Wave Life Sciences
Corporate Presentation

May 3, 2023

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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.

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Emerging leader in RNA medicines

Multi-modal drug discovery and development platform to address new areas of disease biology
RNA editing, splicing and silencing

Differentiated, clinical-stage RNA medicines pipeline with first-in-class RNA editing programs

Strategic collaborations to expand and advance pipeline (GSK and Takeda)

Multiple pipeline and platform catalysts expected in 2023 and beyond

Well-capitalized with expected cash runway into 2025

GMP manufacturing

Strong and broad IP position[1]

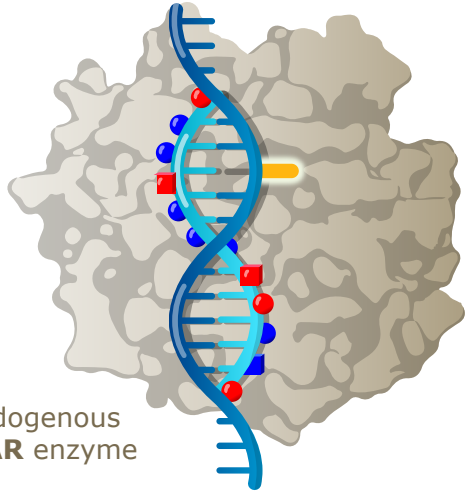
Wave Life Sciences is an RNA medicines company committed to delivering life-changing treatments for people battling devastating diseases

[1]stereopure oligonucleotides and novel backbone chemistry modifications

RNA medicines allow matching disease target to therapeutic modality

RNA Base Editing

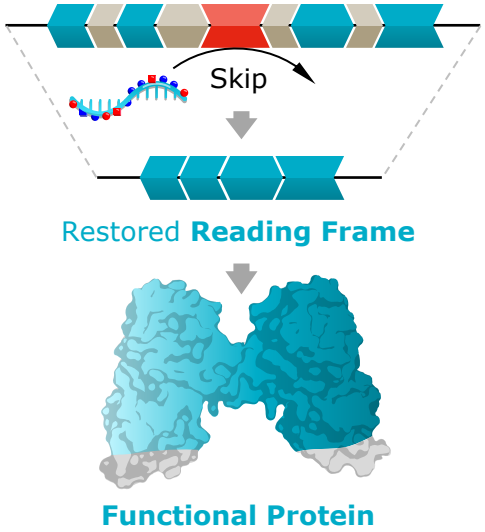
- Efficient editing of RNA bases to **restore** or **modulate** protein production



Endogenous **ADAR** enzyme

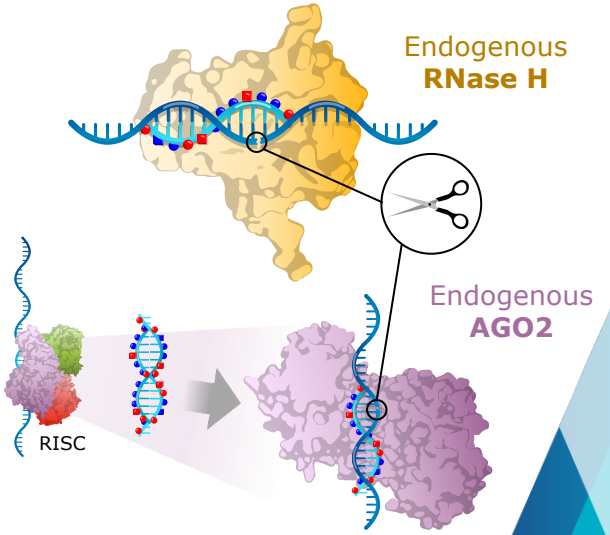
Splicing

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



Silencing

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



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Robust RNA medicines pipeline with first-in-class RNA editing programs

Program	Discovery	Preclinical	Clinical	Rights	Patient population (US & Europe)
RNA EDITING					
WVE-006 SERPINA1 (AATD)				GSK exclusive global license	200K
Multiple undisclosed				100% global	-
SPLICING					
WVE-N531 Exon 53 (DMD)			Phase 1/2	100% global	2.3K
Other exons (DMD)				100% global	Up to 18K
SILENCING: ANTISENSE					
WVE-003 mHTT (HD)			Phase 1/2	Takeda 50:50 Option	25K Manifest (SNP3) 60K Pre-Manifest (SNP3)
WVE-004 C9orf72 (ALS and FTD)			Phase 1/2	Takeda 50:50 Option	4K (C9-ALS) 26K (C9-FTD)
SCA3 (ATXN3)				Takeda 50:50 Option	8K
SILENCING: RNAi					
Undisclosed				100% global	-

Through GSK collaboration, Wave can advance up to three collaboration programs and GSK can advance up to eight collaboration programs

AATD: Alpha-1 antitrypsin deficiency; DMD: Duchenne muscular dystrophy; HD: Huntington's disease; ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; SCA3: Spinocerebellar ataxia 3

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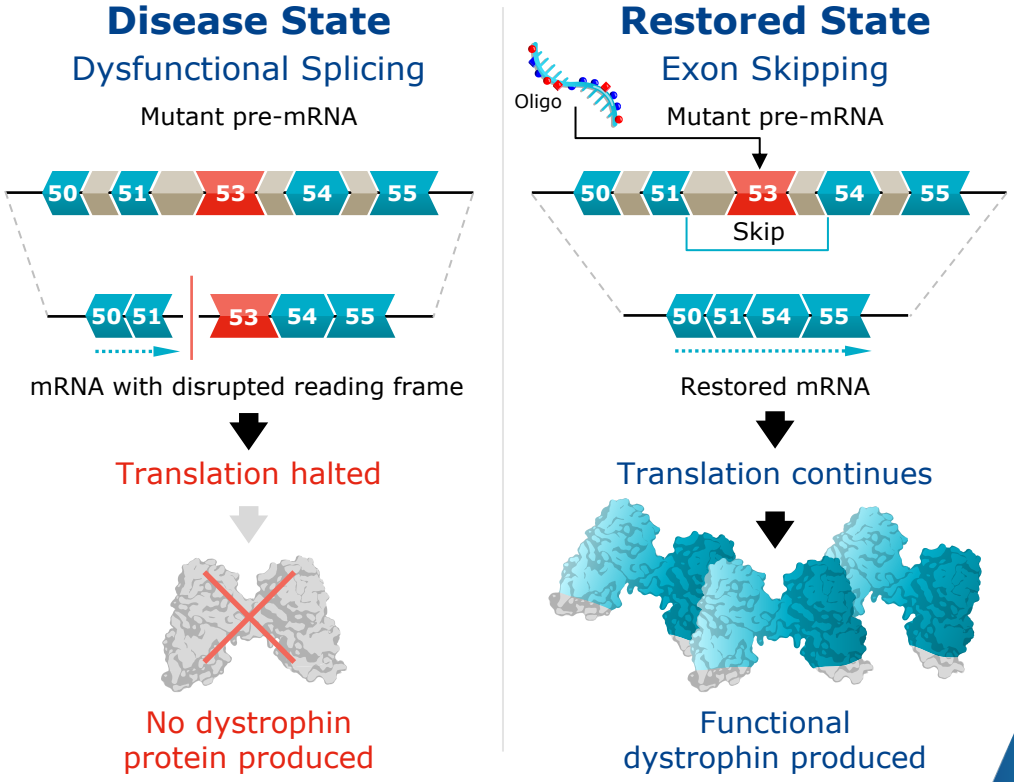
WVE-N531

Duchenne muscular dystrophy

Duchenne muscular dystrophy

- **Genetic mutation in dystrophin gene prevents the production of dystrophin protein**, a critical component of healthy muscle function
- **Impacts approx. 1 in every 5,000 newborn boys each year**; approx. 20,000 new cases annually worldwide
  - Approx. 8-10% are amenable to exon 53 skipping
- **Dystrophin protein established by FDA as surrogate endpoint** reasonably likely to predict benefit in boys[1] for accelerated approval in DMD
- Increasing amount of functional dystrophin expression over minimal amount shown with approved therapies is expected to result in greater benefit for boys with DMD

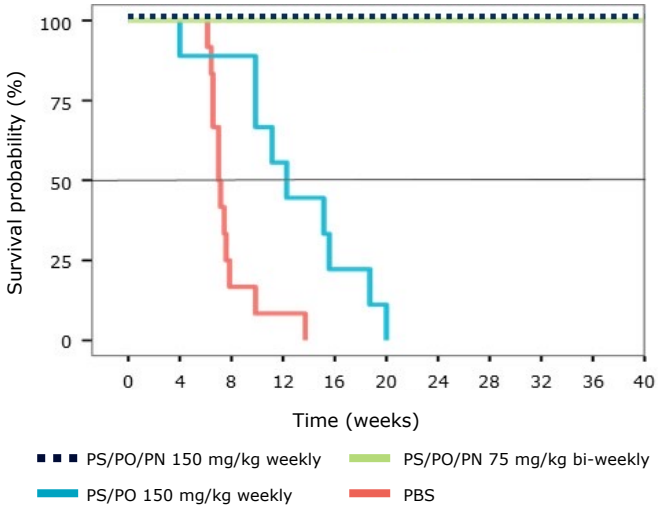


[1]Vyondys: www.fda.gov; viltepso; www.fda.gov; Exondys; www.fda.gov; Amondys: www.fda.gov

Preclinical data supported advancing WVE-N531 to clinical development

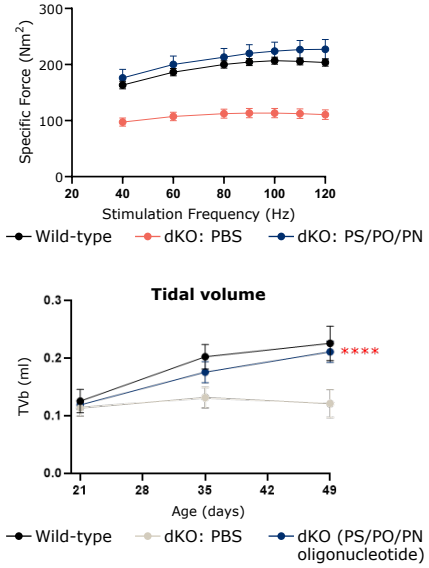
PN chemistry improved function and survival in dKO mice

100% survival at time of study termination



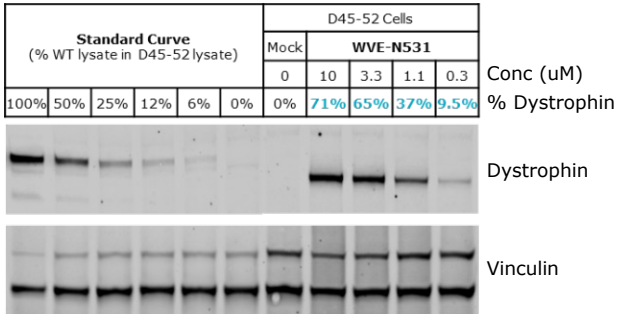
Note: Untreated, age-matched mdx mice had 100% survival at study termination [not shown]

Restored muscle and respiratory function to wild-type levels



WVE-N531: Dystrophin restoration of up to 71% *in vitro*

Western Blot normalized to primary healthy human myoblast lysate



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

In multidose portion of study, patients received three biweekly 10 mg/kg doses

Single ascending intra-patient doses

Initial cohort

- **Boys with DMD amenable to exon 53 skipping**

1 mg/kg

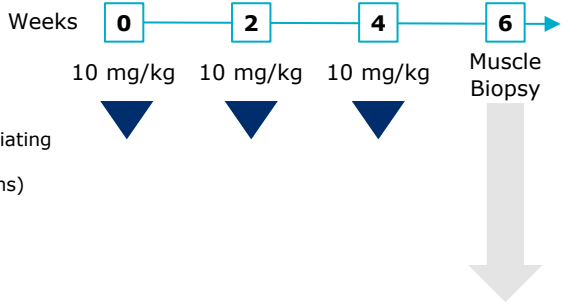
3 mg/kg

6 mg/kg

10 mg/kg

Period before initiating multidosing (~1 – 2 months)

Multidosing at 10 mg/kg every other week



Data include:

- WVE-N531 muscle concentrations
- WVE-N531 localization
- Exon skipping
- Dystrophin protein

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Dose WVE-N531

WVE-N531 in DMD: Delivered positive proof-of-concept data in 4Q 2022

- High exon skipping and muscle concentrations after three biweekly 10 mg/kg doses
- Similar exon skipping regardless of mutation
  - Patient 1: del48-52
  - Patient 2: del45-52
  - Patient 3: del51-52
- PK analysis indicated 25-day half-life in plasma
- WVE-N531 appeared safe and well-tolerated

Patient	Tissue Source	Tissue concentration (µg/g)	% Exon skipping by RT-PCR	Dystrophin by Western blot (% of normal)
1	Deltoid	85.5	61.5	0.24
2	Deltoid	33.5	49.8	0.23
3	Bicep	8.3	47.9	0.34

Mean muscle concentration: 42 µg/g

Mean exon skipping: 53%

Mean dystrophin: 0.27% of normal (BLQ)

Data presented March 22, 2023 at Muscular Dystrophy Association Clinical and Scientific Conference

Biopsies collected ~2 weeks post-last dose (3 biweekly doses of 10 mg/kg)
Data cut-off: December 6, 2022

42 µg/g = 6.1 µM

BLQ: Below level of quantification (1%)

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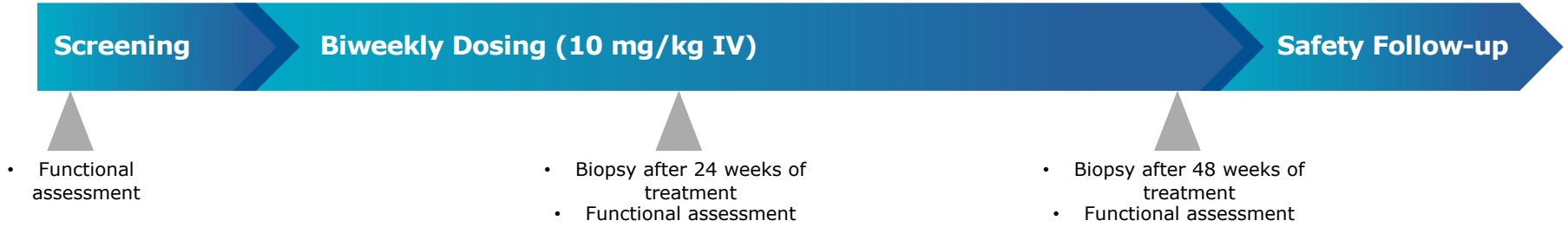
Initiating Part B, a potentially registrational Phase 2 clinical trial of WVE-N531



- **Design**: Phase 2, open-label, 10 mg/kg every other week, up to 10 patients
- **Endpoints**: Dystrophin (powered for >5% of normal), safety/tolerability, pharmacokinetics, functional assessments (incl. NSAA and others)
- **Biopsies**:
  - After 24 weeks of treatment
  - After 48 weeks of treatment
- **Data from Part B expected in 2024**

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IV: intravenous; NSAA: North star ambulatory assessment

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GSK Collaboration and WVE-006 for Alpha-1 antitrypsin deficiency (AATD)

Strategic collaboration with GSK to develop transformative RNA medicines for genetically defined diseases

- ✓ **$170 million upfront to Wave** (cash and equity[1])
- ✓ Additional research support funding
- ✓ Potential for **up to $3.3 billion in milestones**[2]
- ✓ Expands Wave's pipeline

Extends cash runway into 2025

PRISM

Multiple value drivers to Wave

Milestone / royalties	Milestone / royalties	Genetic targets
GSK granted exclusive global license to WVE-006 for AATD	**GSK to advance up to eight collaboration programs**	**Wave to leverage GSK's genetic insights**
Up to $225 million in development and launch milestones	Up to $1.2 billion in aggregate in initiation, development and launch milestones	Wave to advance up to three wholly owned collaboration programs (or more pending agreement with GSK) [3]
Up to $300 million in sales-related milestones	Up to $1.6 billion in aggregate in sales-related milestones	
Double-digit tiered royalties as a percentage of net sales up to high-teens	Tiered royalties as a percentage of net sales up to low-teens	
Development and commercialization responsibilities transfer to GSK after completion of first-in-patient study	Development and commercialization responsibilities transfer to GSK at development candidate	

First-in-class RNA editing program

Collaboration leverages Wave's unique stereopure, PN-chemistry containing PRISM™ platform, including **editing**, **splicing**, **silencing** (RNAi and antisense)

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[1]$120 million in cash and $50 million equity investment received in January 2023, [2]Initiation, development, launch, and commercialization milestones for WVE-006 and programs progressed during initial 4-year research term (8 GSK collaboration programs) [3]GSK eligible to receive tiered royalty payments and commercial milestones from Wave

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

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

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

WVE-006 (GalNAc-conjugated AIMer)

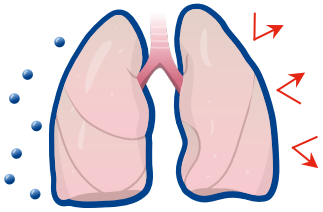
Edited *SERPINA1* mRNA enables wild-type M-AAT protein production

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

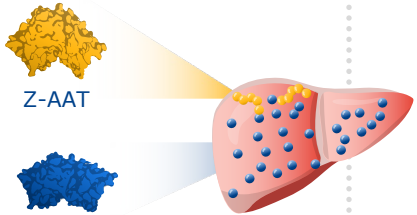
1) Restore circulating, functional wild-type M-AAT

2) Reduce Z-AAT protein aggregation in liver

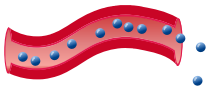
3) Retain M-AAT physiological regulation



M-AAT reaches lungs to protect from proteases



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



M-AAT secretion into bloodstream

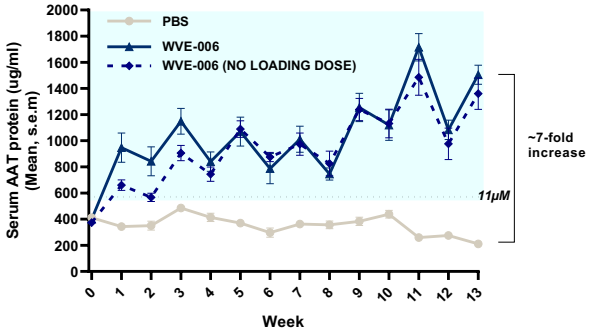
AAT: Alpha-1 antitrypsin Strnad *et al*., 2020 *N Engl J Med* 382:1443-55; Blanco *et al*., 2017 *Int J Chron Obstruct Pulmon Dis* 12:561-69; Remih *et al.,* 2021 *Curr Opin Pharmacol* 59:149-56.

WVE-006 in AATD: First-in-class RNA editing candidate approaching the clinic

Potentially comprehensive approach to address both lung and liver manifestations of AATD

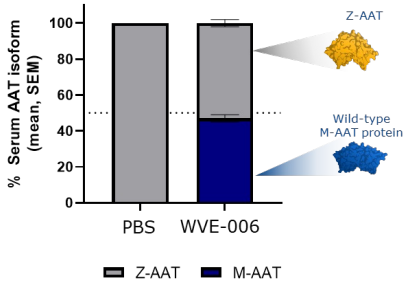
Increased AAT protein in NSG-PiZ mice

WVE-006 treatment results in serum AAT protein levels >11 uM in NSG-PiZ mice



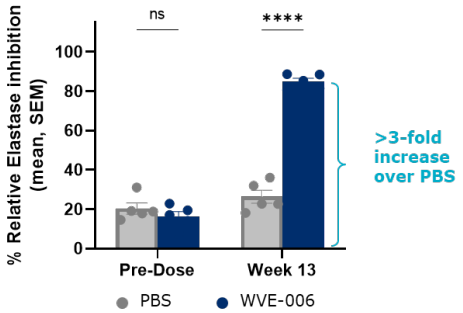
Confirmed restored wild-type M-AAT protein

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



Demonstrated functionality of M-AAT protein

Serum neutrophil elastase inhibition activity in NSG-PiZ mice

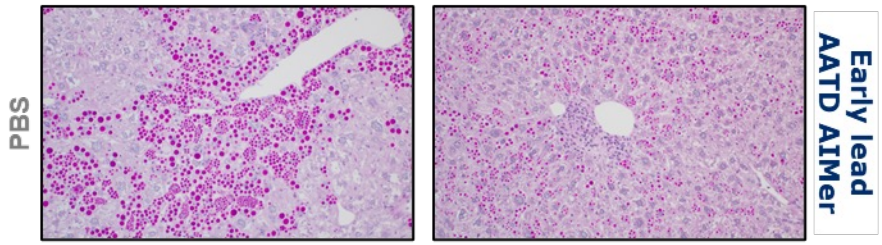


CTA submissions for first-in-human study expected in 2H 2023

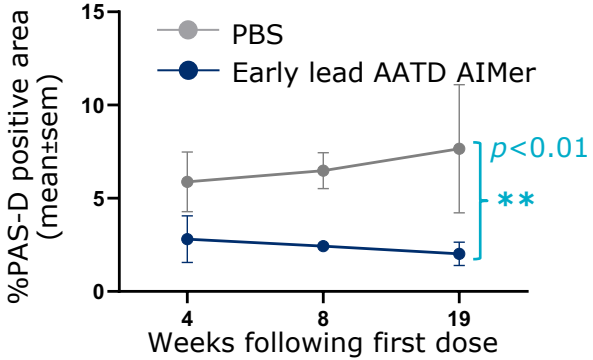
AATD: Alpha-1 antitrypsin deficiency; M-AAT protein: wild-type AAT protein; WVE-006 administered subcutaneously (10 mg/kg bi-weekly) in 7-week old NSG-PiZ mice (n=5 per group); Loading dose: 3 x 10 mg/kg at Day 0. Left: Liver biopsies collected at wk 13 (1 wk after last dose) and SERPINA1 editing quantified by Sanger sequencing; Right: Total serum AAT protein quantified by ELISA; Stats: Two-Way ANOVA with adjustment for multiple comparisons (Tukey)

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

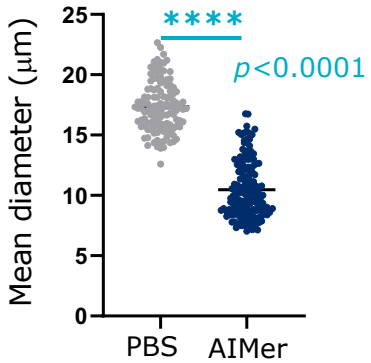
PAS-D staining
(19 weeks)



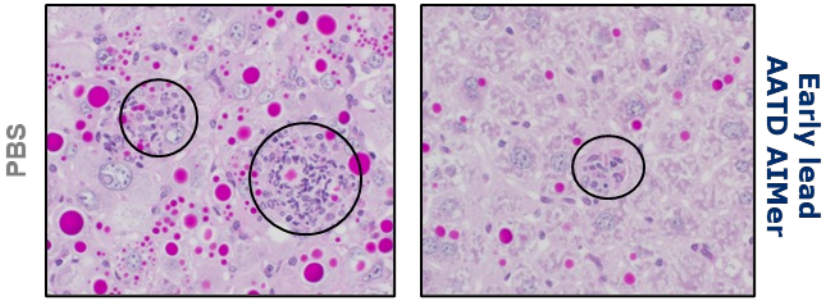
PAS-D-positive area



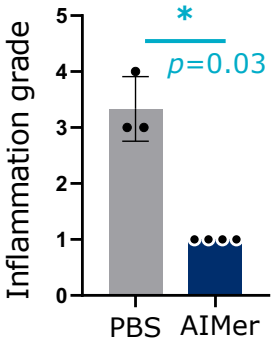
PAS-D globule size
(19 weeks)



Lobular inflammation
(19 weeks)



Lobular inflammation
(19 weeks)



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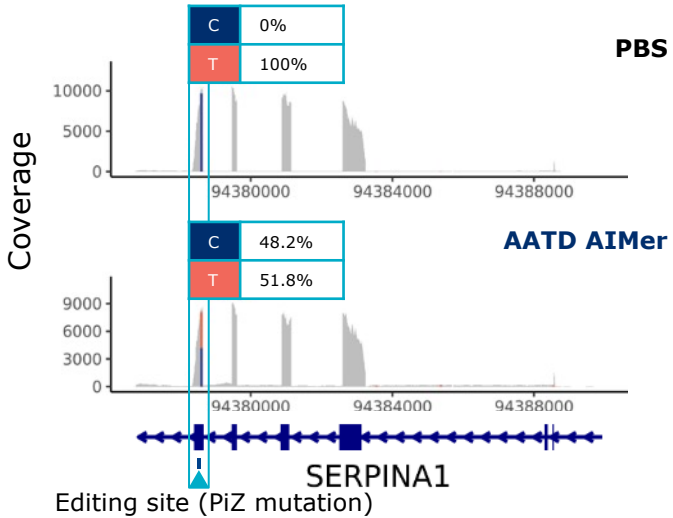
Early lead pre-optimization AATD AIMer (SA1-5) administered in hu*ADAR/SERPINA1* mice (8–10 wKs old); lower left: 20x liver images PAS-D stained, 19 weeks; Quantification of PAS-D positive staining, Stats 2-way ANOVA; Right: Quantification lobular inflammation grade (Grade based on # of inflammatory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

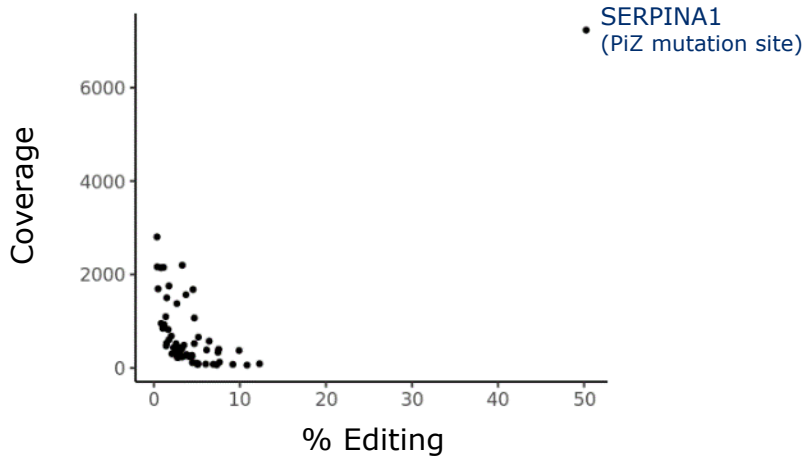
AIMer-directed editing is highly specific in mice

No bystander editing observed on SERPINA1 transcript

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



RNA editing across transcriptome
(mouse liver)



Dose 3x10 mg/kg (days 0, 2, 4) SC with AATD AIMer (SA1 – 4). Liver biopsies day 7. RNA-seq to quantify on-target SERPINA1 editing, to quantify off-target editing reads mapped to entire mouse genome; plotted circles represent sites with LOD>3 (N=4), SERPINA1 edit site is indicated

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WVE-004

Amyotrophic Lateral Sclerosis (ALS)

Frontotemporal Dementia (FTD)

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

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

Different manifestations across a clinical spectrum

Amyotrophic Lateral Sclerosis (ALS)

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

Frontotemporal Dementia (FTD)

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

Including patients with C9-associated ALS, FTD or both

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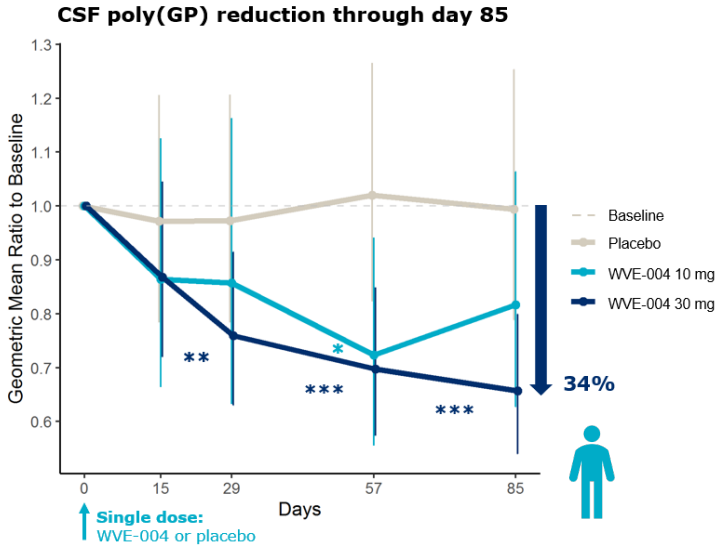
Sources: Balendra et al, EMBO Mol Med, 2017; Brown et al, NEJM, 2017, DeJesus-Hernandez et al, Neuron, 2011. Renton et al, Neuron, 2011. Zhu et al, Nature Neuroscience, May 2020, Stevens et al, Neurology 1998

WVE-004 in C9-ALS/FTD: Successful translation of preclinical data to clinic

- PK/PD modeling using preclinical *in vivo* models predicted pharmacodynamically active starting dose
- **Additional single- and multi-dose biomarker and safety clinical data expected in 1H 2023 from following cohorts:**
  - 20 mg single dose
  - 30 mg single dose
  - 60 mg single dose
  - 10 mg monthly dosing
  - 10 mg quarterly dosing

Target engagement in patients supported advancing FOCUS-C9 clinical study



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 cut-off: March 24, 2022

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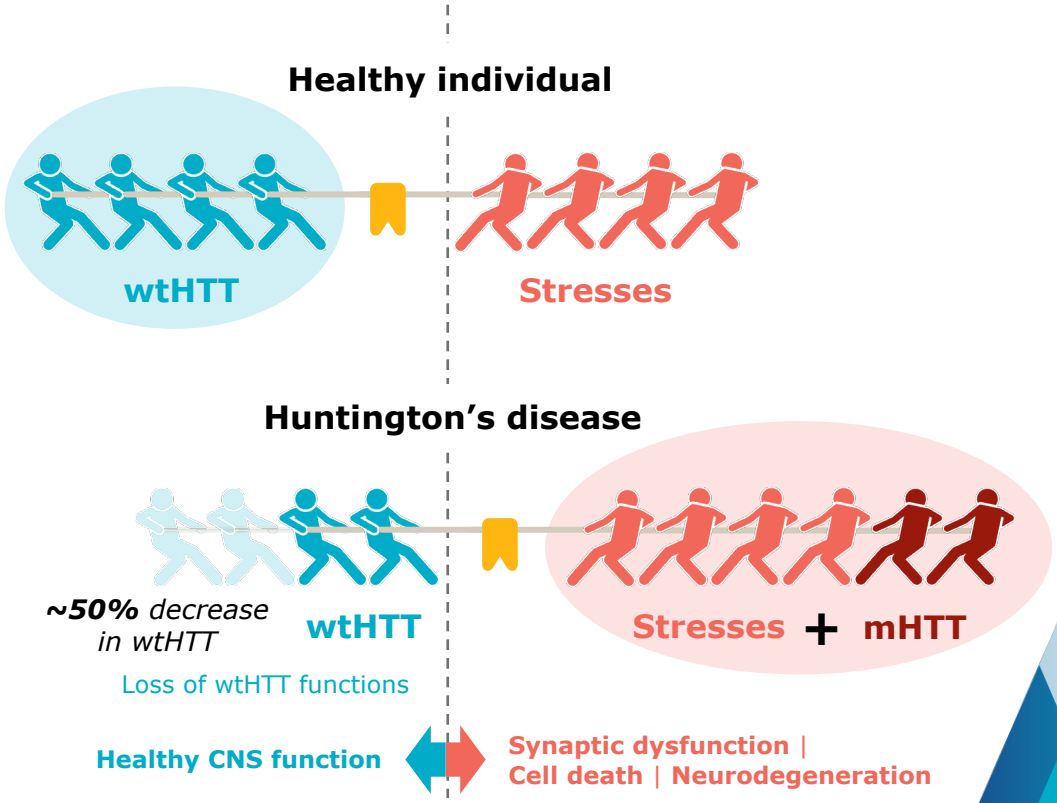
WVE-003

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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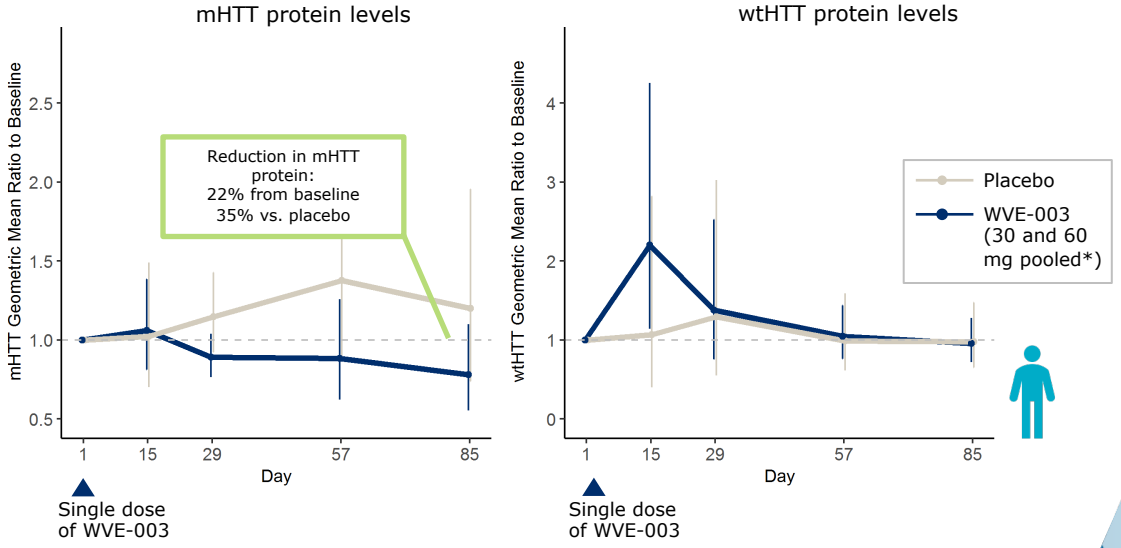
WVE-003: First-in-class allele-selective candidate for HD

- mHTT protein reductions observed in single dose cohorts (Sep. 2022)
- wtHTT protein levels appear consistent with allele-selectivity
- Generally safe and well-tolerated
- **Additional single-dose and multi-dose biomarker and safety clinical data expected in 2H 2023**

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



mHTT: mutant huntingtin protein; wtHTT: wild-type huntingtin protein

*Pooled considering no apparent dose response between 2 cohorts; Data cut-off: August 29, 2022

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AIMers

RNA base editing capability

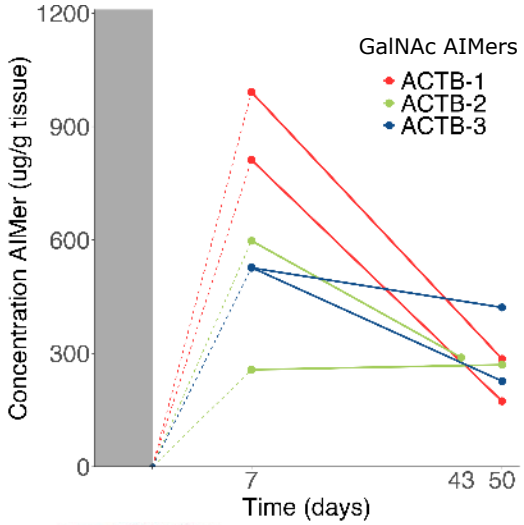
Proof-of-concept preclinical RNA editing data published in *Nature Biotechnology* (March 2022)

nature biotechnology ARTICLES

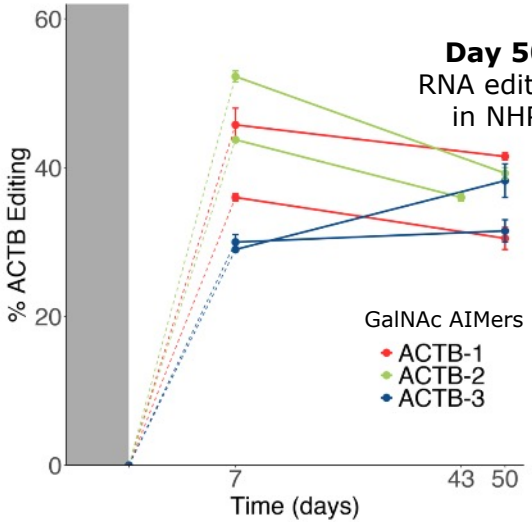
Endogenous ADAR-mediated RNA editing in non-human primates using stereopure chemically modified oligonucleotides

- 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)

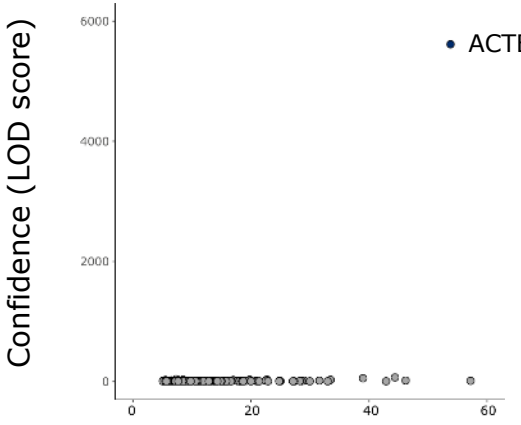


Substantial and durable editing in NHP liver *in vivo* (PD)



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

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

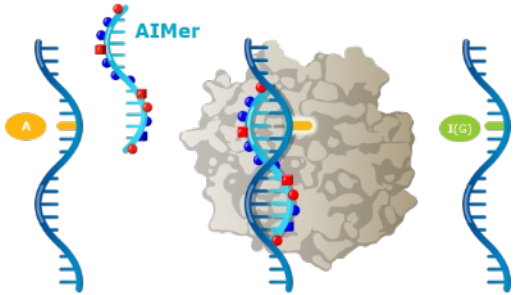
Expanding addressable disease target space using AIMers to activate pathways and upregulate expression

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

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

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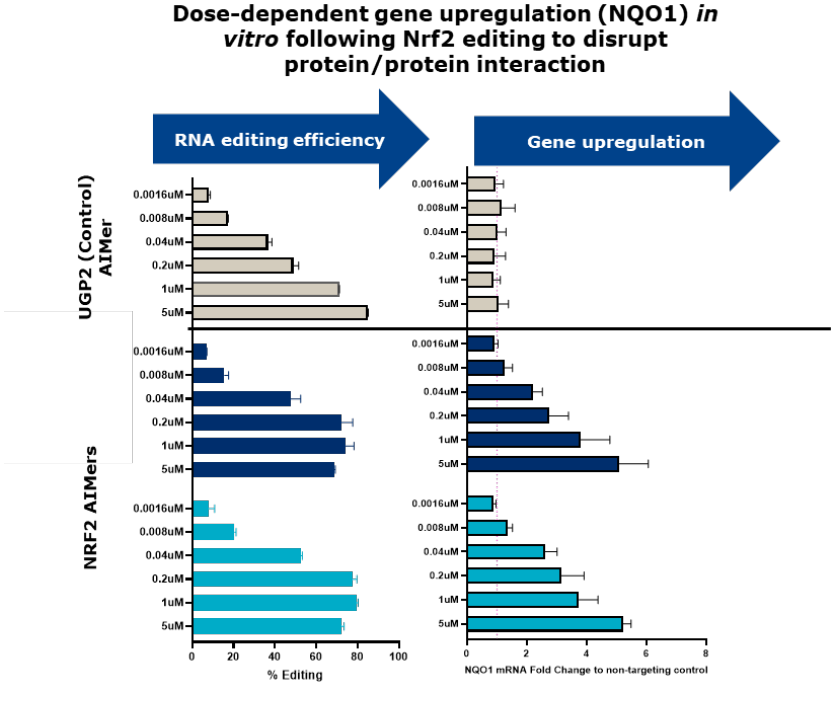
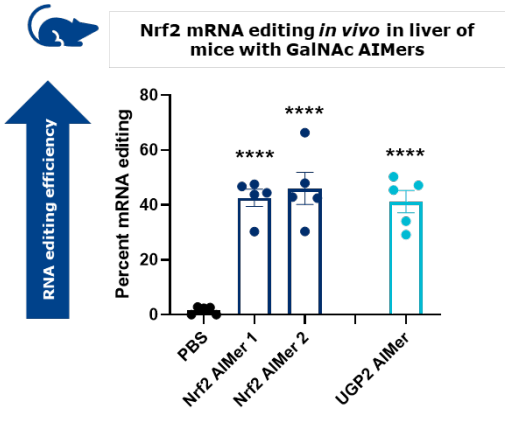
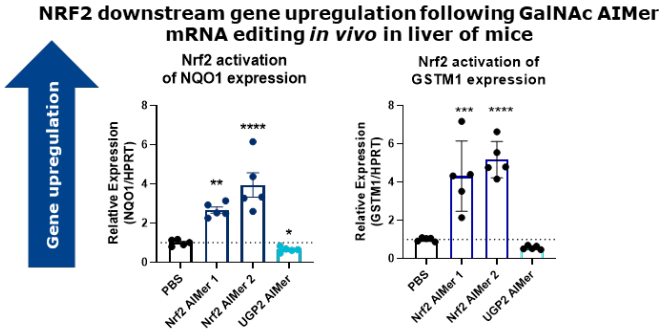
POC: proof of concept

Modulation of protein-protein interactions: AIMers enable activation of gene pathway *in vivo* with single edit







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

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

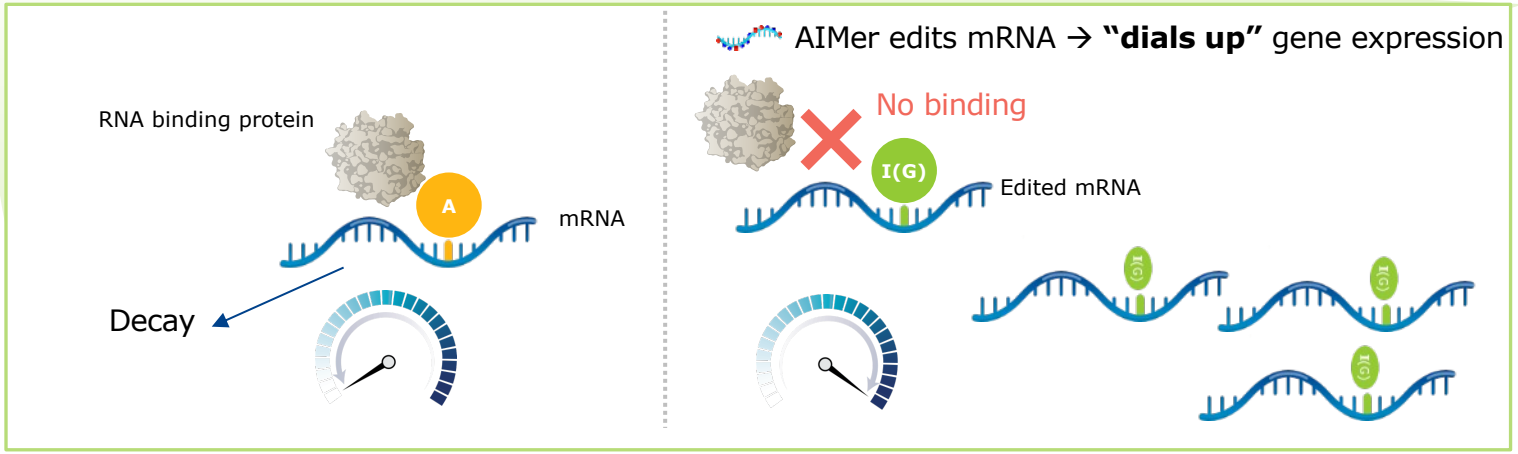
RNA binding proteins recognize sequence motifs to regulate various mRNA properties

Stability
- Enhance or inhibit mRNA decay

Transport
- Intracellular localization

Processing
- Splicing
- Capping
- PolyA usage

Protein production
- Translational efficiency



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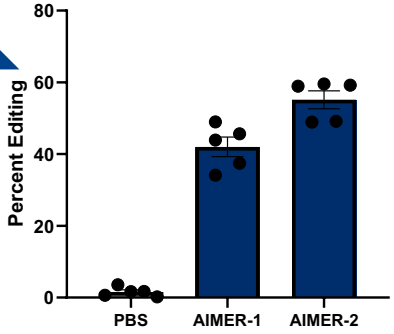
AIMers upregulate mRNA and downstream serum protein *in vivo* above anticipated threshold

Target A (undisclosed liver target)

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

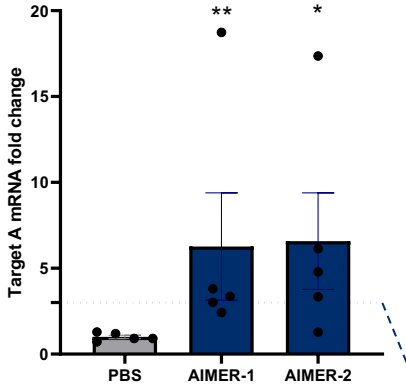
RNA editing

mRNA editing
7 days post-initial dose
GalNAc AIMer

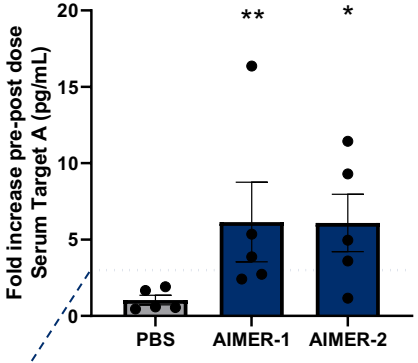


Upregulation

mRNA upregulation
7 days post-initial dose
GalNAc AIMer



Protein upregulation
7 days post-initial dose
GalNAc AIMer



Potential threshold for benefit

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

hADAR mouse dosed subcutaneously 3 x 10 mg/kg GalNAc-conjugated AIMer or PBS days (0, 2, 4), taken down at day 7

WAVE®
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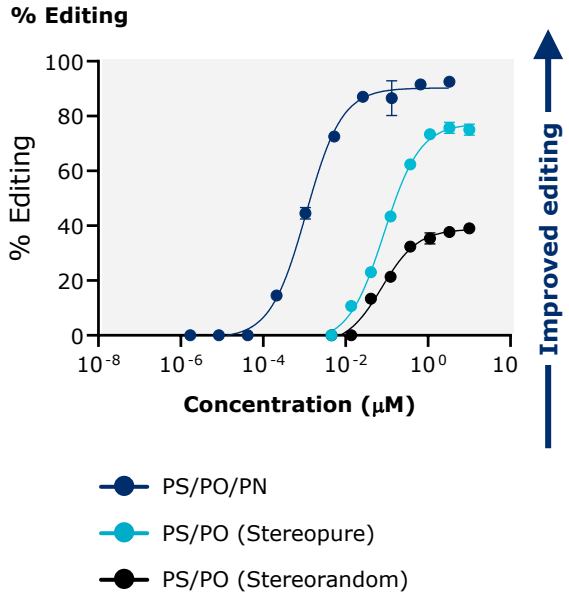
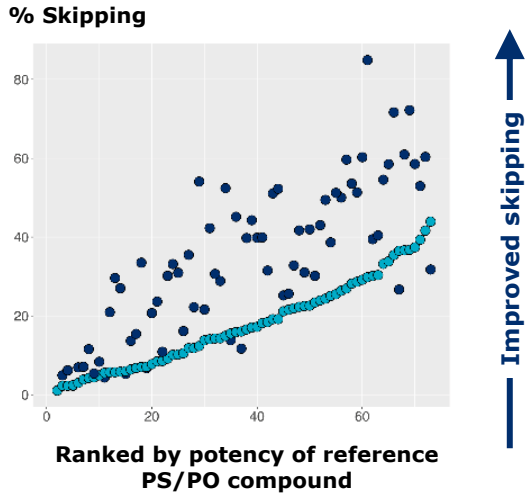
Wave's discovery and drug development platform

Proprietary PN chemistry enhances potency across modalities

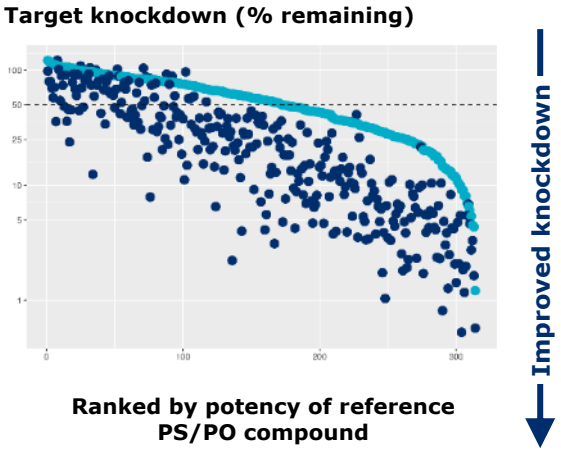
RNA Editing



Splicing



Silencing



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

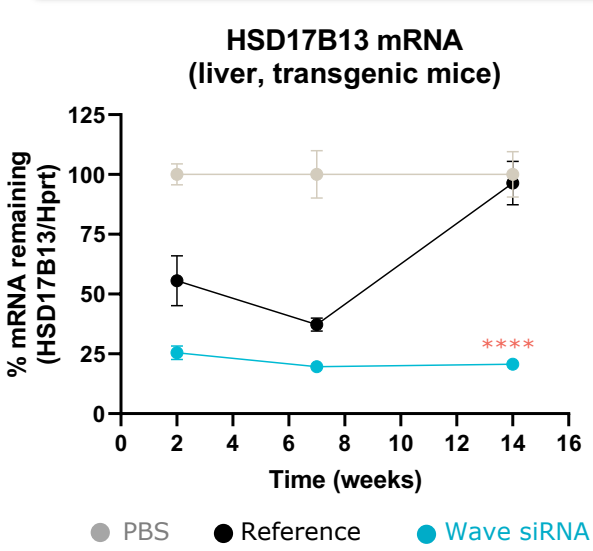
Potential for best-in-class RNAi enabled by Wave's PRISM platform

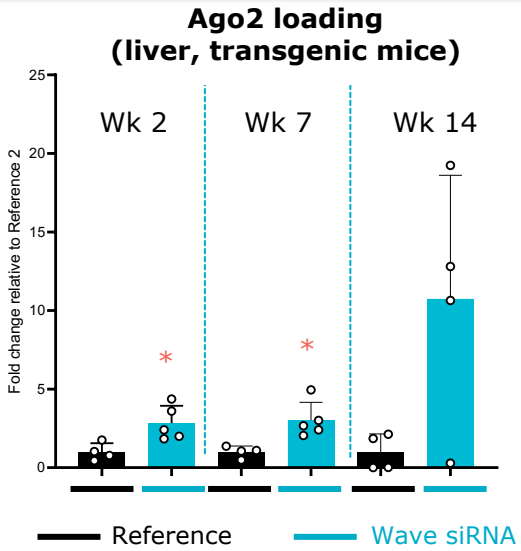
Nucleic Acids Research

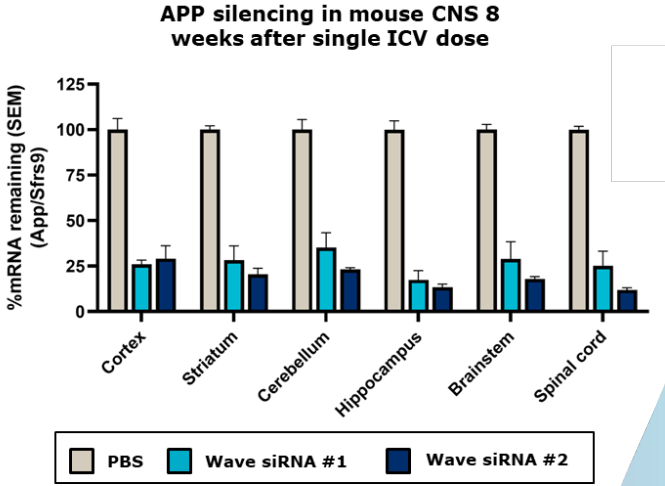
Impact of stereopure chimeric backbone chemistries on the potency and durability of gene silencing by RNA interference

- Unprecedented Ago2 loading following administration of single subcutaneous dose

- First in vivo study of unconjugated siRNAs demonstrated 70-90% APP silencing across six brain regions in mouse CNS at 8 weeks







RNAi is one of multiple Wave modalities being advanced in strategic research collaboration with GSK

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Left, Middle: Mice expressing human *HSD17B13* transgene treated (3 mg/kg)siRNA or PBS, liver mRNA, guide strand concentration, Ago2 loading quantified. Stats: Two-way ANOVA with post-hoc test * P<0.05, ****P<0.0001. Liu et al., 2023 *Nuc Acids Res* doi: 10.1093/nar/gkad268; Right: ICV: Intracerebroventricular; APP: Amyloid precursor protein ; CNS: central nervous system; B6 mice were administered PBS or 100 µg of APP siRNA by ICV injection on day 0 (n=7). Mice euthanized 8 weeks after administration. Taqman qPCR assays used for RNA PD, relative fold changes of *App* to *Sfrs9* mRNA normalized to percentage of PBS group. All treated group show *P*≤0.0001 compared to PBS group in 2way ANOVA.

Delivering on pipeline and platform catalysts

RNA EDITING

WVE-006 for AATD
Most advanced RNA editing candidate & potential best-in-class approach for AATD

WVE-006 CTA submissions expected in 2H 2023

Expansion opportunities in liver, CNS and kidney

SPLICING

WVE-N531 for DMD
Potential best-in-class approach with highest exon skipping reported

Dosing in potentially registrational clinical trial expected in 2023; data expected in 2024

Expansion opportunities in other exons, as well as other muscle diseases and CNS

ANTISENSE SILENCING

WVE-003 for HD
First-in-class wtHTT-sparing approach

Data expected 2H 2023

WVE-004 for ALS/FTD
Variant-selective approach for C9orf72

Data expected 1H 2023

Enables discussion on next steps with Takeda

RNAi

Newest modality in Wave platform
Preclinical data suggest best-in-class potential for Wave RNAi capability

Hepatic, CNS and beyond

DISCOVERY PIPELINE & COLLABORATIONS

Anticipate investor event in 3Q 2023 during which Wave will demonstrate how it is continuing to extend its leadership in RNA editing and share preclinical data on new wholly-owned programs

Advance collaboration activities with GSK, with potential for additional cash inflows in 2023 and beyond

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Realizing a brighter future for people affected by genetic diseases

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