Unlocking the Edit-Verse: Combining Machine Learning & Multiple AIMer Applications to Build a High-Impact RNA Editing Pipeline

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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.

Building a leading RNA medicines company

Multi-modal drug discovery and development platform

- Therapeutic candidates that optimally address disease **biology**
- **RNA editing, siRNA, splicing, antisense**
- Best-in-class oligonucleotide **chemistry**

Differentiated RNA medicines pipeline

- Clinical data updates expected in 2024 from **AATD**, **DMD**, **HD** clinical programs
- INHBE clinical trial initiation for **obesity** expected 1Q 2025
- Initiated first-ever clinical trial in **RNA editing** for AATD

Strategic collaborations (GSK and Takeda)

In-house GMP manufacturing

Strong and broad IP

Well capitalized with cash runway into 4Q 2025*

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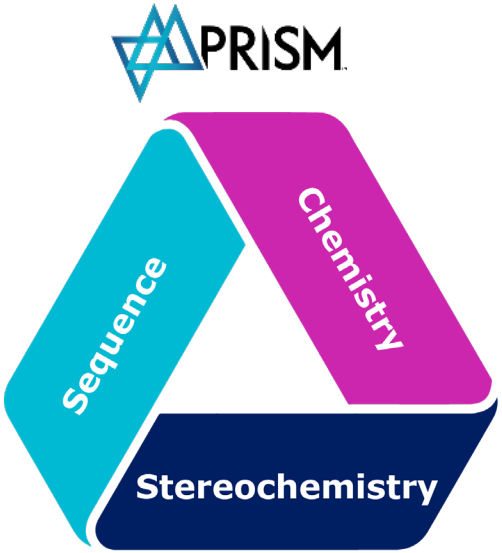
*Cash runway does not include potential future milestones or opt-in payments under GSK and Takeda collaborations
AATD: Alpha-1 antitrypsin deficiency, DMD: Duchenne muscular dystrophy, HD: Huntington's disease

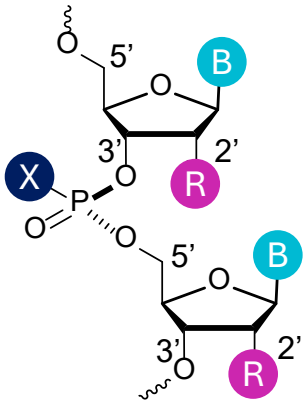
Wave has driven foundational advances in nucleic acid chemistry to expand platform technologies and develop next generation of RNA therapeutics

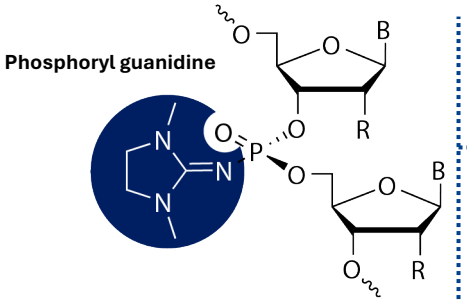
Further information can be found in recent platform publications

Silencing | **Splicing** | **Editing (AIMers)**

Wave's PRISM™ platform enables application of best-in-class chemistry across modalities, including RNA editing







B **Base**

R **2'-Ribose**

X **Stereochemistry and backbone modification**

O: Phosphodiester
S: Phosphorothioate
N: Phosphoryl guanidine

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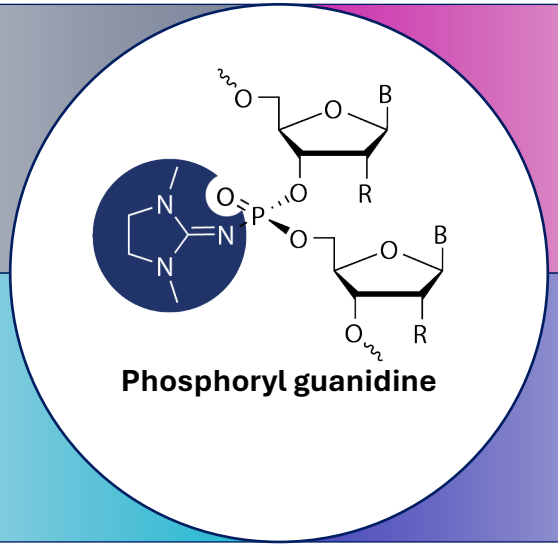
PN backbone chemistry was a significant advance in oligonucleotide chemistry; significantly improves potency, distribution and durability

Chemical impact

- Neutral backbone
- Reduced number of charges
- Hydrophobic
- Chiral center
- Chimeric backbone
- Combo with 2'-modifications

Pharmacological impact

- Nuclease resistance/stability
- Titrating plasma protein binding
- Increased cellular uptake



Phosphoryl guanidine

Biological impact

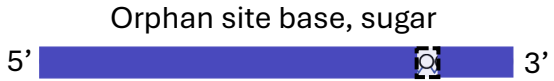
- Differential enzyme recognition
- Enhanced potency, durability and tissue exposure in mice compared with controls

Potential therapeutic impact

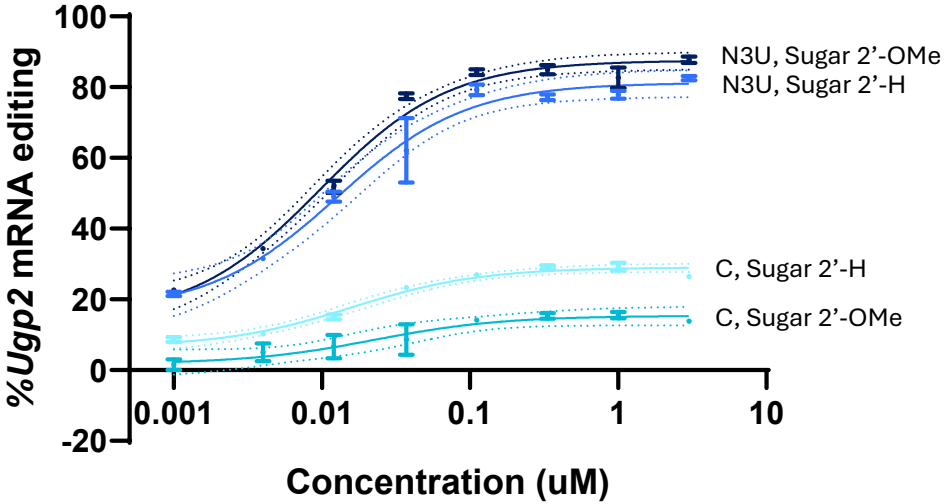
- Anticipated improvements across modalities based on preclinical studies

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

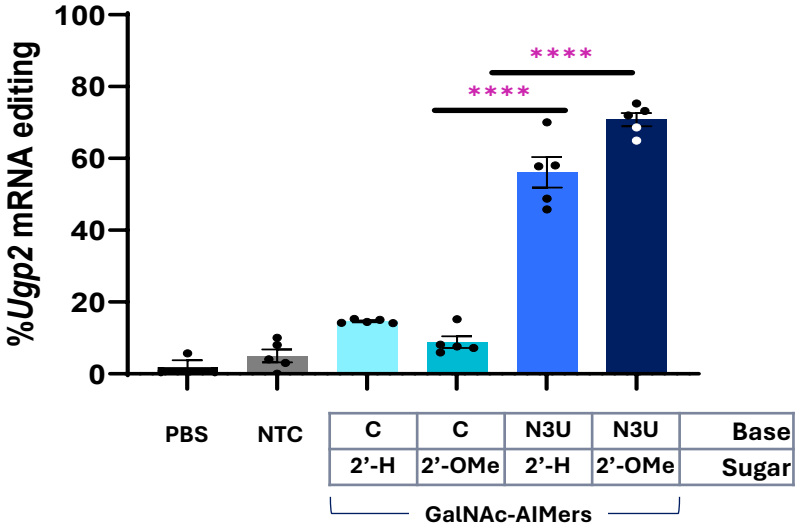
Proprietary and unique chemistry supports efficient editing *in vivo* with GalNAc-AIMers



RNA editing in primary mouse hepatocytes (GalNAc mediated delivery)

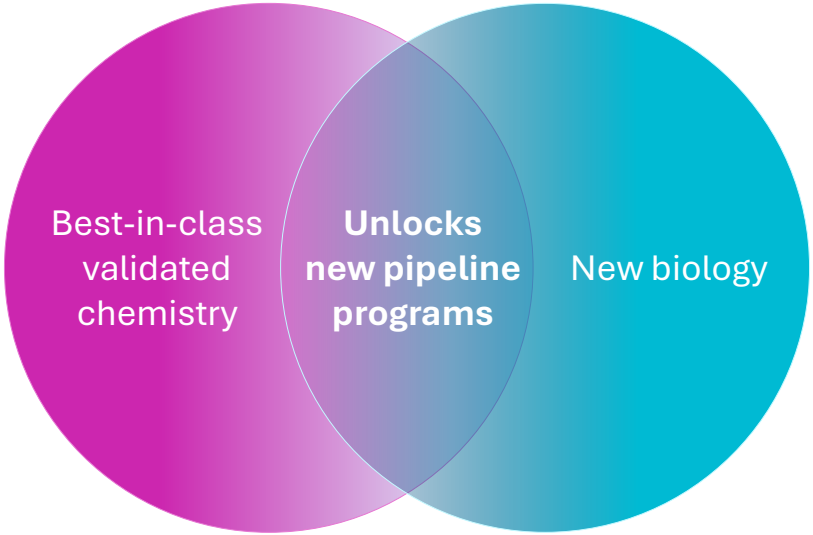


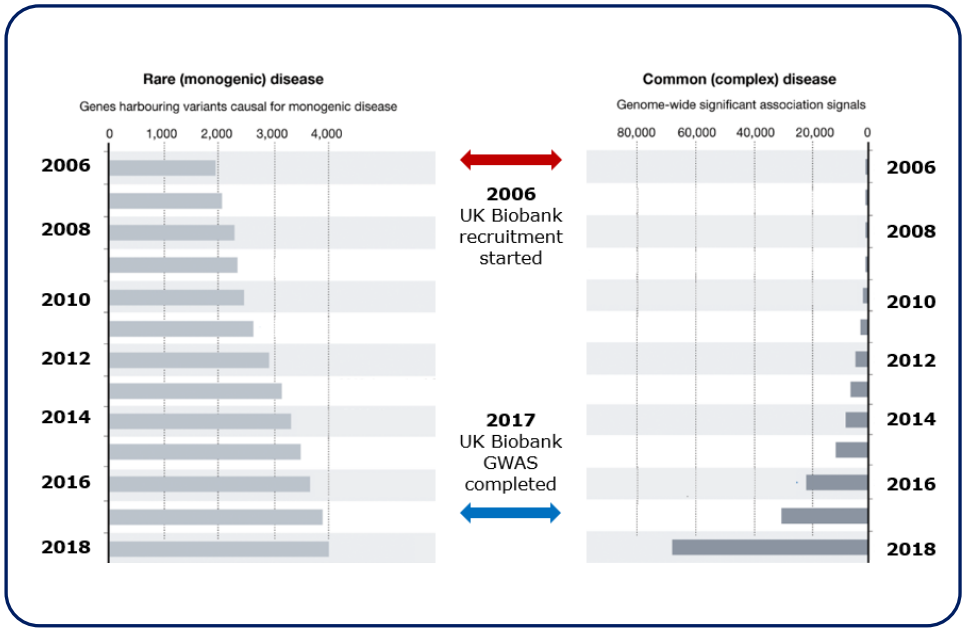
RNA editing *in vivo* liver (GalNAc mediated delivery)



Left: GalNAc-conjugated AIMers targeting *Ugp2* dosed in primary hepatocytes isolated from hADAR1-p110 hemizygous knock-in mice. Data: mean ± SEM. Dashed lines: 95% CI.
Right: 8-week-old transgenic hADAR-p110 knock-in mice dosed with PBS (black) or GalNAc-conjugated AIMer subcutaneously (day 0, 2, 4) and evaluated for UGP2 editing on day 7.
NTC: Non-targeting control, targeting *ACTB*. **** p<0.0001

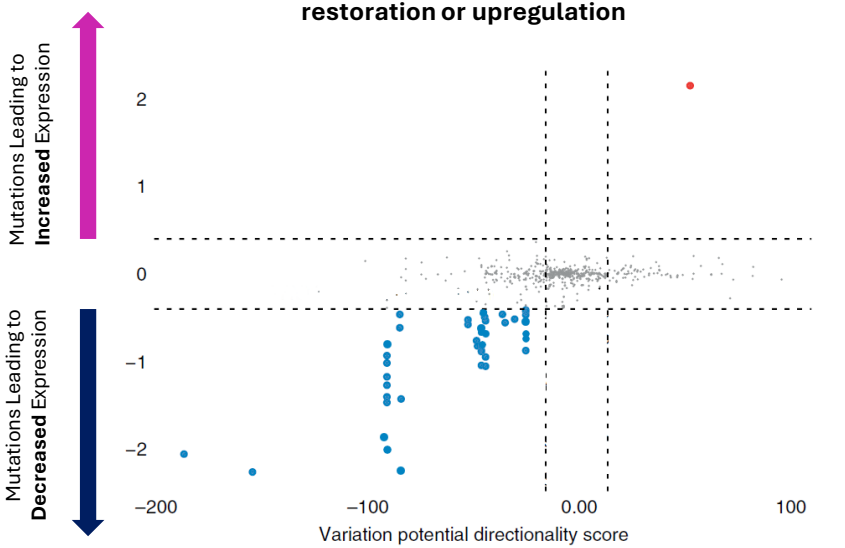
Combining best-in-class chemistry with novel biology and genetic insights: Opportunities for new high-impact medicines





Majority of disease associated mutations are predicted to decrease protein expression

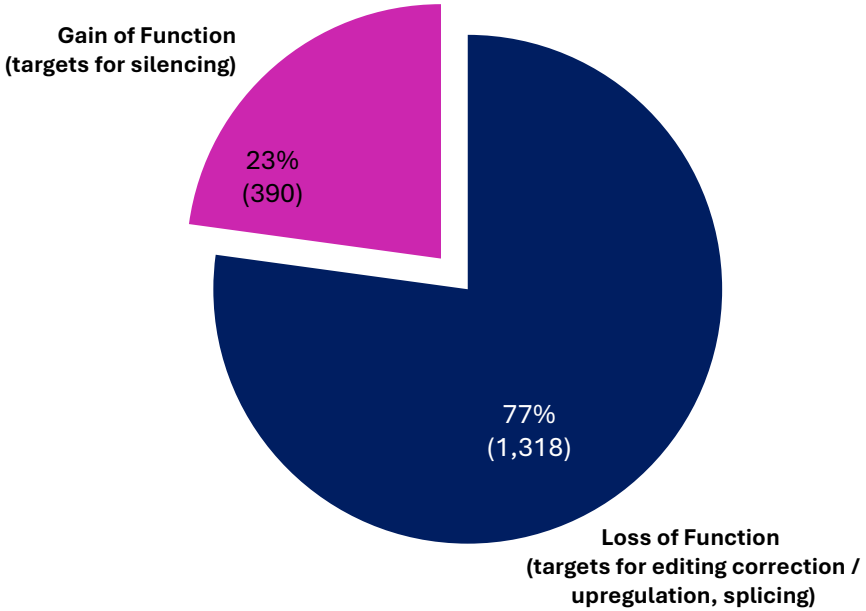
Mutations most commonly require protein restoration or upregulation



Adapted from Zhou, 2018

- *Potential disease targets requiring **upregulation***
- *Potential disease targets requiring **silencing***

Diseases in OMIM with gain of function or loss of function description



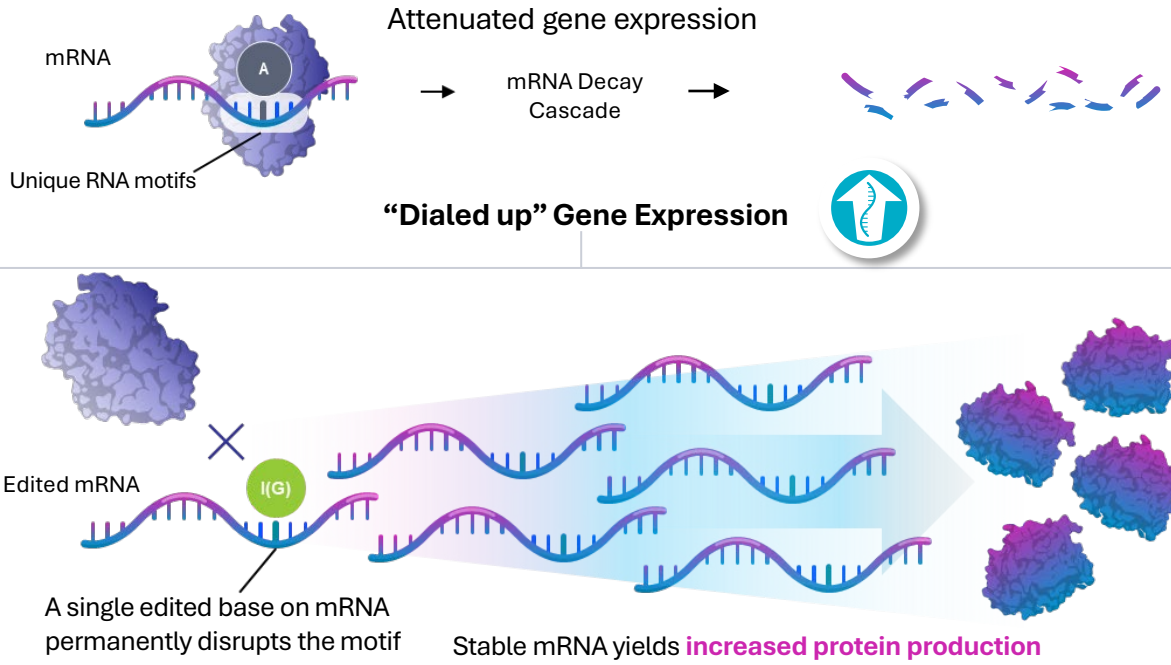
Wave's AIMers offer multiple applications for restoring protein function

Restore or correct protein function

- Correct G-to-A driver mutations with AIMers

WVE-006
(GalNAc-AIMer)
AATD

Upregulate expression to increase endogenous protein activity



Mapping the “Edit-verse”

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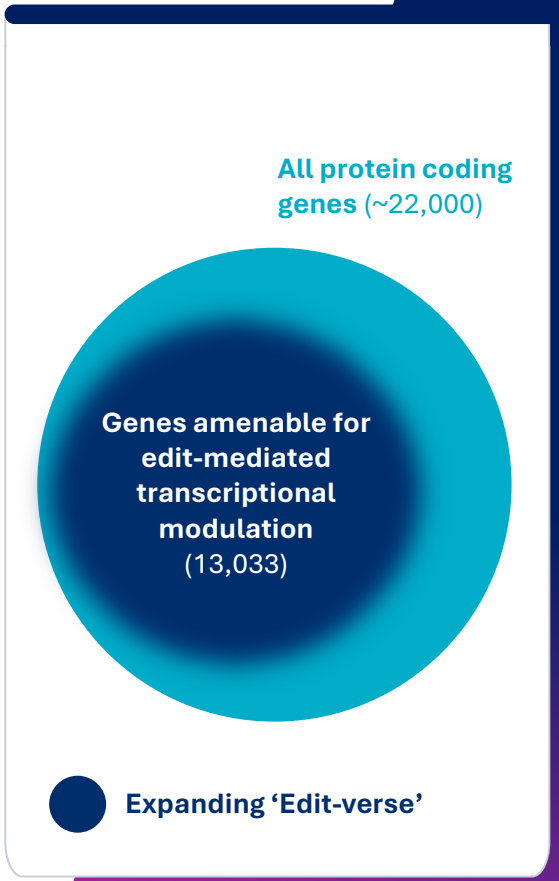
The AIMer-targetable ‘Edit-Verse’ is substantial

- **The Edit-verse is the editable gene-disease universe, including upregulation**
- **>13,000 protein coding genes** with a high-probability[1] of being amenable to transcriptional regulation with A-to-G editing
- Model development ongoing to expand access to **more protein-coding genes** and expand the Edit-verse

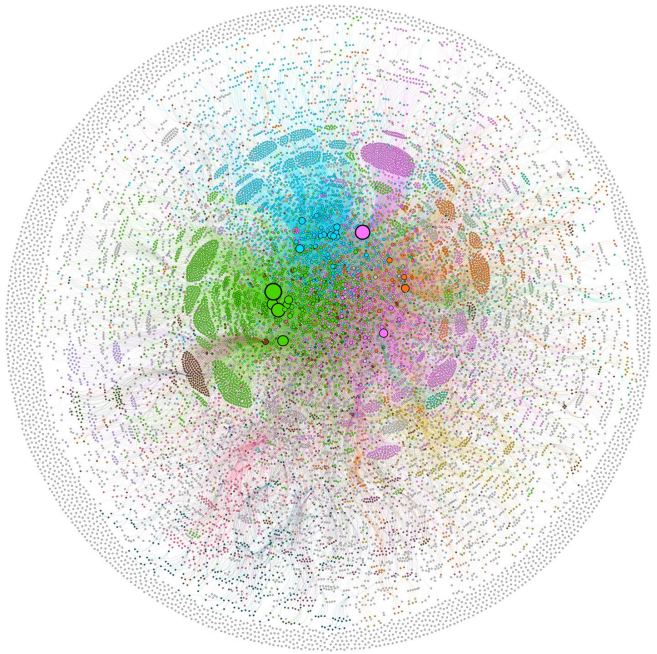


[1](score >95th p-tile)

Mapping the RNA editing target universe

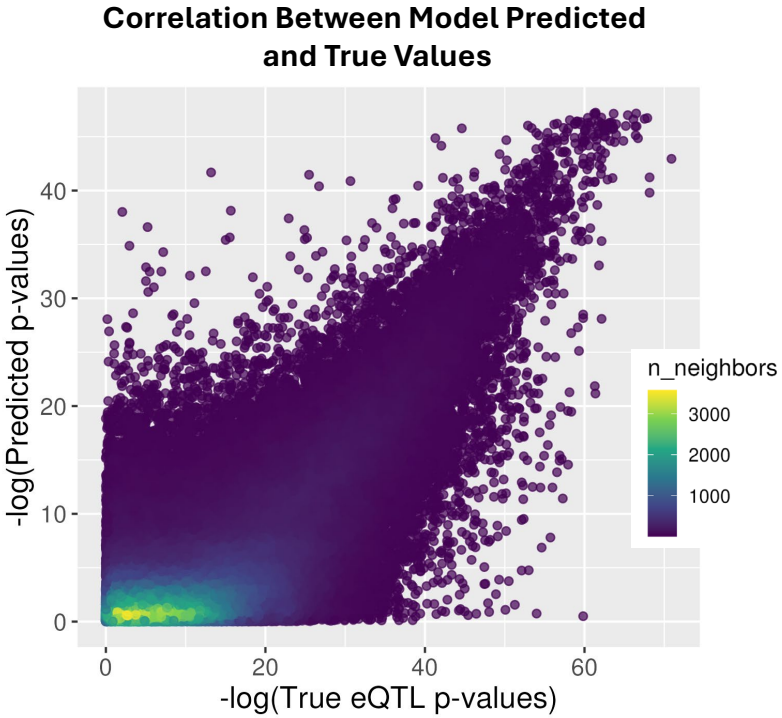
- The editable gene-disease network, **“The Edit-Verse”,** is enormous and includes coding and non-coding regions of transcripts
- The **upregulation target universe** is particularly interesting because many diseases are associated with reduced protein expression:
  - Haploinsufficient and hypomorphic variants
  - Regulatory variants
- Upregulation offers the potential to address multiple pathogenic mutations **with a single therapy**

Gene-Disease Network



Wave's deep learning model predicts novel edit sites that impact transcriptional regulation

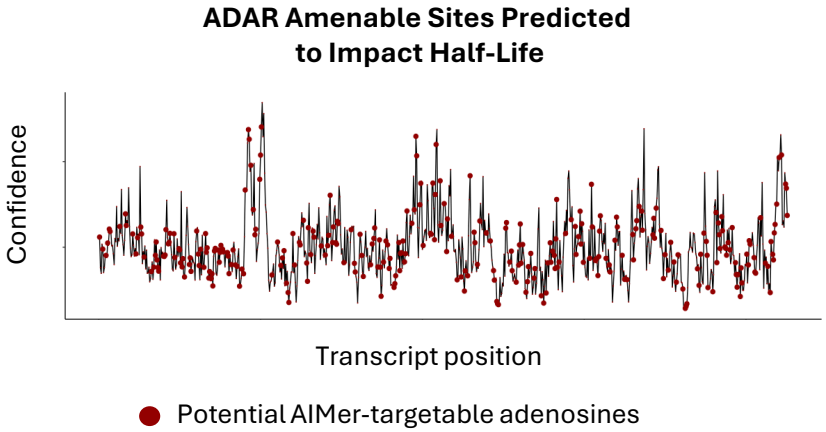
- Proprietary model constructed using large expression quantitative trait loci (eQTL) databases that can predict the impact of editing on gene expression
- Model achieved good predictive accuracy on known eQTLs
- Results include long list of novel eQTL sites where an A-to-G edit, never-before observed in nature, confidently predicts changes in transcript levels for >50% of proteome
- Ongoing model development is expected to expand Edit-verse further

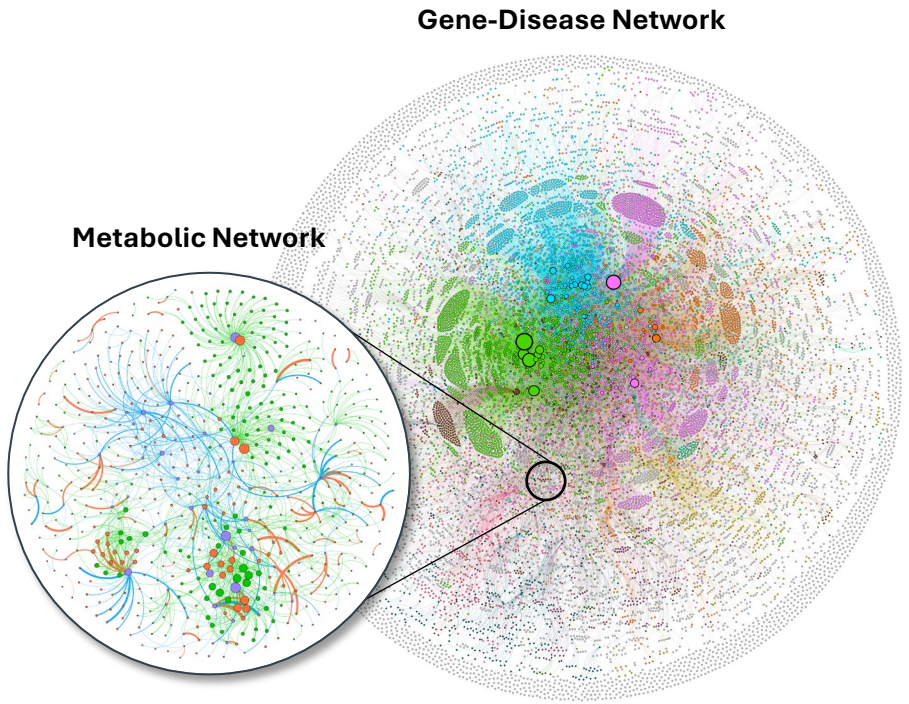


Chen et al, 2022: doi.org/10.1038/s41588-022-01102-2; Zhou et al, 2018: doi.org/10.1038/s41588-018-0160-6

Identify AIMer-mediated upregulation opportunities in disease sub-networks

- For instance, we can zoom into network for the hyperlipidemia and energy intake GWAS phenotypes, which contains 96 genes and disease-pathway associations
- We can then make editing predictions for any in-network gene of interest





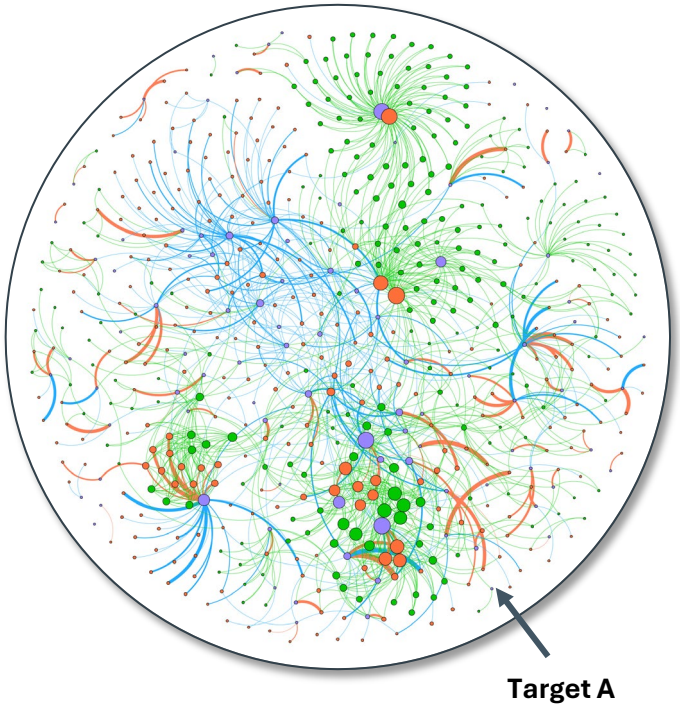
Mining the “Edit-verse”

Edit-verse subnetwork reveals “Target A”: Metabolic syndrome target uniquely suited for AIMer upregulation

Target A

- Liver target for upregulation, non-incretin therapy
- Strongly implicated in metabolic disease, with indirect causation in familial disorders
- Few therapies today provide weight loss in this specific patient population
- Estimate 90 million potential patients in the US and Europe with metabolic syndrome and obesity
- Serum protein levels and biomarkers available to assess target engagement

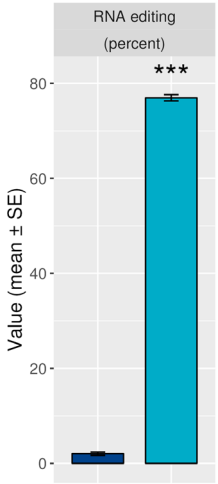
Metabolic Network



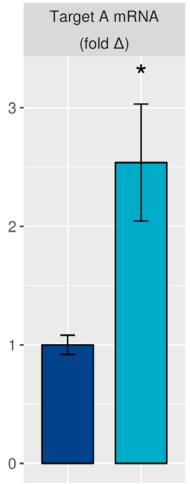
First preclinical *in vivo* PoC: upregulating endogenous protein to restore healthy metabolic phenotype

>75% RNA editing led to >2-fold increase of mRNA, and similar degree of protein upregulation *in vivo* with GalNAc-AIMer in young DIO mice

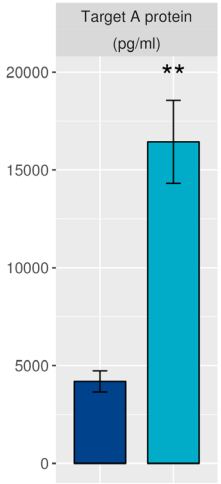
RNA editing



mRNA upregulation



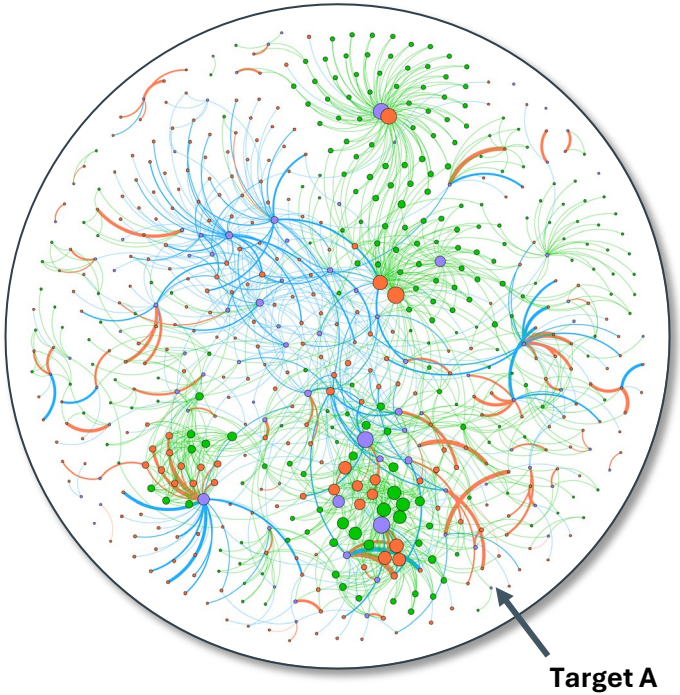
Increased protein



Treatment
PBS
AIMer Target A

p<0.05 *
p<0.001 **
p<0.0001 ***

Metabolic Network

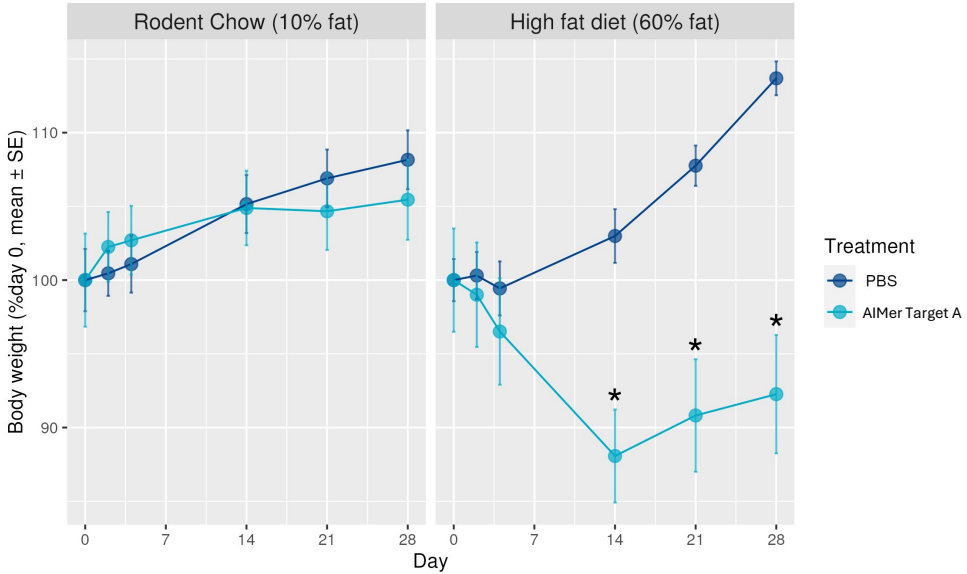


PoC: proof-of-concept Analysis of terminal endpoints (day 31) is shown. Each variable was analyzed using Welch's two-sided t-test. Significance was evaluated a $p<0.05$.

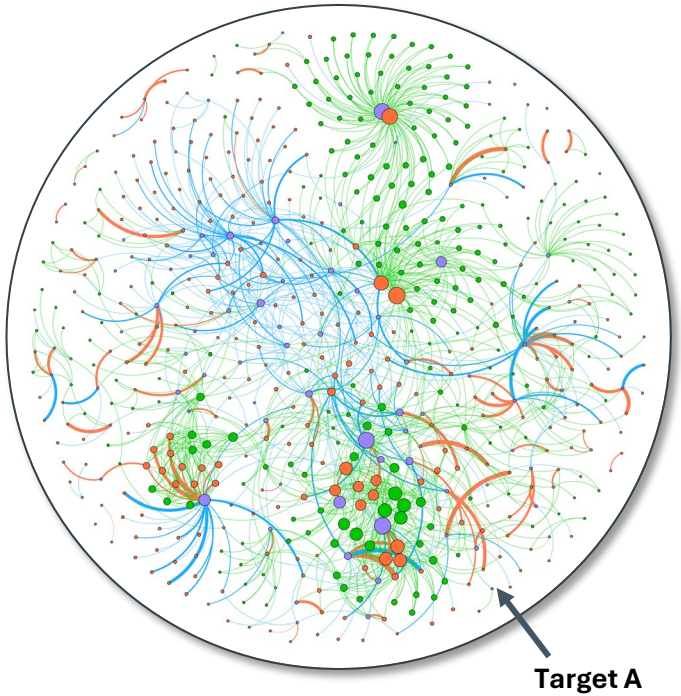
Substantial upregulation of protein induces weight loss

- ~3-fold upregulation of Target A protein with GalNAc-AIMer led to weight reduction in DIO mice

Significant Weight Loss



Metabolic Network

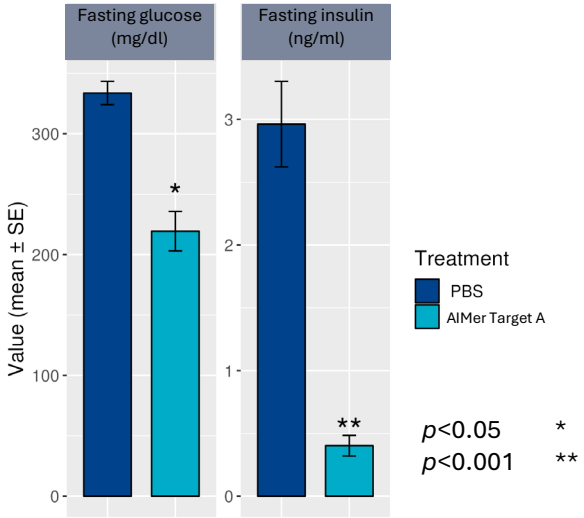


Body weight data were analyzed using a linear mixed effects model to assess the fix effects of diet, time and treatment, controlling for the initial day 0 body weight (continuous covariate) and subject (random effect). Fasted glucose and insulin data (from study termination, day 31) was analyzed using Welch's two-sided t-test. Significance was evaluated at $p<0.05$.

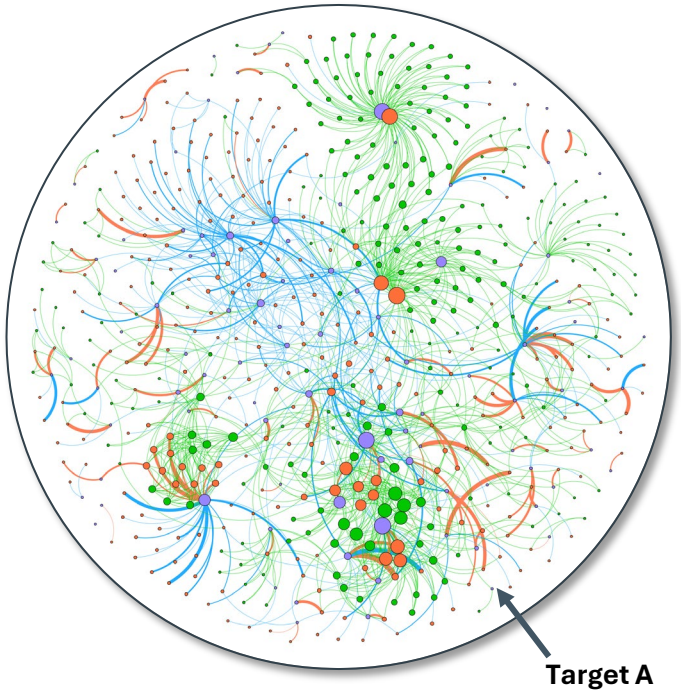
Upregulation of Target A protein improves insulin sensitivity

- ~3-fold upregulation of Target A protein with GalNAc-AIMer led to improved insulin sensitivity in DIO mice

Improved Insulin Sensitivity



Metabolic Network



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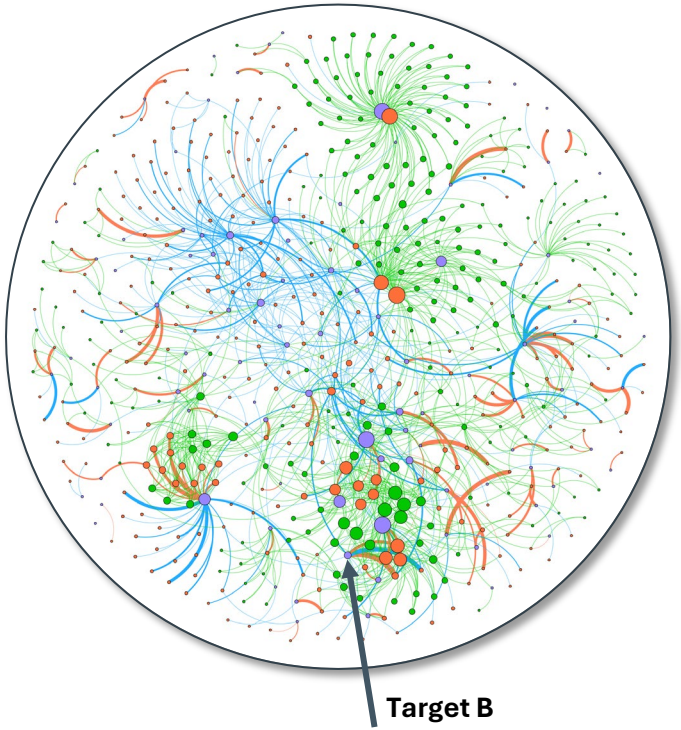
Target B upregulation offers a first-in-class therapeutic approach for hyperlipidemia

Target B

- Liver target for upregulation
- Hyperlipidemia; first-in-class therapeutic approach
- Estimate ~3 million target patients in US and Europe
- Serum biomarkers available to assess target engagement and efficacy
- Potential clinically meaningful benefit of >2 fold upregulation of target mRNA

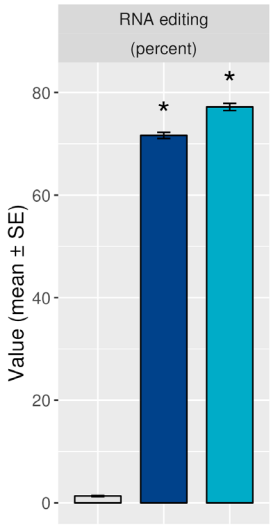
Metabolic Network



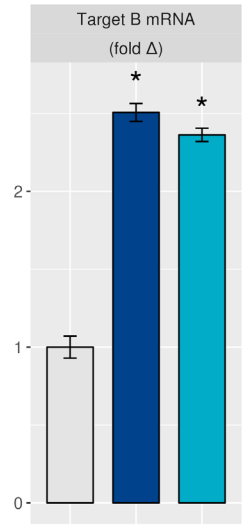
>70% editing achieves ~2-fold upregulation with corresponding increase in protein

Primary human hepatocytes *in vitro*

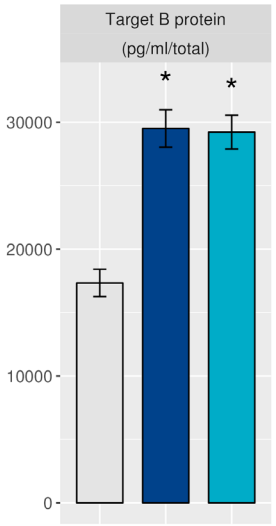
RNA editing



mRNA upregulation

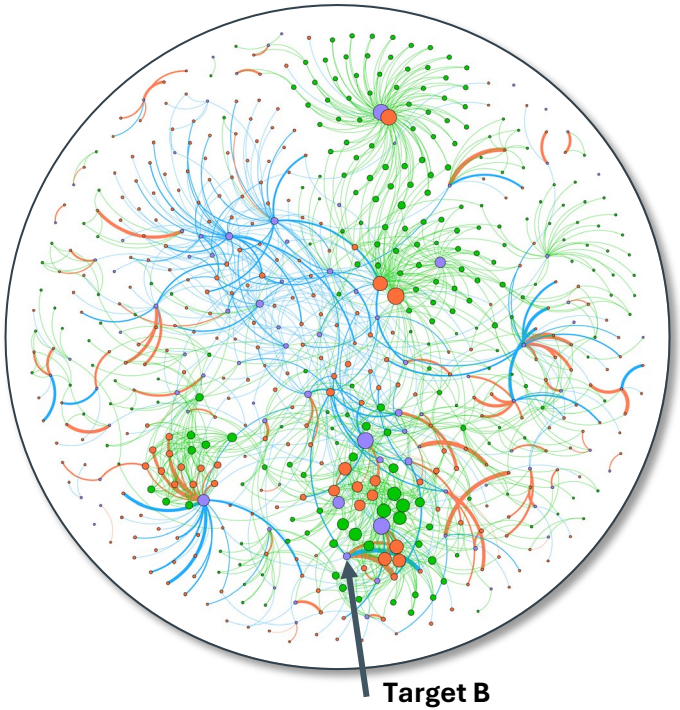


Protein increase



*p<0.0001

Metabolic Network

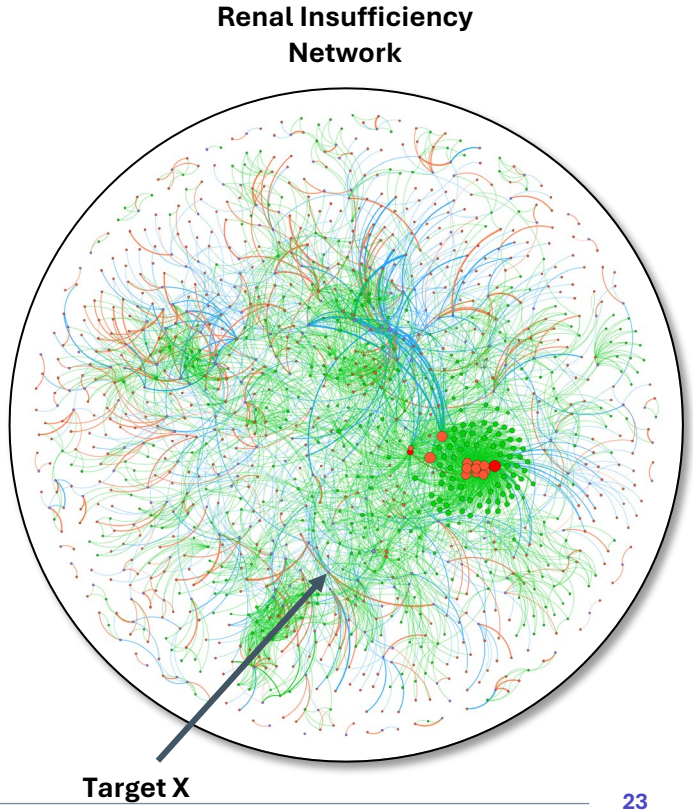


Variable were analyzed with ANOVA and Tukey's HSD. Significance was evaluated at p<0.0001.

Upregulation of liver Target X stops decline in kidney function

Target X

- Liver target for upregulation
- Target X produces a secreted protein to treat kidney disease
- Estimate ~170K target patients in US and Europe
- Therapeutic rationale supported by genetic insights, PheWAS, and observational data
- Plasma biomarkers available to assess target engagement
- ~2-fold upregulation in secreted protein expected to be clinically meaningful

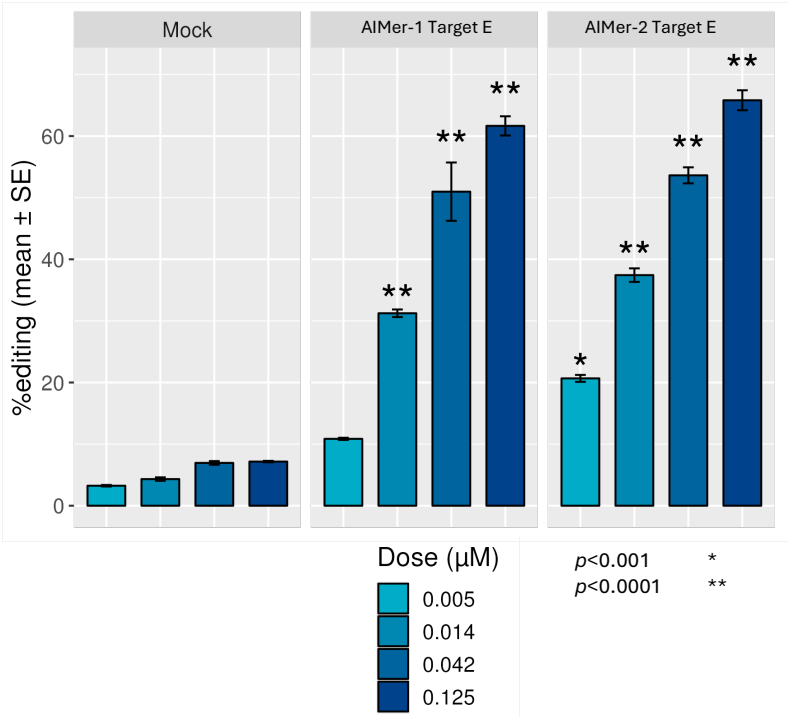


Building on success of AATD: Target E correction restores normal metabolism in rare genetic disease

Target E

- Liver target for correction
- Rare genetic disease
- High unmet need population not addressed with current therapeutic options
- ~17,000 patients addressable with correction approaches in US and Europe
- Fully translatable serum biomarker
- ~15-30% editing expected to deliver clinically meaningful benefit

Proof-of-concept RNA editing in human primary hepatocytes



Two-way ANOVA (Treatment, Dose) and Tukey's HSD. Significance was evaluated at $p<0.05$, GalNAc-AIMers.

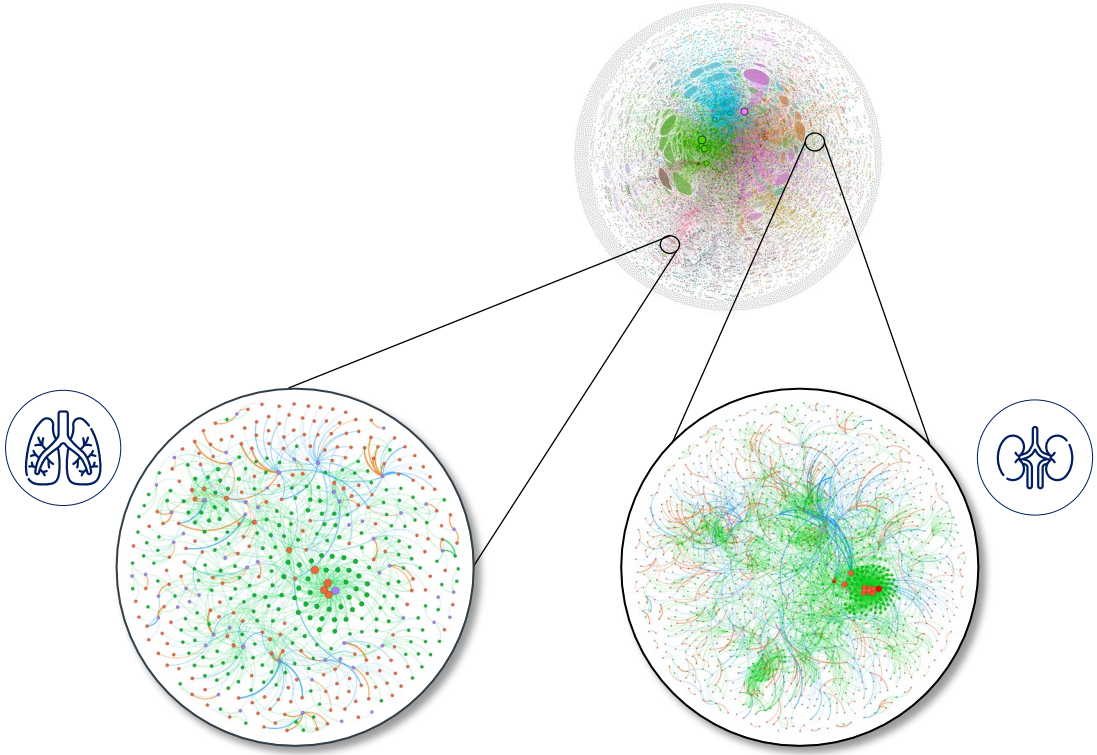
AIMer targetable diseasomes in extra-hepatic organs

Hepatic

- Target A
- Target B
- Target X
- Target E

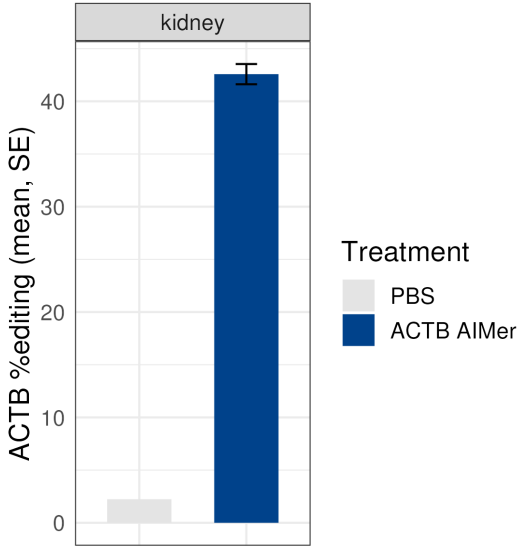
Extra-hepatic

- Target F
- Target G

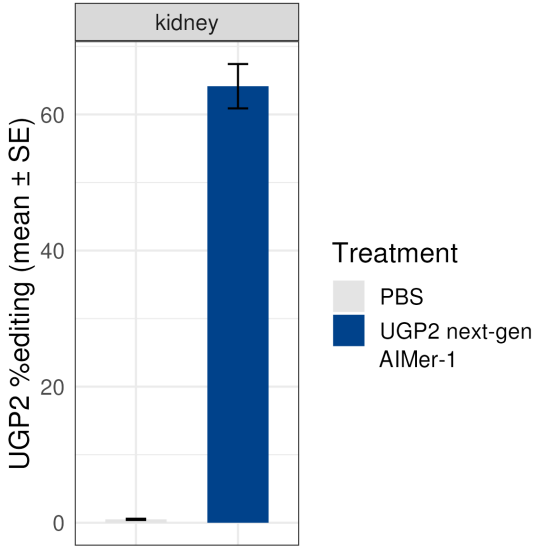


AIMers deliver to proximal and distal convoluted tubules of kidney and achieve substantial editing

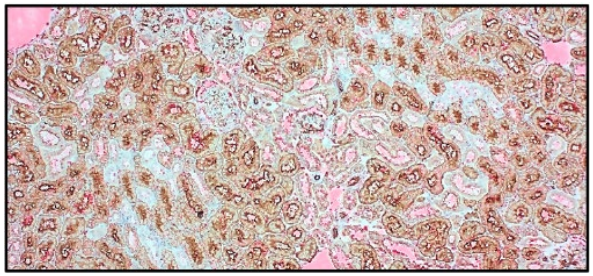
~40% editing of ACTB in NHP
1-week post-single dose (SC)



~60% editing of UGP2 in mice
1-week post single dose (IV)



AIMers (red) accumulated in proximal convoluted tubules (brown) in the NHP kidney following subcutaneous administration

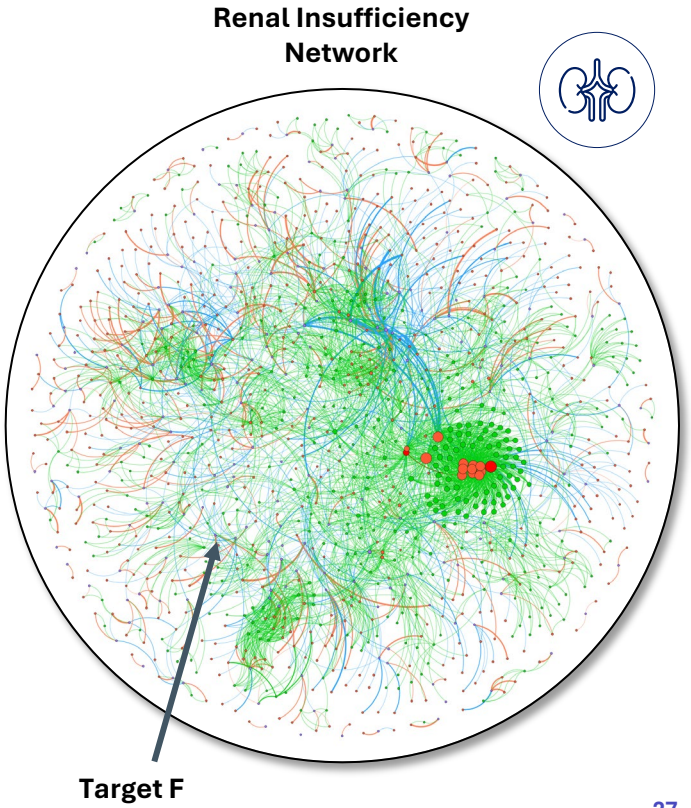


Left: Monian et al., 2022 published online Mar 7, 2022; doi: 10.1038.s41587-022-01225-1; SC: subcutaneous; IV: intravenous

Upregulation of Target F restores kidney function in a rare genetic kidney disease

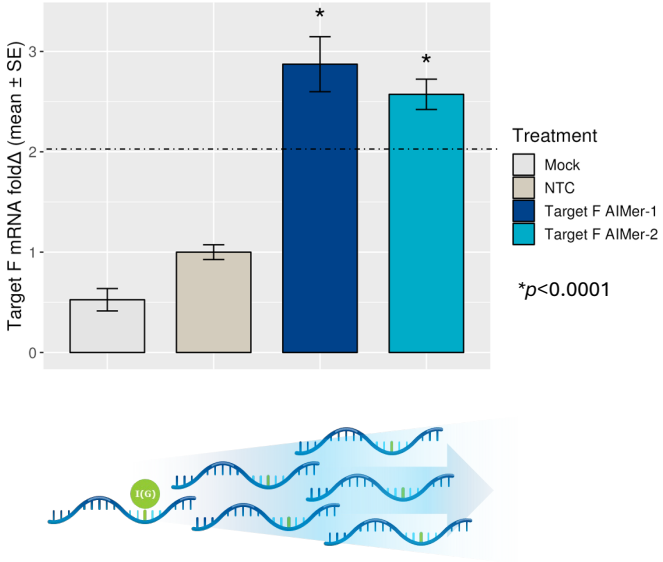
Target F

- Kidney target for upregulation
- Rare genetic kidney disease that leads to ESRD and need for dialysis / transplantation; High unmet need with few treatment options currently available
- ~85K patients in US and Europe addressable with upregulation approach
- Urinary biomarkers available to assess upregulation
- Clinically meaningful benefit may be achieved with 2-fold upregulation

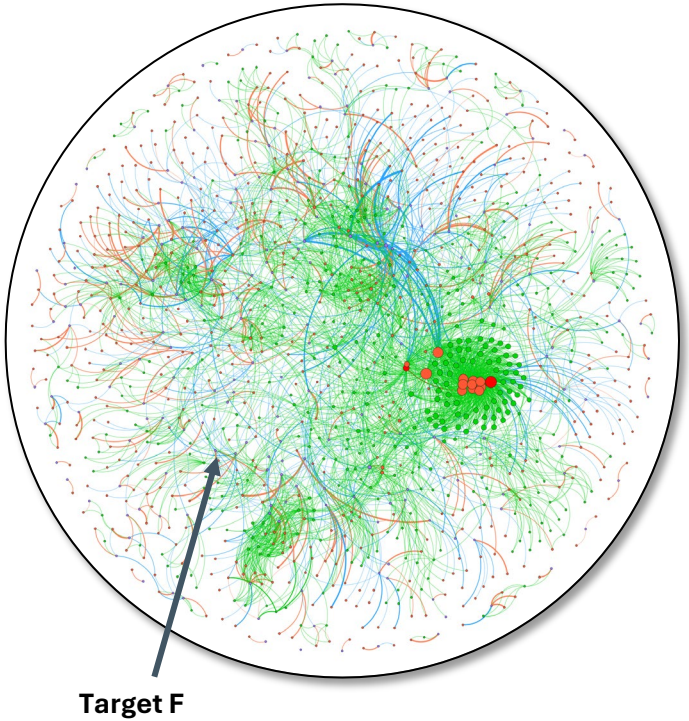


Achieved >2-fold upregulation of Target F mRNA *in vitro* with RNA editing

Upregulation of Target F mRNA in Human kidney tubular epithelial cells



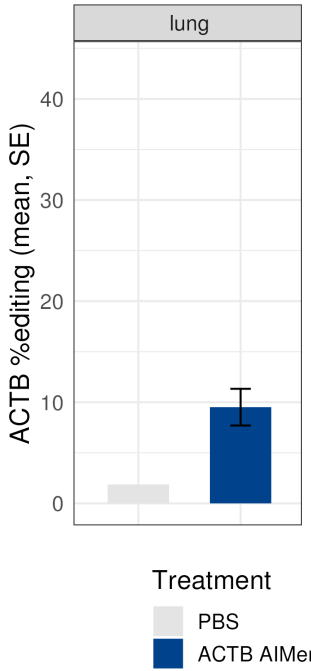
Renal Insufficiency Network



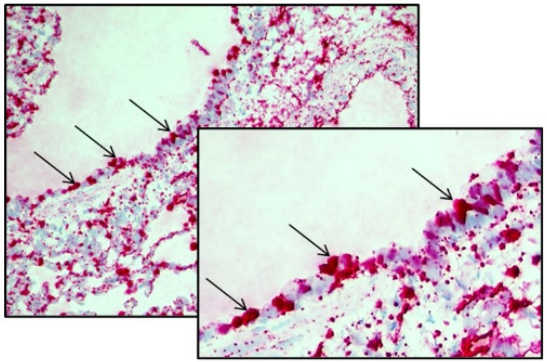
One-Way Anova; samples compared to NTC with Tukey's HSD test. Significance evaluated at p<0.0001.

Proprietary AIMer modifications enhance delivery to lung tissue and achieve significant editing *in vivo*

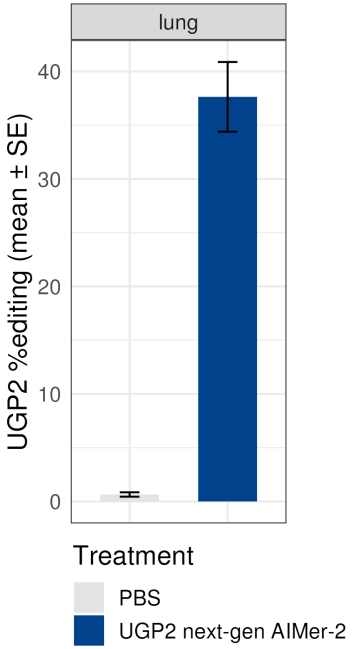
~10% editing of ACTB in NHP 1-week post-single dose (SC)



ACTB AIMer (red) delivery to bronchial epithelial cells (arrows)



>35% editing of UGP2 in mice 1-week post single dose (IV)



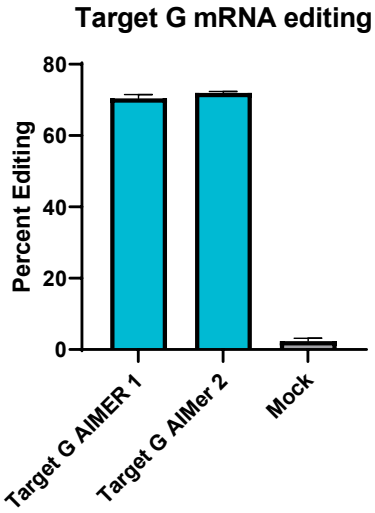
Left: Monian et al., 2022 published online Mar 7, 2022; doi: 10.1038.s41587-022-01225-1

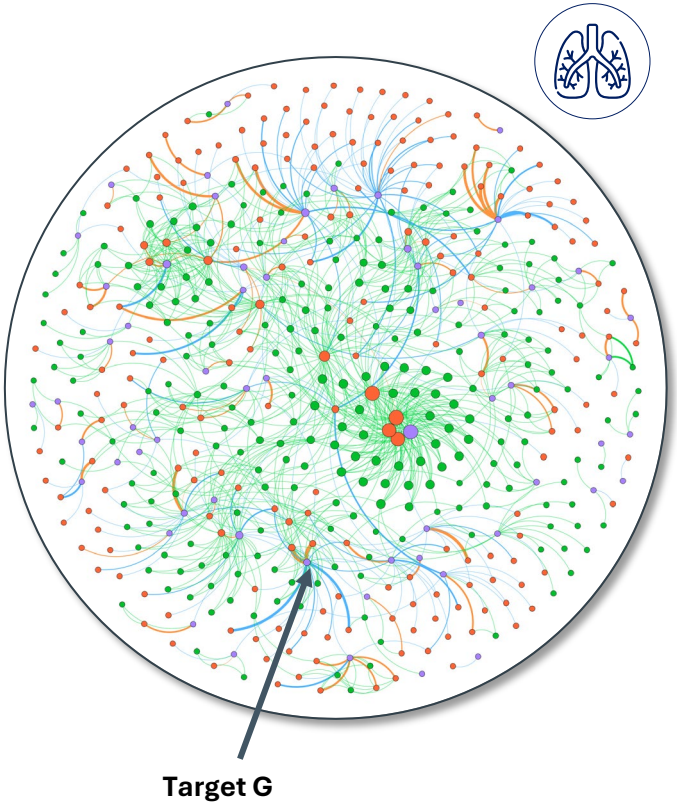
Correction of Target G mutation restores protein function in patients with a genetic lung disease

Target G

- Lung disease target for correction
- Genetic lung disease with target patient population not addressed with available therapies
- ~5K patients amenable to correction approaches in US and Europe
- Clinically meaningful benefit expected with 20% correction
- Established clinical regulatory pathway

In vitro





Multiple RNA editing opportunities to build high-value pipeline beyond WVE-006

Potential to advance any combination of targets into preclinical development

	Hepatic (GalNAc-AIMers)				Extra-Hepatic (AIMers)	
	Target A	**Target B**	**Target X**	**Target E**	**Target F**	**Target G**
Approach	Upregulation	Upregulation	Upregulation	Correction	Upregulation	Correction
Tissue	Liver	Liver	Liver	Liver	Kidney	Lung
Therapeutic Area	Metabolic	Metabolic	Renal	Rare	Renal	Rare
Estimated Patients (US and Europe)	~90M	~3M	~170K	~17K	~85K	~5K

- The Edit-verse is substantial and still expanding
- Advancing work for a diverse set of undisclosed targets addressing areas of high unmet need, including both rare and prevalent diseases

New preclinical data on advancing RNA editing programs expected in 2024

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