



Analyst & Investor Day

Spotlight on RNA editing and RNAi

AATD, obesity and beyond

October 29, 2025

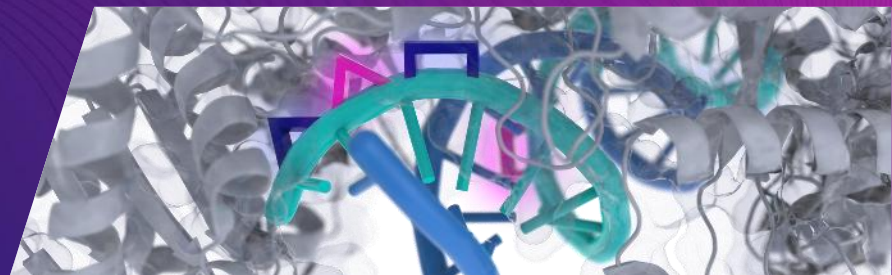
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Today's agenda

Presentation	Speaker
Welcome and introduction	Kate Rausch Vice President, Investor Relations & Corporate Affairs
Opening remarks	Paul Bolno, MD, MBA President and Chief Executive Officer
RNA Editing	
WVE-006: RNA Editing (AIMer) for AATD	Chris Wright, MD, PhD Chief Medical Officer
WVE-008: PNPLA3 AIMer for liver disease	Erik Ingelsson, MD, PhD Chief Scientific Officer
RNAi	
WVE-007: INHBE siRNA for obesity	Erik Ingelsson, MD, PhD Chief Scientific Officer
	Chris Wright, MD, PhD Chief Medical Officer
PRISM platform innovations	Chandra Vargeese, PhD Chief Technology Officer
Closing remarks	Paul Bolno, MD, MBA President and Chief Executive Officer
Q&A	All

Opening remarks



Paul Bolno, MD, MBA

President and CEO



Our Mission

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

WAVE[®]
LIFE SCIENCES



Leveraging best-in-class chemistry and genetic insights to build a leading RNA medicines company

Target selection

Human genetic or clinical support Leverage genetic databases and clinical data

Translational path Select suitable modality and tissue delivery that leverages unique Wave chemistry

Novelty and unmet need Focus on first/best-in-class opportunities

Best-in-class oligonucleotide platform



Clinically-validated oligonucleotide chemistry (including PN, stereochemistry)

Clinical translation

WVE-006 Pioneering RNA editing
AATD

WVE-007 Novel approach to reduce
Obesity fat, preserve muscle

WVE-N531 Potential
DMD best-in-class profile

WVE-003 Leading in
HD allele-selective silencing

AI-driven continuous learnings

Strong and broad IP

In-house GMP manufacturing

What you'll hear today: Spotlight on RNA editing and RNAi

RNA editing

- First-ever clinical translation of RNA editing achieved with **WVE-006** for AATD, **including restoration of dynamic protein production**
- **WVE-008**, a wholly-owned **RNA editing candidate for PNPLA3 liver disease**, building on successful clinical translation of Wave's editing capability

RNAi

- **INLIGHT**: Dose-dependent mean Activin E reductions post-single **WVE-007** dose in clinic; exceeding levels that led to weight loss in preclinical studies; durability supports once or twice per year dosing
- Multiple upcoming INLIGHT clinical data updates expected, including body composition and body weight starting in 4Q 2025

Platform innovation

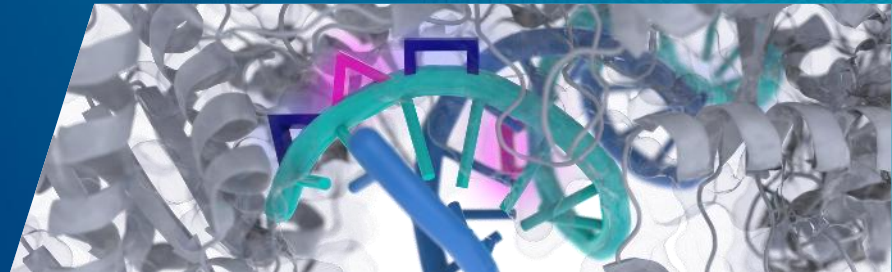
- **Extra-hepatic capabilities**: enable tuning of siRNA to achieve potent and durable silencing across multiple extra-hepatic tissues; RNA editing also achieved across multiple tissues
- **Novel therapeutic modality**: capability to simultaneously edit and silence two unique targets with a single oligonucleotide construct

Positive INHBE target engagement data update demonstrates rapid acceleration from target to successful clinical translation

Robust, diversified RNA medicines pipeline including first-in-class RNA editing and RNAi programs

Program	Discovery	IND / CTA Enabling Studies	Clinical	Rights	Patient population (US & Europe)
RNA EDITING					
WVE-006 (GalNAc) SERPINA1 (AATD)				GSK exclusive global license	200K
WVE-008 (GalNAc) PNPLA3 (liver disease)				100% global	9M
GalNAc / extra-hepatic Multiple				100% global	--
RNAi					
WVE-007 (GalNAc) INHBE (Obesity)				100% global	175M (>1 billion globally)
GalNAc / extra-hepatic Multiple				100% global	--
SPLICING					
WVE-N531 Exon 53 (DMD)				100% global	2.3K
Other exons (DMD)				100% global	Up to 18K
ALLELE-SELECTIVE SILENCING					
WVE-003 mHTT (HD)				100% global	25K Symptomatic (SNP3) 60K Pre-Symptomatic (SNP3)

WVE-006: RNA editing (AlMer) for AATD



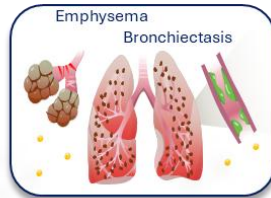
Chris Wright, MD, PhD
Chief Medical Officer



Alpha-1 antitrypsin deficiency impacts multiple organ systems

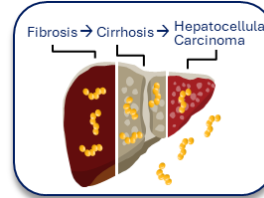
- AATD is a rare, inherited genetic disorder; commonly caused by G-to-A point mutation in SERPINA1 gene
- Aggregation of mutant Z-AAT protein in hepatocytes and lack of functional, wild-type M-AAT drives liver and lung pathology, respectively
- **~200,000 people in US and Europe are homozygous (Pi*ZZ genotype), which is the leading type of severe AATD with high risk of lung and/or liver pathology**

Lung pathology



Lung damage occurs during exacerbations that induce an inflammatory acute phase response, when more AAT protein is needed for protection

Liver pathology



Progressive liver disease results from Z-AAT-induced proteotoxic stress

Correcting mutation with RNA editing is expected to address risk for both lung and liver pathology

AATD has limited treatment options

Treatment options that prevent lung pathology

Weekly IV augmentation therapy is only approved treatment option

- No protective increase in AAT protein levels during acute phase response without additional IV infusions

Treatment goal

Minimize episodic exacerbations and associated lung damage

Treatment options that address liver pathology

No approved therapies to prevent or reverse liver pathology

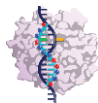
- IV augmentation therapy does not decrease Z-AAT protein aggregation in liver

Treatment goal

Decrease Z-AAT protein

WVE-006: Potential first-in-class, convenient therapy for AATD that addresses both liver and lung manifestations of the disease

WVE-006 (RNA editing)



Proprietary chemistry



Highly specific
(no bystanders)



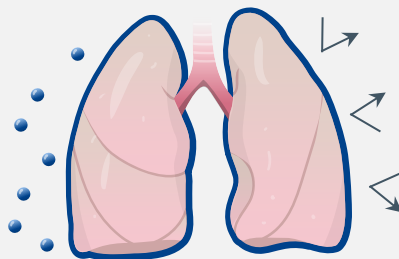
Subcutaneous injection (GalNAc)



Infrequent dosing



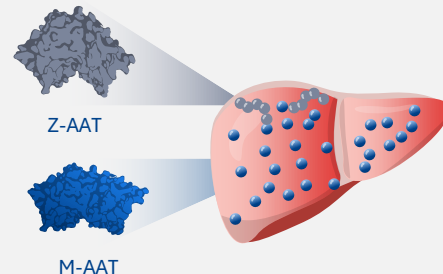
Restore circulating M-AAT and physiological AAT protein production



M-AAT reaches lungs to protect from proteases and **reduce risk of lung pathology**



Reduce Z-AAT protein aggregation in liver



RNA correction replaces mutant Z-AAT protein with wild-type M-AAT protein to **reduce risk of liver pathology**

RNA editing aims to increase M-AAT and restore physiological AAT production during acute phase response

Homozygous Pi*ZZ

No healthy M-AAT

AAT levels increase during acute phase response

Risk of lung pathology

Risk of liver pathology



No



High



High

Goal:
~50% editing
to shift Pi*ZZ
individuals
to AAT function
consistent with
Pi*MZ genotype

Heterozygous Pi*MZ

AAT protein of >11uM, >50% M-AAT



Yes



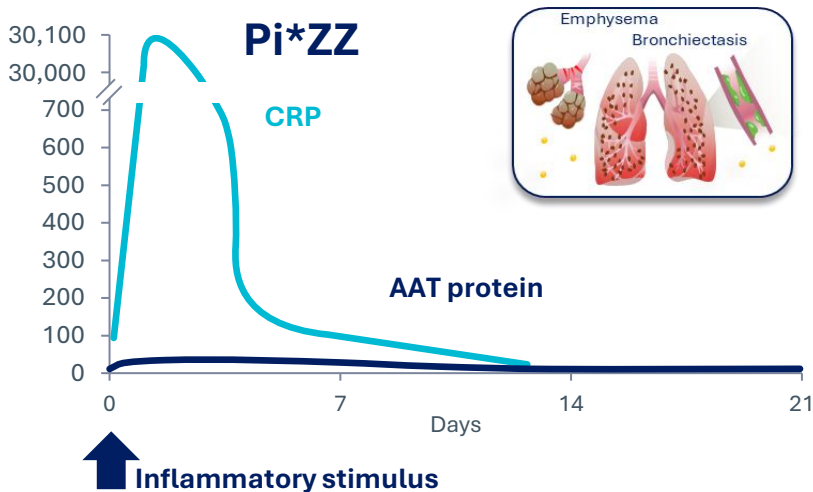
Low



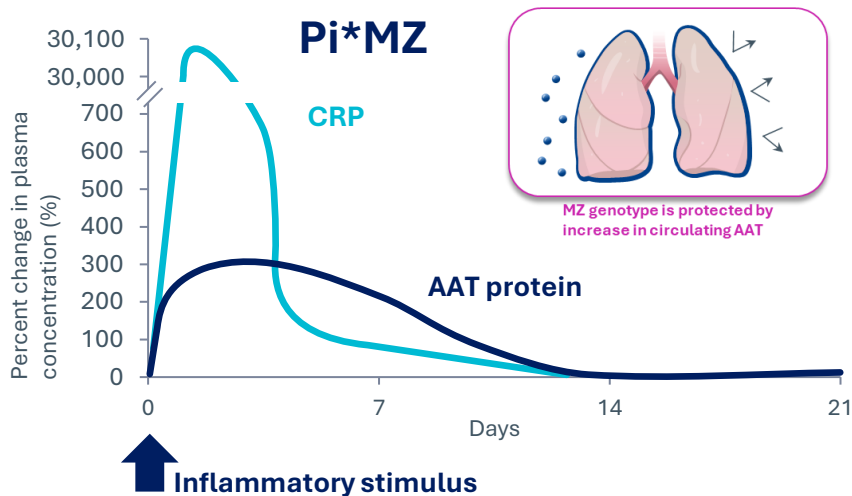
Low

RNA editing aims to restore production of dynamic and therapeutically relevant levels of AAT protein in Pi*ZZ individuals during acute phase response

Lung damage occurs during exacerbations, when more AAT protein is needed for protection



AAT protein has protective functions and is produced during acute phase response



RNA editing has potential to restore dynamic AAT response to inflammation

WVE-006 achieved key treatment goals of restoring MZ phenotype

Total AAT levels exceeded 11 μM , production of wild-type M-AAT of greater than 50%, restored physiological AAT production

Plasma AAT of ~13 μM

- Protein levels associated with lower risk of AATD liver and lung diseases

400 mg single dose

12.8 μM total AAT

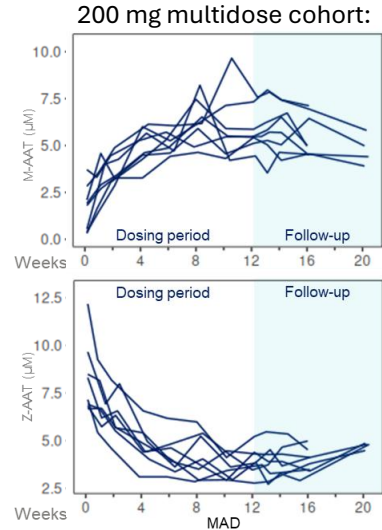
200 mg multidose

11.9 μM total AAT

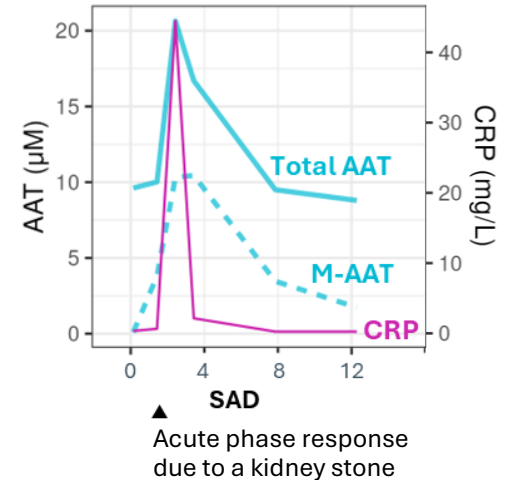
Wild-type M-AAT protein of 64% of total, reduction in Z-AAT

Wild-type M-AAT

Mutant Z-AAT



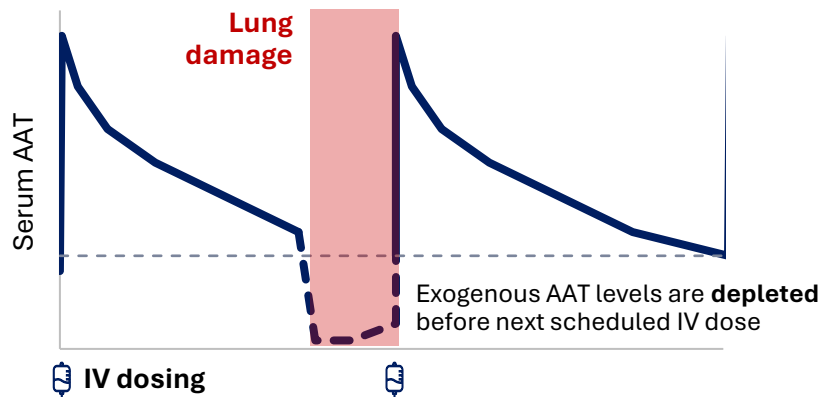
AAT reached >20 μM during an acute phase response



WVE-006 enables endogenous AAT production during an acute phase response while augmentation therapy leaves patients at risk

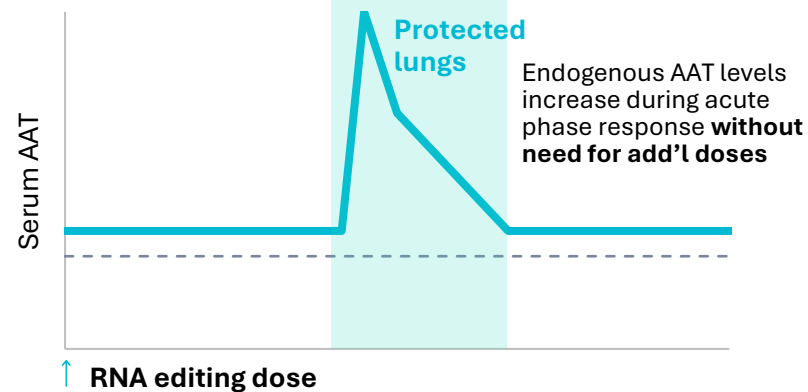
Illustrative model of impact of acute phase response

Augmentation therapy



- Augmentation therapy has **no impact** on liver disease

WVE-006 treatment approach



- WVE-006 also reduces levels of Z-AAT

WVE-006 therapeutic goal is to restore dynamic AAT physiology; augmentation therapy goal is to maximize AAT levels as dynamic response is not enabled

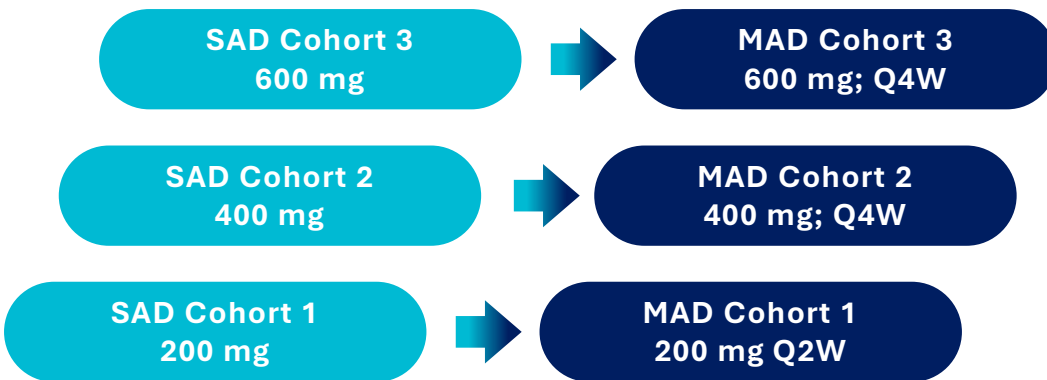
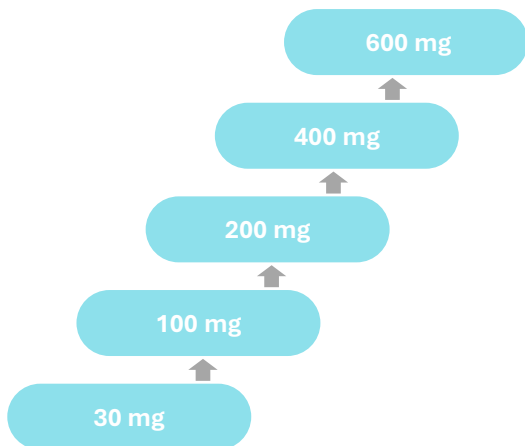
RestorAATion-2 clinical trial ongoing; 400 mg MAD data expected in 1Q 2026 and 600 mg SAD and MAD data expected in 2026



RestorAATion-1: Healthy Volunteers

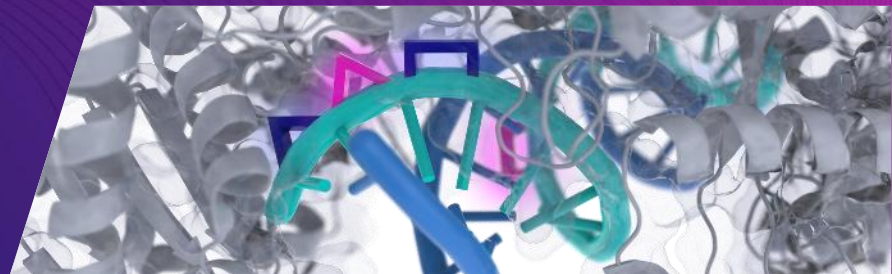
RestorAATion-2: AATD Patients

SAD → MAD Multi-dosing complete



Study key objectives		
Safety and tolerability	Pharmacokinetics	Serum M-AAT levels

WVE-008: PNPLA3 AIMer for liver disease



Erik Ingelsson, MD, PhD

Chief Scientific Officer



RNA editing program: WVE-008 (PNPLA3 AIMer) for liver diseases

Clinically-validated RNA editing

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

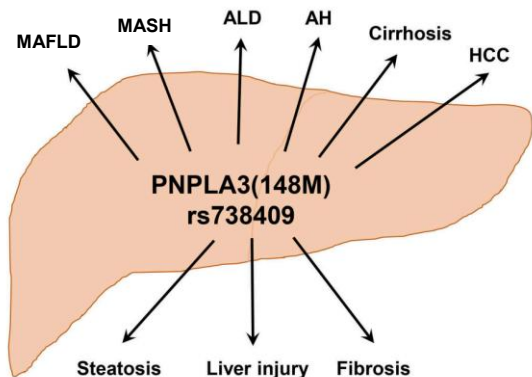
WVE-008 for PNPLA3 I148M

- Strong foundation in human genetics
- Over 9 million homozygous PNPLA3-I148M patients with liver disease in US and Europe
- GalNAc-RNA editing approach uniquely aims to restore PNPLA3 function to fully address disease

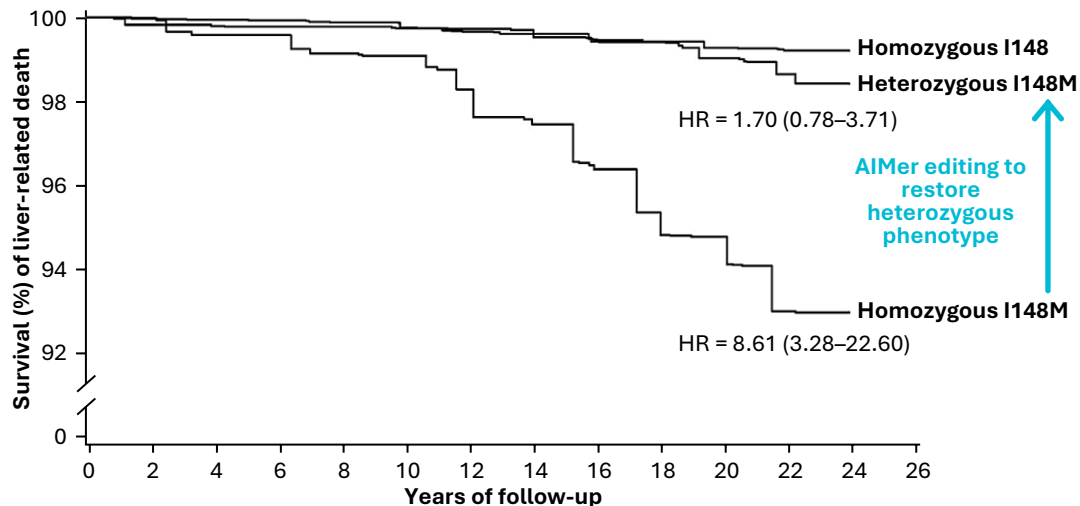
People homozygous for PNPLA3 I148M are at high risk for liver disease

Over 9 million homozygous PNPLA3-I148M patients with liver disease in US and Europe

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



>50% RNA editing would support restoration of heterozygous phenotype with lower risk of liver complications and death

Homozygous PNPLA3 I148M carriers with MASH tend to have more severe disease and urgent need for effective treatment options

MASH in PNPLA3 I148M non-carriers

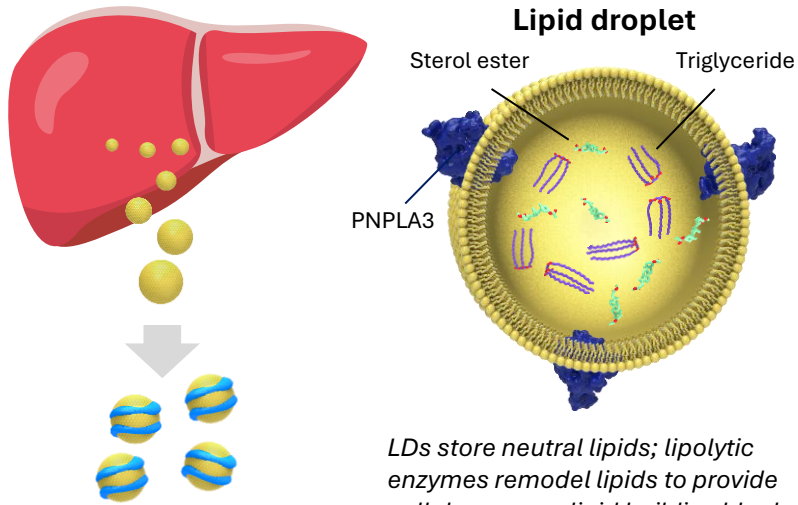
- Enrichment for metabolic cofactors including:
 - Obesity
 - Type 2 Diabetes
 - Hypertension
- Polygenetic background and strongly influenced by environmental factors
- Only treatment options are non-precision medicines primarily targeting steatosis and earlier stages of MASH

MASH in Homozygous PNPLA3 I148M carriers

- Subset of MASH population with more severe disease
 - Faster progression to advanced fibrosis and end-stage liver disease
- Account for ~90% of lean (normal weight) MASH
- Up to 25% of all MASH are homozygous for PNPLA3 I148M, even higher in lean MASH and advanced MASH
- No treatment options targeted to this population

PNPLA3 has a critical role in lipid metabolism in the liver

PNPLA3 balances triglyceride storage and secretion



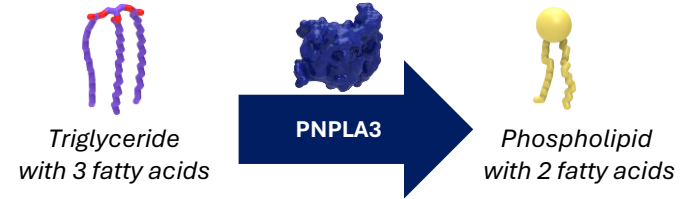
LDs store neutral lipids; lipolytic enzymes remodel lipids to provide cellular energy, lipid building blocks

PNPLA3 expression on LDs is dynamic, increases in response to food

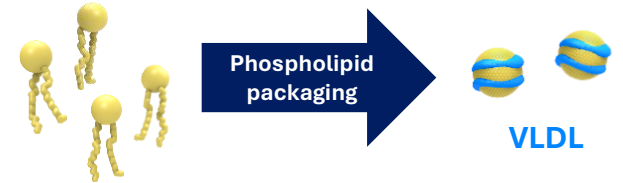
Tg-rich VLDL released into circulation, supply lipids to peripheral tissues

PNPLA3 supports lipid remodeling, lipid mobilization, and retinol metabolism

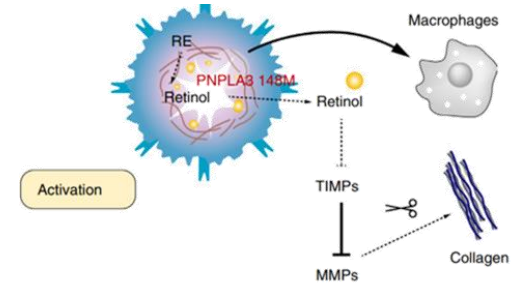
PNPLA3 supports lipid remodeling



PNPLA3 drives lipid mobilization from liver

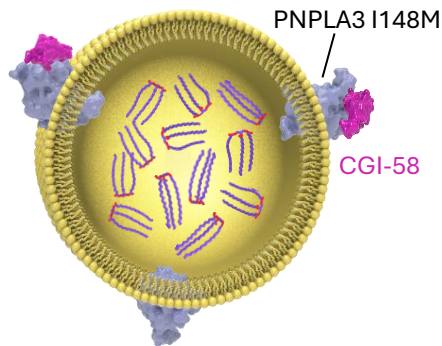


PNPLA3 regulates retinol balance in liver



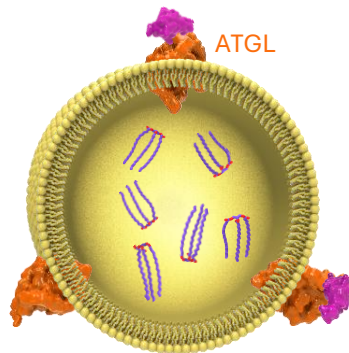
RNA editing is expected to restore PNPLA3 function to treat across the stages of liver diseases

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

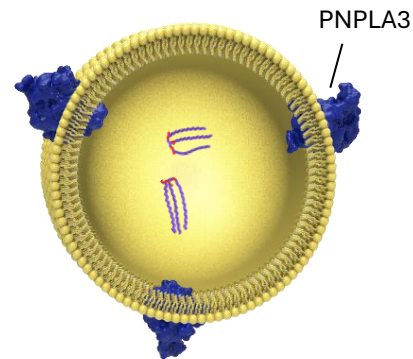
Silencing PNPLA3 may only partially address disease



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

✓ RNA editing approach

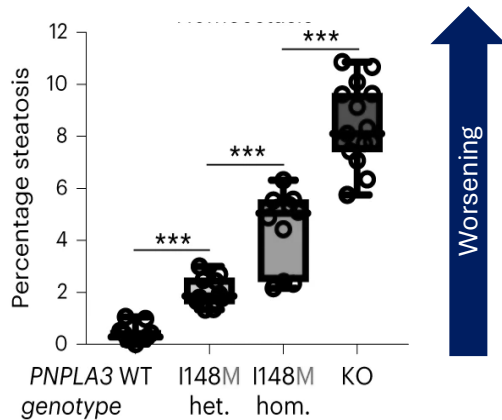
PNPLA3 correction expected to restore function, counter liver disease



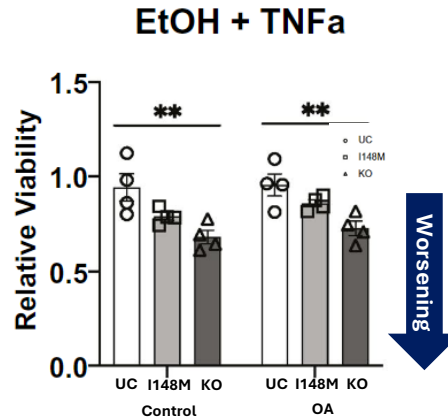
- Restores full PNPLA3 activity
- **Restores lipid mobilization, reverses steatosis, fibrosis, ballooning, and inflammation**

Silencing of PNPLA3 in normal liver may worsen basal physiological functions

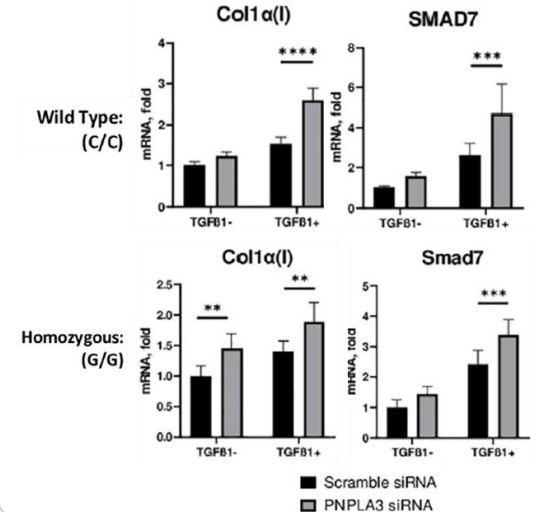
Silencing PNPLA3 worsens steatosis in iPSC-derived human liver organoids²



Silencing PNPLA3 increases inflammation-induced liver cell death in human primary hepatocytes³



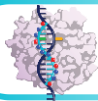
PNPLA3 siRNA exacerbates the fibrotic response in hepatic stellate cells¹



Functional PNPLA3 is imperative for liver health beyond improvements in steatosis

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

WVE-008
(RNA editing)



Proprietary chemistry



Subcutaneous injection (GalNAc)

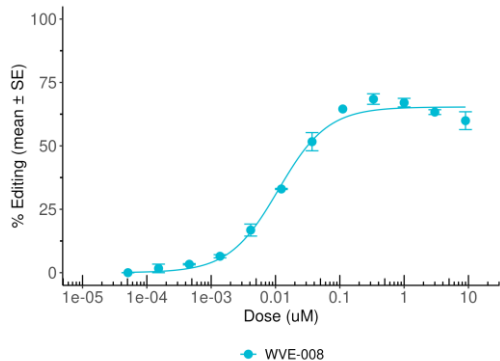


Potential for infrequent dosing

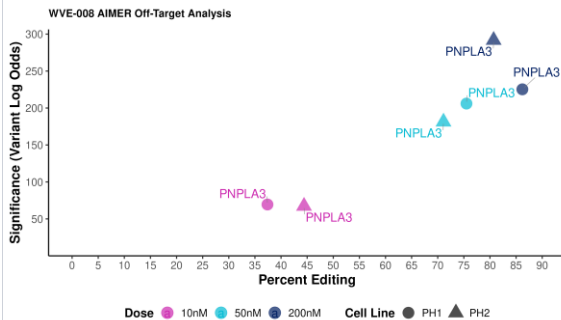


Highly specific editing

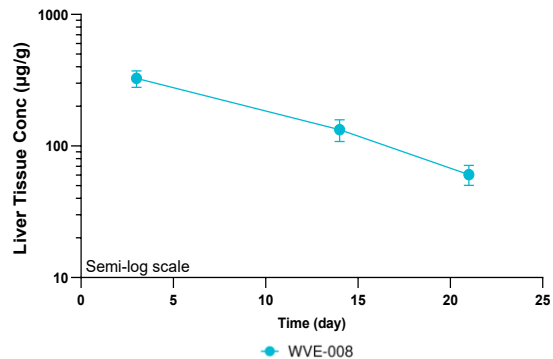
Potent editing with WVE-008



Highly specific editing with WVE-008



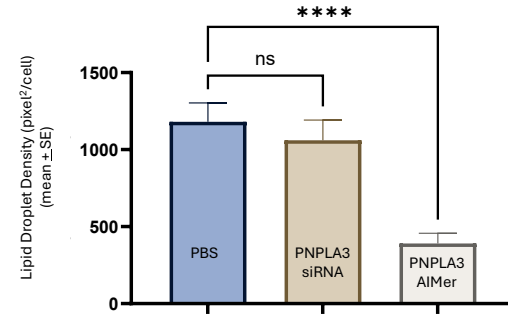
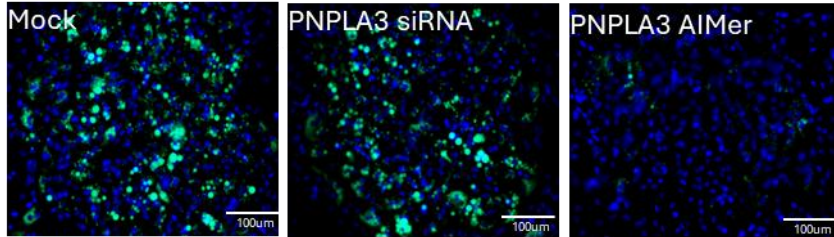
Tissue exposure supports excellent delivery



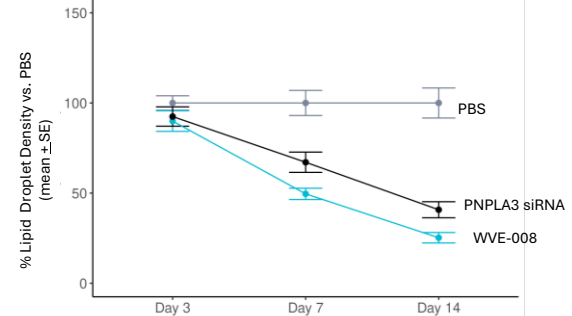
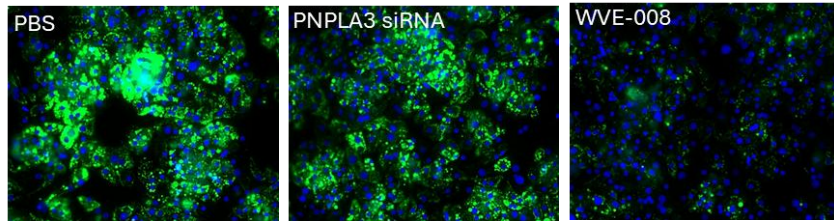
WVE-008 builds on the clinical translation of Wave's RNA editing capability

AIMers achieve efficient editing of PNPLA3, leading to reduction of liver fat

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



CTA filing for WVE-008 expected in 2026

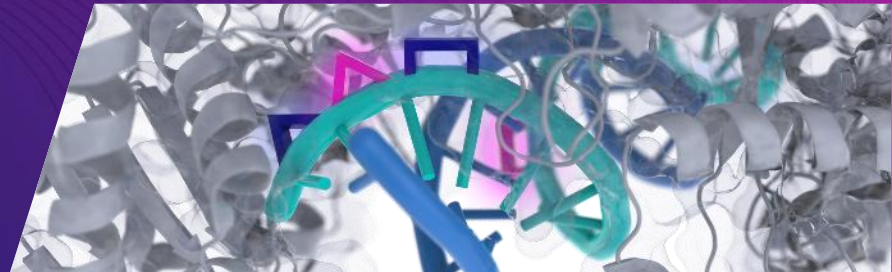
- Large addressable patient population with no disease modifying treatment options targeting PNPLA3 I148M-driven liver disease
- PNPLA3 preclinical data demonstrates ability to restore functional PNPLA3 with RNA editing, restoring lipid regulation for improvement of liver health
- WVE-008 candidate selected, builds on successful clinical translation of Wave's RNA editing capability
- Clinical development planning underway for a first-in-human clinical study
 - Leveraging previously genotyped populations to identify homozygous I148M carriers
 - Initial study to enroll homozygous carriers to assess safety, tolerability, pharmacokinetics and pharmacodynamic endpoints

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

Robust AIMer pipeline, including extra-hepatic targets



WVE-007: INHBE GalNAc-siRNA



Erik Ingelsson, MD, PhD
Chief Scientific Officer



Obesity is a metabolic disease with a treatment paradigm ripe for disruption

Advancing WVE-007, a GalNAc-siRNA, as a novel, long acting, muscle sparing approach for obesity

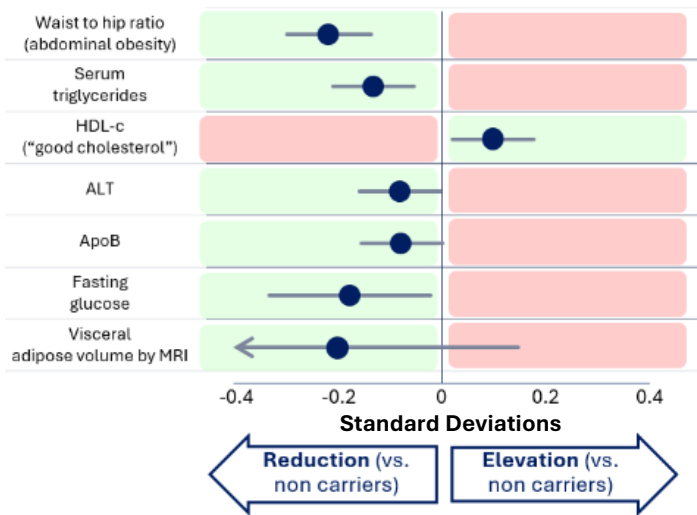


- Adults with obesity have higher risk for many serious health conditions, including heart disease, type 2 diabetes, and some forms of cancer¹
- GLP-1s are current standard of care for weight loss, but impact is often limited by:
 - Loss of muscle mass²
 - Poor tolerability³
 - Frequent dosing⁴
 - High discontinuation rates^{5,6}

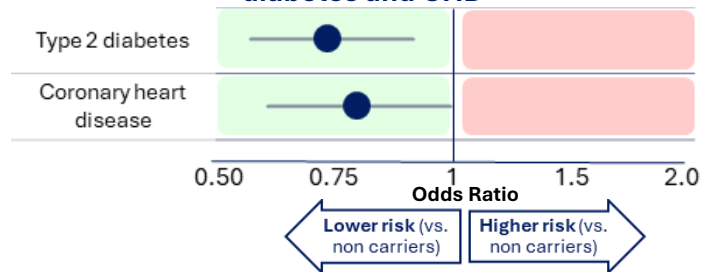
> 1 billion people living with obesity globally

Human genetic data demonstrate that heterozygous INHBE LoF carriers have a healthy metabolic profile

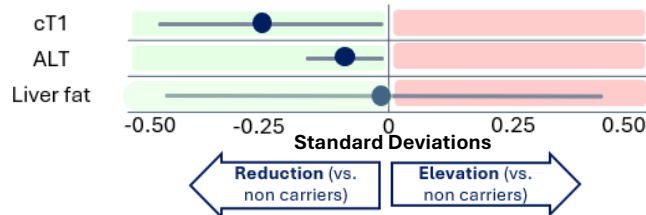
Heterozygous INHBE LoF carriers have favorable traits: lower abdominal obesity, lower triglycerides, higher HDL-c



Heterozygous INHBE LoF carriers have lower risk of Type 2 diabetes and CHD



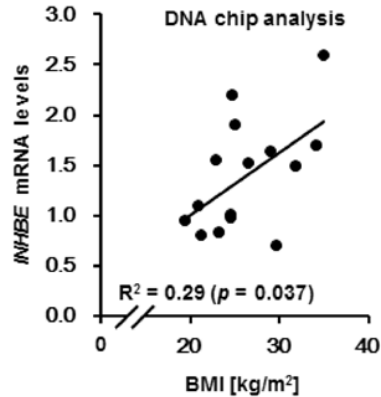
Favorable association with liver traits



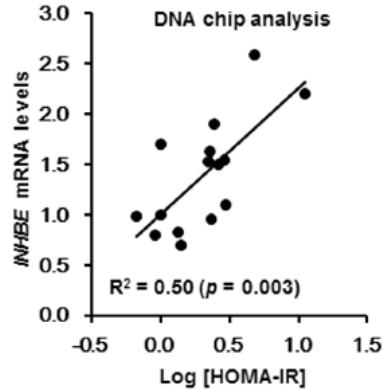
Silencing INHBE mRNA by $\geq 50\%$ is expected to recapitulate the healthy metabolic profile of heterozygous INHBE loss of function (LoF) carriers

Lower INHBE mRNA levels are associated with better metabolic health

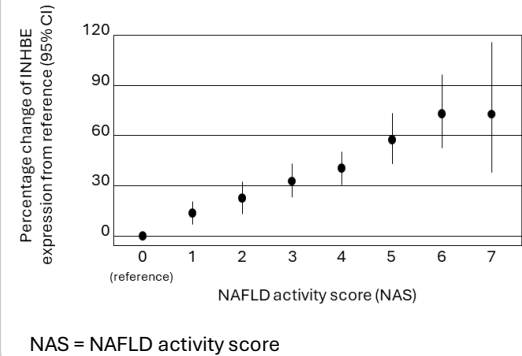
Adiposity is associated with INHBE mRNA¹



Insulin resistance is associated with INHBE mRNA¹



MAFLD is associated with INHBE expression²

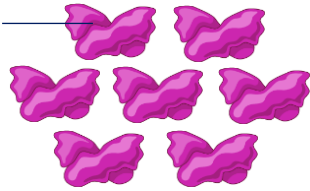


Silencing of INHBE mRNA is expected to lead to fat loss and restore metabolic health

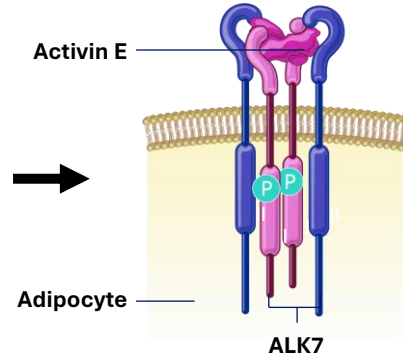
Silencing INHBE mRNA has potential to treat obesity and associated metabolic diseases

Release of **dimerized** INHBE subunits creates hepatokine **Activin E**

Activin E



Binds to and **activates** **ACVR1C (ALK7)** receptor in adipose tissue

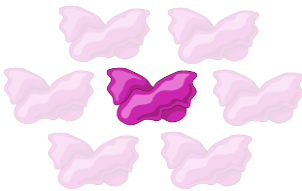


Block adipose lipolysis

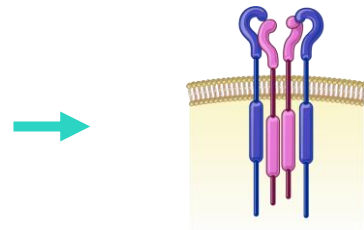


Increased abdominal adiposity leads to **obesity, CVD and T2D**

Reduction of INHBE mRNA with GalNAc-siRNA



Reduced release of hepatokine **Activin E**



Diminished activation of **ACVR1C (ALK7)** receptor in adipose tissue

Increased adipose lipolysis and shrink adipocytes

Decreased abdominal adiposity leads to **weight loss and reduced risk for CVD and T2D**

WVE-007: Potential best-in-class INHBE-siRNA that leverages proprietary chemistry for enhanced interactions with Ago2, better silencing

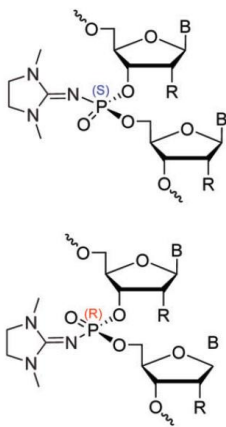
WVE-007 (siRNA)

✓ Proprietary, clinically validated chemistry

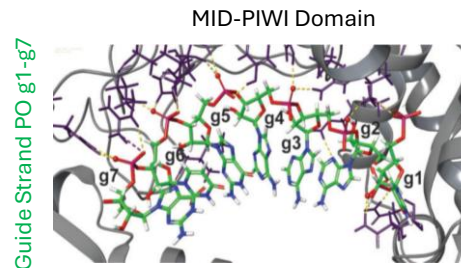
✓ Subcutaneous injection (GalNAC)

✓ Potential for infrequent dosing (1 – 2x year)

Phosphoryl guanidine (PN)



Rational design Ago2



Builds beyond siRNA NAR publication

WVE-007: Nucleic Acids Research 2023, Vol. 52, No. 9
<https://doi.org/10.1093/nar/gkad268>

Published online: 04 April 2023

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

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Received December 16, 2022; Revised March 04, 2023; Editorial Decision March 07, 2023; Accepted March 07, 2023

ABSTRACT

We report the systematic investigation of the impact of RNA backbone (RNA) glycols on the potency and durability of gene silencing by RNA interference (RNAi) using an Ago2-mediated silencing. The incorporation of stereorep chimeric and conformationally rigid and flexible RNA backbones into siRNA backbones improved the potency and durability of gene silencing by RNAi. The stereorep chimeric RNA backbones showed improved potency and durability of gene silencing by RNAi compared with the reference siRNA. The improved potency and durability of gene silencing by RNAi were associated with enhanced interactions between the siRNA and the MID-PIWI domain of Ago2. The improved potency and durability of gene silencing by RNAi were associated with enhanced interactions between the siRNA and the MID-PIWI domain of Ago2. The improved potency and durability of gene silencing by RNAi were associated with enhanced interactions between the siRNA and the MID-PIWI domain of Ago2.

INTRODUCTION

The RNAi pathway is a conserved mechanism for gene silencing and is a key component of the innate immune system. RNAi is a natural antiviral defense mechanism in plants and invertebrates. In mammals, RNAi is primarily used for gene silencing in the context of viral defense and cancer therapy. RNAi is a natural antiviral defense mechanism in plants and invertebrates. In mammals, RNAi is primarily used for gene silencing in the context of viral defense and cancer therapy. RNAi is a natural antiviral defense mechanism in plants and invertebrates. In mammals, RNAi is primarily used for gene silencing in the context of viral defense and cancer therapy.

Wave's siRNA has demonstrated >10x improvement in Ago2 loading versus reference compounds

Single doses of INHBE GalNAc-siRNA result in dose-dependent weight loss and reduction of visceral fat, without affecting muscle mass, in DIO mice



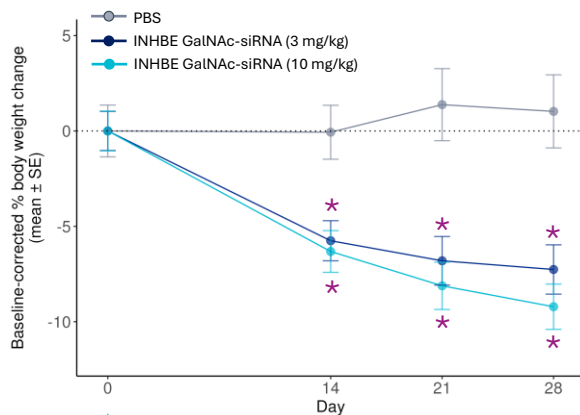
Reduction in body weight



Reduction in visceral fat

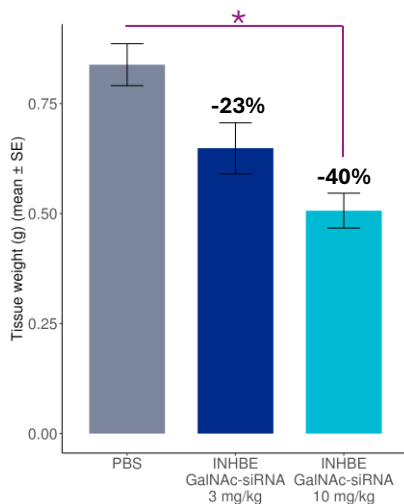


No muscle loss

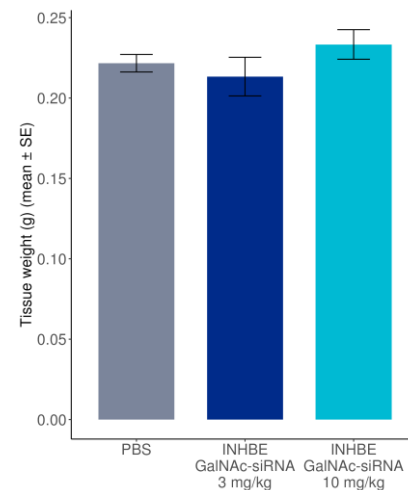


Single dose INHBE GalNAc-siRNA

Epididymal fat weight (Day 28)



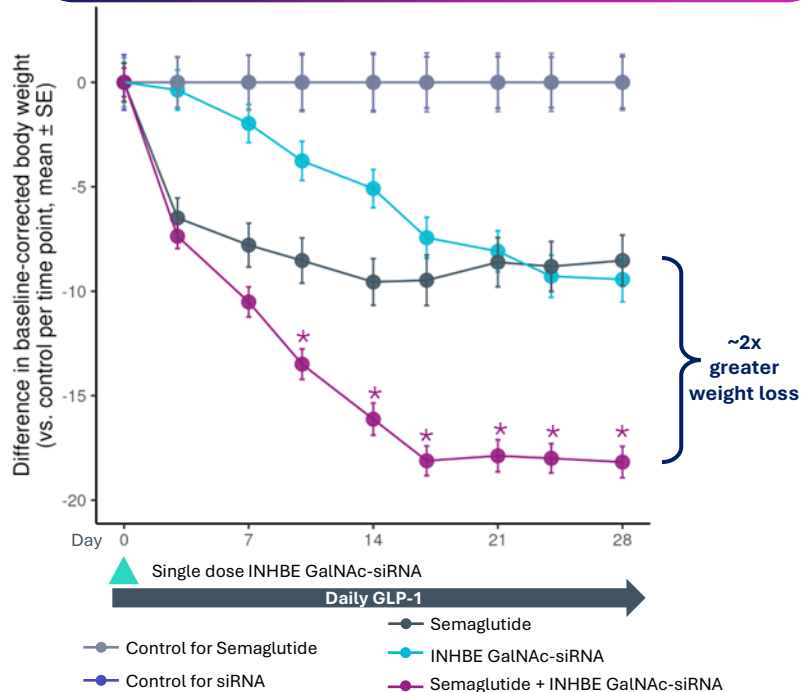
Quadriceps weight (Day 28)



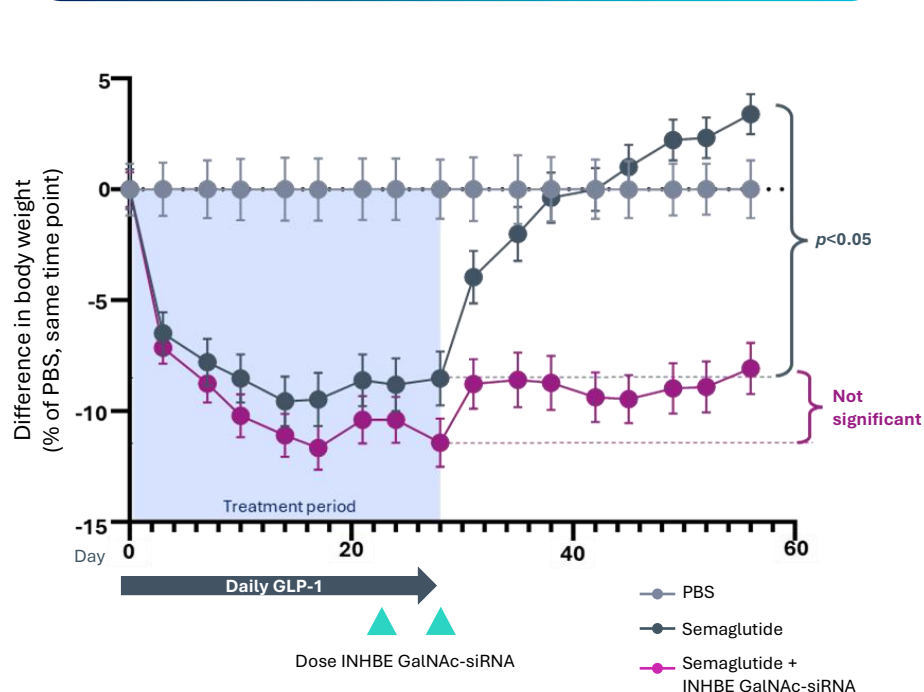
Preclinical data support INHBE GalNAc-siRNA as a single agent for healthy weight loss

INHBE GalNac-siRNA can be used synergistically with GLP-1s or to curtail weight regain after the cessation of treatment with GLP-1

✓ Combined with GLP-1: Greater weight loss

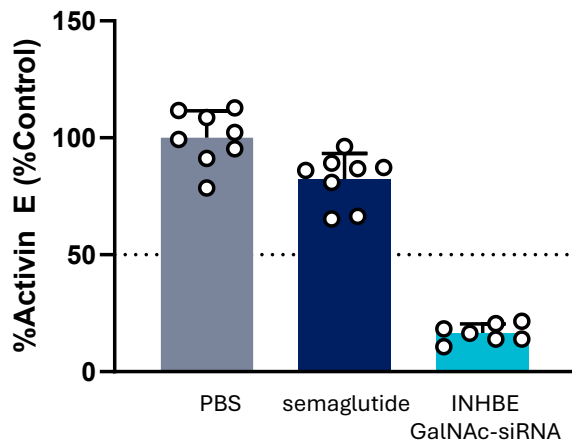


✓ After cessation of GLP-1: Curtails weight re-gain

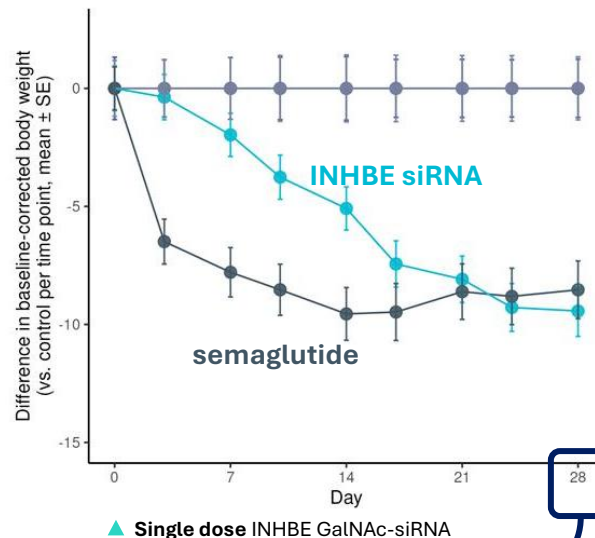


Potent and durable Activin E reduction of greater than 70% in preclinical models delivers weight loss similar to GLP-1

Durable Activin E reduction one-month following a single dose

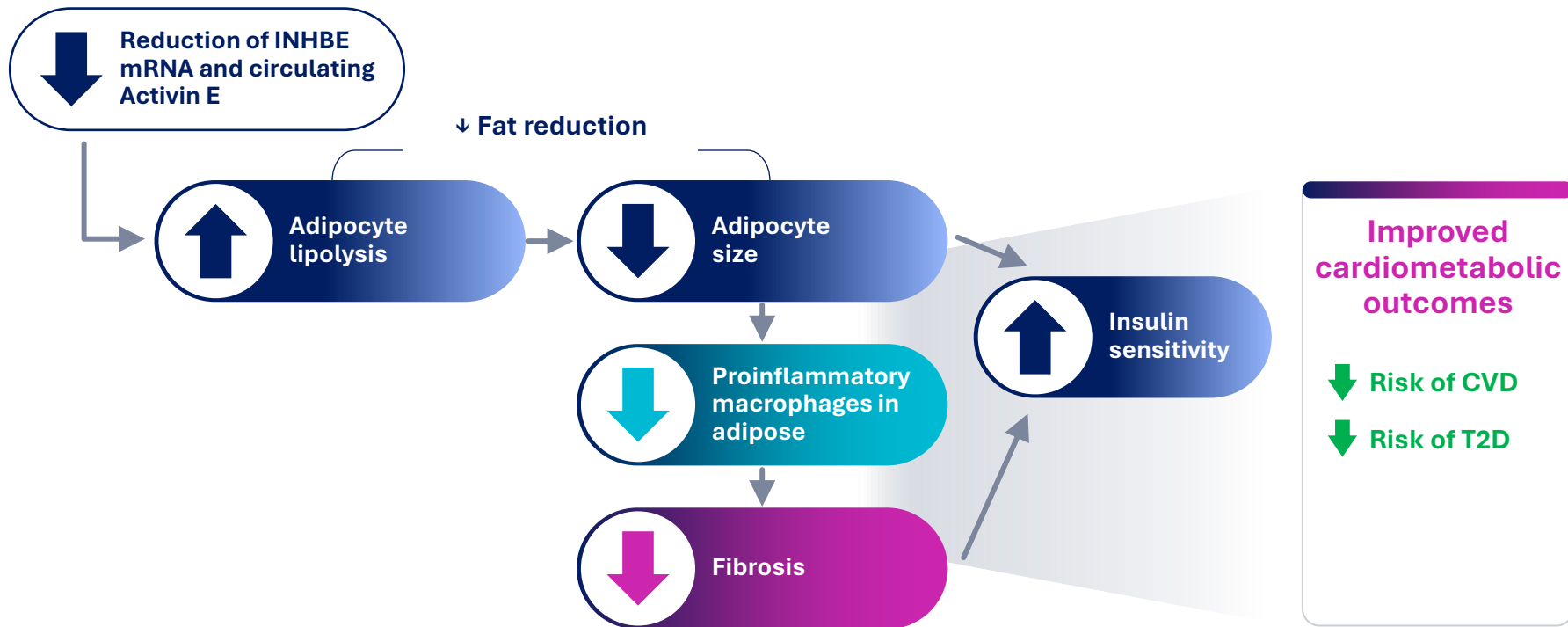


Weight loss with INHBE GalNAc-siRNA **more gradual** versus semaglutide



Treatment with INHBE GalNAc-siRNA expected to improve key measures of cardiometabolic health

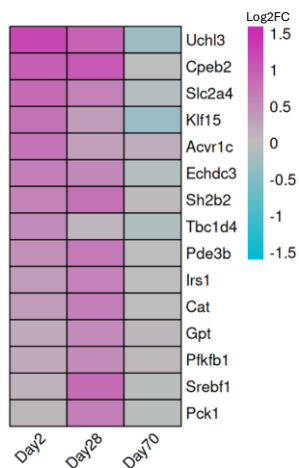
Measures of metabolic improvements



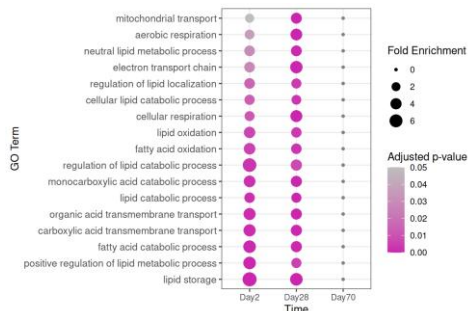
INHBE siRNA improves insulin sensitivity, cellular energetics, and beiging of white adipose tissue

Upregulation

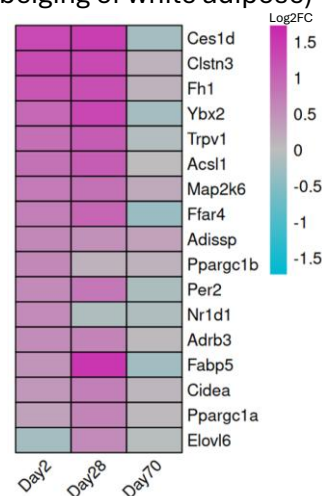
Insulin sensitivity



Fatty acid utilization for energy production

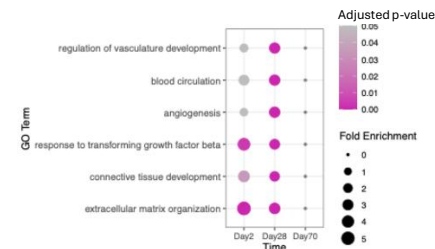


Adaptive thermogenesis (beiging of white adipose)



Downregulation

Adipose remodeling and fibrosis pathways

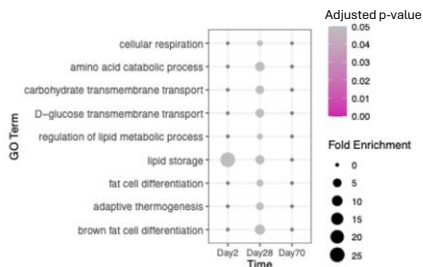


Suppressing adipose remodeling and fibrosis in inguinal subcutaneous adipose

INHBE siRNA improves cellular energetics while suppressing inflammation and fibrosis in mesenteric visceral adipose

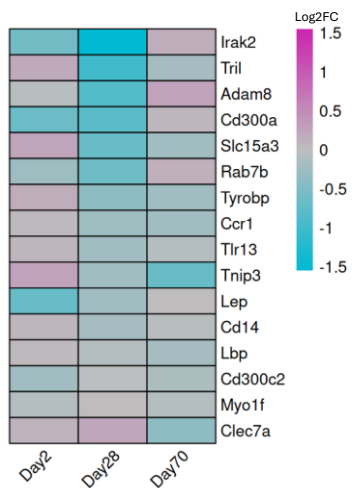
Upregulation

Glucose utilization, thermogenesis, and lipid metabolism (consistent with inguinal subcutaneous adipose)

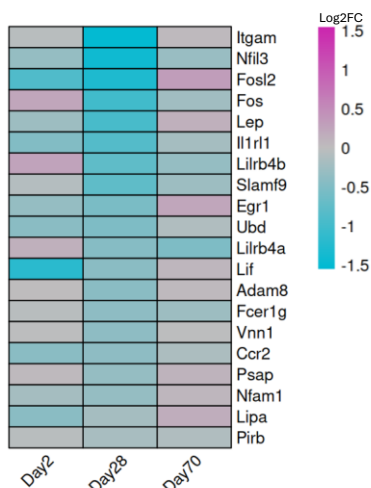


Downregulation

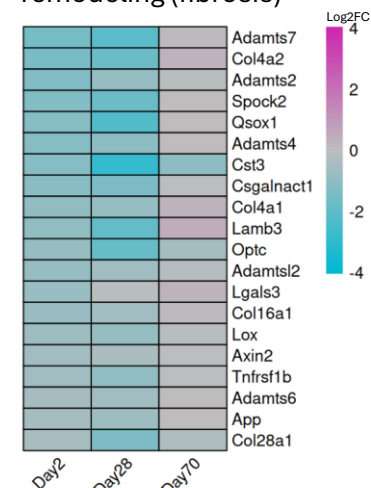
Innate immunity



Cytokine release



Extracellular matrix remodeling (fibrosis)



Anticipated improvement in plasticity of adipose tissues with downregulation

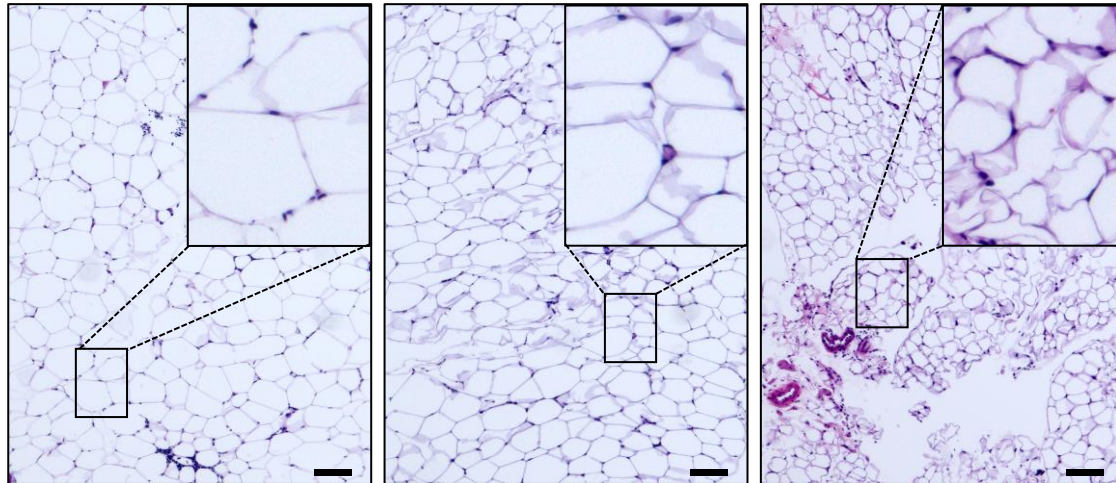
A single dose of INHBE GalNAc-siRNA led to shrinkage of adipocytes in DIO mice

DIO

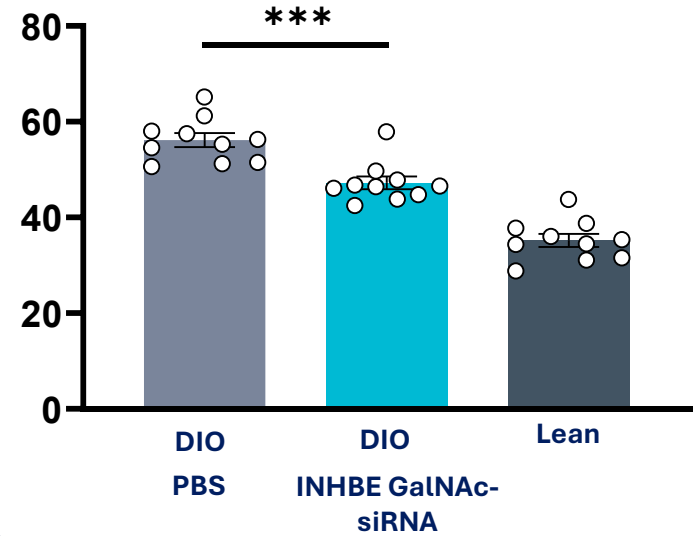
Lean

PBS

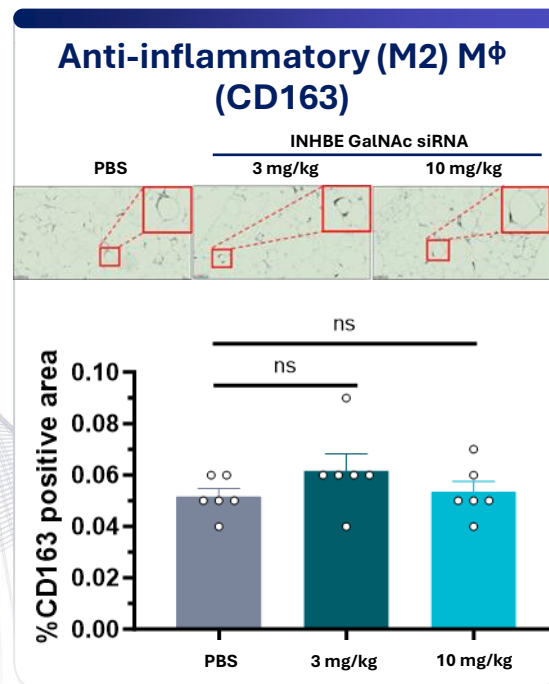
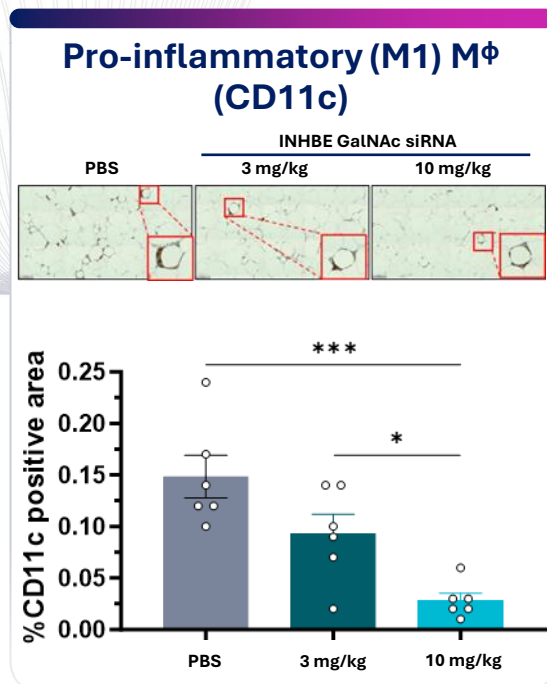
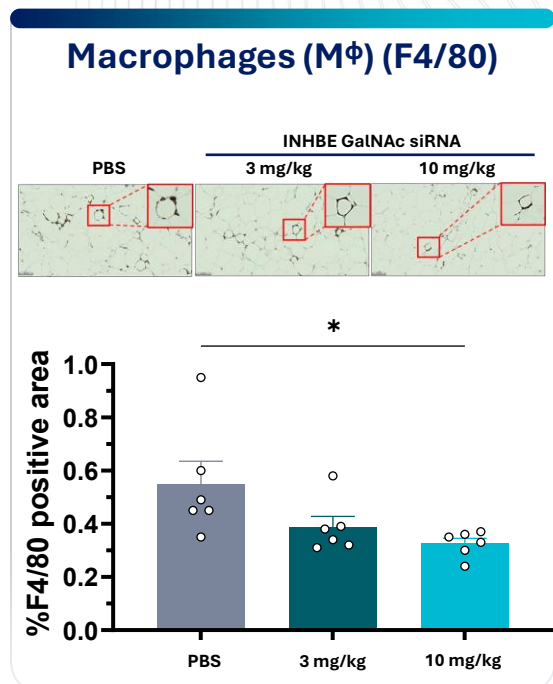
INHBE GalNAc-siRNA



Mean adipocyte diameter
(μm)

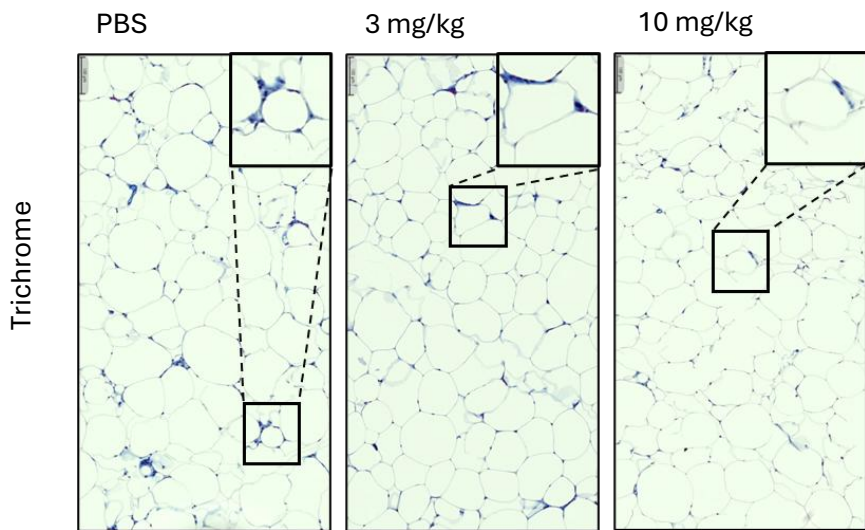


A single dose of INHBE siRNA led to a lower inflammatory state of visceral adipose tissues in DIO mice, with strong suppression of pro-inflammatory M1 macrophages in visceral fat

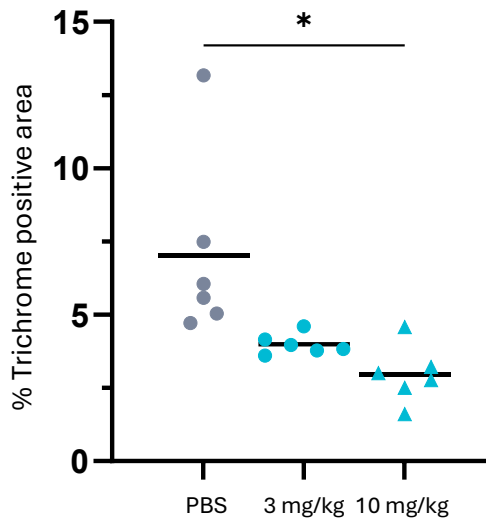


Lowering of inflammatory state of epiWAT visceral fat induced by single dose of INHBE siRNA resulted in 58% reduction of adipose fibrosis

Reduced staining illustrates decreased tissue fibrosis



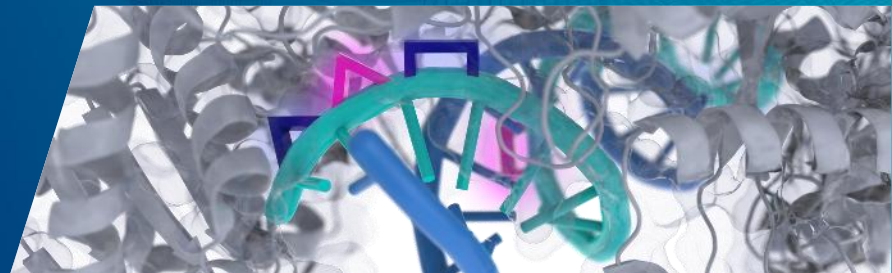
Fibrosis in mouse adipose (Day 56)



WVE-007 has potential to be a convenient therapeutic option to drive fat loss, while preserving muscle

- Human genetic data of INHBE LoF carriers support potential for INHBE-siRNA to drive healthy metabolic outcomes
- WVE-007 siRNA includes proprietary chemistry, including PN-chemistry and unique design to support highly potent and durable silencing
- Potent and durable INHBE mRNA reduction of >70% observed in preclinical studies
- Treatment with INHBE GalNAc-siRNA expected to improve key measures of cardiometabolic health based on preclinical data
- WVE-007 is currently being evaluated as monotherapy in ongoing INLIGHT clinical study

INLIGHT clinical study and target engagement update



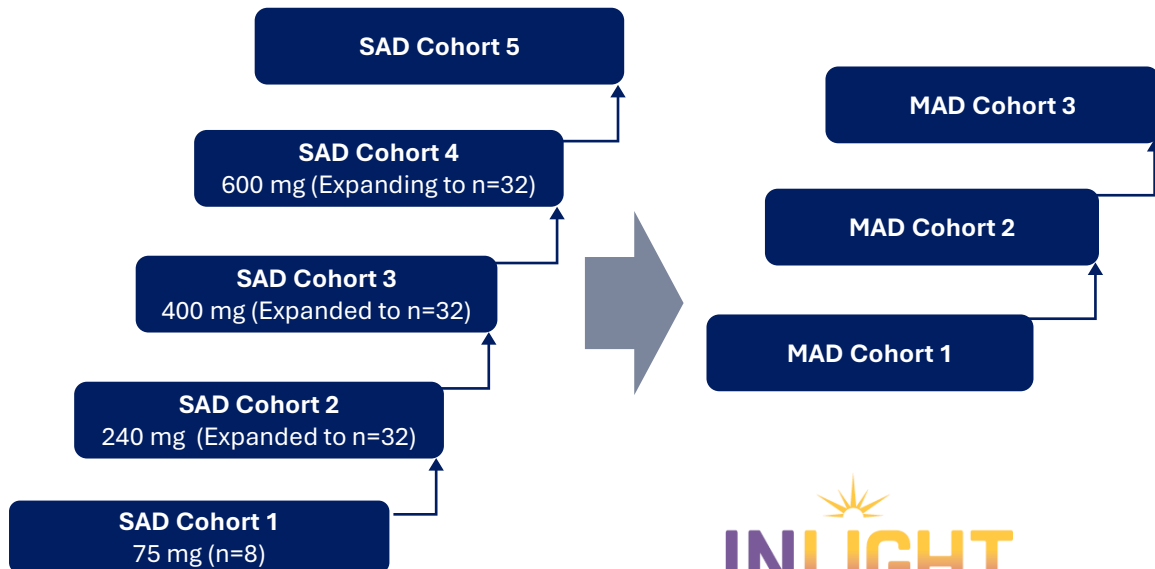
Chris Wright, MD, PhD
Chief Medical Officer



INLIGHT: Dose escalation continues in single-dose portion, follow-up ongoing from multiple therapeutic cohorts

Randomized, double-blind, placebo-controlled (3:1) study of ascending doses of WVE-007

- **Objective:** Assess dose safety, tolerability, PK and PD
- **Key study criteria:**
 - **HbA1c:** <5.9
 - **BMI:** 28 – 35 kg/m² (SAD)
- **Key measurements**
 - **Primary:** Safety and tolerability
 - **Secondary:** PK, Activin E
 - **Exploratory PD:**
 - Body weight
 - Body composition (including DEXA)
 - Biomarkers
- Multiple clinical trial sites, including US



**INLIGHT**

Today's update: Activin E biomarker data from single-dose Cohorts 1, 2 and 3

Cohort 3
400 mg

Cohort 2
240 mg

Cohort 1
75 mg

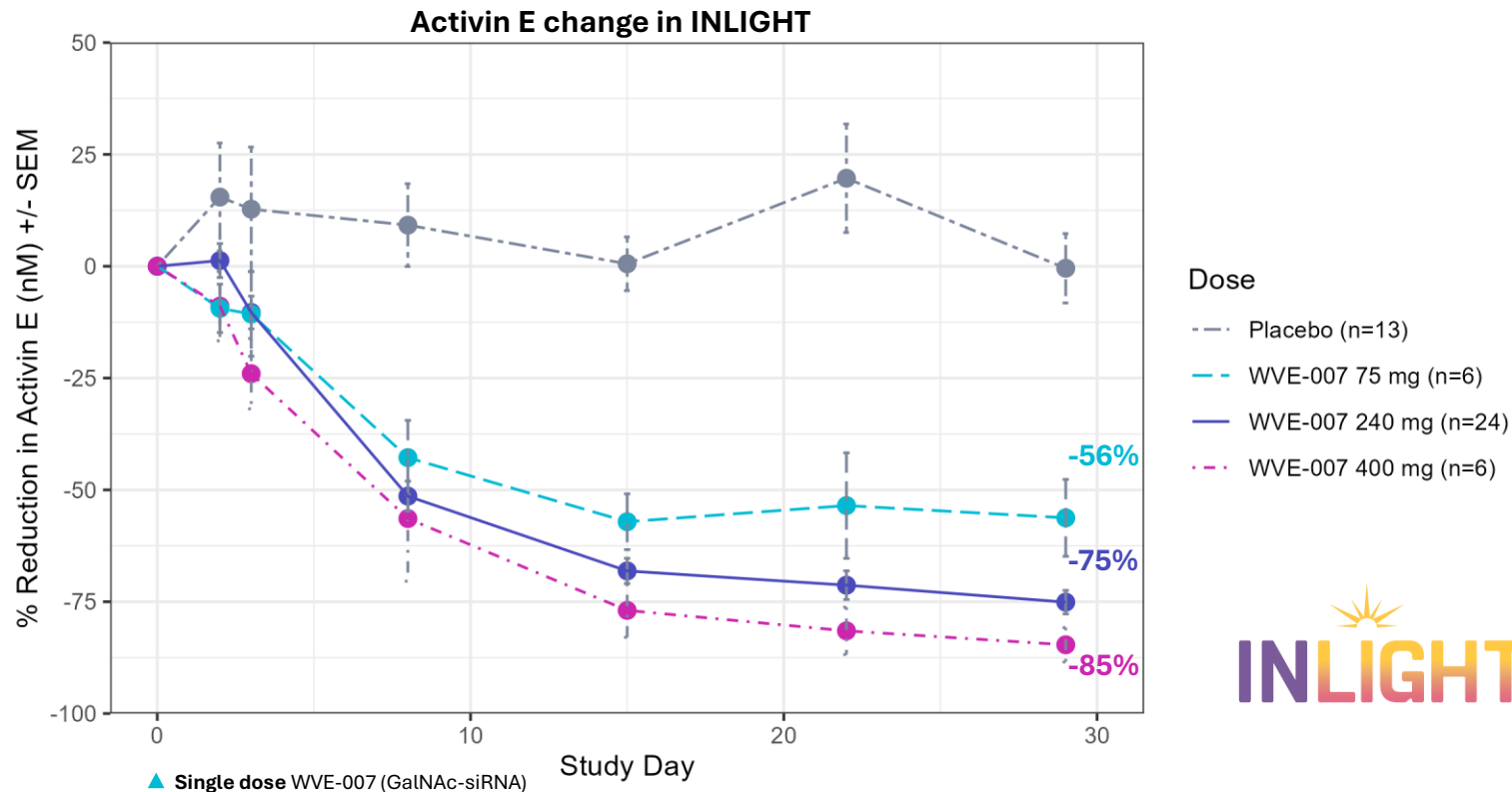
Activin E biomarker data includes

- 1 month of follow-up (Day 29) from Cohort 3 (n=8)
- 1 month of follow-up (Day 29) from Cohort 2 (n=32)
- 6 months of follow-up (Day 169) from Cohort 1 (n=8)



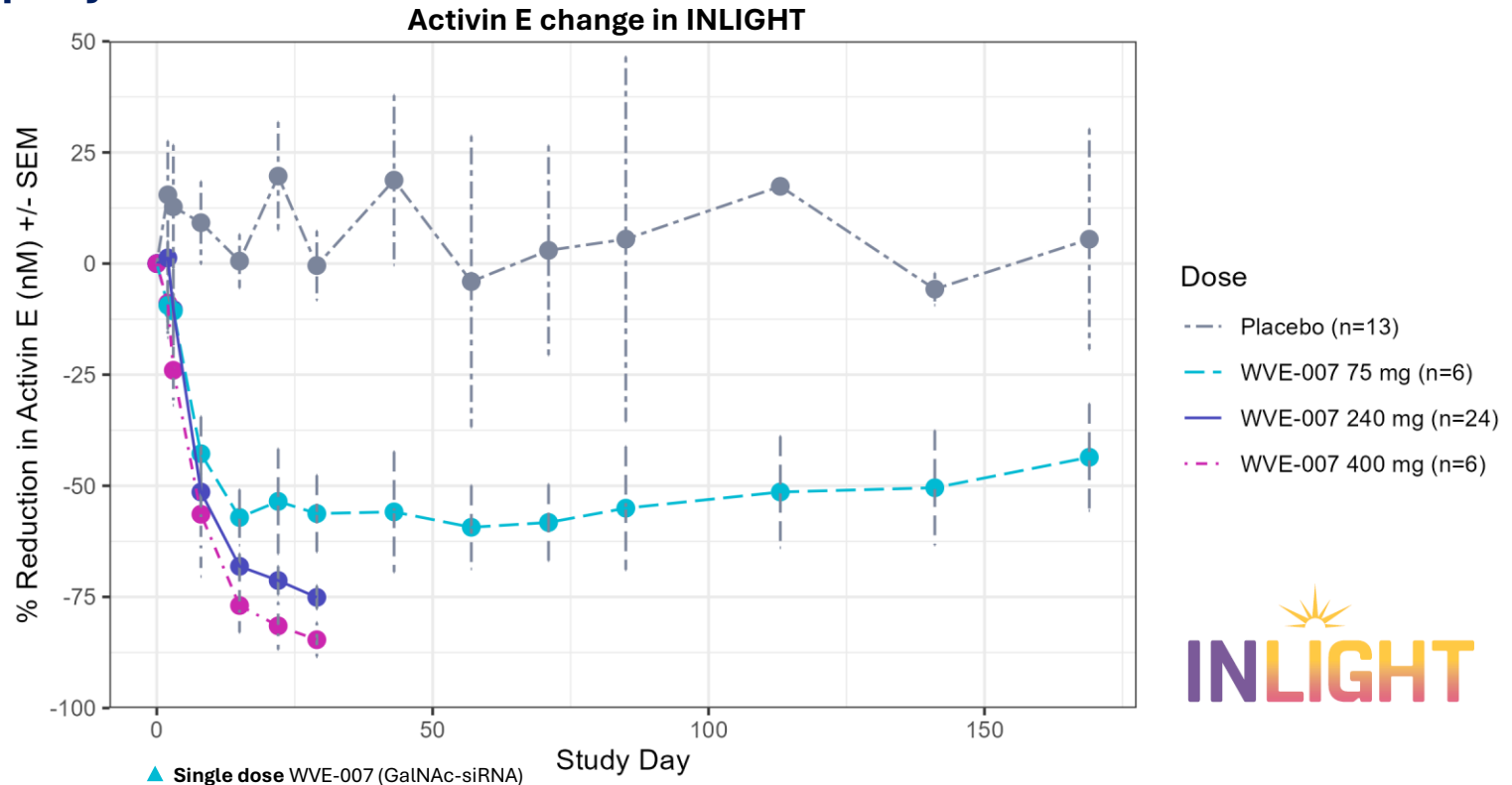
WVE-007 is safe and well tolerated to date; no discontinuations

Highly significant, dose dependent Activin E reductions following a single dose of WVE-007



INLIGHT

Highly durable Activin E reductions with WVE-007 supporting dosing once or twice per year

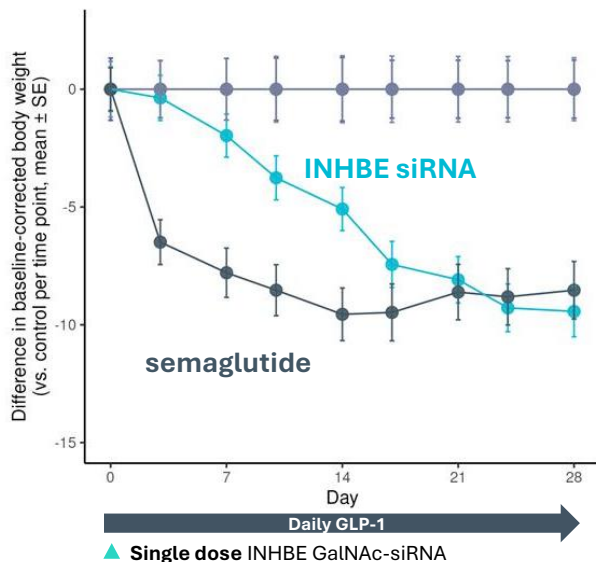


INLIGHT

Clinical Activin E reductions after single dose of WVE-007 exceed levels leading to weight loss in preclinical studies

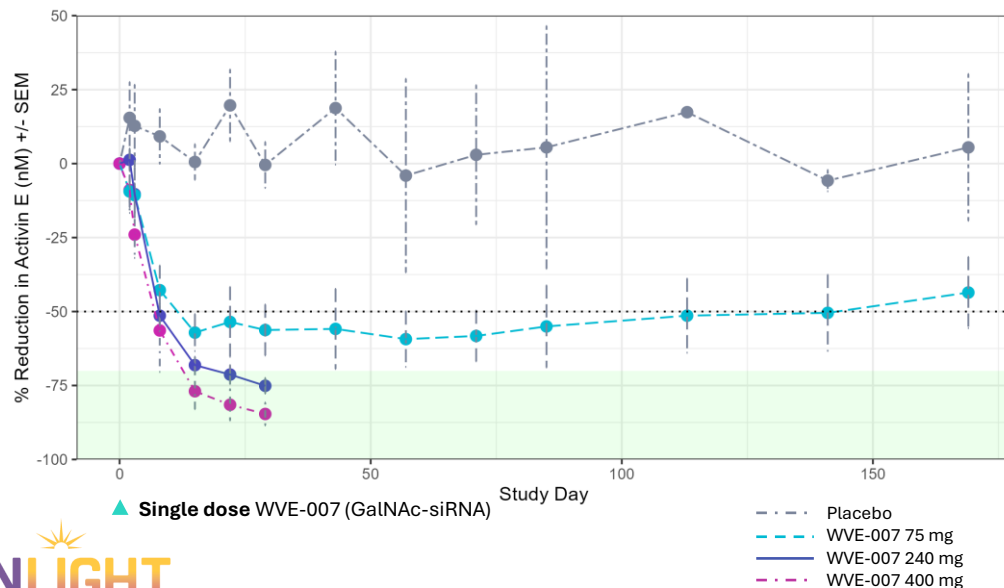
Preclinical studies

>70% Activin E reductions led to weight loss



INLIGHT clinical trial

>70% Activin E reductions achieved



INLIGHT includes evaluations across multiple cohorts and follow-up periods to detect metabolic, body composition improvements, and weight loss



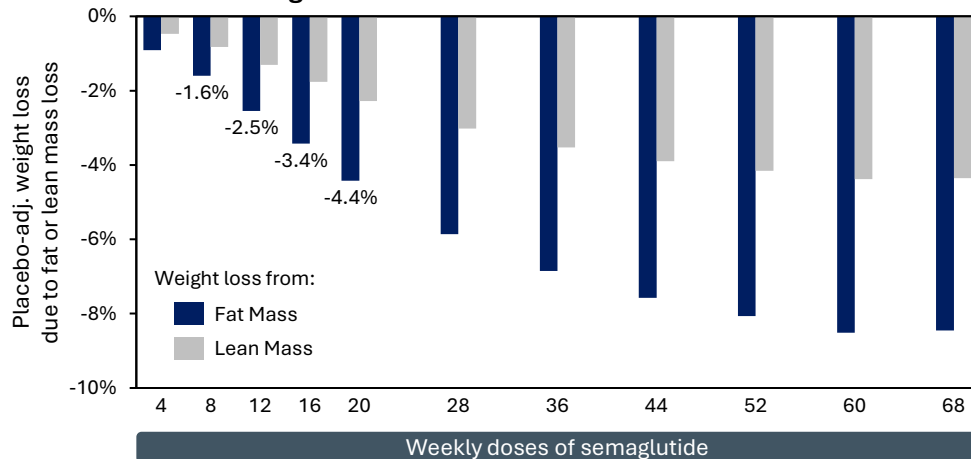
Single dose cohorts



INLIGHT initial clinical data updates aim to achieve:

Activin E	Potent, durable reductions achieved
Associated biomarkers	Signals of metabolic improvement
Fat mass	Reductions
Lean mass	No reductions (preservation)
Body weight	Reductions

Semaglutide Clinical Study (STEP-1): Placebo-Adjusted Weight Loss from Fat and Lean Mass Reduction



WVE-007 aims to achieve fat loss on par with semaglutide by 6 months post-single dose

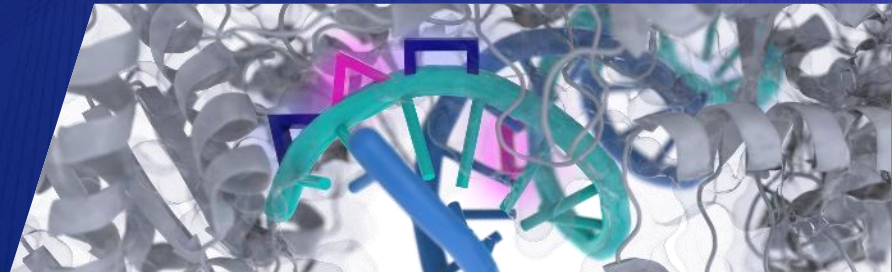
Multiple near-term clinical anticipated data updates for WVE-007, including body weight and body composition

Clinical target engagement update:

- WVE-007 led to dose-dependent, potent and durable Activin E reductions in INLIGHT clinical study
 - Activin E reductions exceed levels that led to weight loss in preclinical models
 - Potential for once or twice yearly dosing
- Safe and well-tolerated to date; 600 mg ongoing (Cohort 4)
- Follow-up ongoing with multiple clinical data updates expected starting in 4Q 2025



SpiNA: Advancing a best-in-class siRNA capability



Chandra Vargeese, PhD

Chief Technology Officer



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

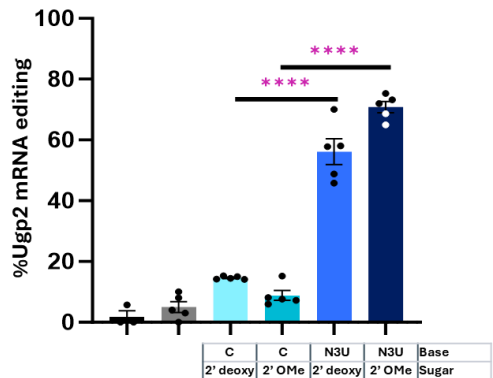
Single well-defined compounds

✓ Optimize stereochemistry

✓ Optimize pharmacological profiles

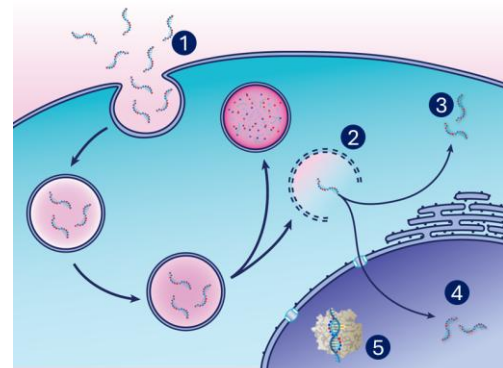
✓ Optimize sequence

Novel base and sugar chemistry modifications



Addition of base modifications led to dramatic increase RNA editing efficiency

Novel backbone modifications

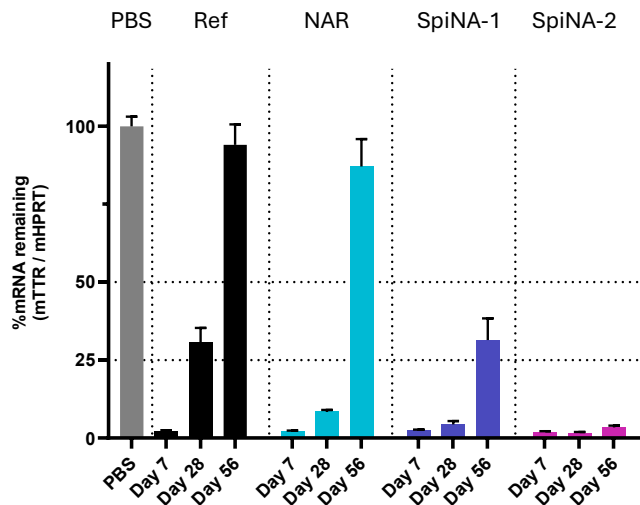


Addition of PN modification increases: Cell uptake, endosomal release, residency, nuclear uptake, target engagement

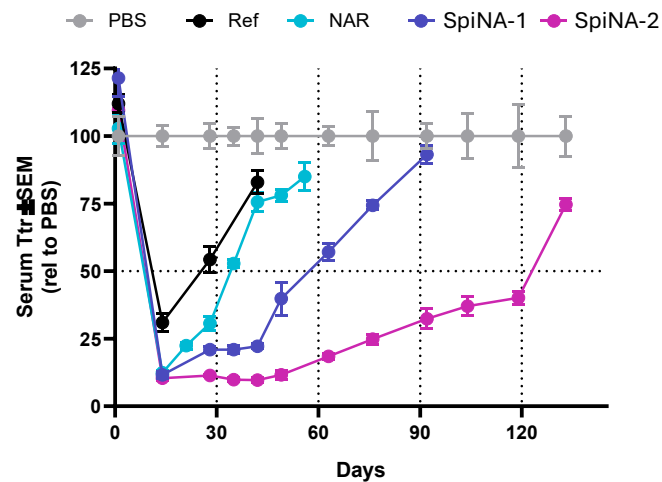
Substantial improvements in duration of activity and potency achieved through chemistry optimization with SpiNA GalNAc-siRNAs

SpiNA: Stereopure interfering Nucleic Acid

mRNA silencing following single dose

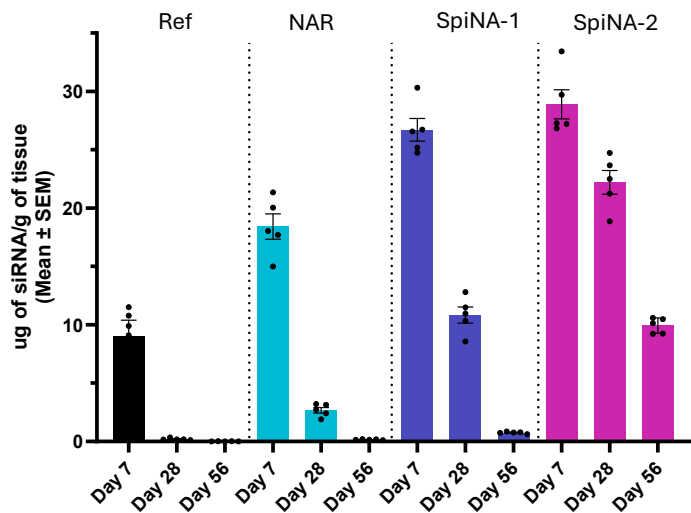


Protein reduction following single dose

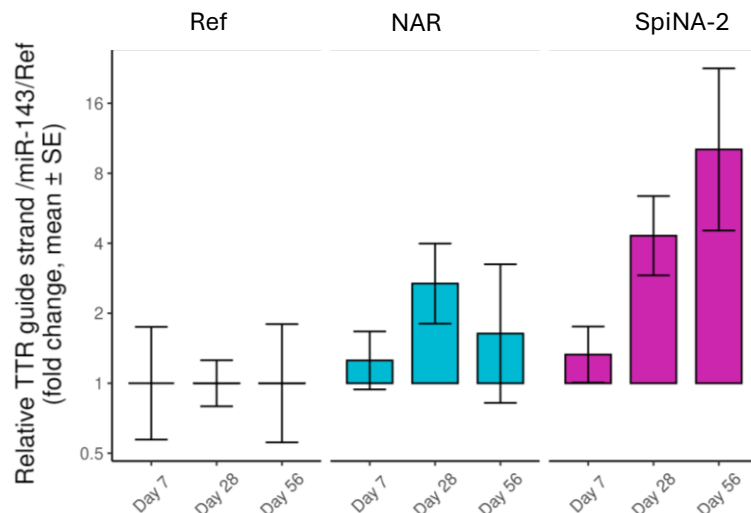


SpiNA GalNAc-siRNAs demonstrate >10-fold improvement in Ago2 loading versus reference siRNAs

siRNA pharmacokinetics



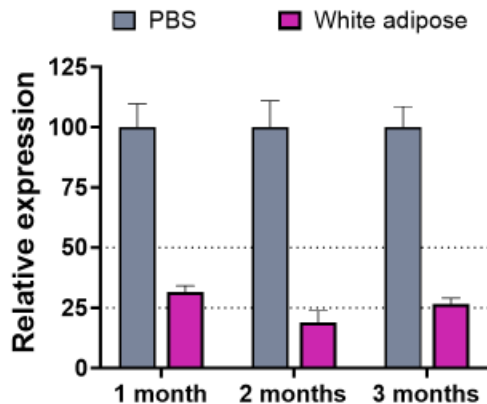
siRNA Ago2 loading



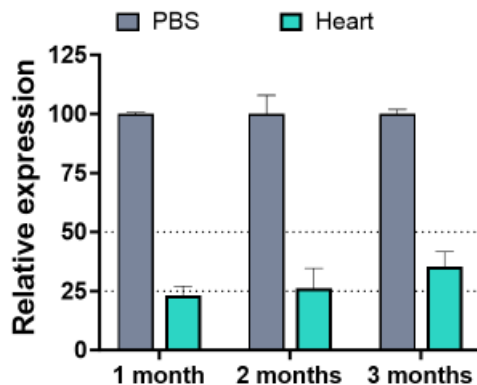
PN variants in SpiNA achieve robust and durable target engagement in extrahepatic tissues

Silencing was durable out to at least 3 months following single, subcutaneous dose

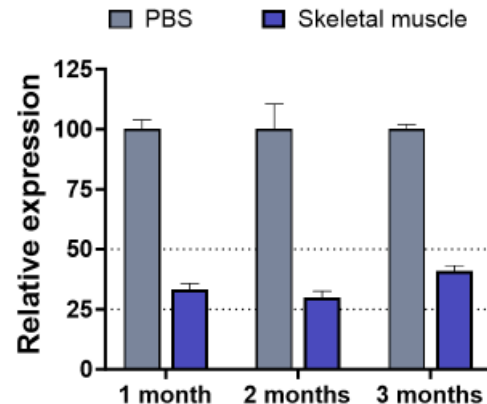
SpiNA Targeting White Adipose Tissue



SpiNA Targeting Heart



SpiNA Targeting Skeletal Muscle

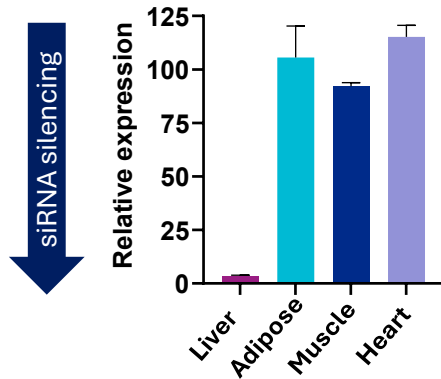


Directing silencing to high priority extrahepatic tissues in mice using siRNA

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

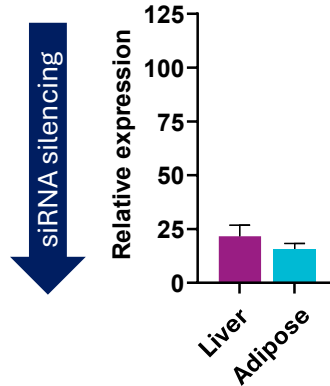
GalNAc + PN

Liver Targeting siRNA

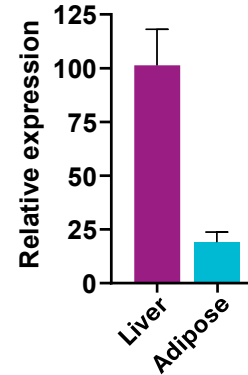


Non-GalNAc + PN variants

Liver and Adipose Targeting siRNA



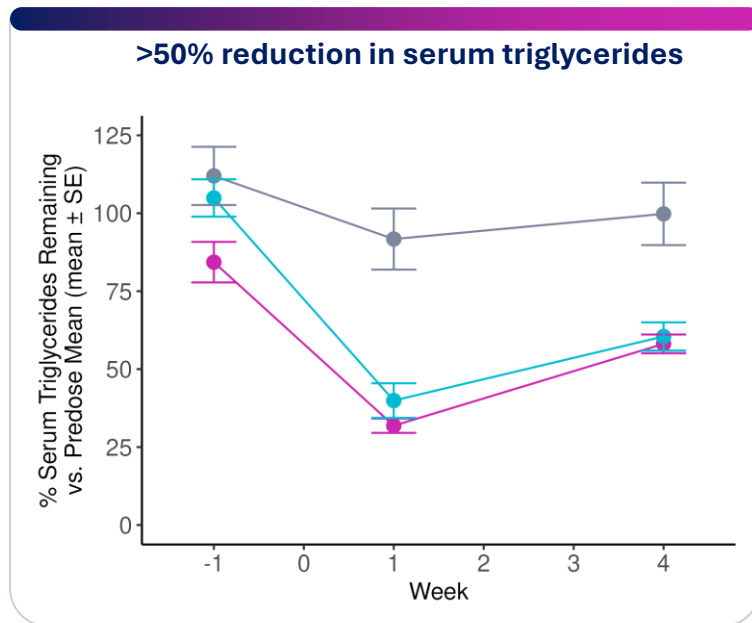
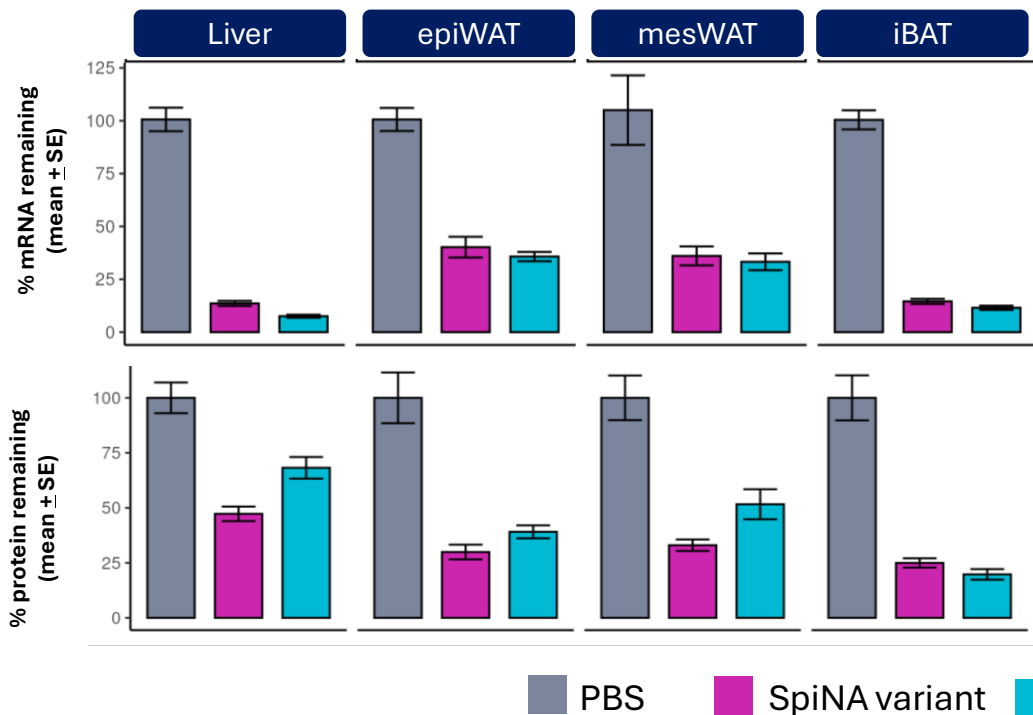
Adipose Targeting siRNA



In vivo silencing at 8 weeks following a single dose

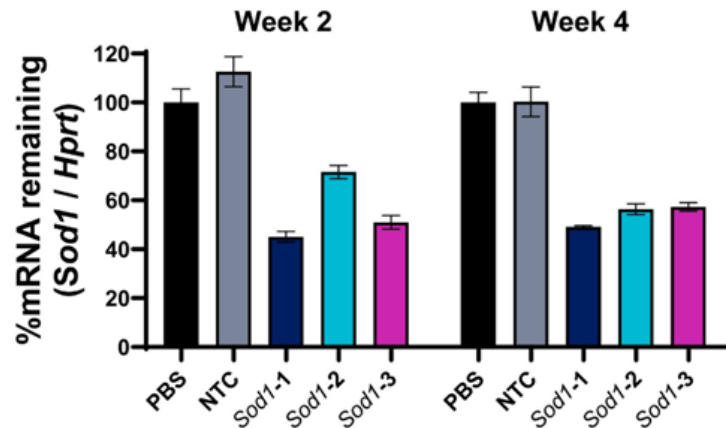
Robust and consistent knockdown of mRNA and protein in liver and adipose achieved with a single dose

Effectively reduce fasting serum triglycerides in mice



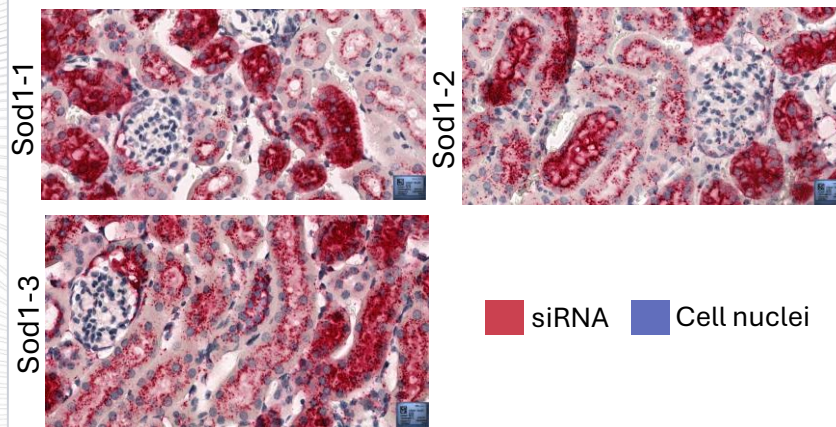
Early generation SpiNA variants drove durable 50% knockdown with broad distribution and activity across cell types with a single dose

Early generation SOD1 mRNA knockdown

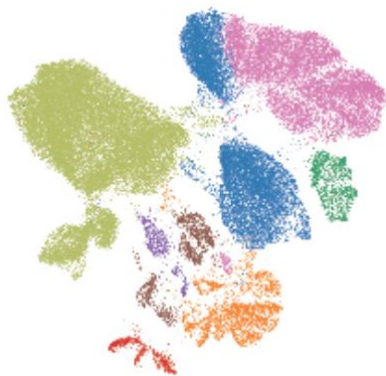


Single 10 mg/kg SC dose

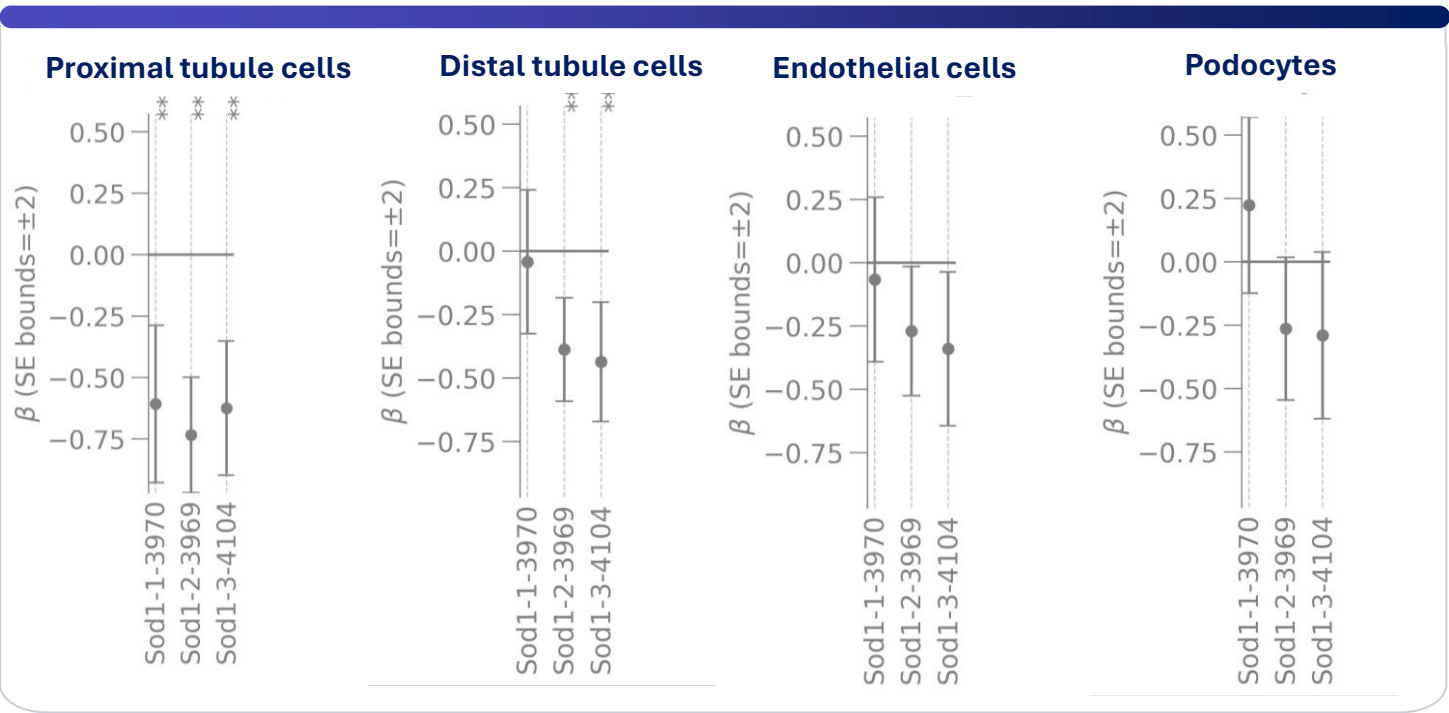
Broad distribution in kidney



Single cell RNA-seq analysis demonstrates knockdown in various cell types in the kidney

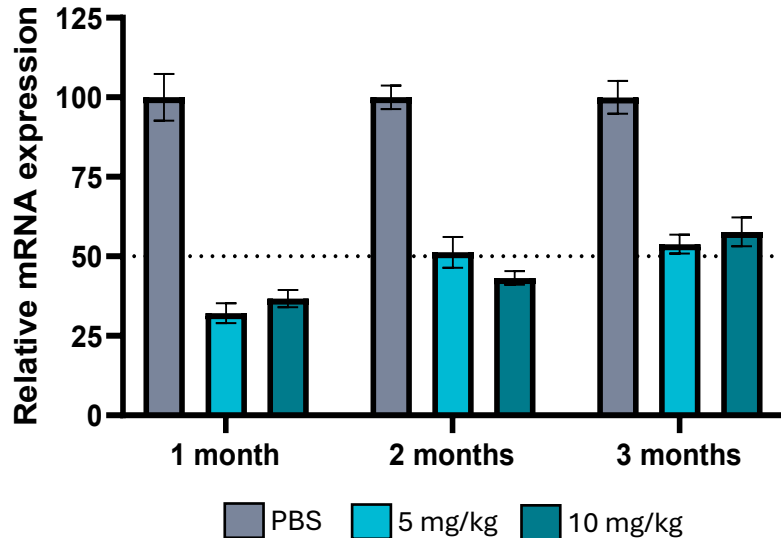


- Distal tubule cells
- Endothelial cells
- Intercalated cells
- Macrophages
- Mesangial cells
- Podocytes
- Principal cells
- Proximal tubule cells

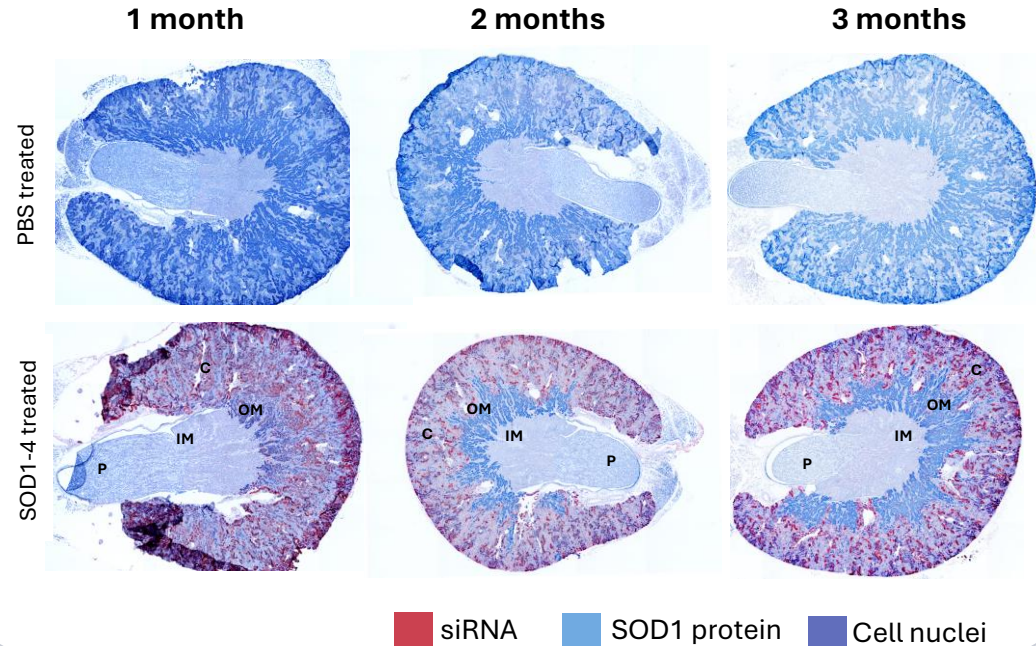


SpiNA variant drove 75% mRNA knockdown and sustained 50% knockdown up to 3 months post single dose with broad distribution and protein reduction in kidney

SOD1 mRNA knockdown



Broad distribution and Protein Reduction



SpINA variant achieves broad distribution in kidney with corresponding protein reduction through 3 months post single 5 mg/kg dose

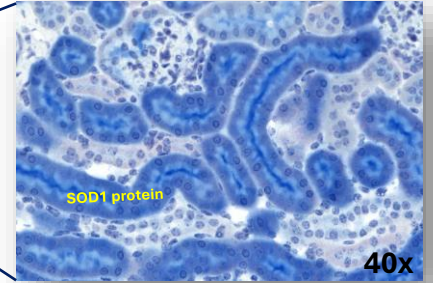
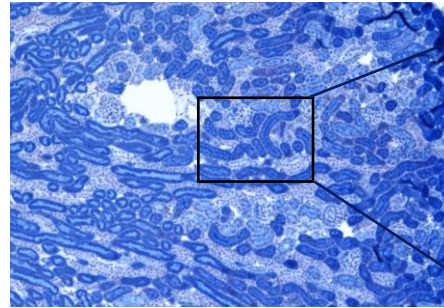
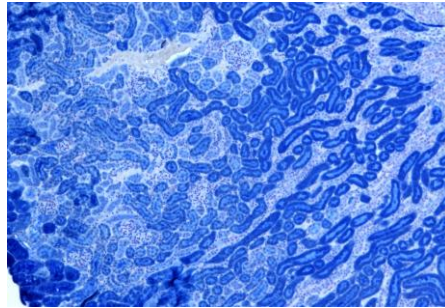
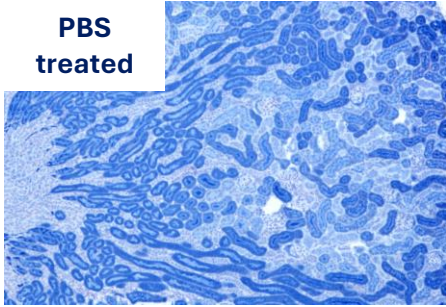
Protein Reduction

1 month

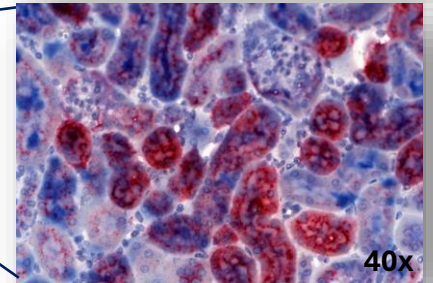
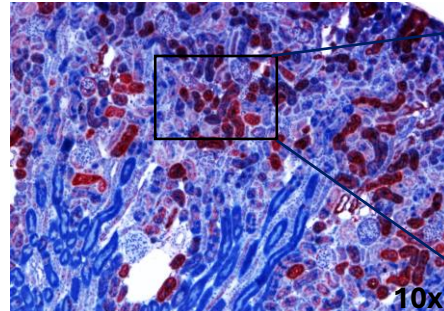
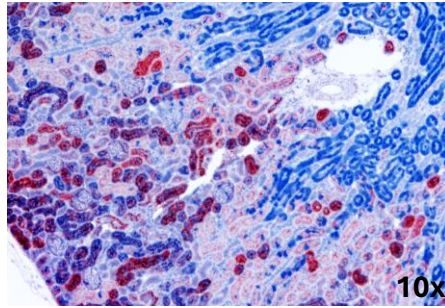
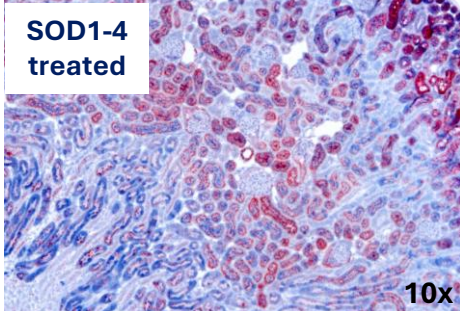
2 months

3 months

PBS
treated



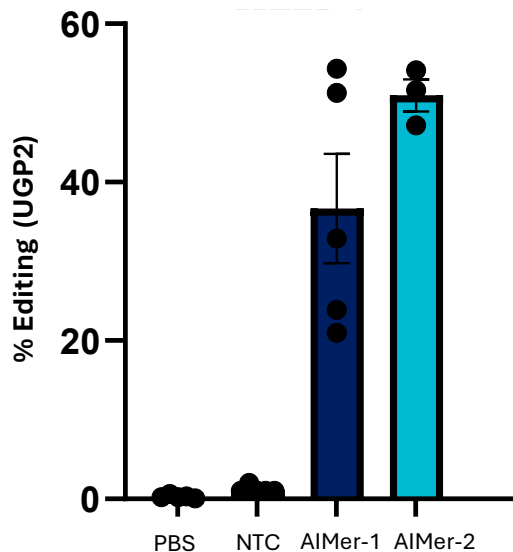
SOD1-4
treated



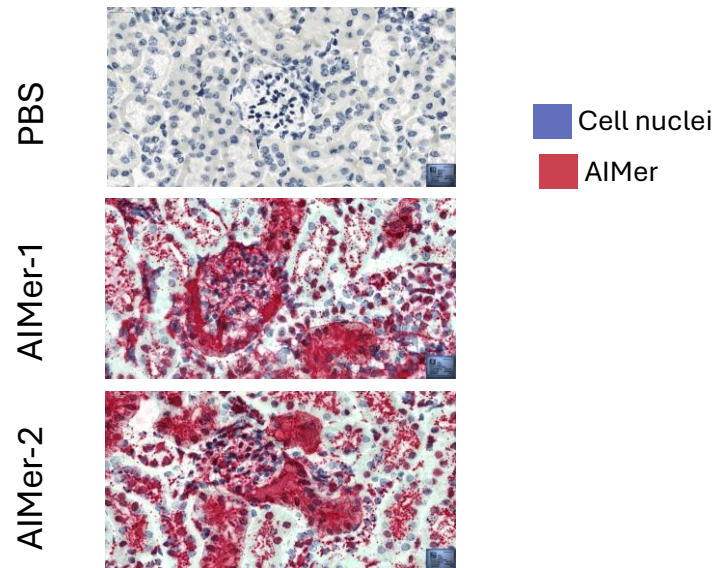
■ siRNA ■ SOD1 protein ■ Cell nuclei

Initial AIMer optimization leads to improved editing, duration, and distribution in kidney

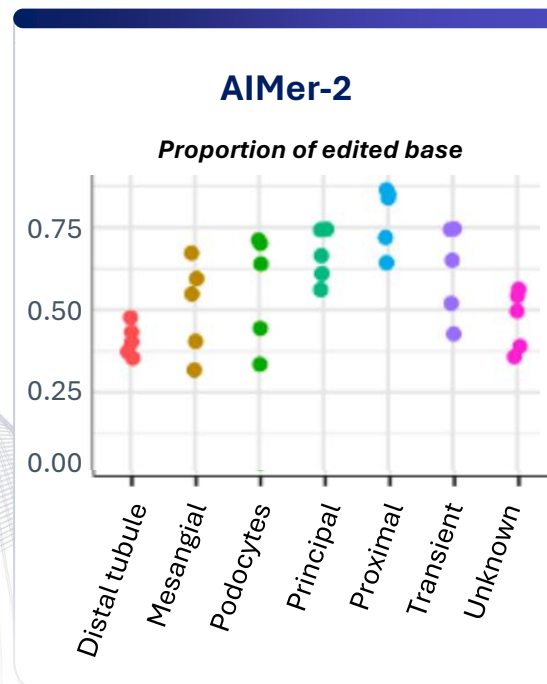
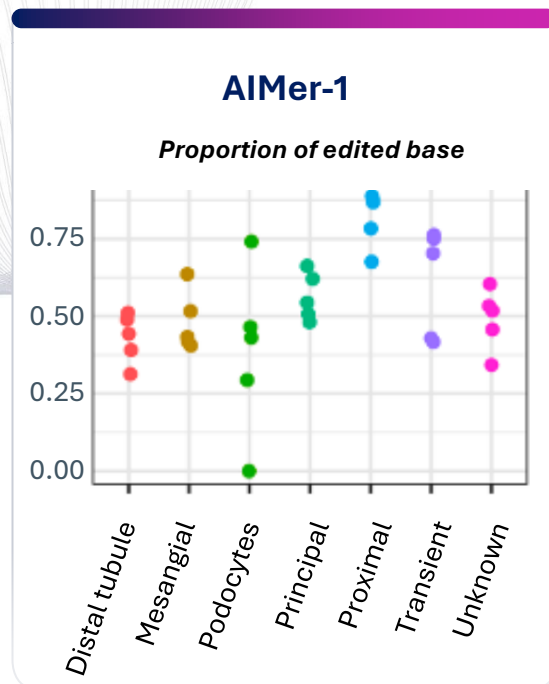
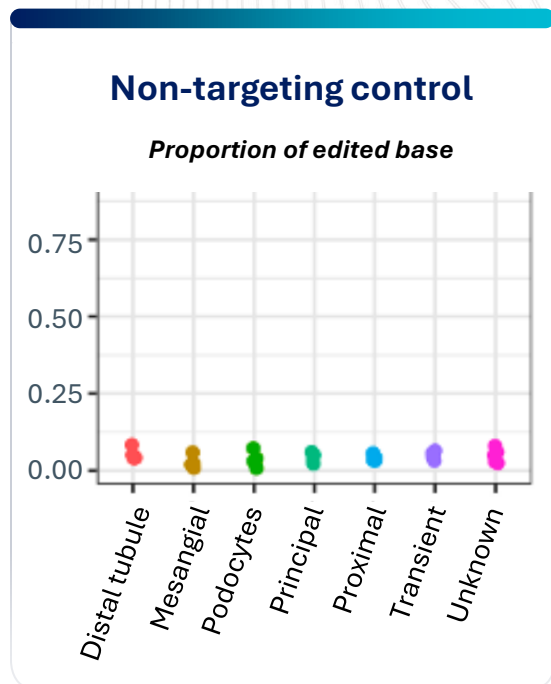
~50% editing 1 week post dose



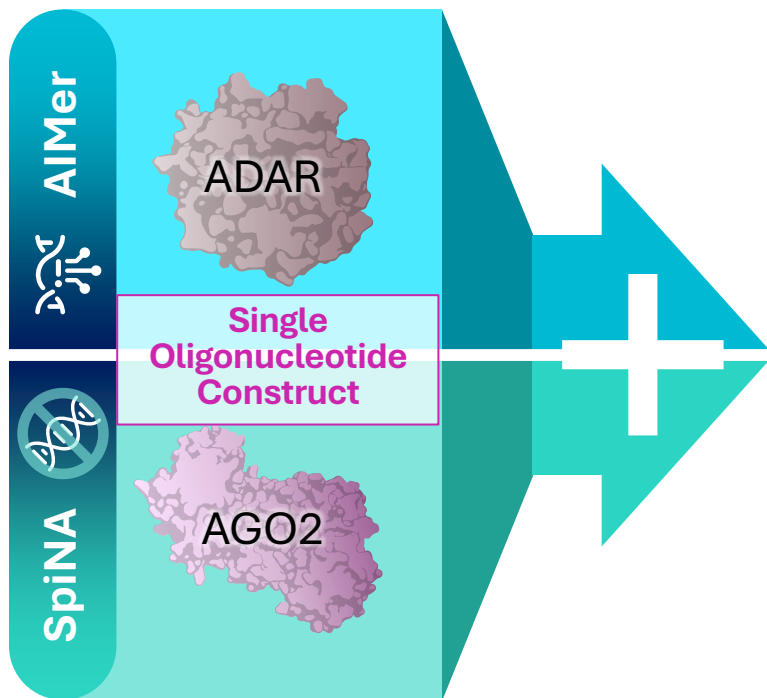
Broad distribution



Single cell RNA-seq analysis shows efficient editing in multiple cell types in the kidney

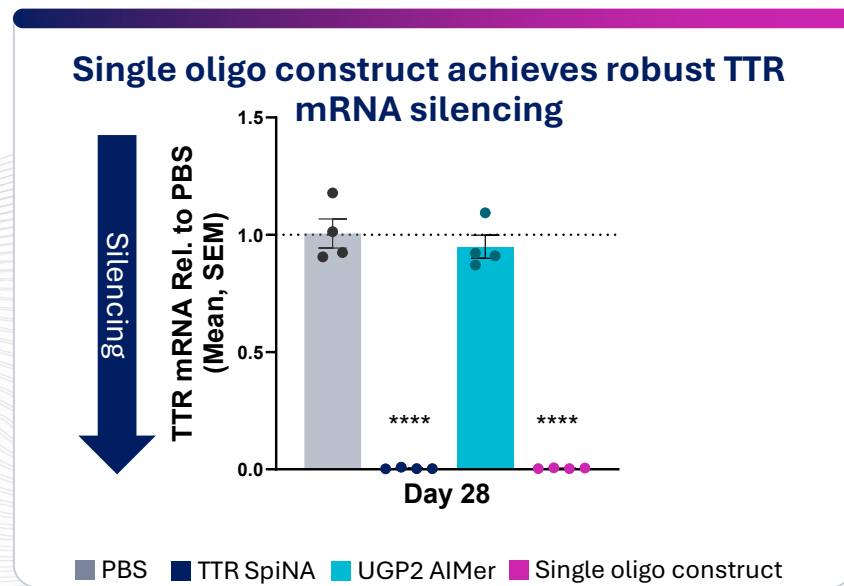
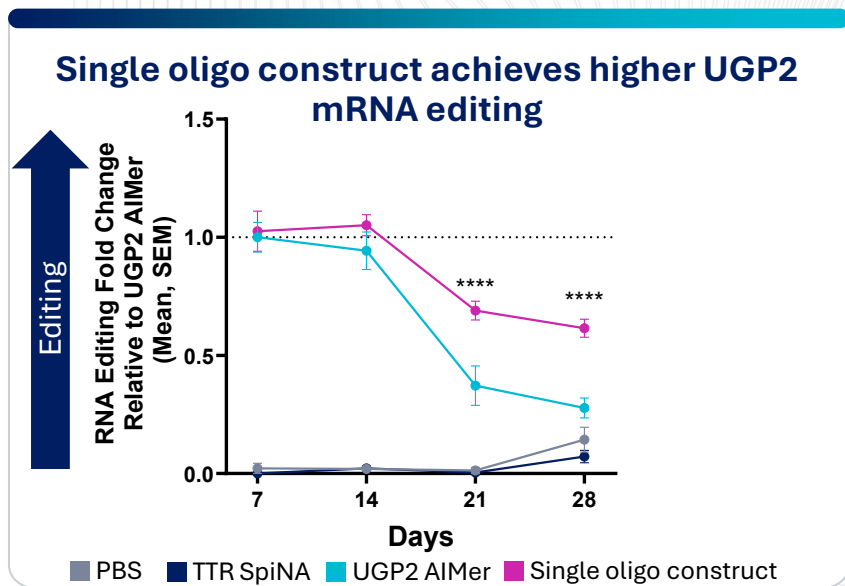


Reimagining RNA medicines: Combining modalities to simultaneously knockdown and edit RNA with single oligonucleotide construct



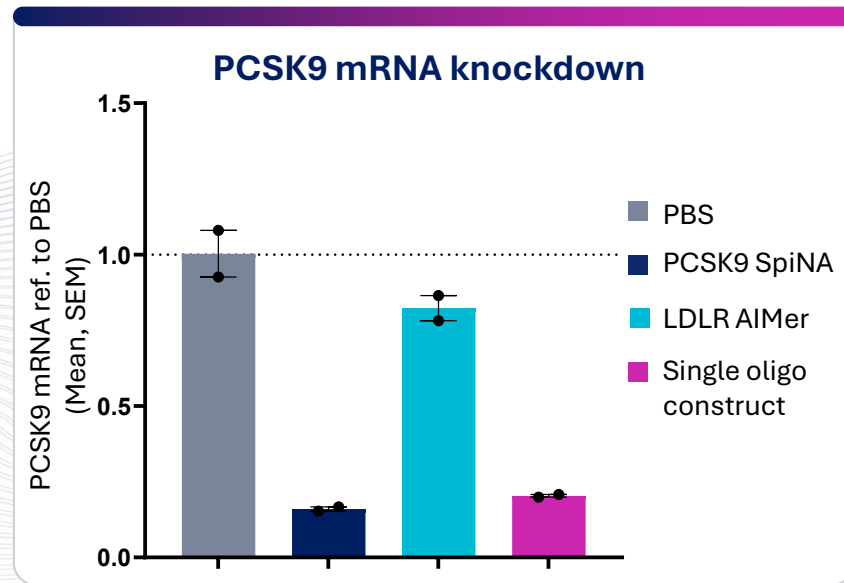
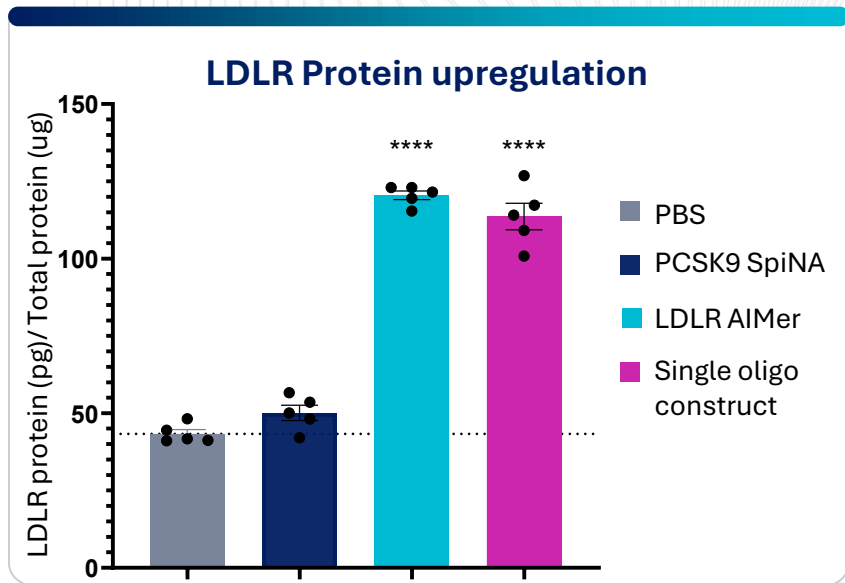
- ✓ Engage both endogenous Ago2 and ADAR enzymes
- ✓ Silence one target, while simultaneously editing or upregulating another unique target
- ✓ Unlock complex indications that require engaging multiple targets
- ✓ May continue to increase durability of editing

Increased editing and knockdown engaging both ADAR and Ago2 with single oligonucleotide construct *in vivo* with single dose



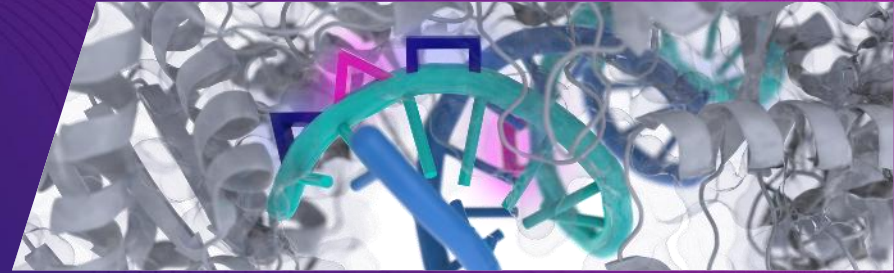
Single GalNAc-conjugate oligonucleotide construct demonstrate more durable editing than traditional AIMers with comparable knockdown *in vivo*

Single GalNAc-conjugated oligonucleotide construct can simultaneously upregulate and silence protein *in vitro*



Demonstrates potential to address complex indications that require engaging multiple targets

Closing remarks



Paul Bolno, MD, MBA

President and CEO



Reimagining RNA medicines: Today's updates

- **Rapidly advancing WVE-006: first-in-class RNA editing therapeutic for AATD**
 - RestorAATion-2 Cohort 3 underway at 600 mg; 400 mg multidose data expected in 1Q 2026, 600 mg single and multidose data expected 2026
- **Building on successful translation of RNA editing with WVE-008 for PNPLA3 liver disease**
 - Potential first-in-class, disease modifying therapy; large patient population with high unmet need
 - CTA filing on track for 2026
- **Highly significant, dose-dependent mean reductions of Activin E up to 85% with WVE-007 in INLIGHT**
 - Exceeding Activin E reductions that led to weight loss in preclinical studies; potential for dosing 1 – 2x per year; safe and well tolerated to date
 - WVE-007 aims to achieve fat loss on par with semaglutide by 6 months post-single dose
 - Multiple clinical data updates expected, including body composition and body weight, starting 4Q 2025
- **Platform innovations: extra-hepatic delivery and an emerging new modality**
 - PN variants enable tuning of SpiNA (potential best-in-class siRNA format) for extra-hepatic silencing
 - Emerging modality adds capability to simultaneously edit and silence two unique targets with a single oligonucleotide construct

Poised for significant and sustained growth driven by editing and siRNA



**RNA
Editing**

WVE-006
AATD

WVE-008

PNPLA3 Liver Disease

Other hepatic targets

Extra-hepatic targets



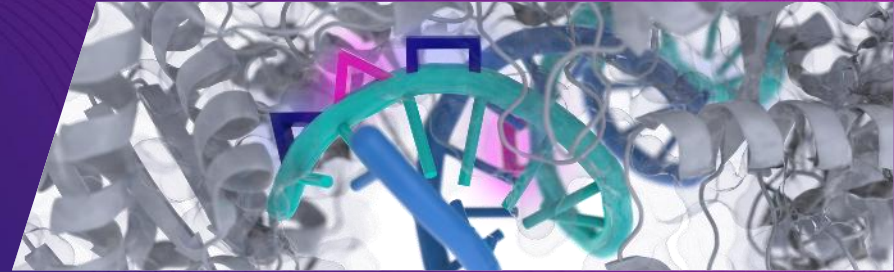
RNAi

WVE-007
Obesity

Other hepatic targets

Extra-hepatic targets

Q&A



**Spotlight on RNA editing
and RNAi**

Research Day 2025



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