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Unlocking Therapeutic RNA Editing

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3rd RNA Editing Summit: April 5-7, 2022

Forward-looking statements

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

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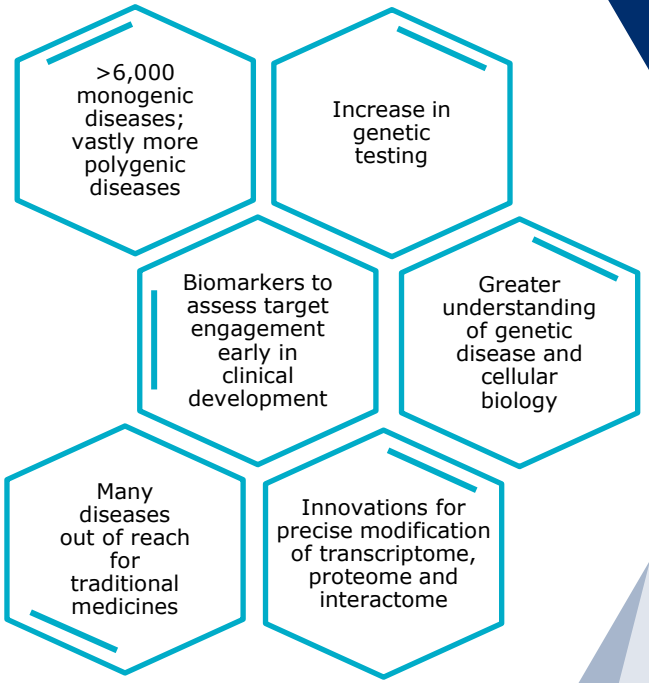
Building a leading genetic medicines company

LEVERAGING THE ONGOING GENETIC REVOLUTION



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

PRISM

Innovative Platform

Stereopure oligonucleotides

Novel backbone modifications (PN chemistry)

Silencing, splicing, and editing modalities

Strong and broad IP position[1]

Diversified Pipeline

CNS: ALS, FTD, HD

Muscle: DMD

Hepatic diseases: AATD

Clinical Expertise

Multiple global clinical trials

Innovative trial designs

GMP Manufacturing

Internal manufacturing capable of producing oligonucleotides at scale

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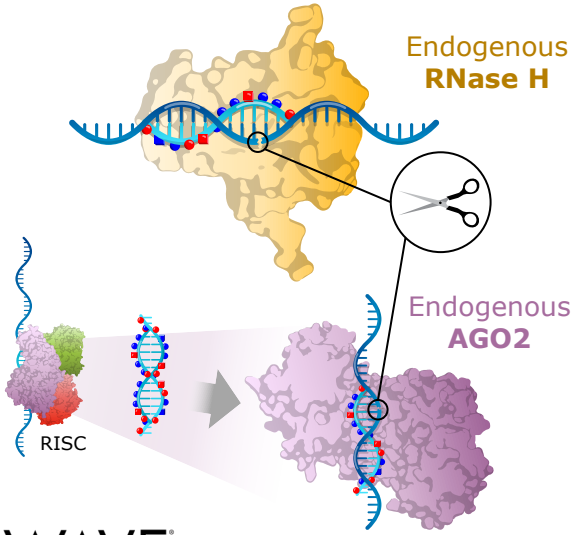
ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; HD: Huntington's disease; DMD: Duchenne muscular dystrophy; AATD: Alpha-1 antitrypsin deficiency

[1]stereopure oligonucleotides and novel backbone chemistry modifications

Harnessing the biological machinery in our cells to treat genetic diseases

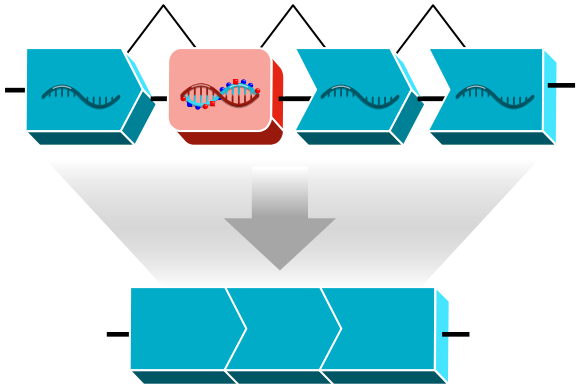
Silencing

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



Splicing

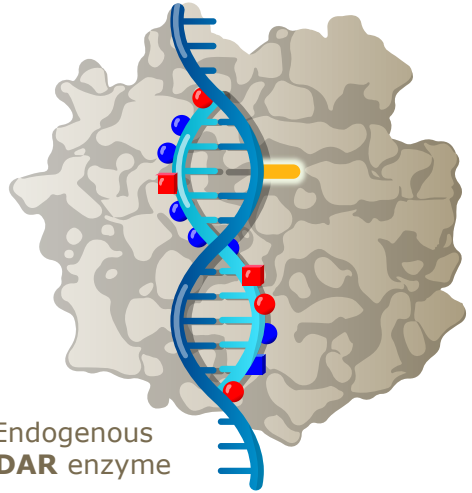
- Restore RNA transcripts and **turn on** protein production



Restored **Reading Frame**

RNA Base Editing

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



Endogenous **ADAR** enzyme

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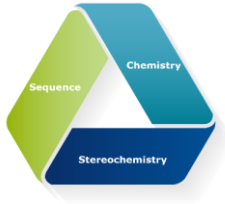
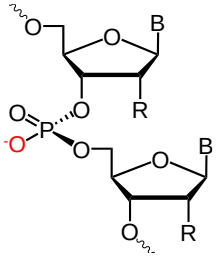
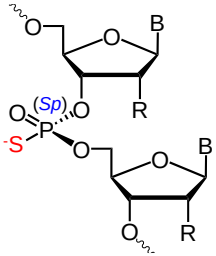
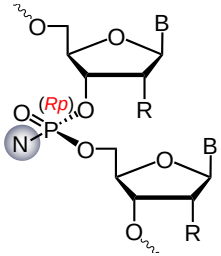
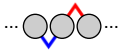
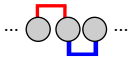
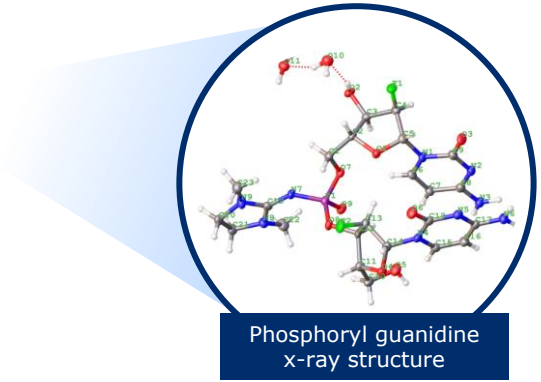
Innovating backbone chemistry modifications: PN chemistry



PRISM backbone linkages

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



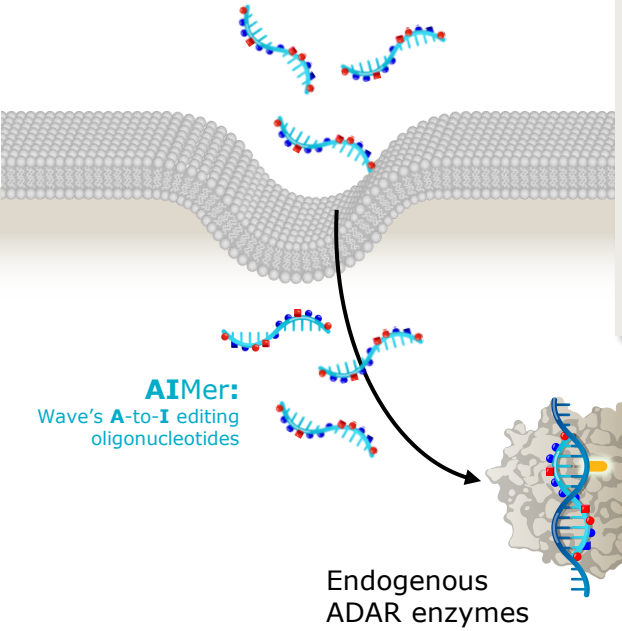
Phosphoryl guanidine x-ray structure

example

PO: phosphodiester PS: phosphorothioate PN: phosphoryl-guanidine

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

Free-uptake of chemically modified oligonucleotides
(No need for LNPs or viral vectors)



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

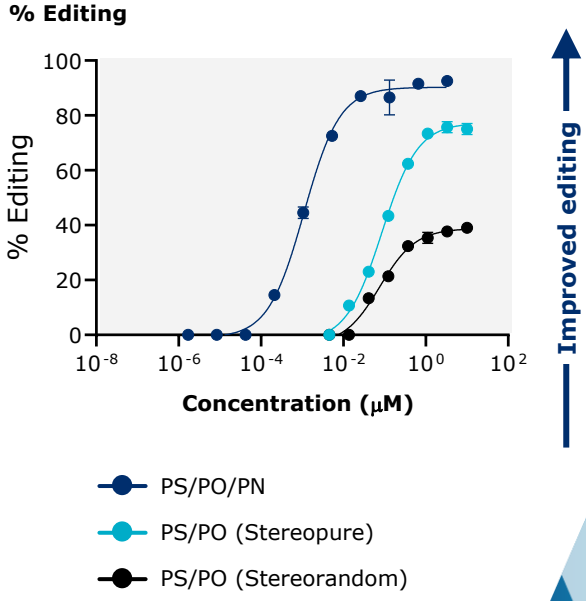
Endogenous ADAR enzymes

ADAR enzymes

- First publication (1995) using oligonucleotide to edit RNA with endogenous ADAR[1]
- Catalyze conversion of A-to-I (G) in double-stranded RNA substrates
- A-to-I (G) edits are one of the most common post-transcriptional modifications
- ADAR1 is ubiquitously expressed across tissues, including liver and CNS

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

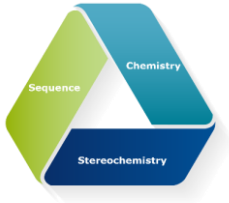
Editing



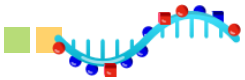
[1]Woolf et al., PNAS Vol. 92, pp. 8298-8302, 1995

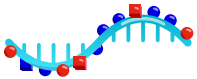
AIMers: Realizing potential of therapeutic RNA editing by harnessing endogenous ADAR

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



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





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

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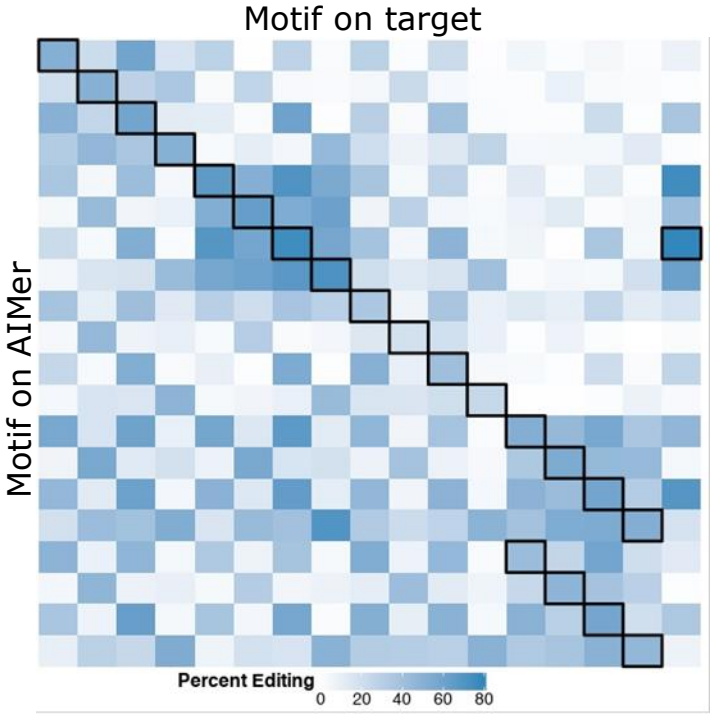
Optimization of every dimension to inform future rational design of AIMers

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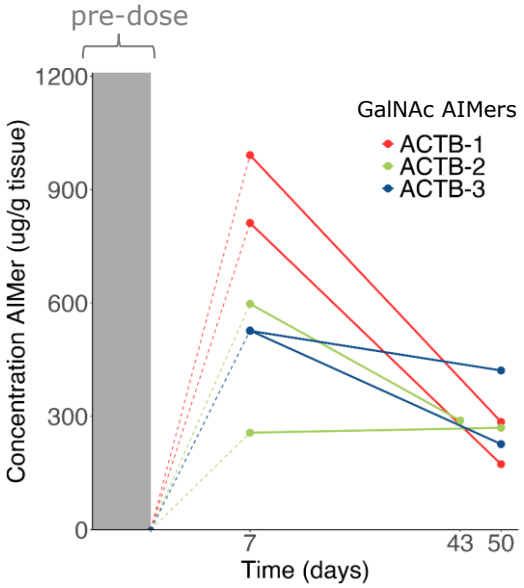
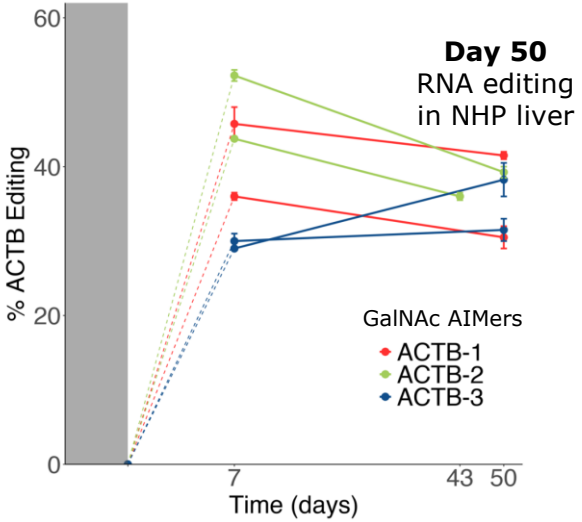
Stability of AIMers enables durable and specific editing out to Day 50 in liver of NHPs

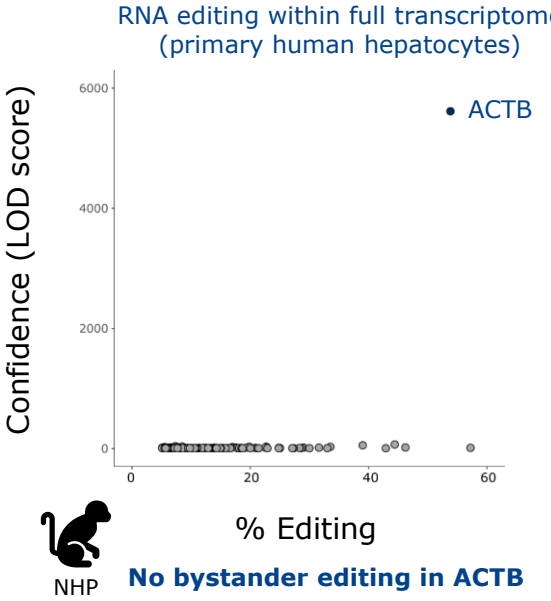
AIMers detected in liver of NHP at day 50



Substantial and durable editing in NHP liver *in vivo*

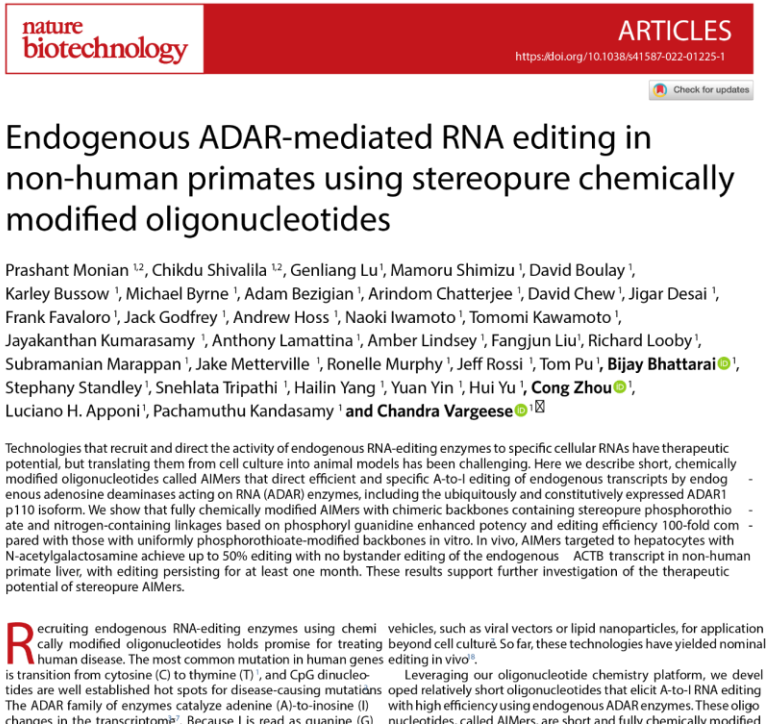


ADAR editing with ACTB AIMer is highly specific



AIMer tissue concentration (left) and editing activity (middle) in liver after 5 mg/kg SC injections on days 1-5; Right: Hepatocytes treated with 1 μM AIMer, 48 hrs later RNA collected, RNAseq conducted using strand-specific libraries to quantify editing; plotted circles represent sites with LOD>3. NHP: non-human primate; ACTB: Beta-actin; Monian et al., 2022 published online Mar 7, 2022; doi: 10.1038.s41587-022-01225-1

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



nature biotechnology

ARTICLES

https://doi.org/10.1038/s41587-022-01225-1

Check for updates

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

Prashant Monian [1,2], Chikdu Shivalila [1,2], Genliang Lu [1], Mamoru Shimizu [1], David Boulay [1], Karley Bussow [1], Michael Byrne [1], Adam Bezigian [1], Arindom Chatterjee [1], David Chew [1], Jigar Desai [1], Frank Favaloro [1], Jack Godfrey [1], Andrew Hoss [1], Naoki Iwamoto [1], Tomomi Kawamoto [1], Jayakanthan Kumarasamy [1], Anthony Lamattina [1], Amber Lindsey [1], Fangjun Liu [1], Richard Looby [1], Subramanian Marappan [1], Jake Metterville [1], Ronelle Murphy [1], Jeff Rossi [1], Tom Pu [1], **Bijay Bhattarai** [1], Stephany Standley [1], Snehlata Tripathi [1], Hailin Yang [1], Yuan Yin [1], Hui Yu [1], **Cong Zhou** [1], Luciano H. Apponi [1], Pachamuthu Kandasamy [1] **and Chandra Vargeese** [1]✉

Technologies that recruit and direct the activity of endogenous RNA-editing enzymes to specific cellular RNAs have therapeutic potential, but translating them from cell culture into animal models has been challenging. Here we describe short, chemically modified oligonucleotides called AIMers that direct efficient and specific A-to-I editing of endogenous transcripts by endogenous adenosine deaminases acting on RNA (ADAR) enzymes, including the ubiquitously and constitutively expressed ADAR1 p110 isoform. We show that fully chemically modified AIMers with chimeric backbones containing stereopure phosphorothioate and nitrogen-containing linkages based on phosphoryl guanidine enhanced potency and editing efficiency 100-fold compared with those with uniformly phosphorothioate-modified backbones in vitro. In vivo, AIMers targeted to hepatocytes with N-acetylgalactosamine achieve up to 50% editing with no bystander editing of the endogenous ACTB transcript in non-human primate liver, with editing persisting for at least one month. These results support further investigation of the therapeutic potential of stereopure AIMers.

Recruiting endogenous RNA-editing enzymes using chemically modified oligonucleotides holds promise for treating human disease. The most common mutation in human genes is transition from cytosine (C) to thymine (T) [1], and CpG dinucleotides are well established hot spots for disease-causing mutations [2]. The ADAR family of enzymes catalyze adenine (A)-to-inosine (I) changes in the transcriptome [3]. Because I is read as guanine (G) vehicles, such as viral vectors or lipid nanoparticles, for application beyond cell culture. So far, these technologies have yielded nominal editing in vivo [4–6].

Leveraging our oligonucleotide chemistry platform, we developed relatively short oligonucleotides that elicit A-to-I RNA editing with high efficiency using endogenous ADAR enzymes. These oligonucleotides, called AIMers, are short and fully chemically modified

- Specificity *in vitro* & *in vivo* (NHPs)
- *In vitro-in vivo* translation (NHPs)
- GalNAc conjugation
- Foundational AIMer SAR

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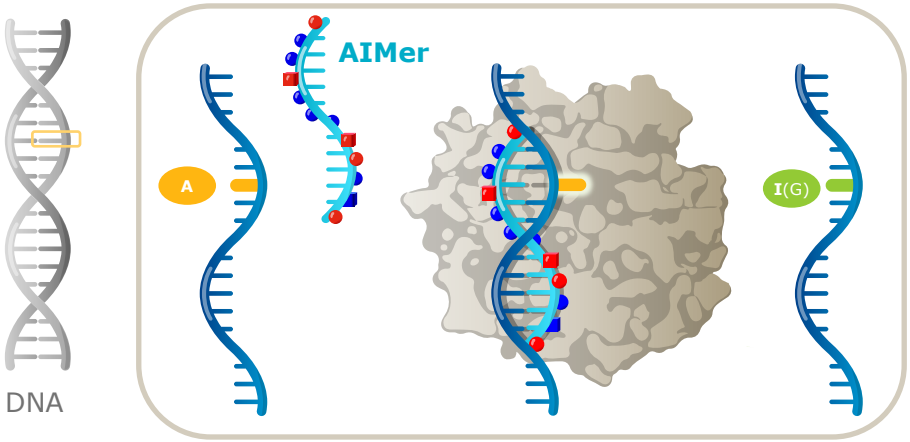
Monian et al., 2022 published online Mar 7, 2022; doi: 10.1038.s41587-022-01225-1
SAR structure-activity relationship

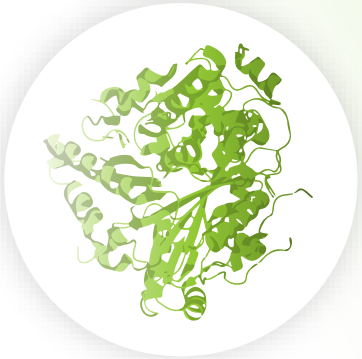
ADAR editing enables correction of single-point mutations to restore functional protein

Restore functional protein



Restore or correct expression

Example therapeutic areas



- AATD (*Lead AIMer program*)
- Rett syndrome

- Initial focus on correcting driver mutations of genetic hepatic diseases with clinically-proven GalNAc-mediated delivery
- 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]

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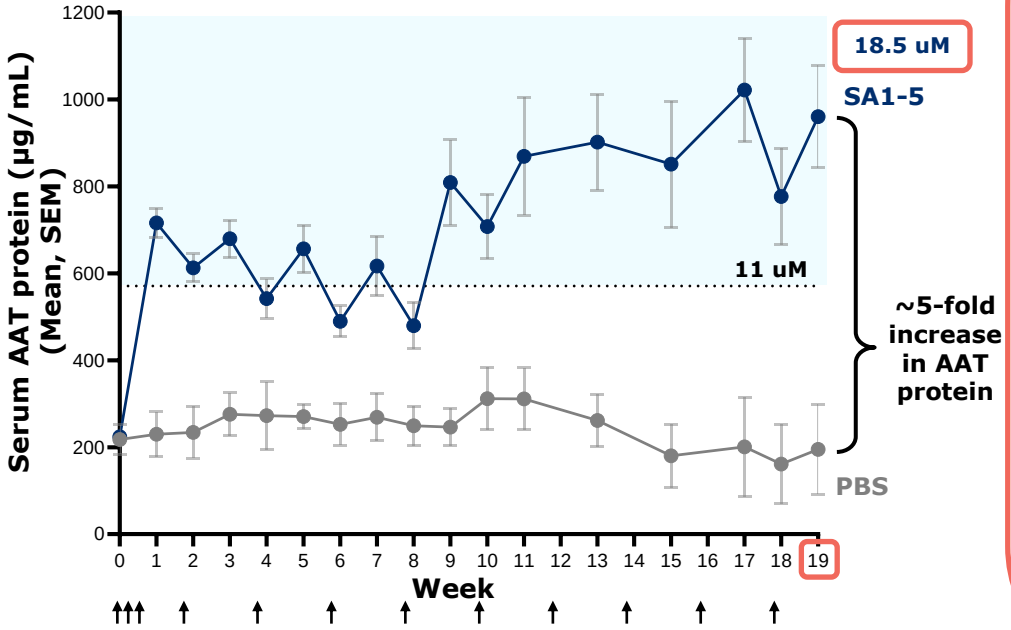
SNP: single nucleotide polymorphism A: Adenosine I: Inosine G: Guanosine
[1]ClinVar database [2]Keeling KM et al., Madame Curie Bioscience Database 2000-2013

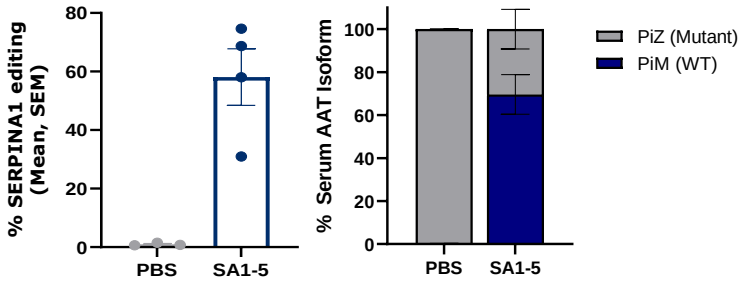
AATD: Analyses suggest functional effects in mouse liver at 19 weeks

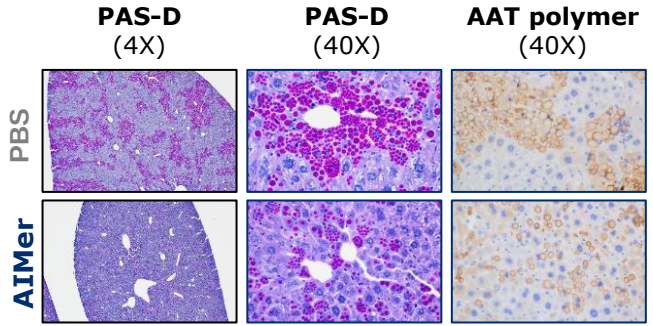
GalNAc-AIMer results in serum AAT protein levels >11 uM at week 19



10 mg/kg AIMer dose

~60% RNA editing & ~70% serum M-AAT protein (week 19 data)

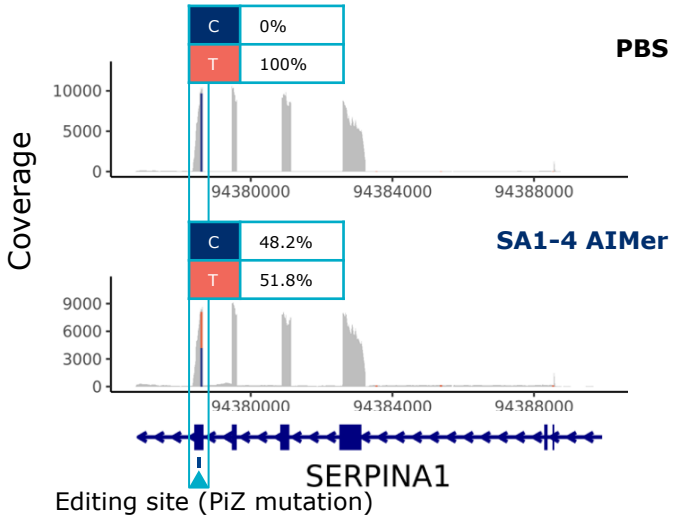




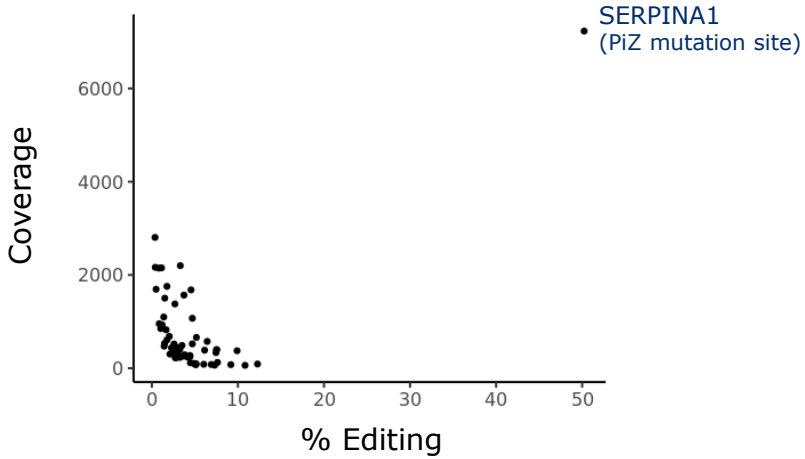
AIMer (SA1-5) administered in hu*ADAR/SERPINA1* mice (8–10 weeks old) Left: Total serum AAT protein quantified by ELISA. Right: Liver biopsies collected at week 19 (one week after last dose); SERPINA1 editing was quantified by Sanger sequencing; Proportion of AAT protein in serum measured by mass spec, total AAT protein quantified by ELISA; images from liver biopsies stained with PAS-D or AAT-polymer specific antibody

AIMer-directed editing is highly specific in mice

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



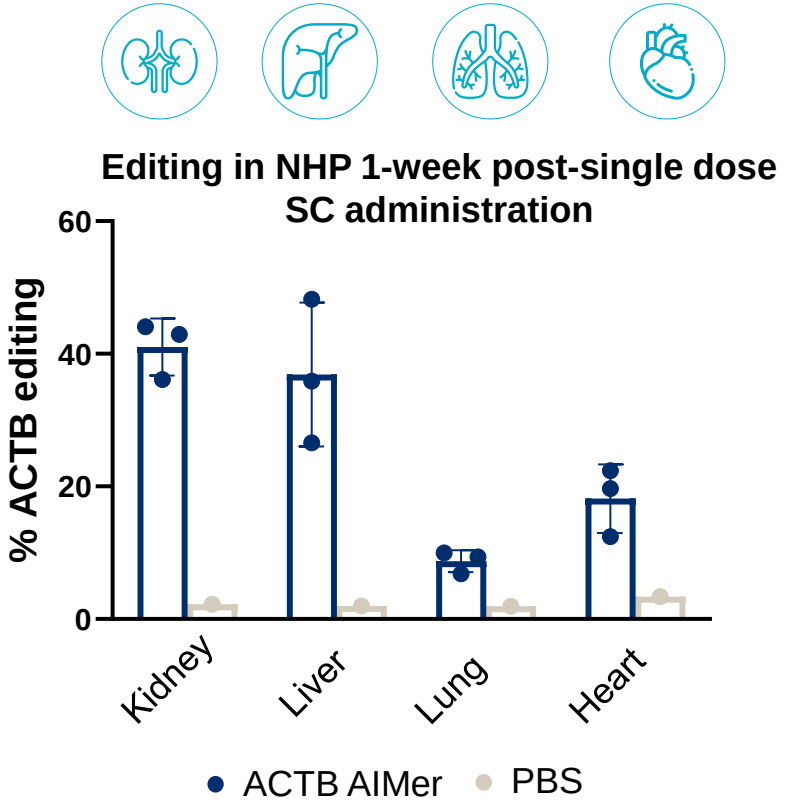
RNA editing across transcriptome
(mouse liver)



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

Removing GalNAc: Productive editing in multiple NHP tissues with unconjugated systemic AIMer delivery

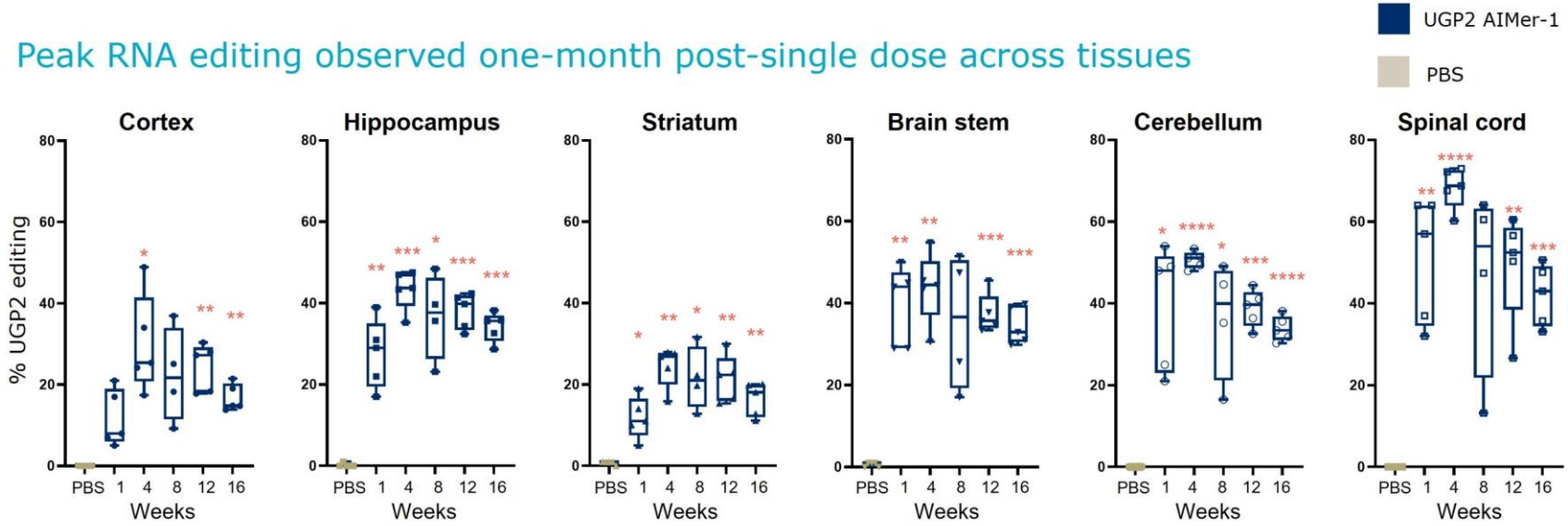
- NHP study demonstrated productive editing in kidney, liver, lung and heart with single subcutaneous dose



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

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

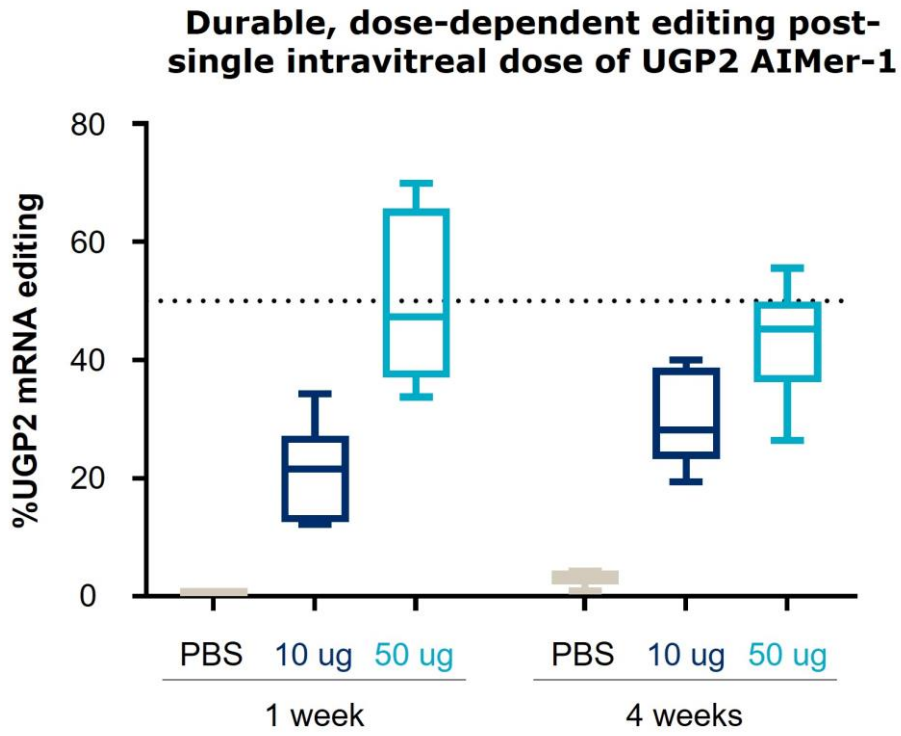
Peak RNA editing observed one-month post-single dose across tissues



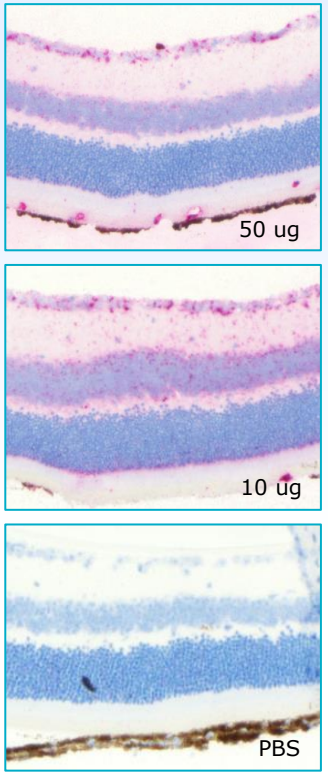
Peak editing	30%	>40%	25%	>40%	50%	>65%

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

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



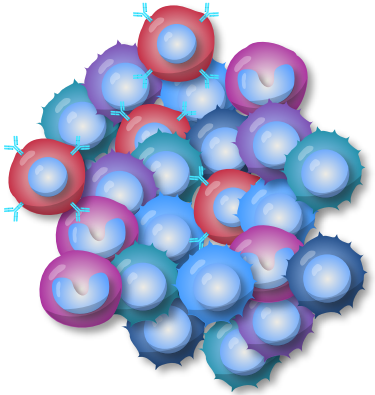
AIMers in retina at 4 weeks



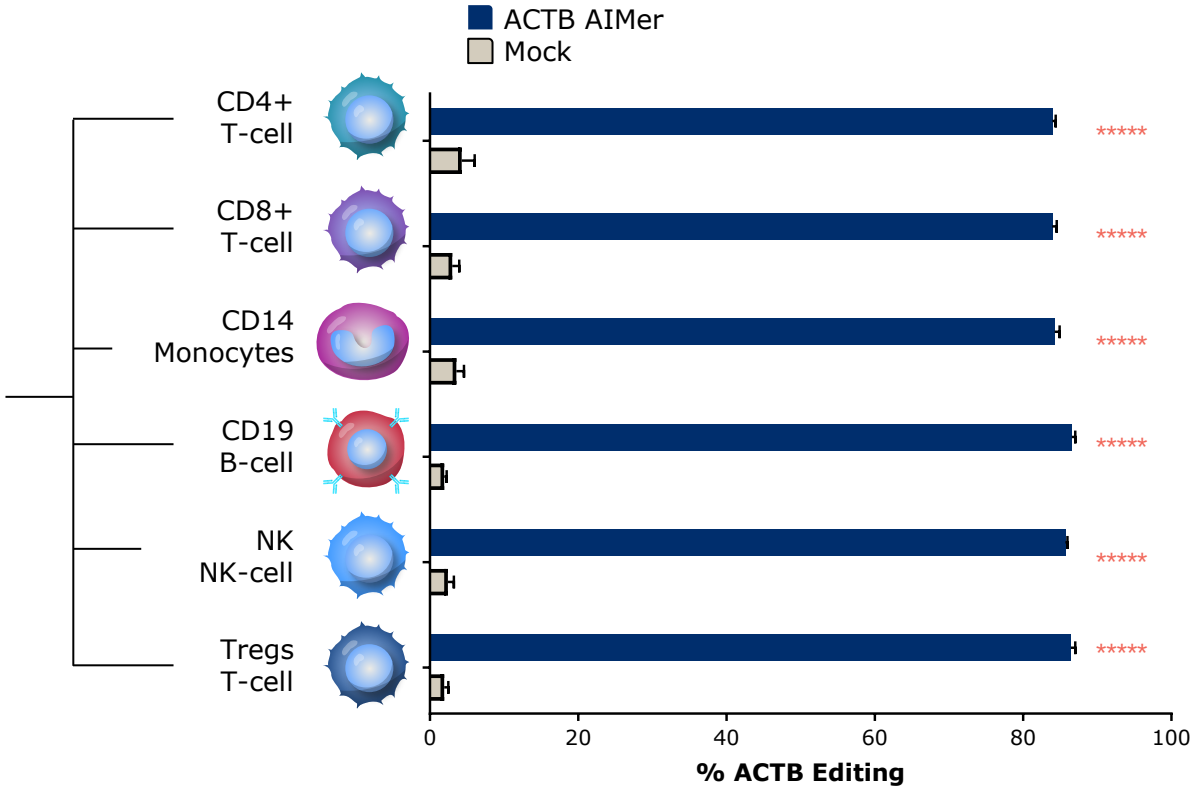
Mice received a single IVT injection (10 or 50 ug AIMer), and eyes were collected for RNA analysis and histology 1 or 4 weeks later. Left: editing evaluated by Sanger sequencing, and % RNA editing calculated with EditR. Right: FFPE and RNA scope assay specific for AIMer, red = oligo, blue = nuclei. Posterior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

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

Human peripheral blood mononuclear cell (PBMC)



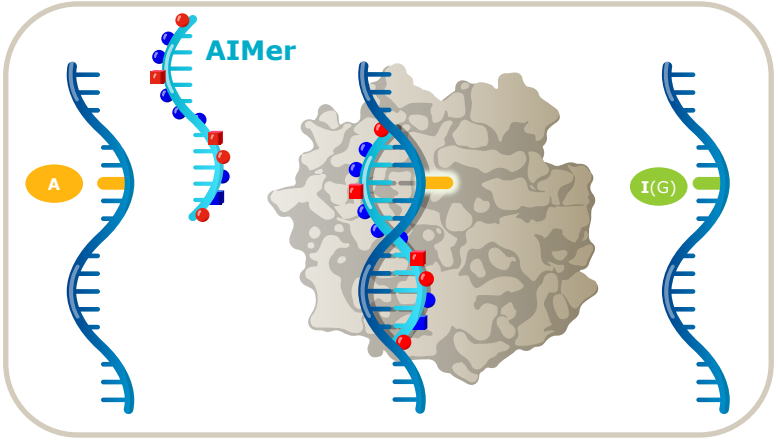
Activate (PHA) → Dose → Sort



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

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

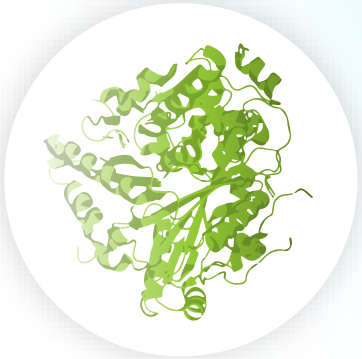
Modulate protein-protein interaction

Post-translational modification

Alter folding (stability)

Alter processing

Example therapeutic areas



- Cardiometabolic
- Oncology
- Immunology
- Neurological disorders

- Opens wide range of therapeutic applications with large patient populations

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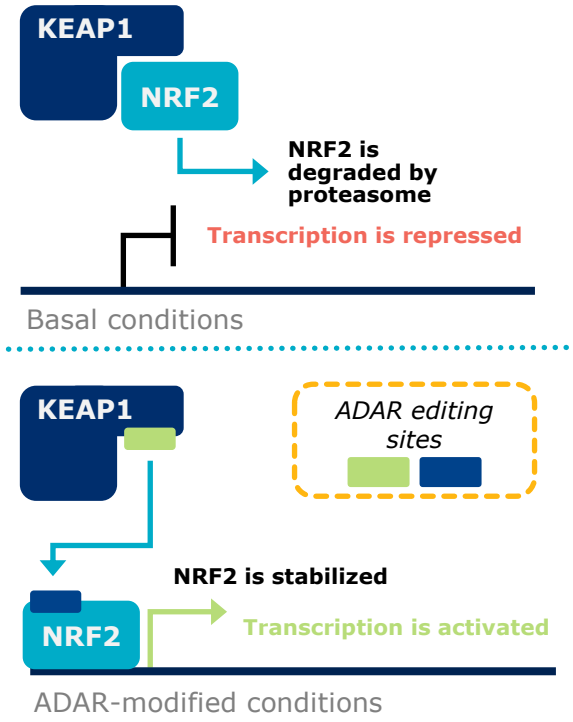
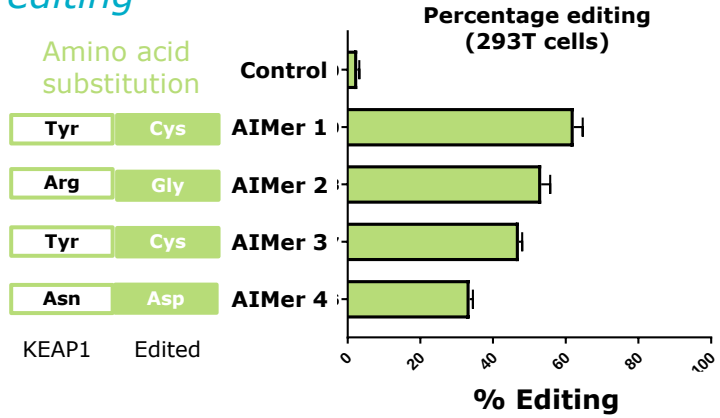
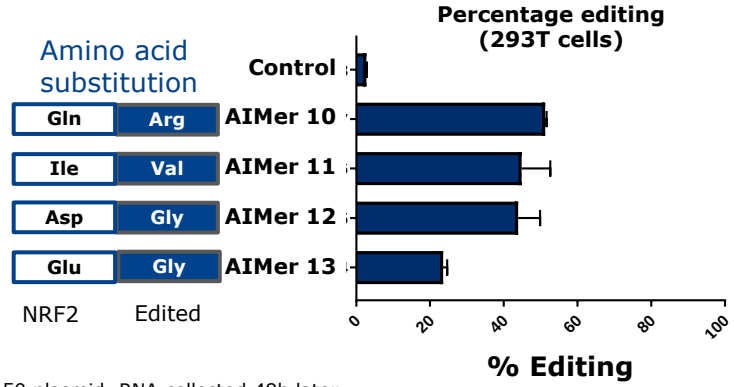
Apply AIMers to modify protein-protein interactions



KEAP1 editing

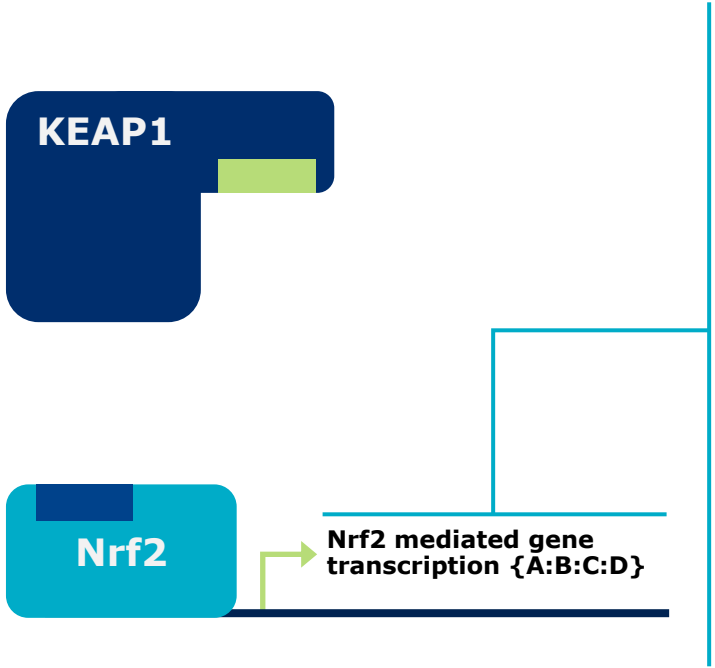


NRF2 editing

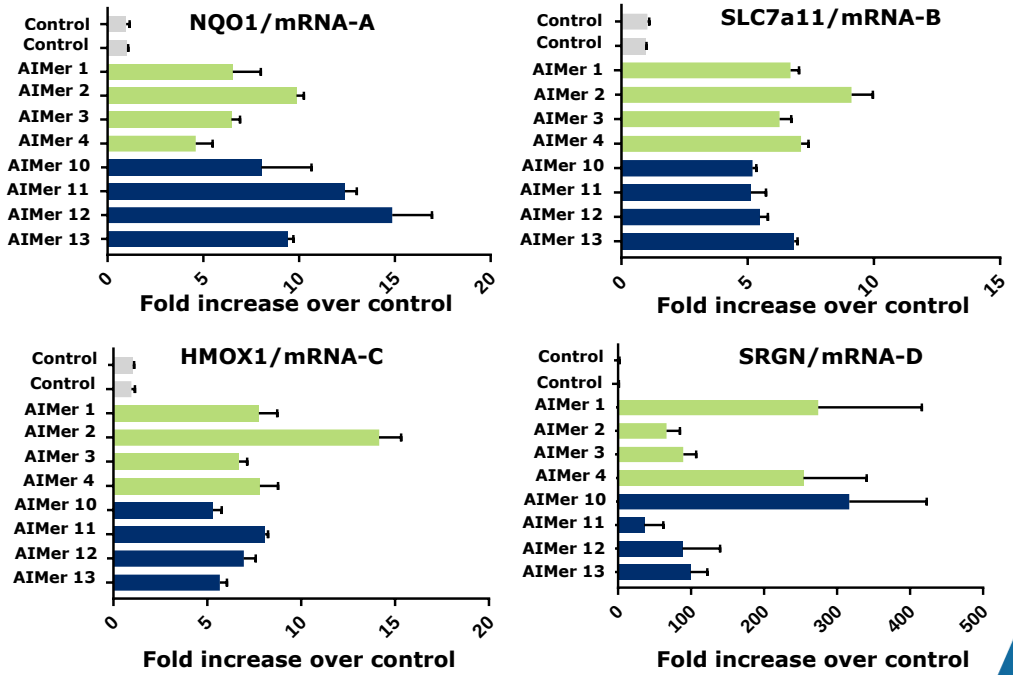


293T cells transfected with 20 nM of AIMer, ADAR-p110 or ADAR-p150 plasmid. RNA collected 48h later, editing quantified by PCR and Sanger (n=2).

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)

Summary

- Wave was built on premise of using short, stereopure oligonucleotides to engage endogenous biological machinery
- AIMers reflect 10+ years of optimization and learning through PRISM:
  - Leverages endogenous ADAR proteins
  - Uses proprietary chemistry: control of stereochemistry and PN chemistry
  - Incorporates deep understanding of SAR to guide design principles
  - Amenable to multiple routes of administration
- GalNAc-conjugated AIMers restore M-AAT protein above therapeutically relevant levels
- Unconjugated AIMers achieve potent, specific and durable editing across a multitude of targets and tissues
- AIMers also have potential to address non-monogenic diseases and larger populations

Q&A

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