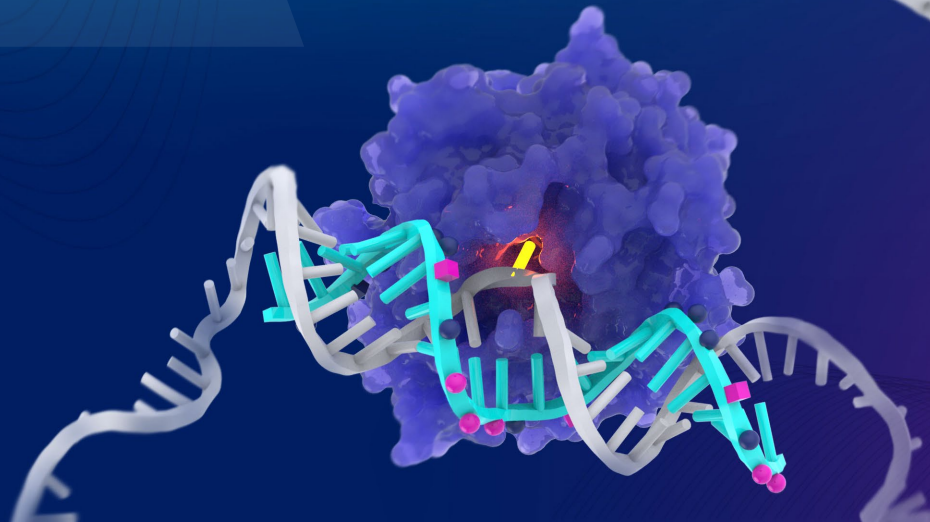
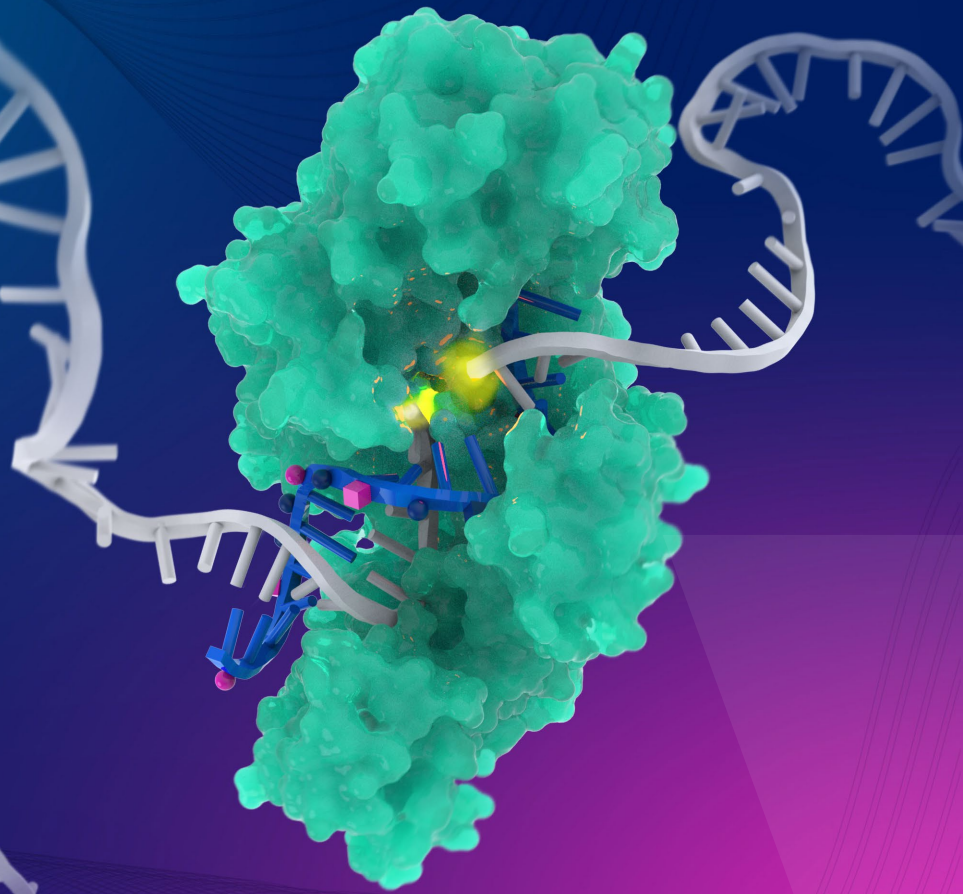
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Research Day 2026





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.

Today's agenda

Presentation	Speaker
Opening remarks	**Paul Bolno, MD, MBA** President and Chief Executive Officer
RNA editing for PNPLA3 liver disease	
From genetic risk to genetic correction: The future of PNPLA3 liver disease	**Arun J. Sanyal, MD, FAASLD** Professor of Medicine, Physiology, and Molecular Pathology at VCU Medical Center
WVE-008: PNPLA3 AIMer for liver disease	**Erik Ingelsson, MD, PhD** Chief Scientific Officer
PRISM® platform innovations	
RNAi (SpiNA design) differentiation and clinical translation	
Unlocking extra-hepatic delivery with PN conjugates	**Chandra Vargeese, PhD** Chief Technology Officer
Bifunctional modalities: Silence, edit or upregulate	
Wrap-up	
Closing remarks	**Paul Bolno, MD, MBA** President and Chief Executive Officer
Q&A	**All**

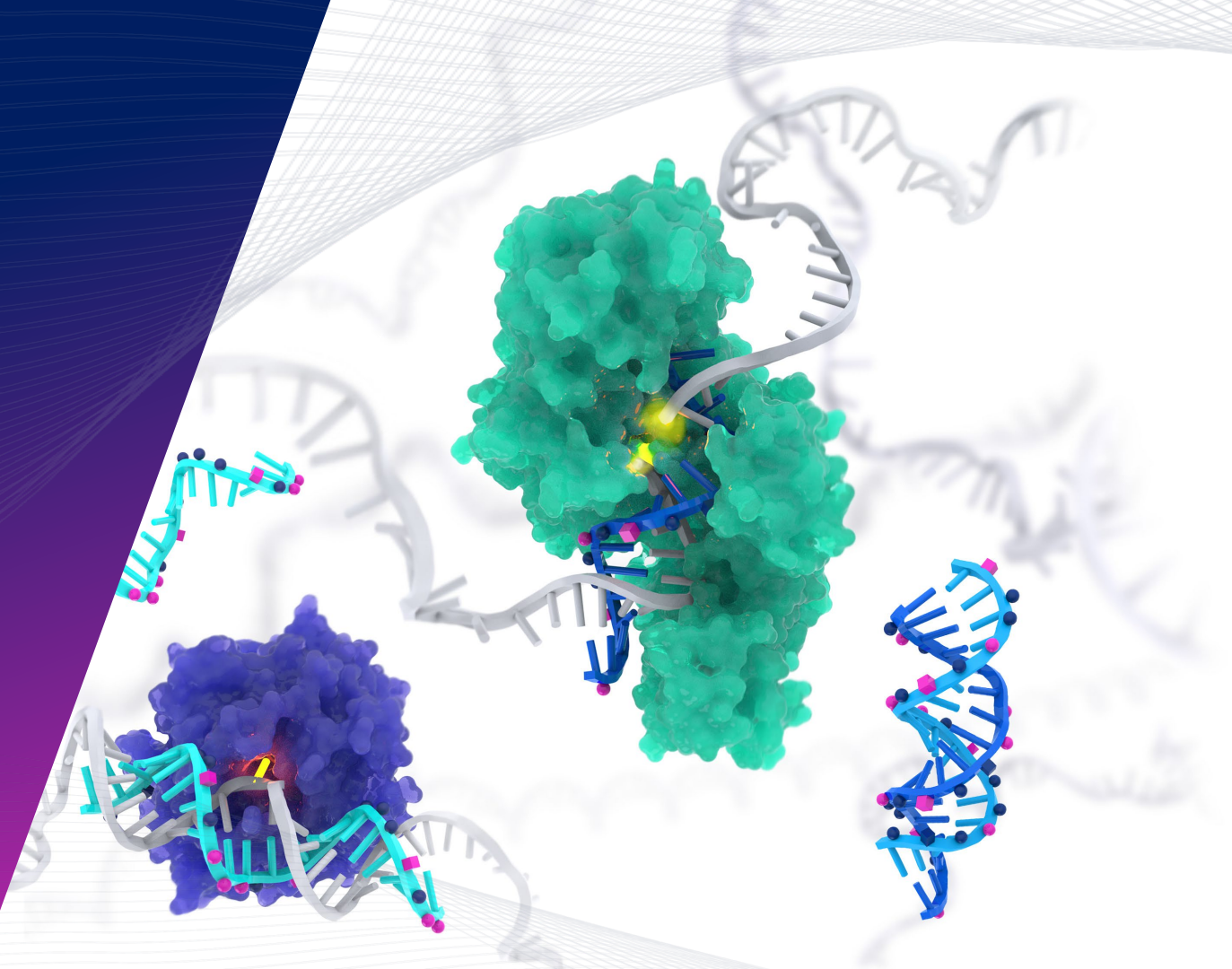
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Opening Remarks

Paul Bolno, MD, MBA

President and CEO





Our Mission

To unlock the broad potential of RNA medicines to transform human health

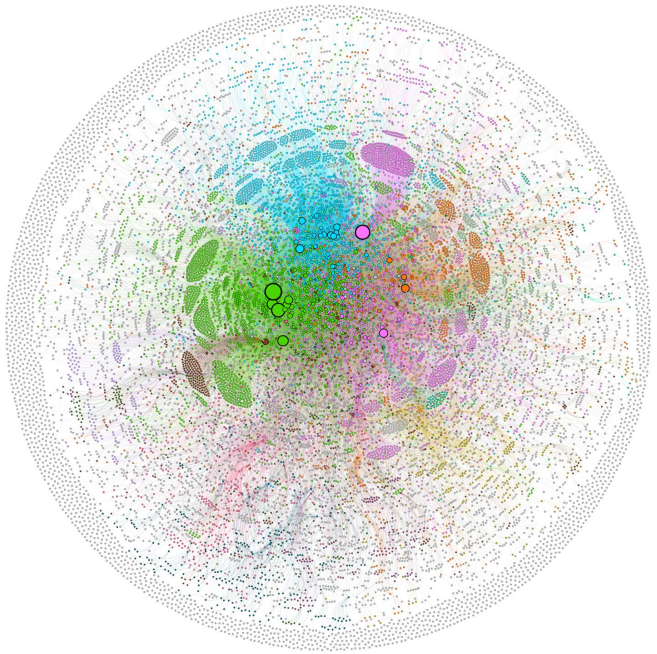


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Unlocking the potential of RNA medicines

- Wave is developing a **toolbox of therapeutic modalities** that target the **transcriptome** to turn on, switch off, modulate the expression of genes, or modulate multiple targets
- We are in the midst of a **revolution in human genetics** bringing a greater understanding of the genetic and molecular drivers of disease
- There are over 6,000 genetically defined diseases, comprised of both **rare diseases** and a rapidly growing number of strong targets for **common diseases**
- An increase in **genetic testing** has enabled identification of individuals likely to benefit from treatment with precision RNA medicines

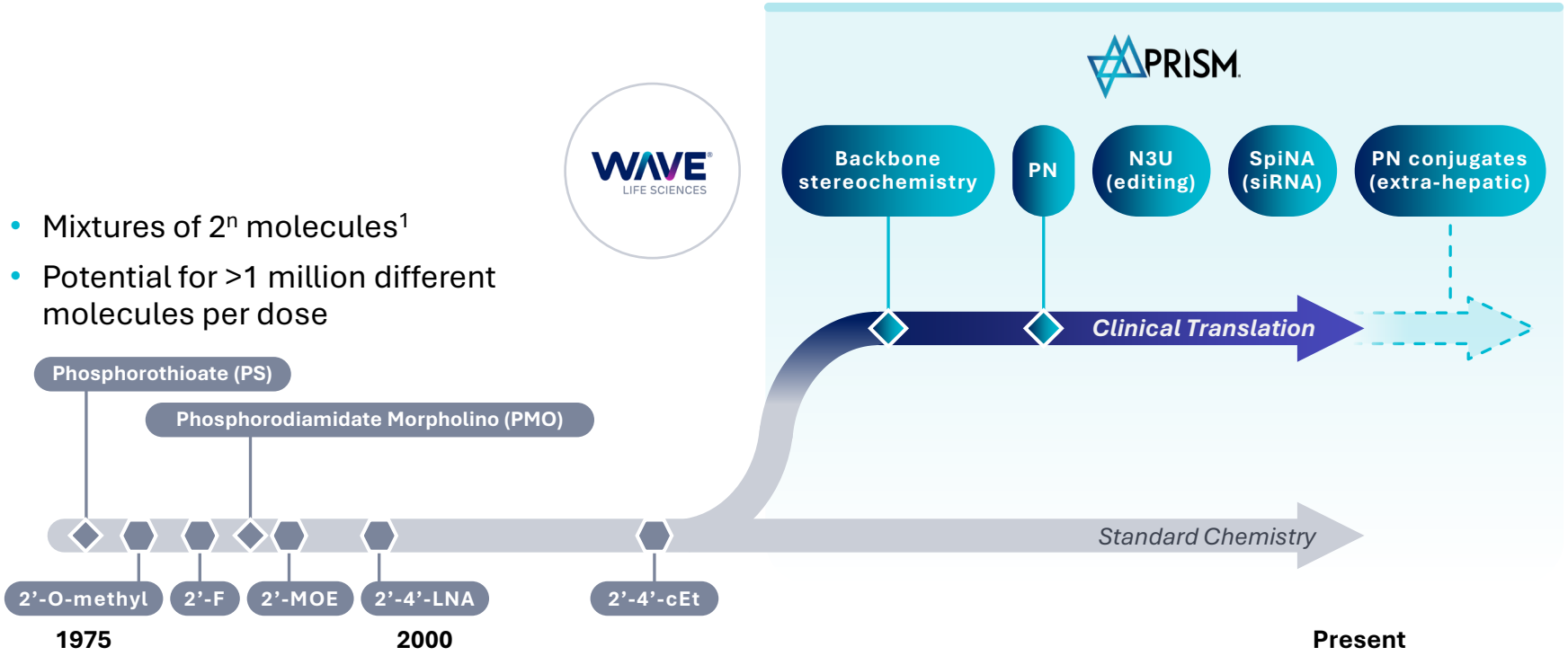
Gene-Disease Network



A network of rare and common diseases and associated phenotypes with strong genetics support (Data source: GWAS Catalog)

PRISM® platform has unlocked novel and proprietary advances in oligonucleotide design that are now translating in the clinic

- Mixtures of 2^n molecules[1]
- Potential for >1 million different molecules per dose



1. n=number of chiral centers

PRISM® platform is continuously improving

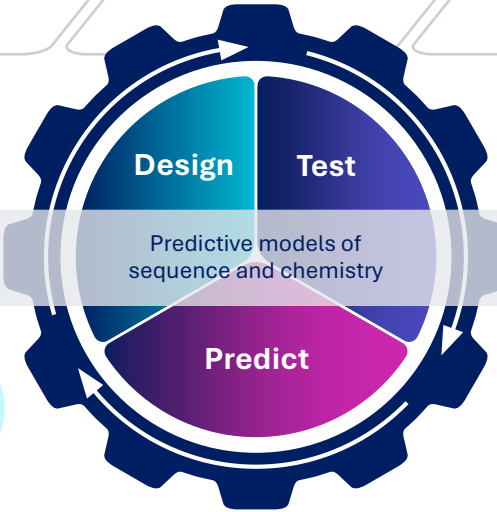
Select targets strongly supported by human genetics

Pair the **modality** that best addresses the target

Design & optimize with PRISM chemistry:

Advance clinical candidates **rapidly** and **reproducibly**

Scalable, cost-effective manufacturing



AI/ML across the workflow…

Human genetics (UK Biobank, FinnGen, All of Us, others)

Analyze target biology, delivery, biomarkers, and feasibility

Predictive models of sequence and chemistry

Cross-program modeling of design principles

Synthesis models predict and design more efficiently

Model-guided design

Models score millions of candidate chemistries to prioritize those for synthesis

Learning across programs

Standard backbones build shared training data across programs

Design principles refined program after program, applied across the pipeline

What you will hear today:

RNA editing

Arun J. Sanyal, MD, FAASLD
PNPLA3 liver disease and opportunity for RNA editing

WVE-008 (GalNAc-AIMer)
PNPLA3 RNA editing program advancing towards clinic

PRISM® platform innovations

siRNA
SpiNA design: innovations are translating in clinic

PN conjugates
Beyond GalNAc: Unlocking extra-hepatic delivery to multiple tissues

Bifunctional modalities
Silence, edit, upregulate two unique targets

Guest speaker: Arun J. Sanyal, MD, FAASLD

Professor of Medicine, Physiology, and Molecular Pathology in the Division of Gastroenterology at Virginia Commonwealth University (VCU) Medical Center



Professor of Medicine, Physiology, and Molecular Pathology in the Division of Gastroenterology at VCU

Director of the Stravitz-Sanyal Institute for Liver Disease and Metabolic Health

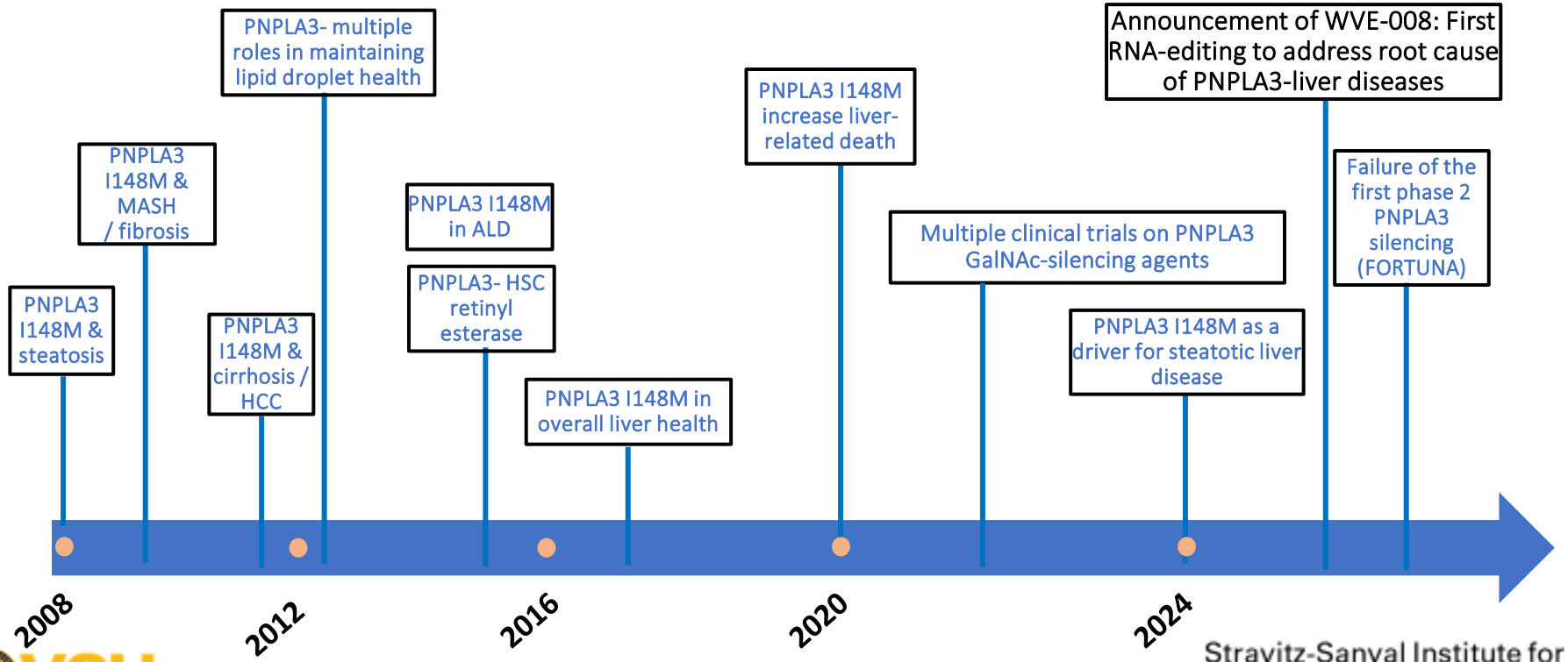
- Arun J. Sanyal, MD, is ranked in the top 0.1% of all biomedical scientists by Stanford University rankings.
- Dr. Sanyal serves as Chairman of the NIH NASH Clinical Research Network, the NIMBLE and MASH track projects of FNIH, and the Liver Forum for NASH and fibrosis.
- He chaired the hepatobiliary pathophysiology study section of the NIH and was a founding member of the Hepatology committee of the American Board of Internal Medicine.
- He has also served as Secretary as well as President of the American Association for the Study of Liver Diseases.
- Dr. Sanyal has authored more than 500 articles in the highest tier journals such as the New England Journal of Medicine, Lancet, and Nature Medicine. He has an H-index of 163 and his work was cited almost 18,000 times in previous year alone.
- He has pioneered the development of diagnostics and therapeutics for end stage liver disease and fatty liver disease and currently leads multiple global trials for this condition.
- He is the recipient of the American Liver Foundation (ALF) 2026 National Legacy Gala Leadership Award, Distinguished Mentorship Award from the American Gastroenterological Association, and the Distinguished Scientific Achievement Award from the American Liver Foundation in 2017 and the Distinguished Achievement Award from the AASLD in 2018.

From Genetic Risk to Genetic Correction: The Future of PNPLA3 Liver Disease

Arun J. Sanyal M.D.

Z Reno Vlahcevic Professor of Medicine
Director, Stravitz-Sanyal Institute for Liver Disease and Metabolic Health
Virginia Commonwealth University School of Medicine

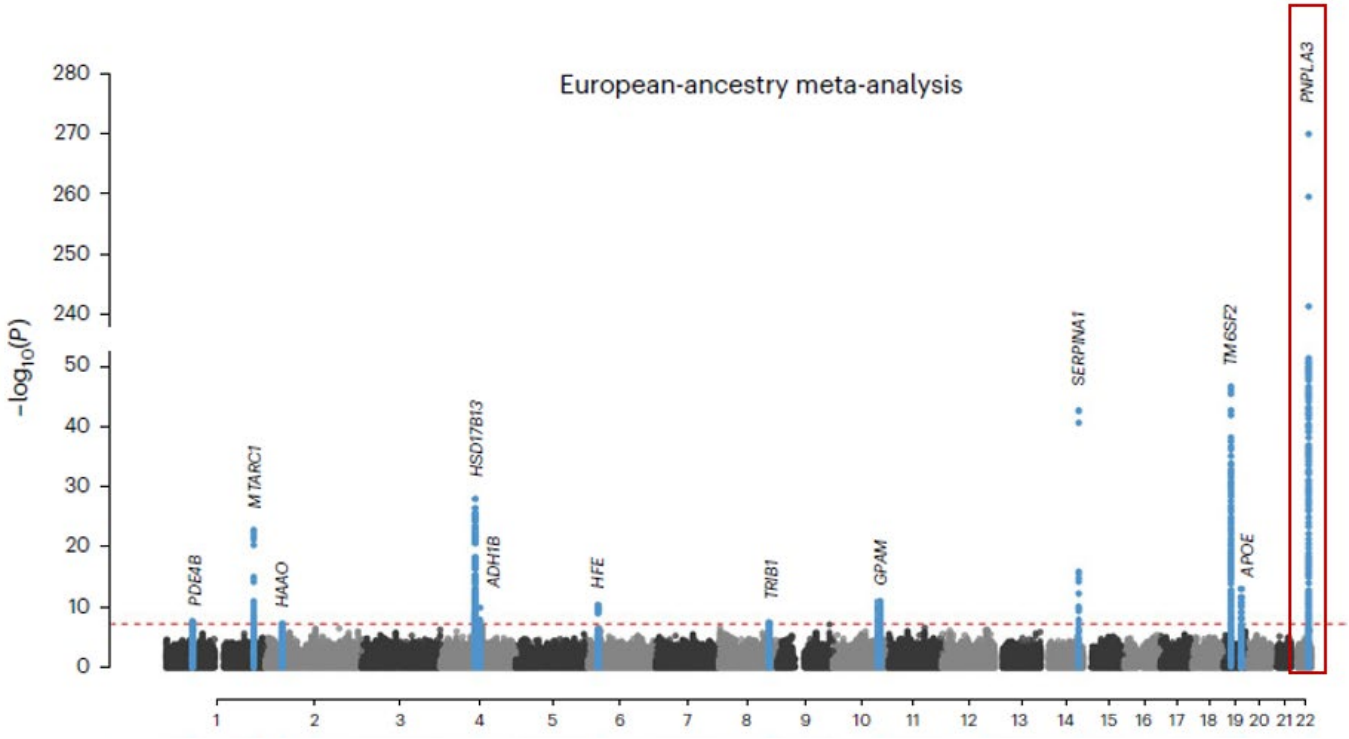
Discovery of PNPLA3 I148M (rs738409) association with liver disease transformed hepatology through human genetics



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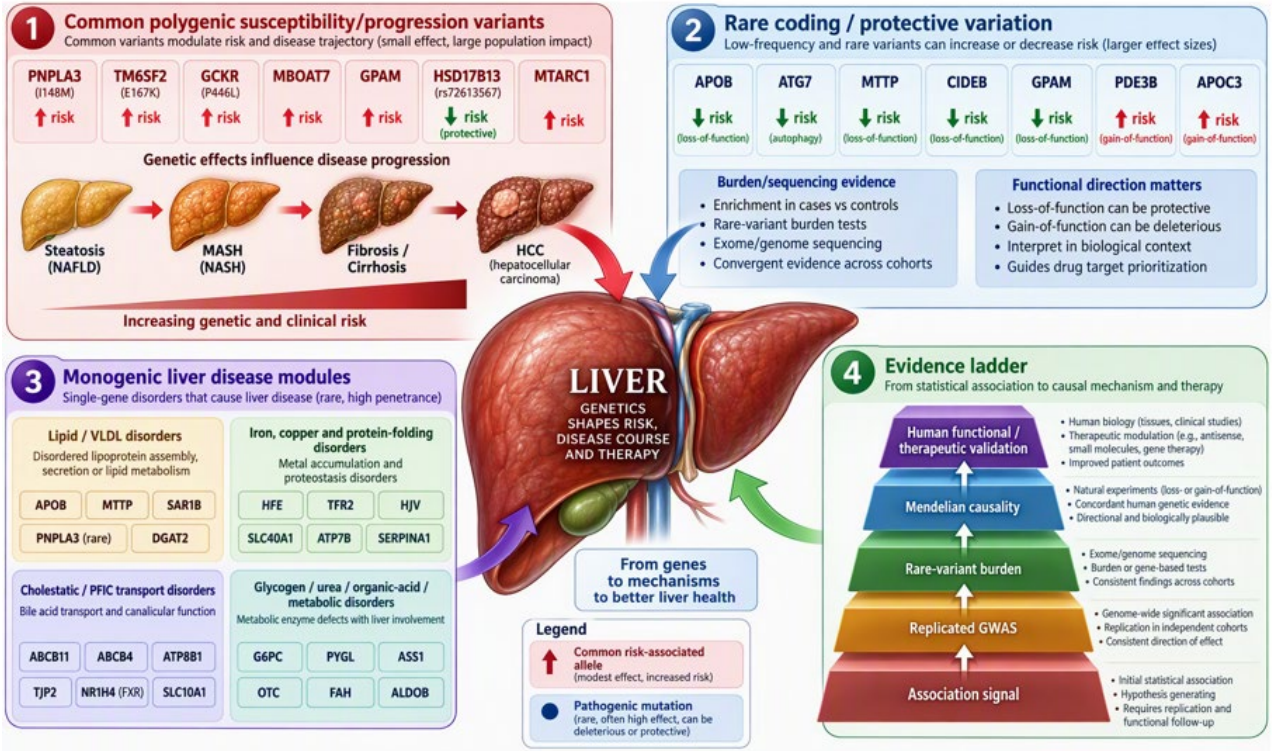
Stravitz-Sanyal Institute for Liver Disease and Metabolic Health

PNPLA3 I148M demonstrates strong association with liver cirrhosis (GWAS analyses)



Ghouse, J. et al. Nature Genetics 2024, 56, 827

PNPLA3 I148M is the clearest genotype-defined MASLD/MASH target

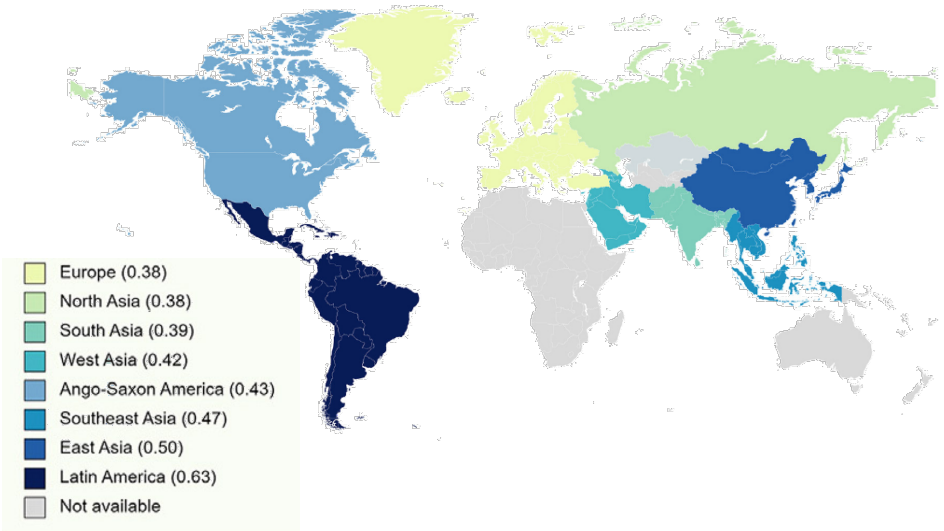


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Global prevalence of PNPLA3 rs738409 variant in MASLD / MASH patients by world region

G-allele Frequency of PNPLA3 I148M among MASLD Patients



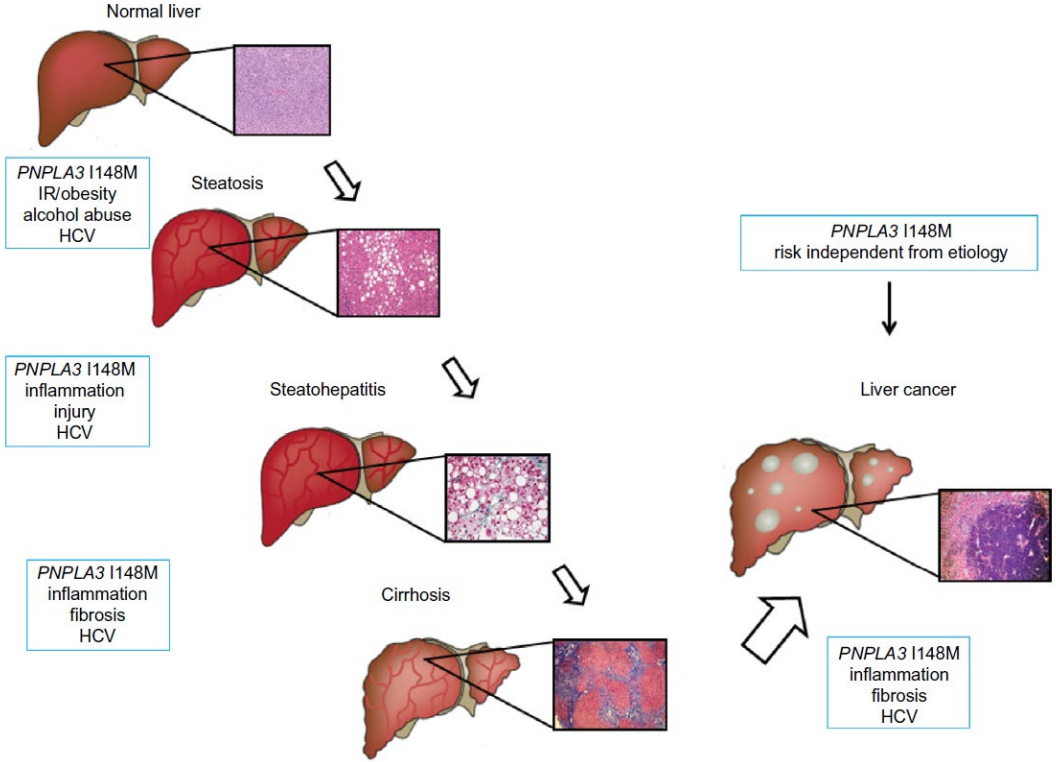
Country / Region	Est Prevalence of MASLD with Homozygous PNPLA3 I148M
United States	18M
Europe (Germany, France, Italy, Spain, UK)	12M
China	75M
Japan	10M
Mexico	15M

Souza, M., et al. Journal of Clinical and Experimental Hepatology 2025, 15, 102495
Younossi, Z., et al. Hepatology 2023, 77, 1335

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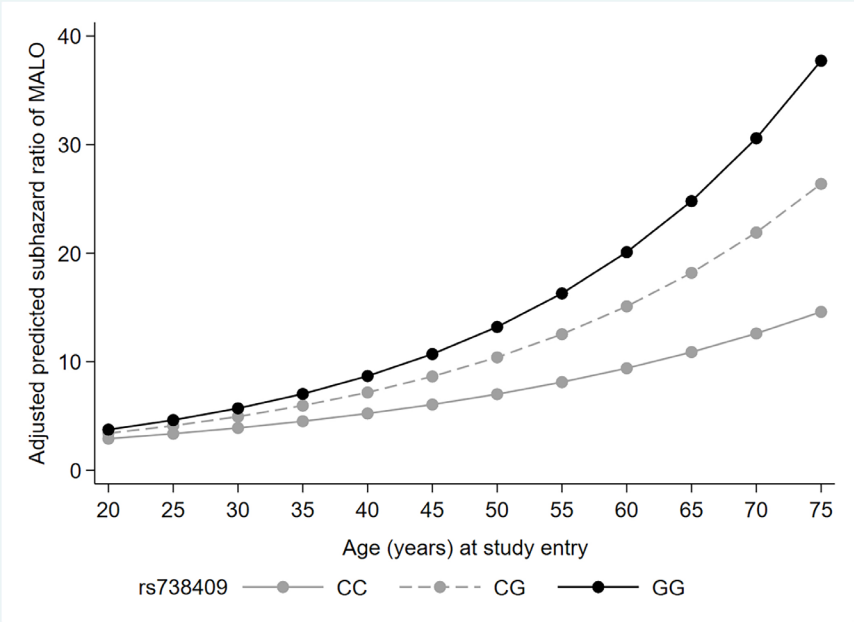
PNPLA3 I148M is the strongest genetic risk factor for fibrosis and HCC



Bruschi, F., et al. Hepatic Medicine: Evidence and Research 2017:9 55–66

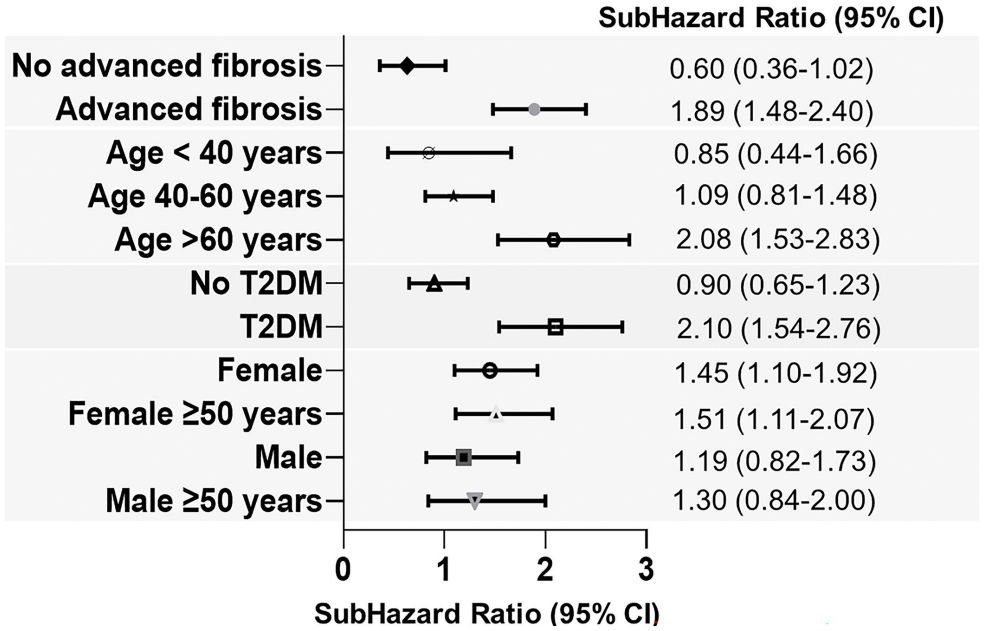
Homozygous PNPLA3 I148M leads to faster MASLD disease progression and worse outcome

Effect of age on the risk of MALO at strata of PNPLA3 genotypes



Chalasani et al, 2024

Effect of PNPLA3 G-allele on risk of MALO at strata of exposures



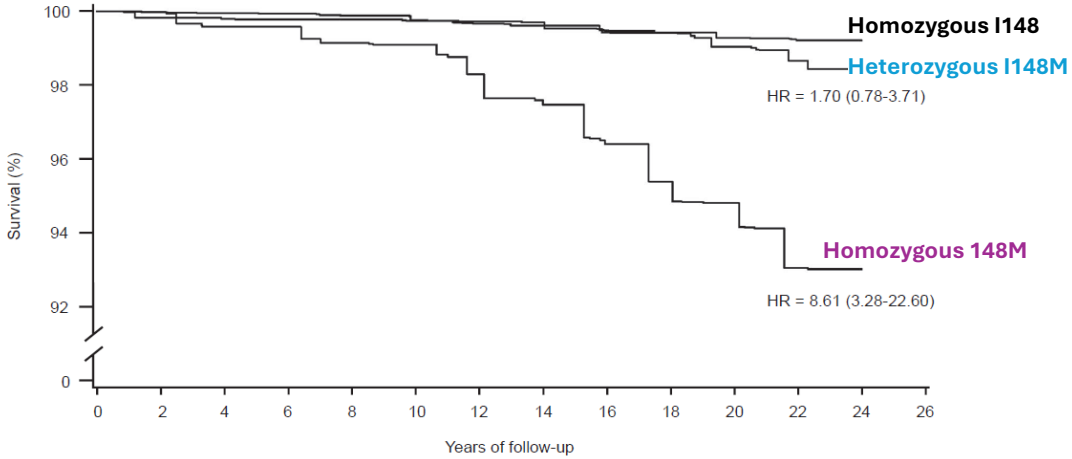
Vilar Gomez et al, 2025

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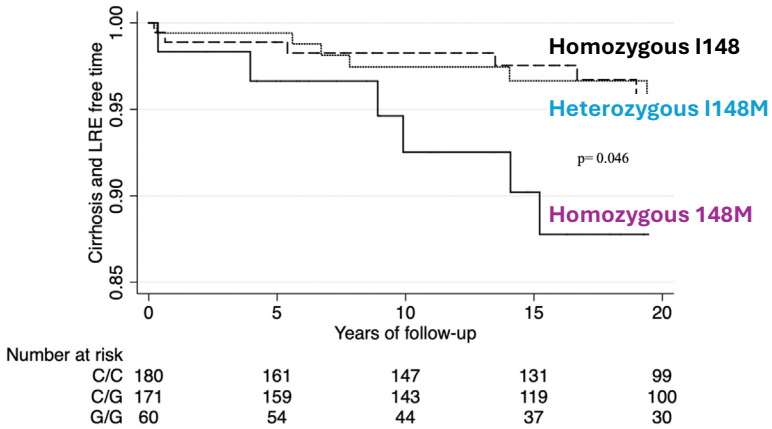
PNPLA3 I148M is associated with poorer prognosis

Multivariate-adjusted cumulative liver disease mortality by *PNPLA3* I148M genotype



NHANES data: Unalp-Arida, et al. Hepatology 2020

Cirrhosis-free survival time in NAFLD patients without advanced fibrosis



Swedish cohort study: Ekstedt, et al. Liver Intl 2022

- *PNPLA3* GG is associated with decompensation or composite end point, after adjusting for age, gender, diabetes, and BMI (aOR 1.64, 95% CI 1.19-2.25) in the IU cohort of ~ 800 NAFLD patients prospectively followed
- NASH CRN analyses are ongoing

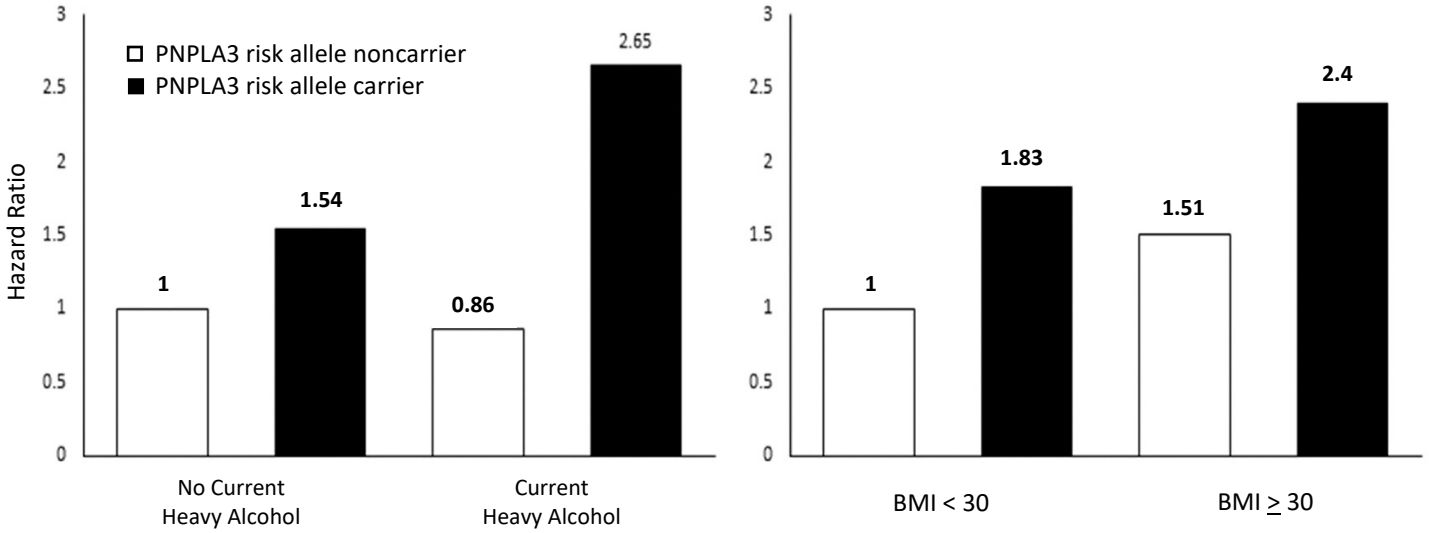
Thrift, A. et al. Clin Gastroenterol Hepatol. 2024 22(9): 1858

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Effect of PNPLA3 I148M is amplified with obesity and alcohol use

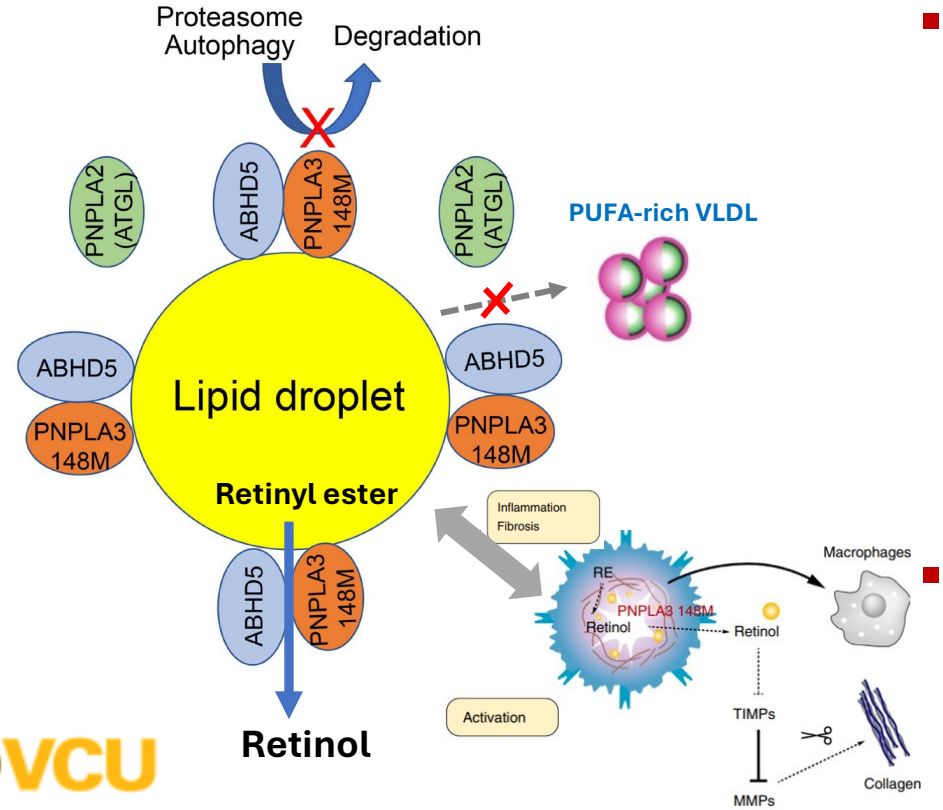
Cirrhosis patients with both genetic risk (*PNPLA3*) and heavy alcohol or obesity are at highest risk for HCC



Thrift, A. et al. Clin Gastroenterol Hepatol. 2024 22(9): 1858

Stravitz-Sanyal Institute for Liver Disease and Metabolic Health

How PNPLA3 I148M mutation worsens fibrosis and exacerbates MASH progression



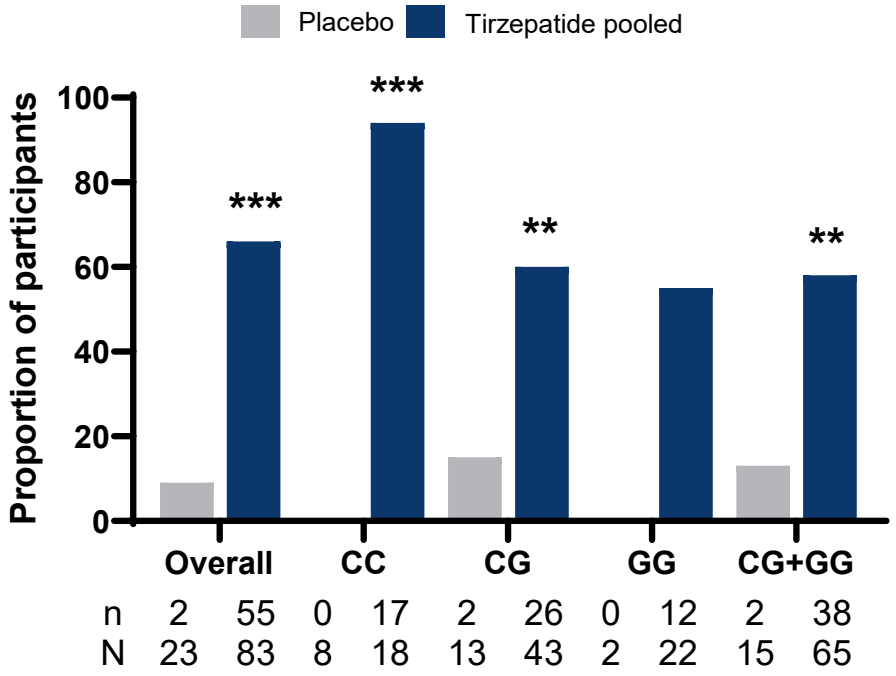
- **Issues with I148M mutation:**
  - ✓ Disrupts lipid-droplet remodeling in hepatocytes, retains triglycerides and promotes **steatosis & inflammation**
  - ✓ Impairs retinyl ester hydrolysis in hepatic stellate cells and accelerates **fibrosis**
  - ✓ Attenuates proteosome autophagy and further exacerbates **MASH progression**

- **PNPLA3 biology supports RNA editing over silencing approach**

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Liver Disease and Metabolic Health

MASH resolution with Tirzepatide was weaker in G-allele (mutant) carriers than in CC (wild-type) carriers



- Significantly more participants achieved MASH resolution without worsening of fibrosis with tirzepatide vs. placebo in the overall population, CC, CG and CG+GG combined
- The placebo-corrected treatment effect of tirzepatide was significantly higher with CC vs CG+GG combined (p=0.033)†

†Interaction between the treatment effect of tirzepatide and genotype (CC versus CG + GG); p = 0.033

Sanyal et al. (2024) TLM24

*p<0.05; **p<0.01; ***p<0.001 for comparison vs. placebo.
N=total number with measure; n=participants achieving the endpoint.

Why is mutation correction through RNA editing an optimal solution for PNPLA3 I148M liver disease ?

- PNPLA3 interacts with regulatory proteins and enzymes on lipid droplet to maintain hepatic lipid homeostasis.

→ Mutation correction restores lipid homeostasis, reduces steatosis and prevents liver injury.

- PNPLA3 plays critical roles in control of hepatic retinol homeostasis, inflammation and oxidative stress. In turn, the I148M mutation promotes fibrosis and MASH progression.

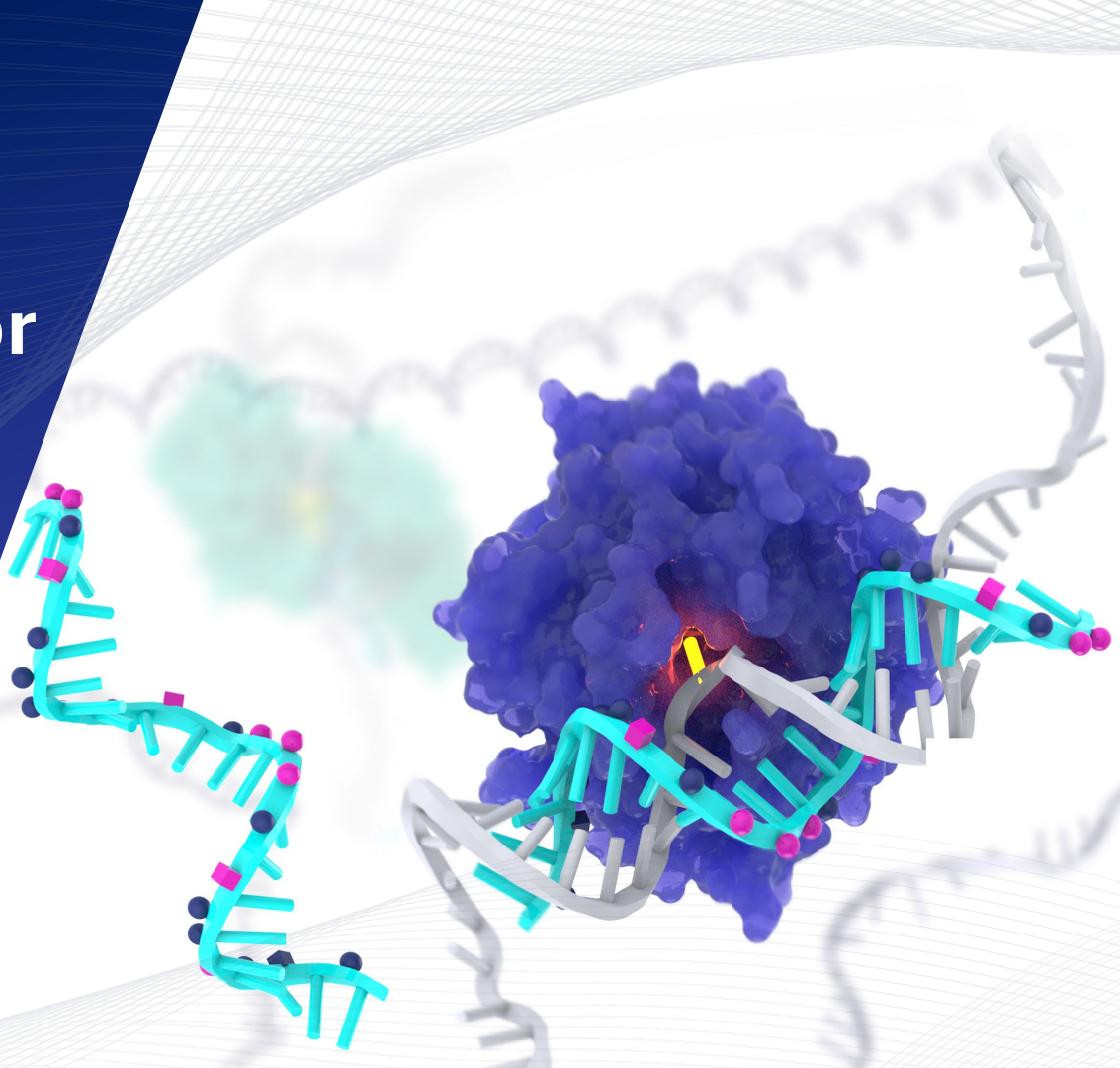
→ Mutation correction attenuates hepatic inflammation and oxidative stress. Consequently, it will lead to lowering of fibrosis and MASH resolution.

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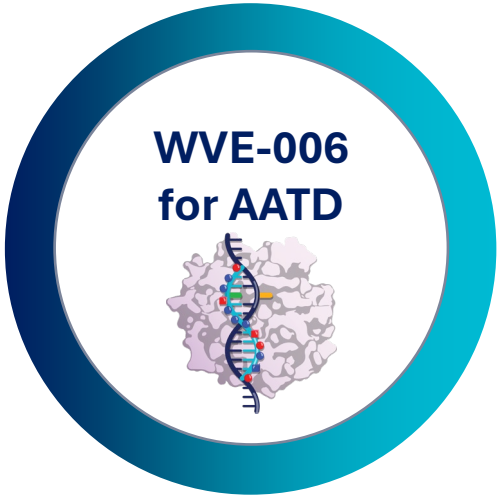
WVE-008: PNPLA3 AIMer for Liver Disease

Erik Ingelsson, MD, PhD
Chief Scientific Officer





Clinical translation of WVE-006 unlocks broad opportunity in RNA editing



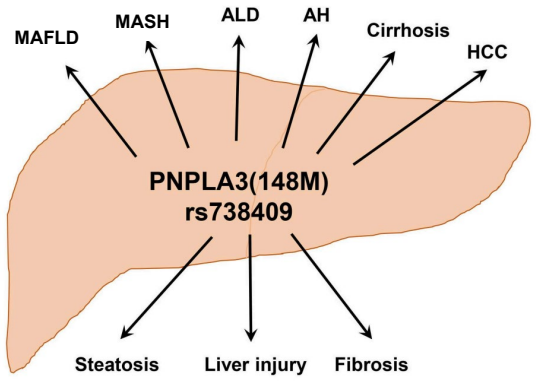
Wave is the leading RNA editing company

- Efficient and consistent editing
- Restore dynamic physiological response
- Durable RNA editing supporting infrequent dosing
- Generally safe and well tolerated

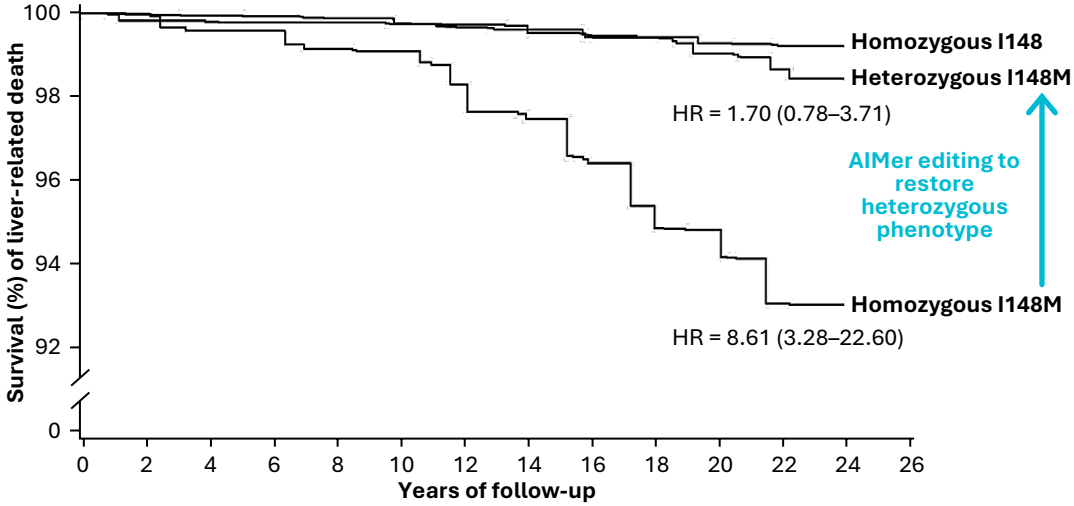
WVE-008 for PNPLA3 I148M liver disease

GalNAc-RNA editing approach uniquely aims to restore PNPLA3 function to fully address genetic liver disease

Homozygous PNPLA3 I148M carriers have significantly higher risk of multiple liver diseases



Heterozygous carriers have 80% lower risk of liver-related death as compared to homozygous carriers



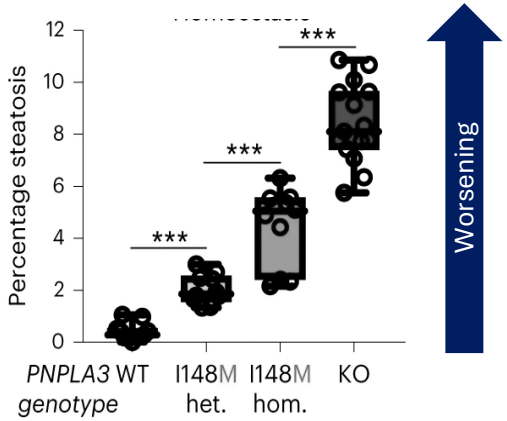
Over nine million homozygous PNPLA3 I148M individuals with genetic liver disease in US and Europe

1. Carlsson, B., et al. 2020 *Aliment Pharmacol Ther.*; 2. Unalp-Arida and Ruhl 2020 *Hepatology*; 3. Dong, XC, 2019 *Front. Med*. 4. Liver International, 2025; 45:e16133

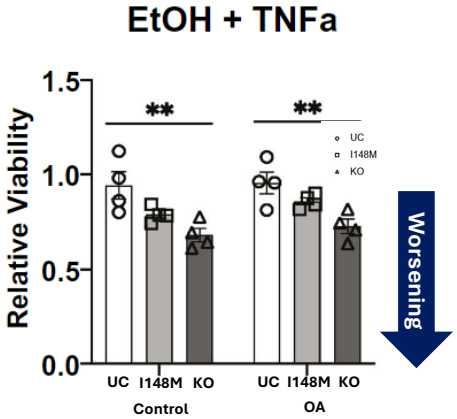
MAFLD, Metabolic dysfunction-associated fatty liver disease; MASH, Metabolic dysfunction-associated steatohepatitis; ALD, alcoholic liver disease; AH, Alcohol-associated hepatitis; HCC, hepatocellular carcinoma

Silencing of PNPLA3 in normal liver may worsen basal physiological functions

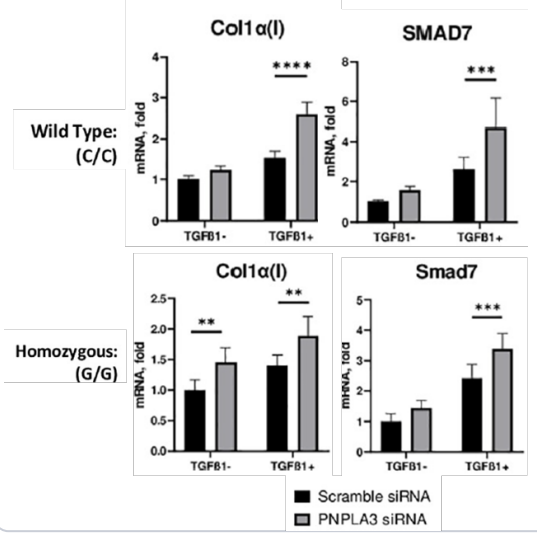
Silencing PNPLA3 worsens steatosis in iPSC-derived human liver organoids[2]



Silencing PNPLA3 increases inflammation-induced liver cell death in human primary hepatocytes[3]



PNPLA3 siRNA exacerbates the fibrotic response in hepatic stellate cells[1]



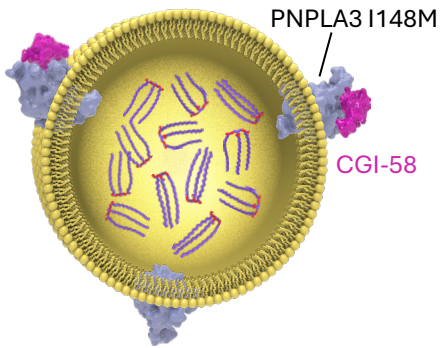
Functional PNPLA3 is imperative for liver health beyond improvements in steatosis

1. Rady, B, et al. 2021 PLoS ONE 2021; 2. Hendriks, D, et al. 2023 Nat Biotechnol; 3. Tilson, SG, et al. 2021 Hepatology

RNA editing is expected to restore PNPLA3 function to treat across the stages of liver diseases

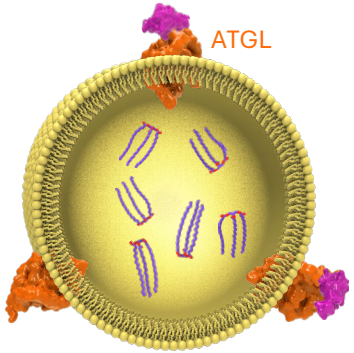
RNA editing approach

PNPLA3 I148M aggravates steatosis and fibrosis through gain-of-function



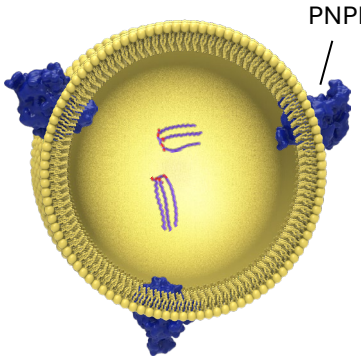
- PNPLA3 I148M accumulates on LDs, sequesters CGI-58, inhibits ATGL's lipase activity and lipid mobilization from ER
- Suppresses retinol metabolism in liver and worsens inflammation and fibrosis
- Promotes liver fat accumulation and fibrosis through activation of stellate cells

Silencing PNPLA3 may only partially address disease



- Creates PNPLA3 loss of function
- ATGL partial rescue for loss PNPLA3
- Silencing will not restore retinol metabolism
- **Fibrosis, ballooning, and inflammation persist**

PNPLA3 correction expected to restore function, counter liver disease



- Restores full PNPLA3 activity
- **Restores lipid mobilization, reverses steatosis, fibrosis, ballooning, and inflammation**

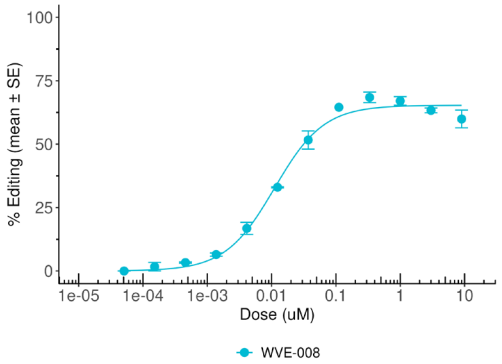
ATGL: adipose triglyceride lipase; CGI-58: co-factor for ATGL; ER endoplasmic reticulum; LDs: lipid droplets; CGI-58 also called ABHD5

Liver International, 2025; 45:e16117; Human Molecular Genetics, (2014) 23(15): 4077–4085

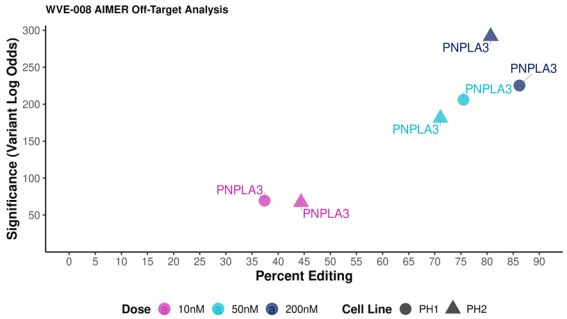
WVE-008: Potential first-in-class, disease modifying therapy for treatment of PNPLA3 I148M-driven liver disease

- Proprietary chemistry
- Subcutaneous delivery (GalNAc)
- Potential for infrequent dosing
- Highly specific editing

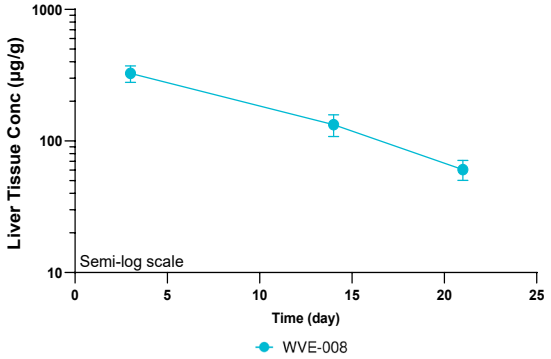
Potent editing with WVE-008



Highly specific editing with WVE-008



Tissue exposure supports excellent delivery

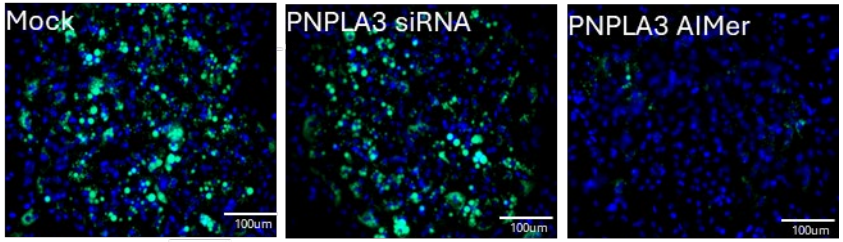


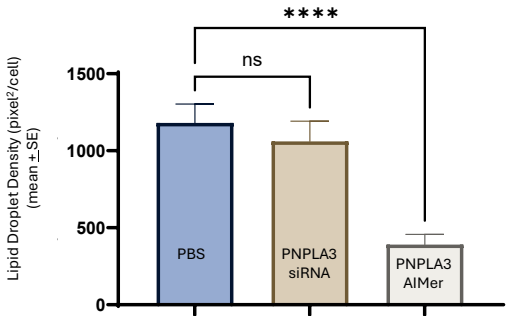
WVE-008 builds on the clinical translation of Wave's RNA editing capability

Left: 4-parameter log-logistic dose response curve; Middle: Analysis utilized RNA-sequencing with two separate primary human hepatocyte cell lines (PH1/2). Variant calling utilized GATK best practices for RNA variant calling using Mutect2 and display A->G evidence found when filtering for variants found in both cell lines and all doses.

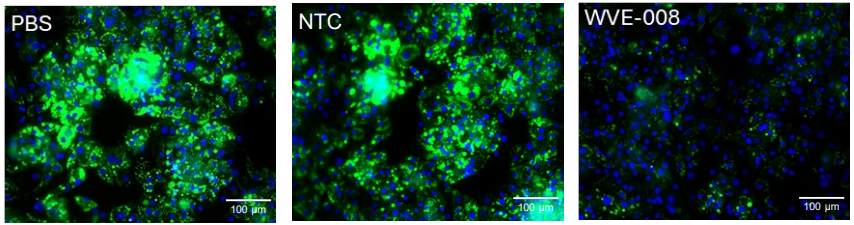
PNPLA3 AIMers achieve efficient editing of PNPLA3, leading to reduction of fat accumulation in hepatocytes

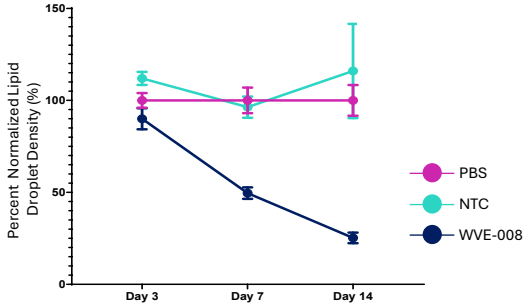
Significant decrease in liver fat with PNPLA3 editing in human HEPATOPAC® model with homozygous I148M





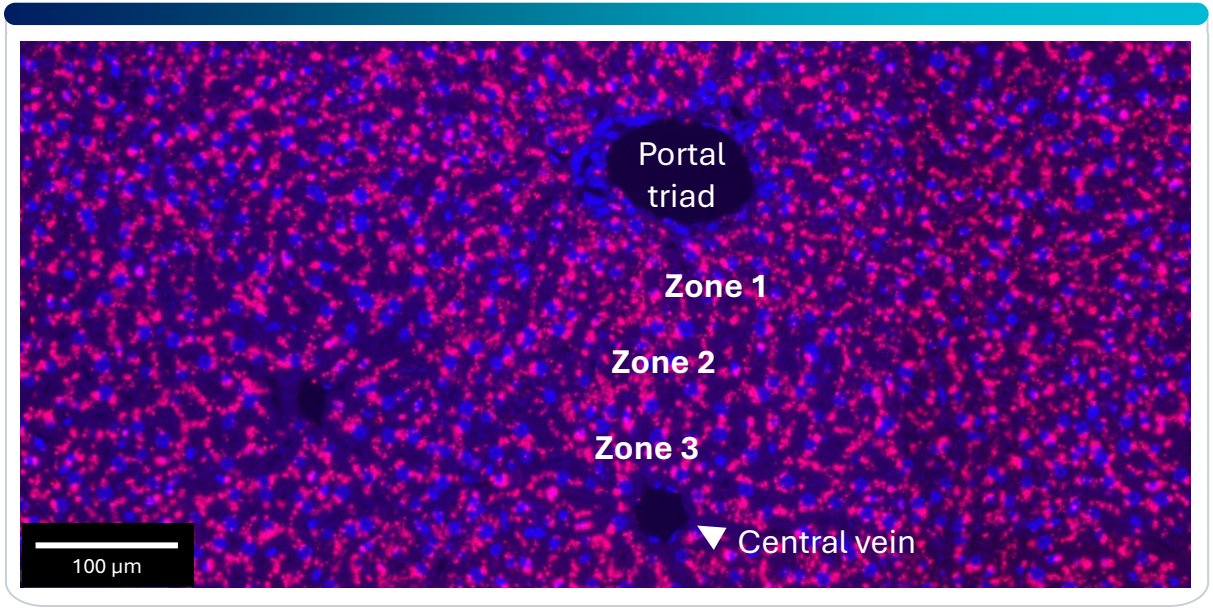
Decrease in liver fat with WVE-008 in monolayer model





One-way ANOVA with Dunnett post hoc test comparisons to Mock **** P< 0.0001

PNPLA3 AIMers distribute evenly across all three zones of liver



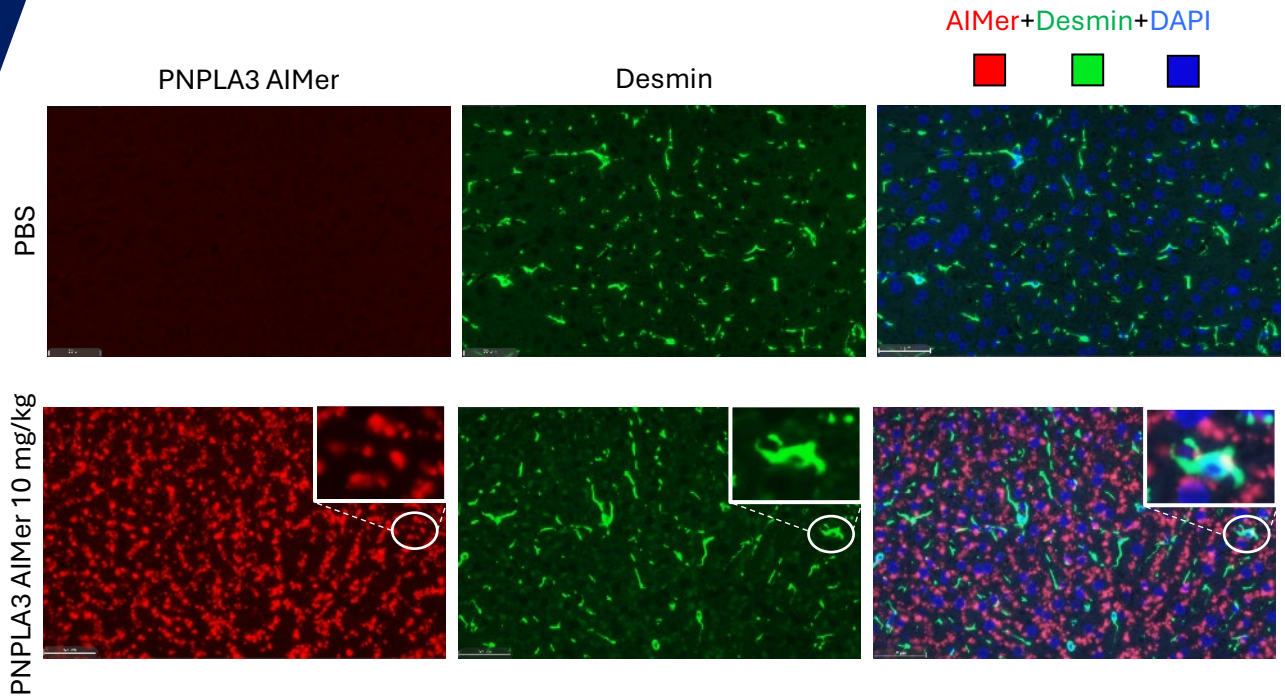
Zone 1:
Periportal hepatocytes

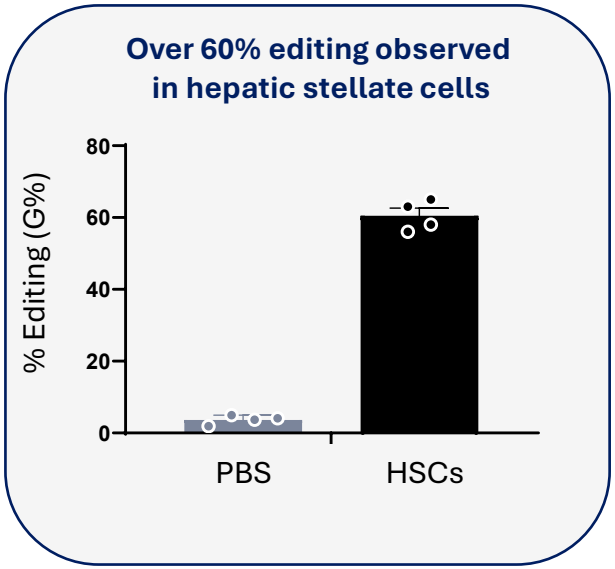
Zone 2:
Intermediate hepatocytes

Zone 3:
Pericentral hepatocytes

Human PNPLA3 I148M transgenic mice were dosed with a single subcutaneous injection of 10, 30 or 100 mg/kg PNPLA3 AIMer or PBS. PNPLA3 AIMer was detected by in situ hybridization in liver tissues collected at 7 days following the initial dose. Red signal: RNAscope ISH probe for detecting PNPLA3 AIMer; Blue signal: DAPI nuclear counterstain

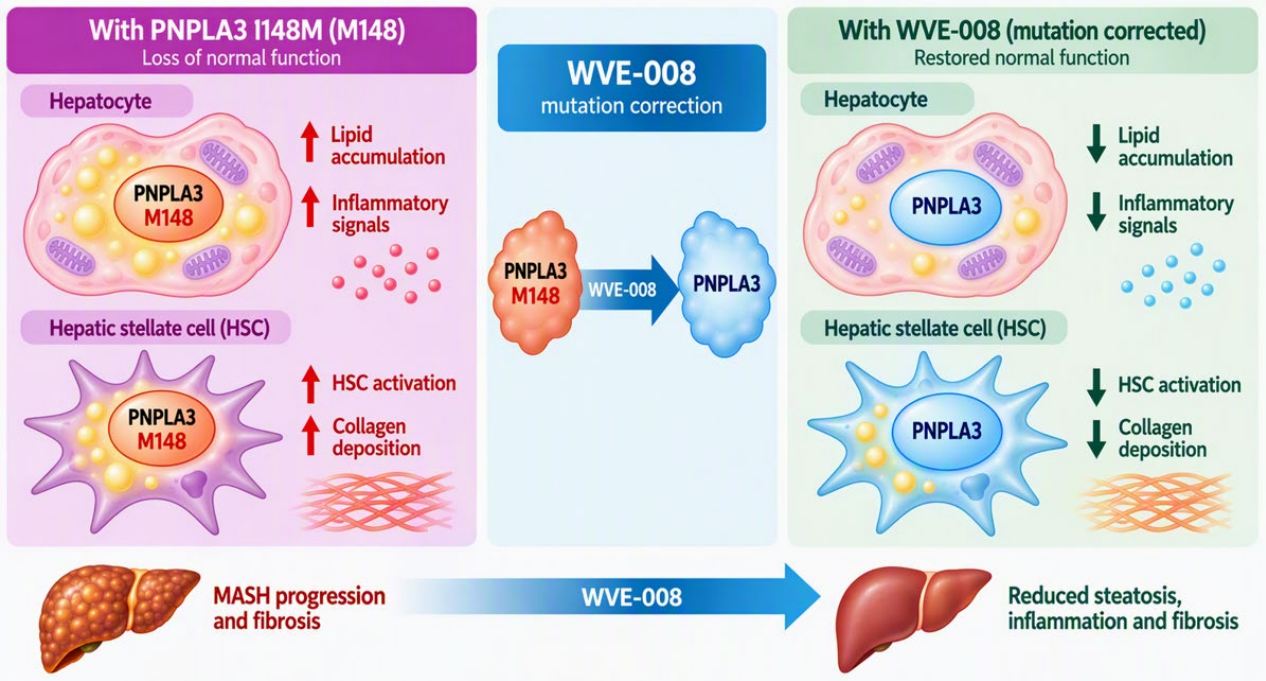
PNPLA3 AIMer presence in hepatic stellate cells supports a direct anti-fibrotic mechanism of RNA editing





Human PNPLA3 I148M transgenic mice were injected with a single (10, 30 and 100mg/kg) subcutaneous dose (n=4) of AIMer-3 or PBS. Immunofluorescence was performed in liver collected at 7 days after the initial dose, PNPLA3 AIMer (red), DAPI (blue, cell nuclei), desmin (green, HSC). The colocalization of PNPLA3 AIMer and desmin was shown in yellow signal. Representative images (20X) from the 10mg/kg and PBS treatment groups were shown here. Images were quantified by HALO, digital pathology image-analysis platform. Each bar represents mean ± SEM of n=4. The %editing in HSC was analyzed by Sanger sequencing of liver tissue collected 7 days after 30mg/kg Q2W for 10 weeks in human PNPLA3 I148M transgenic mice.

WVE-008 corrects I148M mutation and restores its normal function in hepatocytes and hepatic stellate cells



WVE-008 has potential to reduce steatosis, inflammation, and fibrosis, and improve MASH resolution in patients homozygous for PNPLA3 I148M

Potential best-in-class, disease modifying treatment for homozygous PNPLA3 I148M carriers with liver disease

- Large addressable patient population with no treatment options directly targeting PNPLA3 I148M-driven liver disease
- Preclinical data demonstrate:
  - Substantial editing expected to reverse MASH progression
  - Restoration of lipid regulation for improvement of liver health and decreases in liver fat
  - Broad distribution across all three zones of the liver, and in hepatic stellate cells, which supports a direct anti-fibrotic mechanism of RNA editing
- Clinical development planning underway for a first-in-human clinical study
  - Leveraging previously genotyped populations to efficiently identify homozygous I148M carriers
  - Initial study to enroll homozygous carriers to assess safety, tolerability, pharmacokinetics, and pharmacodynamic endpoints

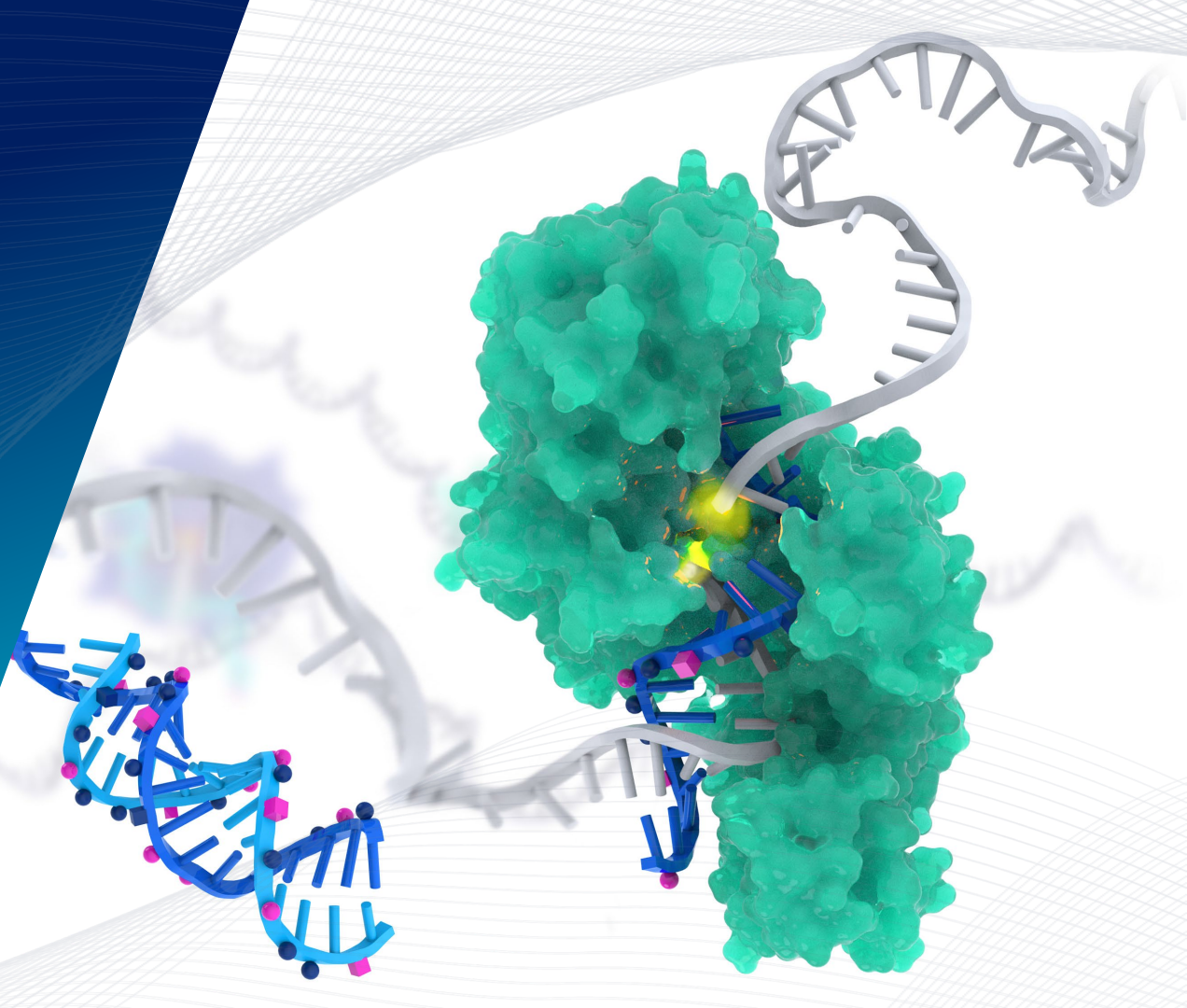
Expect to file Clinical Trial Application (CTA) for WVE-008 in 4Q 2026

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PRISM® Platform Innovations

Chandra Vargeese, PhD
Chief Technology Officer





Today's PRISM® platform update:

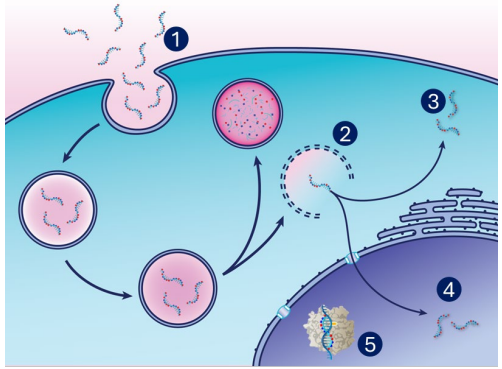
1. RNAi (SpiNA design) differentiation and clinical translation
2. Unlocking extra-hepatic delivery with PN conjugates
3. Bifunctional modalities: Silence, edit or upregulate

For over a decade, Wave has been extending the frontiers of RNA therapies through advances in nucleic acid chemistry

Single well-defined compounds

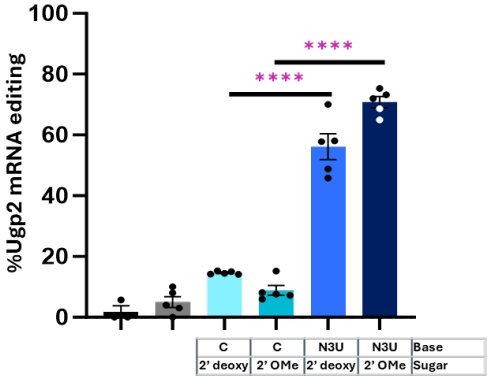
- Optimize stereochemistry
- Optimize pharmacological profiles
- Optimize sequence

Novel backbone modifications



Addition of PN modification increases: Cell uptake, endosomal release, residency, nuclear uptake, target engagement

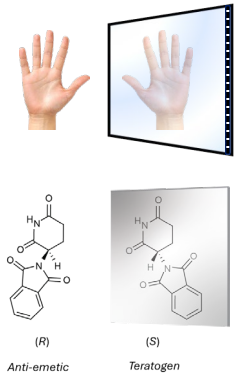
Novel base and sugar chemistry modifications



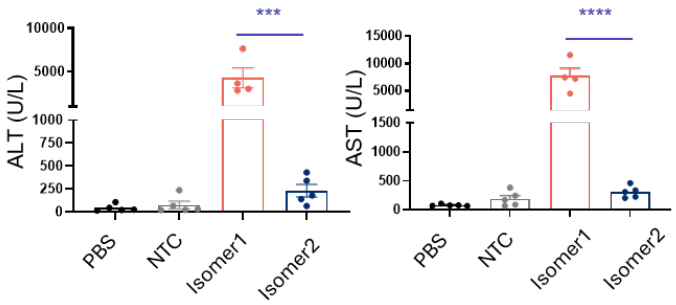
Addition of base modifications led to dramatic increase RNA editing efficiency

Wave's leading chirally-controlled rationally designed stereopure oligonucleotides are translating in clinic

Chirality matters: Backbone stereochemistry affects pharmacology

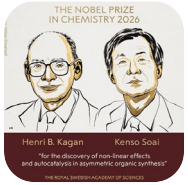


Oligonucleotide isomers with same target engagement can have opposite tolerability profiles



PRISM® platform controls stereochemistry

- ✓ Design and optimization of fully-characterized, single-isomer oligonucleotides can improve pharmacology including potency, duration, and tolerability
- ✓ Chirality enhances Ago2 loading
- ✓ Dominant IP portfolio
- ✓ Unique ability to manufacture and screen stereopure oligonucleotides, without significant increase to cost



Several Nobel Prizes featured stereochemistry, including the 2026 prize in Chemistry

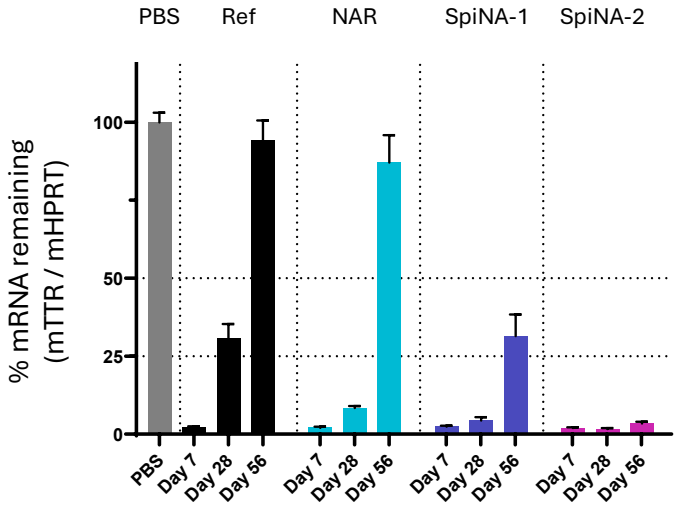
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2021 OTS presentation; nobelprize.org/prizes/chemistry/2026/press-release/

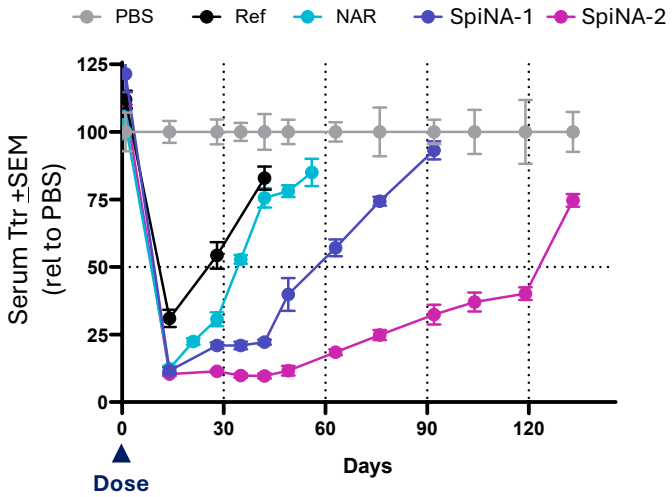
Substantial improvements in duration of activity and potency achieved through chemistry optimization with SpiNA GalNAc-siRNAs

SpiNA: **S**tereo**p**ure **i**nterfering **N**ucleic **A**cid

mRNA silencing following single dose



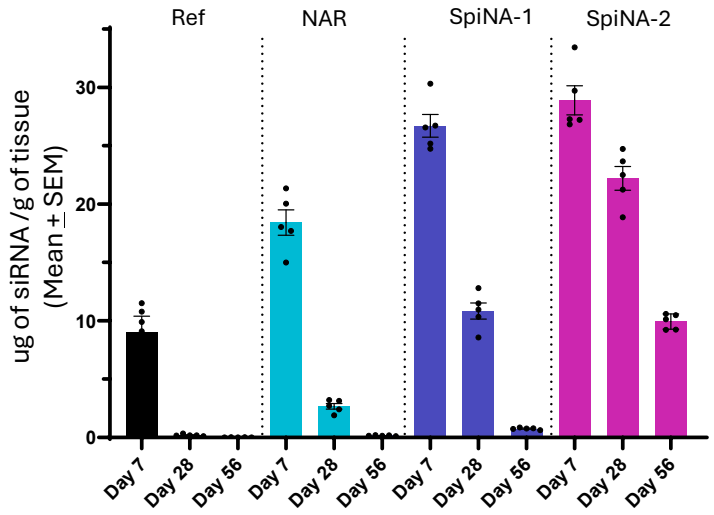
Protein reduction following single dose



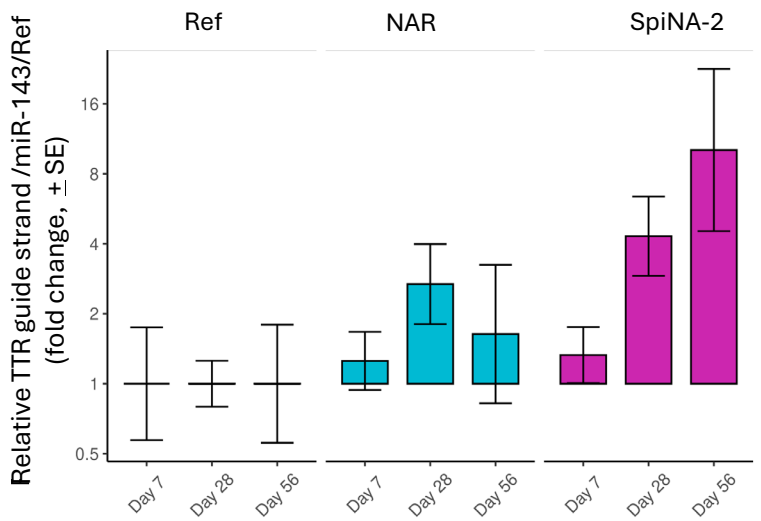
Left: single subcutaneous dose of 2 mg/kg in C57BL/6 mice; Right: single subcutaneous dose of 0.5 mg/kg in C57BL/6 mice
Ref, NAR: Liu et al., 2023 Nucleic Acids Research doi: 10.1093/nar/gkad268

SpiNA GalNAc-siRNAs demonstrate >10-fold improvement in Ago2 loading versus reference siRNAs

siRNA pharmacokinetics



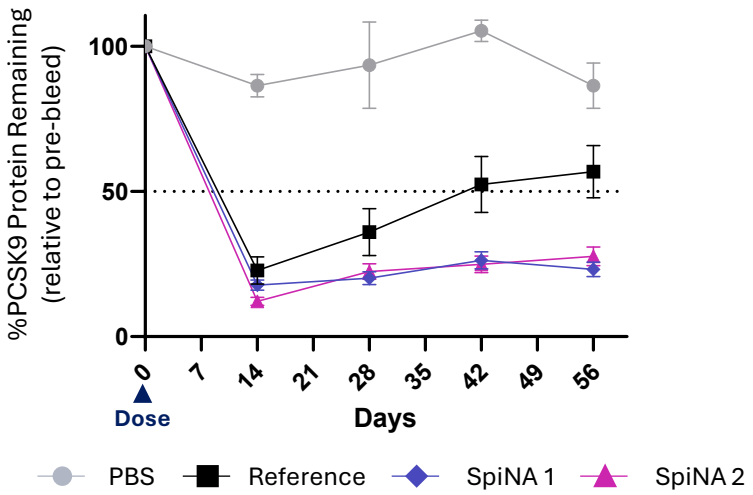
siRNA Ago2 loading



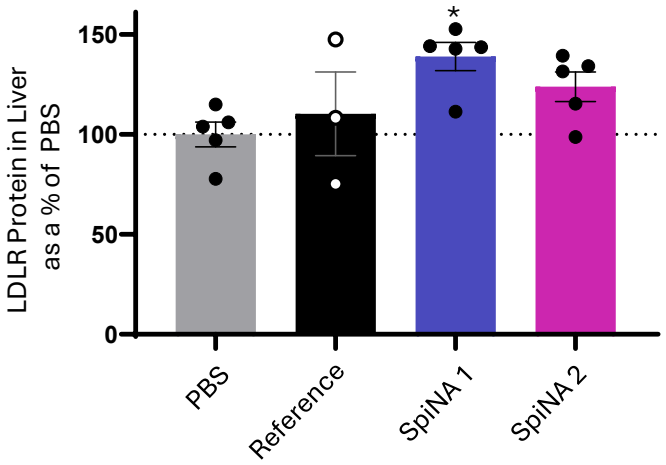
Left: single subcutaneous dose of 2 mg/kg in C57BL/6 mice; Right: single subcutaneous dose of 0.5 mg/kg in C57BL/6 mice;
Ref+NAR: Liu et al., 2023 Nucleic Acids Research doi: 10.1093/nar/gkad268

Substantial improvements in duration and efficacy achieved with PCSK9 SpiNA

PCSK9 protein reduction following single dose



LDLR protein upregulation downstream of PCSK9 knockdown



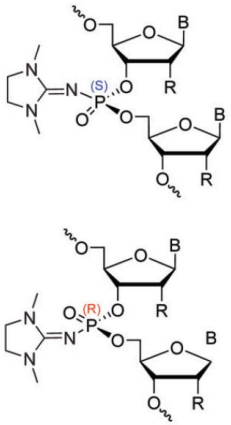
Transgenic mice expressing human PCSK9 were dosed subcutaneously with a single 3 mg/kg dose of indicated GalNAc-siRNA. Serum was collected at indicated timepoints for PCSK9 protein analysis by ELISA. Liver punches were collected at day 56 to analyze hepatic LDLR protein content by ELISA. All results were normalized to PBS treated animals; Bar graph stats: Ordinary one-way ANOVA with Dunnett's multiple comparisons test relative to PBS group. (*) $p \leq 0.05$

WVE-007: Clinical-stage INHBE-siRNA leveraging proprietary chemistry for enhanced interactions with Ago2, better silencing

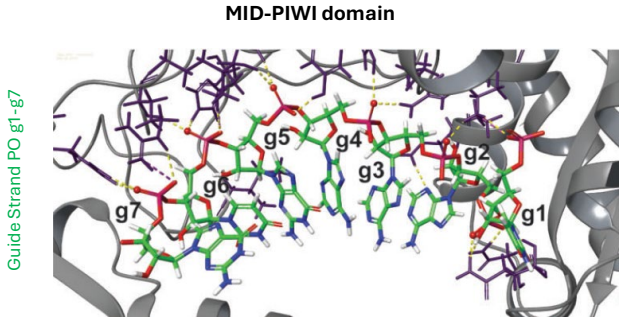
WVE-007 (INHBE GalNAc-siRNA)

- Proprietary, clinically validated chemistry
- Subcutaneous delivery (GalNAc)
- Potential for infrequent dosing (1 – 2x year)

Phosphoryl guanidine (PN)



Rational design
Chirality enhances Ago2 loading

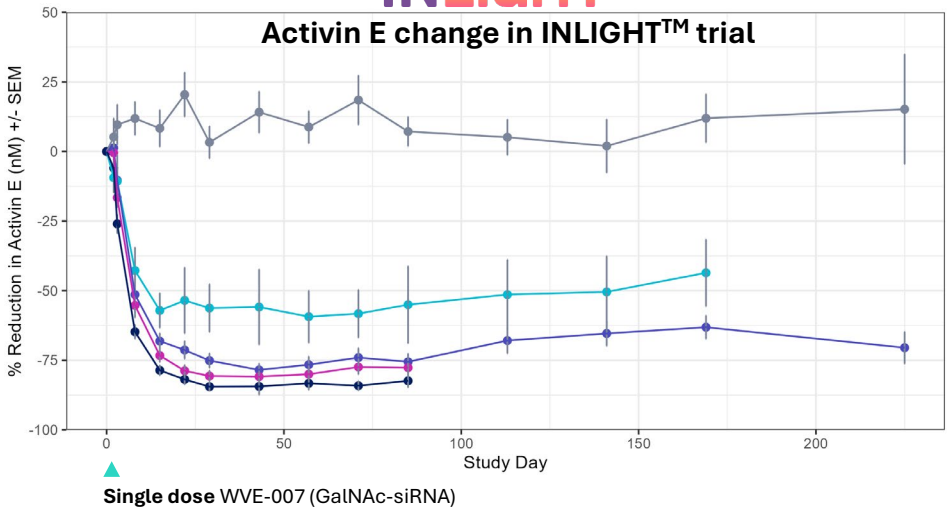


Potent and durable Activin E reductions achieved following a single dose

Liu et al., 2023 Nucleic Acids Research doi: 10.1093/nar/gkad268

SpiNA clinical translation: Potent and durable Activin E reductions observed leading to improvements in body composition following single dose

INLIGHT™



Phase 1 otherwise healthy (SAD)
Lower BMI of ~32 kg/m^2

Improved body composition six months following single 240 mg dose:

- Significant reduction in **visceral fat** (-14%*)
- Reduction in **waist circumference** (-3%)
- Reduction in **total fat** (-5%)
- Stabilization of **lean mass** (+2%)
- Reduction in **body weight** (-1%)

- 400 mg three-month data emphasize impact of baseline body composition on therapeutic effect
- **Durable and dose-dependent** suppression of Activin E sustained through at least 7 months continues to support **1-2x yearly dosing**
- **Generally safe and well tolerated**

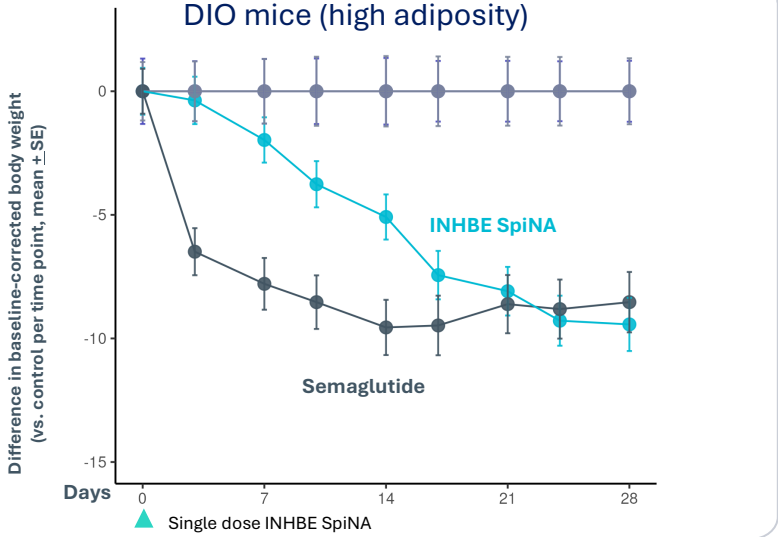
Phase 2a multidose INLIGHT clinical trial enrolling population with higher baseline adiposity and comorbidities with expectations for greater fat loss

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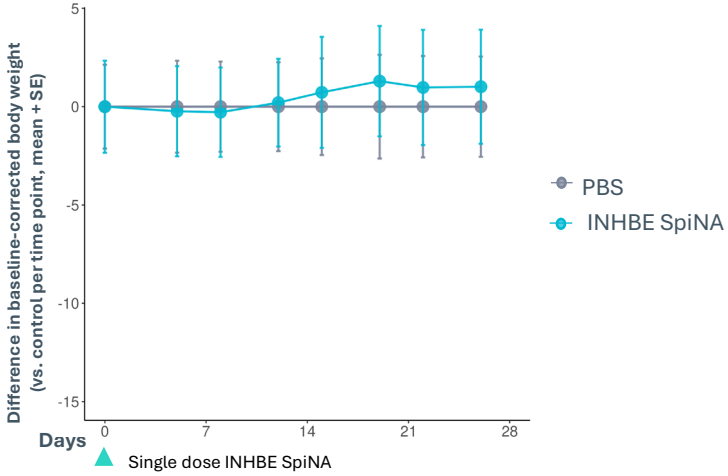
INLIGHT interim Phase 1 data reported March 26, 2026; Left: figure shows sample means and SEMs. All MMRM baseline and placebo comparisons from Day 8 onwards are p<0.003. Right: *p<0.05. All reductions are placebo-adjusted % change from baseline were estimated using an MMRM model with fixed effects for treatment group, visit, treatment-by-visit interaction, and baseline as a covariate; estimates were based on geometric mean ratios.

Single dose of INHBE SpiNA results in weight loss and reduction in visceral fat, without affecting muscle mass, in DIO mice

Single dose drove weight loss on par with semaglutide in mice on high-fat diet



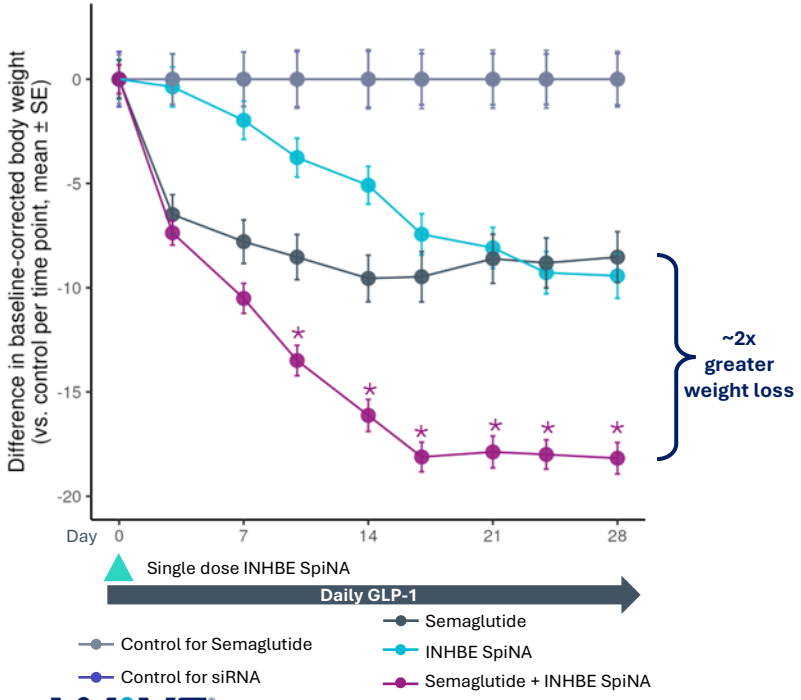
INHBE SpiNA showed no weight loss in lean mice on chow diet



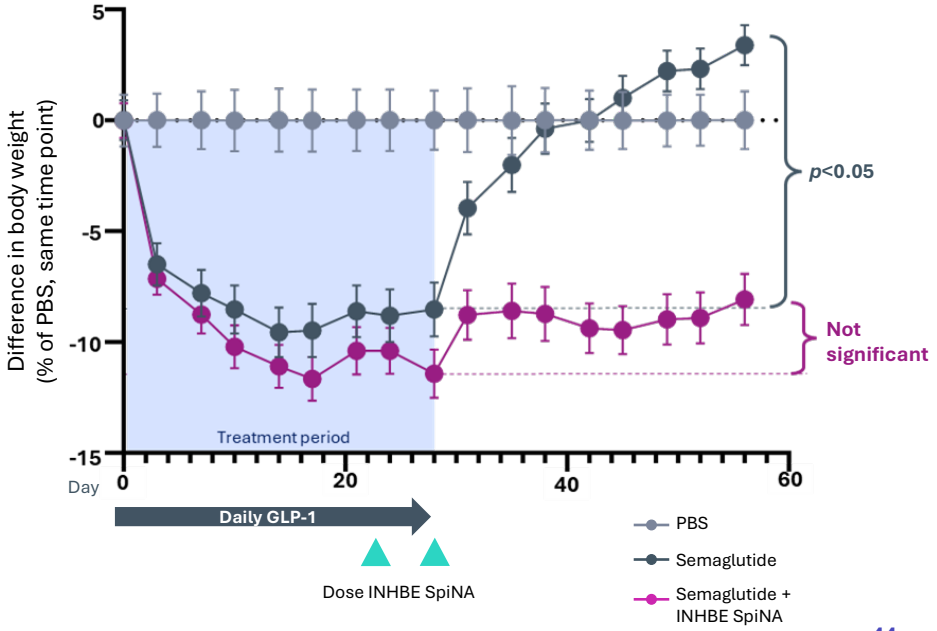
Greater weight loss observed with increased baseline adiposity support Phase 2a design

WVE-007 has potential for use synergistically with GLP-1s or to curtail weight regain after the cessation of treatment with GLP-1, based on preclinical data

Combined with GLP-1: Greater weight loss



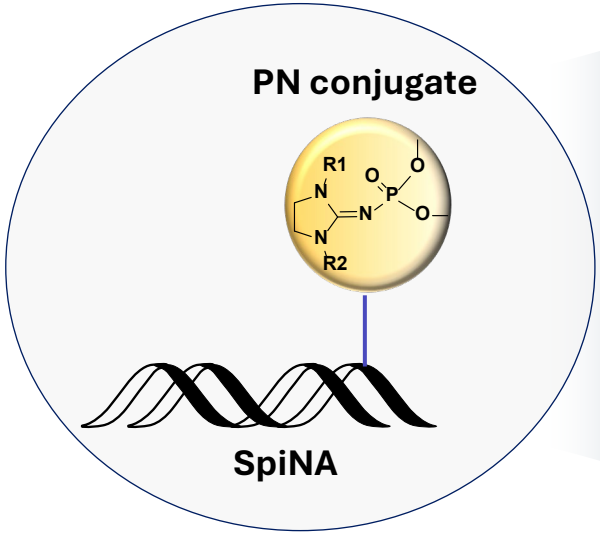
After cessation of GLP-1: Curtails weight regain



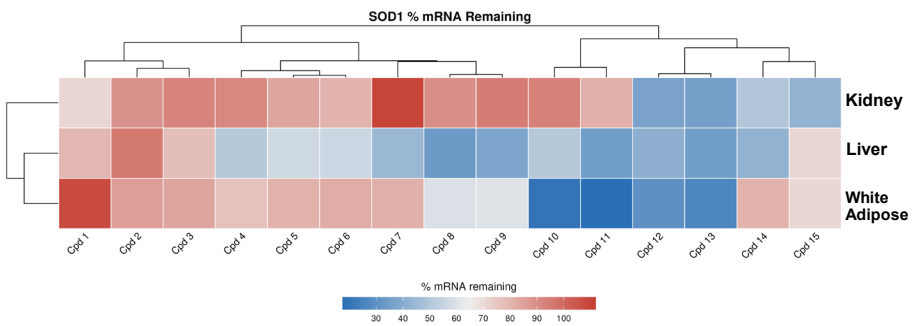
Data from preclinical studies conducted in mice fed with 60% high fat diet; Left: semaglutide10 nmol/kg daily SC in mouse is equivalent to therapeutic dose of 2.4mg weekly SC in human. Left Stats: Linear Mixed Effects ANOVA with post hoc comparisons of marginal treatment effects of Semaglutide vs. Semaglutide + INHBE GalNAc-siRNA per time point * $p < 0.05$; Right Stats: Linear Mixed Effects ANOVA with post hoc comparison of Day 28 vs. Day 56 marginal effects per treatment

Conjugates beyond GalNAc: Ability to tune extra-hepatic delivery using SpiNA PN conjugates

Adjusting chemical properties of PN conjugates with proprietary chemistry



PN conjugates enable delivery to kidney, adipose, liver, or a combination of tissues



Same sequence with different PN conjugates

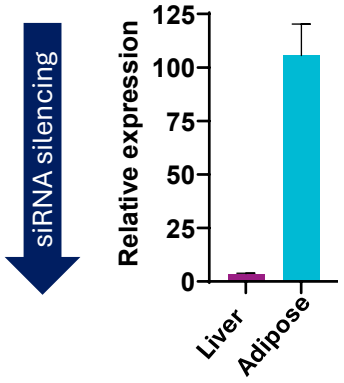
Unique chemical properties of different PN backbones allow for the tunability of delivery

The color scale of the heatmap is standard normal (mean 64.4%, SD = 25.1%).

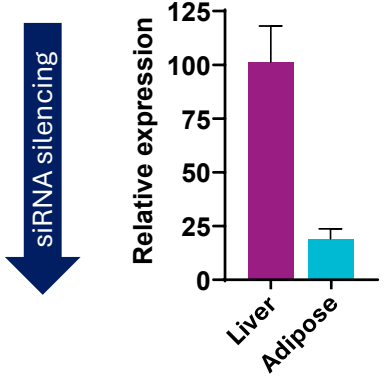
Directing silencing to high-priority extrahepatic tissues in mice using SpiNA

Achieved by changes in physicochemical properties without requirement for LNP or other delivery agents

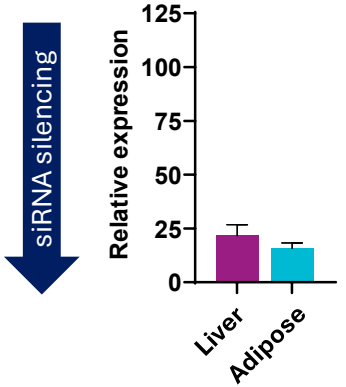
GalNAc conjugates for liver



PN conjugates for adipose



PN conjugates for adipose + liver



Durable silencing at 8 weeks *in vivo* following a single dose

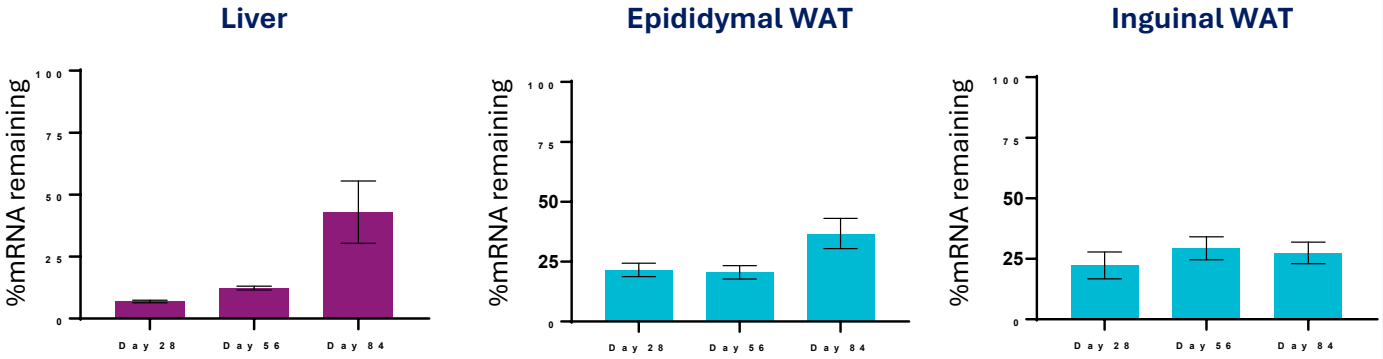
Directing silencing to both liver and adipose in mice using PN conjugates and SpiNA design for cardiometabolic Target A

Human genetics data support that silencing Target A may improve insulin sensitivity

Target A

- Strong association between LoF and risk reduction for CAD and insulin resistance
- Addresses historical challenge in addressing insulin resistance, a key driver of type 2 diabetes
- Current insulin sensitizers have modest efficacy or carry significant safety concerns
- No insulin sensitizer has been approved by FDA in over 25 years

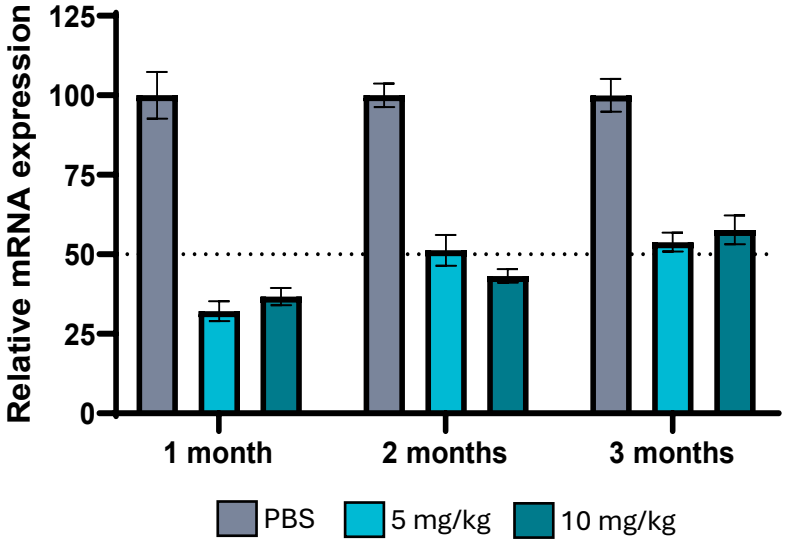
Target A mRNA silencing in liver and adipose tissue



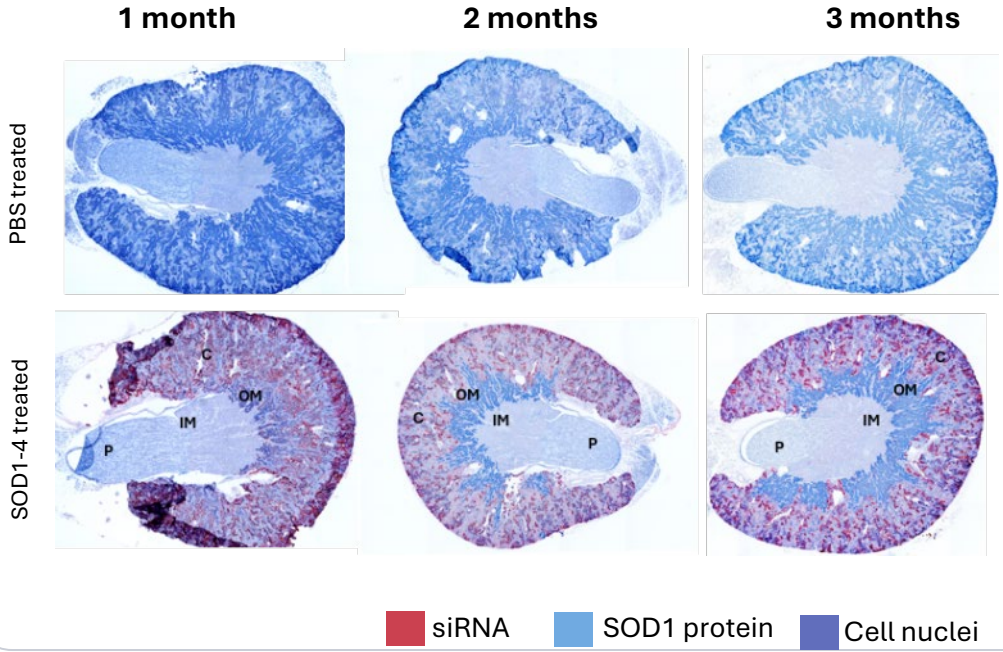
Durability out to three months in both liver and adipose in mice following a single dose

PN conjugate + SpiNA: 75% mRNA knockdown and sustained 50% knockdown up to 3 months post single dose; broad distribution and protein reduction in kidney

SOD1 mRNA knockdown

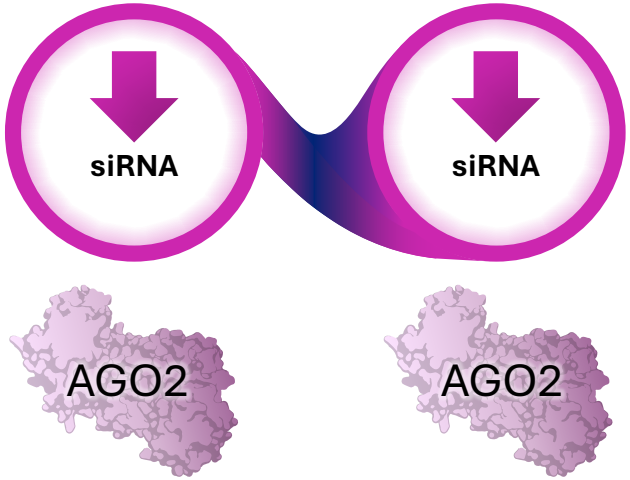


Broad distribution and protein reduction



Left side: Single subcutaneous administration of 5 or10 mg/kg to C57BL/6 mice on D0, necropsy 1,2-,or 3-months post dose. SOD1 mRNA expression assessed in the kidney. Right side: Hematoxylin staining was performed to identify cell nuclei, followed by Immunohistochemistry and miRNAscope staining for SOD1 protein and SOD1 siRNA, respectively. C: cortex; OM: outer medulla; IM: inner medulla; P: papilla.

Bifunctional modalities: Silencing two distinct transcripts with a dual guide single oligonucleotide construct

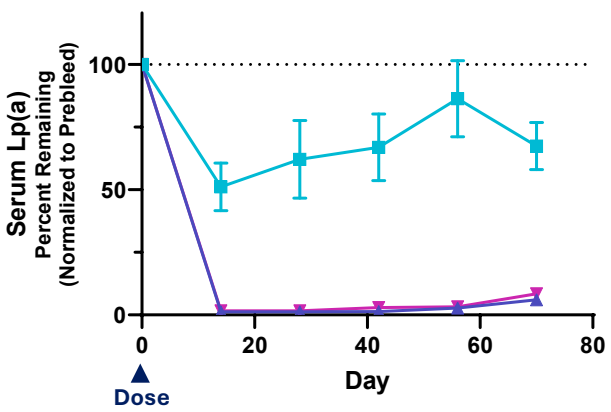


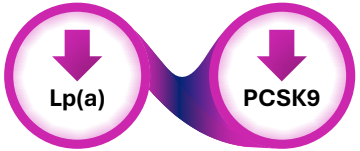
Dual RNAi silencing with a single construct

- ✓ Silence expression of two transcripts simultaneously in the same cell in tissue
- ✓ Requires unique chemistry design
- ✓ Enabled by best-in-class SpiNA design
- ✓ Potential to drive efficiencies in drug development and deliver value to patients, providers, and payers

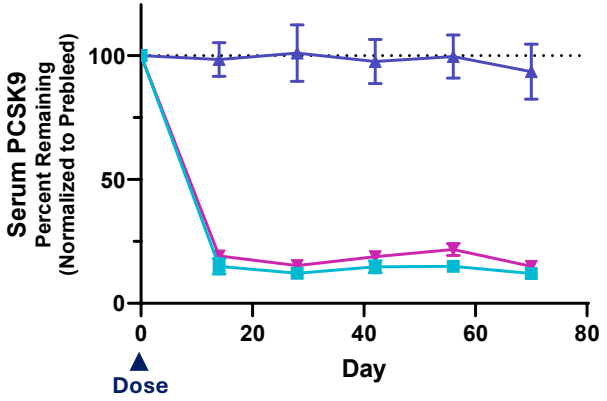
Bifunctional SpiNAs have robust and durable activity comparable to mono SpiNA in mice

Serum Lp(a) knockdown





Serum PCSK9 knockdown

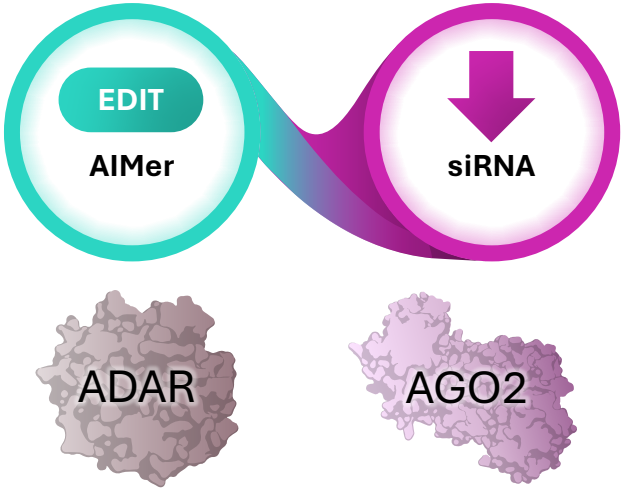


Lp(a) mono SpiNA PCSK9 mono SpiNA Bifunctional Lp(a)-PCSK9

Durable activity supports potential for once or twice-yearly dosing

Transgenic mice expressing either hLPA or hPCSK9 were subcutaneously injected with equimolar concentration of the indicated compounds. Overnight-fasted serum was collected biweekly starting with a pre-bleed on D0. Serum protein was analyzed via ELISA, normalized to the pre-bleed concentration of each animal, and plotted as mean ± SEM. Note: serum Lp(a) concentrations at days 14, 28, 42, and 56 include values below the LLOQ of the ELISA assay; these values are represented as the samples' maximum potential concentration based on the sample dilution used and the LLOQ.

Reimagining RNA medicines: Combining modalities to simultaneously edit, upregulate or silence RNA with a single oligonucleotide construct

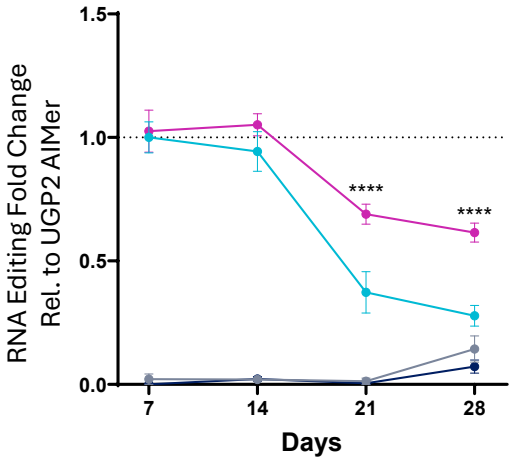


Edit, upregulate, or silence with a single construct

- ✓ Engage both endogenous Ago2 and ADAR enzymes
- ✓ Silence one target, while simultaneously editing or upregulating another unique target
- ✓ Potential to drive efficiencies in drug development and deliver value to patients, providers, and payers
- ✓ May continue to increase durability of editing

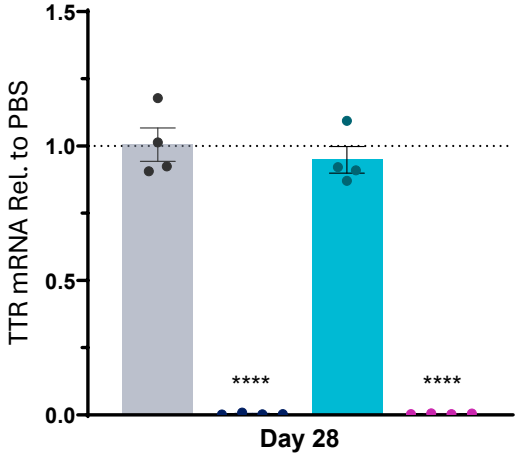
Bifunctional construct improves durability of RNA editing, while preserving mRNA silencing with a single dose *in vivo*

Potent UGP2 mRNA editing





Robust TTR mRNA silencing

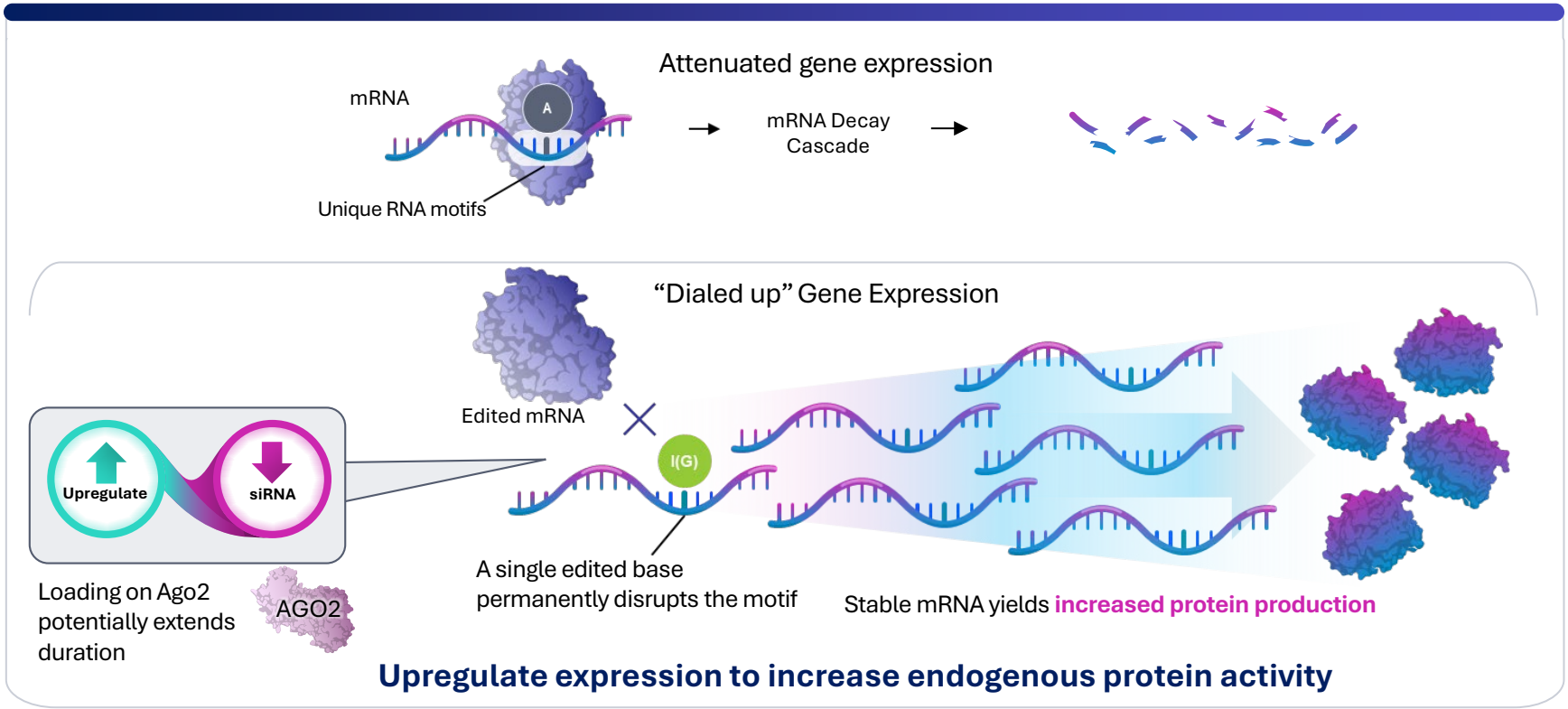


PBS | TTR SpiNA | UGP2 AIMer | Bifunctional UGP2-TTR

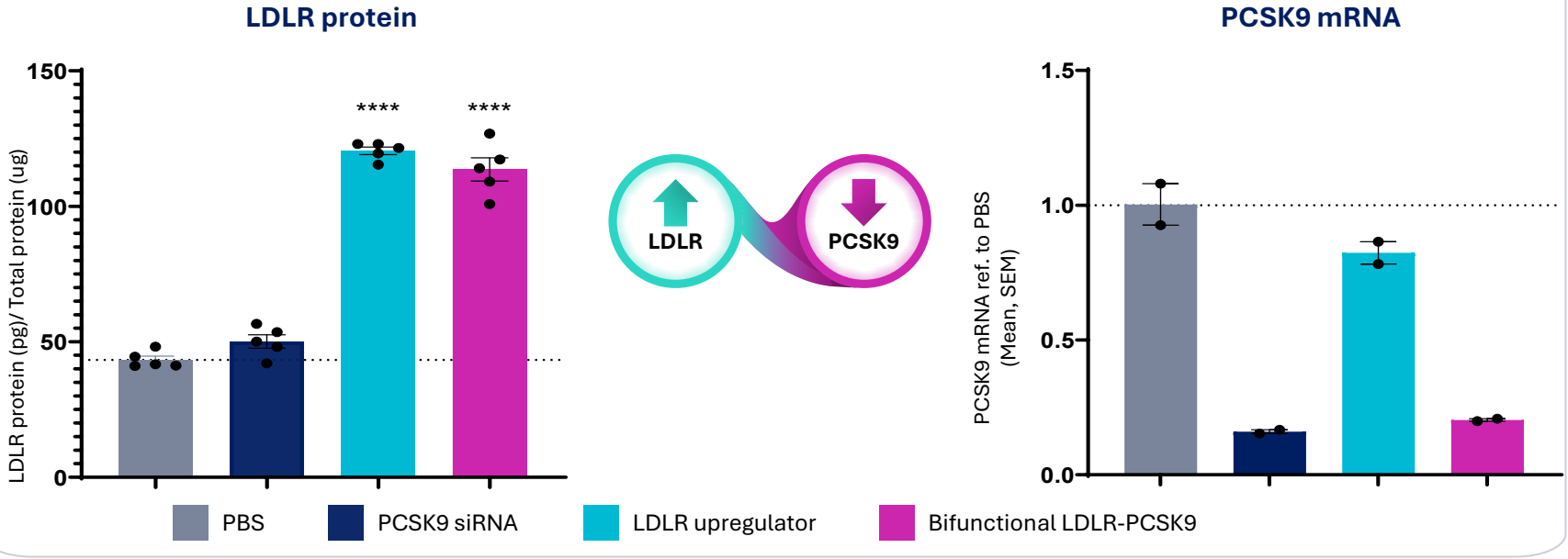
Bifunctional construct demonstrates more durable editing with comparable knockdown *in vivo*

WT C57BL/6J mice were subcutaneously injected with equimolar concentration of indicated compounds, and liver biopsies were collected at indicated timepoints
Left: UGP2 RNA editing was measured by Sanger sequencing and normalized to % editing for UGP2 AIMer at day 7. Stats: 2-way ANOVA with Dunnett post-hoc comparison to AIMer
Right: TTR transcript knockdown was measured by qPCR using the ΔΔCt method. Stats: Welch's One-Way ANOVA with Dunnett's T3 post hoc-comparison ****<0.0001

Upregulators: Engaging ADAR to upregulate gene expression



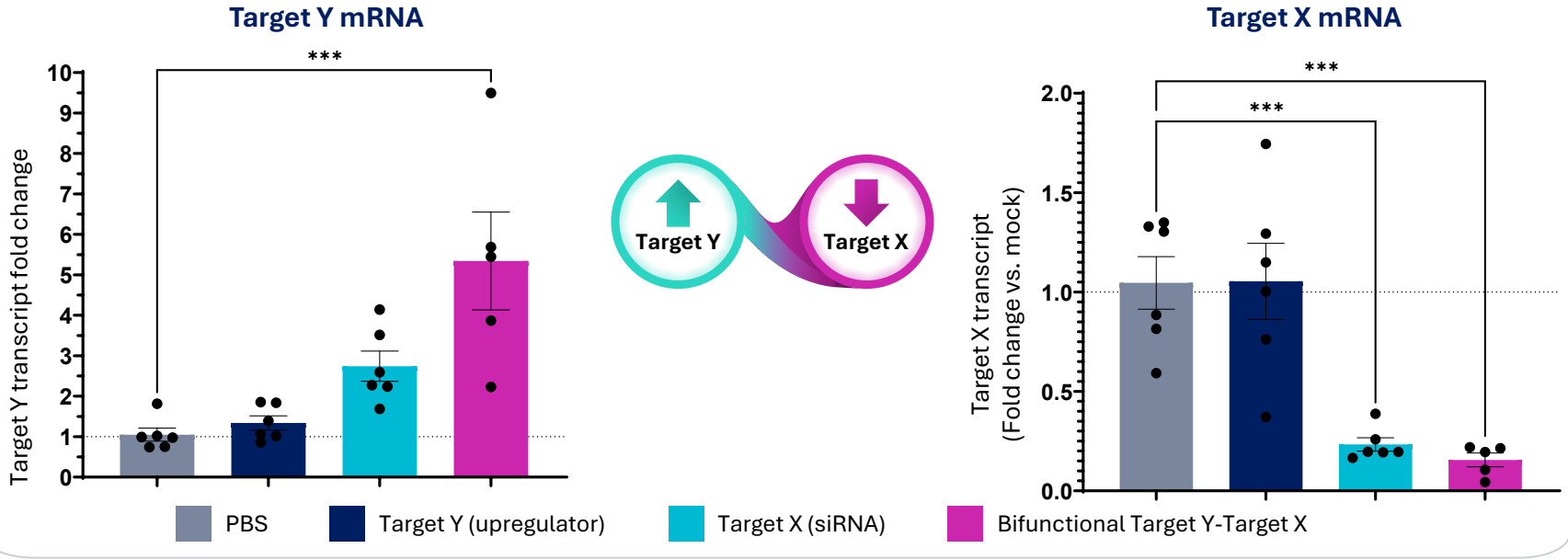
Bifunctional construct: Upregulate + silence two distinct targets with a single GalNAc-conjugated oligonucleotide



Bifunctional LDLR - PCSK9: upregulates and silences simultaneously, without losing efficacy *in vitro*

Primary human hepatocytes were treated *in vitro* with indicated compounds for 96 hours. Left: LDLR protein was measured using an ELISA; Stats: Welch's One-Way ANOVA with Dunnett's T3 post hoc-comparison. Right: PCSK9 transcript was measured by qPCR using the ΔΔCt method

Bifunctional construct demonstrates synergistic effects *in vivo*



Synergistic effect enables bifunctional construct to upregulate Target Y >5-fold, while achieving potent siRNA silencing of Target X

WT C57BL/6J mice were subcutaneously injected with equimolar concentrations of indicated compounds on Days 0,2, 4 and liver biopsies were collected at day 11. Relative amounts of transcript X and Y in the liver were measured by qPCR using the ΔΔCt method. Stats: One-way ANOVA with Dunnett's test adjustment for multiple comparisons vs. PBS

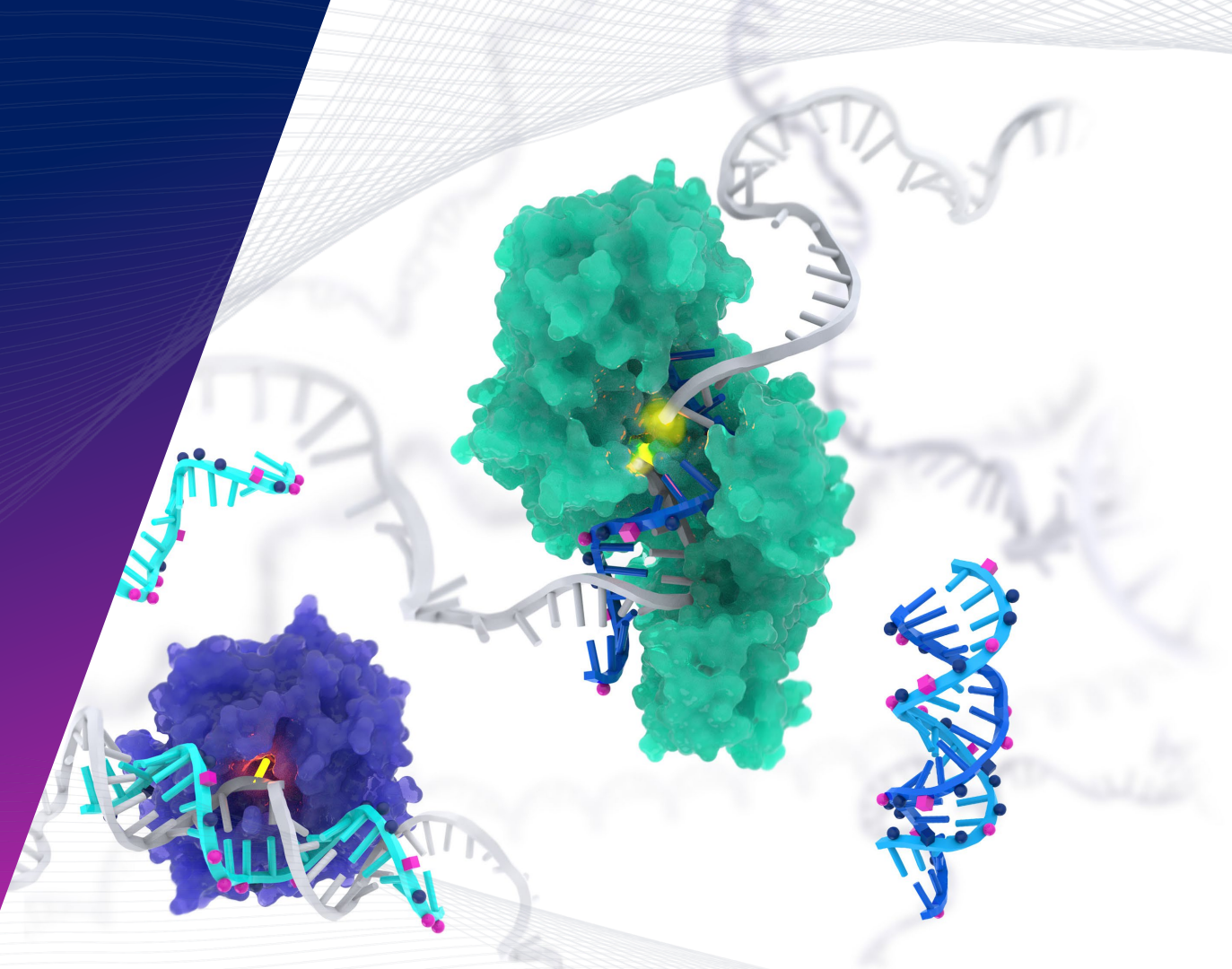
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Closing Remarks

Paul Bolno, MD, MBA

President and CEO

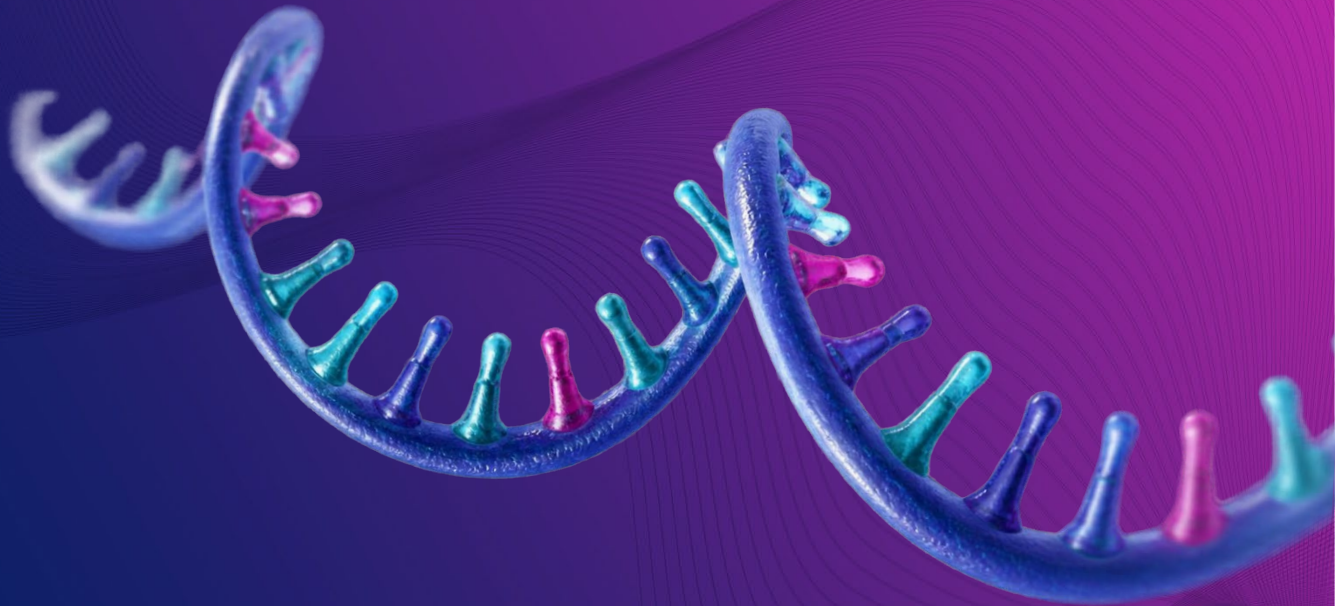




Delivering on our mission to unlock the broad potential of RNA medicines

- **Wave's multi-modal platform combines genetic insights and proprietary chemistry**
  - Oligonucleotide center of excellence: in-house large-dataset integration, rational drug design, multi-model platform, and manufacturing
- **Advancing WVE-008 for PNPLA3 liver disease**
  - Strong support from human genetics, with advantages over siRNA approach
  - CTA filing expected in 4Q 2026
- **SpiNA design translating in the clinic and PN conjugates enabling extra-hepatic targets**
  - WVE-007 has delivered potent and durable target engagement in clinic, supporting potential once or twice-yearly dosing, with a safe and well-tolerated profile
  - PN conjugates enable delivery beyond liver, including to adipose and kidney
- **Bifunctional modalities**
  - Simultaneously silence, edit or upregulate two unique targets with a single construct; potential to increase durability of editing
  - Potential to drive efficiencies in development and deliver value to patients, providers, and payers

Q&A



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