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): January 10, 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 (see General Instruction A.2. below):

☐ 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))

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. ☐

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**

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 January 10, 2022, the Company shared an investor 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	Investor Presentation of Wave Life Sciences Ltd. dated January 10, 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: January 10, 2022

Exhibit 99.1

Wave Life Sciences

Investor Presentation

January 10, 2022

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.

WAVE
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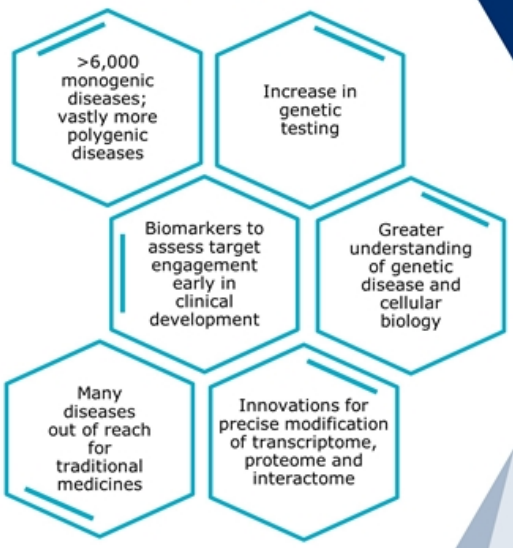
Building a leading genetic medicines company

LEVERAGING THE ONGOING GENETIC REVOLUTION



WAVE LIFE SCIENCES

DRUGGING 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

Ophthalmology

Clinical Expertise

Multiple global clinical trials

Innovative trial designs

GMP Manufacturing

Internal manufacturing capable of producing oligonucleotides at scale

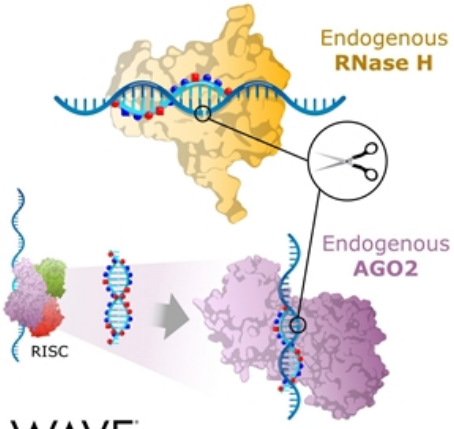
ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; HD: Huntington's disease; DMD: Duchenne muscular dystrophy; AATD: Alpha-1 antitrypsin deficiency

[1]stereopure oligonucleotides and novel backbone chemistry modifications

Biological machinery in our cells can be harnessed to treat genetic diseases

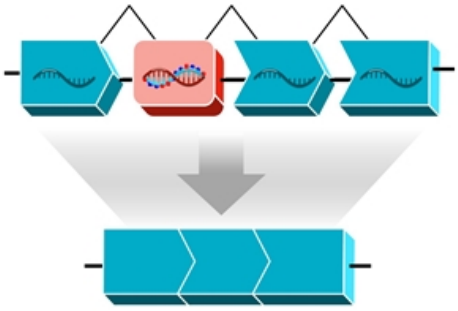
Silencing

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



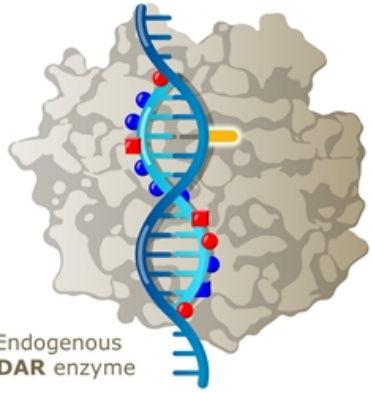
Splicing

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



RNA Base Editing

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



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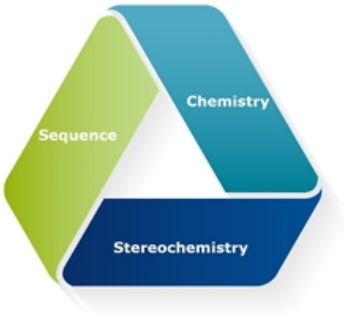
PRISM enables precision modulation of RNA therapeutic properties using unique chemistry toolkit

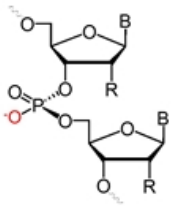
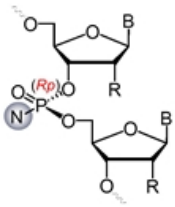
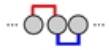
Bases	A, T, C, mC, G, U, other modified bases
2′ modifications	OMe, MOE, F, other modifications
Backbone chemistry	PO, PS, PN
Chiral control of any stereocenter	5′ modifications, backbone modifications

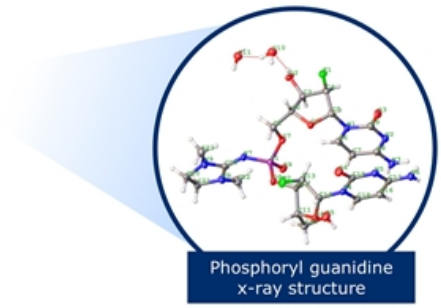


- Potency
- Tissue exposure
- Duration of activity

Innovating stereopure backbone chemistry modifications

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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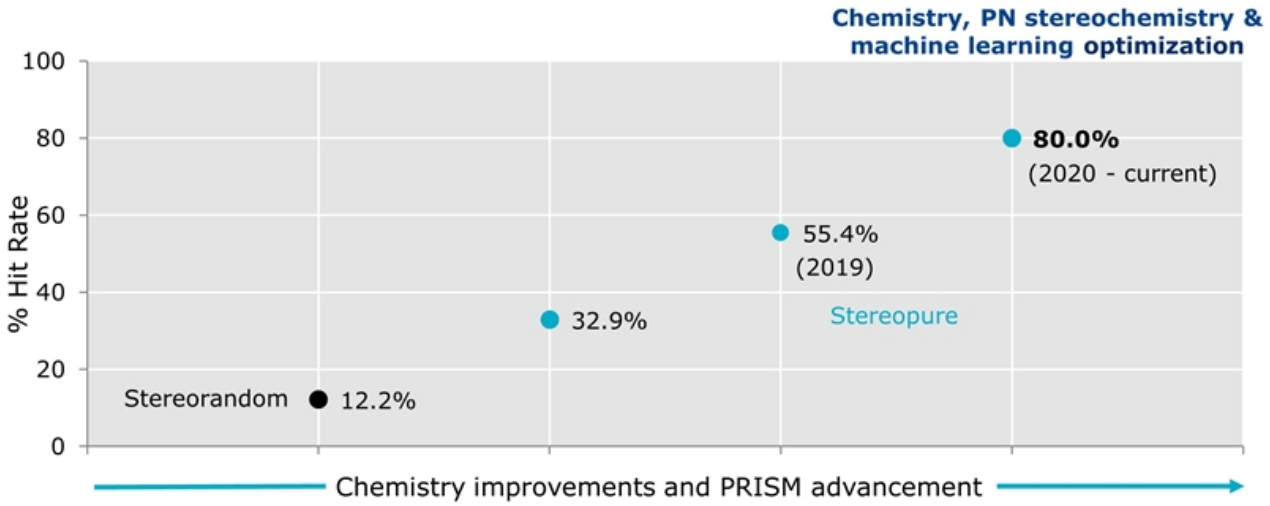
PO: phosphodiester PS: phosphorothioate

Improvements in PRISM primary screen hit rates accelerate drug discovery

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



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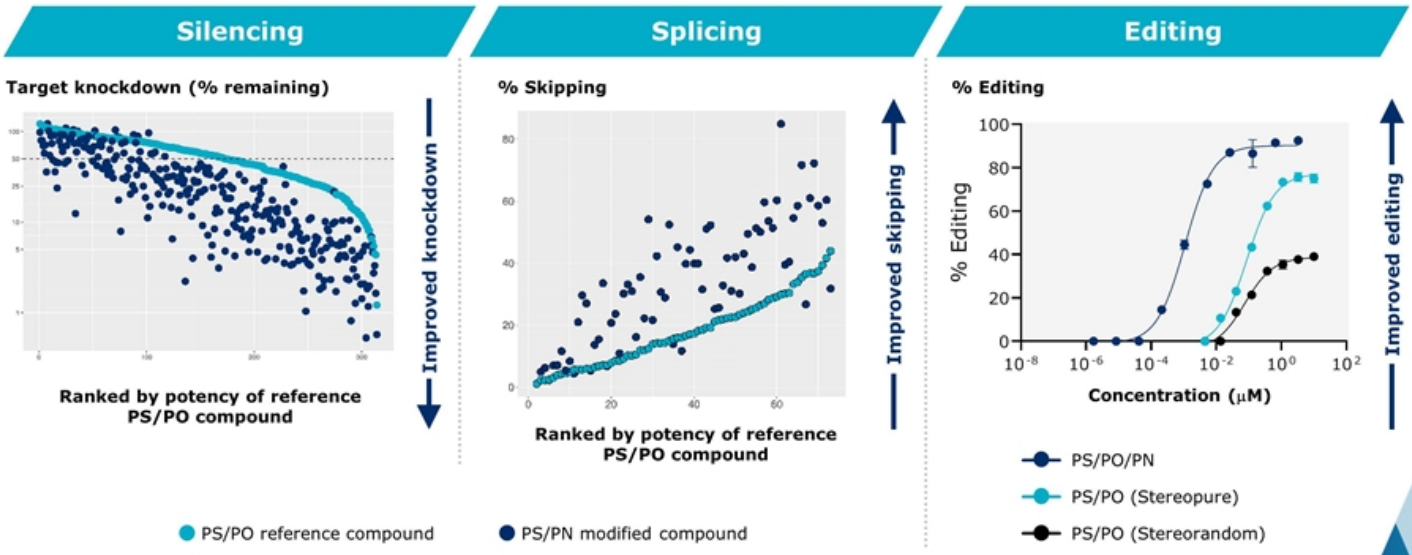
All screens used iPSC-derived neurons; Data pipeline for improved standardization. Hit rate = % of oligonucleotides with target knockdown greater than 50%. Each screen contains >100 oligonucleotides. ML: machine learning

PRISM

Potency is enhanced with addition of PN modifications across modalities



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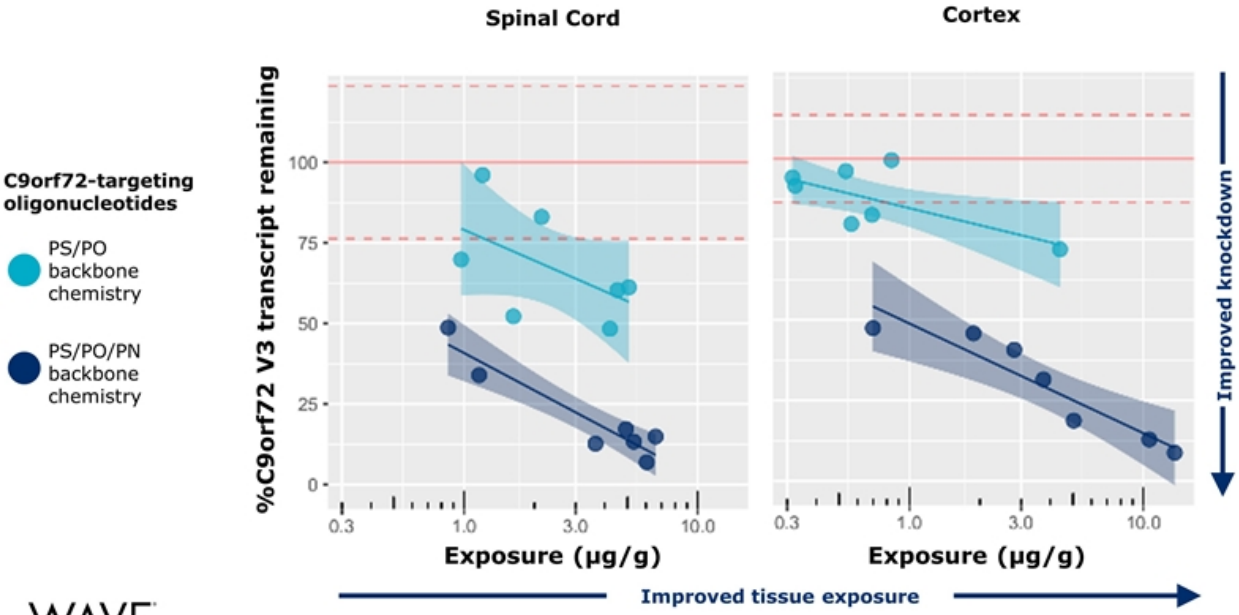
Left: Experiment was performed in iPSC-derived neurons *in vitro*; target mRNA levels were monitored using qPCR against a control gene (HPRT1) using a linear model equivalent of the ΔΔCt method; Middle: DMD patient-derived myoblasts treated with PS/PO or PS/PO/PN stereopure oligonucleotide under free-uptake conditions. Exon-skipping efficiency evaluated by qPCR. Right: Data from independent experiments

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



Target knockdown: Liu, TIDES poster 2021; Oligonucleotide concentrations quantified by hybridization ELISA. Graphs show robust best fit lines with 95% confidence intervals (shading) for PK-PD analysis. Manuscript submitted.

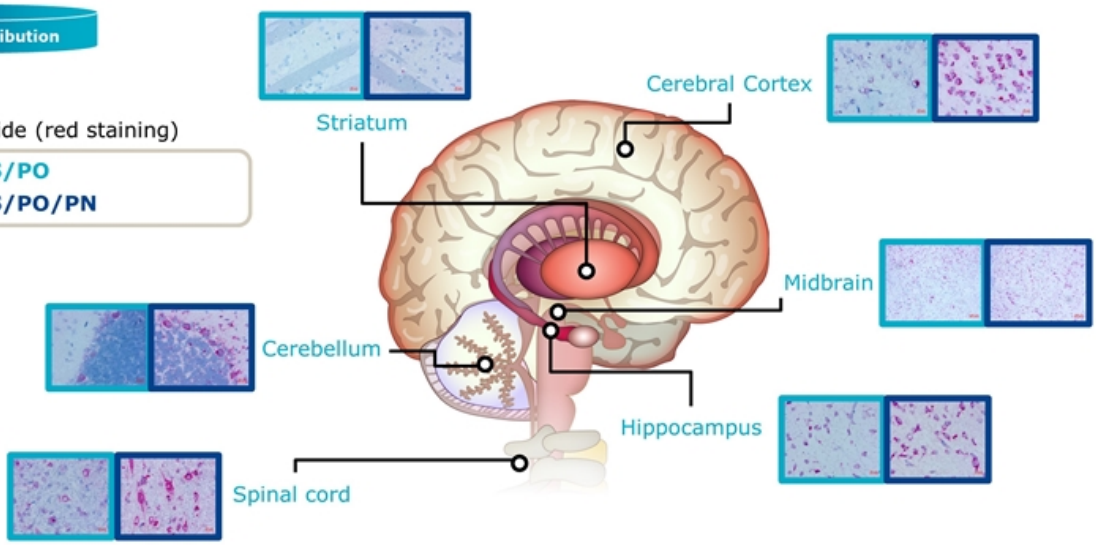
PN chemistry improves distribution to CNS

Distribution of oligonucleotides in NHP CNS 1-month post single IT dose

Tissue distribution

Oligonucleotide (red staining)

Backbone chemistry **PS/PO** **PS/PO/PN**



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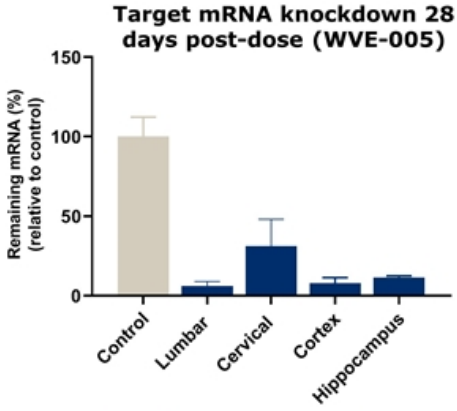
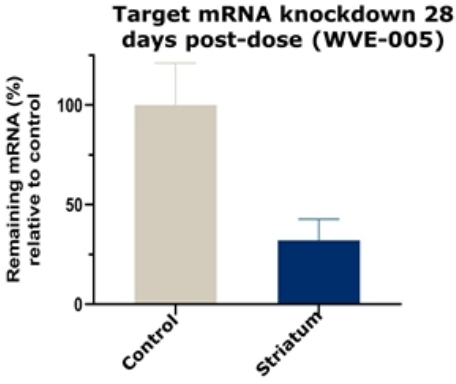
NHPs administered 1x12 mg oligonucleotide or PBS by intrathecal injection/lumbar puncture (IT). CNS tissue evaluated 11 or 29 days after injection (n=6 per group). Oligonucleotide was visualized by ViewRNA (red), and nuclei are counterstained with hematoxylin. Images from day 29.

Single intrathecal dose in NHP leads to substantial and widespread target mRNA reduction throughout the CNS

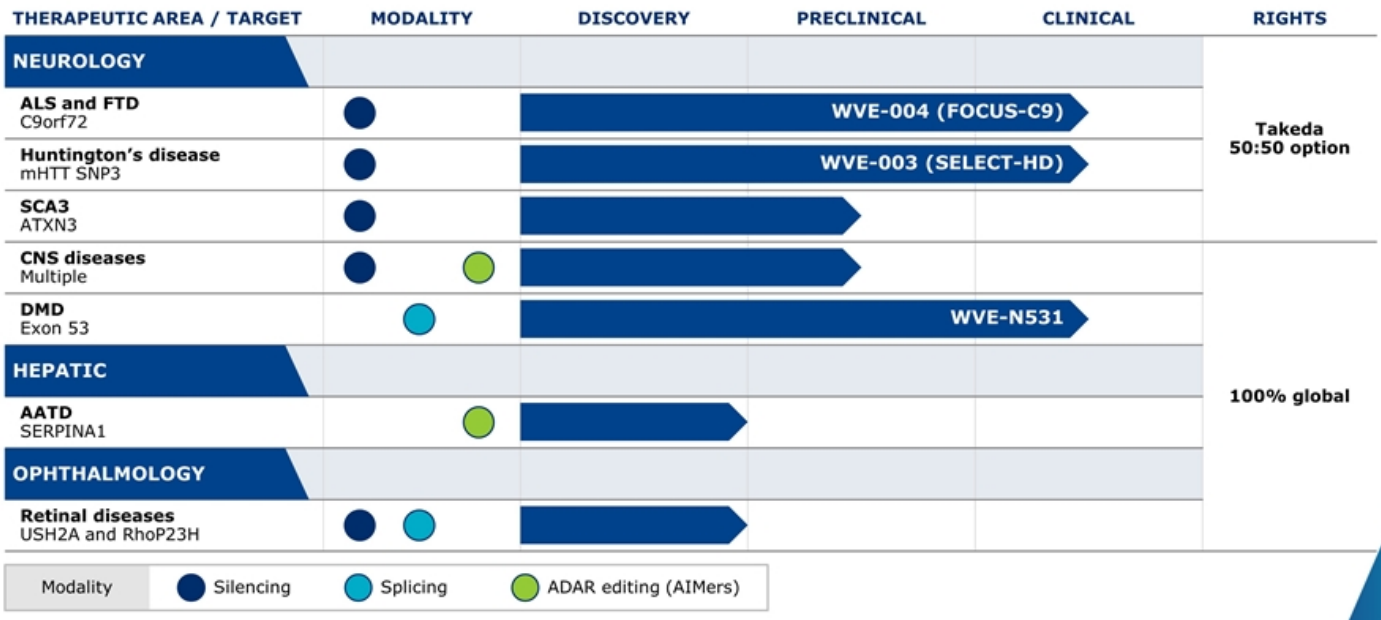




Potential for infrequent IT administration, widespread CNS distribution of PN modified oligonucleotides, and availability of disease biomarkers facilitates development of differentiated CNS portfolio

NHPs: Non-human primates
NHPs were administered 12 mg on day 1 via IT bolus injection; tissue samples were collected from 3 NHPs at 28 days post-dose.

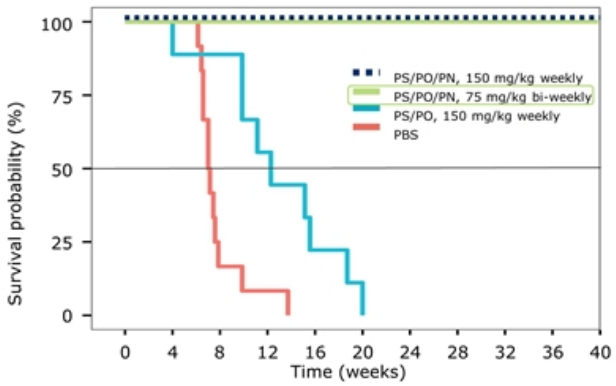
Robust portfolio of stereopure, PN-modified oligonucleotides



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

Dramatic increase in effect with PN-modified splicing oligonucleotide in dKO mouse model

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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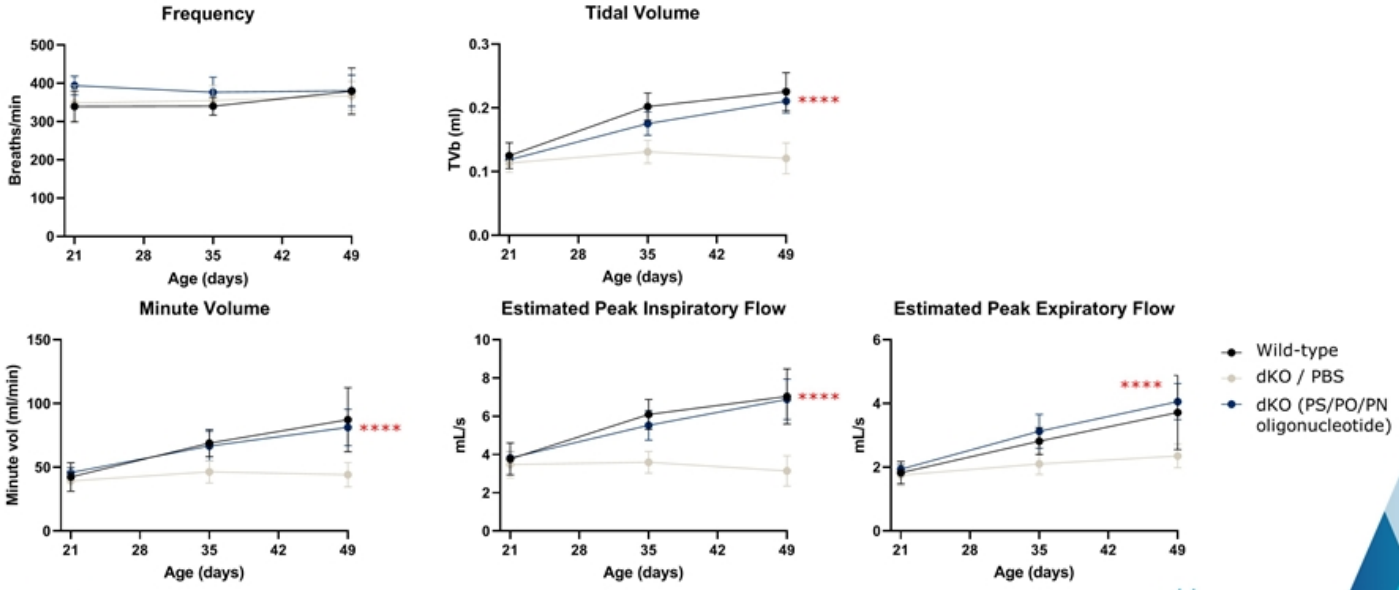
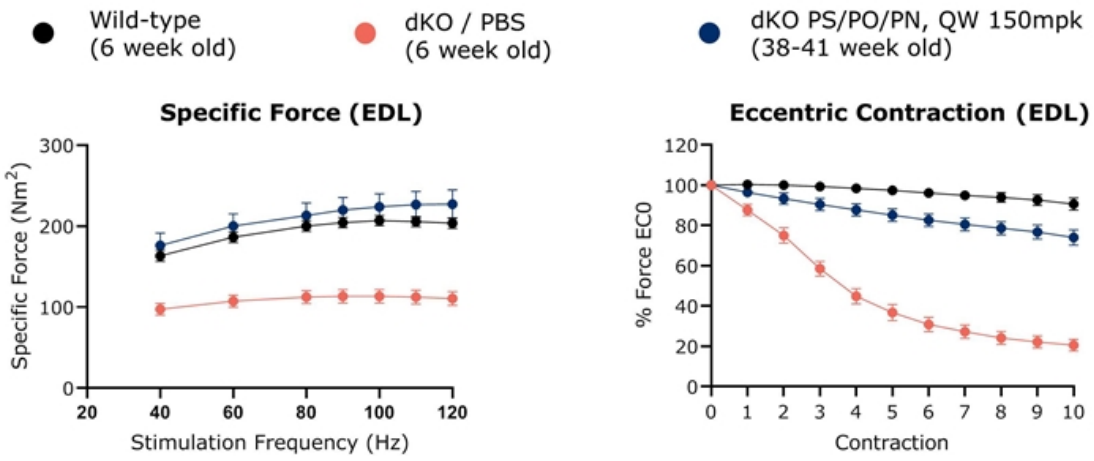
dKO; double knockout mice lack dystrophin and utrophin protein. mdx mice lack dystrophin. dKO: PS/PO/PN 150 mg/kg n= 8 (p=0.0018); PS/PO/PN 75 mg/kg n=9 (p=0.00005); PS/PO n=9 (p=0.0024), PBS n=12 Stats: Chi square analysis with pairwise comparisons to PBS using log-rank test

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



Manuscript in press. 10 day old dKO mice received weekly subcutaneous 150 mg/kg doses of PS/PO/PN splicing compound or PBS. Age-matched C57Bl/6 wild-type mice were also included in study. Data are presented as mean ± s.d. Stats from 2-way ANOVA **** P<0.0001.

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



Mdx/utr-/- mice received weekly subQ 150 mpk dose of PS/PO/PN stereopure oligonucleotide beginning at postnatal day 10. Age-matched *mdx/utr-/-* littermates were treated with PBS, and *wild-type C57BL10* mice were not treated. Electrophysiology to measure specific force and eccentric contraction performed at Oxford University based on Goyenvalle et al., 2010 Mol Therapy 18(1), 198-205.

Clinical trial of WVE-N531 underway

- Unmet need in DMD remains high
- Open-label clinical trial of up to 15 boys with DMD amenable to exon 53 skipping
  - Powered to evaluate change in dystrophin expression
  - Possible cohort expansion driven by assessment of drug distribution in muscle and biomarkers, including dystrophin

Initial cohort

- Ascending 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

Possible cohort expansion

- 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

Dose level and dosing frequency guided by independent committee

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DMD: Duchenne muscular dystrophy

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

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

Different manifestations across a clinical spectrum

Amyotrophic Lateral Sclerosis (ALS)

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

Frontotemporal Dementia (FTD)

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

Including patients with C9-associated disease across phenotypes

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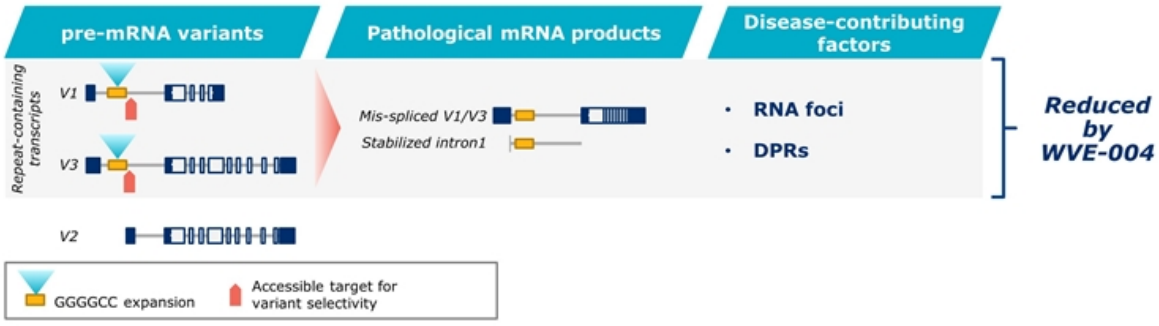
Sources: Balendra et al, EMBO Mol Med, 2017; Brown et al, NEJM, 2017, DeJesus-Hernandez et al, Neuron, 2011. Renton et al, Neuron, 2011. Zhu et al, Nature Neuroscience, May 2020, Stevens et al, Neurology 1998

WVE-004 selectively targets repeat-containing transcripts to address multiple drivers of toxicity

- C9orf72 protein is important for normal regulation of neuronal function and the immune system
- WVE-004 targets hexanucleotide repeat containing transcript variants that lead to loss of normal C9orf72 function and production of pathological mRNA products and toxic dipeptide repeat (DPR) proteins
- Poly-GP is an important DPR transcribed from sense and antisense toxic mRNA transcripts
- Poly-GP is a sensitive biomarker of target engagement and reductions of mRNA transcripts and other toxic proteins by WVE-004
- Neurofilament Light-Chain (NfL) measurements will provide important insight into potential for neuroprotection



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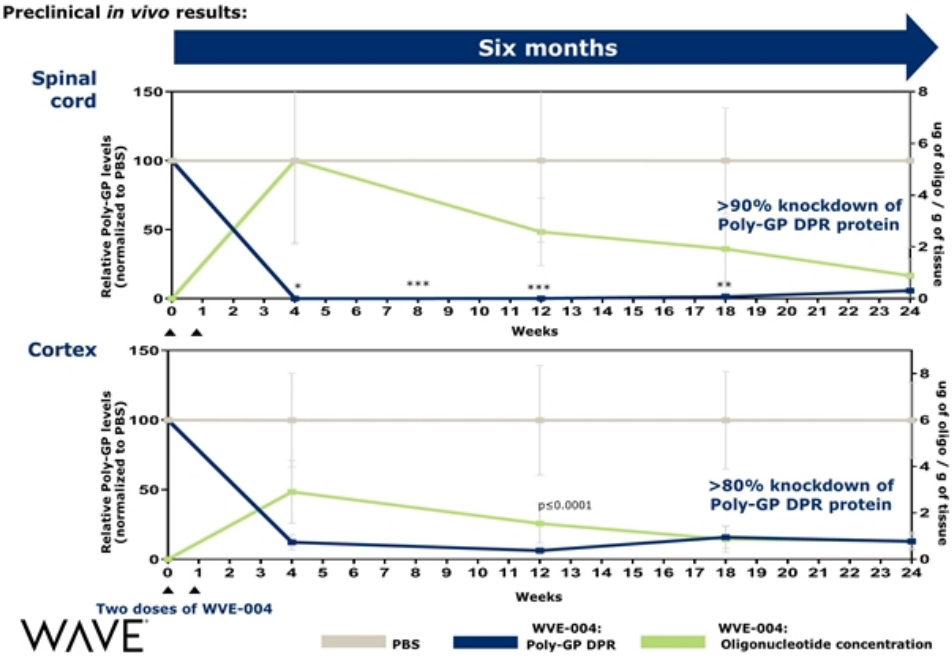
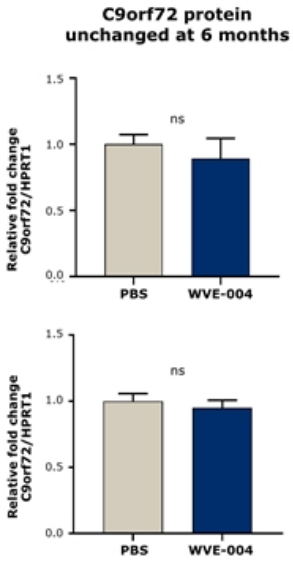
Liu et al, Nature Communications, 2021

Durable reduction *in vivo* of Poly-GP in spinal cord and cortex after 6 months

Preclinical *in vivo* results:





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

FOCUS-C9 clinical trial: Dose level and dosing frequency guided by independent committee

FOCUS C9

Clinical evaluations
- Safety and tolerability
- ALSFRS-R
- CDR-FTDLD
- FVC
- HHD

Key biomarkers:
- PolyGP DPR in CSF
- p75NTRECD in urine
- NfL in CSF

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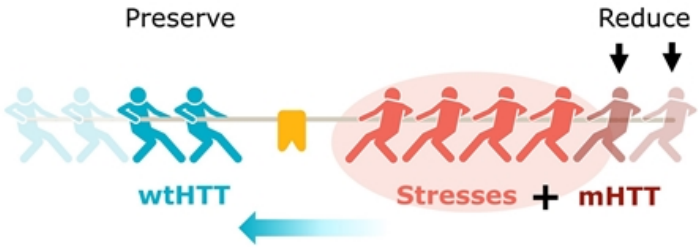
PK: pharmacokinetic

Adaptive cohorts

Allele-selective approach to treating HD

Wave has only allele-selective clinical program in Huntington's disease

- ✓ Target mutant mRNA HTT transcript to reduce mutant HTT protein
- ✓ Preserve wild-type HTT protein reservoir in brain



Only an allele-selective approach is designed to address <u>both</u> toxic gain of function and toxic loss of function drivers of HD

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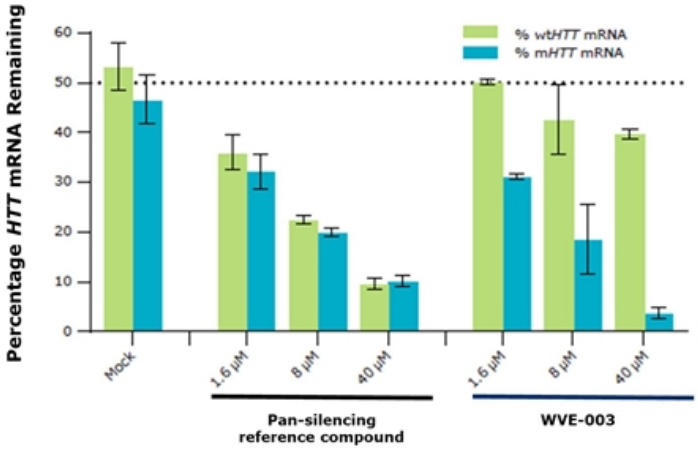
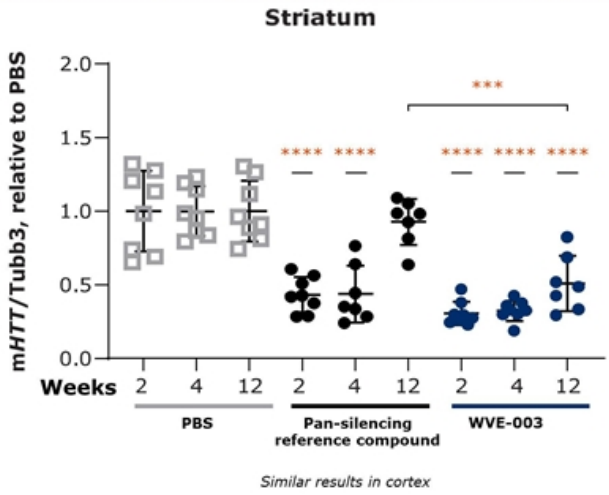
WVE-003 (SNP3) demonstrates selective, potent, and durable reduction of mHTT in preclinical models

Incorporates PN backbone chemistry modifications

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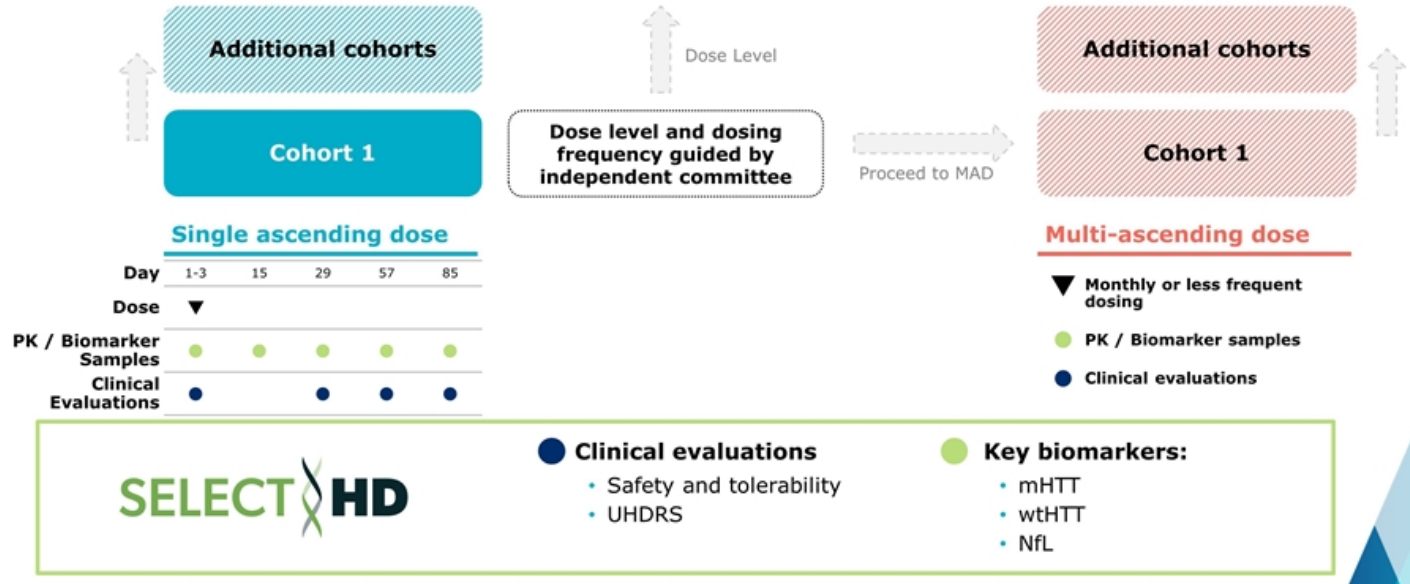
Results from ND50036 iPSC-derived medium spiny neurons. Total *HTT* knockdown quantified by qPCR and normalized to HPRT1. Oligonucleotide or PBS [100 µg ICV injections through cannula on days 1, 3, 5] delivered to BACHD transgenic. Mean ± SD (n=8, **P*<0.0332, ****P*<0.0002, *****P*<0.0001 versus PBS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

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

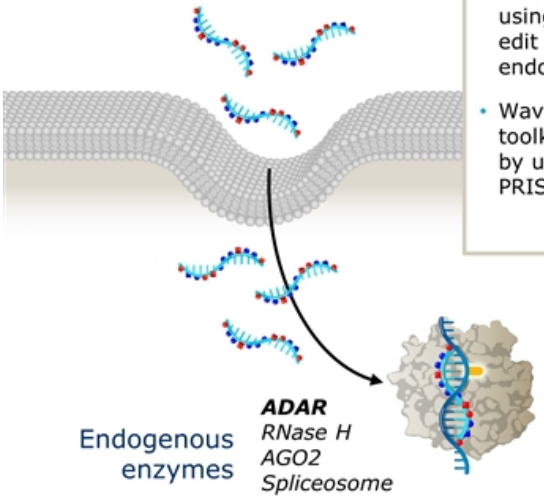
WAVE LIFE SCIENCES

PK: pharmacokinetic

Adaptive cohorts

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

Free-uptake of chemically modified oligonucleotides



- First publication (1995) using oligonucleotide to edit RNA with endogenous ADAR[1]
- Wave goal: Expand toolkit to include editing by unlocking ADAR with PRISM oligonucleotides

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

AIMer:

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

Endogenous enzymes

ADAR
RNase H
AGO2
Spliceosome

ADAR enzymes

- 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

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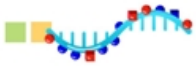
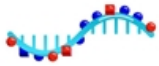
[1]Woolf et al., PNAS Vol. 92, pp. 8298-8302, 1995

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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Opportunity for novel and innovative AIMer therapeutics

Correct driver mutations with AIMers

Examples

AATD

Rett syndrome

Recessive or dominant genetically defined diseases

Restore or correct protein function

- >32,000 pathogenic human SNPs[2] – ~50% ADAR amenable
- Tens of thousands of potential amenable disease variants[1]
- ~12% of all reported disease-causing mutations are single point mutations that result in a premature stop codon[3]

Modulate protein interactions with AIMers

Upregulate expression

Modify function

Modulate protein-protein interaction

Post-translational modification

Alter folding or processing

Examples

Haploinsufficient diseases

Loss of function Neuromuscular

Dementias

Familial epilepsies

Neuropathic pain

- Large patient populations
- Human Reference Interactome documents >50K protein-protein interactions involving >8K proteins[4]
- >90K Post-translational modifications across ~30K proteins mapped,[5] thousands associated with disease[6]

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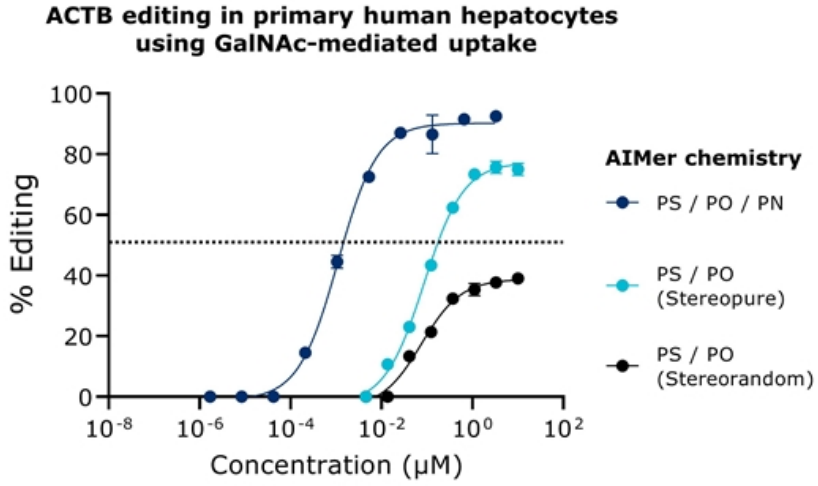
SNP: single nucleotide polymorphism A: Adenosine I: Inosine G: Guanosine
[1]ClinVar database [2]Gaudeli NM et al. *Nature* (2017) [3]Keeling KM et al., Madame Curie Bioscience Database 2000-2013 [4]Luck, K et al. *Nature* (2020)
[5]Prasad, TSK et al. *Nucleic Acids Research* (2009) [6]Huang, K et al. *Nucleic Acids Research* (2016)

Stereochemistry and PN chemistry enhance potency and editing efficiency of AIMers



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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

PRISM

Optimization of every dimension to inform future rational design of AIMers

Heat map for sequence impact on SAR

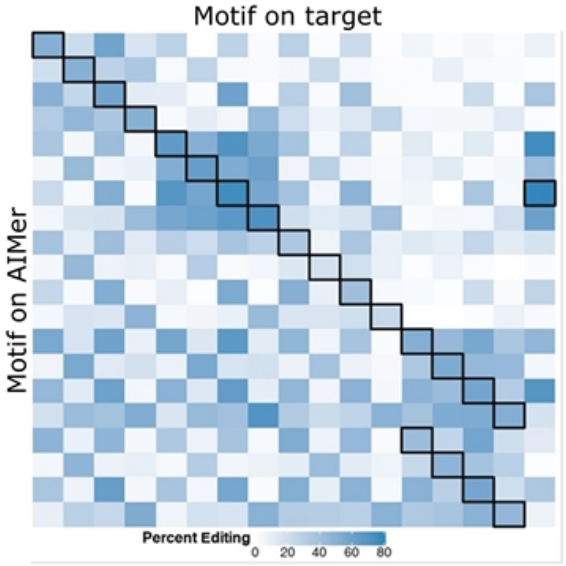
Example: Sequence is one of multiple dimensions for optimization

Sequence space is defined

NNN — AIMer

XAX — mRNA target

- >300 unique AIMers tested containing different base pair combinations
- Identified base modification combinations with high editing efficiency to optimize sequence



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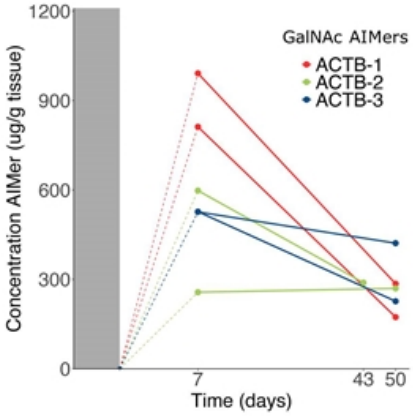
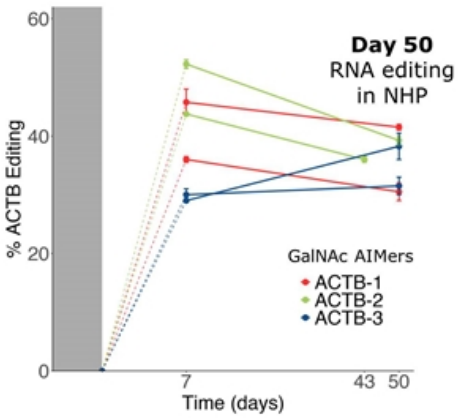
Learnings inform design principles deployed across future targets

Stability of AIMers enables durable and specific editing out to Day 50 in liver of NHPs

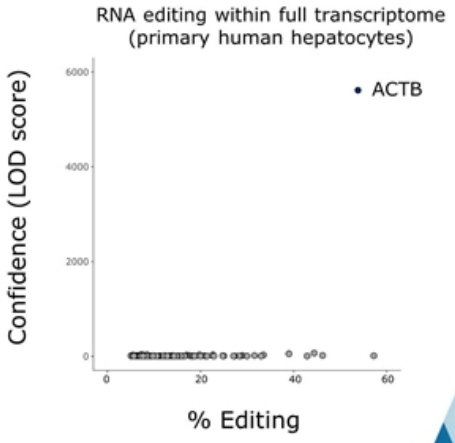
AIMers detected in liver of NHP at Day 50 (PK)



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



ADAR editing with ACTB AIMer is highly specific



RNA editing only detected at editing site in ACTB transcript

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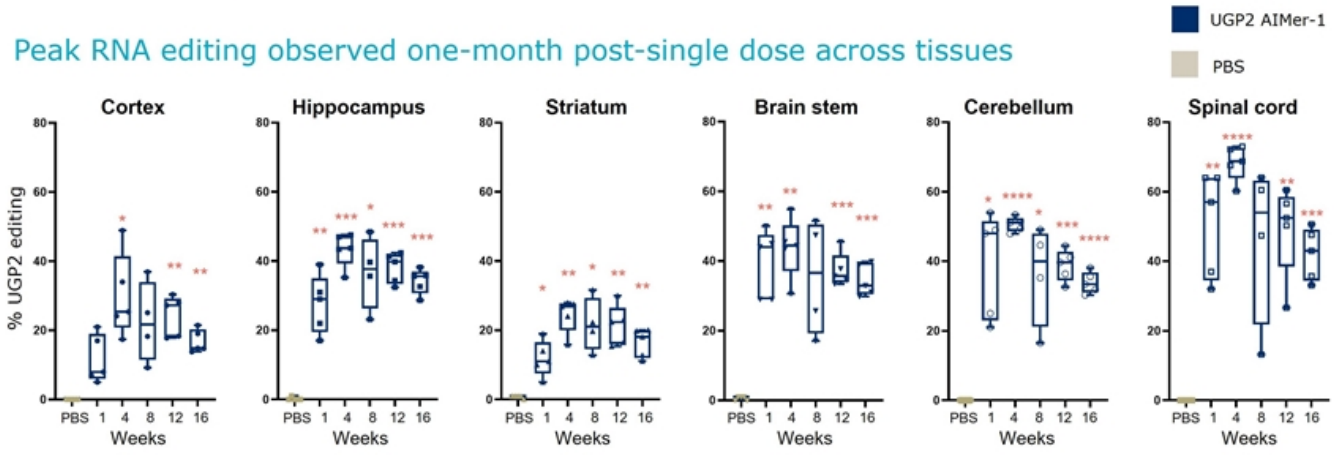
Manuscript in press. Left: AIMer PK C: 5mg/kg SC: Day 1,2,3,4,5; Liver biopsy; Right: Dosed 1um AIMer, 48 hrs later RNA collected, RNAseq conducted using strand-specific libraries to quantify on / off-target editing; plotted circles represent sites with LOD>3. NHP: non-human primate; ACTB: Beta-actin

Substantial *in vivo* RNA editing out to at least 4 months post-single dose in CNS tissues

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



Peak editing	30%	>40%	25%	>40%	50%	>65%

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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

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

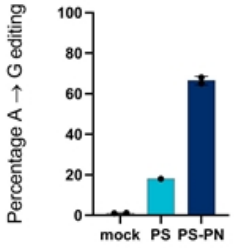
Variant base

ADAR editing site

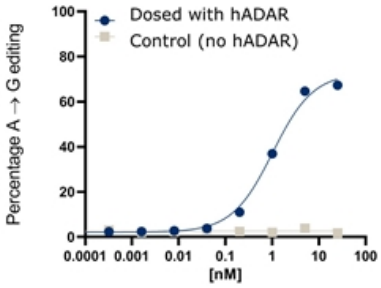
Nonsense mutations found in Rett Syndrome can occur in multiple locations on RNA transcript:

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

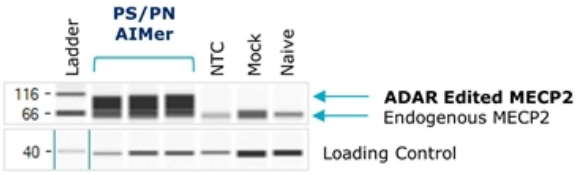
PN chemistry improved editing efficiency *in vitro*



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



Full length MECP2 protein is expressed following ADAR editing



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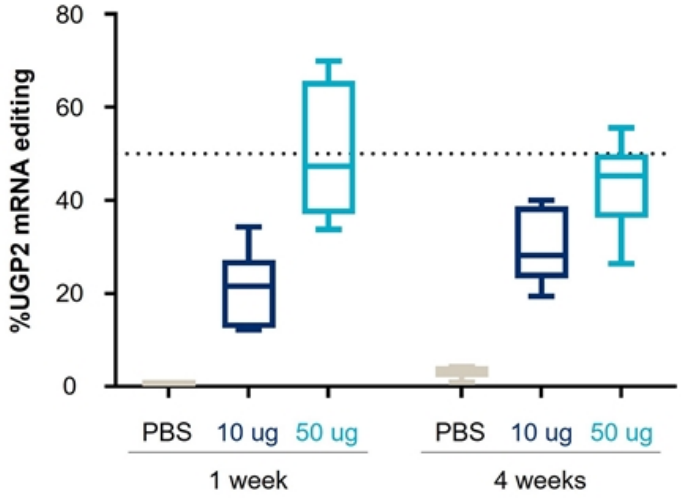
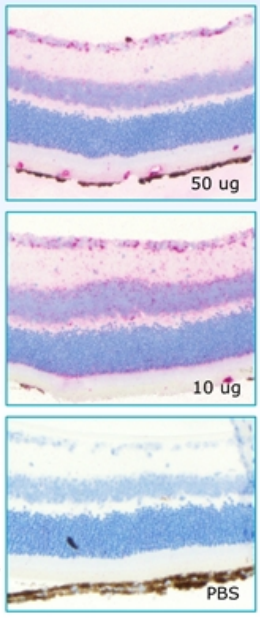
293T cells transfected with both nonsense mutation on MECP2 (GFP-fusion construct) and ADAR plasmids. AIMers transfected for 48h prior to RNA extraction and sequencing. Percentage editing determined by Sanger sequencing. Left: Single dose (25nM) treatment Middle: Full dose response curve (25nM, 5-fold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

ADAR editing: Up to 50% editing *in vivo* in posterior of eye one month post-single IVT dose

Durable, dose-dependent editing post-single intravitreal dose of UGP2 AIMer-1



AIMers in retina at 4 weeks



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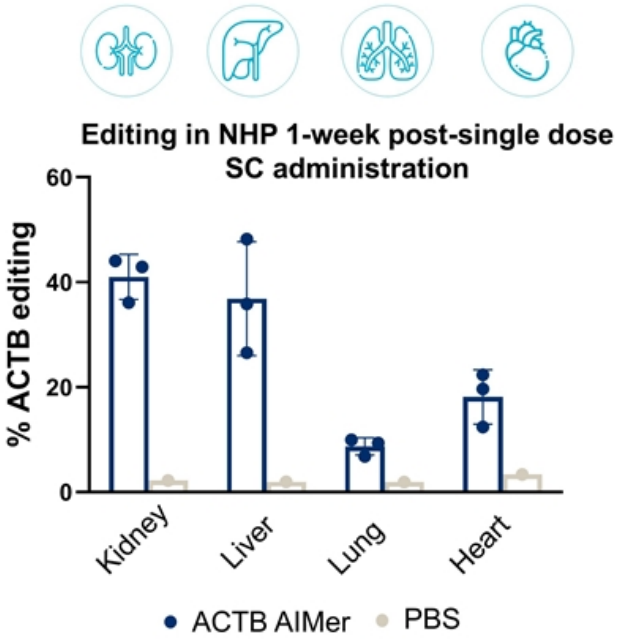
Mice received a single IVT injection (10 or 50 ug AIMer), and eyes were collected for RNA analysis and histology 1 or 4 weeks later. Left: editing evaluated by Sanger sequencing, and % RNA editing calculated with EditR. Right: FFPE and RNA scope assay specific for AIMer, red = oligo, blue = nuclei. Posterior region: retina, choroid, sclera.

Achieving productive editing in multiple NHP tissues with unconjugated systemic AIMer delivery

- ✓ GalNAc-conjugated *(Targeted - subcutaneous)*
- ✓ Unconjugated *(Local – IVT, IT)*
- ✓ **Unconjugated *(Systemic)***

- NHP study demonstrated productive editing in kidney, liver, lung and heart with single subcutaneous dose



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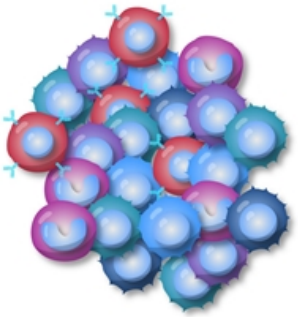
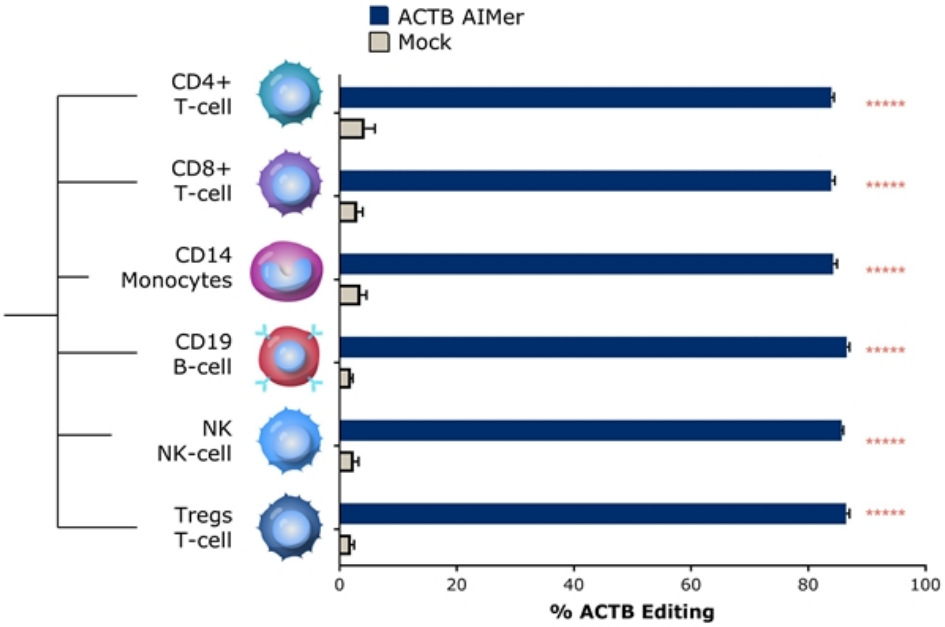
NHP: non-human primate; ACTB: Beta-actin
Dose: 50 mg/kg SC on Day 1 Necropsy for mRNA (ACTB Editing) Day 8

Achieving productive editing in multiple immune cell types with AIMers *in vitro*

Human peripheral blood mononuclear cell (PBMC)



Activate (PHA) → Dose → Sort



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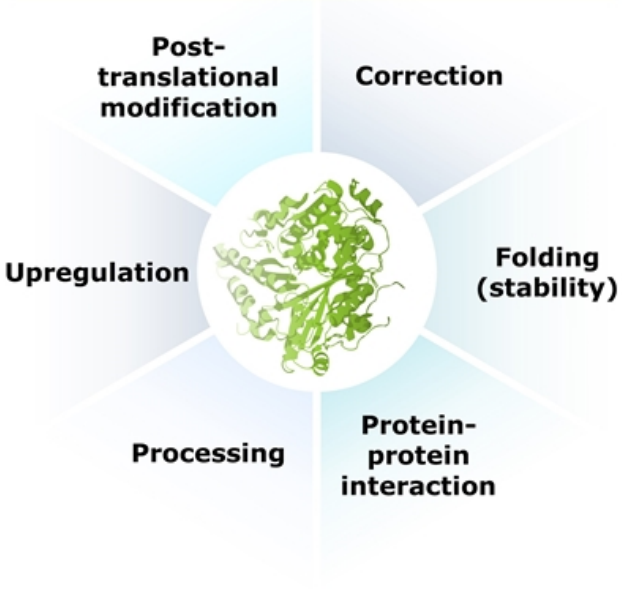
Human PBMCs dosed with 10 uM ACTB AIMers, under activating conditions (PHA). After 4 days, different cell types isolated, quantitated for editing %. ACTB: Beta-actin; Two-way ANOVA followed by post hoc comparison per cell line. P values were Bonferroni-corrected for multiple hypotheses

Expanding addressable disease target space using ADAR editing to modulate proteins

ADAR editing of mRNA

Restore or modify protein function



Impact diseases

Examples:

- Familial epilepsies
- Neuropathic pain
- Neuromuscular disorders
- Dementias
- Haploinsufficient diseases
- Loss of function

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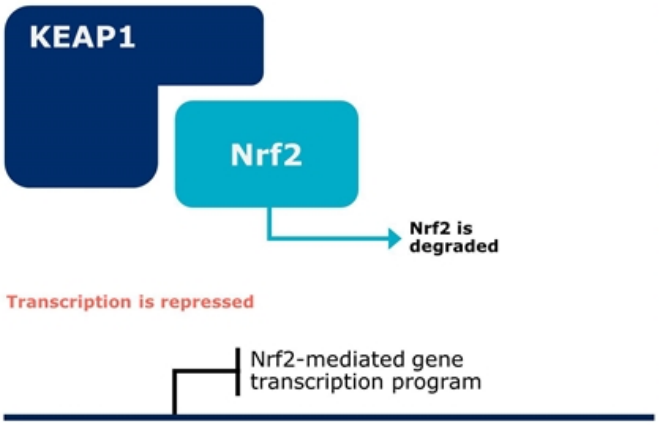
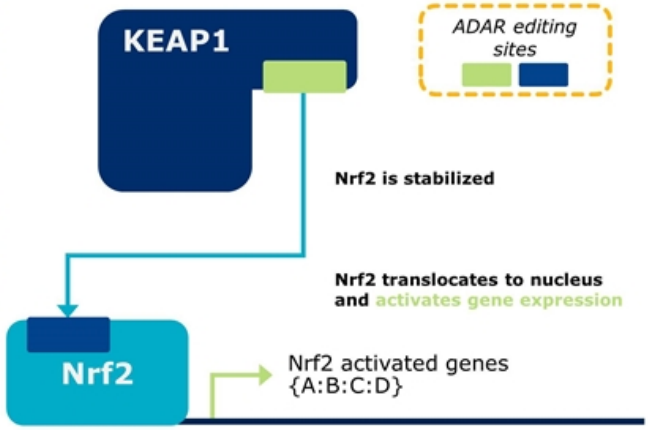
ADAR to modify protein-protein interactions

Basal conditions



KEAP1 binds Nrf2, targeting Nrf2 for proteosomal degradation and repressing Nrf2 mediated gene transcription

ADAR modified pathway



ADAR editing to change one amino acid in KEAP1 or Nrf2 could allow for stabilization of Nrf2 and activation of Nrf2 mediated gene transcription

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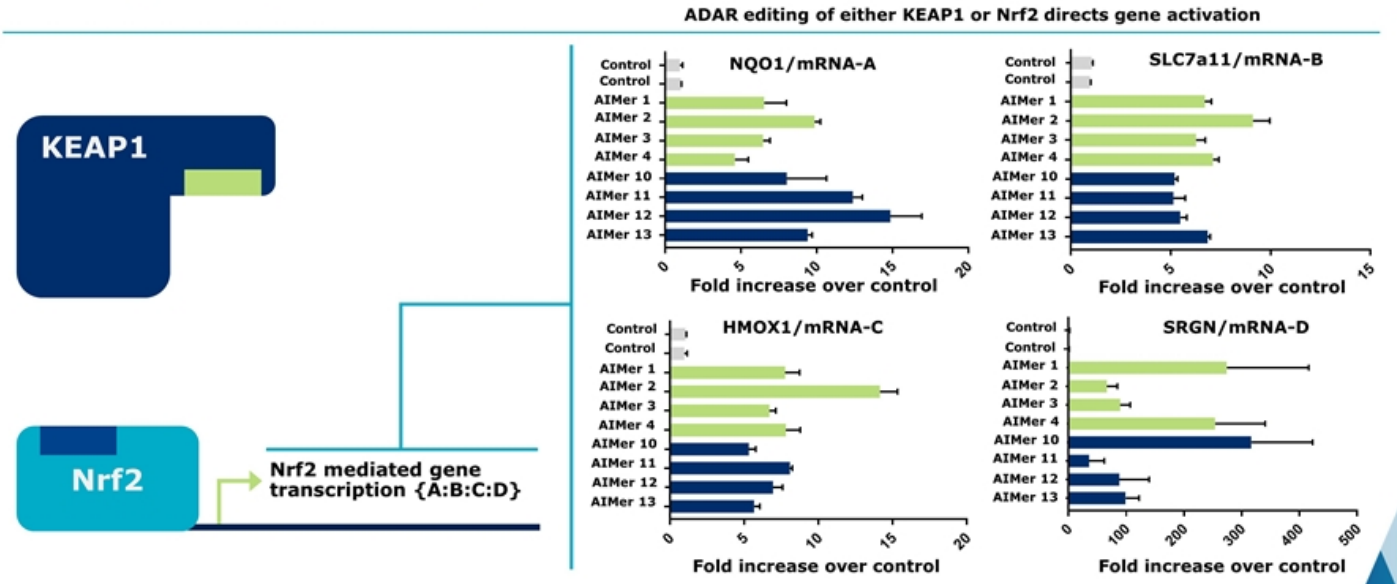
ADAR editing activates multiple genes confirming disrupted protein-protein interaction *in vitro*



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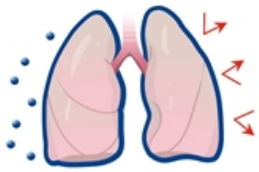
Gene expression quantified by PCR (n=2)

RNA editing is uniquely suited to address the therapeutic goals for AATD

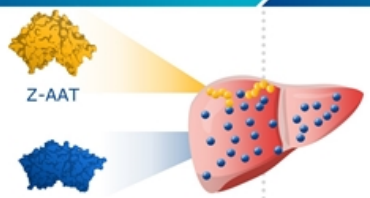
Wave ADAR editing approach addresses all goals of treatment:

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



M-AAT reaches lungs to protect from proteases

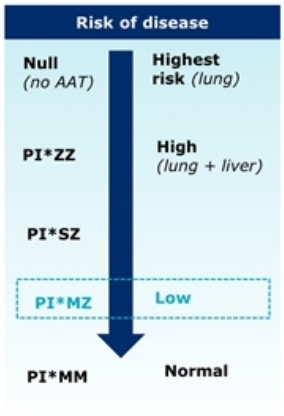
2) Reduce Z-AAT protein aggregation in liver



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

3) Retain M-AAT physiological regulation

M-AAT secretion into bloodstream



Alternative approaches address only a subset of treatment goals:

*Current **protein augmentation** addresses only lung manifestations*

***siRNA** approaches only address the liver disease*

***Small molecule** approaches may address the lung and liver but do not generate wildtype M-AAT*

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

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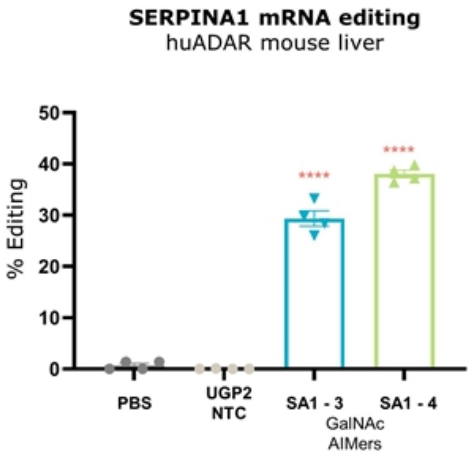
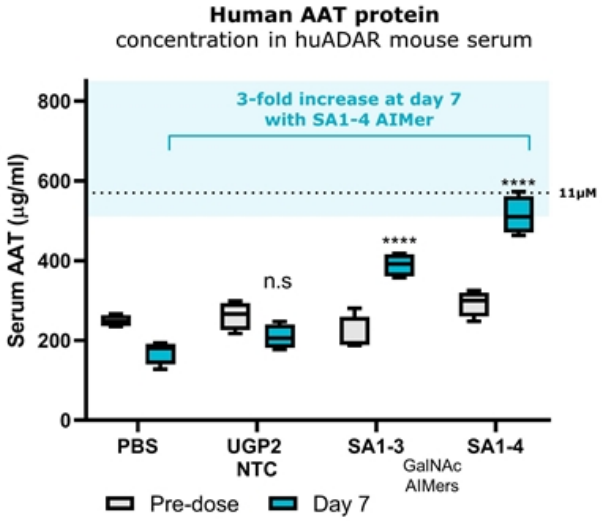
AAT: Alpha-1 antitrypsin; Sources: Strnad 2020; Blanco 2017; Remih 2021

RNA editing of 40% results in therapeutically meaningful increases in circulating AAT protein

SERPINA1 Z allele mRNA editing levels nearing correction to heterozygote (MZ)





AAT serum levels by genotype

PI*MZ: ~3 – 5x increase
PI*SZ: ~2x increase
PI*ZZ: ~3 – 7 uM

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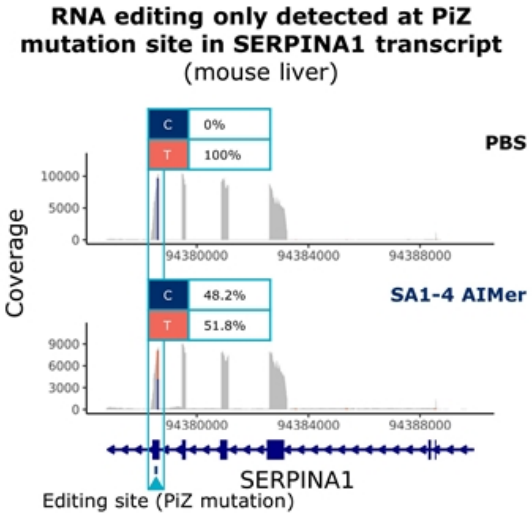
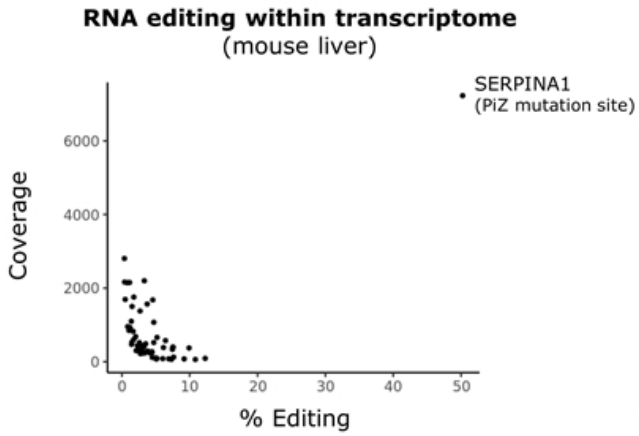
hu*ADAR/SERPINA1* mice administered PBS or 3 x 10 mg/kg AIMer (days 0, 2, and 4) SC. Samples collected day 7. Stats: One-way ANOVA; NTC: non-targeting control; Right: Statistics (ELISA): Matched 2-way ANOVA with correction for multiple comparisons (Bonferroni) was used to test for differences in AAT abundance in treated samples compared to PBS Statistics; de Serres et al., J Intern Med. 2014; NTC: non-targeting control

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

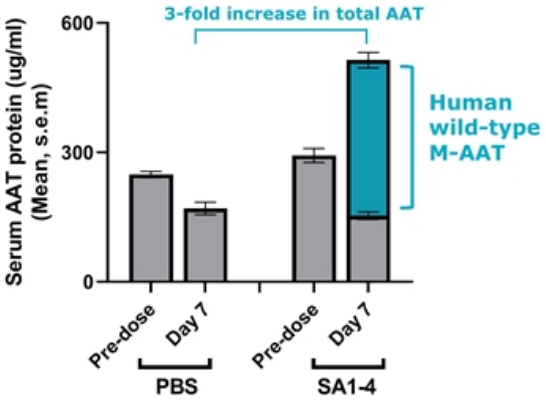




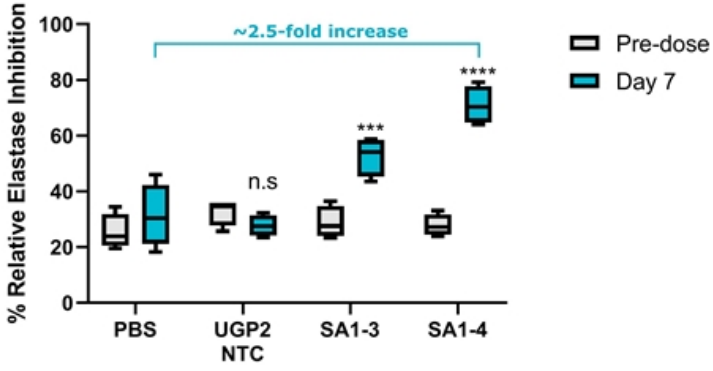
Dose 3 x 10mg/kg days (0, 2, 4) SC. Liver biopsies day 7. RNAseq, To quantify on-target SERPINA1 editing reads mapped to human SERPINA1, to quantify off-target editing reads mapped to entire mouse genome; plotted circles represent sites with LOD>3 (N=4); Analyst and Investor Research Webcast September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

ADAR editing restores circulating, functional M-AAT

Wild-type M-AAT detected with ADAR editing



Significant increase in neutrophil elastase inhibition with ADAR editing



✓ Z allele mRNA editing *in vivo* | ✓ AAT protein increase | ✓ Wild-type M-AAT functional

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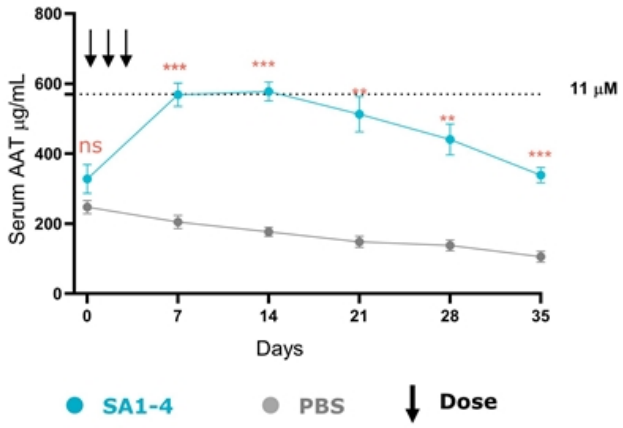
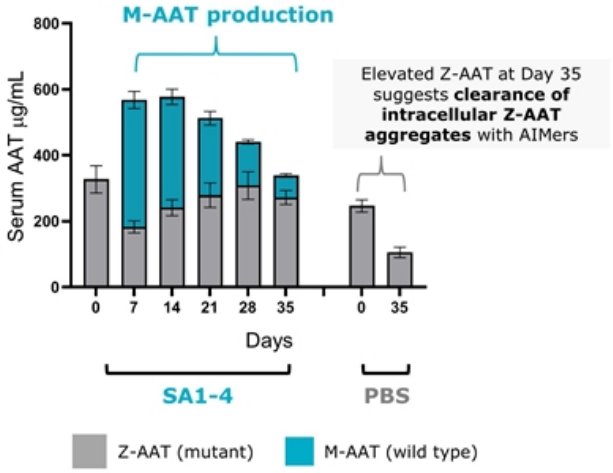
Left: Mass spectrometry and ELISA Right: (Elastase inhibition): Matched 2-way ANOVA with correction for multiple comparisons (Bonferroni) was used to test for differences in elastase inhibition activity in serum collected at day 7 vs pre-dose for each treatment group; NTC: non-targeting control

Increase in circulating human AAT is durable, with restored M-AAT detected one month post last dose

Human AAT serum concentration ≥3-fold higher over 30 days post-last dose



Restored wild-type M-AAT detected over 30 days post-last dose



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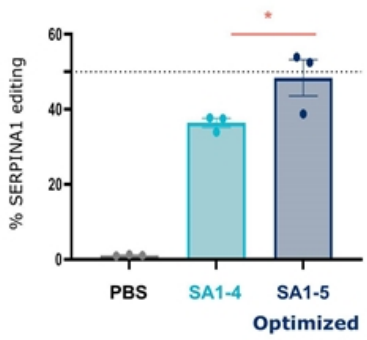
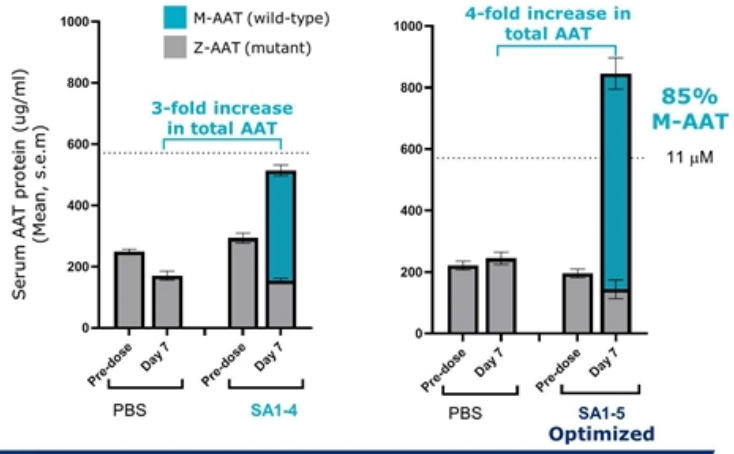
SA1-4: GalNAc AIMer (Left) hu*ADAR/SERPINA1* mice administered PBS or 3 x 10 mg/kg AIMer (days 0, 2, and 4) SC. AAT levels quantified by ELISA. Data presented as mean ± sem. Stats: Matched 2-way ANOVA ns nonsignificant, ** P<0.01, *** P<0.001. (Right) Proportion of AAT in serum, Z type (mutant) or M type (wild type), measured by mass spectrometry, total AAT levels quantified by ELISA

Optimized AIMers achieve ~50% mRNA editing and restore AAT protein well above therapeutic threshold

RNA editing huADAR mouse
(3x5 mg/kg, SC)



AAT protein concentration in serum
(3x10 mg/kg, SC)



- **Additional preclinical data expected in 2022, including reduction in Z-AAT aggregates and changes in liver pathology**
- **AATD AIMer development candidate expected in 2022**

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Left: AIMers administered hu*ADAR/SERPINA1* mice (3x5 mg/kg) on days 0, 2, and 4. Livers collected on day 7, and SERPINA1 editing was quantified by Sanger sequencing (shown as mean ±. sem) Stats: One-way ANOVA was used to test for differences in editing between SA1-4 and other oligos * P<0.05 Right: hu*ADAR/SERPINA1* mice administered PBS or 3 x 10 mg/kg AIMer (days 0, 2, and 4) SC. Proportion of AAT protein in serum measured by mass spec, total AAT protein quantified by ELISA

Upcoming milestones throughout 2022 will unlock opportunities

WVE-004 C9orf72 ALS & FTD	• Clinical data being generated to enable decision making
WVE-003 HD SNP3	• Clinical data being generated to enable decision making
WVE-N531 DMD Exon 53	• Clinical data being generated to enable decision making
AIMer AATD SERPINA1	• Additional preclinical data, including reduction in Z-AAT aggregates and changes in liver pathology • AATD AIMer development candidate expected

Silencing	**CNS** *(Intrathecal)*
Splicing	**Muscle** *(IV)*
ADAR editing	**Liver** *(Subcutaneous GalNAc)*

Success with any current program validates platform and unlocks modalities and tissues

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