



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

Kenneth Longo, PhD, VP, Data Science

Ginnie Yang, PhD, SVP, Translational Medicine

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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\***

# 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



**nature biotechnology**  
THE SCIENCE AND BUSINESS OF BIOTECHNOLOGY

VOLUME 35 NUMBER 9 SEPTEMBER 2017  
www.nature.com/naturebiotechnology

**ILLUSTRATION COMMUNICATIONS**

**ARTICLE** OPEN

**Variant-selective stereorep oligonucleotides protect against pathologies associated with C9orf72 repeat expansion in preclinical models**

Yuanqing Liu<sup>1,2</sup>, Xian Shuwei<sup>1,2</sup>, Huihui Tian<sup>1,2</sup>, Shaohua Bai<sup>1,2</sup>, Muzhao Brant<sup>1</sup>, Michael Byrne<sup>1</sup>, Ann F. Durbin<sup>1</sup>, Xian Shuwei<sup>1,2</sup>, Jiali Shihai<sup>1,2</sup>, Hailin Yang<sup>1,2</sup>, Yuan Yu<sup>1,2</sup>, Amy Dorner<sup>1</sup>, Zhong Zhang<sup>1</sup>, Chaoxi Vargayese<sup>1,2</sup> & Robert H. Brown Jr<sup>1,2</sup>

**Stereorep antisense oligonucleotides Labeling neurons in vivo miRNA expression atlas**

A large C9orf72 repeat expansion in C9orf72 is the most common genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Neuronal degeneration associated with the expansion arises from a loss of C9orf72 protein, the accumulation of RNA foci, the expansion of dipeptide repeat (DPR) protein, or all three factors. We report the discovery of a novel repeating sequence that is common to all C9orf72 transcripts but enables neuronal knockdown of repeat-containing transcripts in multiple animal models and CRISPR transgenic mice. We systemically oligonucleotides that all target this site and demonstrate that their penetrance of oligo knockdowns into brain tissue chemically and systemically using single in vivo stereorep oligonucleotide injections. Stereorep oligonucleotides without dipeptide repeat expression. Their degradation, including protein, nucleic acid, and C9orf72 expression modulation from gene silencing. We hypothesize that targeting C9orf72 with stereorep oligonucleotides may be a viable therapeutic approach for the treatment of C9orf72-associated neurodegenerative disorders.

Published online 2 February 2017

Nature Reviews Molecular Cell Biology 2017, Vol. 18, No. 9

**NAR Breakthrough Article**

**Impact of guanidine-containing backbone linkages on stereorep antisense oligonucleotides in the CNS**

Pachamuthu Kandasamy<sup>1</sup>, Yuanqing Liu<sup>1</sup>, Vincent Aduda, Sandeep Akar, Rowshan Alam, Ann F. Durbin, David Boulay, Kellie Burgess, Marketa Brana, Marissa Casanova, Kenneth Longo<sup>1</sup>, Gerliang Lu<sup>1</sup>, Subramanian Marappan, Khos Luu, Sneha Tripathi, Erin Parcell Estabrook, Jiali Shihai, Huihui Tian, Anthony Lanatino, Qianqi Pi, Brett Schrand, Frank Favaro, Mugisha Baghera, Arindom Chatterjee, Jagar Desai<sup>1</sup>, Tomonori Kawamura, Gensheng Liu, Jiaa Metterville, Minjia Sannarawong, Priyanka Shiva Prakashai, Hailin Yang, Yan Yu, Hai Yu, Paloma M. Giugiarone, Michael Byrne, Pachamuthu Kandasamy and Chandra Vargasee<sup>1,2</sup>

Published online 16 October 2016

**Impact of stereorep chimeric backbone chemistry on the potency and durability of gene silencing by RNA interference**

Wu Liu<sup>1</sup>, Nooki Iwamoto<sup>1</sup>, Subramanian Marappan, Khos Luu, Sneha Tripathi, Erin Parcell Estabrook, Jiali Shihai, Huihui Tian, Anthony Lanatino, Qianqi Pi, Brett Schrand, Frank Favaro, Mugisha Baghera, Arindom Chatterjee, Jagar Desai<sup>1</sup>, Tomonori Kawamura, Gensheng Liu, Jiaa Metterville, Minjia Sannarawong, Priyanka Shiva Prakashai, Hailin Yang, Yan Yu, Hai Yu, Paloma M. Giugiarone, Michael Byrne, Pachamuthu Kandasamy and Chandra Vargasee<sup>1,2</sup>

Published online 16 October 2016

**Abstract**

Here, we report the systematic investigation of stereorep phosphorothioate (PS) and phosphorothioate (PT) linkages in stereorep antisense oligonucleotides. We demonstrate that stereorep antisense oligonucleotides with PS and PT linkages are more potent and durable in silencing mouse and human targets (TfR and HSP70) in mouse hepatocytes in vivo compared with non-stereorep antisense oligonucleotides. The PS and PT linkages have beneficial effects on increased neuronal susceptibility to amyotrophic lateral sclerosis (ALS) in transgenic mice. The PS and PT linkages have beneficial effects on increased neuronal susceptibility to amyotrophic lateral sclerosis (ALS) in transgenic mice. The PS and PT linkages have beneficial effects on increased neuronal susceptibility to amyotrophic lateral sclerosis (ALS) in transgenic mice.

## Splicing

**Control of backbone chemistry and chirality boost oligonucleotide splice-switching activity**

Pachamuthu Kandasamy<sup>1</sup>, Graham McCloy<sup>1</sup>, Mamoru Shimizu<sup>1</sup>, Nayantara Kothari<sup>1</sup>, Rowshan Alam<sup>1</sup>, Nooki Iwamoto<sup>1</sup>, Jayanthina Kumarasamy<sup>1</sup>, Gopal R. Bonemissen<sup>1</sup>, Adam Bezigan<sup>1</sup>, Omang Chivatkar<sup>1</sup>, David C. Butler<sup>1</sup>, Michael Byrne<sup>1</sup>, Katarzyna Chwalatka<sup>1</sup>, Kay E. Davies<sup>1</sup>, Jagar Desai<sup>1</sup>, Ann F. Durbin<sup>1</sup>, Ruth Eberling<sup>1</sup>, Ben Edwards<sup>1</sup>, Jack Godfrey<sup>1</sup>, Andrew Hosa<sup>1</sup>, Fangjun Lu<sup>1</sup>, Kenneth Longo<sup>1</sup>, Gerliang Lu<sup>1</sup>, Subramanian Marappan<sup>1</sup>, Jacopo Oleri<sup>1</sup>, Ki-Hyeon Paik<sup>1</sup>, Erin Parcell Estabrook<sup>1</sup>, Chikita Shivalila<sup>1</sup>, Mavee Trachbani<sup>1</sup>, Tomomi Kawamura<sup>1</sup>, Jayanthina Kumarasamy<sup>1</sup>, Anthony Lanatino<sup>1</sup>, Amber Lindsey<sup>1</sup>, David Liu<sup>1</sup>, Richard Lough<sup>1</sup>, Subramanian Marappan<sup>1</sup>, Jiaa Metterville<sup>1</sup>, Roselle Murphy<sup>1</sup>, Jeff Ross<sup>1</sup>, Tom Pu<sup>1</sup>, Bijay Bhattarai<sup>1</sup>, Stephen Standley<sup>1</sup>, Sneha Tripathi<sup>1</sup>, Hailin Yang<sup>1</sup>, Yan Yu<sup>1</sup>, Hai Yu<sup>1</sup>, Cong Zhou<sup>1</sup>, Luciano A. Vargasee<sup>1,2</sup>

Published online 21 January 2017

**Abstract**

Although repeat regulatory approval of antisense oligonucleotides (ASOs) for the treatment of neurodegenerative diseases such as Duchenne muscular dystrophy has been an advance for the field of neurodegenerative diseases, ASOs are still limited clinically due to poor pharmacology. To overcome limitations of existing ASOs, we engineered chimeric stereorep oligonucleotides with phosphorothioate (PS) and phosphorothioate (PT) backbones. We demonstrate that these PS and PT stereorep oligonucleotides have markedly improved pharmacology and efficacy compared with PS and PT oligonucleotides, preventing premature death and improving motor survival in mice for at least 280 days in a dystrophic mouse model with an aggressive phenotype. We demonstrate that PS and PT stereorep oligonucleotides have improved potential for continued neuroprotection against the oligonucleotide backbone. More specifically, we conclude that chimeric stereorep oligonucleotides are a promising splice-switching modality with potential for the treatment of neurodegenerative diseases.

## Editing (AIMers)

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

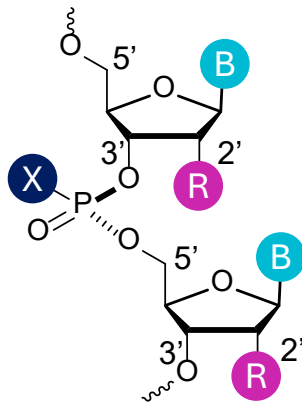
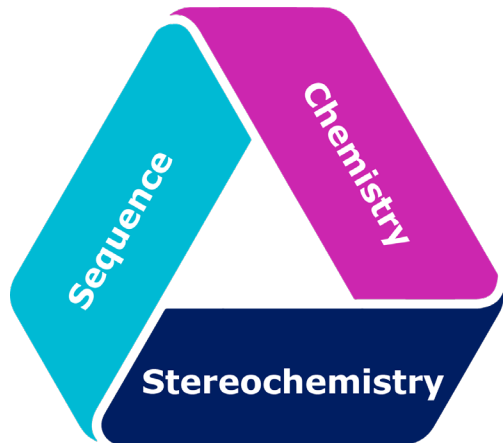
Prashant Mani<sup>1</sup>, Chikita Shivalila<sup>1</sup>, Gensheng Liu<sup>1</sup>, Mamoru Shimizu<sup>1</sup>, David Boulay<sup>1</sup>, Karley Russow<sup>1</sup>, Michael Byrne<sup>1</sup>, Adam Bezigan<sup>1</sup>, Arindom Chatterjee<sup>1</sup>, Jagar Desai<sup>1</sup>, Frank Favaro<sup>1</sup>, Jack Godfrey<sup>1</sup>, Andrew Hosa<sup>1</sup>, Nooki Iwamoto<sup>1</sup>, Tomomi Kawamura<sup>1</sup>, Jayanthina Kumarasamy<sup>1</sup>, Anthony Lanatino<sup>1</sup>, Amber Lindsey<sup>1</sup>, David Liu<sup>1</sup>, Richard Lough<sup>1</sup>, Subramanian Marappan<sup>1</sup>, Jiaa Metterville<sup>1</sup>, Roselle Murphy<sup>1</sup>, Jeff Ross<sup>1</sup>, Tom Pu<sup>1</sup>, Bijay Bhattarai<sup>1</sup>, Stephen Standley<sup>1</sup>, Sneha Tripathi<sup>1</sup>, Hailin Yang<sup>1</sup>, Yan Yu<sup>1</sup>, Hai Yu<sup>1</sup>, Cong Zhou<sup>1</sup>, Luciano A. Vargasee<sup>1,2</sup>

Published online 21 January 2017

**Abstract**

Although it is well established that the activity of endogenous ADARs is essential for normal development, endogenous ADAR-mediated RNA editing in non-human primates using stereorep chemically modified oligonucleotides (AIMers) that direct efficient and specific A-to-I editing of endogenous transcripts by endogenous ADARs remains to be demonstrated. Here, we demonstrate that chemically modified oligonucleotides containing AIMers with chimeric backbones containing stereorep phosphorothioate (PS) and PT linkages can induce ADAR-mediated RNA editing in non-human primates. We show that with fully phosphorylated-modified backbones in vivo, in vivo, AIMers targeted to hepatocytes with PS and PT linkages induce A-to-I editing on a 50% editing on a heterologous A-to-I editing substrate in non-human primates. We show that editing percentages for at least one month. These results support further investigation of the therapeutic potential of stereorep AIMers.

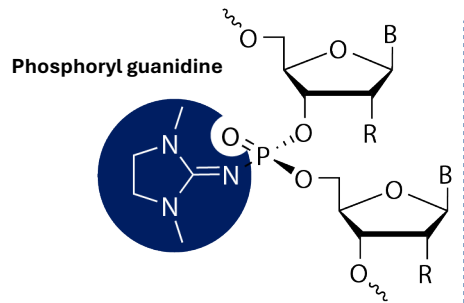
# Wave's PRISM™ platform enables application of best-in-class chemistry across modalities, including RNA editing



(B) Base

(R) 2'-Ribose

(X) Stereochemistry and backbone modification



O: Phosphodiester  
S: Phosphorothioate  
N: Phosphoryl guanidine

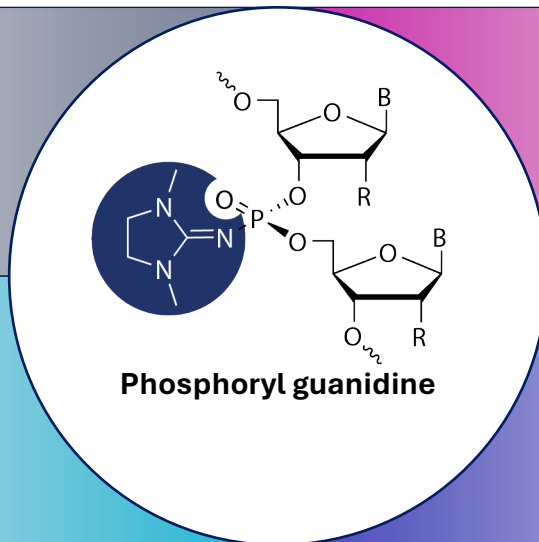
# PN backbone chemistry was a significant advance in oligonucleotide chemistry; significantly improves potency, distribution and durability

## 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



## Biological impact

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

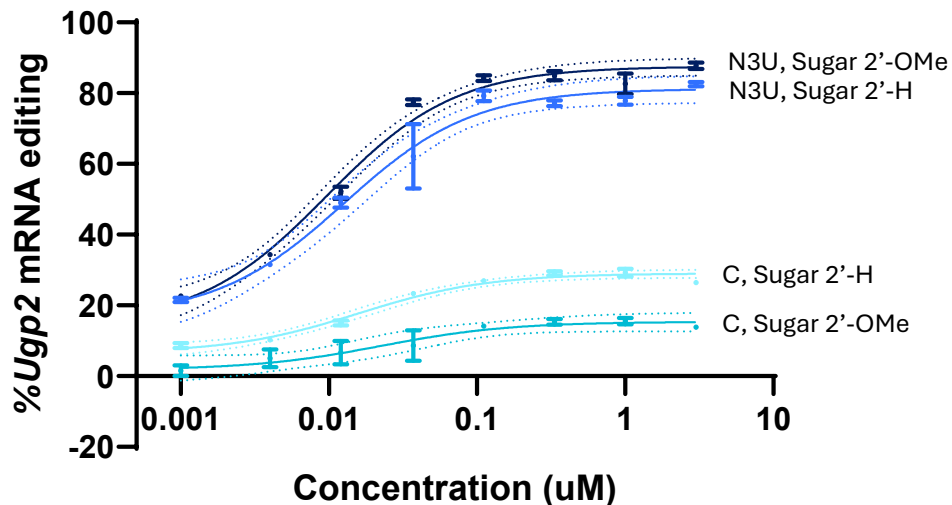
## Potential therapeutic impact

- Anticipated improvements across modalities based on preclinical studies

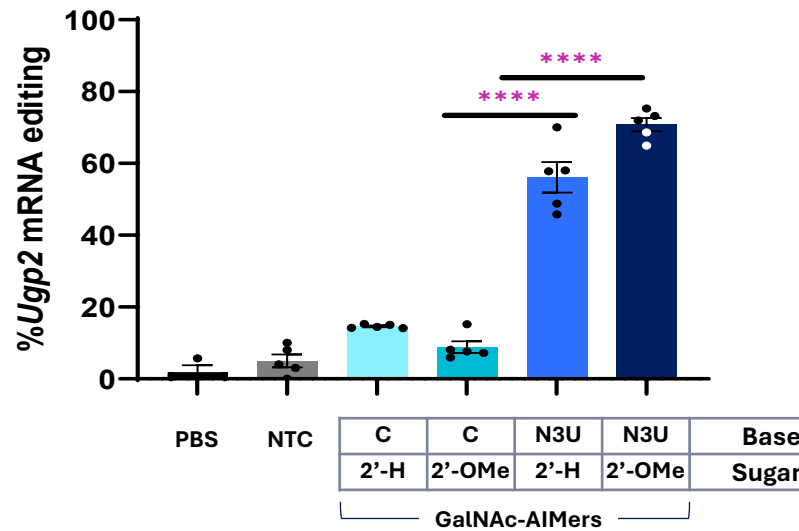
# Proprietary and unique chemistry supports efficient editing *in vivo* with GalNAc-AIMers



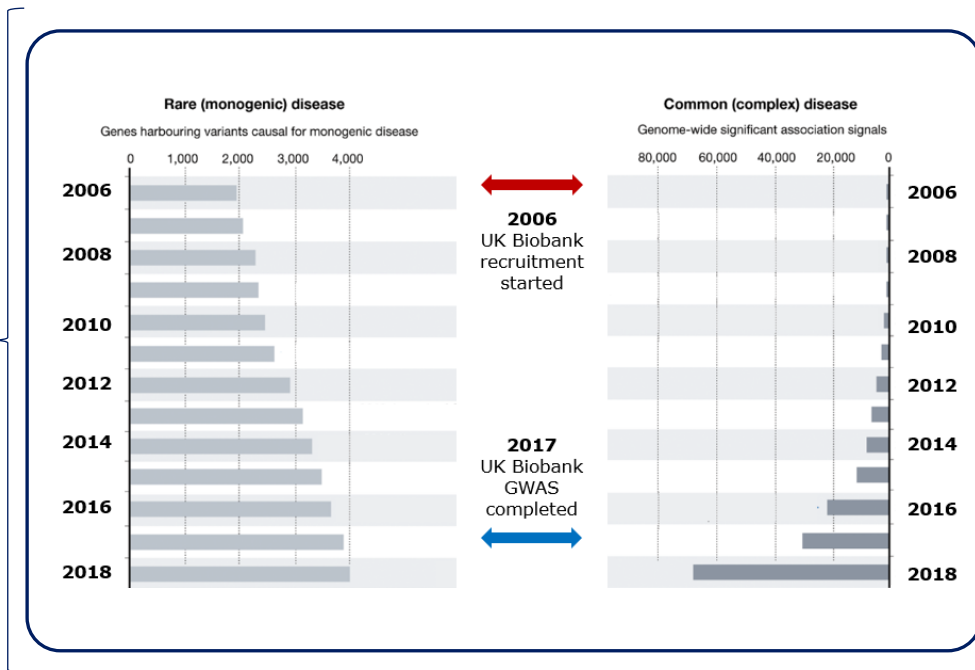
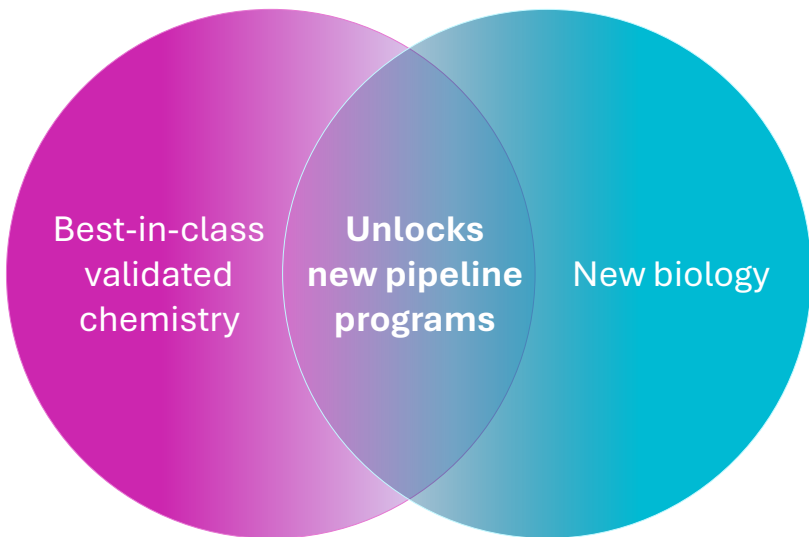
RNA editing in primary mouse hepatocytes (GalNAc mediated delivery)



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

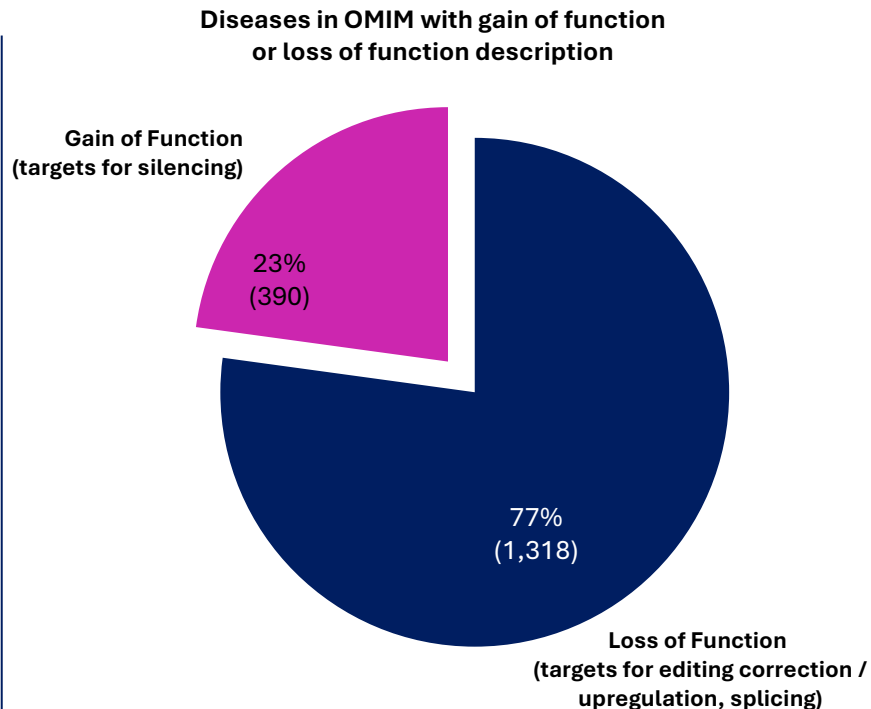
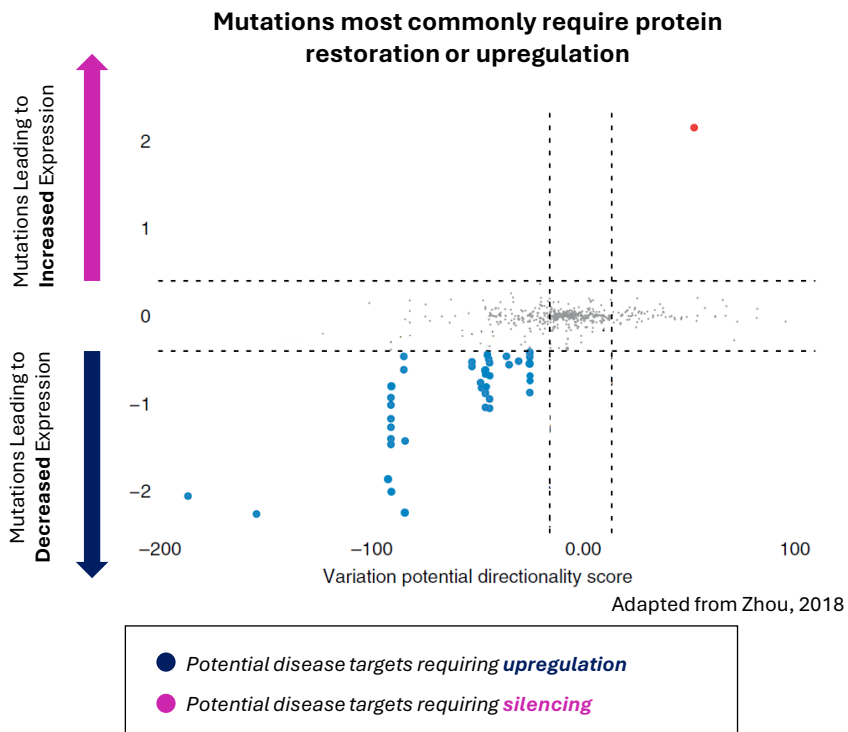


# Combining best-in-class chemistry with novel biology and genetic insights: Opportunities for new high-impact medicines





# Majority of disease associated mutations are predicted to decrease protein expression



# Wave's AIMers offer multiple applications for restoring protein function

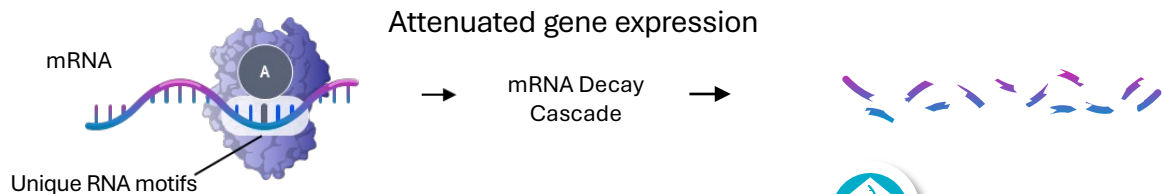
## Restore or correct protein function



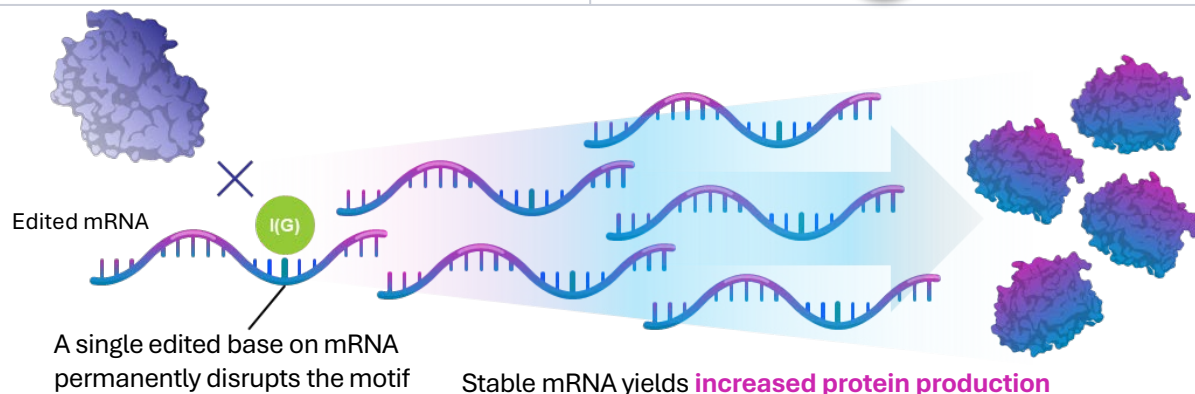
- Correct G-to-A driver mutations with AIMers

**WVE-006**  
(GalNAc-AIMER)  
AATD

## Upregulate expression to increase endogenous protein activity



## “Dialed up” Gene Expression

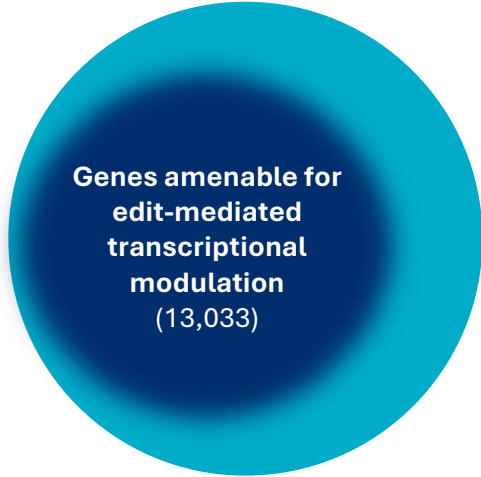


# Mapping the “Edit-verse”

## 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<sup>1</sup> 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

All protein coding genes (~22,000)



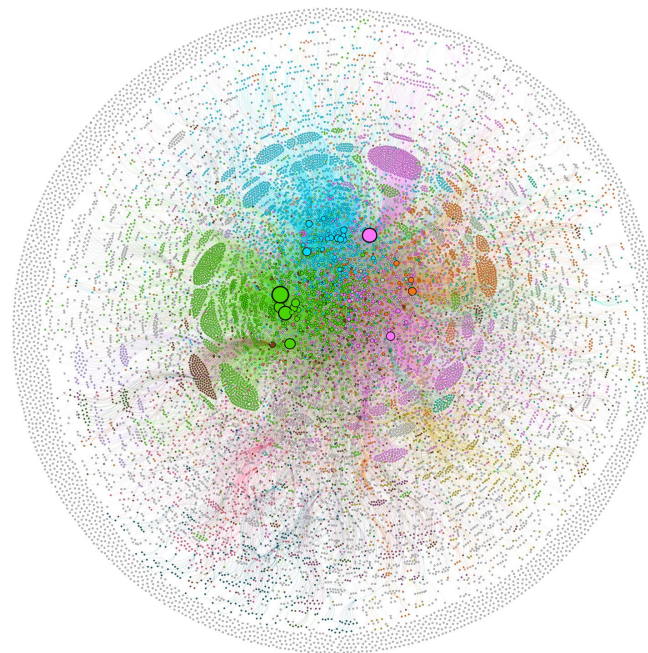
Genes amenable for edit-mediated transcriptional modulation (13,033)

Expanding 'Edit-verse'

# 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**

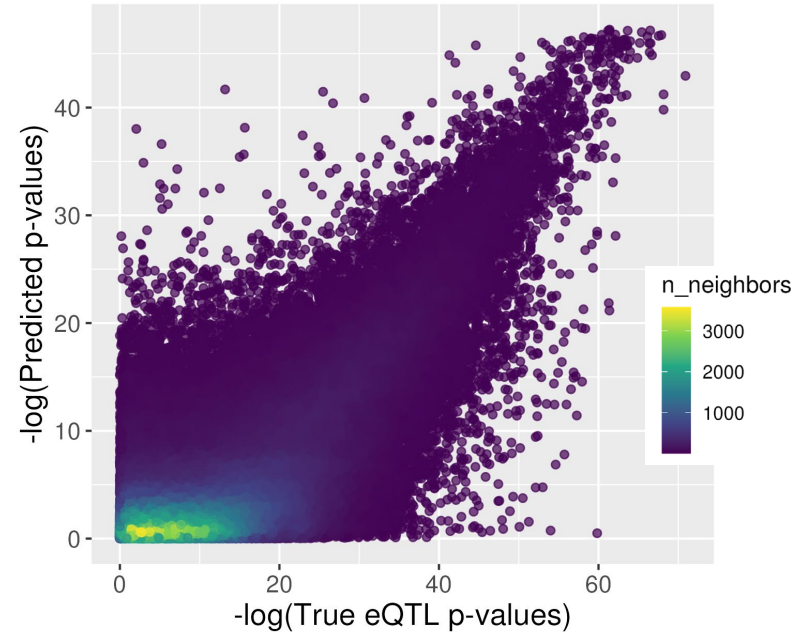
**Gene-Disease Network**



# 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

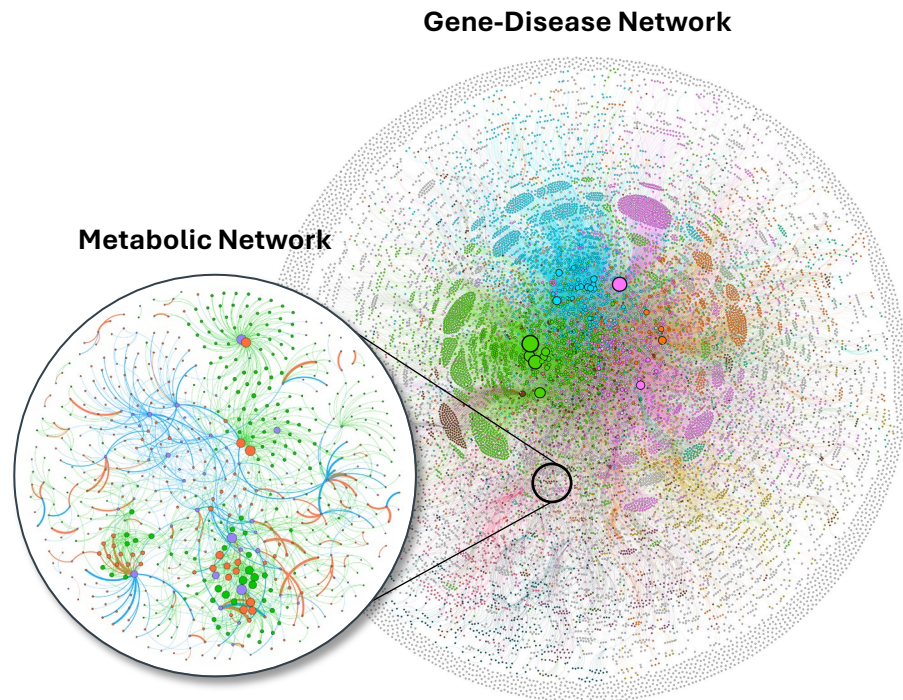
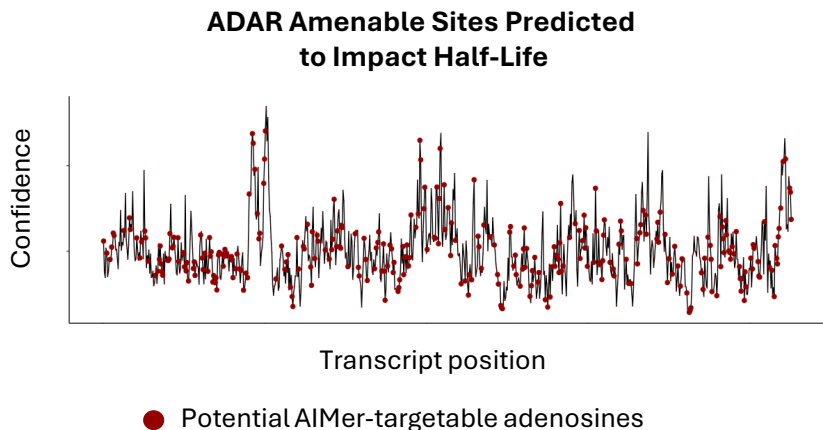
Correlation Between Model Predicted and True Values





# 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”



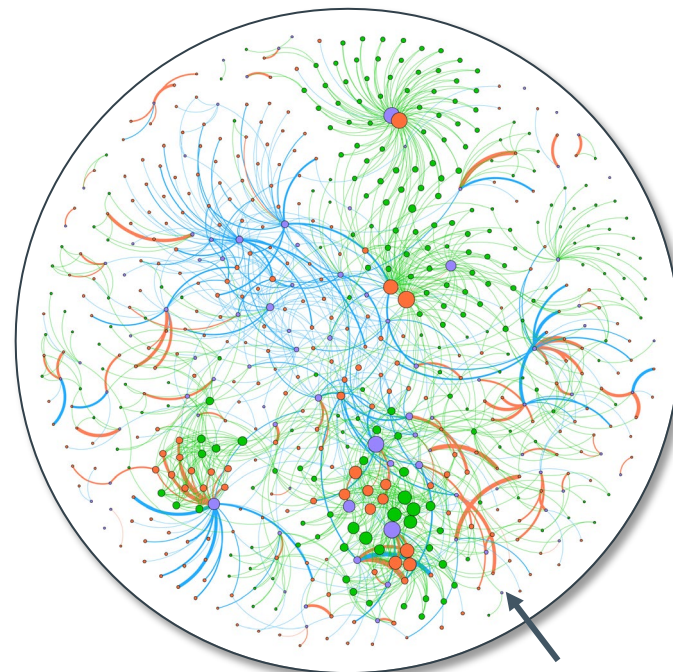


## Edit-verse subnetwork reveals “Target A”: Metabolic syndrome target uniquely suited for AIMER upregulation

### 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

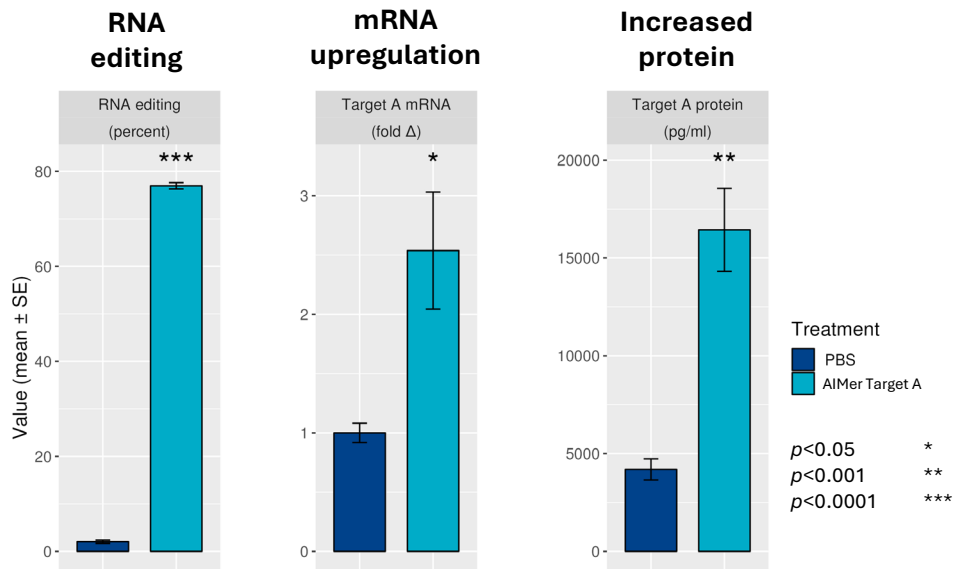


Target A

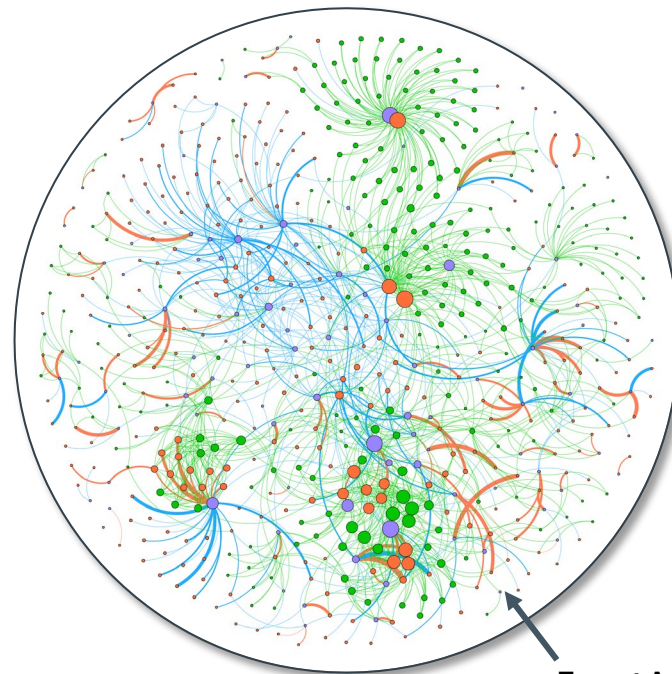


# First preclinical *in vivo* PoC: upregulating endogenous protein to restore healthy metabolic phenotype

>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



Metabolic Network



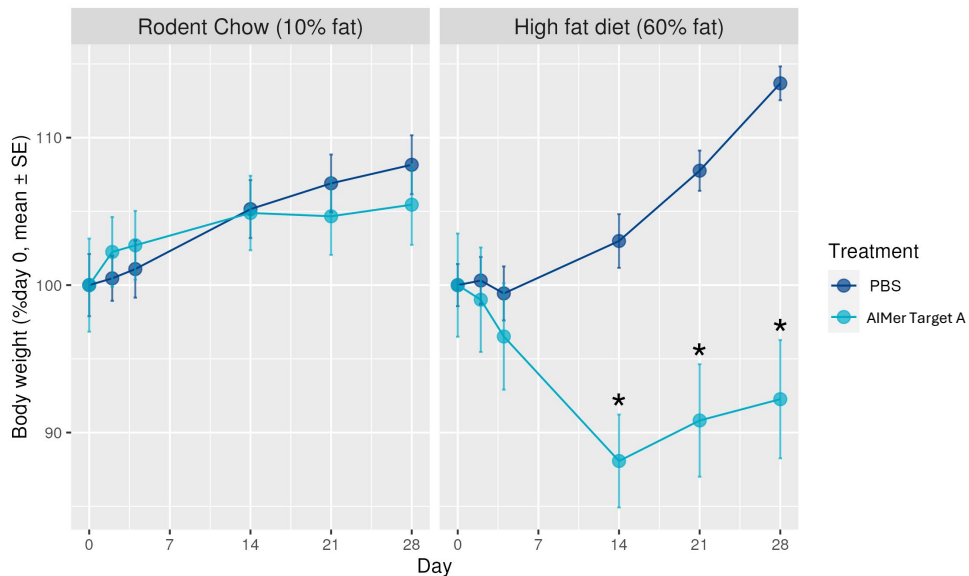
Target A



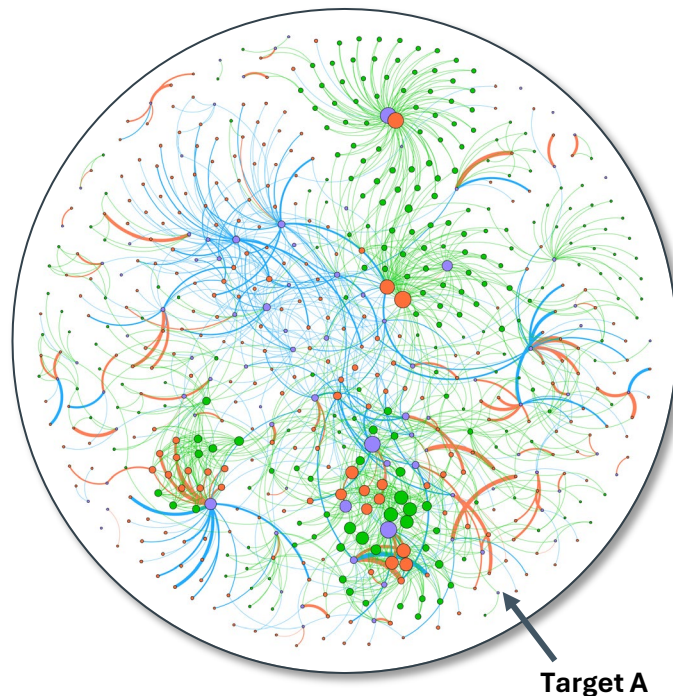
## Substantial upregulation of protein induces weight loss

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

### Significant Weight Loss



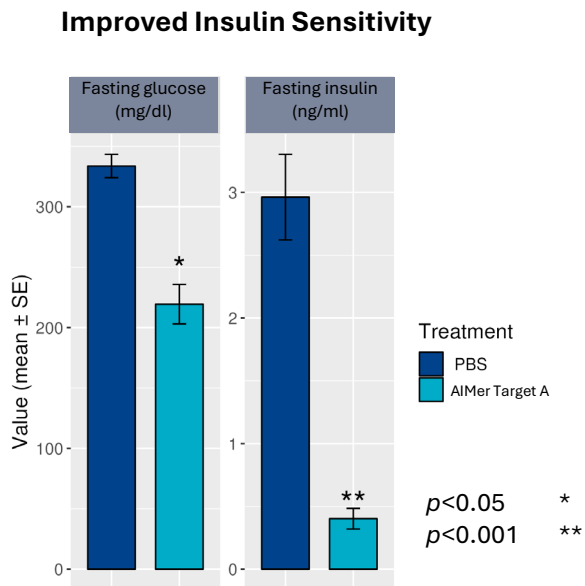
### Metabolic Network



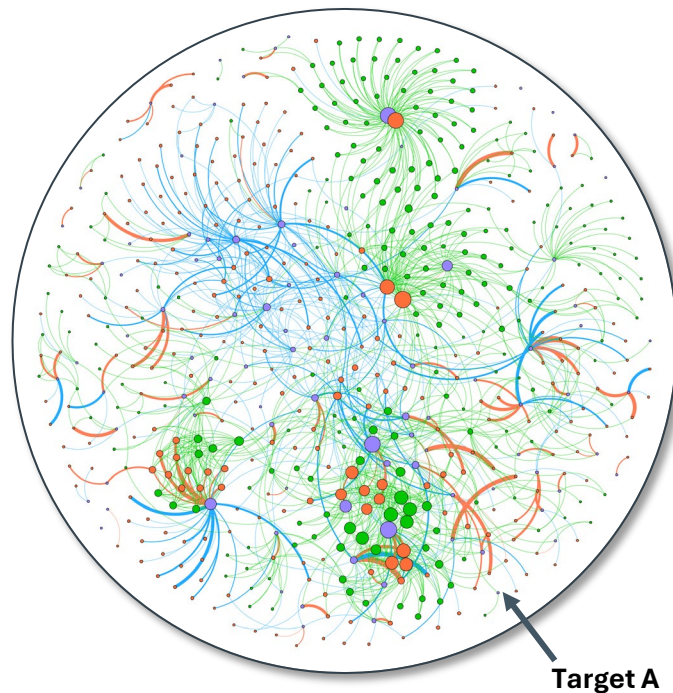


## Upregulation of Target A protein improves insulin sensitivity

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



**Metabolic Network**



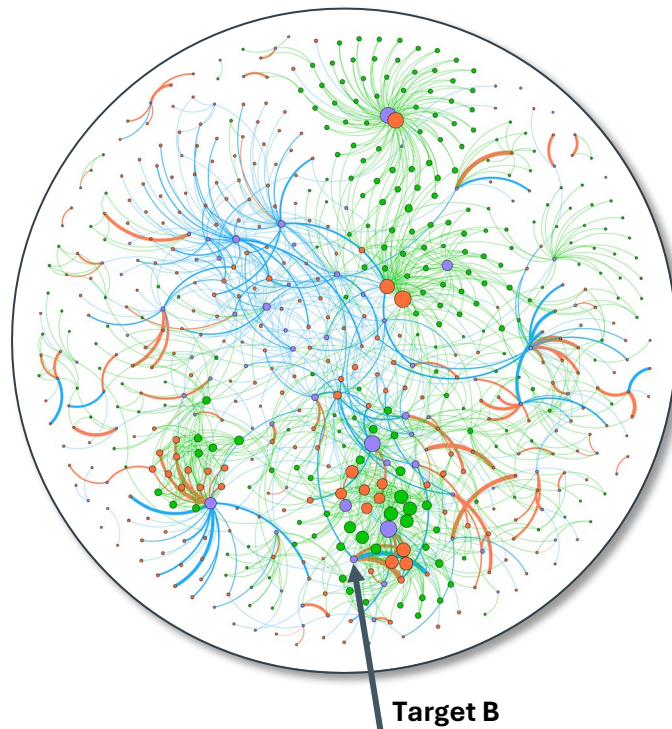


# Target B upregulation offers a first-in-class therapeutic approach for hyperlipidemia

## 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

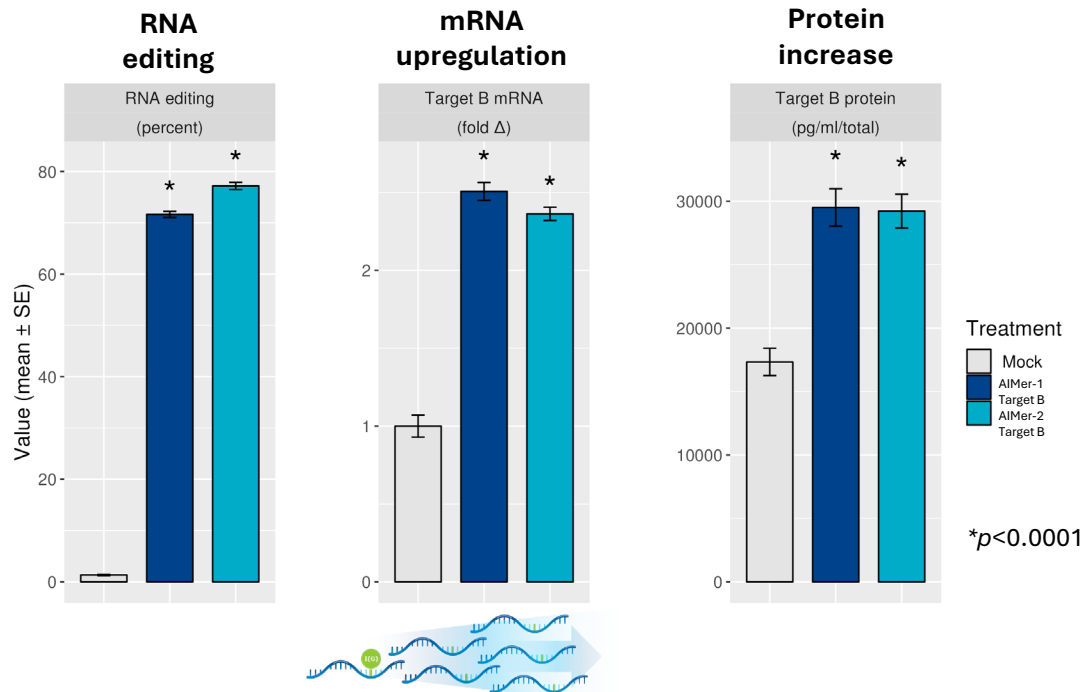




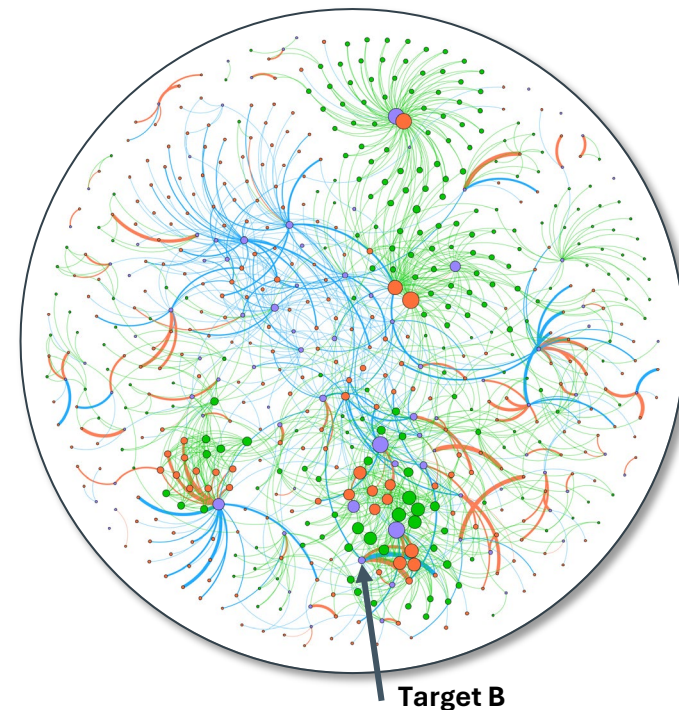


# >70% editing achieves ~2-fold upregulation with corresponding increase in protein

Primary human hepatocytes *in vitro*



## Metabolic Network



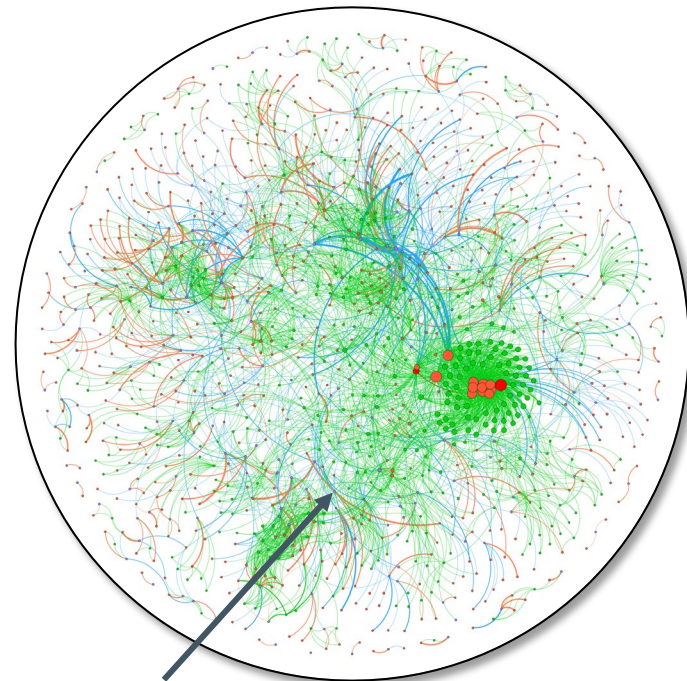


## Upregulation of liver Target X stops decline in kidney function

### 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

### Renal Insufficiency Network



Target X

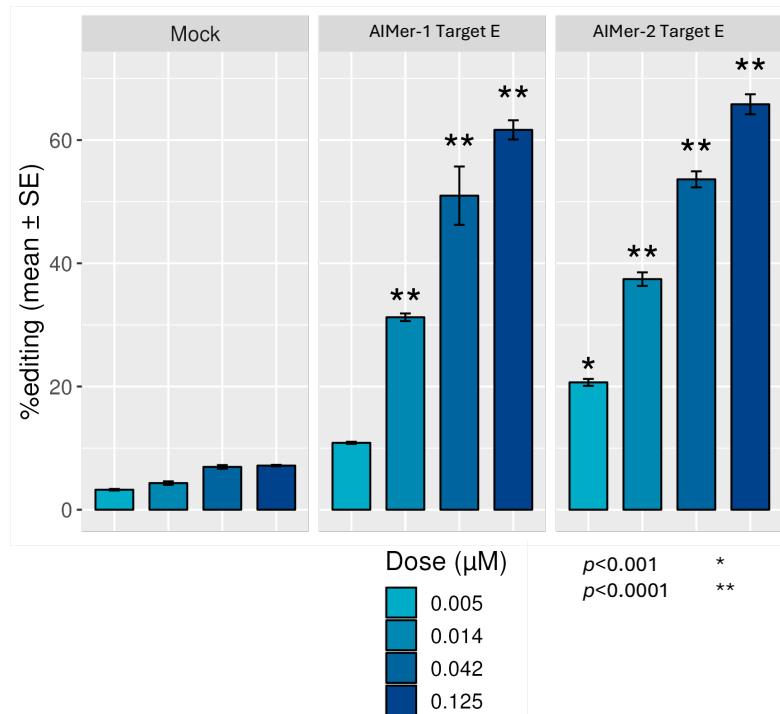


# Building on success of AATD: Target E correction restores normal metabolism in rare genetic disease

## 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





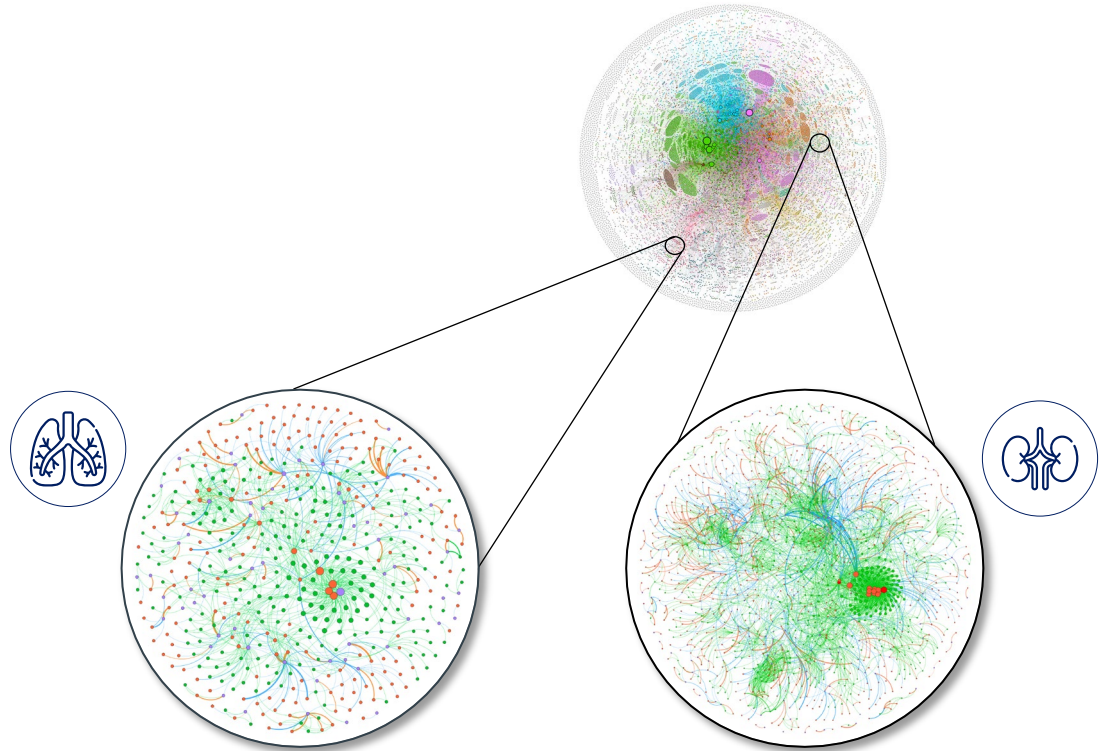
# AIMer targetable diseasesomes in extra-hepatic organs

## Hepatic

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

## Extra-hepatic

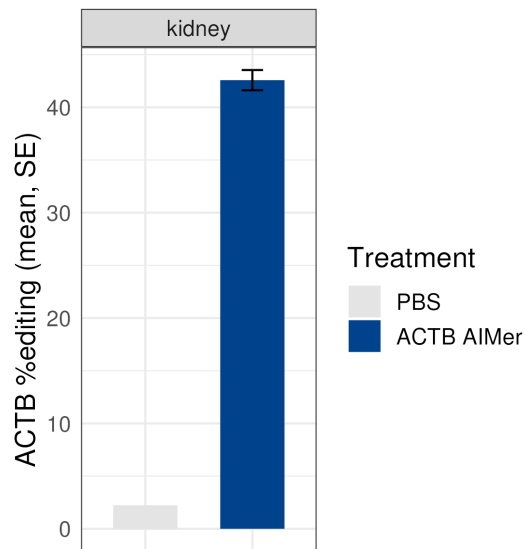
- Target F
- Target G



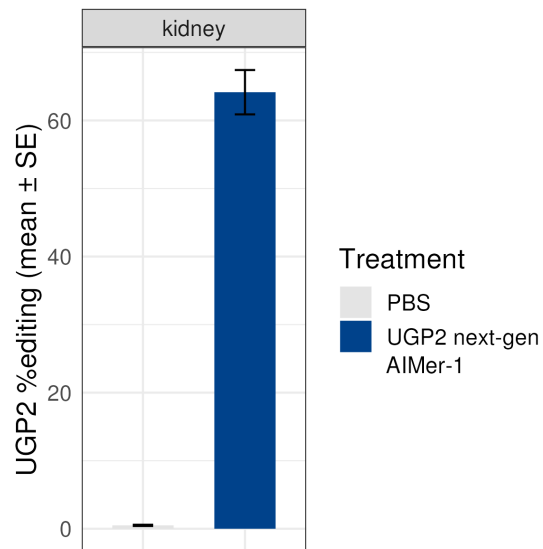
# AIMers deliver to proximal and distal convoluted tubules of kidney and achieve substantial editing



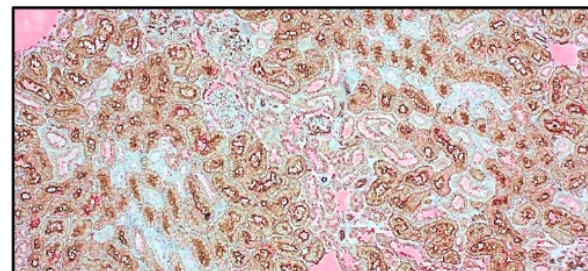
~40% editing of ACTB in NHP  
1-week post-single dose (SC)



~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



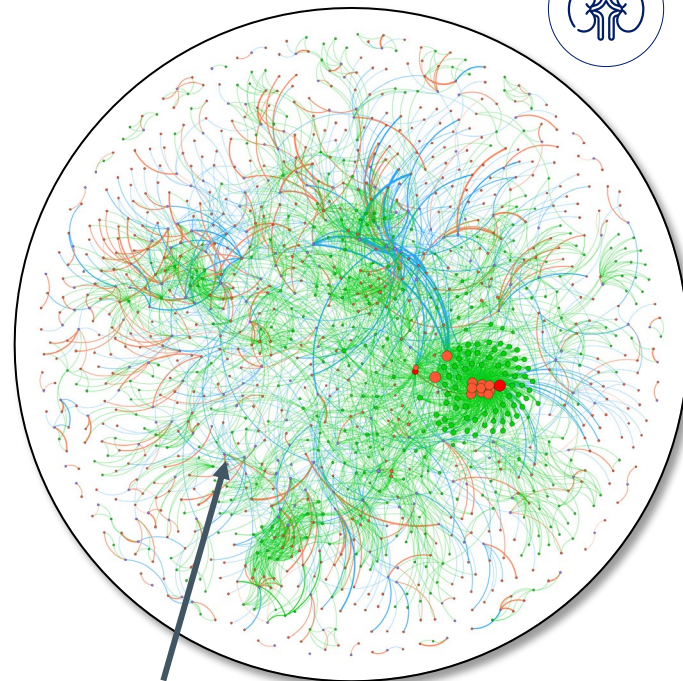


# Upregulation of Target F restores kidney function in a rare genetic kidney disease

## 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

## Renal Insufficiency Network

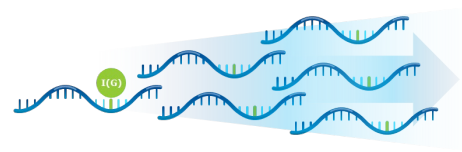
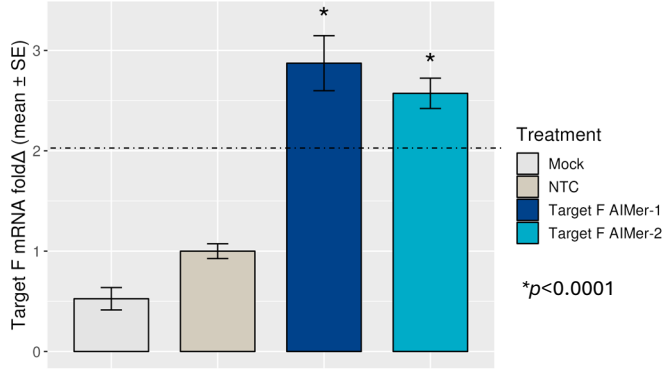


Target F

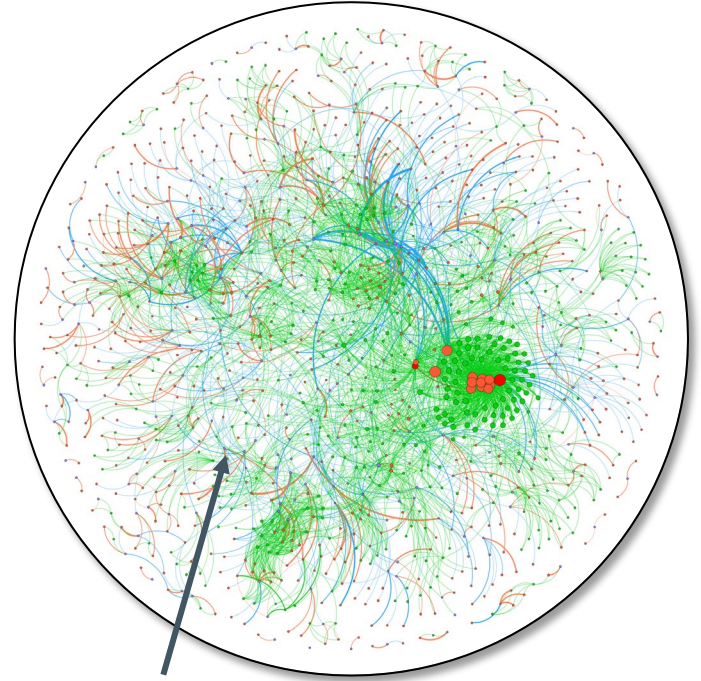


# Achieved >2-fold upregulation of Target F mRNA *in vitro* with RNA editing

Upregulation of Target F mRNA in Human kidney tubular epithelial cells



Renal Insufficiency Network

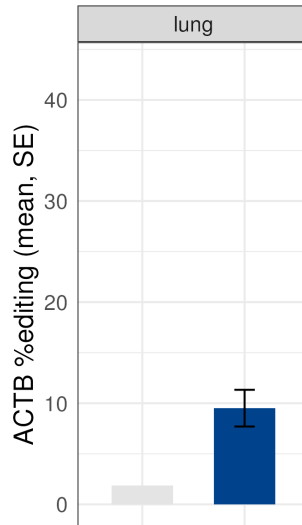


Target F

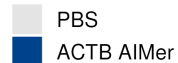


# Proprietary AIMer modifications enhance delivery to lung tissue and achieve significant editing *in vivo*

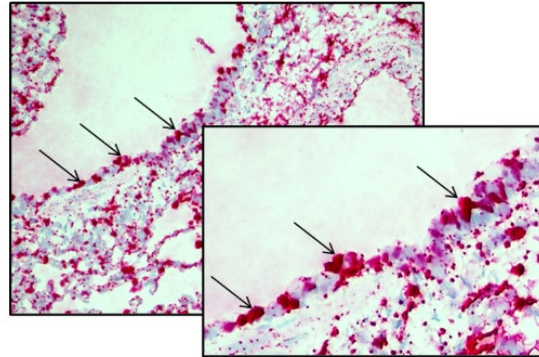
~10% editing of ACTB in NHP 1-week post-single dose (SC)



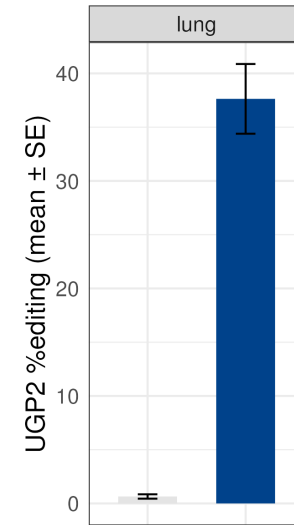
Treatment



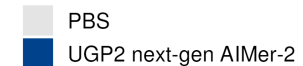
ACTB AIMer (red) delivery to bronchial epithelial cells (arrows)



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



Treatment



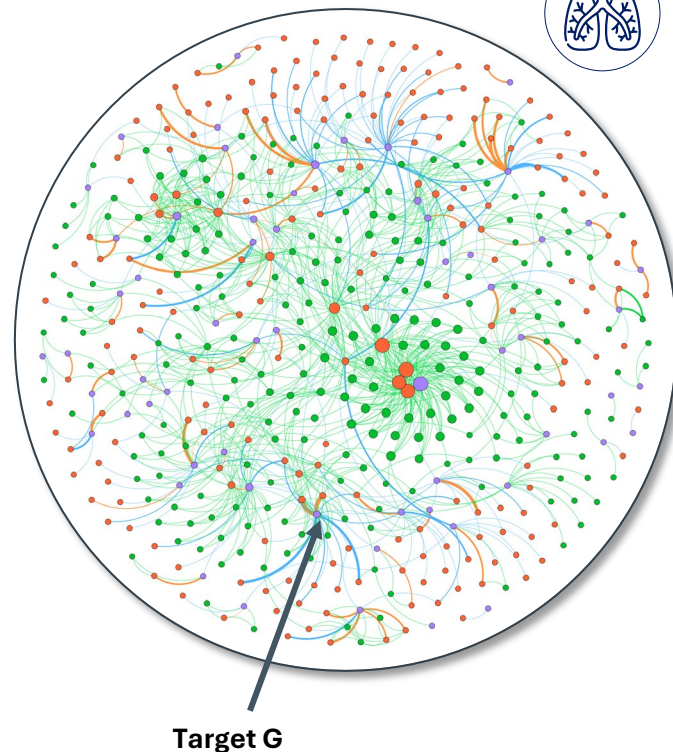
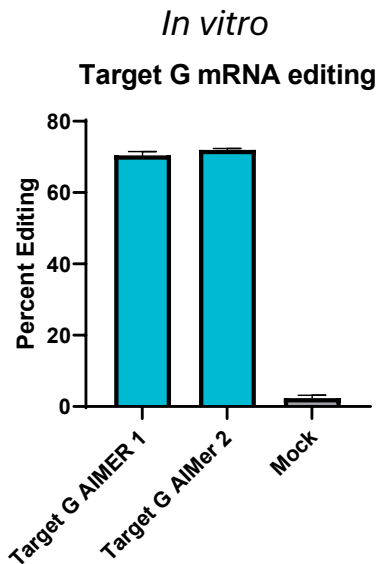


# Correction of Target G mutation restores protein function in patients with a genetic lung disease



## 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



# 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
<b>Approach</b>	Upregulation	Upregulation	Upregulation	Correction	Upregulation	Correction
<b>Tissue</b>	Liver	Liver	Liver	Liver	Kidney	Lung
<b>Therapeutic Area</b>	Metabolic	Metabolic	Renal	Rare	Renal	Rare
<b>Estimated Patients (US and Europe)</b>	~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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