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Wave Life Sciences

Third Quarter 2021 Earnings

November 10, 2021

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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Paul Bolno, MD, MBA

President and CEO

Today's agenda

1. **Business update -** Paul Bolno, MD, MBA, President and CEO
2. **AIMers: Making RNA editing therapeutics a reality -** Chandra Vargeese, PhD, CTO
3. **Therapeutic pipeline -** Michael Panzara, MD, MPH, CMO, Head Therapeutics Disc. and Dev.
4. **3Q 2021 financial update –** Kyle Moran, CFO
5. **Looking ahead -** Paul Bolno, MD, MBA, President and CEO
6. **Q&A**

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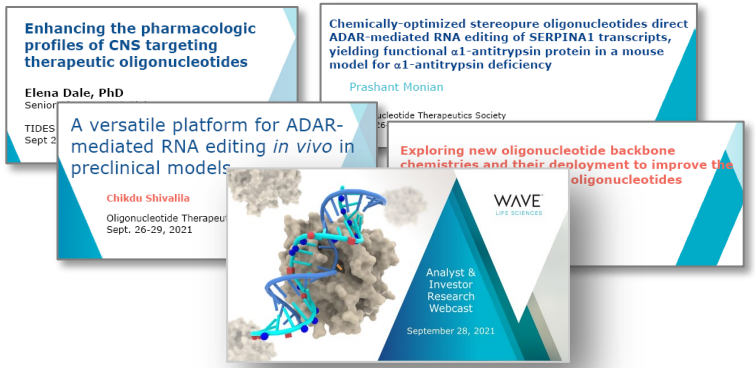
Third quarter 2021 and recent highlights

Capitalized to accelerate RNA editing momentum

- ~$30M aggregate block sale through ATM based on interest from new and existing shareholders



Therapeutic programs expected to drive shareholder value

- Generating data through 2022 to enable decision making
  - IT dosing in CNS underway in FOCUS-C9 (WVE-004) and SELECT-HD (WVE-003) clinical trials
  - IV dosing underway for clinical trial in DMD (WVE-N531)
- AATD AIMer development candidate in 2022

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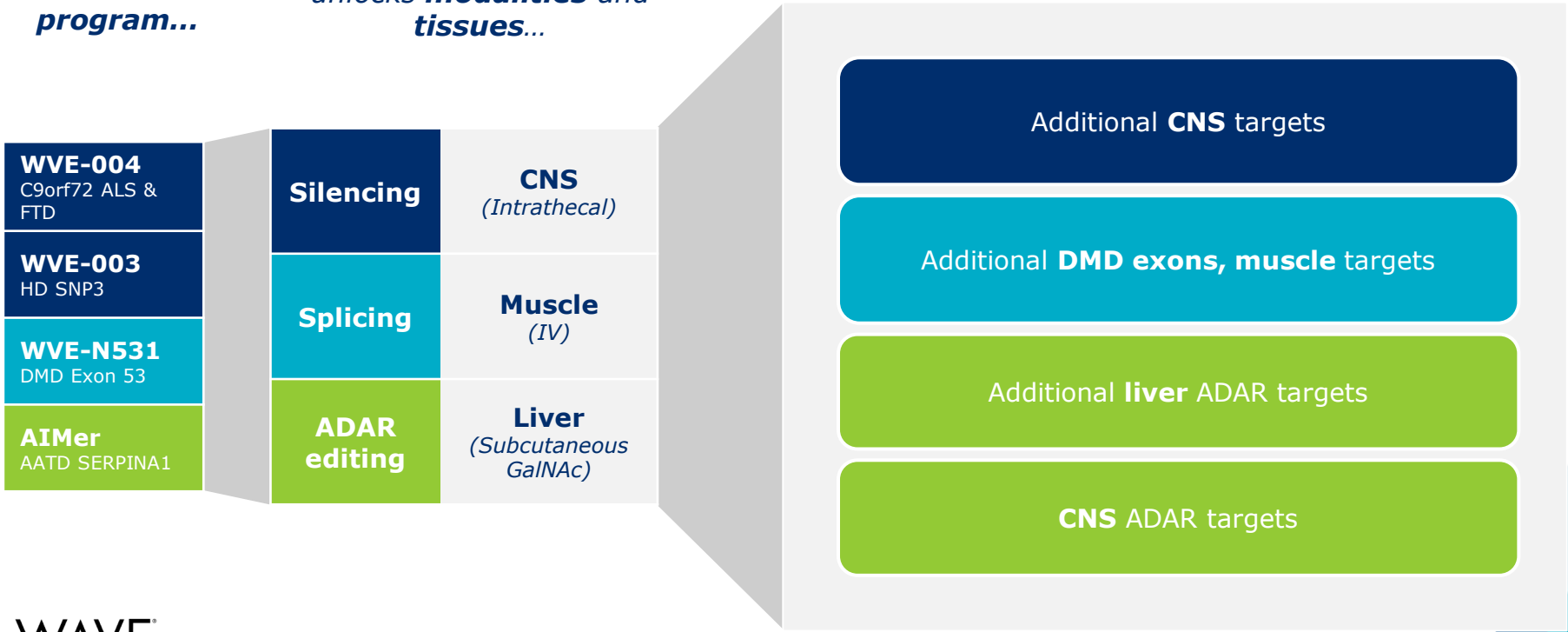
IT: Intrathecal AATD: alpha-1 antitrypsin deficiency DMD: Duchenne muscular dystrophy

Vast opportunities unlocked by any one program

Success with any ***current program…***

…validates platform and unlocks ***modalities*** *and* ***tissues****…*

…and a broad universe of ***targets*** *&* ***indications***



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Opportunity for novel and innovative AIMer therapeutics

Correct driver mutations with AIMers

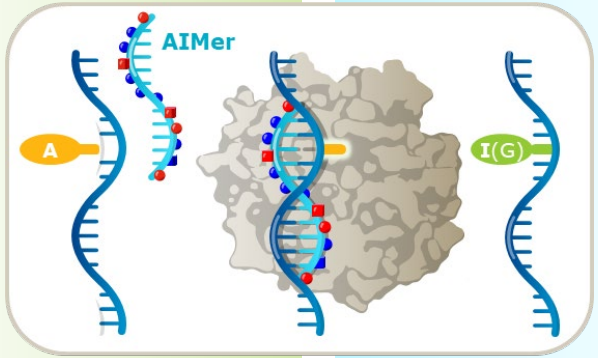
Examples

AATD

Rett syndrome

Recessive or dominant genetically defined diseases

Restore or correct protein function



- >32,000 pathogenic human SNPs[1] – ~50% ADAR amenable
- Tens of thousands of potential amenable disease variants[2]
- ~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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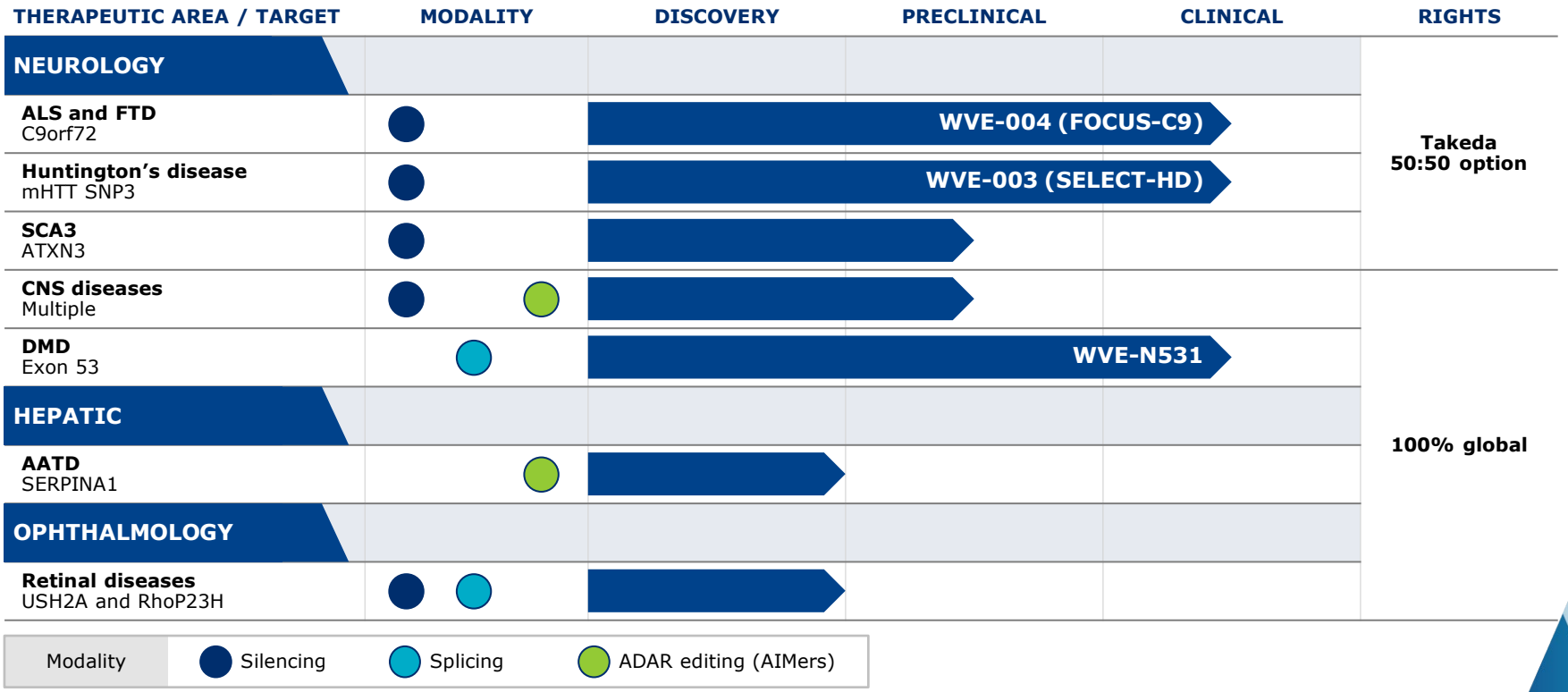
SNP: single nucleotide polymorphism A: Adenosine I: Inosine G: Guanosine

[1]Gaudelli NM et al. *Nature* (2017) [2]ClinVar database [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)

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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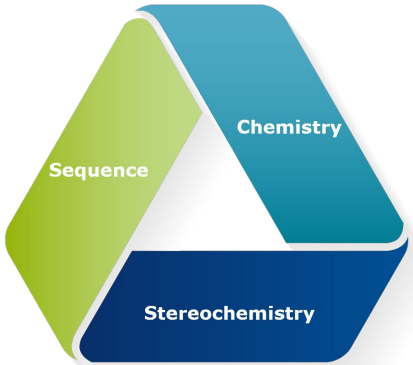
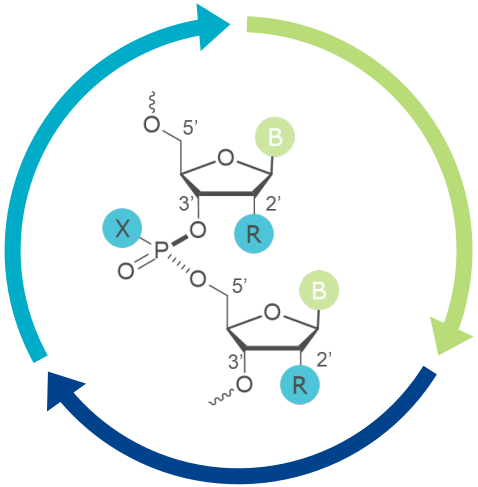
Chandra Vargeese, PhD

Chief Technology Officer

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

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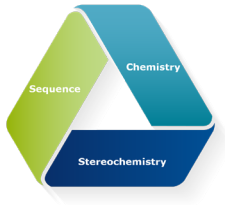
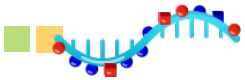
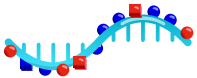
AIMers: Realizing potential of therapeutic RNA editing by harnessing endogenous ADAR

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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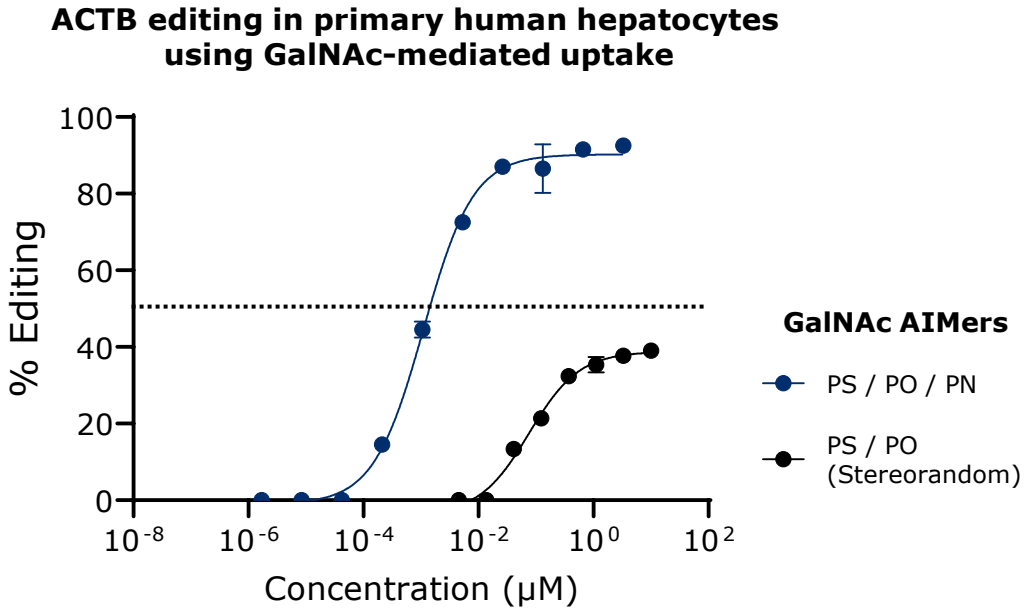
Stereochemistry and PN chemistry enhance potency and editing efficiency of AIMers



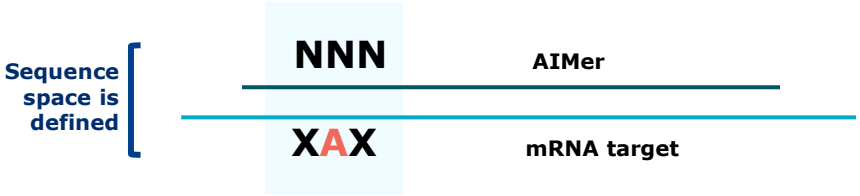
- Stereopure AIMers with PS/PO/PN backbone chemistry achieve:
  - Peak editing of ~90%
  - EC50: ~1.4 nM

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

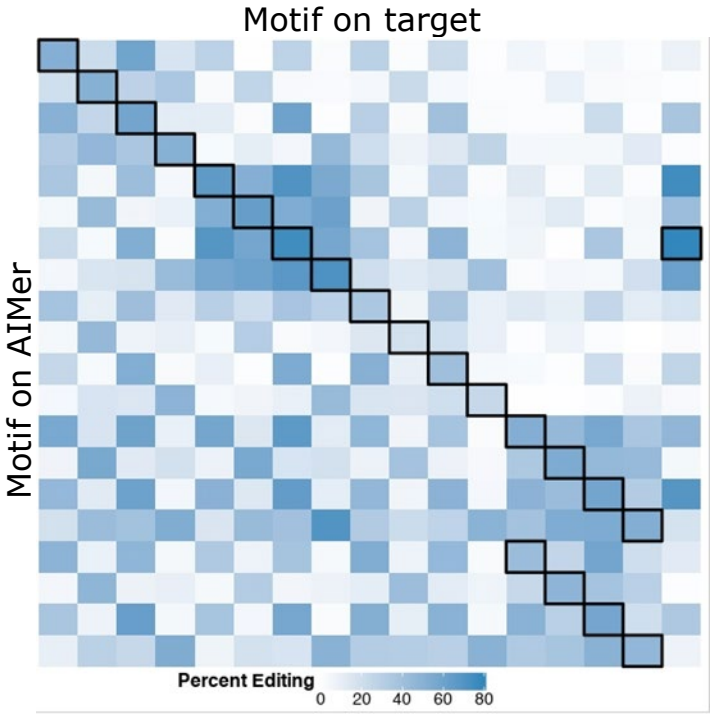
Optimization of every dimension to inform future rational design of AIMers

Heat map for sequence impact on SAR

Example: Sequence is one of multiple dimensions for optimization



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



Learnings inform design principles deployed across future targets

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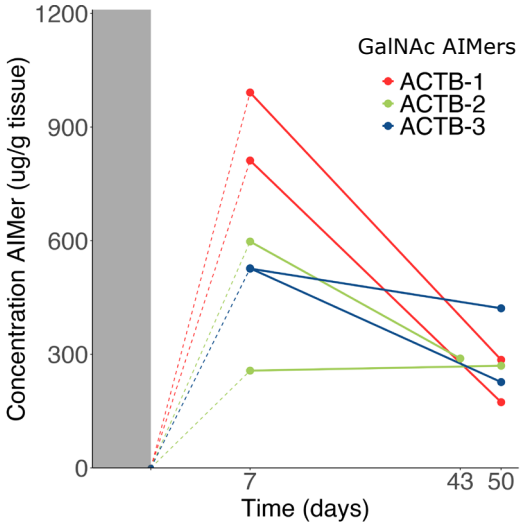
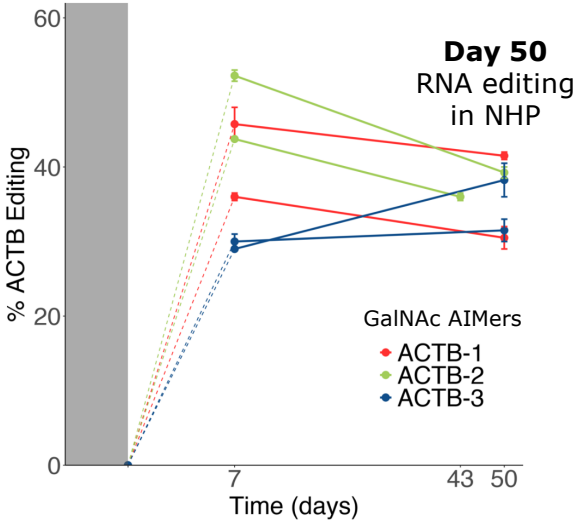
Stability of AIMers enables durable and specific editing out to Day 50 in liver of NHPs

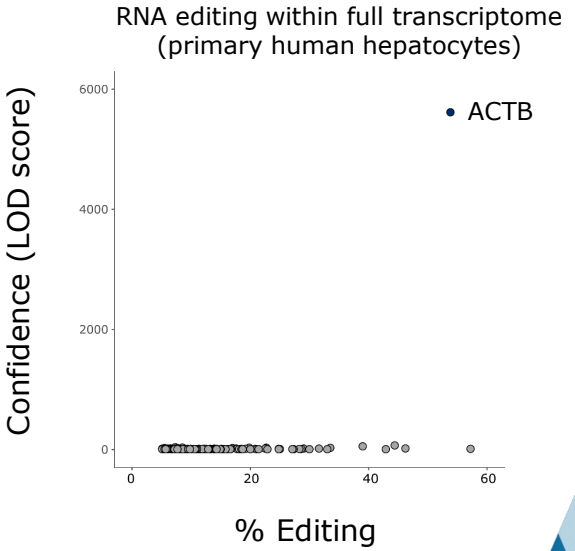
AIMers detected in liver of NHP at Day 50 (PK)



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



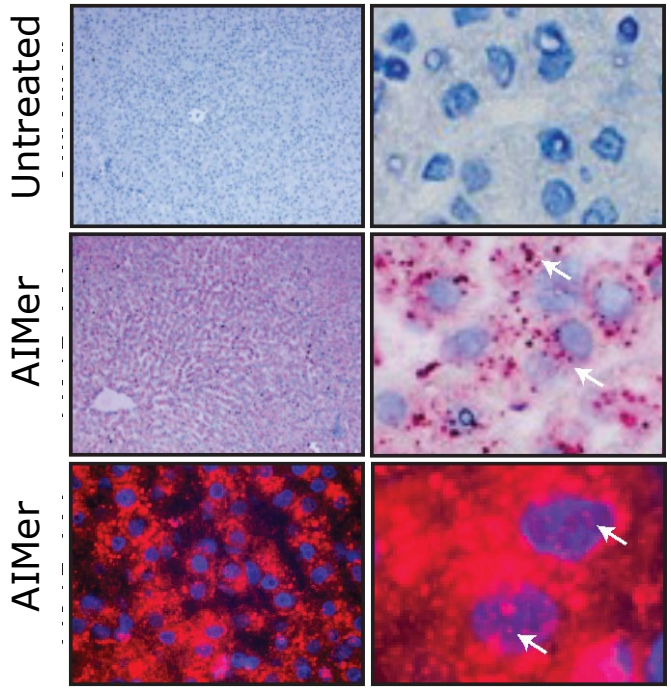
ADAR editing with ACTB AIMer is highly specific



RNA editing only detected at editing site in ACTB transcript

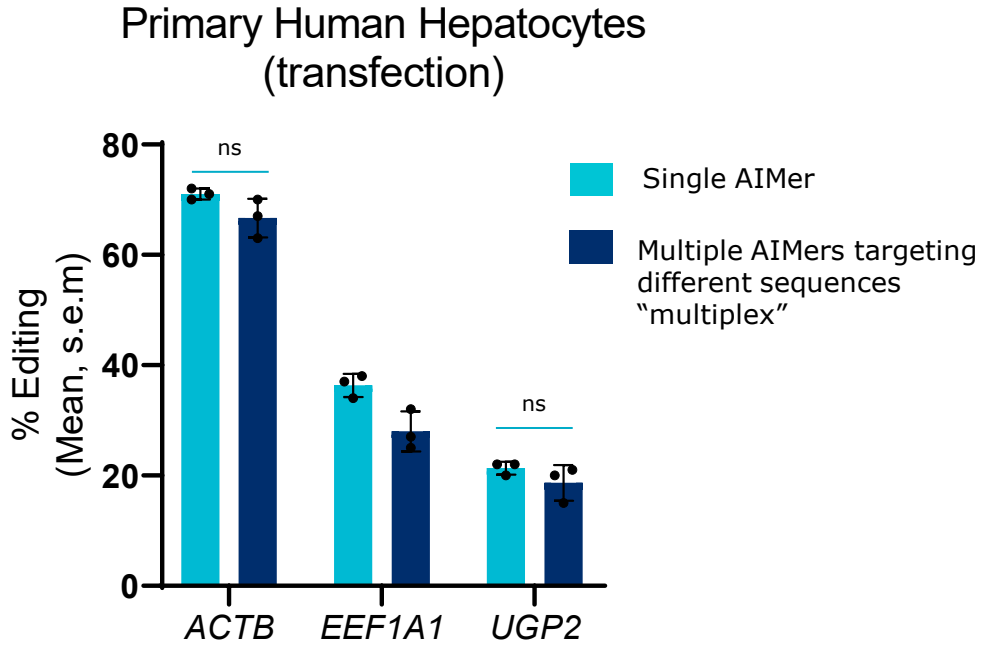
Left: AIMer PK Center: 5mg/kg SC: Day 1,2,3,4,5; Liver biopsy; Right: 1um AIMer, 48 hrs later RNA collected, RNAseq conducted using strand-specific libraries to quantify on / off-target editing; plotted circles represent sites with LOD>3. Manuscript submitted. NHP: non-human primate; ACTB: Beta-actin

AIMers delivery to hepatocytes confirmed in liver biopsies from NHPs at Day 50



ViewRNA images showing NHP liver tissue pre- (untreated) and post-treatment with AIMer. Panels show bright field for ViewRNA (AIMer, red) with hematoxylin (nuclei, blue) or fluorescent field images with Cy3 (AIMer, red) and Hoeschst 33342 (nuclei, blue).

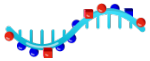
AIMer design principles are compatible across different targets

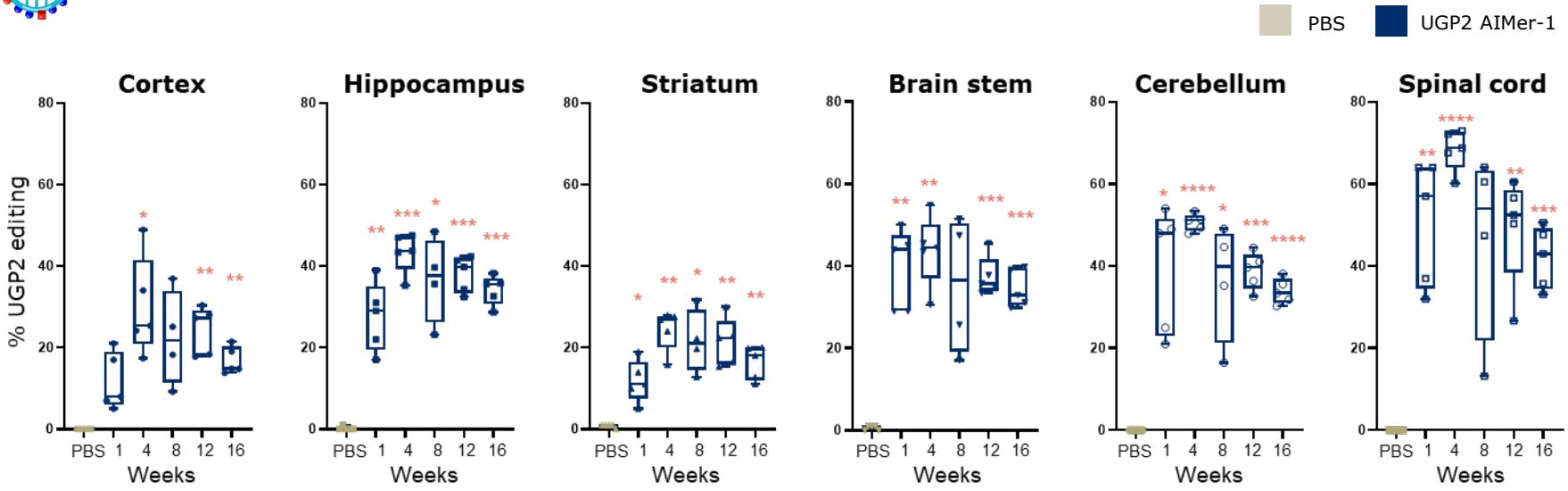


- Endogenous ADAR enzyme supports editing on multiple independent targets
- Editing efficiency comparable even when additional AIMers targeting different sequences are added, suggesting there is a more than sufficient reservoir of ADAR enzyme

Percentage A-to-I editing detected on the indicated transcripts in presence of 20 nM each of a single (Isolated) or multiple (Multiplex) AIMers after transfection of primary human hepatocytes (left). Data are presented as mean ± SEM, n=3. P values as determine by two-tailed Welch's t-test are indicated. NTC non-targeting control. Manuscript submitted.

Unconjugated AIMers: Substantial and durable *in vivo* RNA editing 4 months post-single dose in CNS





	Cortex	Hippocampus	Striatum	Brain stem	Cerebellum	Spinal cord
Peak editing	**30%**	**>40%**	**25%**	**>40%**	**50%**	**>65%**

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

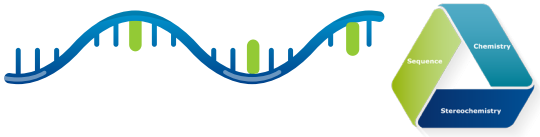
RNA editing of nonsense mutation found in MECP2 (Rett Syndrome) restores functional protein

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

Variant base

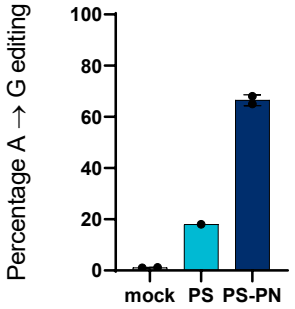
ADAR editing site

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

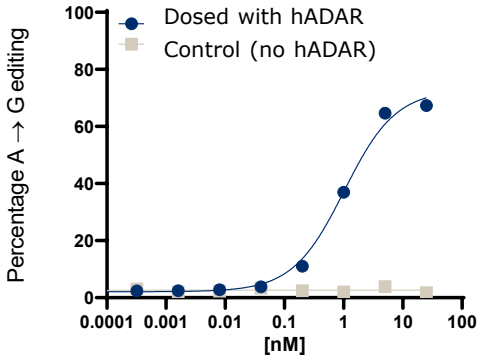


in vitro ADAR editing of over 60% targeting MECP2 disease transcript

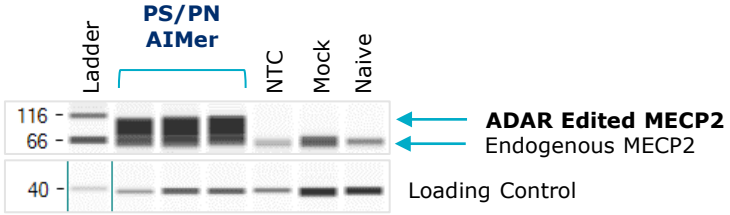
PN chemistry improved editing efficiency *in vitro*



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



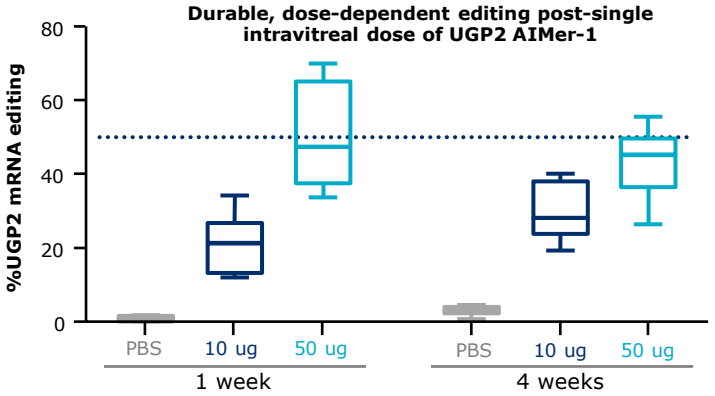
Full length MECP2 protein is expressed following ADAR editing



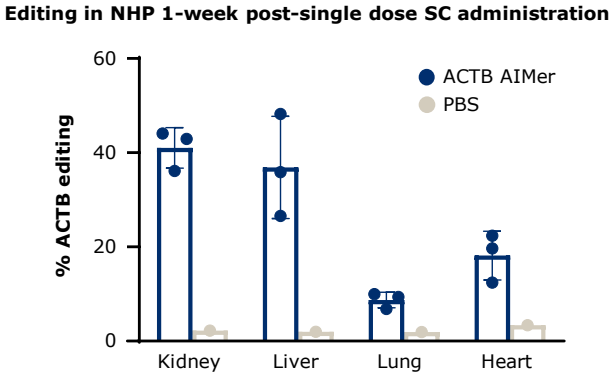
293T cells transfected with nonsense mutation on MECP2 (GFP-fusion construct), ADAR plasmids. AIMers transfected for 48h prior to RNA extraction and sequencing. Percentage editing determined by Sanger sequencing. Left: Single dose (25nM) treatment Middle: Full dose response curve (25nM, 5-fold dilution,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

AIMer pipeline expansion opportunities include targets beyond liver and CNS

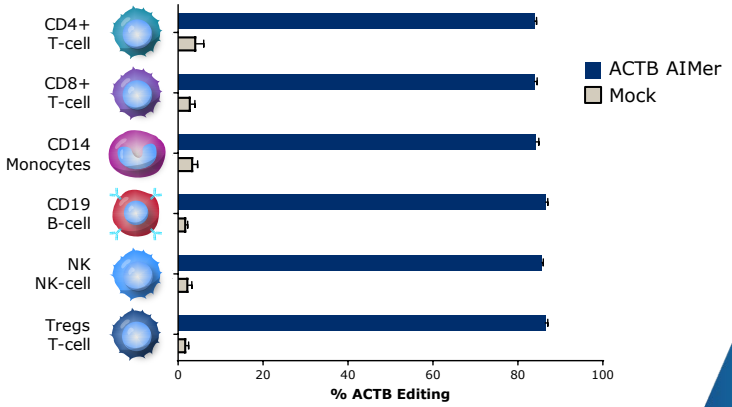
Ophthalmology



Kidney, liver, lung, heart



Immune cells



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GalNAc-AIMers leading the way towards clinical proof-of-concept of ADAR editing

Additional AIMers data to be shared in publications and presentations in 2022

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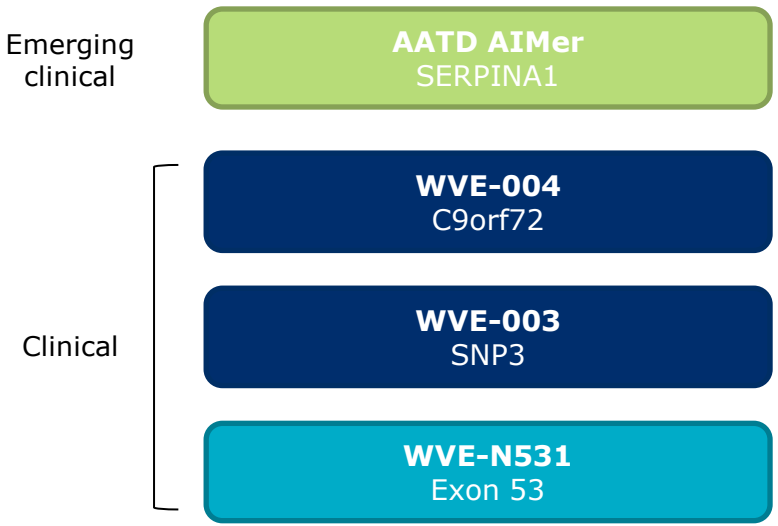
Mike Panzara, MD, MPH

Chief Medical Officer,

Head of Therapeutics

Discovery and Development

Diversified portfolio of therapeutic programs



Milestones in the third-quarter 2021

- ✓ Preclinical data on editing specificity, durability of AAT protein restoration and AIMer optimization (September 2021)
- ✓ Dosing underway in FOCUS-C9 clinical trial (July 2021)
- ✓ Dosing underway in SELECT-HD clinical trial (September 2021)
- ✓ Dosing underway in open-label clinical trial (September 2021)

First clinical trials to evaluate oligonucleotides containing PN chemistry

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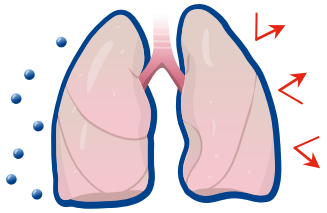
RNA editing is uniquely suited to address the therapeutic goals for AATD

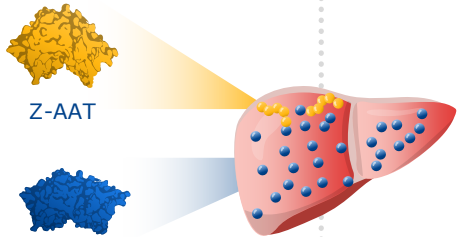
1) Restore circulating, functional wild-type M-AAT

2) Reduce Z-AAT protein aggregation in liver

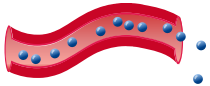
3) Retain M-AAT physiological regulation



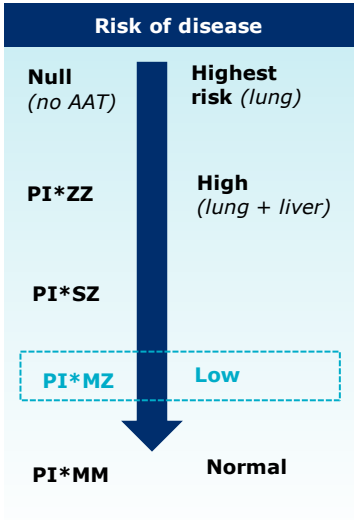
M-AAT reaches lungs to protect from proteases



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



M-AAT secretion into bloodstream



Wave ADAR editing approach addresses all goals of treatment

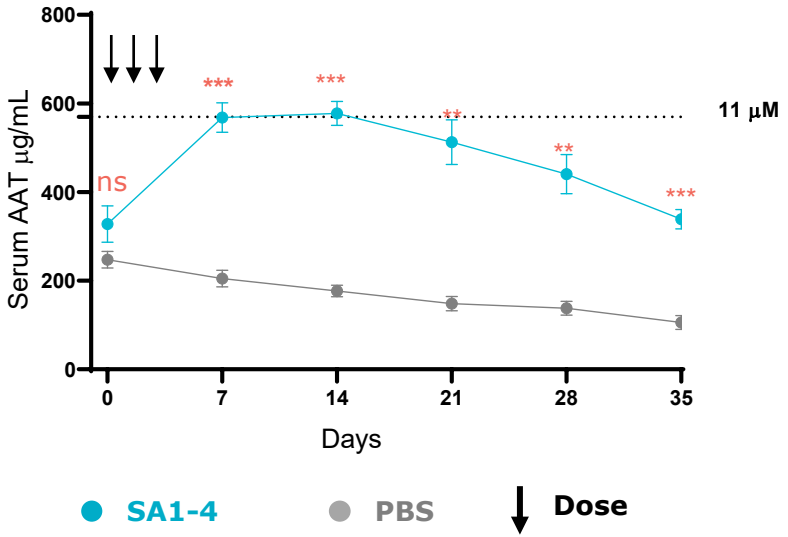
GalNAc-conjugated for subcutaneous delivery

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

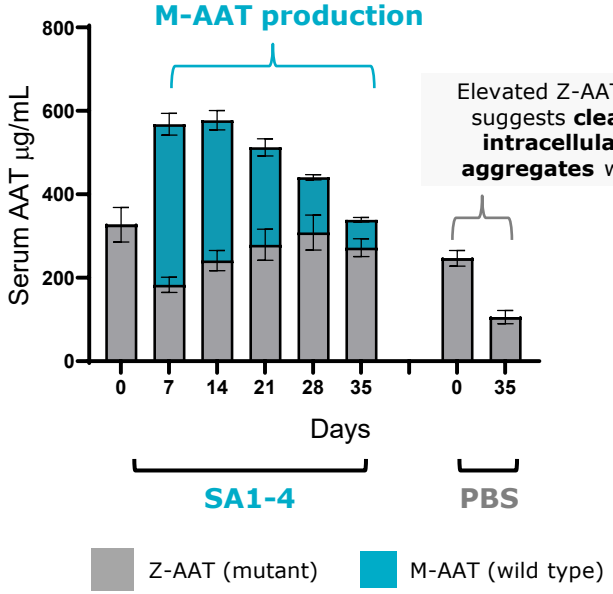
AAT: Alpha-1 antitrypsin; Sources: Strnad 2020; Blanco 2017

Durable restoration of functional, M-AAT protein with ADAR editing

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



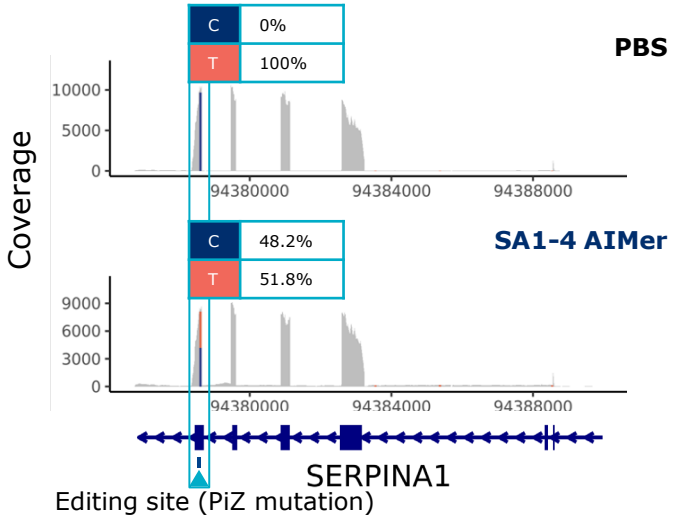
Restored wild-type M-AAT detected over 30 days post-last dose



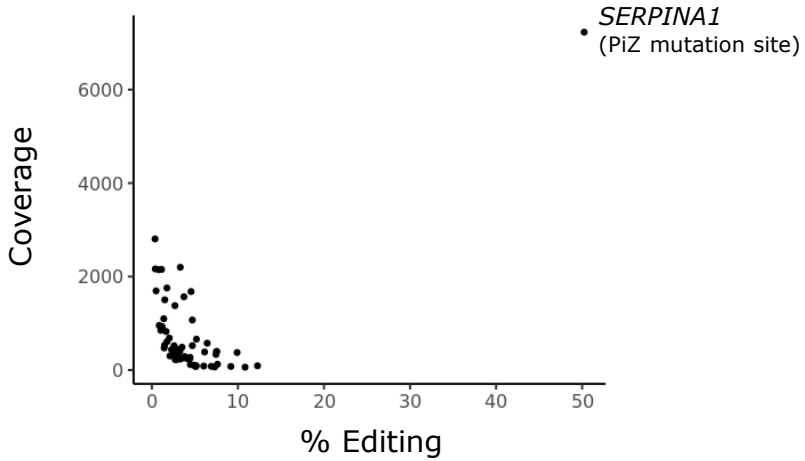
SA1-4: GalNAc AIMer L: hu*ADAR/SERPINA1* mice, PBS, 3 x 10 mg/kg (days 0, 2, 4) SC. ELISA. R: Mass spec, ELISA

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

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



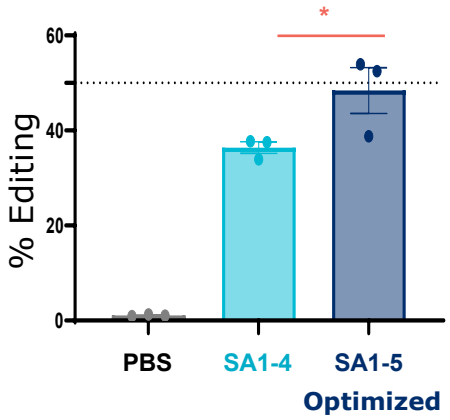
RNA editing within transcriptome
(mouse liver)



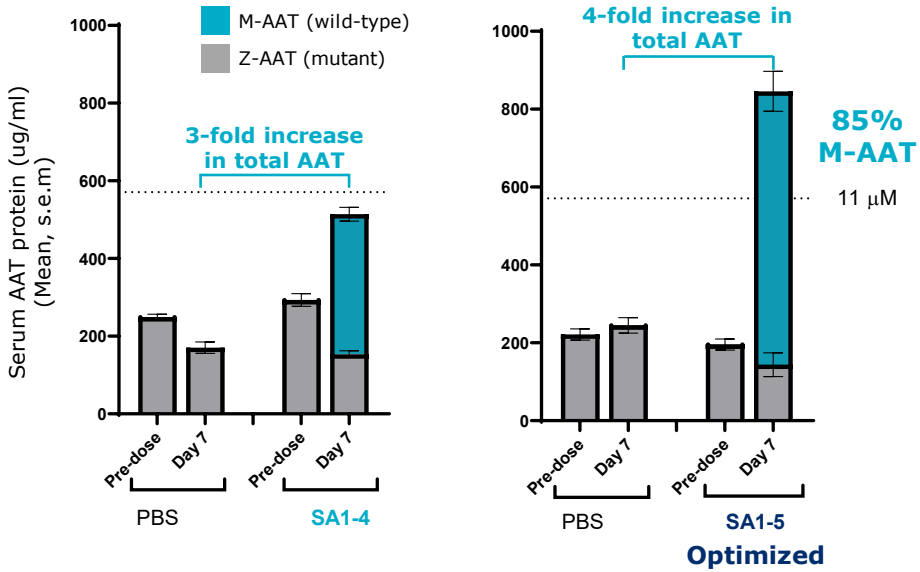
Dose 3 x 10mg/kg days (0, 2, 4) SC. Liver biopsies day 7. RNAseq, To quantify on-target *SERPINA1* editing reads mapped to human *SERPINA1*, to quantify off-target editing reads mapped to entire mouse genome; plotted circles represent sites with LOD>3 (N=4); Analyst and Investor Research Webcast September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

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

SERPINA1 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**

Diversified portfolio of therapeutic programs

First clinical trials to evaluate oligonucleotides containing PN chemistry

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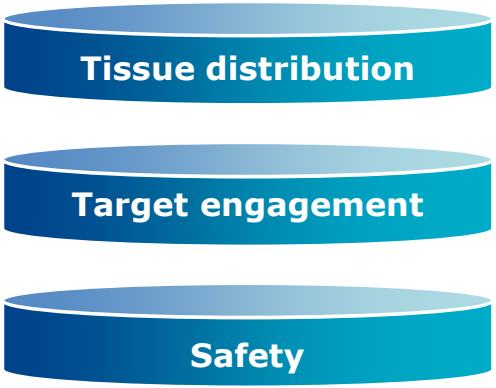
Keys to delivering therapeutic success in CNS

PRISM platform

- ✓ PN backbone modifications in the setting of chiral control and other PRISM advancements improve potency, tissue distribution, and duration of effect
- ✓ Increased emphasis on translational pharmacology

Rational design



Innovative development plans

Selection of relevant biomarkers, clinical endpoints, study duration, dosing regimen

Right target for disease	Right patient population

Current and future unmet need

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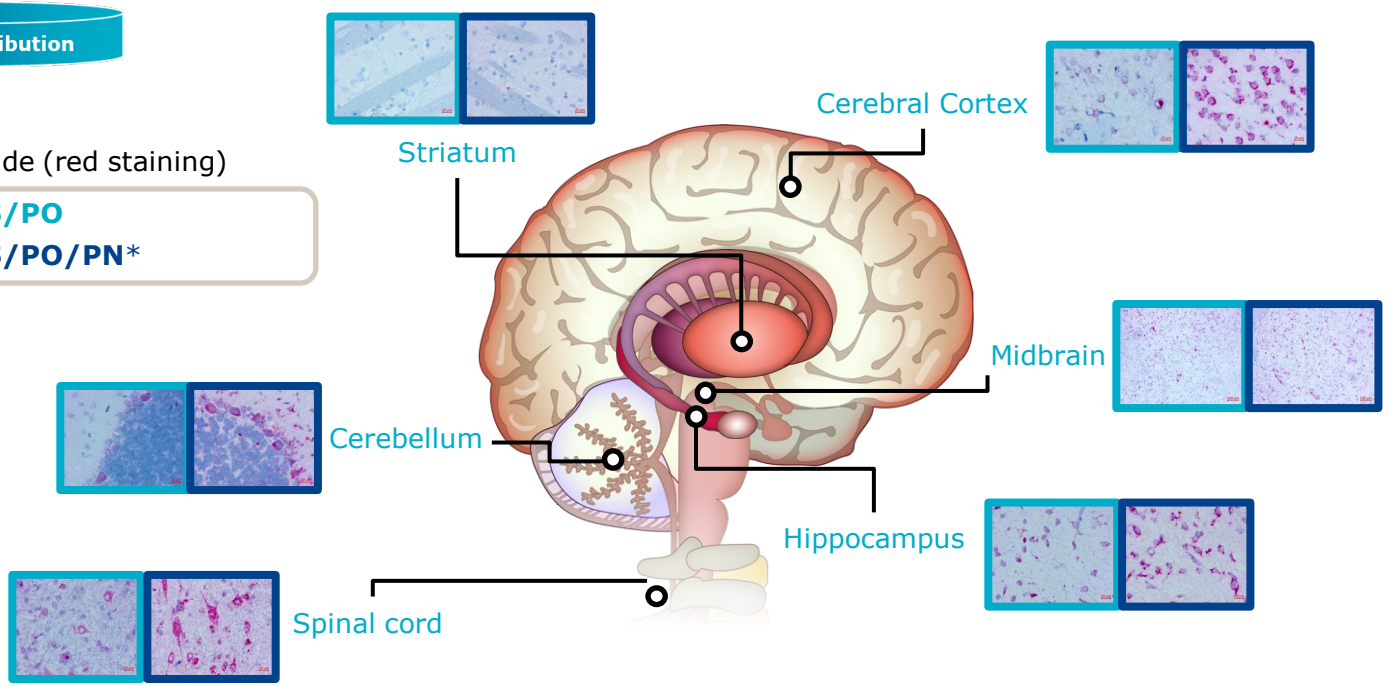
PN chemistry improves distribution to CNS

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

Tissue distribution

Oligonucleotide (red staining)

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



*Isomer 3; 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.

Rational design to achieve target engagement and preclinical tolerability

Unconjugated oligonucleotide administered **ICV**

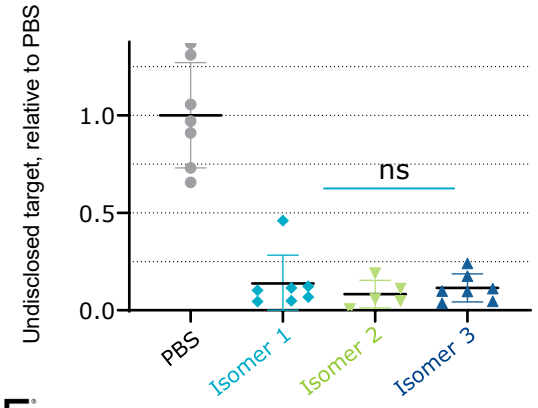
Isomer 1
Isomer 2
Isomer 3

Same sequence, but different backbone stereochemistry

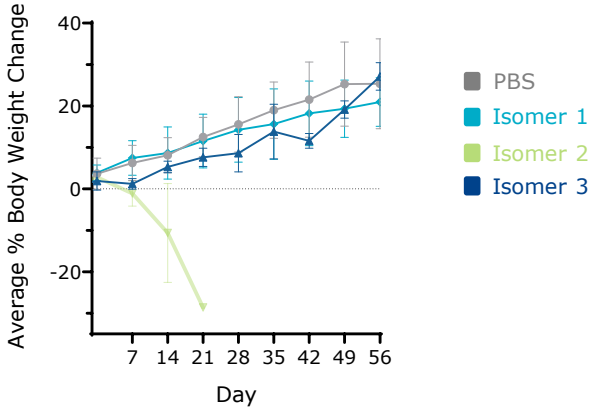
Stereoisomers have **similar** pharmacodynamic effects *in vivo*

Changing backbone stereochemistry leads to **different** tolerability profiles *in vivo*

CNS target knockdown *in vivo*



Percentage body weight change



Left: In a target engagement study, 7 mice administered 2 x 50 ug oligonucleotide or PBS by ICV on days 0 and 7. Tissue collected on day 14. Target mRNA normalized to Tubb3 and plotted relative to PBS. Data presented as mean ± SD (n=7). Stats: One-way ANOVA ns not significant, PBS phosphate buffered saline. Right: wt mouse tolerability study, n=4 administered 100 ug oligonucleotide or PBS by ICV on day 0 and monitored for 8 weeks.

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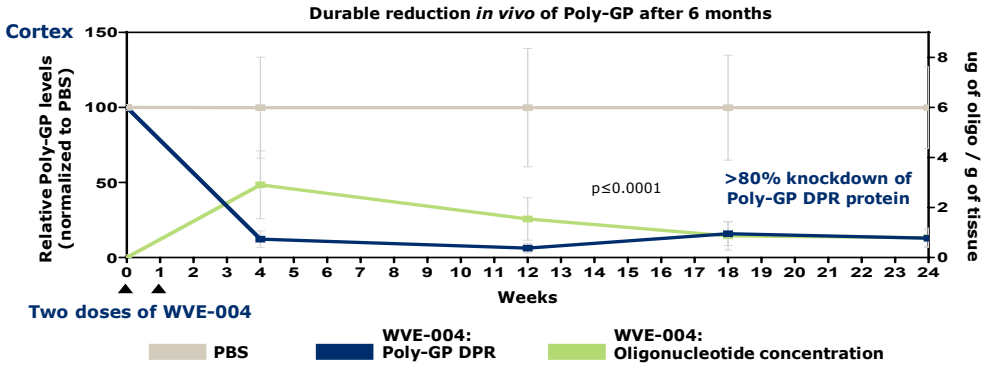
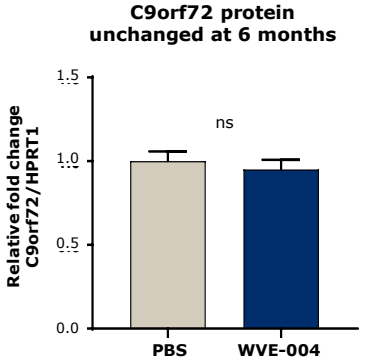
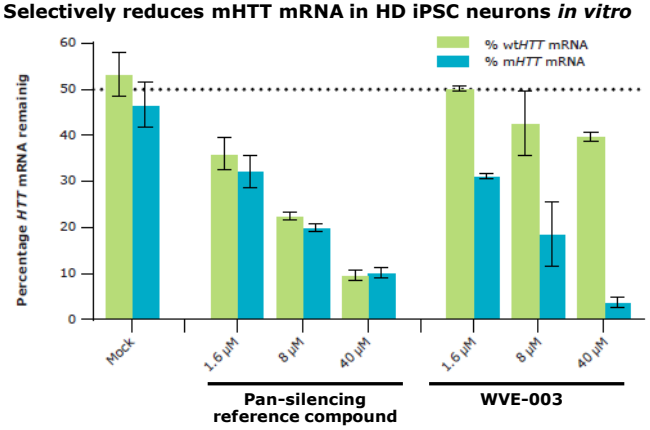
Preclinical data enabled modeling to determine starting doses predicted to be pharmacologically active

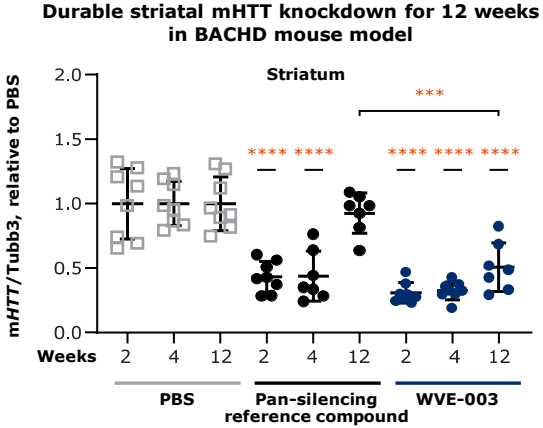
WVE-004
C9of72
ALS / FTD





WVE-003
SNP3
HD





New SNP3 *in vivo* allele-selective silencing data presented at Huntington Study Group (HSG) November 5, 2021

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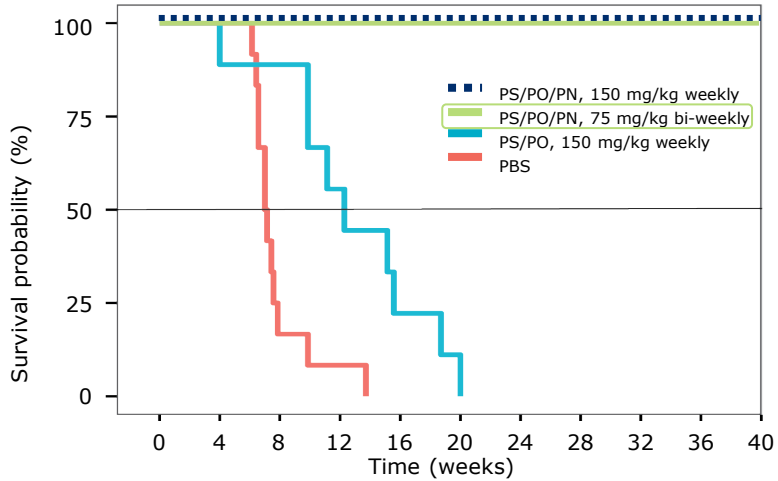
Dramatic increase in effect with PN-modified splicing oligonucleotide in the dKO mouse model

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. Left: Mice with severe disease were euthanized. 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

Innovative and adaptive trial designs to generate data through 2022 to enable decision making

WVE-004
ALS/FTD

FOCUS ON C9

WVE-003
HD

SELECT HD

WVE-N531
DMD

All three studies expected to provide valuable insights into clinical effects of novel PN backbone modifications in the CNS and muscle

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Kyle Moran

Chief Financial Officer

Third quarter 2021 financial results

	Three Months Ended September 30, 2021	Three Months Ended September 30, 2020
Figures are in thousands, except per share amounts		
Revenue	$36,423	$3,450
Operating Expenses:		
Research and Development	31,086	28,275
General and Administrative	12,944	9,590
Total Operating Expenses	44,030	37,865
Net Loss from Operations	(7,607)	(34,415)
Total Other Income, Net	1,337	1,315
Net Loss	($6,230)	($33,100)
Net Loss per Share	**($0.12)**	**($0.86)**

As of September 30, 2021 **Shares Outstanding:** 52.0 million **Cash Balance:** $123.9 million

In October 2021, Wave received an additional $52.1 million, including $22.5 million from Takeda and $29.6 million in proceeds from its ATM equity program.

Wave expects that its existing cash and cash equivalents will enable the company to fund its operating and capital expenditure requirements into 2Q 2023.

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Paul Bolno, MD, MBA

President and CEO

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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Q&A

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Realizing a brighter future for people affected by genetic diseases

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