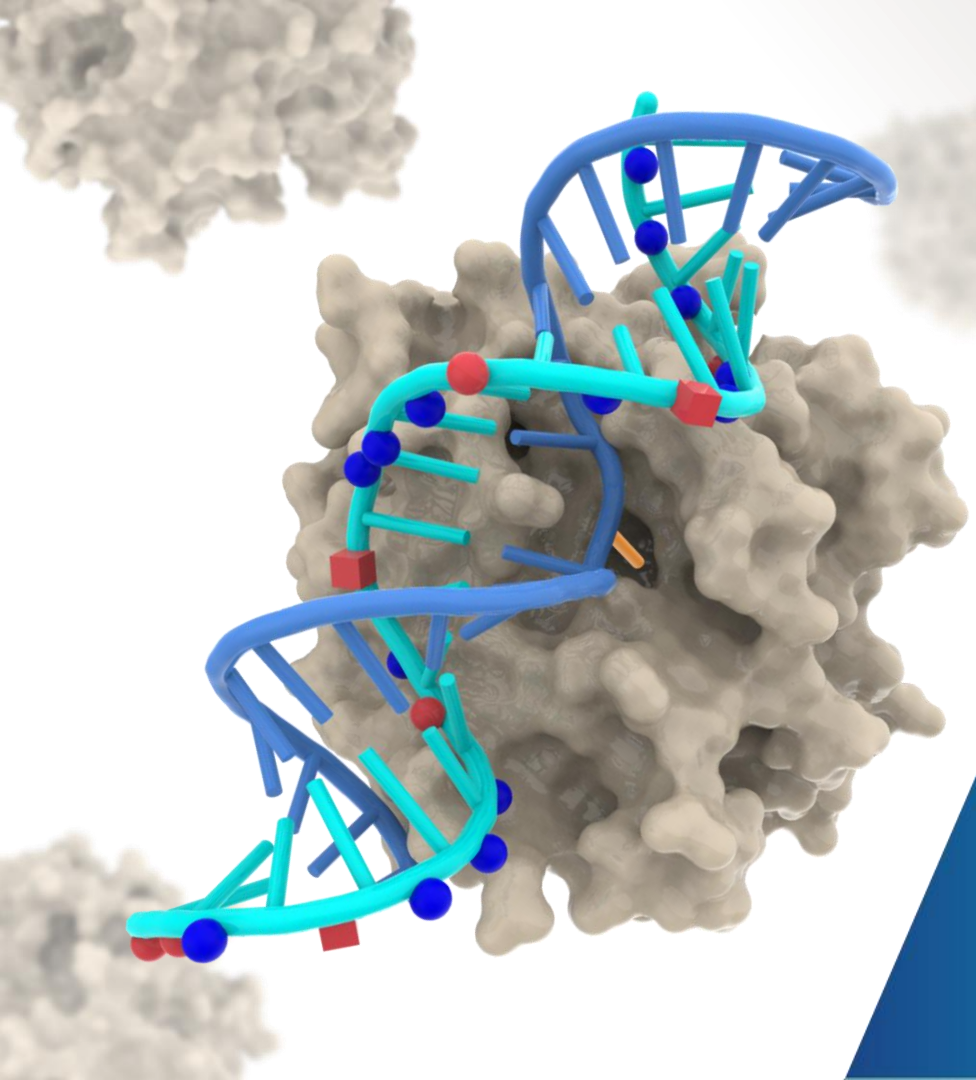


WAVE™
LIFE SCIENCES

Analyst & Investor Research Webcast

September 28, 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.

WAVE™
LIFE SCIENCES

Today's agenda

PRESENTATION	SPEAKER
Opening Remarks	**Paul Bolno, MD, MBA** President and CEO
Applying PRISM Principles for Rational Oligonucleotide Design	**Chandra Vargeese, PhD** Chief Technology Officer
Building a Best-in-Class ADAR Editing Capability: Introducing AIMers	**Chandra Vargeese, PhD** Chief Technology Officer
Advancing ADAR Editing in the CNS	**Ken Rhodes, PhD** SVP, Therapeutics Discovery
Restoring Functional AAT Protein with ADAR Editing: Program Update	**Paloma Giangrande, PhD** VP, Platform & Discovery Sciences Biology
Q&A	
Closing Remarks	**Paul Bolno, MD, MBA** President and CEO

WAVE™ LIFE SCIENCES

Opening Remarks

Paul Bolno, MD, MBA

President and CEO

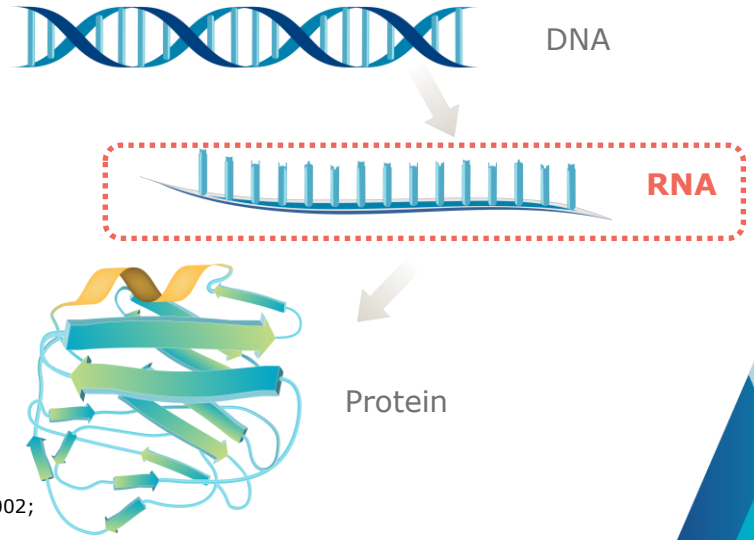
WAVE™ LIFE SCIENCES

We are taking part in a genetic revolution

- **Greater understanding** of genetic drivers of disease and definition at molecular level
- **>6,000** genetically defined diseases
- Increase in **genetic testing** enabling identification of individuals likely to benefit from treatment

Many diseases beyond the reach of traditional treatments

- Wave is developing therapeutics to drug the **transcriptome** to turn on, switch off, or modulate expression of faulty genes



Sources: Shen et al, Genetics Research, 2015; Hopkins et al, Nat Rev Drug Discov, 2002; geneticdiseasefoundation.org

Strategic decision to intervene at RNA level

RNA-targeting therapeutics offer ideal balance of precision, durability, potency, and safety

Address underlying genetic drivers of disease

Defined path to commercialization

Simplified delivery

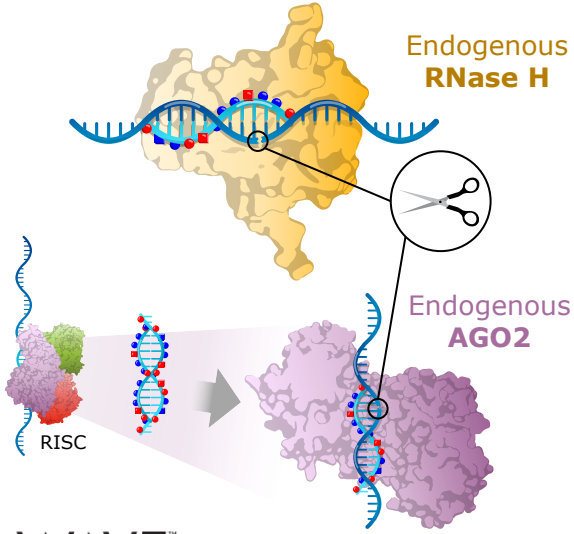
Durable effects to enable infrequent dosing

WAVE™ LIFE SCIENCES

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

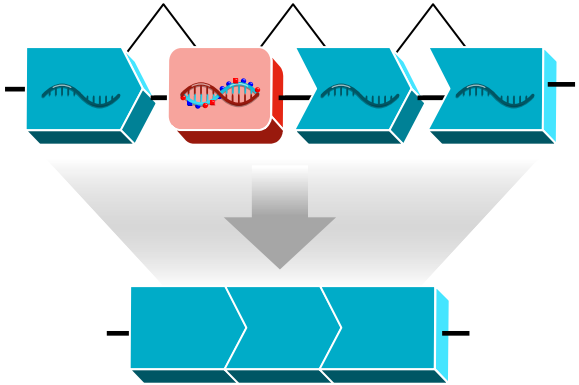
Silencing

- **Oligonucleotide-directed delivery** of RNA to regulate enzymes



Splicing

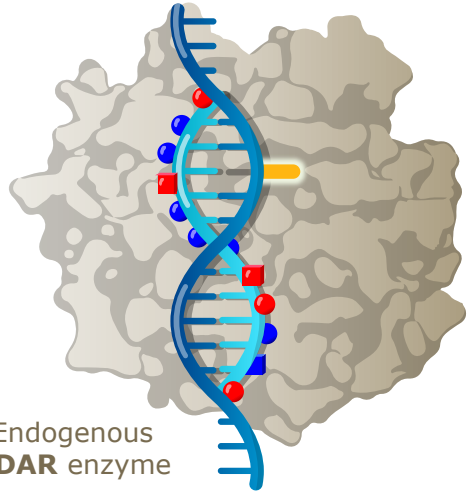
- Leverages **exon skipping machinery** to restore a working transcript



Restored **Reading Frame**

Editing

- Efficient editing of RNA bases using **endogenous ADAR**



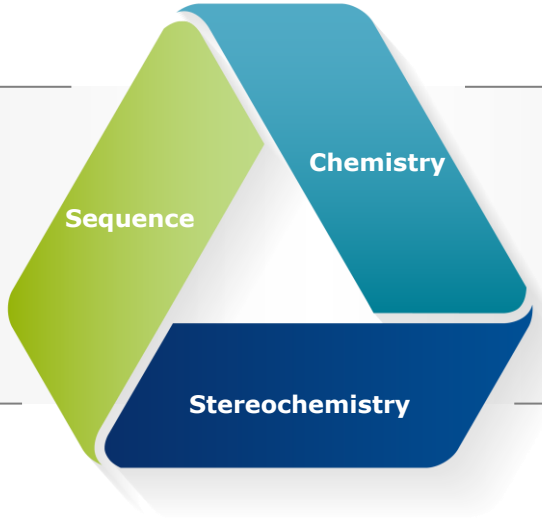
Endogenous **ADAR** enzyme

WAVE™ LIFE SCIENCES

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

DESIGN

Unique ability to construct single isomers and control three structural features of oligonucleotides to efficiently engage biological machinery



OPTIMIZE

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

Built-for-Purpose Candidates to Optimally Address Disease Biology

Silencing | Splicing | RNA Editing

WAVE LIFE SCIENCES

Wave is the leader in chirally-controlled rationally designed stereopure oligonucleotides

Stereochemistry is a reality of chemically-modified nucleic acid therapeutics

Current therapeutics with chiral backbone modifications:

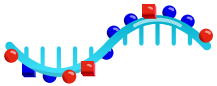
- **Antisense oligonucleotides**
- **siRNA**
- **Exon-skipping oligonucleotides**
- **mRNA therapeutics**
- **RNA guide strands**

Chirality matters: affects pharmacology of oligonucleotides *in vitro* and *in vivo*

Increasingly recognized by leaders in nucleic acid therapeutics:

PRISM controls stereochemistry throughout drug discovery and development process

Enables design and optimization of fully-characterized, **single-isomer** RNA therapeutics

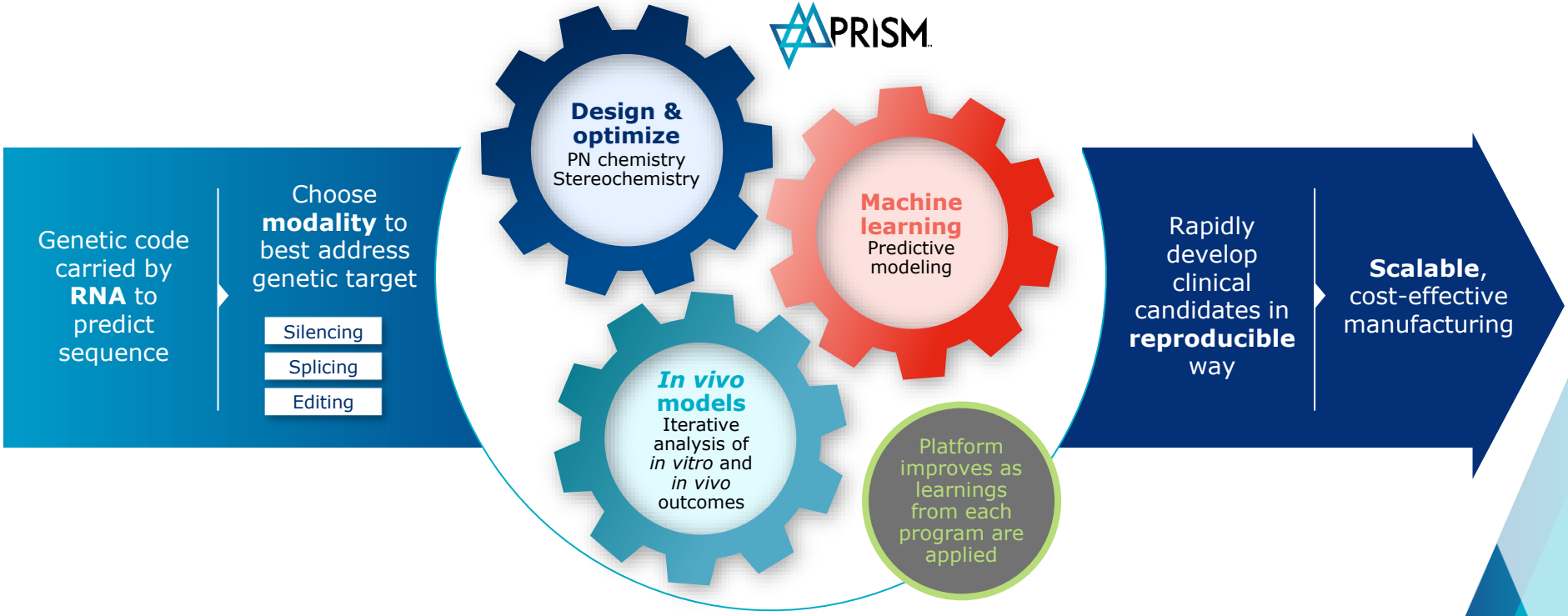


Dominant IP portfolio and unique ability to manufacture and screen stereopure oligonucleotides

WAVE™ LIFE SCIENCES

Jahns et al., NAR, 2021; Hansen, et al. 2021; Funder, Albaek et al. 2020

PRISM platform is continuously improving

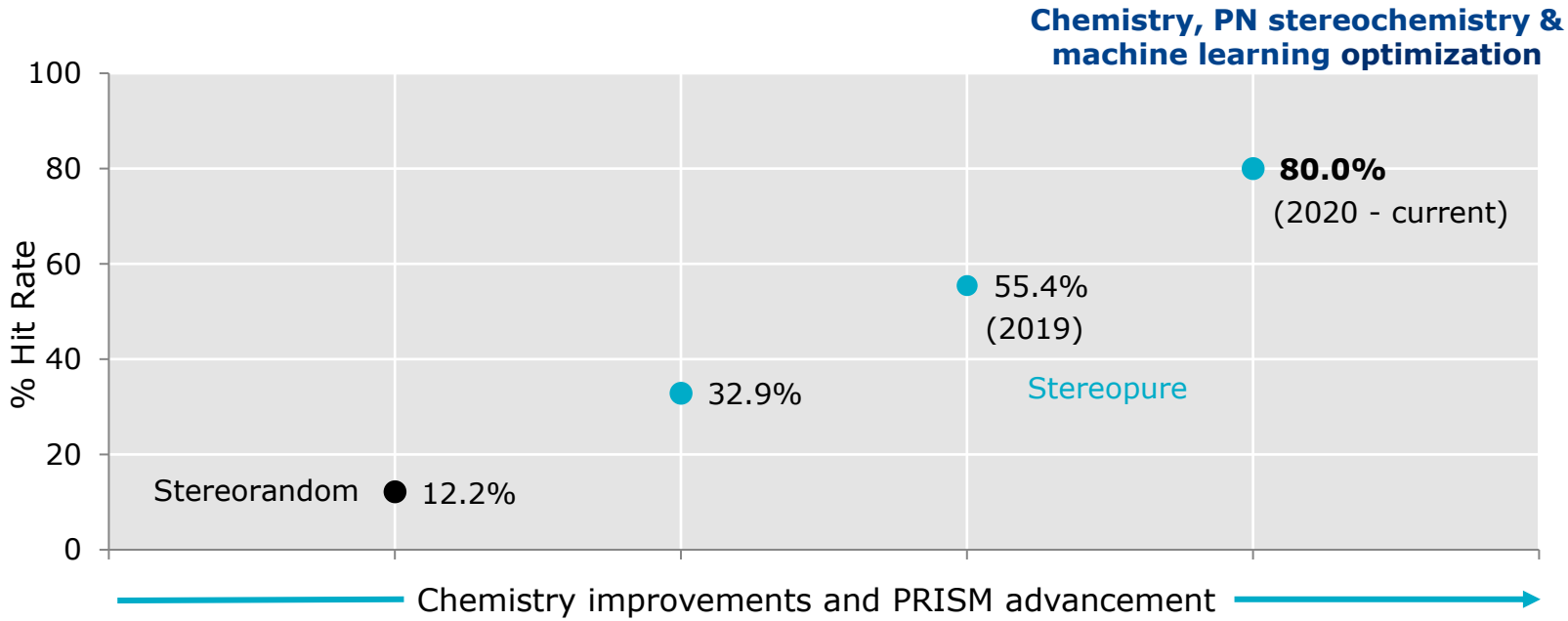


Continuous definition of design principles deployed across programs

WAVE LIFE SCIENCES

Improvements in PRISM primary screen hit rates accelerate drug discovery

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



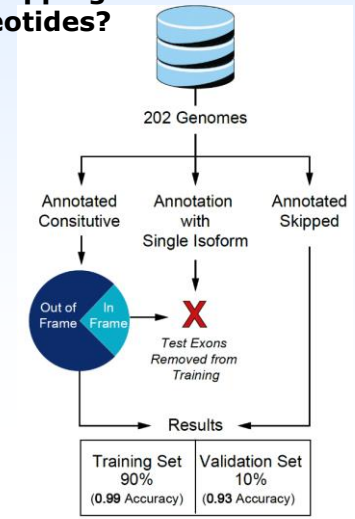
All screens used iPSC-derived neurons; Data pipeline for improved standardization. Hit rate = % of oligonucleotides with target knockdown greater than 50%. Each screen contains >100 oligonucleotides. ML: machine learning

Data sciences enable prediction of new potential therapeutic exon-skipping targets

Model trained on millions of known protein sequences

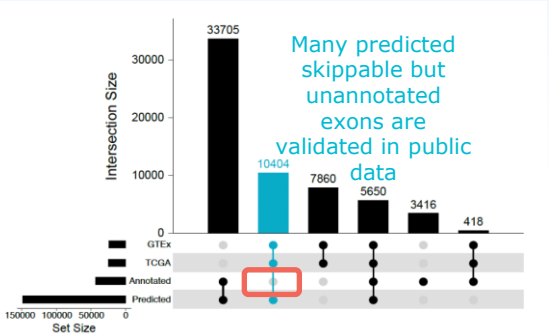
Is an exon amenable to exon-skipping oligonucleotides?

PRISM



Predicts skippable exons that are currently undiscovered

Identified >10,000 exons that are predicted to be skippable but are currently unannotated



Identifies clinically relevant genes with skippable exons

Identified ~2,500 potential exon-skipping targets with oligonucleotide therapeutics as compared ~100 identified skippable in literature

Experimentally confirmed (PubMed)

~100 genes

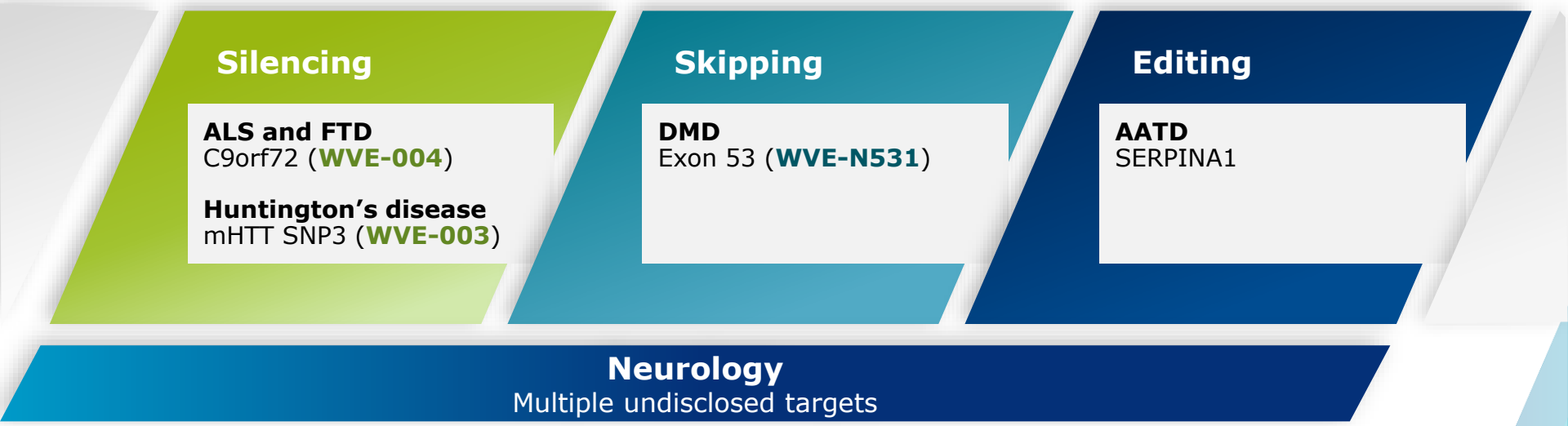
Exon ByPASS predicted

~2500 genes

WAVE LIFE SCIENCES

Exon ByPASS: predicting Exon-skipping Based on Protein Amino acid SequenceS; Data presented at OTS 2021. Manuscript submitted

Advancing programs using multiple modalities



ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; DMD: Duchenne muscular dystrophy; AATD: Alpha-1 antitrypsin deficiency

Building a leading genetic medicines company

- Scientific approach focused on unlocking the body's own ability to treat genetic disease
- PRISM platform enables multiple modalities for built-for-purpose therapeutics
- Leading the way in rationally designed stereopure oligonucleotides with innovative backbone chemistry
- Robust portfolio of PN-modified, stereopure oligonucleotides, including three programs in clinic and multiple ADAR editing discovery programs

WAVE™ LIFE SCIENCES

Applying PRISM Principles for Rational Oligonucleotide Design

Chandra Vargeese, PhD

Chief Technology Officer

WAVE™ LIFE SCIENCES

PRISM platform enables rational drug design

Sequence

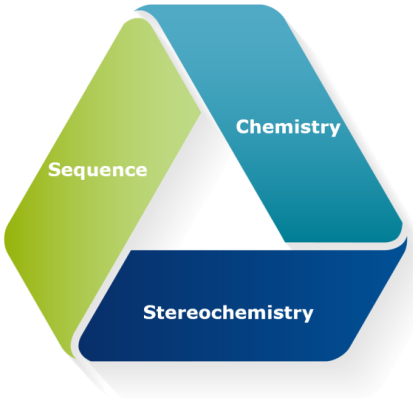
B: bases

A, T, C, mC, G, U,
other modified bases

Stereochemistry

Chiral control of
any stereocenter

5′ modifications,
backbone modifications



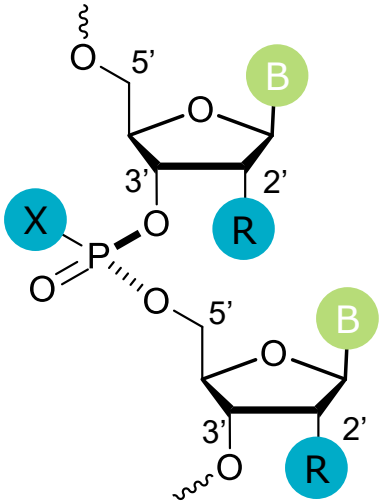
Chemistry

R: 2′ modifications

OMe, MOE, F,
other modifications

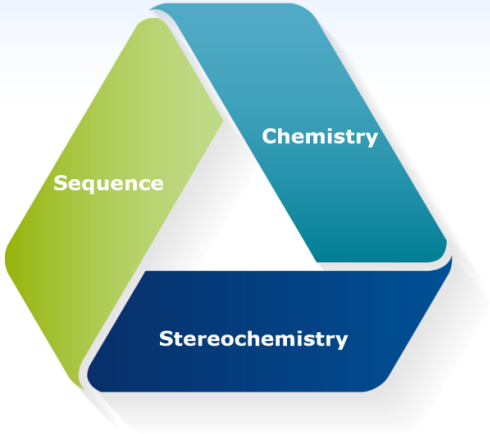
X: backbone chemistry

PO, PS, PN

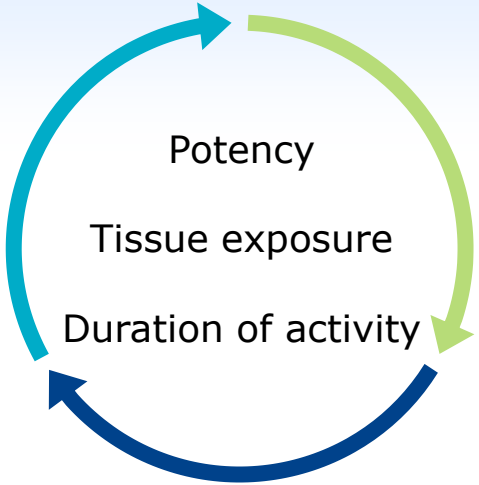


Optimization framework compatible across different modalities

Interplay between key **structural** components of oligonucleotides…



..to modulate key aspects of **activity**…



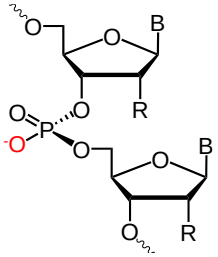
… and apply to multiple **therapeutic modalities**

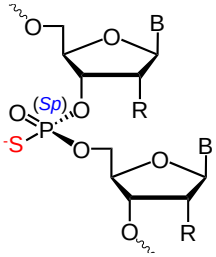
- Silencing
- Splicing (exon-skipping)
- ADAR editing

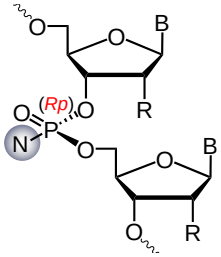
Innovating new backbone chemistry modifications

PRISM backbone linkages

PO | **PS** | **PN**

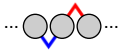






Chirality
None

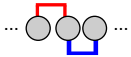
Negative charge



Chirality

PS backbone *Rp*
PS backbone *Sp*

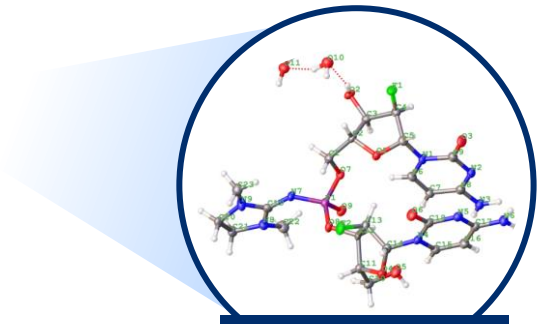
Negative charge



Chirality

PN backbone *Rp*
PN backbone *Sp*

Neutral charge



Phosphoryl guanidine x-ray structure

example

PO: phosphodiester PS: phosphorothioate

Rationally placed stereopure PN modifications enhance pharmacology across modalities

Adding PN linkages benefits all PRISM modalities…

Silencing	• Efficient engagement of RNase H or Ago2
Splicing	• Efficient uptake in the cell nucleus
Editing	• Efficient engagement of ADAR

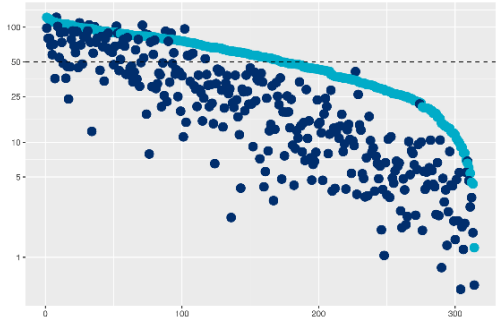
… and improves key pharmacological drivers of translation

Potency	• Target knockdown, splicing or editing
Exposure	• In the right tissues, cells and cellular compartments
Durability	• Enabling infrequent administration

Potency is enhanced with addition of PN modifications across modalities

Silencing

Target knockdown (% remaining)

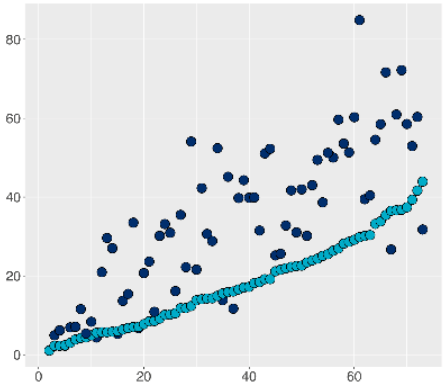


Ranked by potency of reference PS/PO compound

Improved knockdown

Splicing

% Skipping

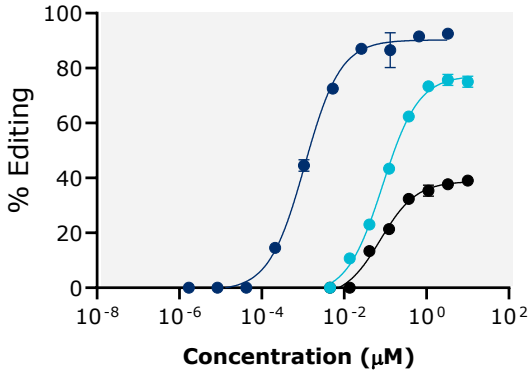


Ranked by potency of reference PS/PO compound

Improved skipping

Editing

% Editing



Improved editing

PS/PO/PN
PS/PO (Stereopure)
PS/PO (Stereorandom)

PS/PO reference compound

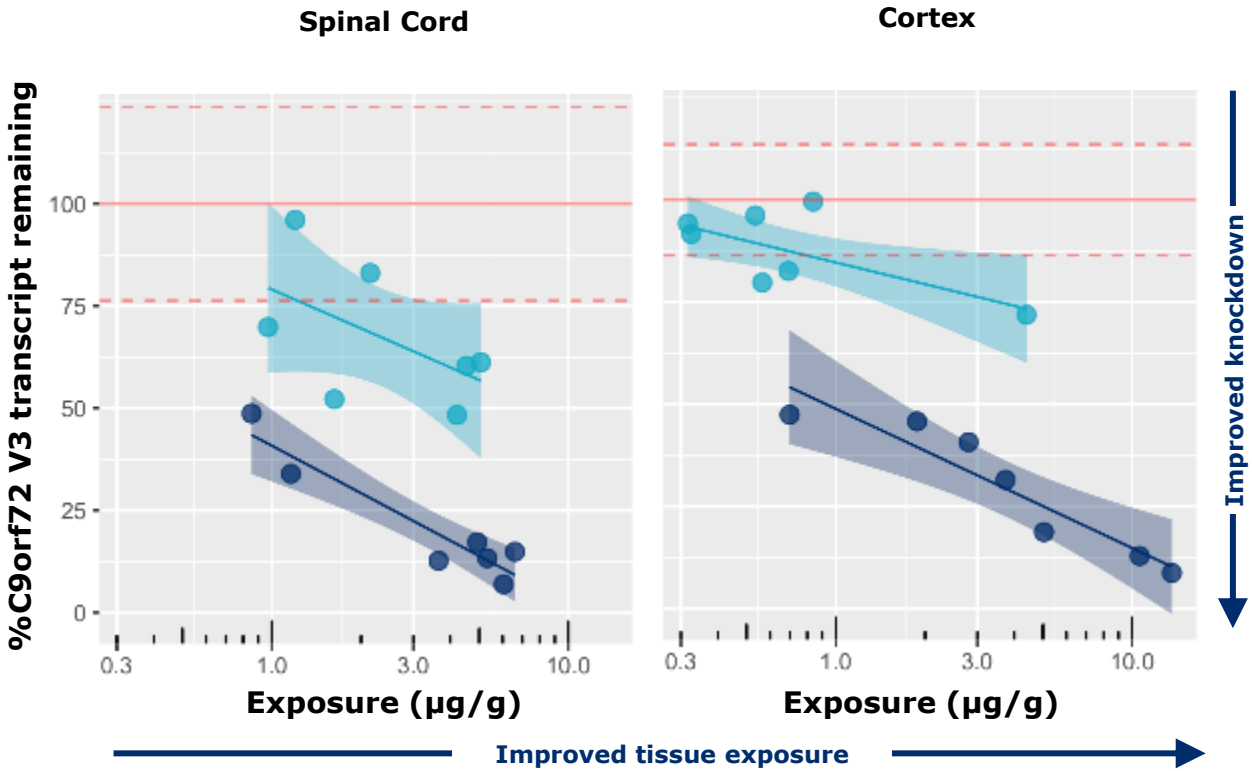
PS/PN modified compound

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*

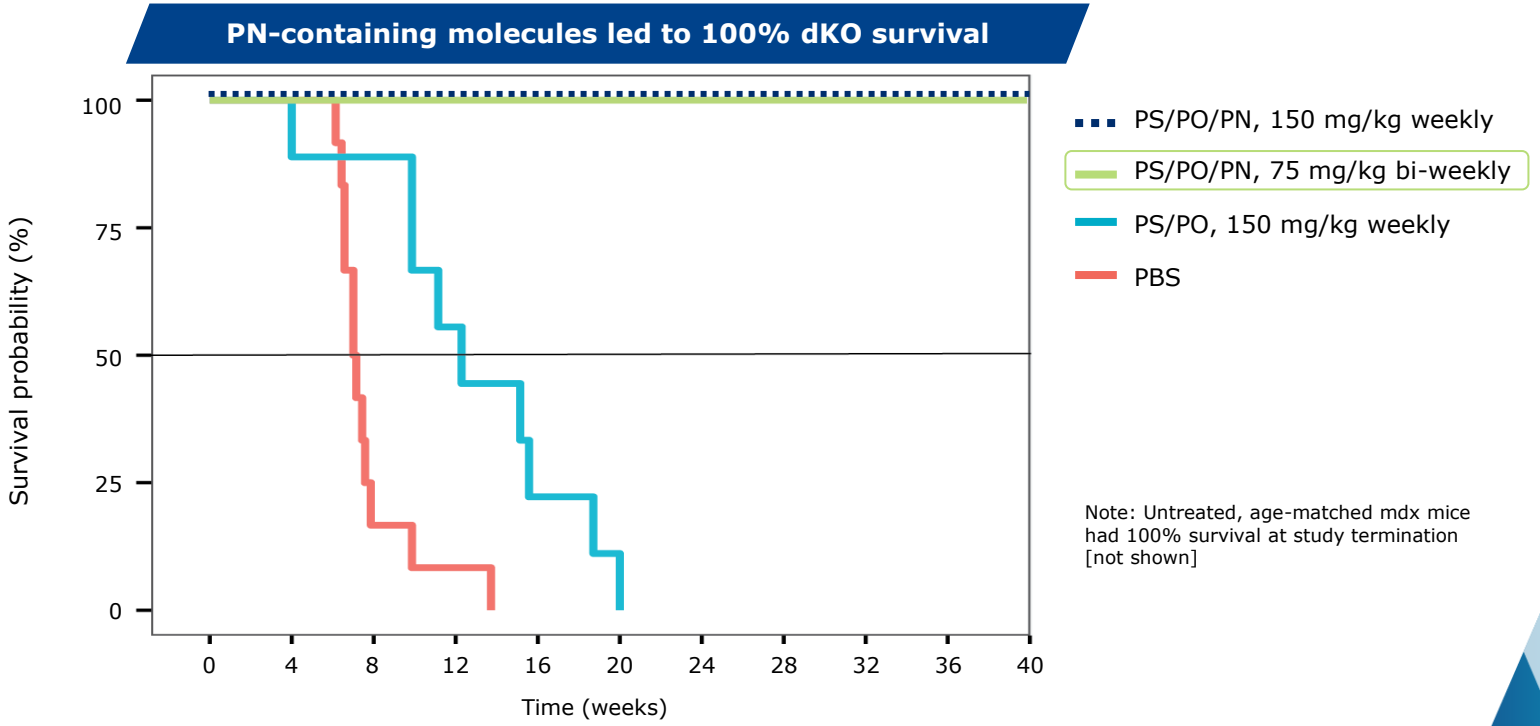
C9orf72-targeting oligonucleotides

- PS/PO backbone chemistry
- PS/PO/PN backbone chemistry



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.

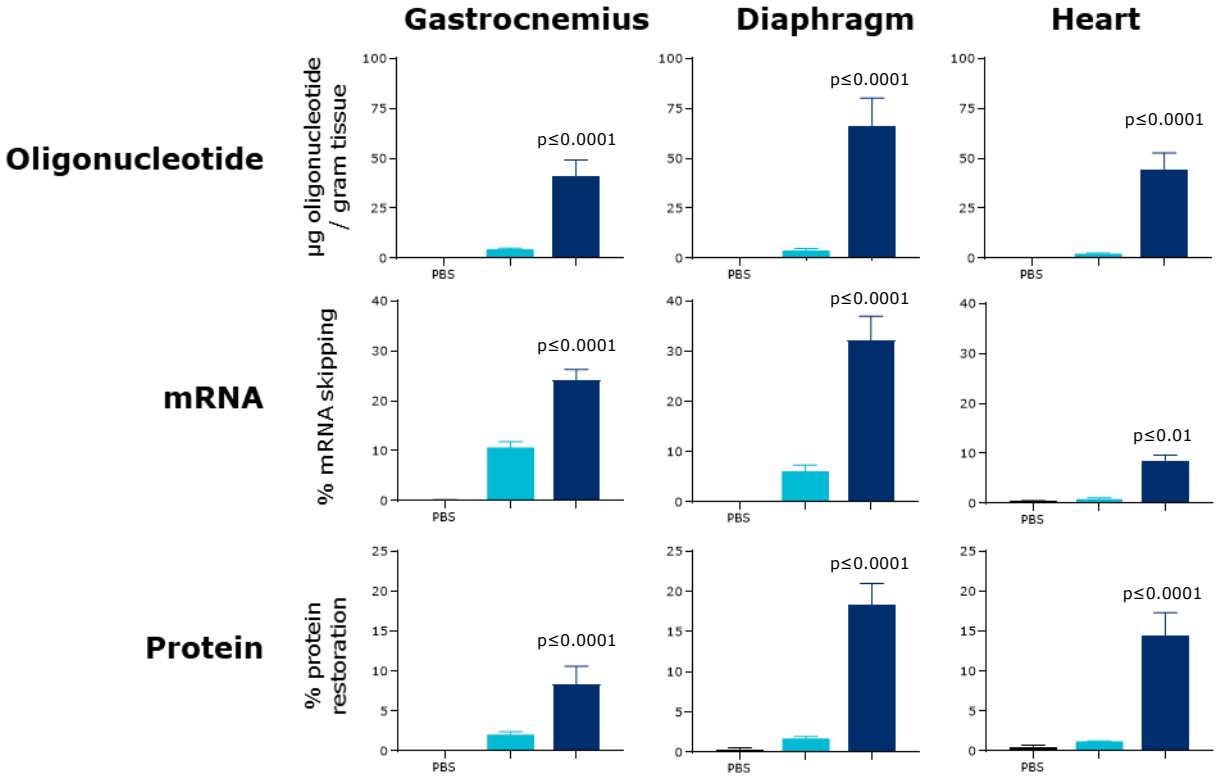
Adding PN chemistry modifications led to overall survival benefit in dKO model



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

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. Manuscript submitted.

PN chemistry improves exposure and target engagement in key tissues

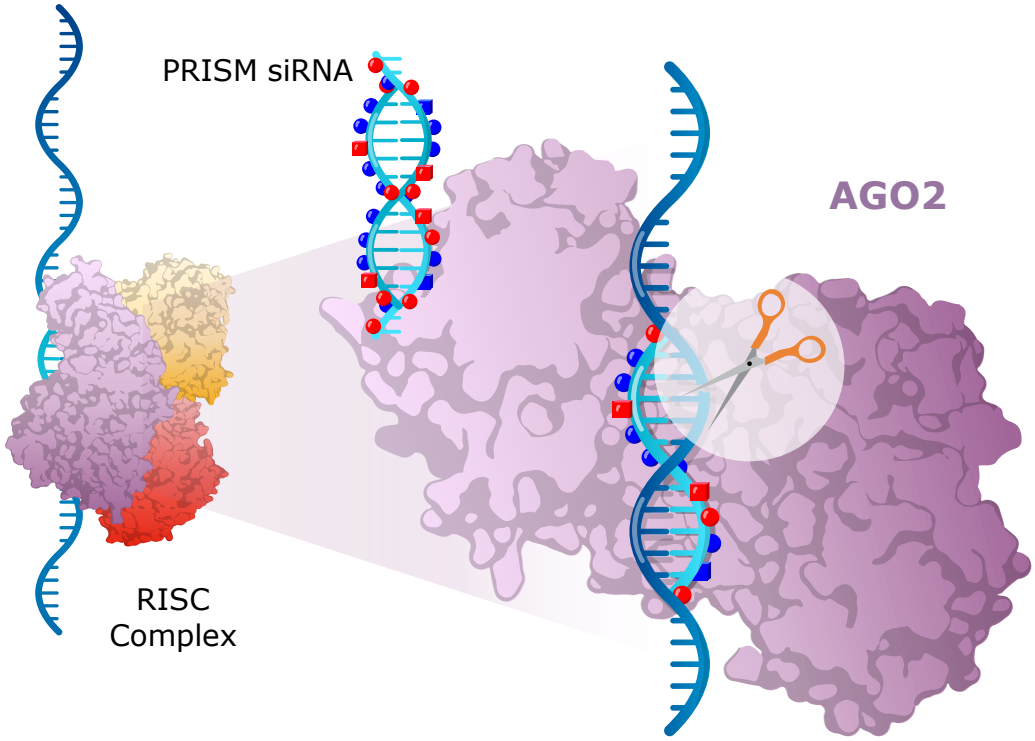


Exon-skipping oligonucleotides

- PS/PO backbone chemistry
- PS/PO/PN backbone chemistry

6x weekly 75 mg/kg subcutaneous doses; Sample collected 2 days after last dose. Manuscript submitted

PRISM principles applied to another class of silencers: siRNA

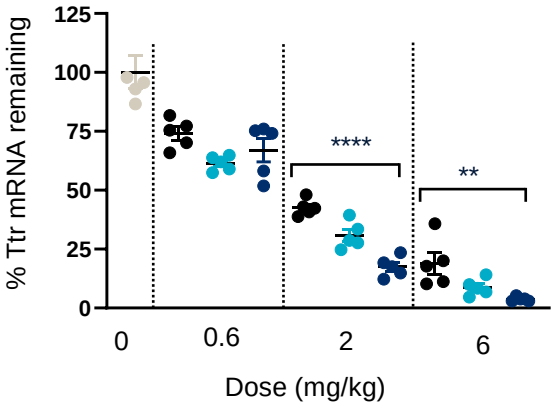


Application of PRISM principles to siRNA improves another class of silencers

PN chemistry improves potency and durability of ESC format

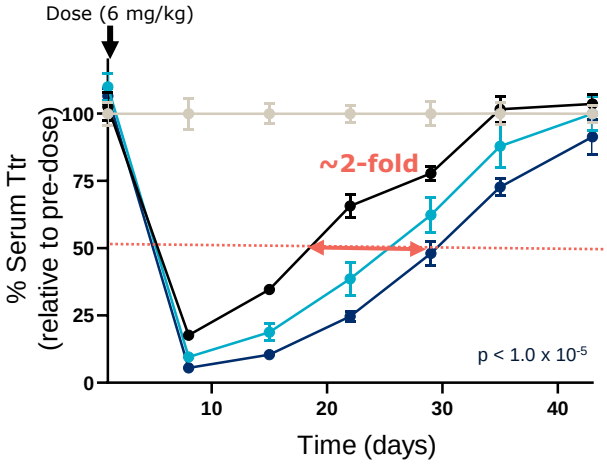
Potency

mTtr mRNA (liver)



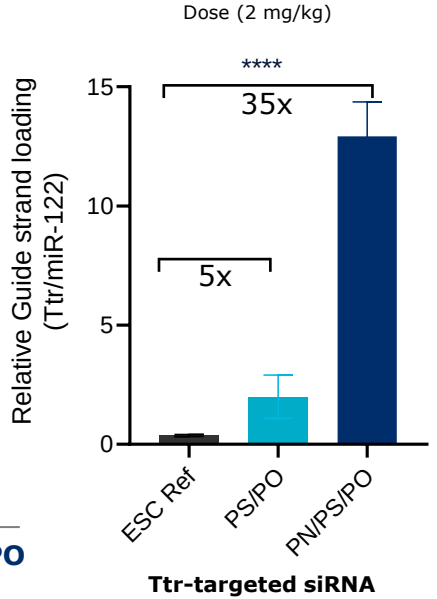
Durability

mTTR protein (serum)



Ago2-loading

Guide strand-Ago2 IP (liver)



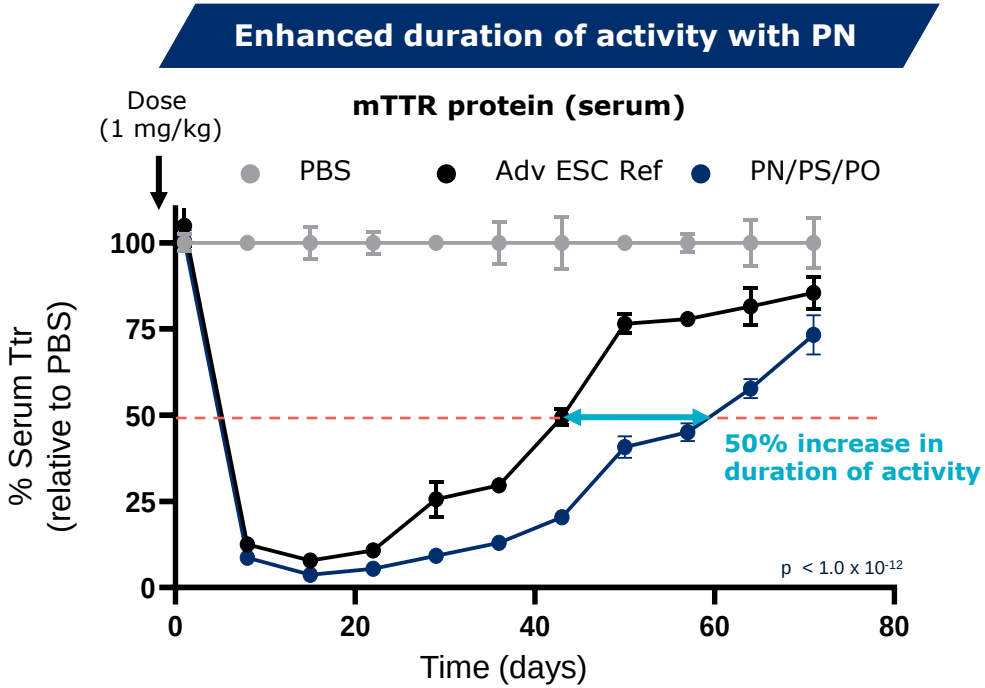
siRNA chemistry

PBS | ESC Ref | PS/PO | PN/PS/PO

(Left) C57Bl/6 mice administered single 0.2, 2 or 6 mg/kg subcutaneous dose on day 1. Tissue harvested on day 8. Stats: 2-way ANOVA with post-hoc comparison to ESC. (Middle) Mice received single 6 mg/kg subcutaneous dose on day 1. Serum collected weekly. Stats: 2-way mixed ANOVA with post hoc comparisons PN vs Reference. (Right) As described for left panel (2 mg/kg); Ago2 loading measured by qPCR after immunoprecipitation (IP) and normalized to miR-122; Stats: 1-way ANOVA followed by Tukey's honest significance test. ** P<0.01, *** P<0.001****, P<0.0001. All post-hoc P values Bonferroni-corrected for multiple hypotheses. Reference: Enhanced Stabilization Chemistry

Application of PN chemistry to siRNA: Improving on the state-of-the-art

PN chemistry extends duration of GalNAc-conjugated Advanced ESC format

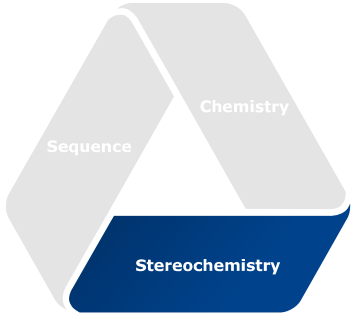


- PN extends 50% knockdown period for GalNAc-conjugated Adv ESC siRNAs
- Further optimization studies are in progress

Mice received a single 1 mg/kg subcutaneous dose on day 1. Serum was collected weekly. Stats: 2-way mixed ANOVA with post hoc comparisons PN vs Reference. P value is Bonferroni corrected for multiple hypotheses.

PRISM provides visibility into effects of backbone stereochemistry within every sequence

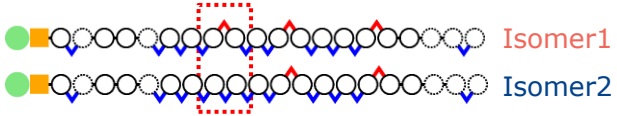
- Backbone stereochemistry impacts pharmacologic properties
- PRISM enables stereochemical control to fully characterize and investigate structure activity relationship (SAR) of each therapeutic candidate
- Standard in small molecule and antibody development



Backbone stereochemistry can be a tool to modulate pharmacologic properties, including tolerability

A single stereoisomeric change can dramatically alter the tolerability profile *in vivo*

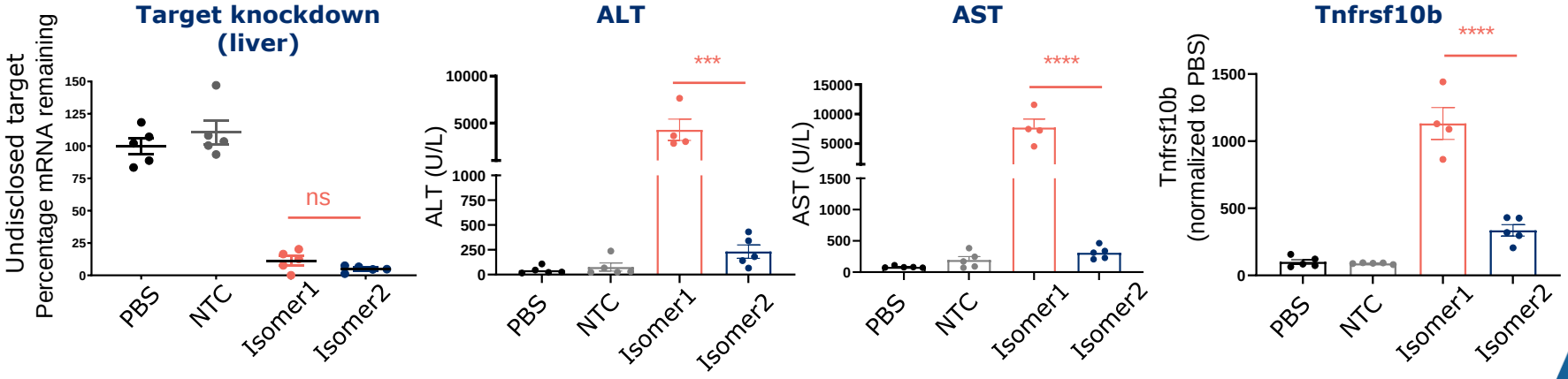
GalNAc conjugated oligonucleotide administered **subcutaneously**



Same sequence and chemical modifications, but different stereochemistry

Stereoisomers have **similar** pharmacodynamic effects

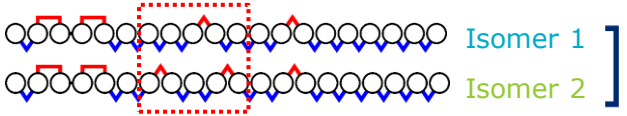
Changing backbone stereochemistry leads to **different** hepatotoxicity profiles *in vivo*



C57Bl/6 mice were administered 5 mg/kg oligonucleotide or PBS by subcutaneous injection on days 1, 3, 5 and 8. Liver tissue was collected on day 11. Target mRNA was normalized to Hprt1. Data are presented as mean ± sem (n=5). Stats: One-way ANOVA ns not significant, PBS phosphate buffered saline, NTC non-targeting control

Stereoisomeric changes can dramatically alter the tolerability profile in the CNS *in vivo*

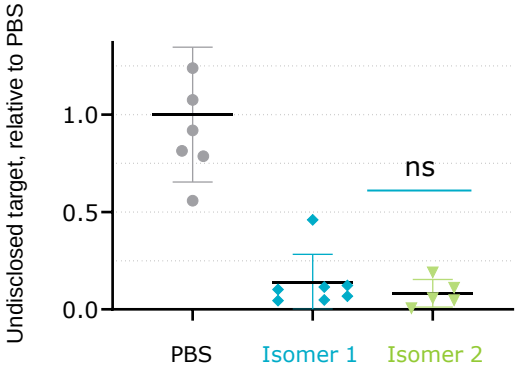
Unconjugated oligonucleotide administered **ICV**



Same sequence and chemical modifications, but different stereochemistry

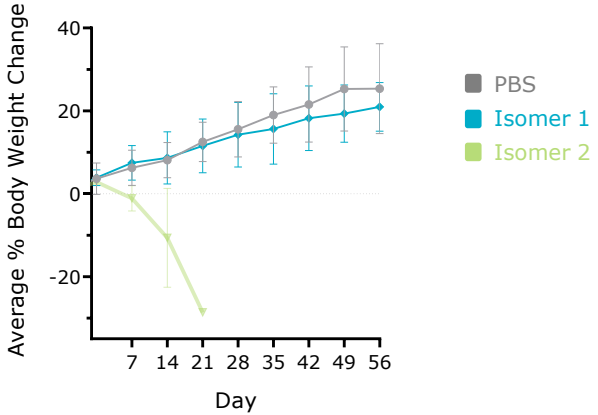
Stereoisomers have **similar** pharmacodynamic effects *in vivo*

CNS target knockdown *in vivo*



Changing backbone stereochemistry leads to **different** tolerability profiles *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: wtmouse tolerability study, n=4 administered 100 ug oligonucleotide or PBS by ICV on day 0 and monitored for 8 weeks.

PRISM enables novel advances in oligonucleotide design for optimization of RNA therapeutics

- PRISM uses deep understanding of interplay between sequence, chemistry and stereochemistry
- Rationally placed PN backbone chemistry modifications improve potency, durability of effect and distribution *in vitro* and *in vivo* across silencing, including RNAi, splicing and editing modalities
- Backbone stereochemistry can be a tool to modulate pharmacologic properties, including tolerability

WAVE™ LIFE SCIENCES

Building a Best-in-Class RNA Editing Capability: Introduction of AIMers

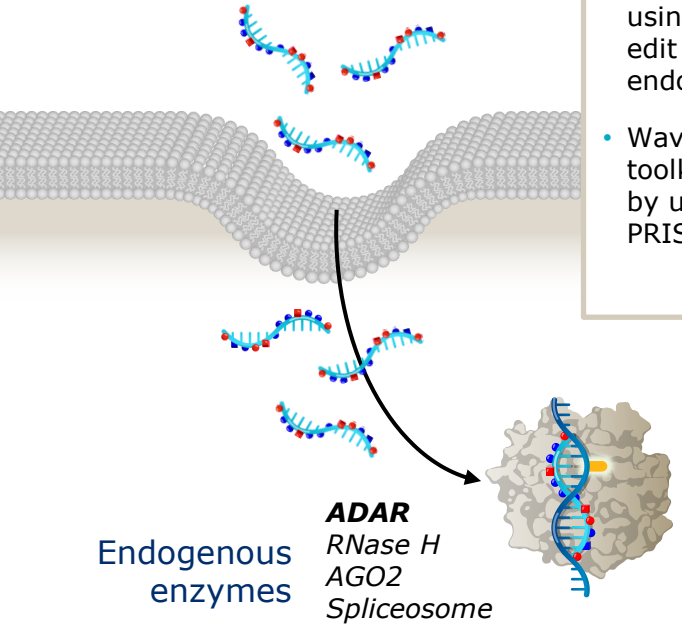
Chandra Vargeese, PhD

Chief Technology Officer

WAVE™ LIFE SCIENCES

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

Free-uptake of chemically modified oligonucleotides



Endogenous enzymes

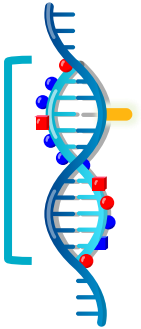
ADAR
RNase H
AGO2
Spliceosome

- 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



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

WAVE LIFE SCIENCES

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

Building best-in-class ADAR editing capability

Topics of discussion

1 Applications

- Restore protein expression
- Modulate protein activity

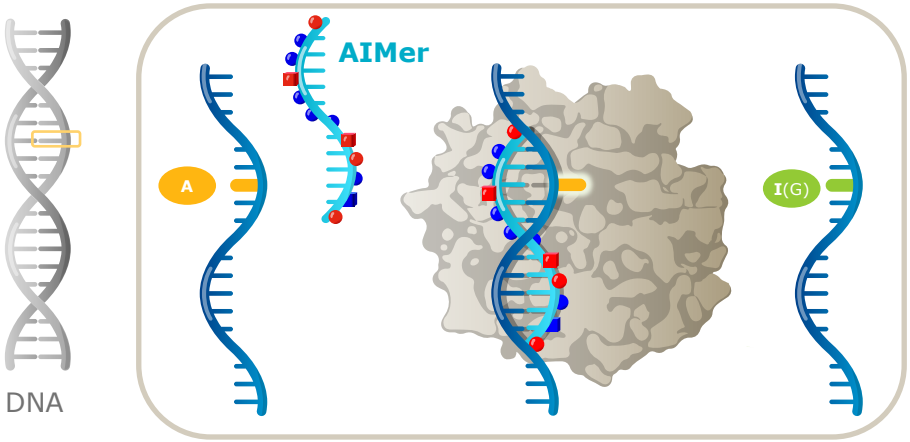
2 Design & Optimize

3 Translation *in vivo*

WAVE™ LIFE SCIENCES

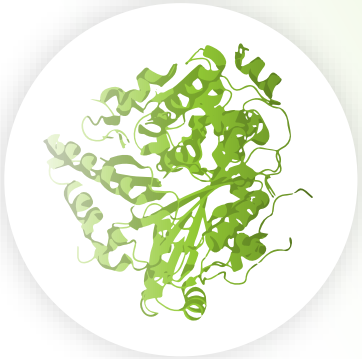
ADAR editing enables correction of single-point mutations to restore functional protein

Restore functional protein



Restore or correct expression

Example therapeutic areas



- AATD
- Rett syndrome
- Recessive or dominant genetically defined diseases

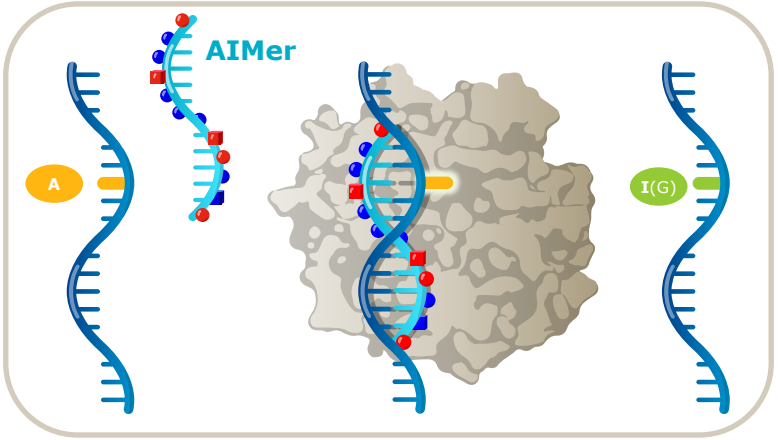
- >32,000 pathogenic human SNPs[2] – nearly half are ADAR amenable (G-to-A mutations)
- Tens of thousands of potential disease variants A-to-I(G) editing could target[1]
- ~12% of all reported disease-causing mutations are single point mutations that result in a premature stop codon[3]

WAVE LIFE SCIENCES

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

ADAR editing to modulate proteins at transcript level opens wide range of large therapeutic applications

Modulate downstream protein interactions with single RNA base edit



Upregulate expression

Modify function

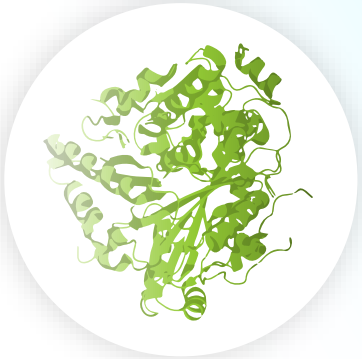
Modulate protein-protein interaction

Post-translational modification

Alter folding (stability)

Alter processing

Example therapeutic areas



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

- Opens wide range of therapeutic applications with large patient populations

WAVE™ LIFE SCIENCES

Building best-in-class ADAR editing capability

Topics of discussion

1 Applications

- Restore protein expression
- Modulate protein activity

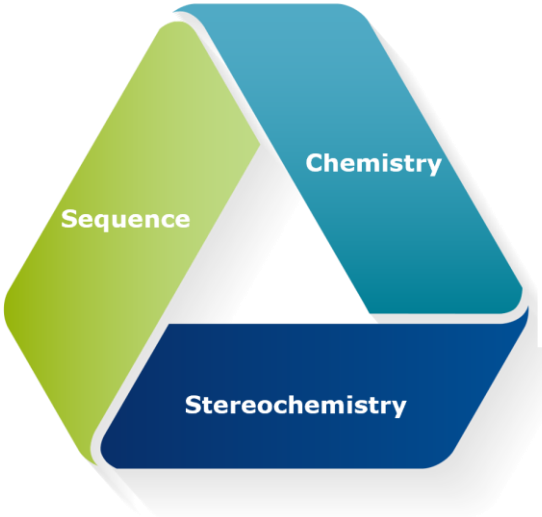
2 Design & Optimize

- Applying unique chemistry capabilities to AIMers enhances editing
- Optimization of chemistry and SAR informs design principles for future rational design

3 Translation *in vivo*

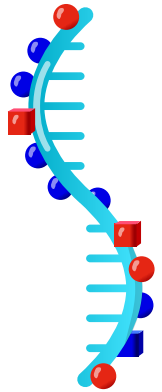
WAVE™ LIFE SCIENCES

Unique chemistry platform enables rational design of AIMers to efficiently recruit ADAR enzymes



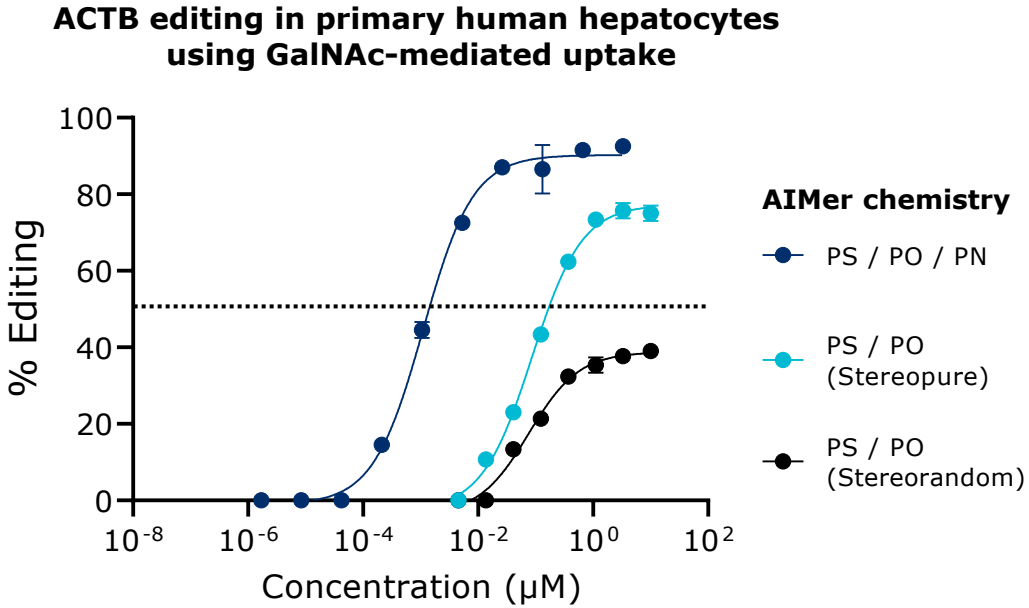
AIMers

- RNA base editing oligonucleotides
- Short, single-stranded
- Fully chemically modified
- Modified nucleobases
- Stereopure PS and PN backbone modifications
- Compatible with targeting ligands



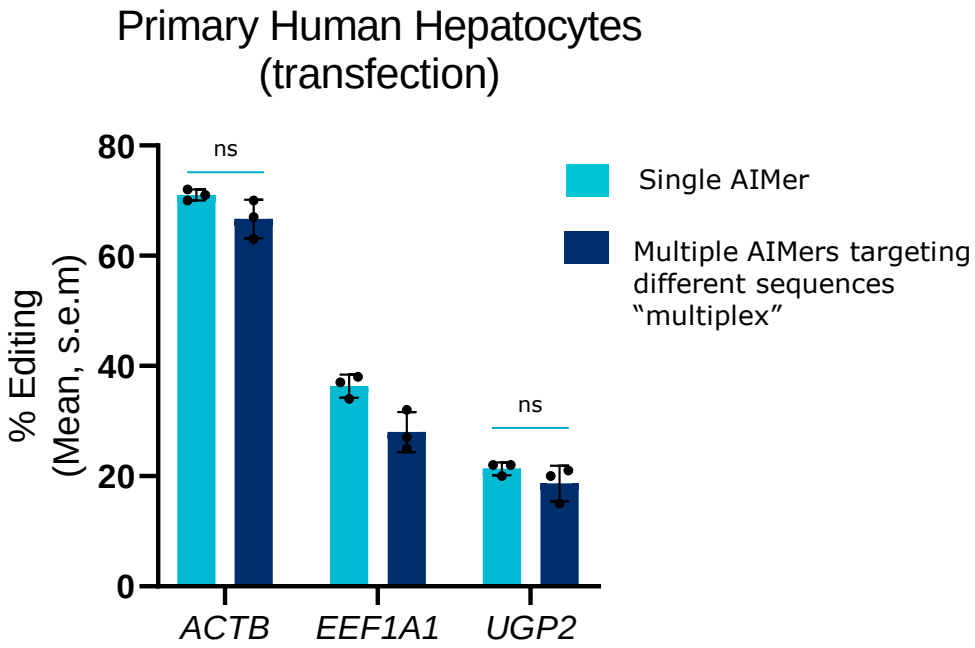
WAVE™ LIFE SCIENCES

Stereochemistry and PN chemistry enhance potency and editing efficiency of AIMers



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

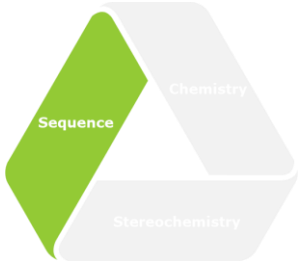
Levels of endogenous ADAR enzyme are not rate limiting for editing



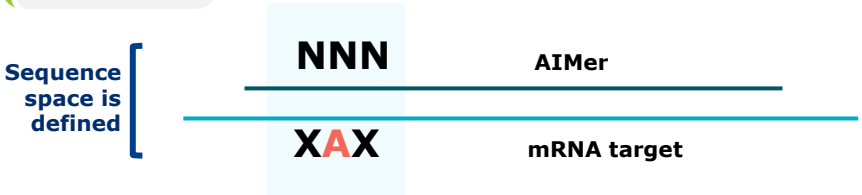
- Endogenous ADAR enzyme supports editing on multiple independent targets
- Editing efficiency comparable even when additional AIMers targeting different sequences are added, suggesting there is a more than sufficient reservoir of ADAR enzyme

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.

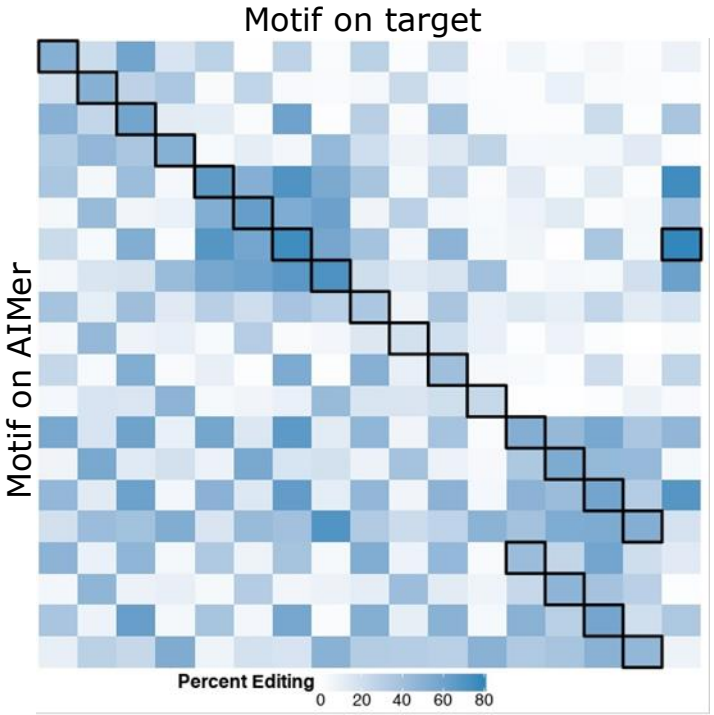
Optimization of every dimension to inform future rational design of AIMers



Sequence is one of multiple dimensions for optimization



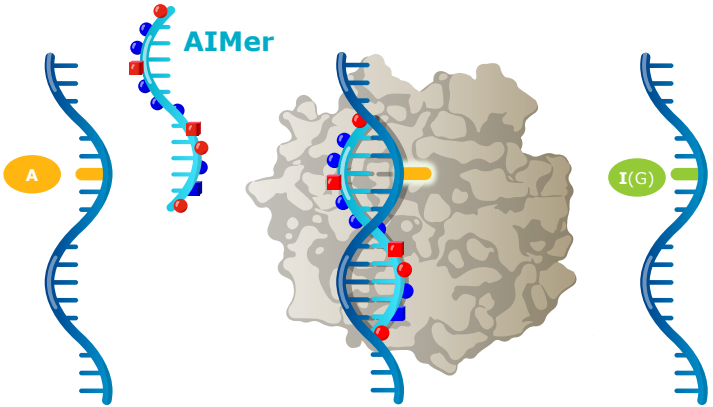
- >300 unique AIMers tested containing different base pair combinations
- Identified base modification combinations with high editing efficiency to optimize sequence



Learnings inform design principles deployed across future targets

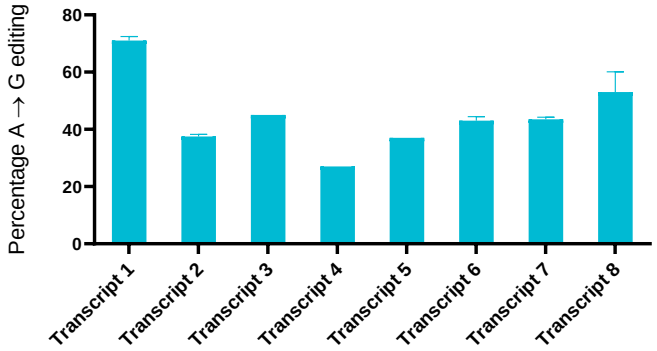
WAVE LIFE SCIENCES

ADAR interacts with double-stranded RNA duplex in a sequence independent way



- The intrinsic function of ADAR is to recognize dsRNA **independent of sequence**

RNA-editing design applicable across targets *in vitro* in primary human hepatocytes



- Editing achieved across several distinct RNA transcripts
- Supports potential for technology to be applied across variety of disease targets

WAVE LIFE SCIENCES

Data presented at 1st International Conference on Base Editing – Enzymes and Applications (Deaminet 2020). Manuscript submitted.

Building best-in-class ADAR editing capability

Topics of discussion

1 Applications

- Restore protein expression
- Modulate protein activity

2 Design & Optimize

- Applying unique chemistry capabilities to AIMers enhances editing
- Optimization of chemistry and SAR informs design principles for future rational design

3 Translation *in vivo*

- GalNAc-conjugated AIMers: liver
- Unconjugated AIMers: CNS, ophthalmology and beyond

WAVE™ LIFE SCIENCES

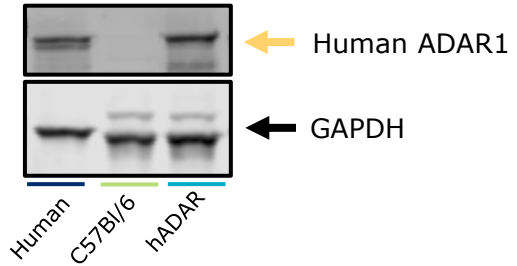
huADAR mouse enables optimization of AIMers to human ADAR

huADAR mouse

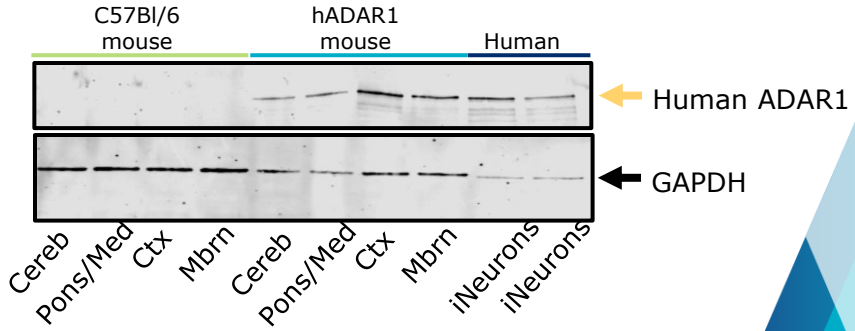
Genotype	
✓	huADAR/mADAR
	Human ADAR expressed in all tissues

- Transgenic mouse expressing **human ADAR1**
- Expression of ADAR in liver and neurons in mouse approximates expression in corresponding human tissues

Human ADAR expression in hepatocytes



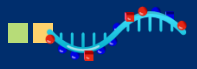
Human ADAR expression in neurons



Western blots showing expression of ADAR1 and GAPDH proteins in the indicated tissue
Left: Protein extracts from human hepatocytes, C57Bl/6 or hADAR1 mouse liver; Right: Protein extracts from cerebellum (Cereb), pons/medulla (pons/med), cortex (Ctx), midbrain (Mbrn), or human iCell neurons (iNeurons)

GalNAc-conjugated AIMers demonstrate proof-of concept of RNA editing in liver

Rapidly advancing first therapeutic program

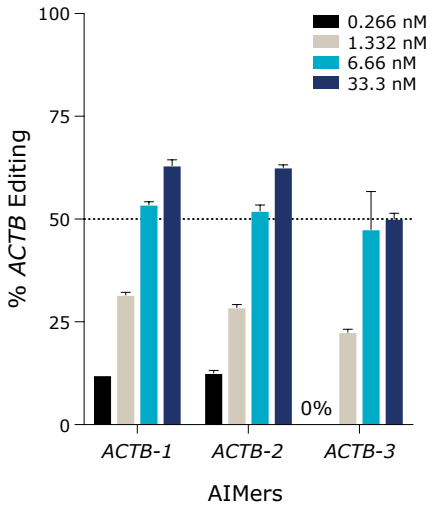
Delivery	Routes of administration	Tissue types	
GalNAc-conjugated 	**Subcutaneous**	**Liver**	**AATD program**
Unconjugated 	IVT Intrathecal (IT)	Ophthalmology Central nervous system (CNS)	

PN-modified AIMers direct potent and durable editing *in vivo*

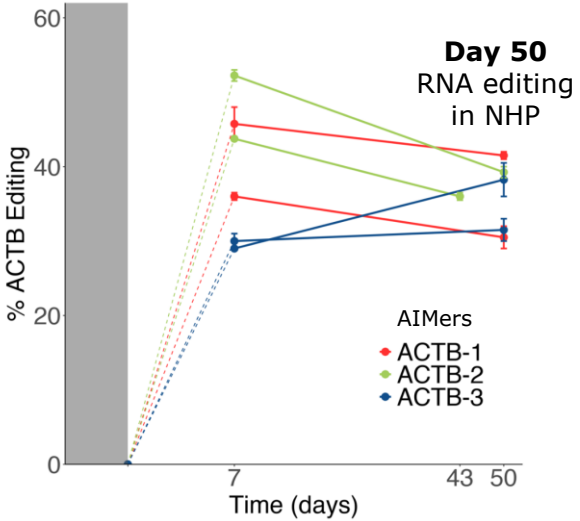
WAVE LIFE SCIENCES

GalNAc-conjugated AIMers support efficient, durable and highly specific ADAR editing in NHPs

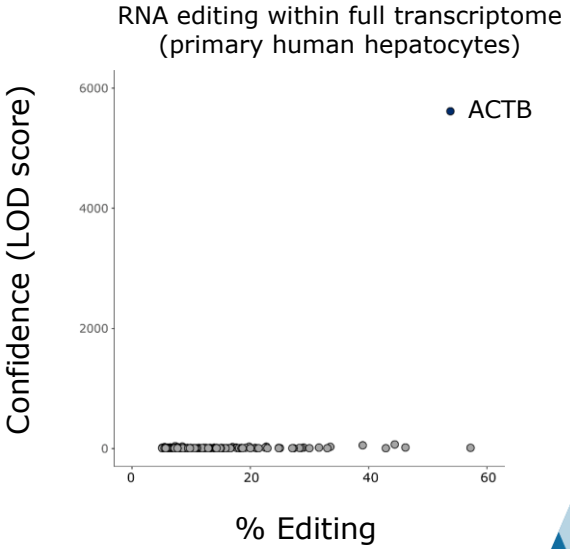
Dose-dependent editing in NHP hepatocytes *in vitro*



Substantial and durable editing in NHP liver *in vivo*



ADAR editing with ACTB AIMer is highly specific

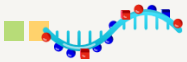


RNA editing only detected at editing site in ACTB transcript

Left: Total RNA harvested, reverse transcribed to generate cDNA, and editing target site amplified by PCR; % Editing quantified from Sanger sequencing using EditR program; Center: 5mg/kg SC: Day 1,2,3,4,5; Liver Biopsy for mRNA (ACTB Editing); Right: Dosed 1um AIMer, 48 hours later RNA collected, RNAseq conducted using strand-specific libraries to quantify on-target ACTB editing and off-target editing; plotted circles represent sites with LOD>3. Manuscript submitted. NHP: non-human primate; ACTB: Beta-actin

Unconjugated AIMers expand tissues amenable to ADAR editing

Opportunity for future pipeline programs

Delivery	Routes of administration	Tissue types
GalNAc-conjugated 	Subcutaneous	Liver
Unconjugated 	**IVT** **Intrathecal (IT)**	**Ophthalmology** **Central nervous system (CNS)**

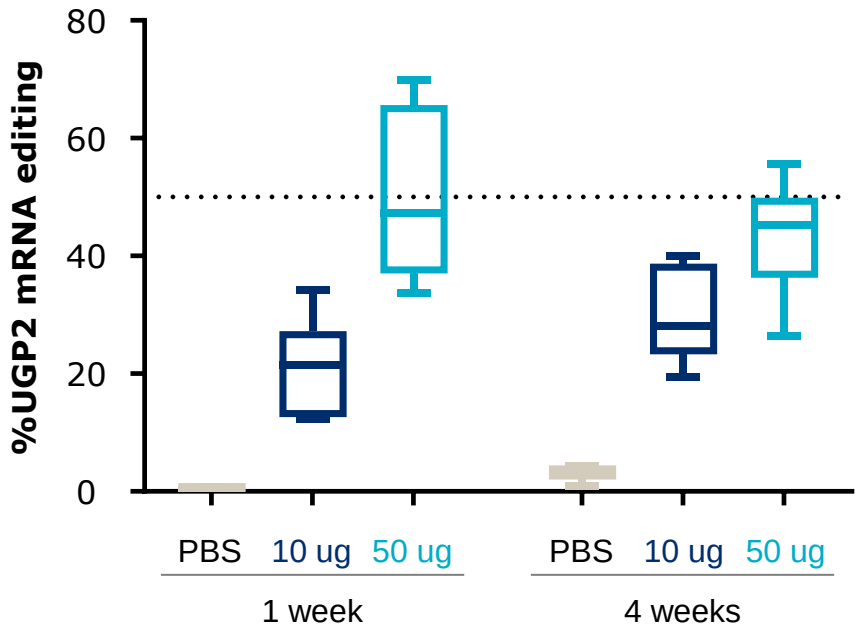
MECP2 and undisclosed exploratory programs

PN-modified AIMers direct potent and durable editing *in vivo*

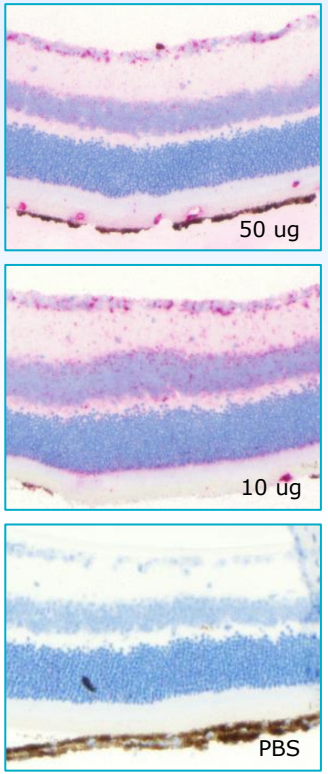
WAVE LIFE SCIENCES

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

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



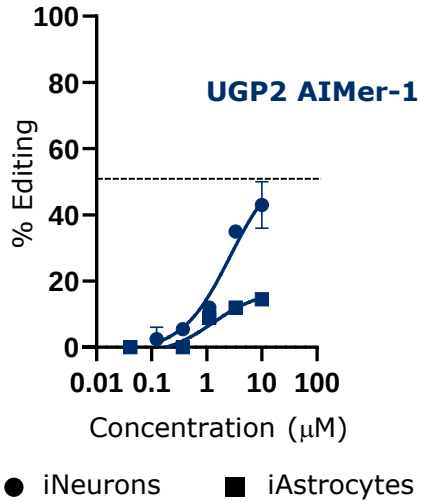
AIMers in retina at 4 weeks



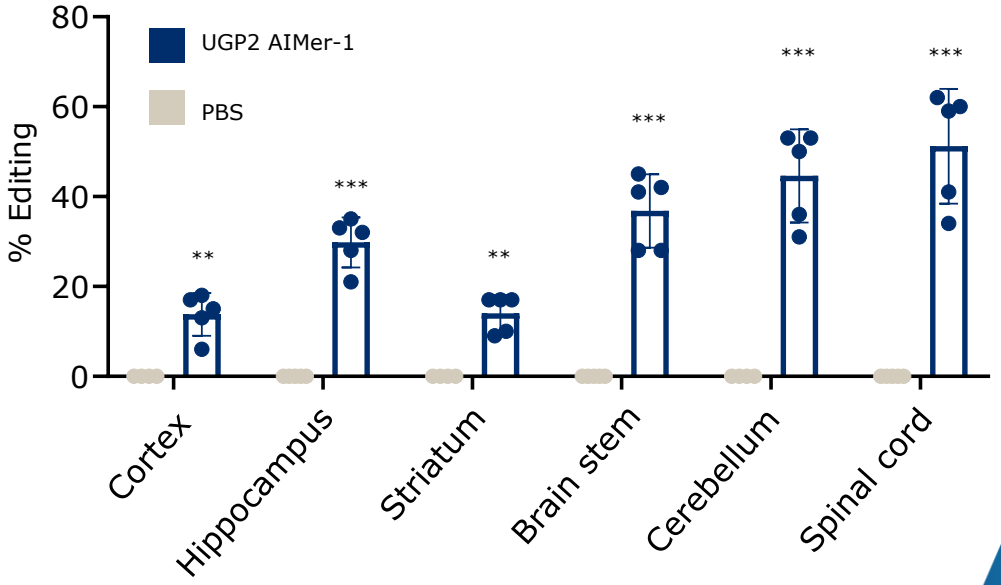
Mice received a single IVT injection (10 or 50 ug AIMer), and eyes were collected for RNA analysis and histology 1 or 4 weeks later. Left: editing evaluated by Sanger sequencing, and % RNA editing calculated with EditR. Right: FFPE and RNA scope assay specific for AIMer, red = oligo, blue = nuclei. Posterior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

AIMers direct editing *in vitro* in multiple CNS cell types and throughout CNS *in vivo*

In vitro dose-response



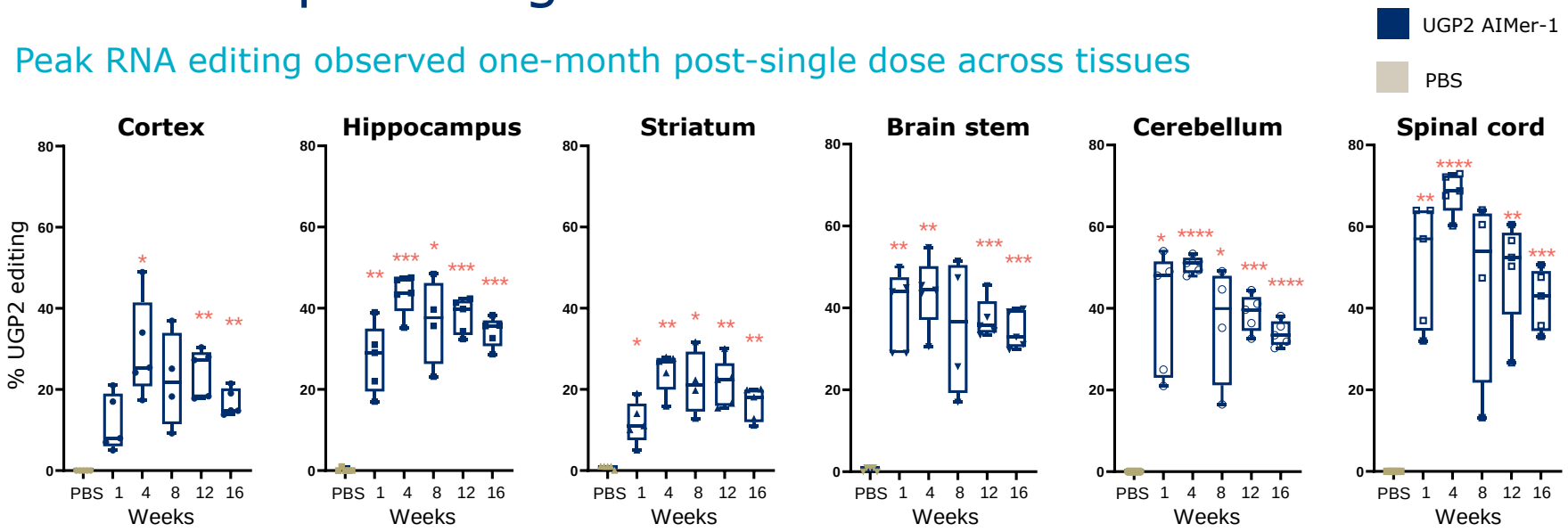
Editing in CNS of hADAR mouse (Single ICV injection, 100 μg)



hADAR: human ADAR; UGP2: Glucose Pyrophosphorylase 2; CNS: central nervous system; Editing observed across all tested tissues of huADAR-transgenic mice. N=5 PBS or single 100 μg ICV dose on day 0, necropsied on day 7. RNA harvested, editing measured by Sanger sequencing. ACTB β-actin; Stats: *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; all comparisons to PBS-treated group by t test (P values Bonferroni corrected)

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

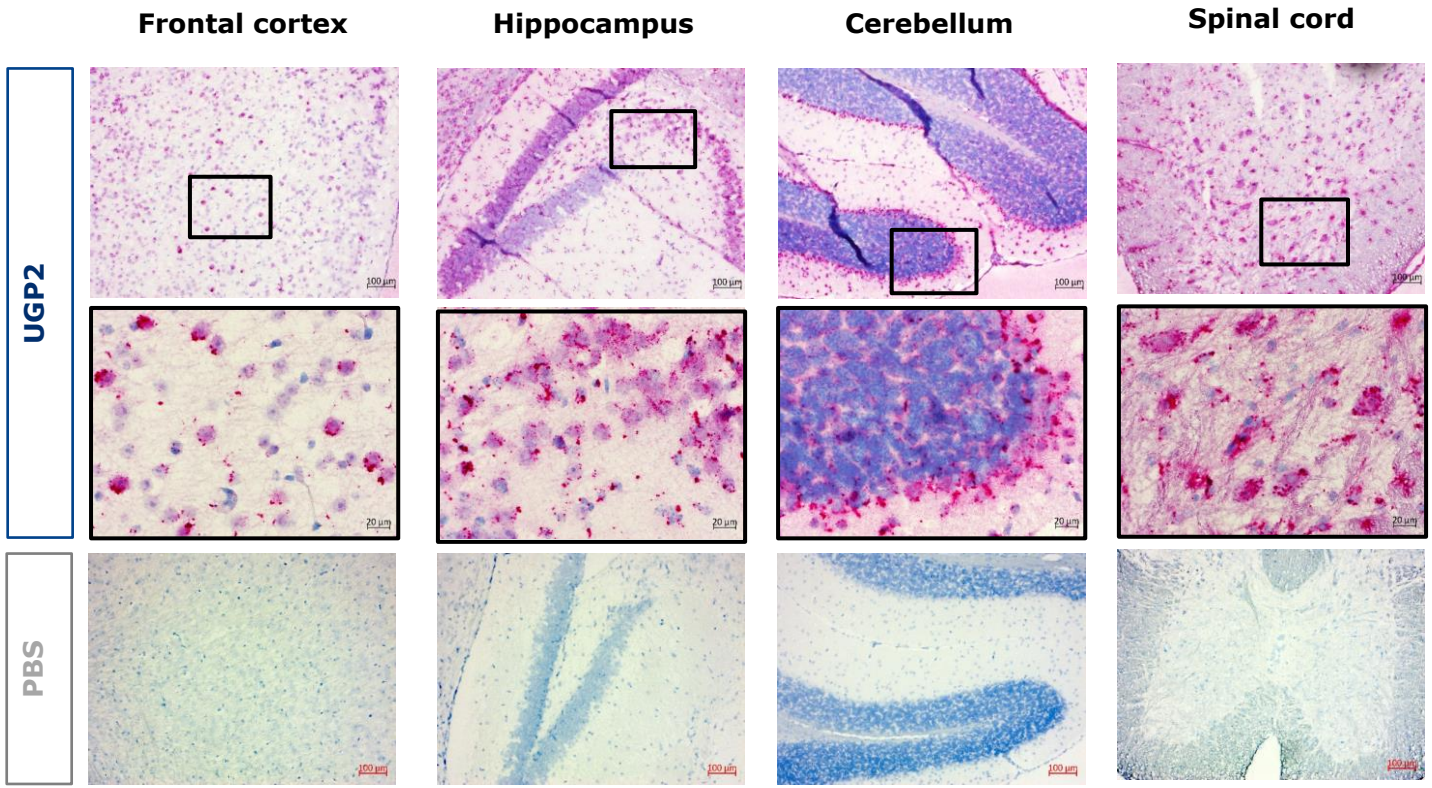
Peak RNA editing observed one-month post-single dose across tissues



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

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

UGP2 AIMer-1 distributes throughout CNS

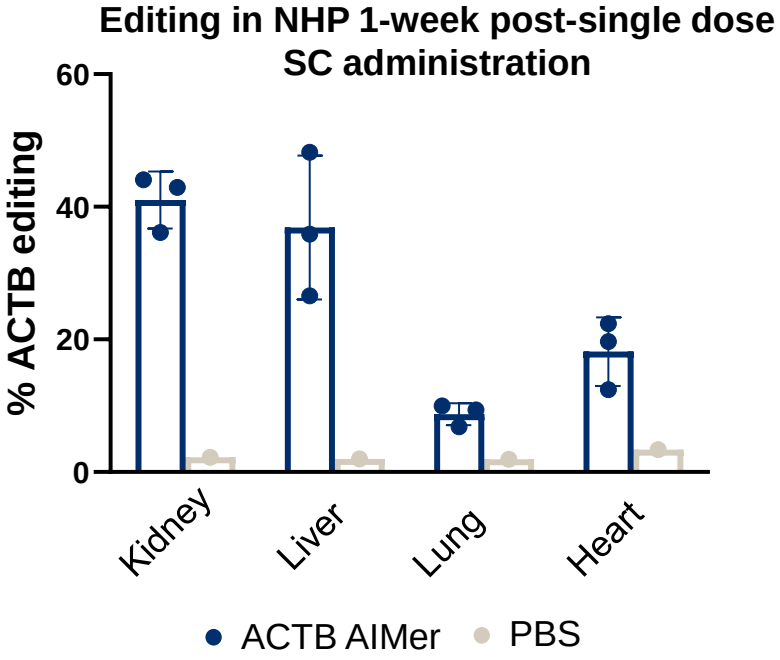


Sections from treated mice 12-weeks after a single 100 μg dose of UGP2-AIMer or PBS (bottom). ViewRNA (red, Fast red) was used to detect oligonucleotides; sections are counterstained with hematoxylin (blue nuclei). Magnification 10X (top & bottom), 40X (middle, oil), 10X

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

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

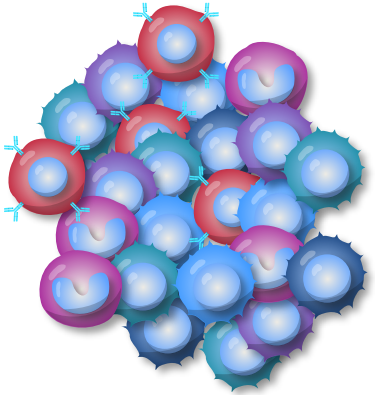
- NHP study demonstrated productive editing in kidney, liver, lung and heart with single subcutaneous dose



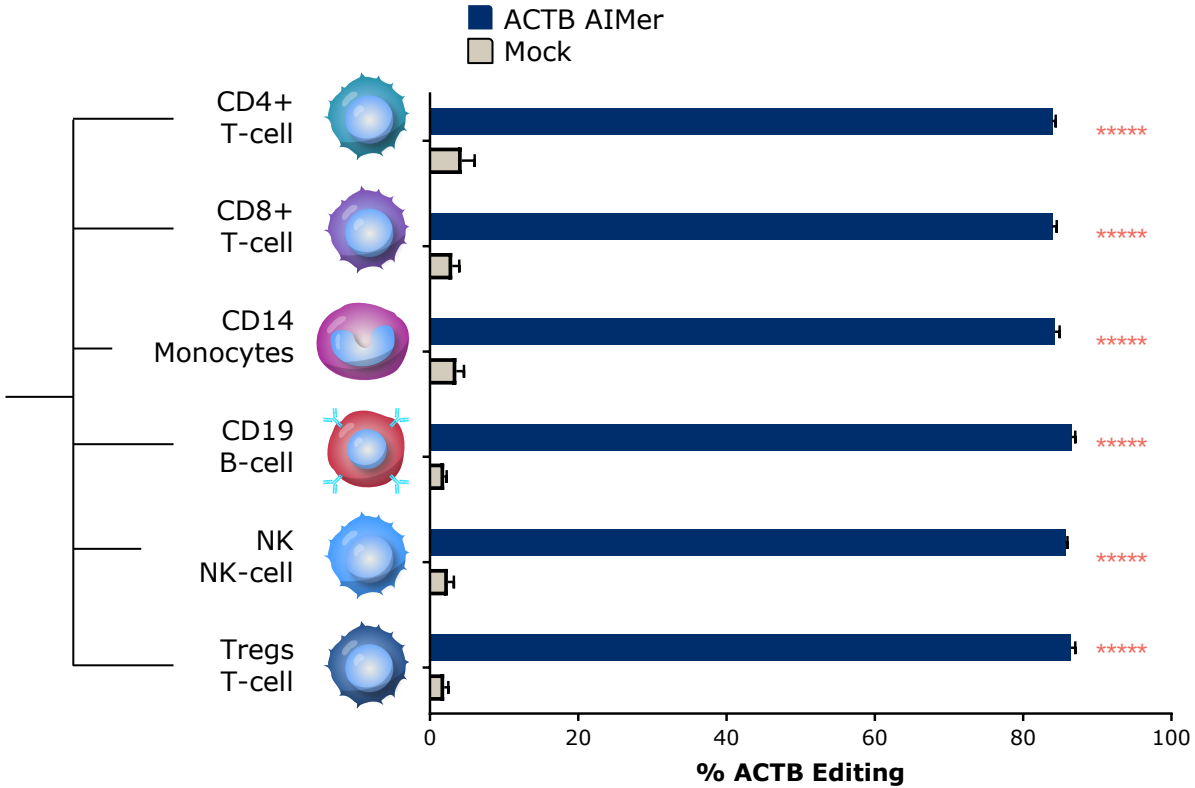
NHP: non-human primate; ACTB: Beta-actin
Dose: 50 mg/kg SC on Day 1 Necropsy for mRNA (ACTB Editing) Day 8

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

Human peripheral blood mononuclear cell (PBMC)



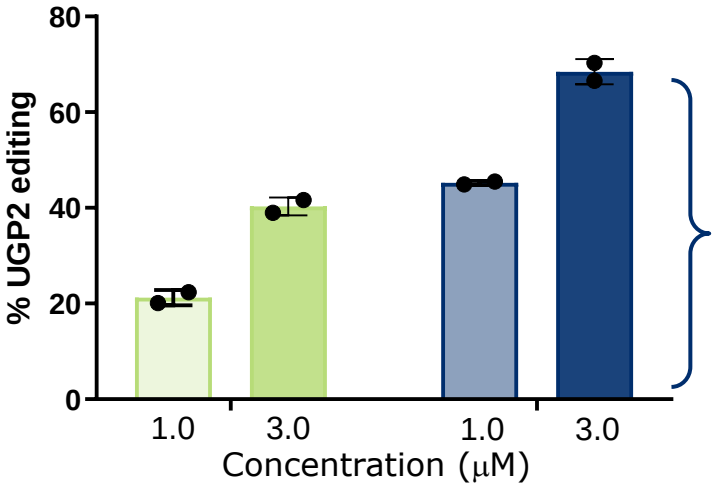
Activate (PHA) → Dose → Sort



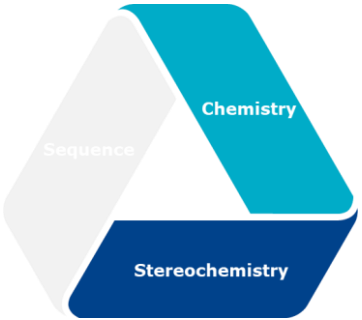
Human PBMCs dosed with 10 uM ACTB AIMers, under activating conditions (PHA). After 4 days, different cell types isolated, quantitated for editing %. ACTB: Beta-actin; Two-way ANOVA followed by post hoc comparison per cell line. P values were Bonferroni-corrected for multiple hypotheses

Ongoing chemistry optimization continues to drive potency gains

***In vitro* dose-response in iCell neurons**

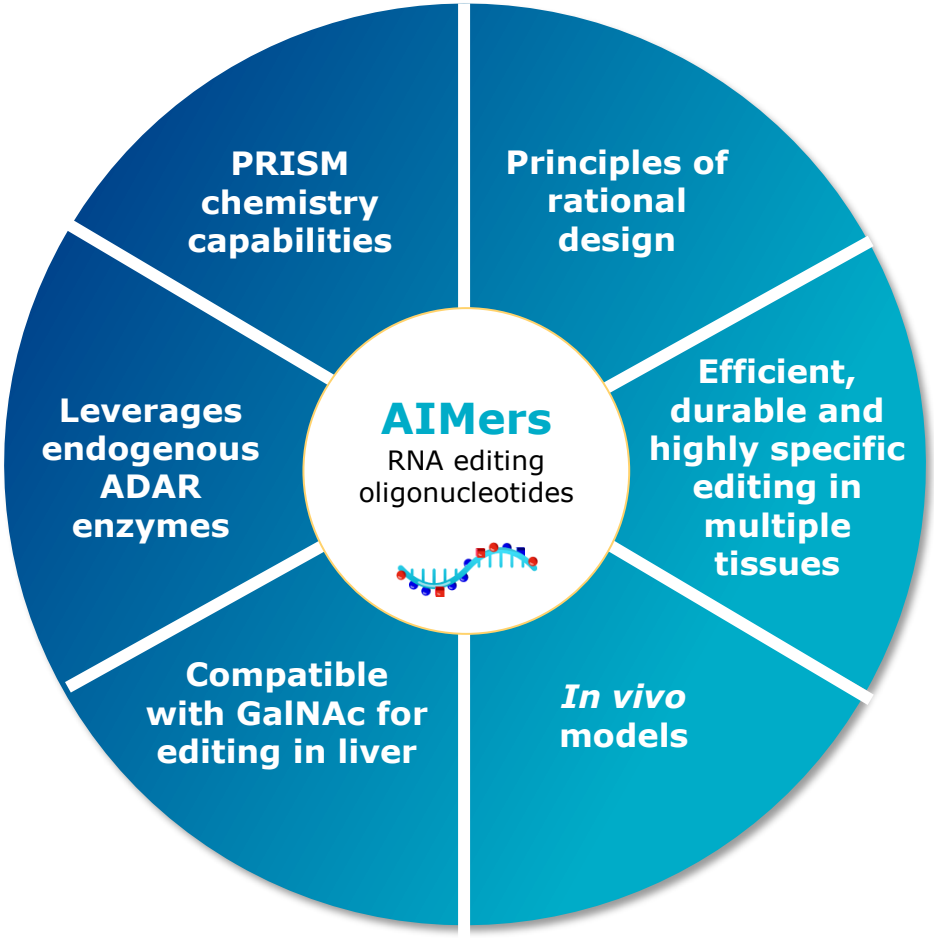


~75% more efficient editing with optimized AIMers



iCell neurons treated with 1 or 3 mM UGP2 AIMer with old (left, blue) or new (right, green) chemistry. Data are mean ± sd.

Rapidly advancing best-in-class ADAR editing capability



WAVE LIFE SCIENCES

Advancing ADAR Editing in the CNS

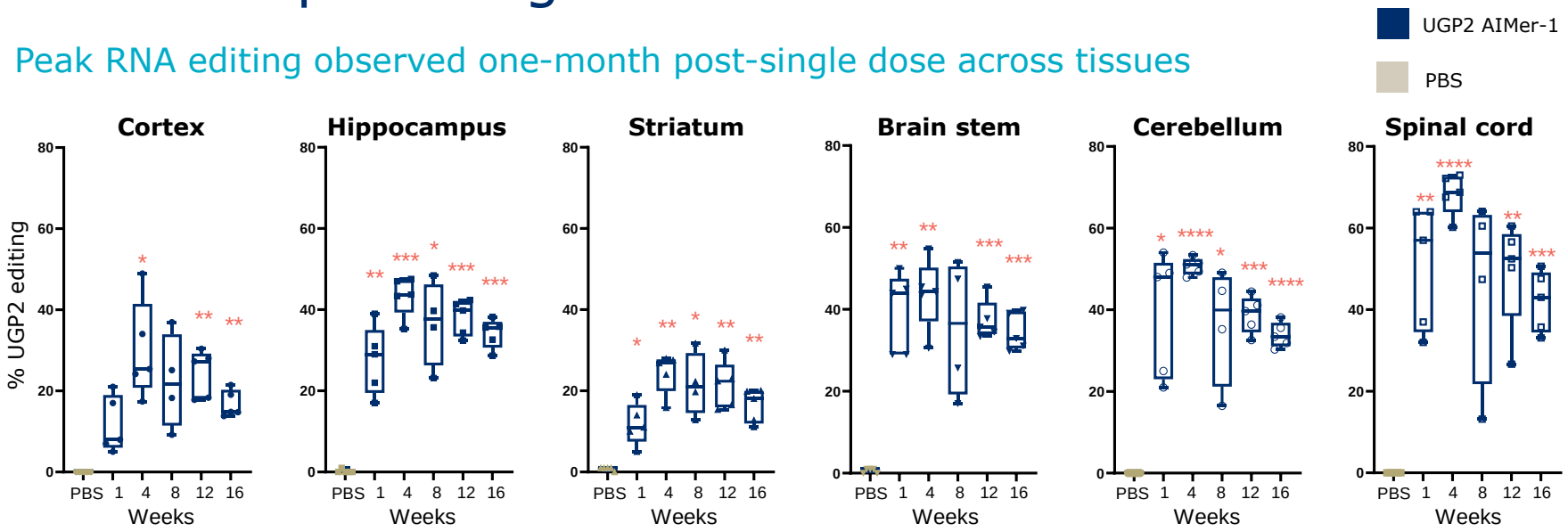
Ken Rhodes, PhD

SVP, Therapeutics Discovery

WAVE™ LIFE SCIENCES

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

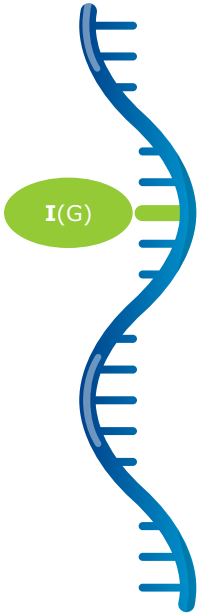


Peak editing	30%	>40%	25%	>40%	50%	>65%

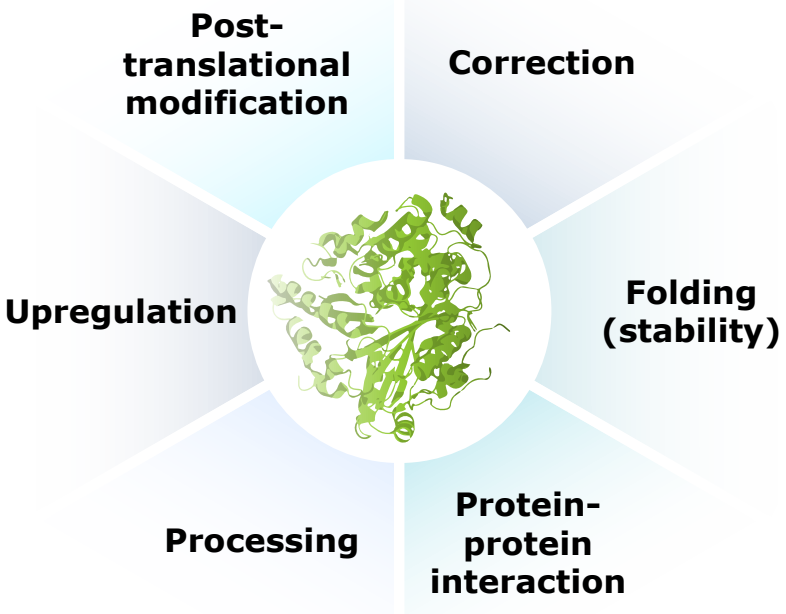
Transgenic huADAR mice administered 100 μg AIMer or PBS on day 0 and evaluated for UGP2 editing across CNS tissues at 1, 4, 8, 12, and 16-weeks post dose. Percentage UGP2 editing determined by Sanger sequencing. Stats: 2-way ANOVA compared to PBS (n=5 per time point per treatment) *P<0.05, **P<0.01,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

Expanding addressable disease target space using ADAR editing to modulate proteins

ADAR editing of mRNA



Restore or modify protein function



Impact diseases

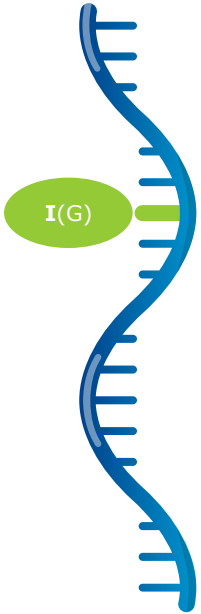
Examples:

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

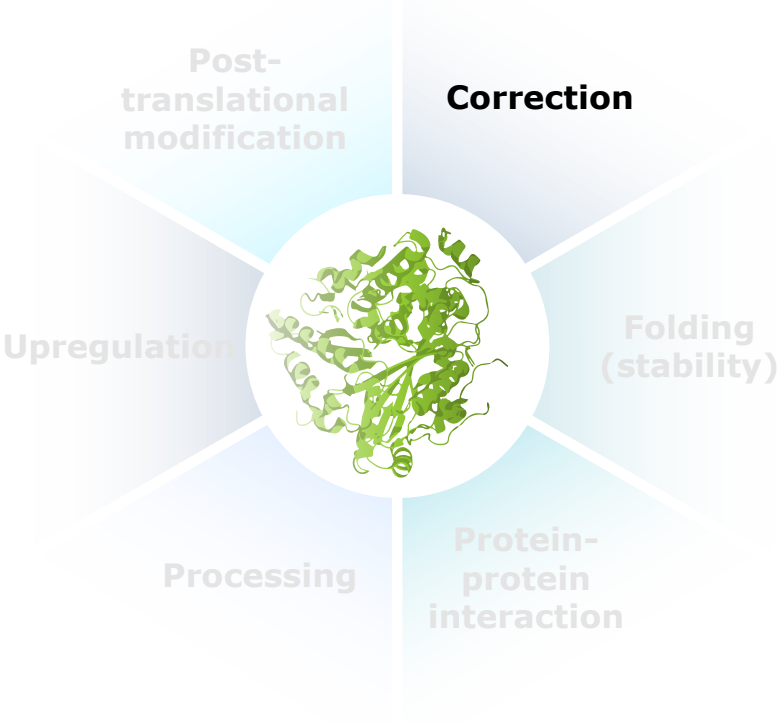
WAVE LIFE SCIENCES

Correct a nonsense mutation using ADAR editing to restore protein expression and function

ADAR editing of mRNA



Downstream protein interactions



WAVE LIFE SCIENCES

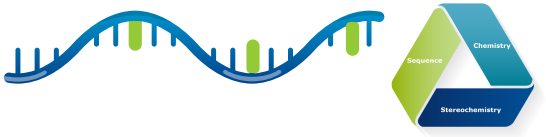
RNA editing of nonsense mutation found in MECP2 (Rett Syndrome) restores functional protein

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

Variant base

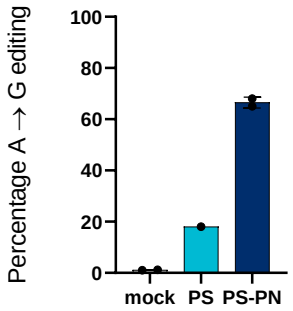
ADAR editing site

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

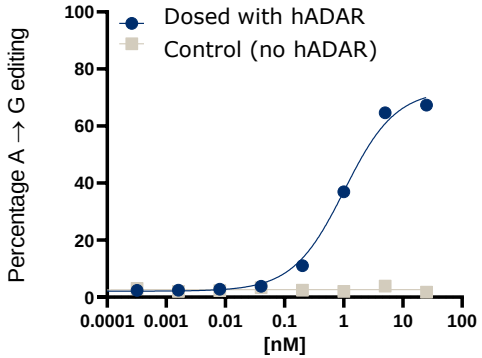


in vitro ADAR editing of over 60% targeting MECP2 disease transcript

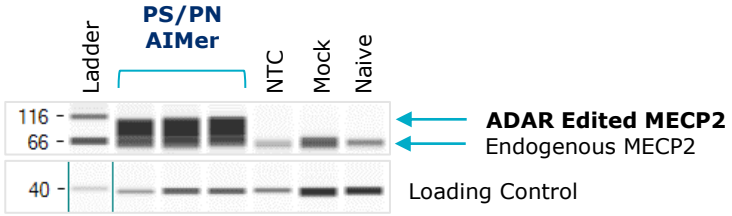
PN chemistry improved editing efficiency *in vitro*



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

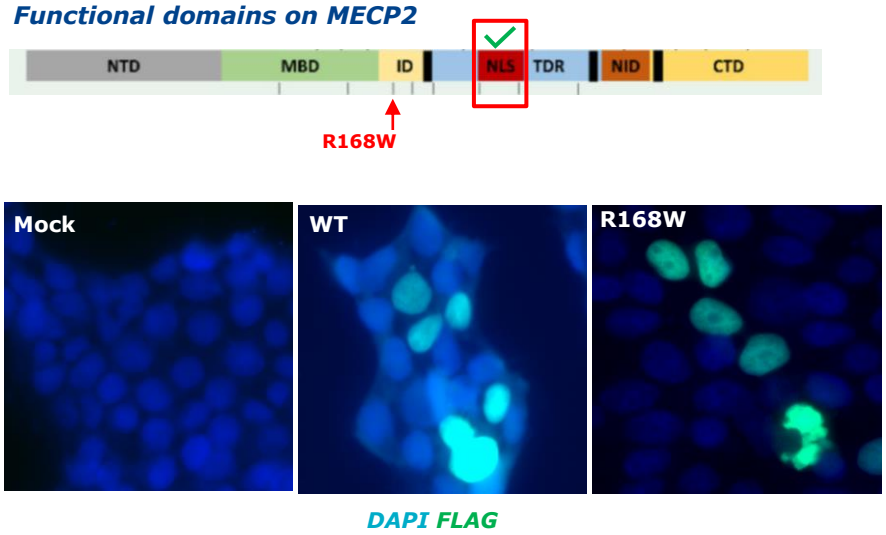


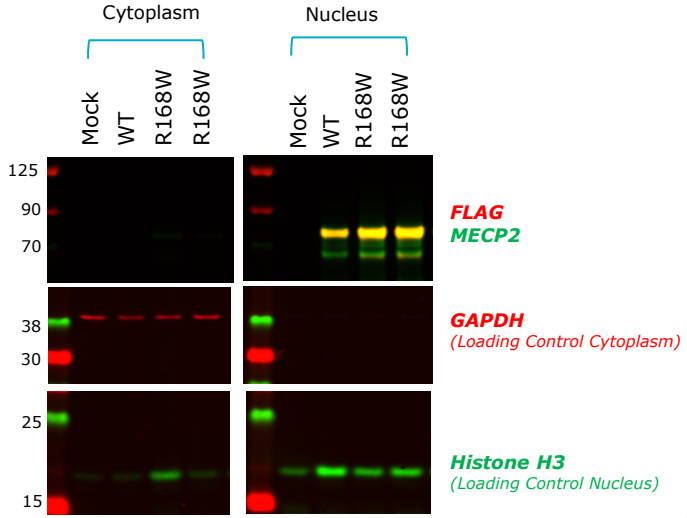
Full length MECP2 protein is expressed following ADAR editing



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

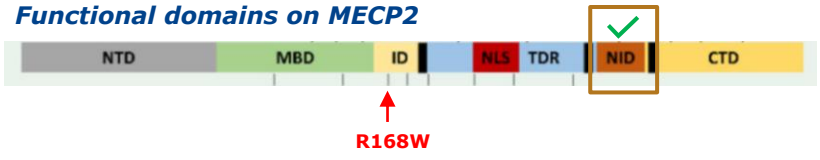
Restored MECP2 retains proper nuclear localization

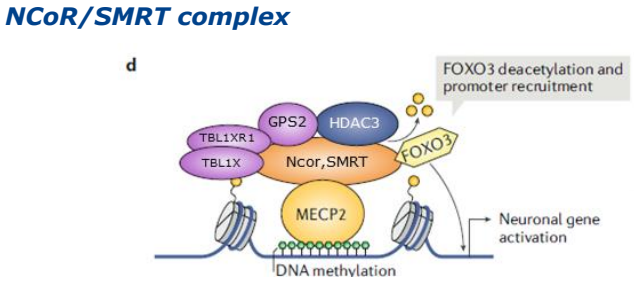


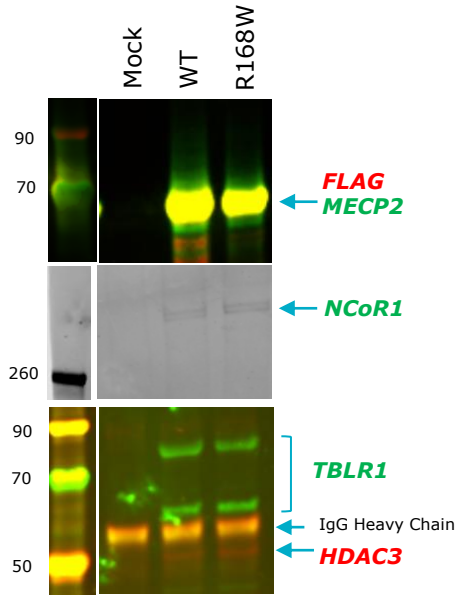


293T cells transfected with plasmids containing either wildtype or R168W MECP2 (FLAG-fusion construct) for 72hr. Left: Immunofluorescence staining with anti-FLAG monoclonal antibody (green), nuclei were counterstained with DAPI (blue). Right: Western blot analysis of cellular fractionation to isolate cytoplasm and nucleus. Mock, WT MECP2, and two biological replicates of MECP2 (R168W) transfected 293T cells probed for FLAG-tagged MECP2 protein.

Restored MECP2 binds to coregulatory proteins and recruits HDAC3, further suggesting functional restoration







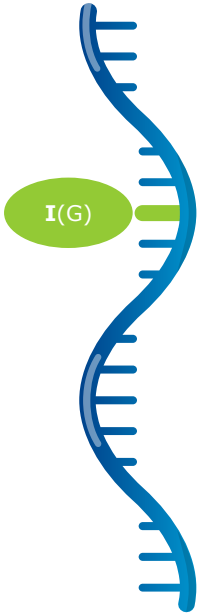
NCoR1 - Transcriptional coregulatory proteins that facilitates the recruitment of HDAC3 to DNA promoter regions
TBLR1 - Scaffold protein facilitating assembly of multi-protein complexes
HDAC3 – Histone deacetylase that removes acetyl group from histones, allowing histones to wrap DNA more tightly and suppress target gene expression

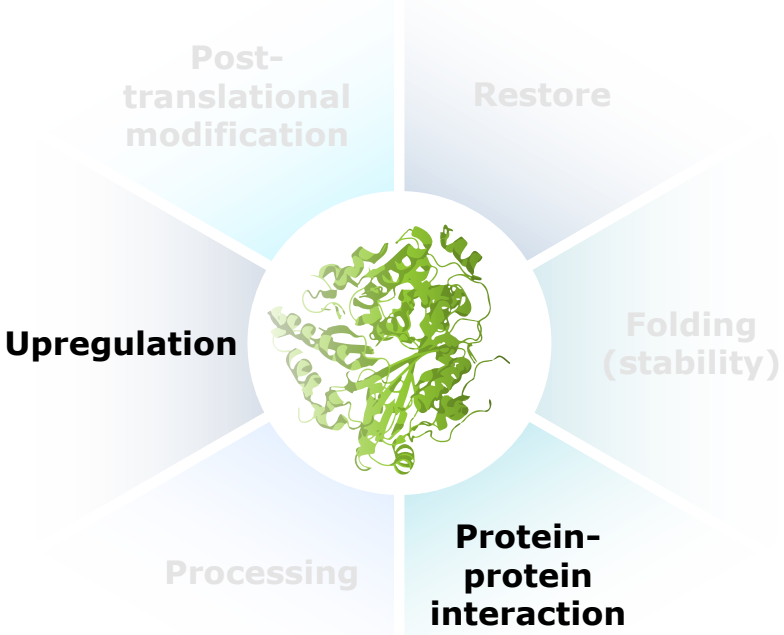
293T cells transfected with plasmids containing either wildtype or R168W MECP2 (FLAG-fusion construct). Transfected for 72h prior to nuclear extraction and immunoprecipitation with anti-FLAG tagged magnetic beads. Right: Western blot analysis of immunoprecipitation eluates probed for FLAG-tagged MECP2 protein and NCoR1/SMRT complex.

ADAR editing to modulate protein-protein interactions: upregulating gene expression

ADAR editing of mRNA

Downstream protein interactions

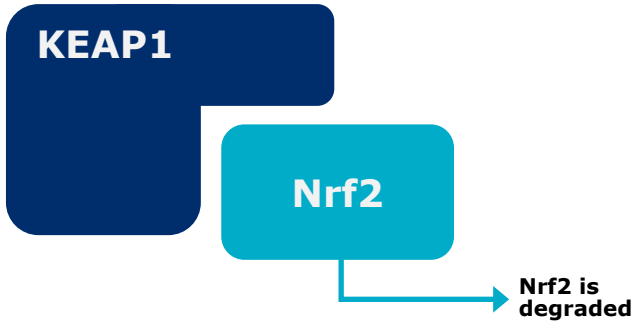




WAVE LIFE SCIENCES

ADAR to modify protein-protein interactions

Basal conditions



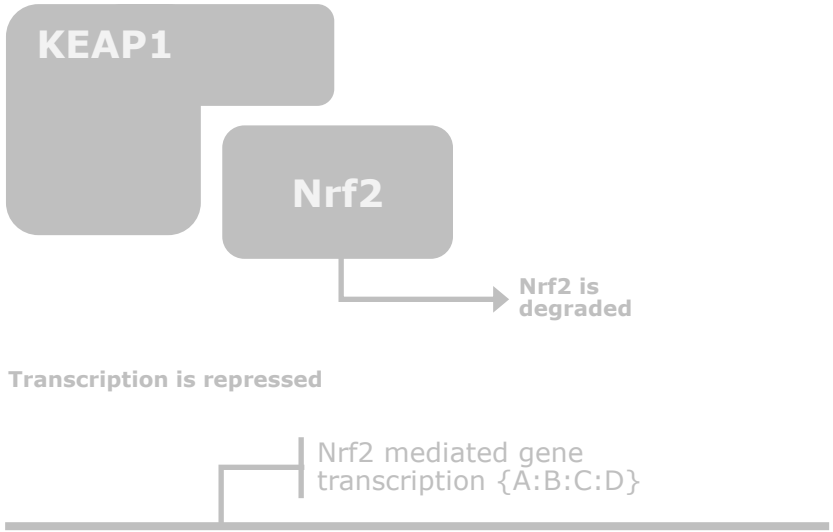
Transcription is repressed

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

WAVE LIFE SCIENCES

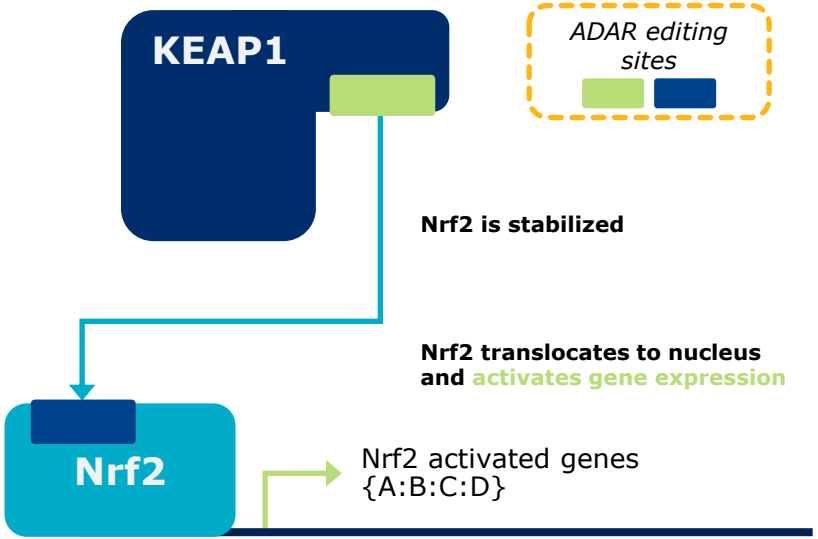
ADAR to modify protein-protein interactions

Basal conditions



KEAP1 binds Nrf2, destabilizing Nrf2 and repressing Nrf2 mediated gene transcription

ADAR modified pathway



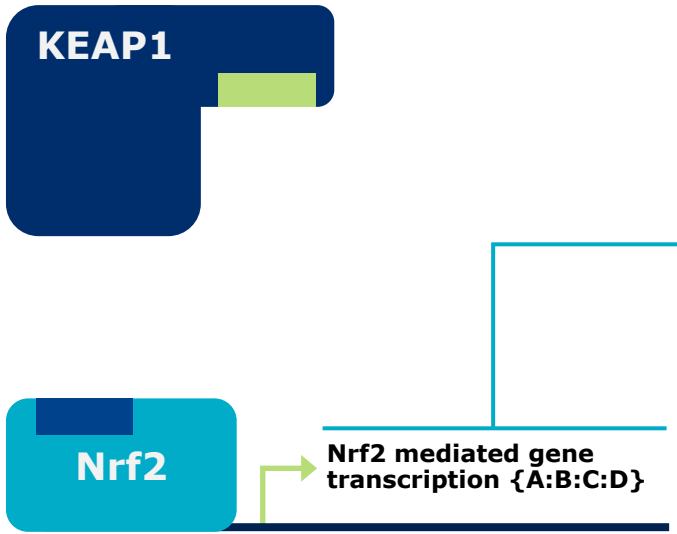
ADAR editing to change one amino acid in KEAP1 or Nrf2 could allow for stabilization of Nrf2 and activation of Nrf2 mediated gene transcription

WAVE LIFE SCIENCES

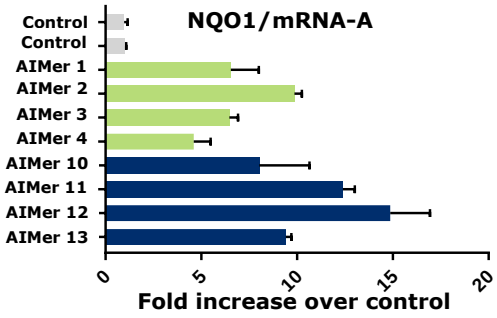
ADAR editing alters multiple amino acids on two different proteins *in vitro*

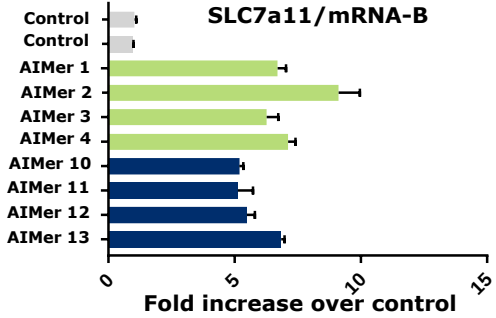
293T cells transfected with 20nM of AIMer, ADAR-p110 or ADAR-p150 plasmid. RNA collected 48h, editing quantified by PCR and Sanger (n=2).

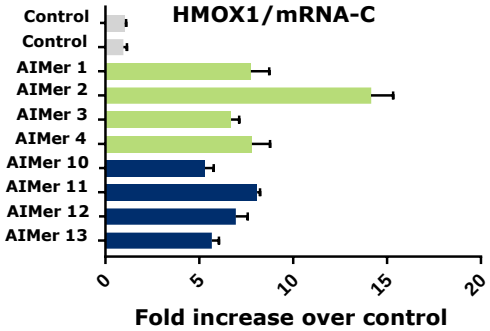
ADAR editing activates multiple genes confirming disrupted protein-protein interaction *in vitro*

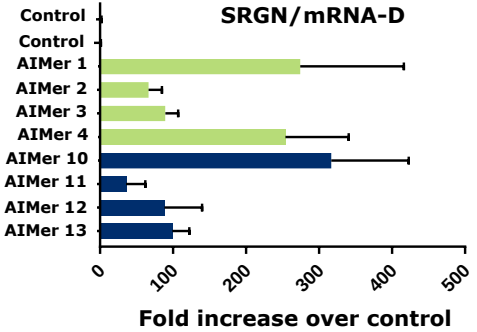


ADAR editing of either KEAP1 or Nrf2 directs gene activation









Gene expression quantified by PCR (n=2)

ADAR editing expands target universe in CNS

- PN chemistry expands addressable CNS disease target space, enabling protein restoration and protein modulation by leveraging shared learnings across ADAR programs
  - Editing of UGP2 *in vivo* in CNS tissues is durable out to 4 months
  - Discovery-stage MECP2 program for Rett Syndrome demonstrates restoration of functional MECP2 protein with ADAR editing *in vitro* to correct nonsense mutation
  - Disrupting protein–protein interactions enables access to new mechanisms

WAVE™ LIFE SCIENCES

Restoring Functional AAT Protein with ADAR Editing: Program Update

Paloma Giangrande, PhD

VP, Platform Discovery Sciences

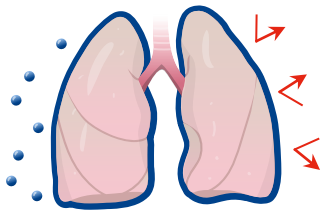
WAVE™ LIFE SCIENCES

Leading RNA editing program provides optimal approach for treatment of AATD

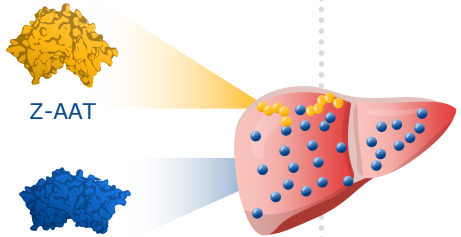
1) Restore circulating, functional wild-type M-AAT

2) Reduce Z-AAT protein aggregation in liver

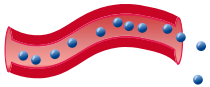
3) Retain M-AAT physiological regulation



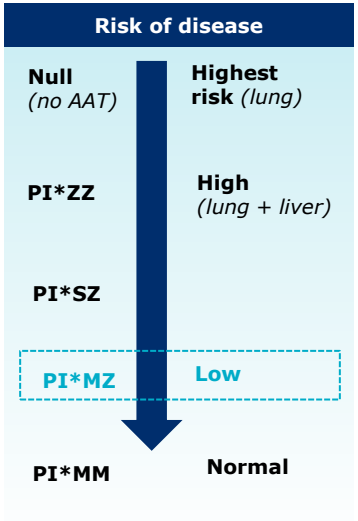
M-AAT reaches lungs to protect from proteases



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

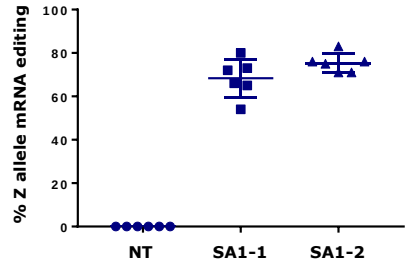
Today’s update on AATD program

WAVE™ LIFE SCIENCES

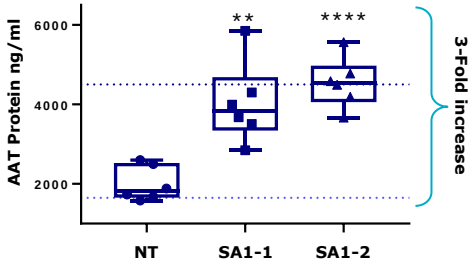
Focused on restoring wild-type M-AAT *in vivo*

In vitro proof of concept

SERPINA1 Z allele mRNA editing



AAT protein concentration in media



In vivo proof of concept

SERPINA1 mouse

Genotype
✓ huSERPINA1-Pi*Z
Human Z-AAT protein expressed in liver

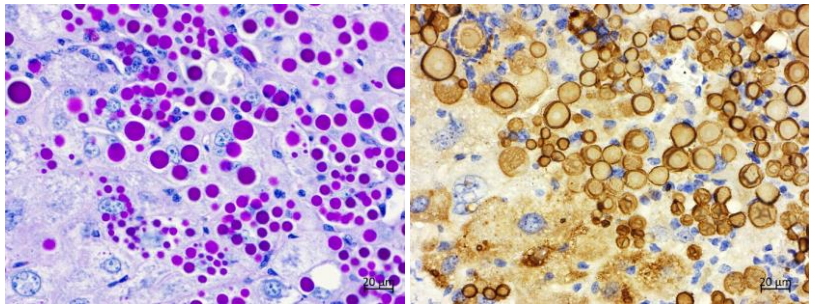
huADAR mouse

Genotype
✓ huADAR
Human ADAR expressed in all tissues

SERPINA1-Pi*Z/huADAR

Genotype	Pathology
✓ huADAR	Liver pathology, Z-AAT protein in serum and liver
✓ huSERPINA1-Pi*Z	

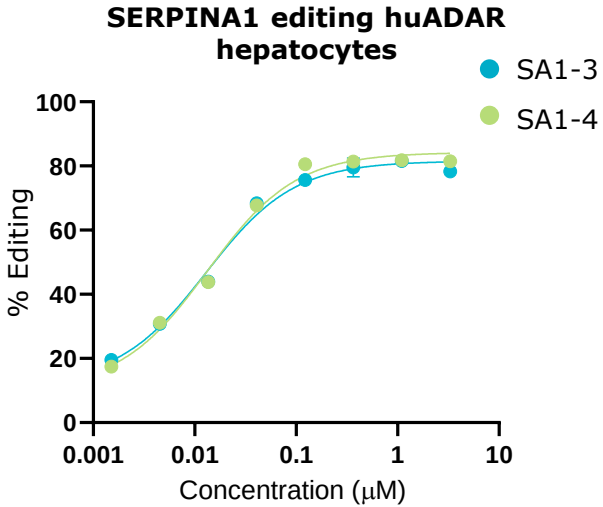
Liver AAT aggregation observed in AATD is recapitulated in mouse model

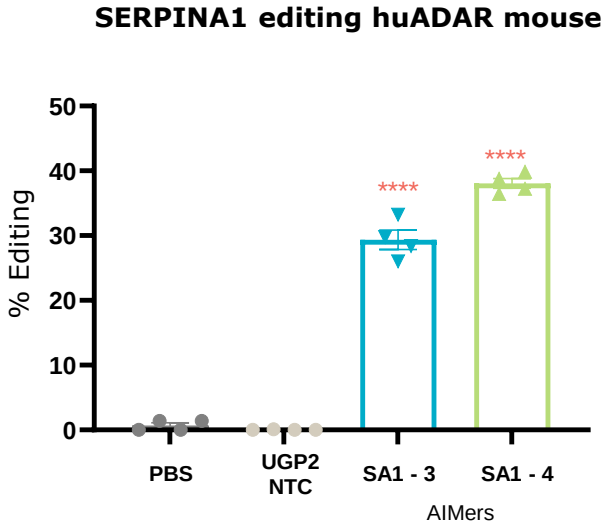


AATD: Alpha-1 antitrypsin deficiency, Z-AAT: mutated protein, M-AAT: wild-type human AAT protein
(Left) Hematoxylin and PAS stain and (Right) immunohistochemistry for AAT protein with hematoxylin counterstain in the huADAR/AATD mouse liver

Achieving 40% editing of Z allele mRNA at single time point

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





- GalNAc-conjugated compounds
- Up to 40% editing of Z allele mRNA in liver of transgenic human ADAR mice at day 7

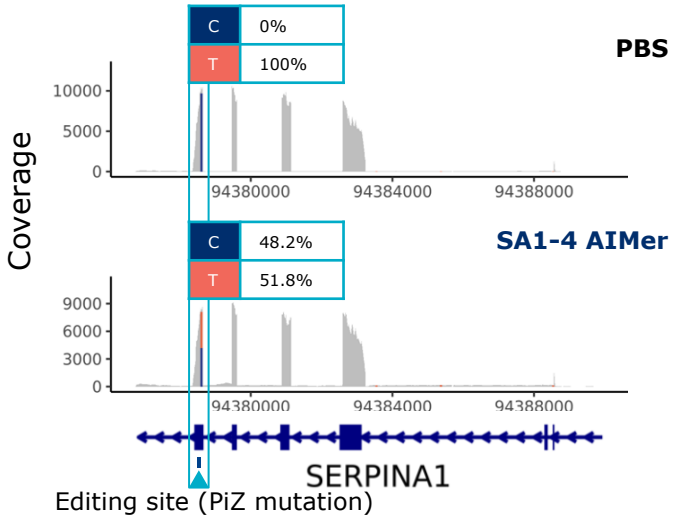
Z allele mRNA editing *in vivo* | **AAT protein increase** | **Wild-type M-AAT functional**

WAVE LIFE SCIENCES

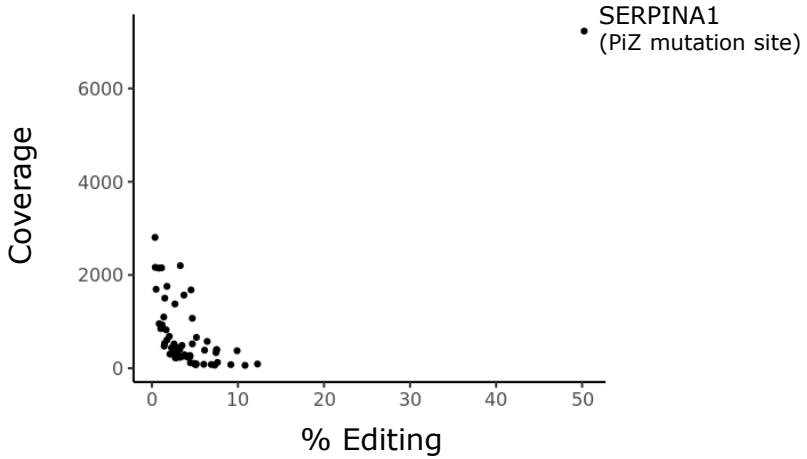
hu*ADAR/SERPINA1* mice administered PBS or 3 x 10 mg/kg AIMer (days 0, 2, and 4) SC. Samples collected day 7. Stats: One-way ANOVA; NTC: non-targeting control

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)



Highly specific Z allele mRNA editing *in vivo*

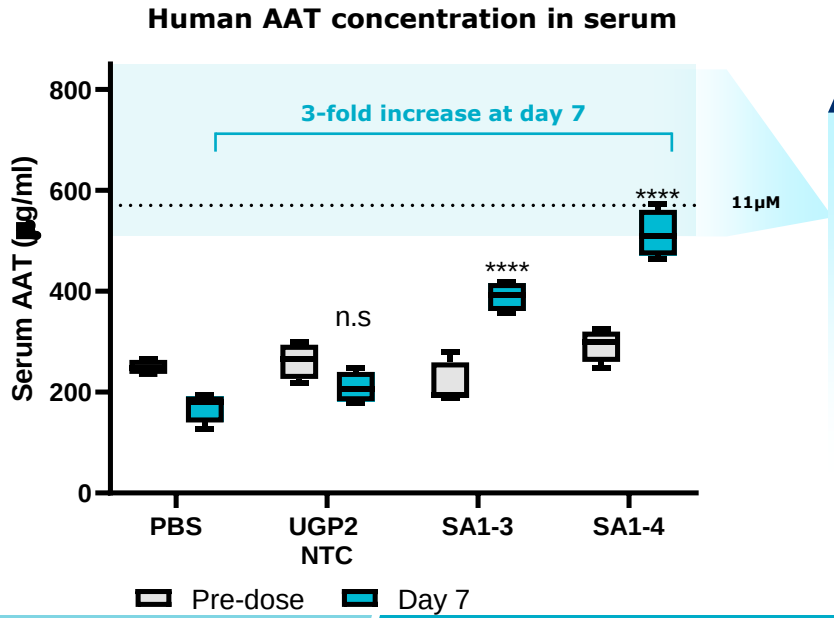
AAT protein increase

Wild-type M-AAT functional

Mice were at dosed at 3 x 10mg/kg on days 0, 2, and 4 SC. Liver biopsies were collected on day 7. RNAseq was conducted using strand-specific libraries. To quantify on-target SERPINA1 editing reads were mapped to human SERPINA1 and to quantify off-target editing reads were mapped to entire mouse genome; plotted circles represent sites with LOD>3 (N=4)

Achieving therapeutically meaningful increases in circulating human AAT protein

3-fold increase in circulating human AAT as compared to PBS at initial timepoint



AAT serum levels by genotype

PI*MZ	~3 to 5-fold increase
PI*SZ	~2-fold increase
PI*ZZ	~3 – 7 uM

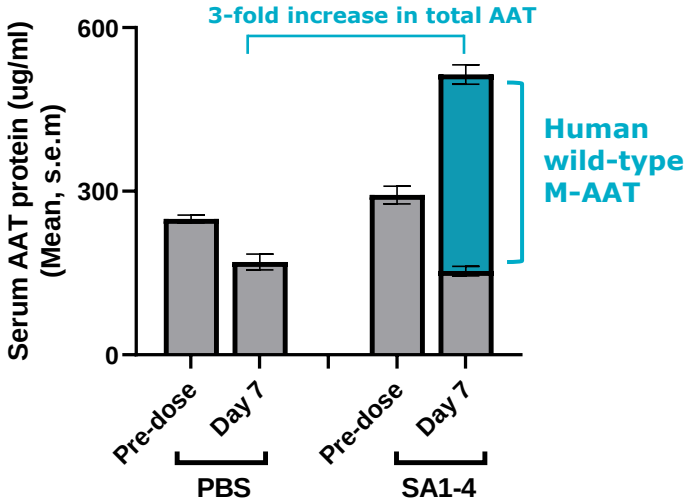
✓ Z allele mRNA editing *in vivo* | ✓ AAT protein increase | Wild-type M-AAT functional

WAVE LIFE SCIENCES

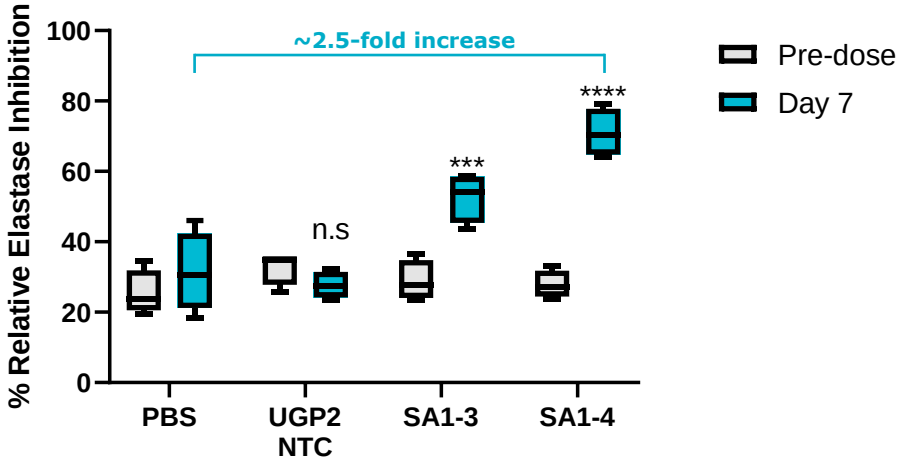
Statistics (ELISA): Matched 2-way ANOVA with correction for multiple comparisons (Bonferroni) was used to test for differences in AAT abundance in treated samples compared to PBS Statistics; de Serres et al., J Intern Med. 2014; NTC: non-targeting control

ADAR editing 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*

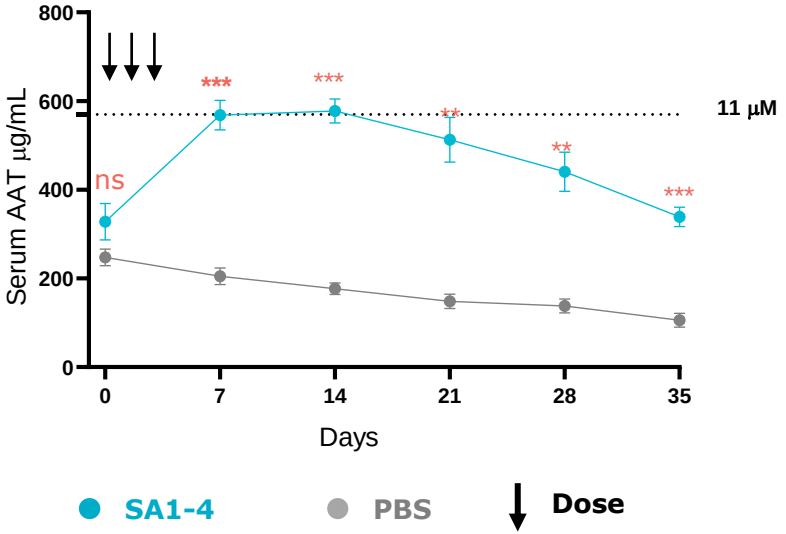
✓ AAT protein increase

✓ Wild-type M-AAT functional

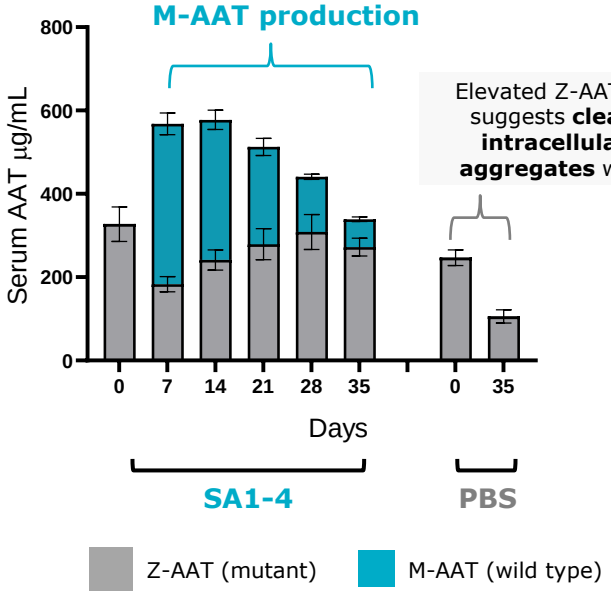
Left: Mass spectrometry and ELISA Right: (Elastase inhibition): Matched 2-way ANOVA with correction for multiple comparisons (Bonferroni) was used to test for differences in elastase inhibition activity in serum collected at day 7 vs pre-dose for each treatment group; NTC: non-targeting control

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



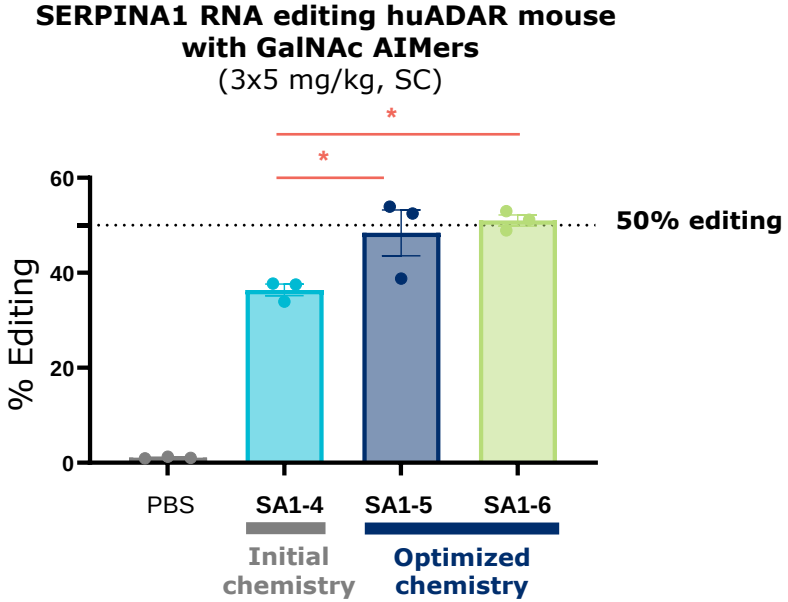
Elevated Z-AAT at Day 35 suggests **clearance of intracellular Z-AAT aggregates** with AIMers

WAVE LIFE SCIENCES

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

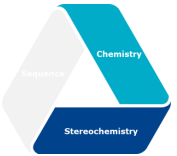
Optimization further improves potency

50% mean editing observed with half dose in mice at Day 7



Chemistry optimization:

- ✓ Increases Z allele mRNA editing efficiency



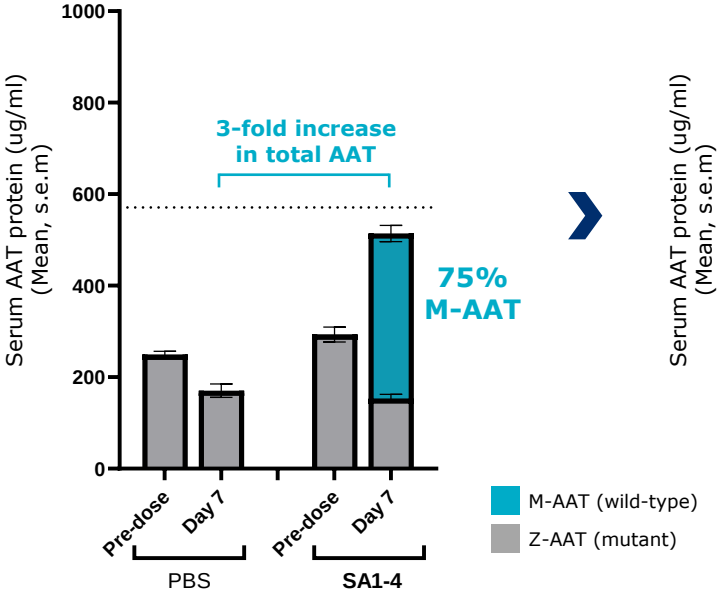
AIMers administered hu*ADAR/SERPINA1* mice (3x5 mg/kg) on days 0, 2, and 4. Livers collected on day 7, and SERPINA1 editing was quantified by Sanger sequencing (shown as mean ±. sem) Stats: One-way ANOVA was used to test for differences in editing between SA1-4 and other oligos * P<0.05

Optimization further improves M-AAT restoration

4-fold increase in AAT protein (>15uM) relative to PBS at Day 7 with optimized AIMer

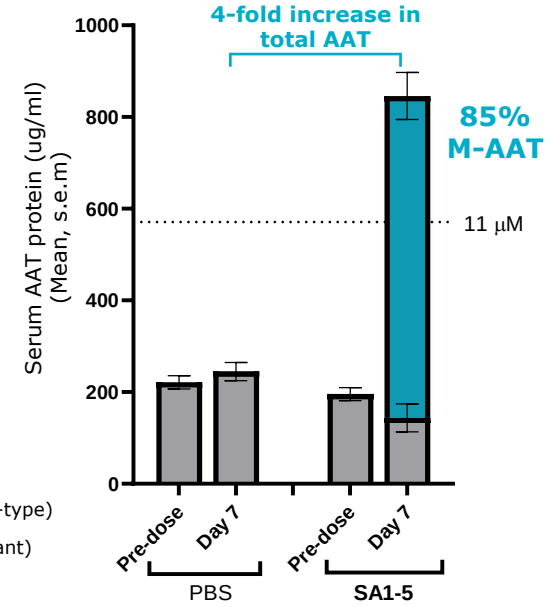
Initial chemistry

AAT concentration in serum



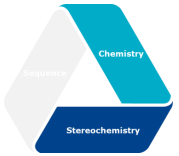
Optimized chemistry

AAT concentration in serum



Chemistry optimization:

- ✓ Increases Z allele mRNA editing efficiency
- ✓ Higher fold-increase in circulating AAT protein relative to control
- ✓ Greater percentage of restored wild-type M-AAT protein relative to total AAT



WAVE LIFE SCIENCES

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, Z type or M type, measured by mass spectrometry, total AAT protein levels quantified by ELISA.

AATD development candidate expected in 2022

Demonstrate restoration of functional M-AAT

- ✓ GalNAc-conjugated AIMers restore therapeutically meaningful levels of functional, wild-type M-AAT

Assess specificity and duration of effect

- ✓ ADAR editing is highly specific
- ✓ Restored, circulating wild-type M-AAT in serum at 1-month post-last dose

Chemistry optimization to improve potency

- ✓ Chemistry optimization of AIMers further increases potency
- ✓ Optimized AIMers restore AAT in serum by 4-fold (>15uM) at Day 7
- ✓ Restored wild-type M-AAT at 85% of total AAT

Path to development candidate

- Ongoing and planned preclinical studies assessing durability, dose response and PK/PD
- Assessment of reduction in Z-AAT aggregates and changes in liver pathology

WAVE™ LIFE SCIENCES

Closing Remarks

Paul Bolno, MD, MBA

President and CEO

WAVE™ LIFE SCIENCES

Q&A

Dr. Paul Bolno
President and
Chief Executive Officer

Dr. Chandra Vargeese
Chief Technology Officer

Dr. Ken Rhodes
SVP, Therapeutics Discovery

Dr. Paloma Giangrande
VP, Platform Discovery
Sciences, Biology

WAVE™
LIFE SCIENCES

WAVE™
LIFE SCIENCES

Realizing a brighter future for people affected by genetic diseases

For more information:
Kate Rausch, Investor Relations
krausch@wavelifesci.com
617.949.4827