

# **siRNA-INHBE Silencing in Mice Confirms Human Genetic Data and Supports the Vision for Next Generation Anti-Obesity Treatment**

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May 13, 2025

# Forward-looking statements

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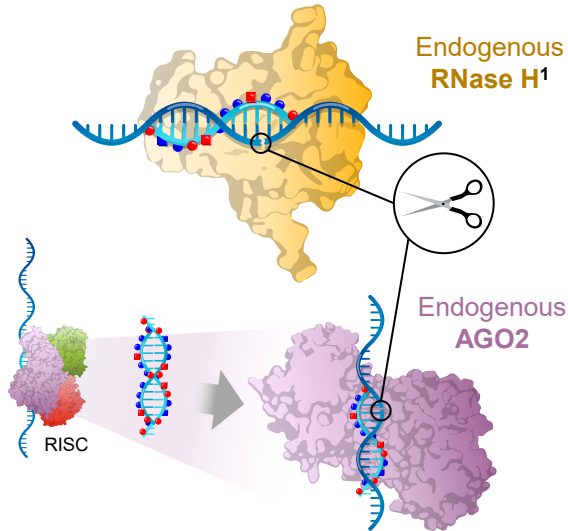
## Disclosures

- **Hsiu-Chiung (Ginnie) Yang**, Wei Liu, Keith Bowman, Michael Byrne, Cynthia Caracta, Jigar Desai, Naoki Iwamoto, Pachamuthu Kandasamy, Tomomi Kawamoto, Anthony Lamattina, Fangjun Liu, Ken Longo, Khoa Luu, Subramanian Marappan, Lola Owen, Qianli Pan, Priyanka Prakasha, Himali Shah, Kuldeep Singh, Stephany Standley, Kris Taborn, Carina Thomas, Hailin Yang, Chandra Vargeese, and Erik Ingelsson are employees of Wave Life Sciences

# Wave's PRISM<sup>®</sup> platform capitalizes on new genetic insights and harnesses the biological machinery in our cells to modulate RNA expression

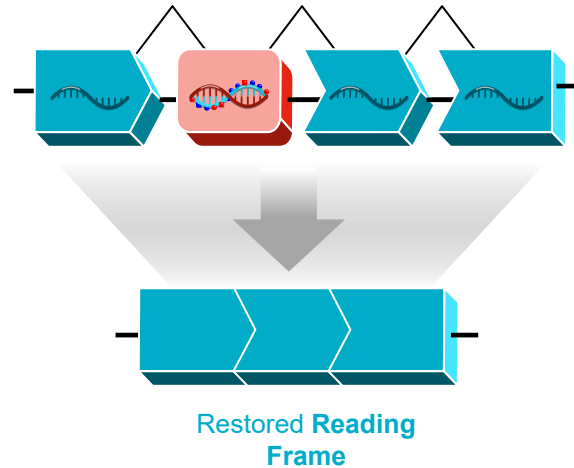
## Silencing

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



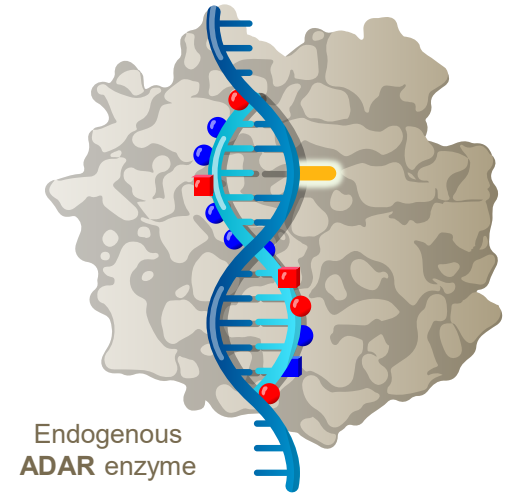
## Splicing

- Restore RNA transcripts and **turn on** protein production<sup>2</sup>



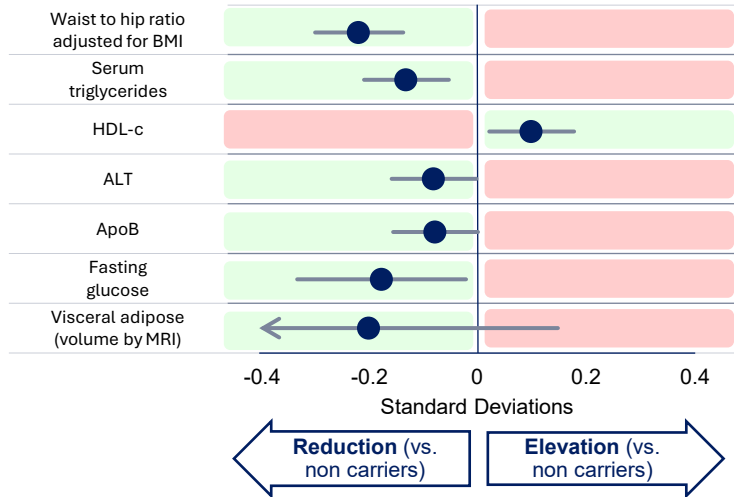
## RNA Base Editing

- Efficient editing of RNA bases to **restore**<sup>3</sup> or **modulate** protein production

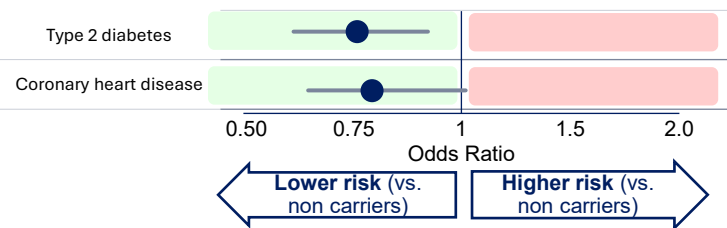


# Human genetic data demonstrate that heterozygous *INHBE* LoF carriers have a healthy metabolic profile

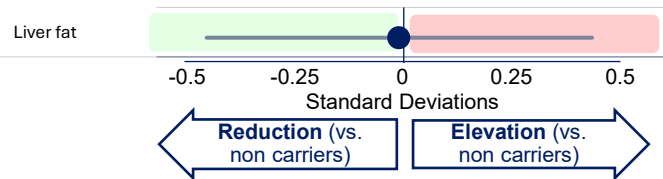
Heterozygous *INHBE* LoF carriers have favorable traits: lower abdominal obesity, lower triglycerides, higher HDL-c



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



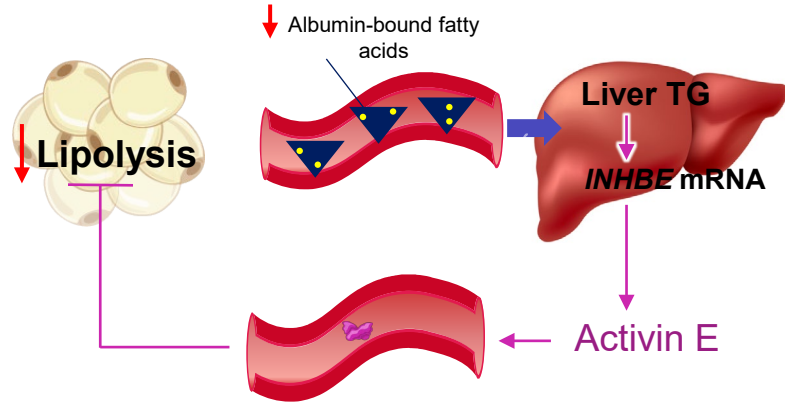
Heterozygous *INHBE* LoF carriers have no difference in liver fat



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

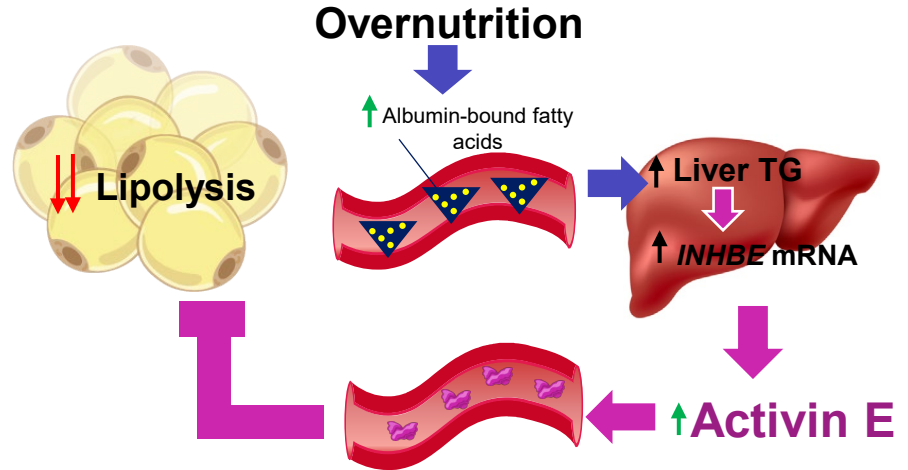
# Activin E is a lipolysis suppressor that is upregulated in obesity

## Healthy weight



*Normal Activin E keeps fat burning low during non-fasting periods in healthy weight subjects*

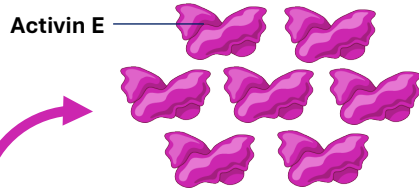
## Obesity



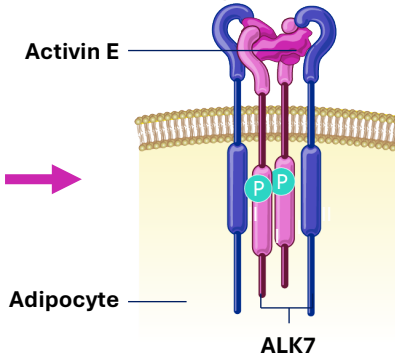
*Increased Activin E restricts fat burning in chronic overnutrition and increases adiposity*

# How INHBE GalNAc-siRNA might address obesity-associated metabolic disease

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



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



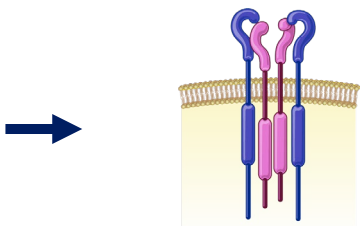
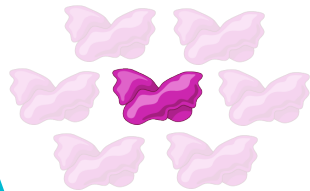
Block adipose lipolysis



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

**GalNAc-siRNA**

**Reduced** release of hepatokine **Activin E**



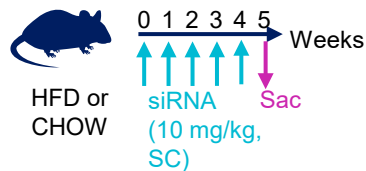
**Diminished** activation of **ACVR1C (ALK7)** receptor in adipose tissue

**Increased** adipose lipolysis and shrink adipocytes

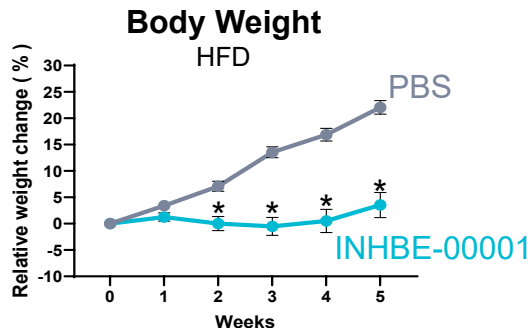


**Decreased** abdominal adiposity leads to **weight loss, reduced risk for CVD and T2D**

# INHBE GalNAc-siRNAs durably suppress weight gain in mice

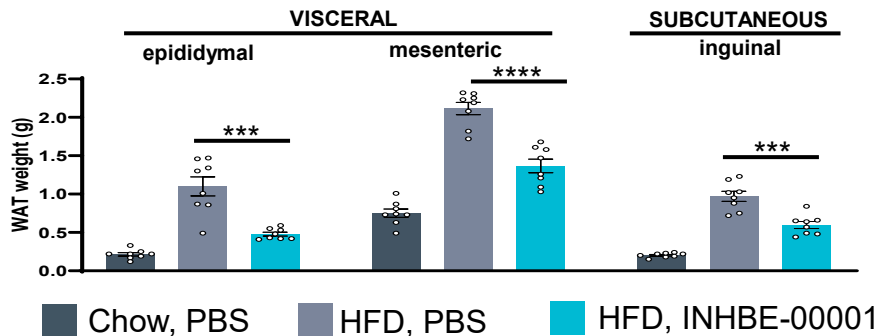


INHBE-00001: Wave's prior design<sup>1</sup> siRNA



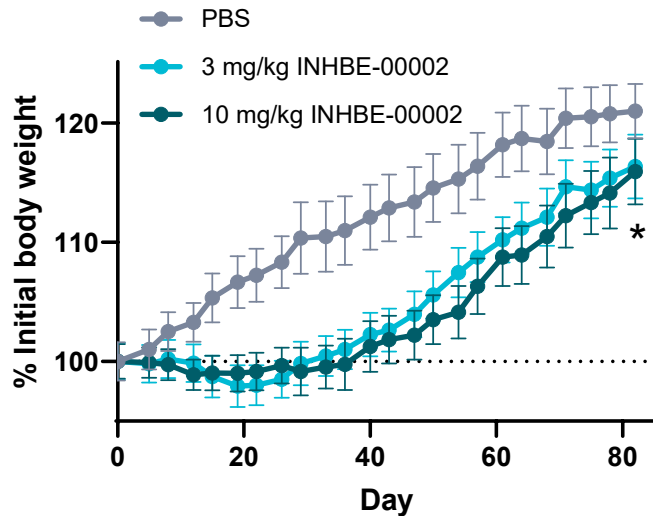
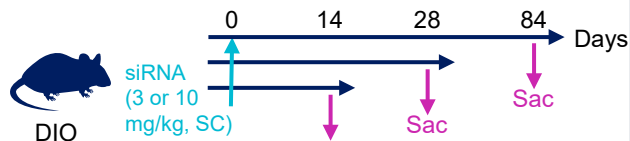
## White Adipose Tissue Weight

Week 5



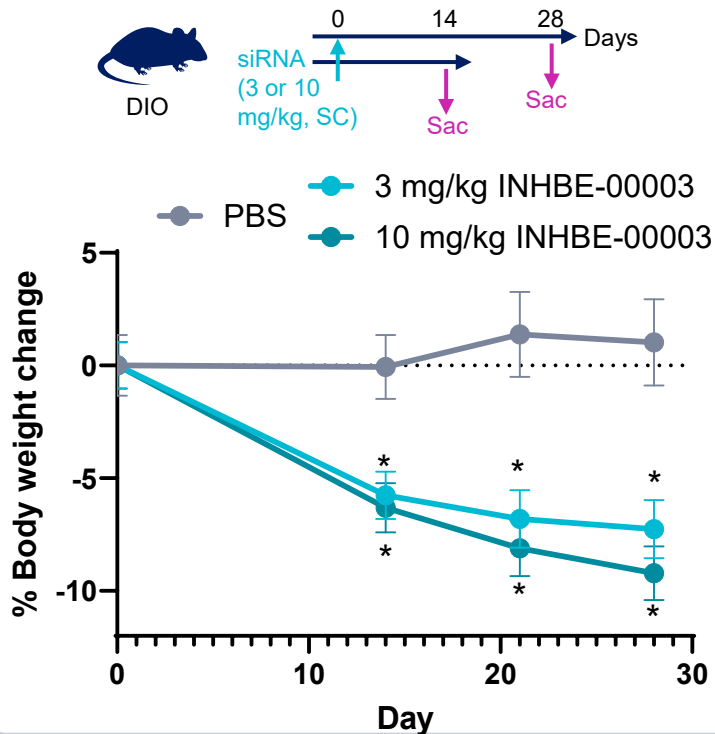
## Body Weight 84 Days

INHBE-00002: Wave's new design siRNA

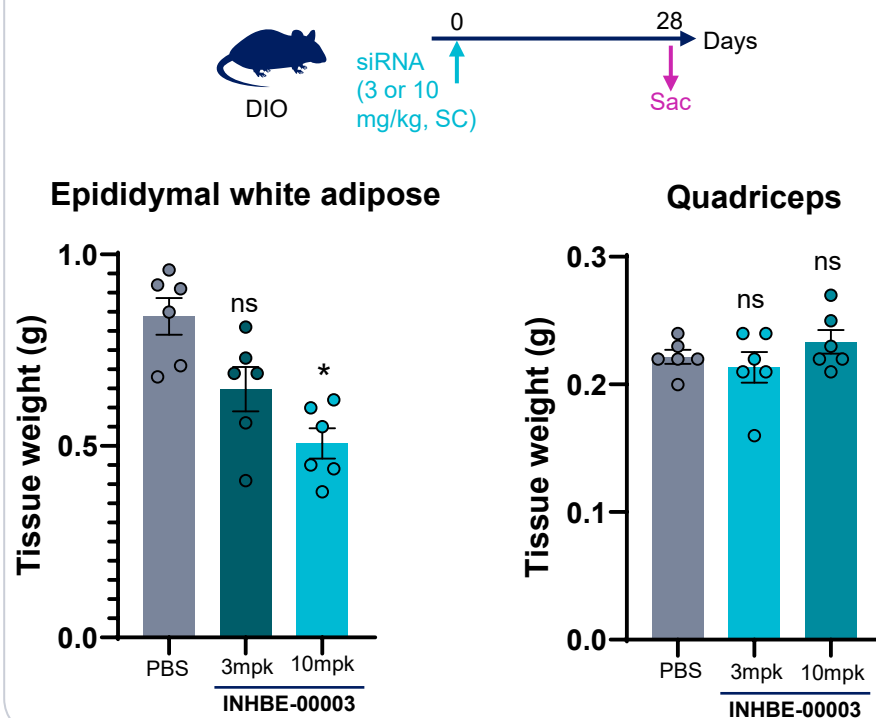


# A single dose of INHBE GalNAc-siRNA leads to weight loss driven by fat loss without loss of muscle mass

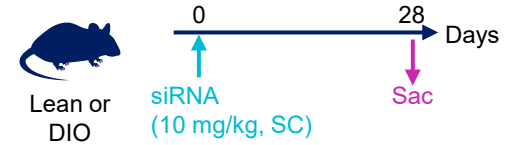
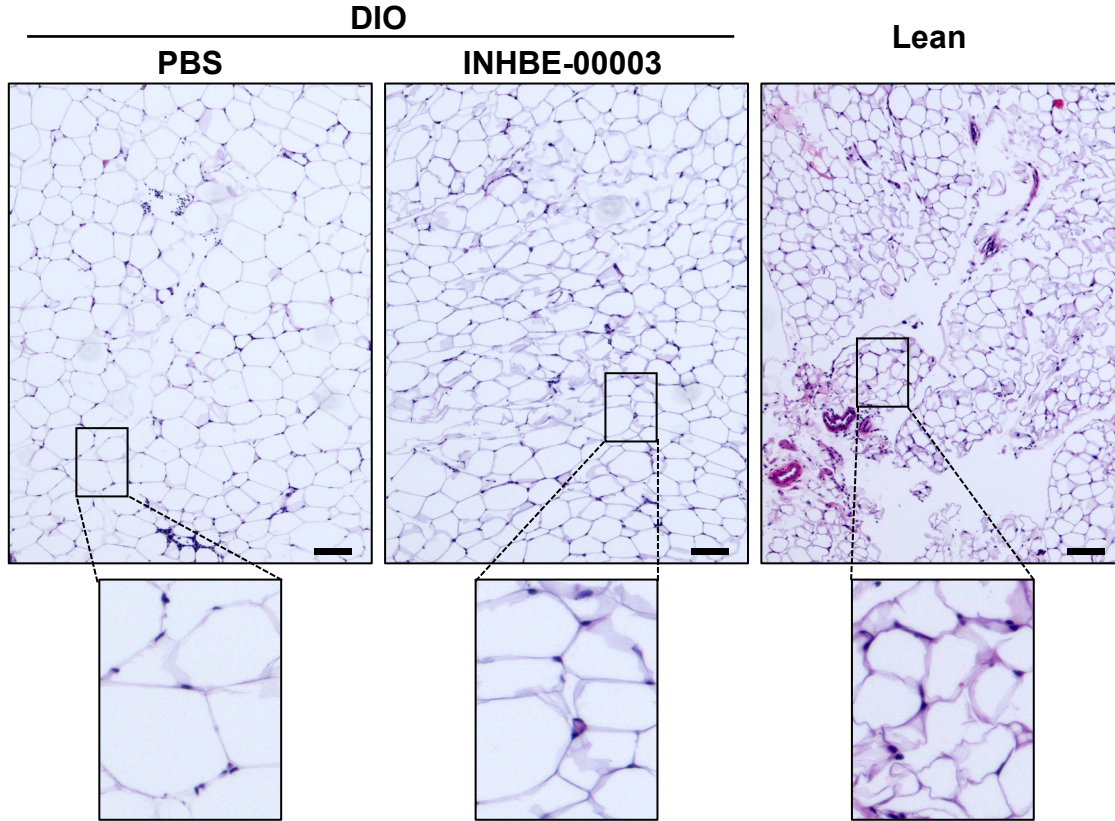
## Body Weight



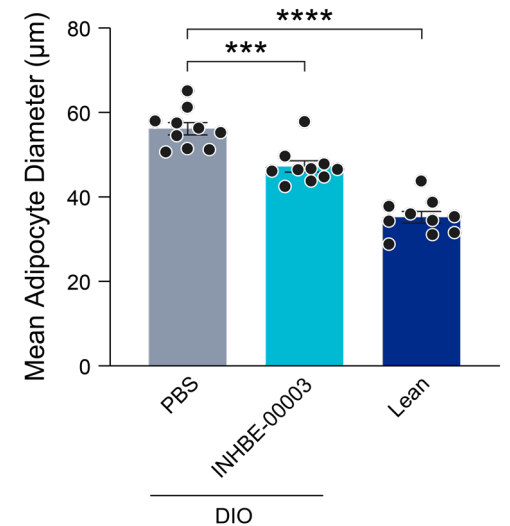
## Tissue Weight



# INHBE GalNAc-siRNA decreases adipocyte size in MesWAT of DIO mice

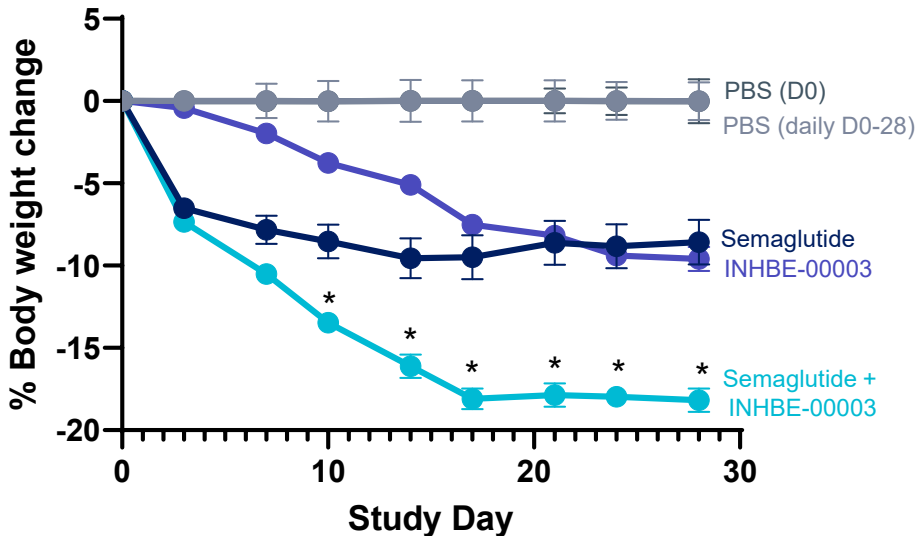


## Mean Adipocyte Diameter

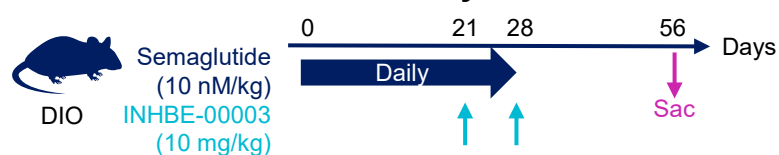
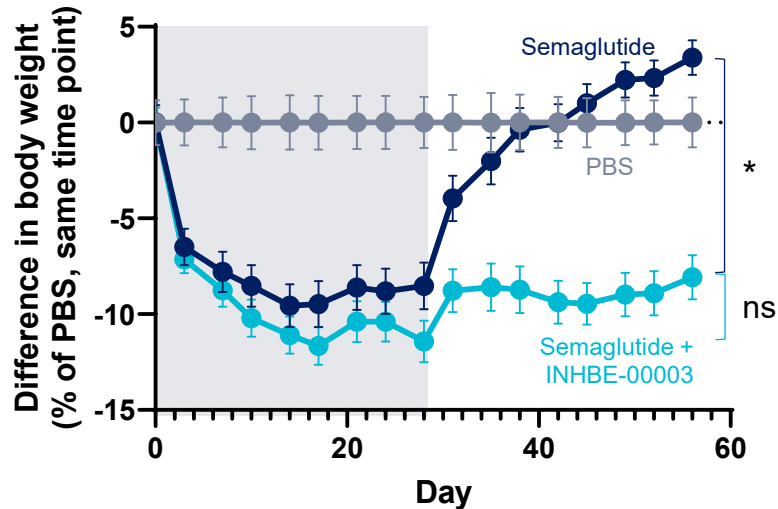


# INHBE GalNAc-siRNA augments semaglutide-induced weight loss in DIO mice

✓ ~2x greater overall weight loss when added to GLP-1



✓ Curtails weight regain after the cessation of GLP-1



## Preclinical data support potential semi-annual or annual dosing of an INHBE GalNAc-siRNA across multiple treatment settings

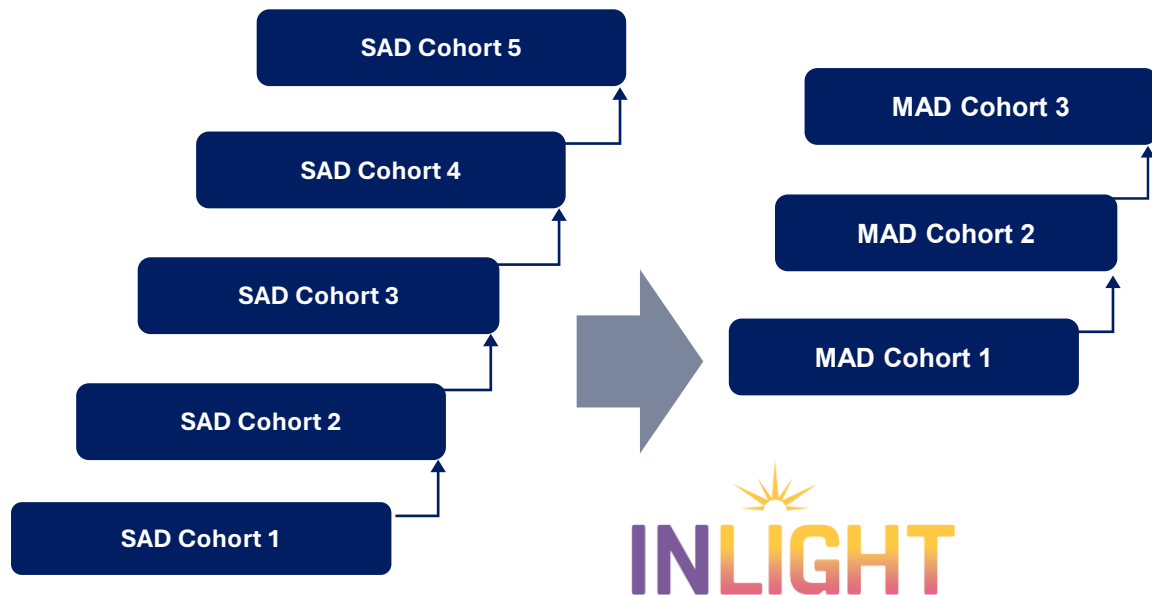
- ✓ **Monotherapy:** provide healthy weight loss with potent loss of fat mass and preservation of muscle mass
- ✓ **Add-on to GLP-1s:** increase weight loss with GLP-1 therapy or reduce dose of GLP-1 drugs
- ✓ **Maintenance:** for patients who stop treatment with GLP-1 therapy

# INLIGHT: Phase 1 trial of WVE-007 in adults living with overweight or obesity, otherwise healthy

Randomized, double-blind, placebo-controlled study of ascending doses of investigational WVE-007, a GalNAc-siRNA targeting *INHBE* mRNA

## Trial Design

- **Objective:** Assess dose safety, tolerability, PK and PD
- **Key measurements**
  - **Primary:** Safety and tolerability
  - **Secondary:** PK, Activin E
  - **Exploratory PD:**
    - Body weight
    - Body composition
    - Metabolic health
    - Biochemical markers



Dosing is ongoing in INLIGHT with clinical data expected in 2H 2025

# Summary

- Preclinical data show that in DIO mice, *Inhbe* GalNAc-siRNAs:
  - lower expression of *Inhbe* mRNA
  - reduce body weight
  - positively impact body composition
  - double weight loss, when added on to semaglutide
  - curtail weight regain upon cessation of semaglutide
- Preclinical data support potential to use WVE-007 across multiple treatment settings: as a monotherapy, as an add-on to GLP-1s, and for weight maintenance after cessation of GLP-1s
- WVE-007 is a novel, long acting, muscle sparing approach for obesity.
  - Dosing for the INLIGHT phase 1 clinical trial of WVE-007 in overweight and obesity is ongoing; data expected in second half 2025.

# Acknowledgements

- Thanks to all colleagues and contributors to **Wave Life Sciences** and our collaborators.
- Nicole Neuman, Wave Life Sciences, assisted in preparing this presentation.

## Silencing (RNase H and Ago2)

**NAR Breakthrough Article**  
Impact of guanine-containing backbone linkages on stereore antisense oligonucleotides in the CNS

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

**Variant-selective stereore oligonucleotides protect against pathologies associated with C9orf72-repeat expansion in mice**

**Stereore antisense RNA expression**

**Preclinical evaluation of stereore antisense oligonucleotides for allele-selective lowering of mutant HTT**

**Introduction**  
The RNA interference (RNAi) pathway, or the mechanism by which short double-stranded (ds) RNA molecules silence gene expression, has become an important tool for gene silencing in research and medicine. This gene silencing pathway is conserved in mammalian cells with few exceptions. To leverage the sequence diversity for targeting non-protein-coding RNA (ncRNA), we recently developed a new generation of RNAi molecules, called stereore oligonucleotides (SOs). The RNAi pathway for stereore oligonucleotides is potent and highly specific for target gene silencing. We demonstrate that these chimeric stereore oligonucleotides are markedly improved pharmacology and efficacy compared with 19-mer dsRNA. Despite their enhanced potency and efficacy, SOs do not show any toxicity in mice. We also demonstrate that these stereore oligonucleotides are highly effective in silencing mutant huntingtin (mHTT) in a mouse model with an aggressive phenotype. These data demonstrate that chimeric stereore oligonucleotides can be used to target specific ncRNAs in a tissue-specific manner. We hypothesize that targeting mHTT with SOs may be a viable therapeutic approach for the treatment of C9orf72-related disorders.

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## Splicing

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

**Introduction**  
Elevated splicing abnormalities, a type of splice-switching technology, are observed in adult-onset neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). However, the underlying mechanism of this pathology is not fully understood. We demonstrate that the RNAi pathway for stereore oligonucleotides is potent and highly specific for target gene silencing. We demonstrate that these chimeric stereore oligonucleotides are markedly improved pharmacology and efficacy compared with 19-mer dsRNA. Despite their enhanced potency and efficacy, SOs do not show any toxicity in mice. We also demonstrate that these stereore oligonucleotides are highly effective in silencing mutant huntingtin (mHTT) in a mouse model with an aggressive phenotype. These data demonstrate that chimeric stereore oligonucleotides can be used to target specific ncRNAs in a tissue-specific manner. We hypothesize that targeting mHTT with SOs may be a viable therapeutic approach for the treatment of C9orf72-related disorders.

## Editing

**Rational design of base, sugar and backbone modifications improves ADAR-mediated RNA editing**

**Introduction**  
ADARs are a family of mammalian RNA deaminases that induce A-to-I RNA editing through interaction with endogenous adenosine targets. This process is essential for normal brain function. However, the underlying mechanism of this process is not fully understood. We demonstrate that the RNAi pathway for stereore oligonucleotides is potent and highly specific for target gene silencing. We demonstrate that these chimeric stereore oligonucleotides are markedly improved pharmacology and efficacy compared with 19-mer dsRNA. Despite their enhanced potency and efficacy, SOs do not show any toxicity in mice. We also demonstrate that these stereore oligonucleotides are highly effective in silencing mutant huntingtin (mHTT) in a mouse model with an aggressive phenotype. These data demonstrate that chimeric stereore oligonucleotides can be used to target specific ncRNAs in a tissue-specific manner. We hypothesize that targeting mHTT with SOs may be a viable therapeutic approach for the treatment of C9orf72-related disorders.



Selected Wave publications: PMC10201370, PMC9092894, PMID 35256816, PMC9177980, PMC9178015, PMC8780851, PMC7804567, PMID 28829437, DOI: 10.1016/j.omtn.2024.102246; DOI: 10.1093/nar/gkae681; DOI: 10.1093/nar/gkae681

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