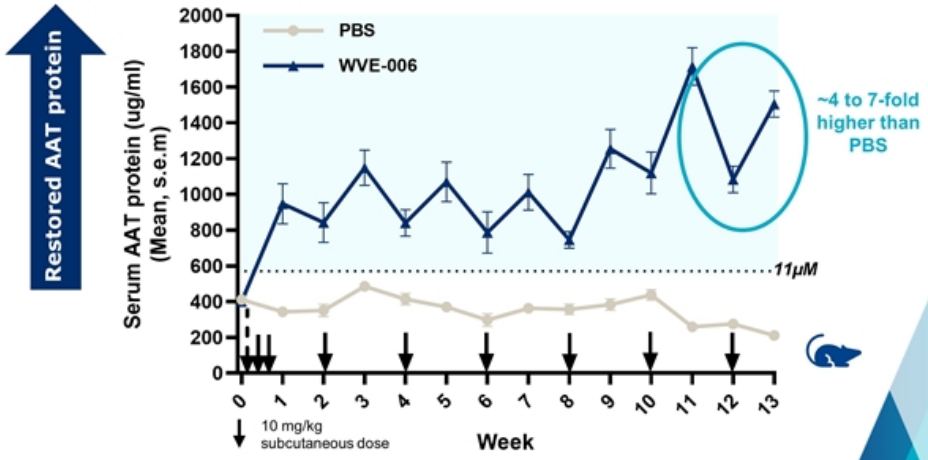
GalNAc AIMer (SA1-5) administered bi-weekly (10 mg/kg) following initial loading dose (3 x 10 mg/kg) in hu*ADAR/SERPINA1* mice (8–10 weeks old); Left: Neutrophil elastase inhibition assay (pre-dose, week 19 serum samples), Stats: Mixed effects analysis P<0.001; Right: 20x images from liver stained with PAS-D at 19 weeks ** p<0.01

WVE-006 results in circulating AAT protein levels well above established 11µM threshold *in vivo*

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

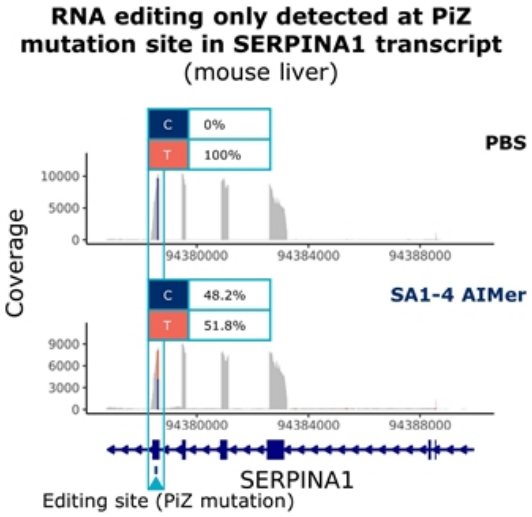


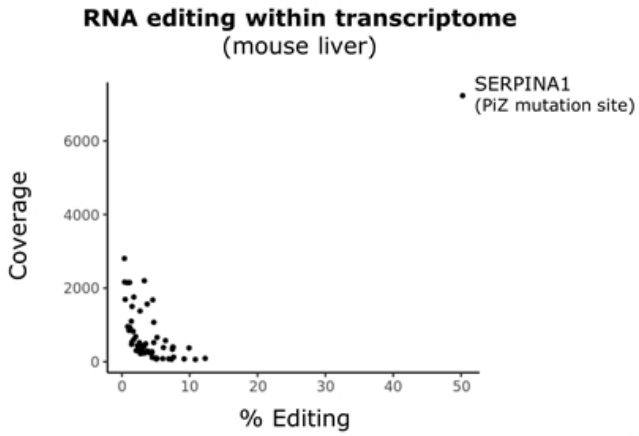
WVE-006 treatment results in serum AAT protein levels >11 uM in AATD mouse model (NSG-PiZ mice)



WVE-006 is a GalNAc-conjugated AIMer (A to I(G) RNA base editing oligonucleotide); WVE-006 administered in 7-week old NSG-PiZ mice (n=5 per group); 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)

ADAR editing is highly specific; no bystander editing observed on SERPINA1 transcript

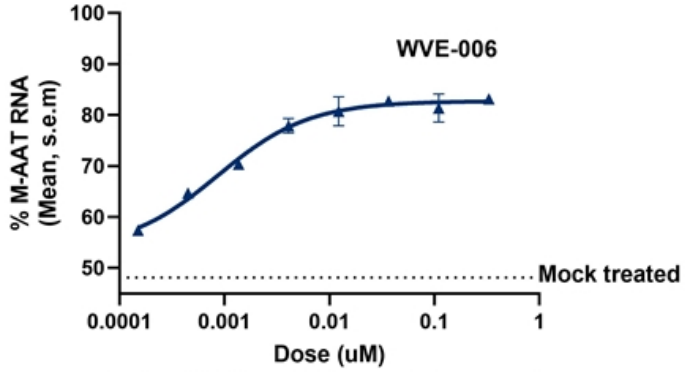




Dose 3 x 10mg/kg days (0, 2, 4) SC. Liver biopsies day 7. RNAseq, To quantify on-target SERPINA1 editing reads mapped to human SERPINA1, to quantify off-target editing reads mapped to entire mouse genome; plotted circles represent sites with LOD>3 (N=4); Analyst and Investor Research Webcast September 28, 2021

WVE-006 results in efficient editing in primary human hepatocytes, further supporting strong candidate profile

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%

- ✓ Efficient SERPINA1 and circulating AAT protein restoration *in vivo* demonstrated in AATD mouse model
- ✓ Concentration-dependent RNA editing *in vitro* demonstrated in primary human hepatocytes (MZ genotype)
- ✓ IND-enabling activities underway

CTA submissions for WVE-006 expected in 2023

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Primary human hepatocytes from an MZ donor treated with WVE-006 (GalNAc AIMer) at indicated doses for 48 hrs; SERPINA1 editing was quantified by Sanger sequencing

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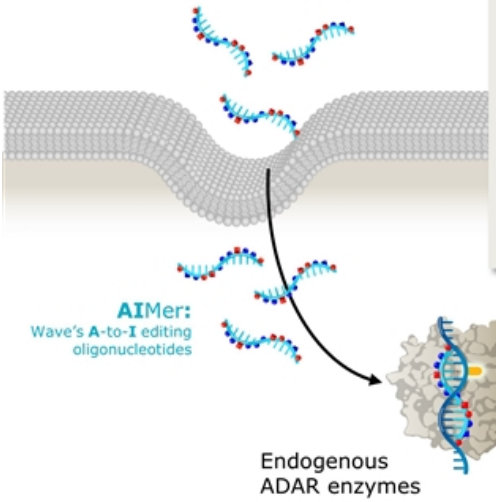
AIMers

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)



AIMer:
Wave's **A**-to-**I** editing oligonucleotides

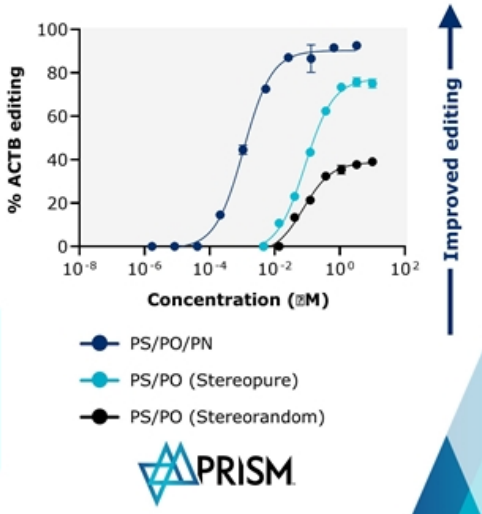
Endogenous ADAR enzymes

ADAR enzymes

- First publication (1995) using oligonucleotide to edit RNA with endogenous ADAR[1]
- 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



PRISM

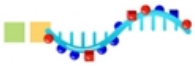
WAVE LIFE SCIENCES

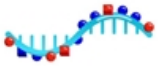
[1]Woolf et al., PNAS Vol. 92, pp. 8298-8302, 1995; Right: Data from independent experiments; Total RNA was harvested, reverse transcribed to generate cDNA, and the editing target site was amplified by PCR and quantified by Sanger sequencing

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

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

Efficient ADAR recruitment	Stability	Delivery and intracellular trafficking	Beyond liver
• AIMer design principles • SAR developed to design AIMers for different targets	• Decade of investment and learnings to improve stability of single-stranded RNAs	• GalNAc compatible for targeted liver delivery • Endosomal escape and nuclear uptake	• AIMer design also works for delivery to CNS and other tissue types
Potent and specific editing *in vivo*	**Potential for infrequent dosing**	**Subcutaneous dosing**	**IT, IVT, systemic dosing**





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

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SAR: structure-activity relationship

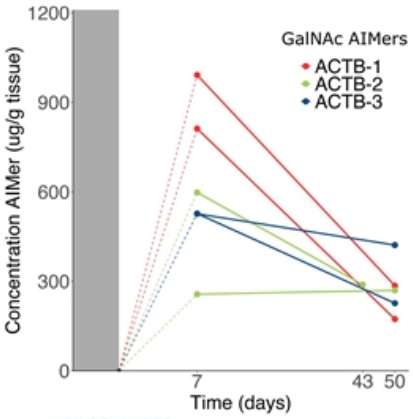
Proof-of-concept preclinical RNA editing data published in *Nature Biotechnology* (March 2022)

nature biotechnology ARTICLES

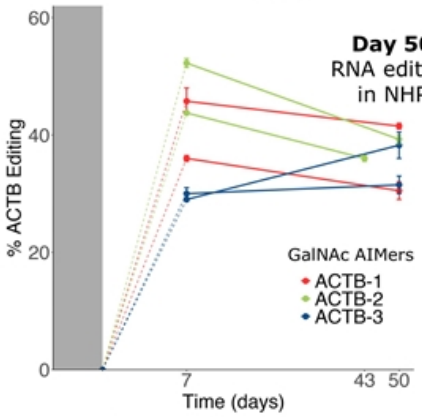
Endogenous ADAR-mediated RNA editing in non-human primates using stereopure chemically modified oligonucleotides

- 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)

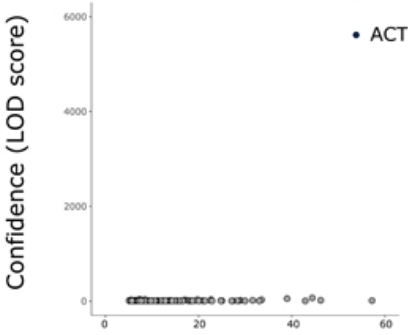


Substantial and durable editing in NHP liver *in vivo* (PD)



ADAR editing with ACTB AIMer is highly specific

RNA editing within full transcriptome (primary human hepatocytes)



RNA editing only detected at editing site in ACTB transcript

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

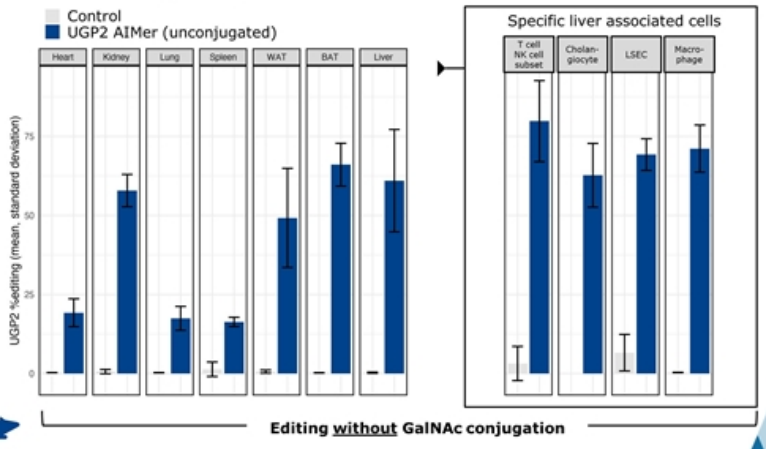
Systemic *in vivo* editing without delivery vehicles

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

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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

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

Correct G-to-A driver mutations with AIMers

✓ **Restore or correct protein function**

WVE-006 (GalNAc AIMer)
AATD

Modulate protein interactions with AIMers

- ✓ **Modulate protein-protein interaction** — *Achieved POC*
- ✓ **Upregulate expression** — *Achieved POC*
- Modify function
- Post-translational modification
- Alter folding or processing

Potential to precisely control gene upregulation with a titratable therapeutic approach

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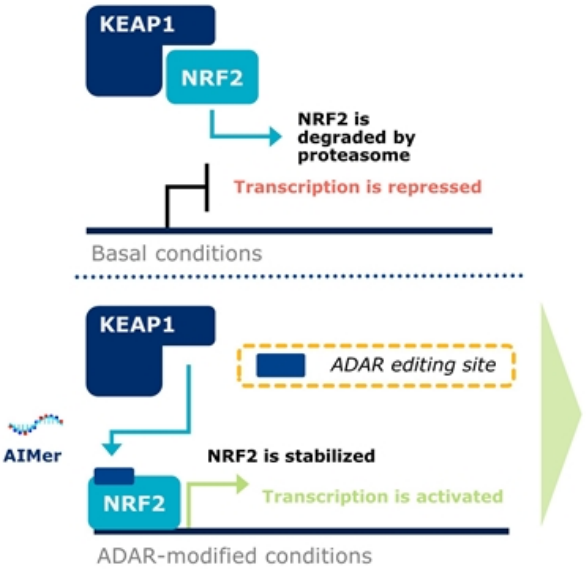
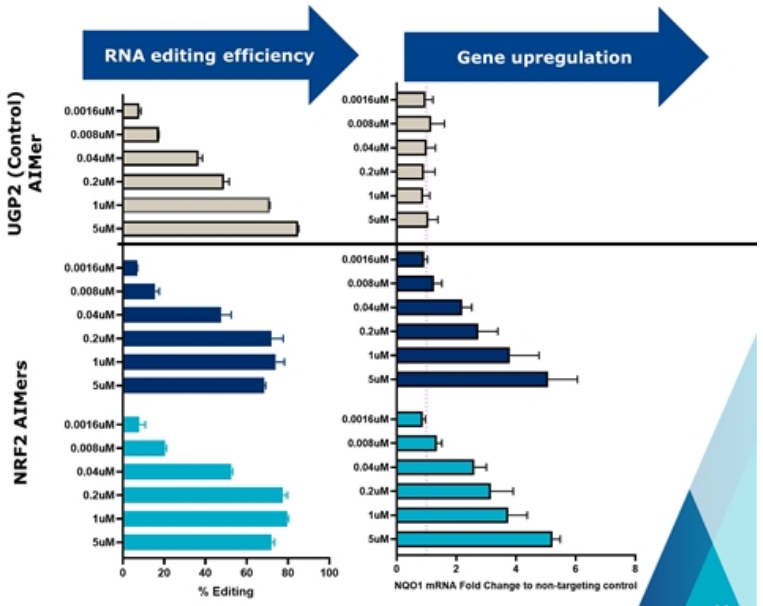
POC: proof of concept

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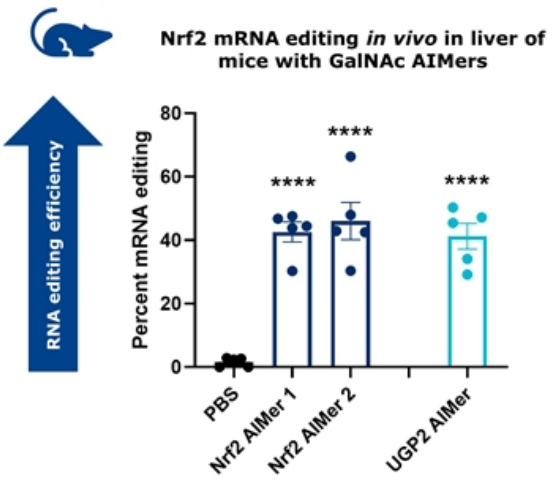
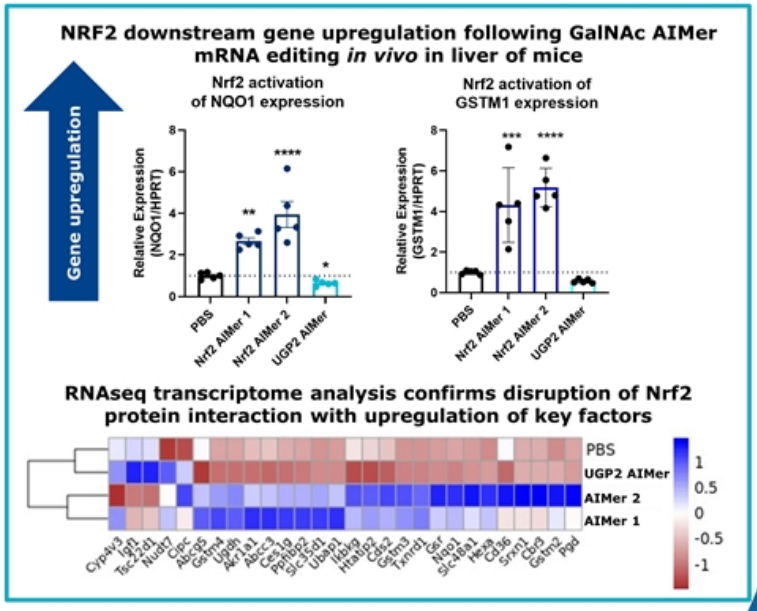
n=2; Primary hepatocytes 48h of treatment with the indicated dose concentration of AIMers

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



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



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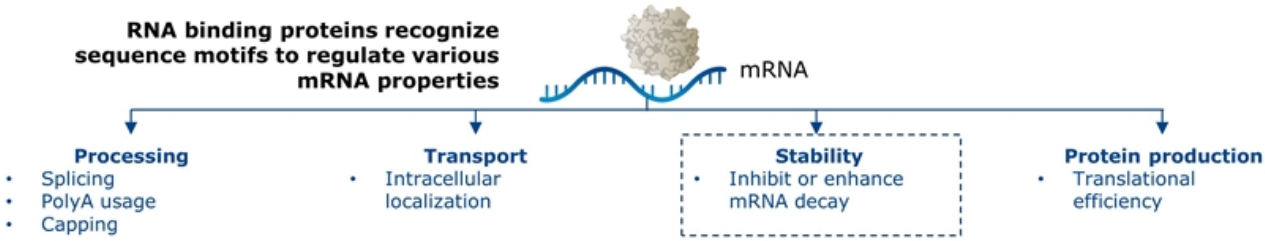
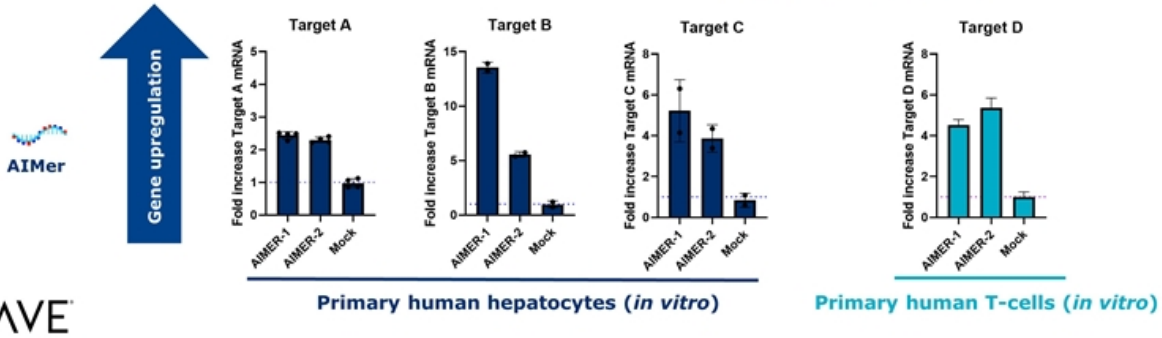
Methods: hADAR C57BL/6 mice dosed subQ (days 0, 2, 4) at 10mg/kg GalNAc-conjugated AIMers. Livers harvested (day 7), analyzed for editing and NQO1 expression via Sanger sequencing or qPCR, respectively. Data analyzed via One-way ANOVA with Tukey's multiple comparison test. Asterisks indicate statistical 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



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



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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

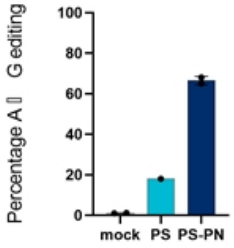
Variant base

ADAR editing site

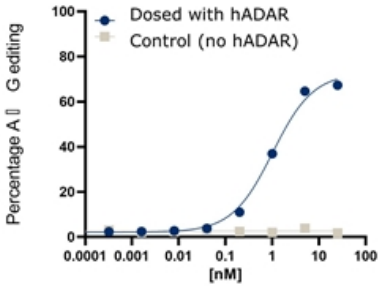
Nonsense mutations found in Rett Syndrome can occur in multiple locations on RNA transcript:

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

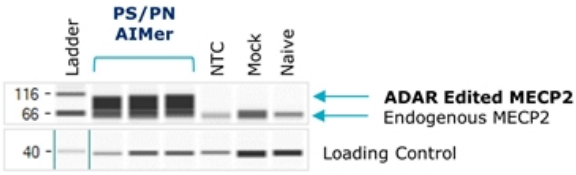
PN chemistry improved editing efficiency *in vitro*



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



Full length MECP2 protein is expressed following ADAR editing



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 naïve 293T cells probed for fusion protein.


WAVE
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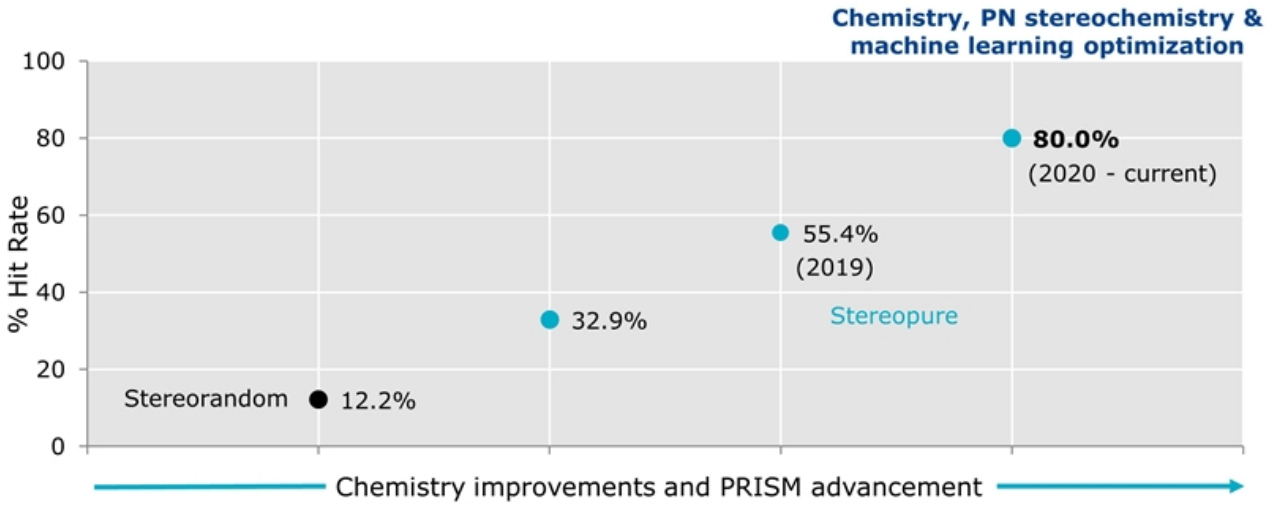
PRISM
Wave's discovery and drug development platform

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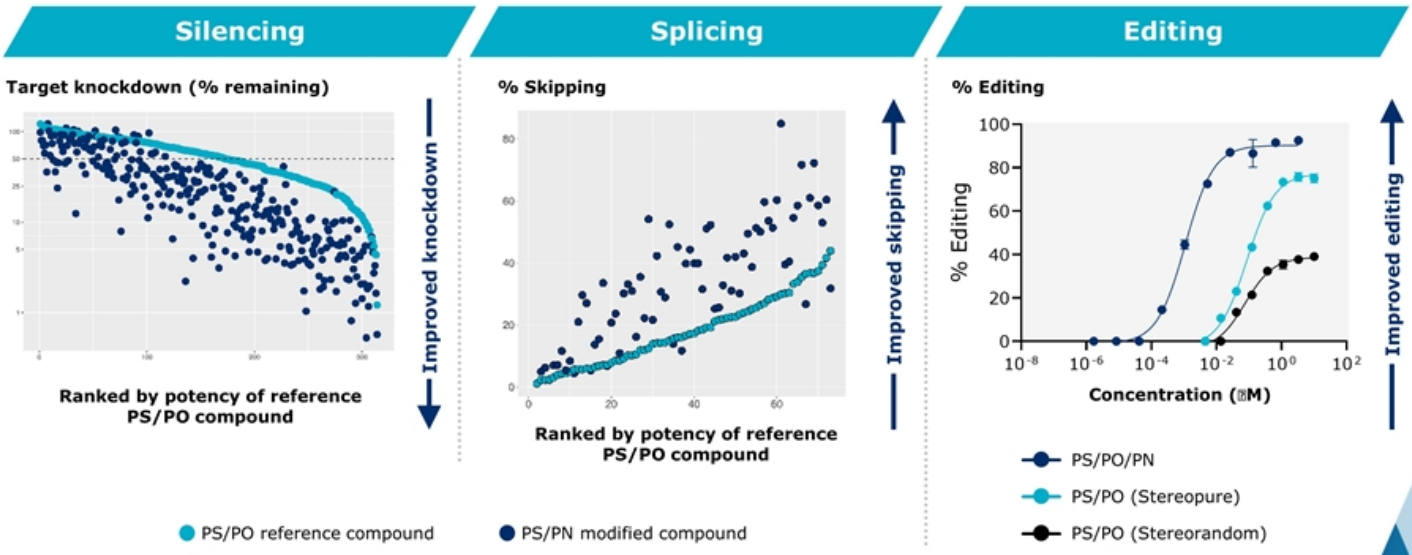
All screens used iPSC-derived neurons; Data pipeline for improved standardization. Hit rate = % of oligonucleotides with target knockdown greater than 50%. Each screen contains >100 oligonucleotides. ML: machine learning

Potency is enhanced with addition of PN modifications across modalities



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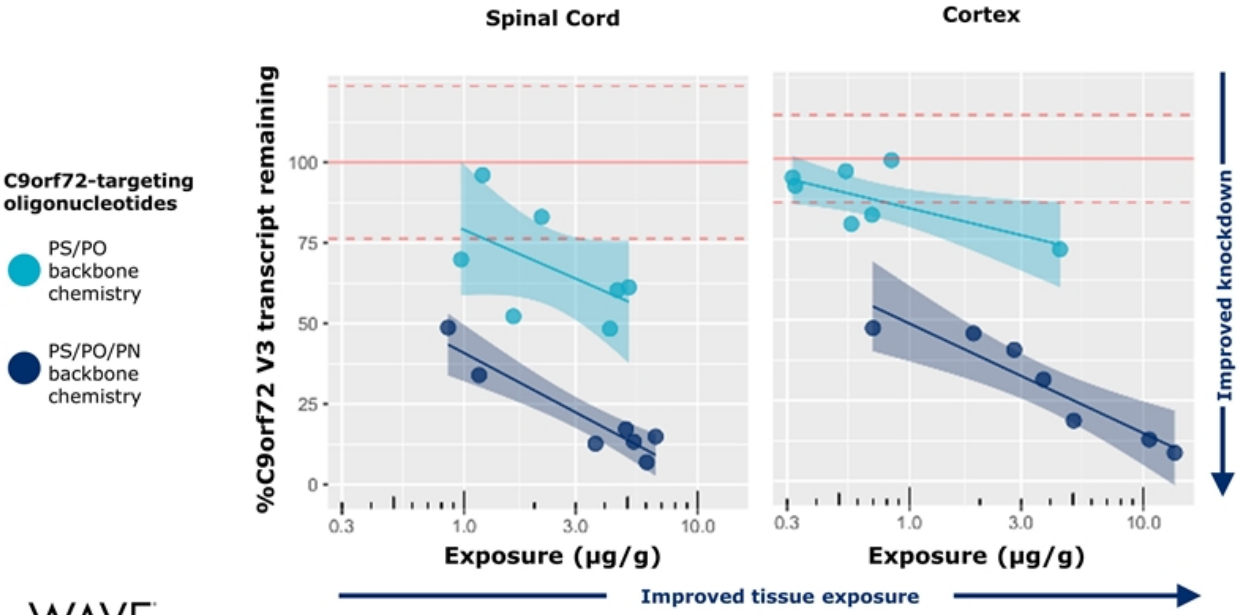
Left: Experiment was performed in iPSC-derived neurons *in vitro*; target mRNA levels were monitored using qPCR against a control gene (HPRT1) using a linear model equivalent of the DDCt method; Middle: DMD patient-derived myoblasts treated with PS/PO or PS/PO/PN stereopure oligonucleotide under free-uptake 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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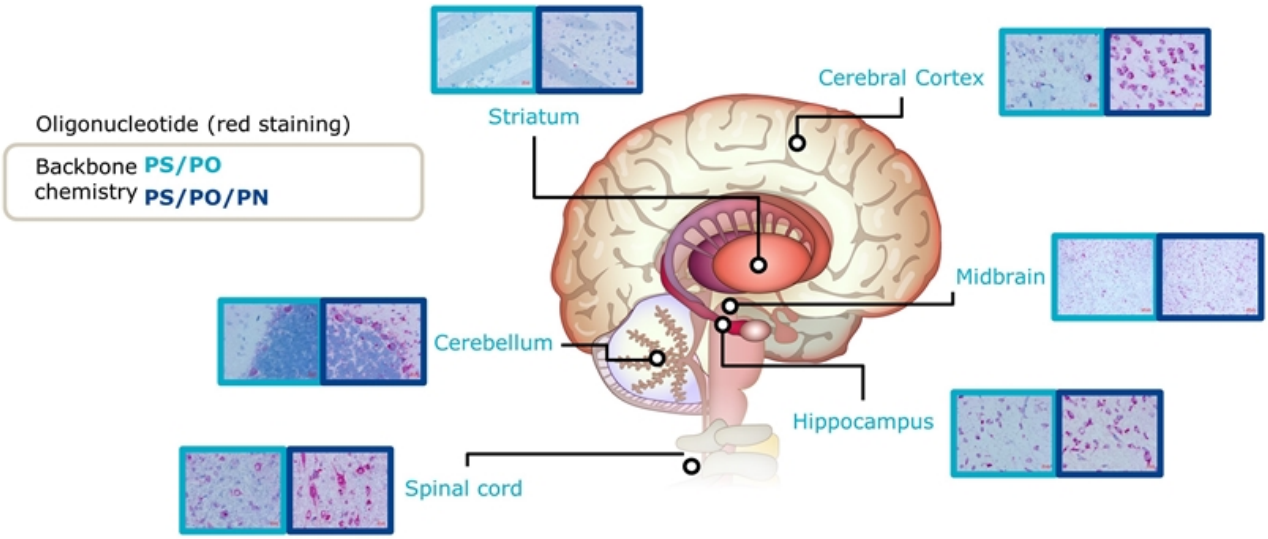
Oligonucleotide concentrations quantified by hybridization ELISA. Graphs show robust best fit lines with 95% confidence intervals (shading) for PK-PD analysis; Liu et al. Molecular Therapy Nucleic Acids 2022; Kandasamy et al., Nucleic Acids Research, 2022, doi: 10.1093/nar/gkac037

PN chemistry improves distribution to CNS

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



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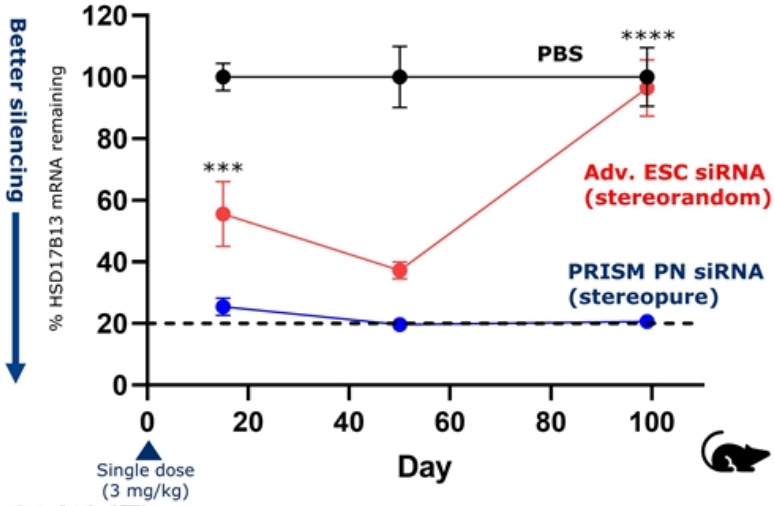
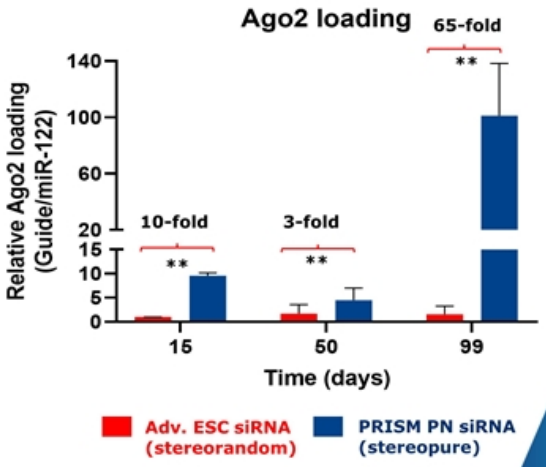
NHPs administered 1x12 mg oligonucleotide or PBS by intrathecal injection/lumbar puncture (IT). CNS tissue evaluated 11 or 29 days after injection (n=6 per group). Oligonucleotide was visualized by ViewRNA (red), and nuclei are counterstained with hematoxylin. Images from day 29.

PRISM PN siRNA led to unprecedented silencing as compared to state-of-art >3 months after single dose

~80% silencing HSD17B13 mRNA *in vivo* with GalNAc-conjugated PRISM PN siRNA 14 weeks post single dose



PRISM PN siRNA loaded in RISC is significantly greater than Adv. ESC siRNA



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(Left) Proprietary human transgenic mouse model, Post hoc tests derived from Linear Mixed Effects Model with Random subject effects;
(Right) ** P<0.01, 2-way ANOVA

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

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Upcoming milestones

Differentiated RNA therapeutics pipeline with multiple clinical datasets expected in 2H 2022

WVE-004 C9orf72 ALS & FTD	✓ Delivered clinical target engagement data with single doses • Additional single and multidose data in 2H 2022 • Discussions with regulatory authorities regarding next phase of development later in 2022 • Initiate an OLE clinical trial in 2H 2022	**Silencing**	**CNS** *(Intrathecal)*
WVE-003 HD SNP3	• Clinical data to enable decision making in 2H 2022		
WVE-N531 DMD Exon 53	• Clinical data to enable decision making in 4Q 2022	**Splicing**	**Muscle** *(IV)*
WVE-006 AATD	✓ Selected an AATD AIMer development candidate and initiated IND-enabling activities • Submit clinical trial applications in 2023	**ADAR editing**	**Targeted delivery liver** *(Subcutaneous)*

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

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WVE-004 FOCUS-C9 clinical trial (NCT04931862); WVE-003 SELECT-HD clinical trial (NCT05032196); WVE-N531 open-label clinical trial (NCT04906460)

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Realizing a brighter future for people affected by genetic diseases

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