siRNA-INHBE Silencing in Mice Recapitulates Human Genetic Data and Demonstrates Improved Healthy Weight Loss Profile

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Disclosures

- **Hsiu-Chiung (Ginnie) Yang**, Wei Liu, Keith Bowman, Michael Byrne, Cynthia Caracta, Jigar Desai, Anamitra Ghosh, Dhiman Ghosh, Joseph Haegele, Naoki Iwamoto, Pachamuthu Kandasamy, Tomomi Kawamoto, Anthony Lamattina, Ken Longo, Khoa Luu, Subramanian Marappan, Padma Narayanan, Lola Owen, Priyanka Prakasha, Jeanette Rheinhardt, Denise Schwahn, Kuldeep Singh, Stephany Standley, Kris Taborn, Chandra Vargeese, and Erik Ingelsson are employees of Wave Life Sciences

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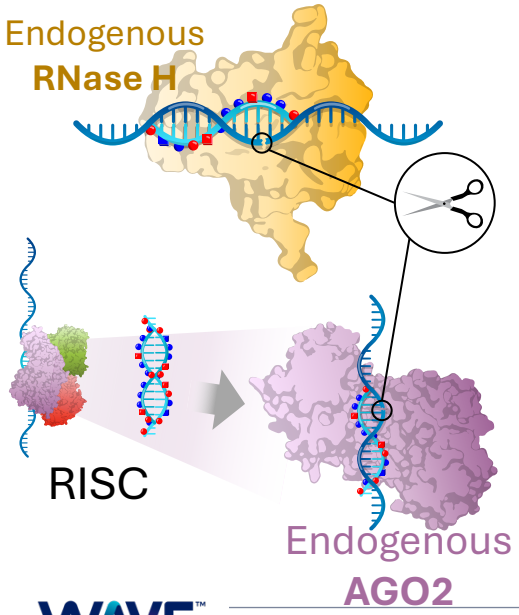
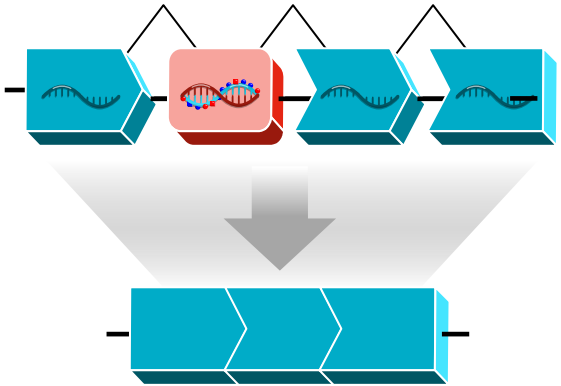
Wave's PRISM® platform uses genetic insights and modulates RNA expression

Silencing

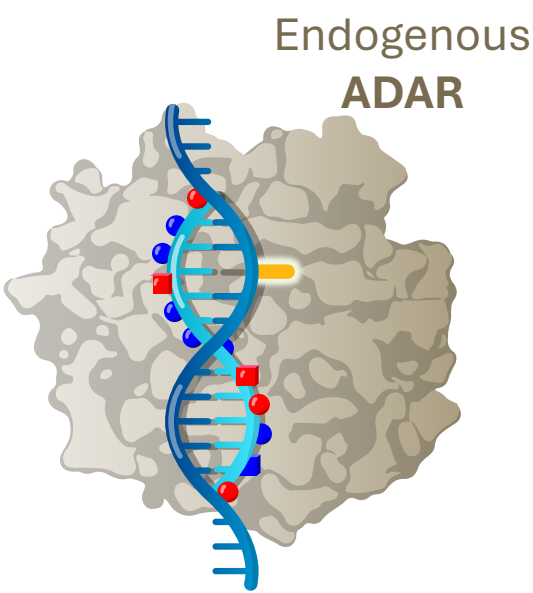


Splicing



Restored **Reading Frame**

RNA Editing



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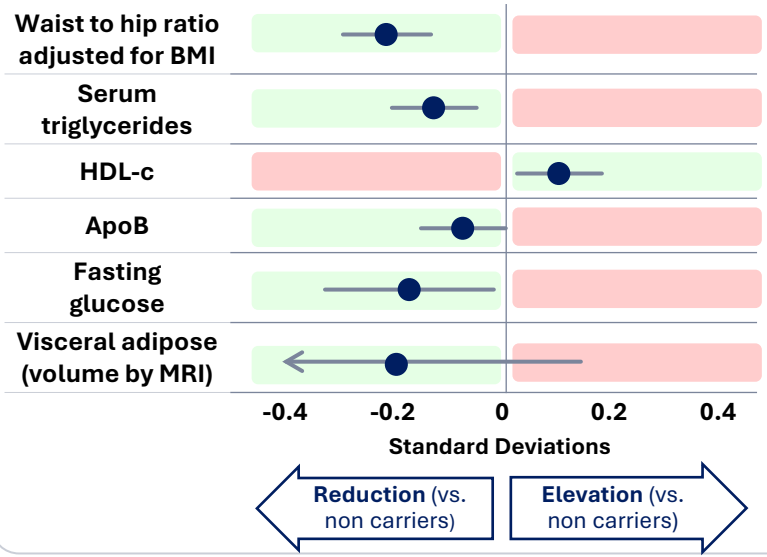
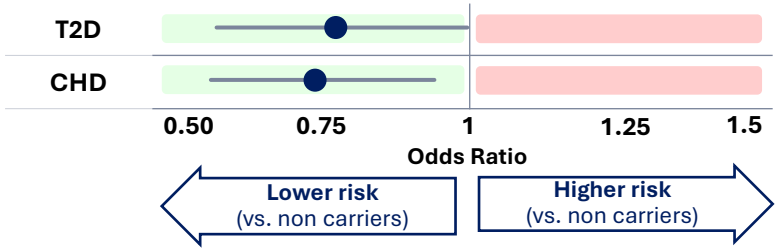
Kandasamy et al., 2022, doi: 10.1093/nar/gkac037; Kandasamy et al., 2022, doi: 10.1093/nar/gkac018; Monian et al., 2022, doi:10.1038/s41587-022-01225-1

Human *INHBE* loss of function (LoF) variant carriers have a healthy metabolic profile

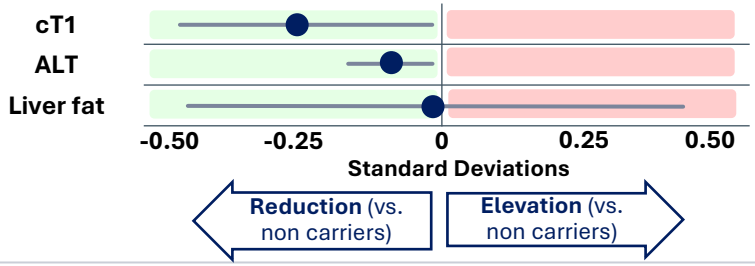
Display favorable metabolic traits



Lower risk of T2D and CHD



Favorable associations with liver traits

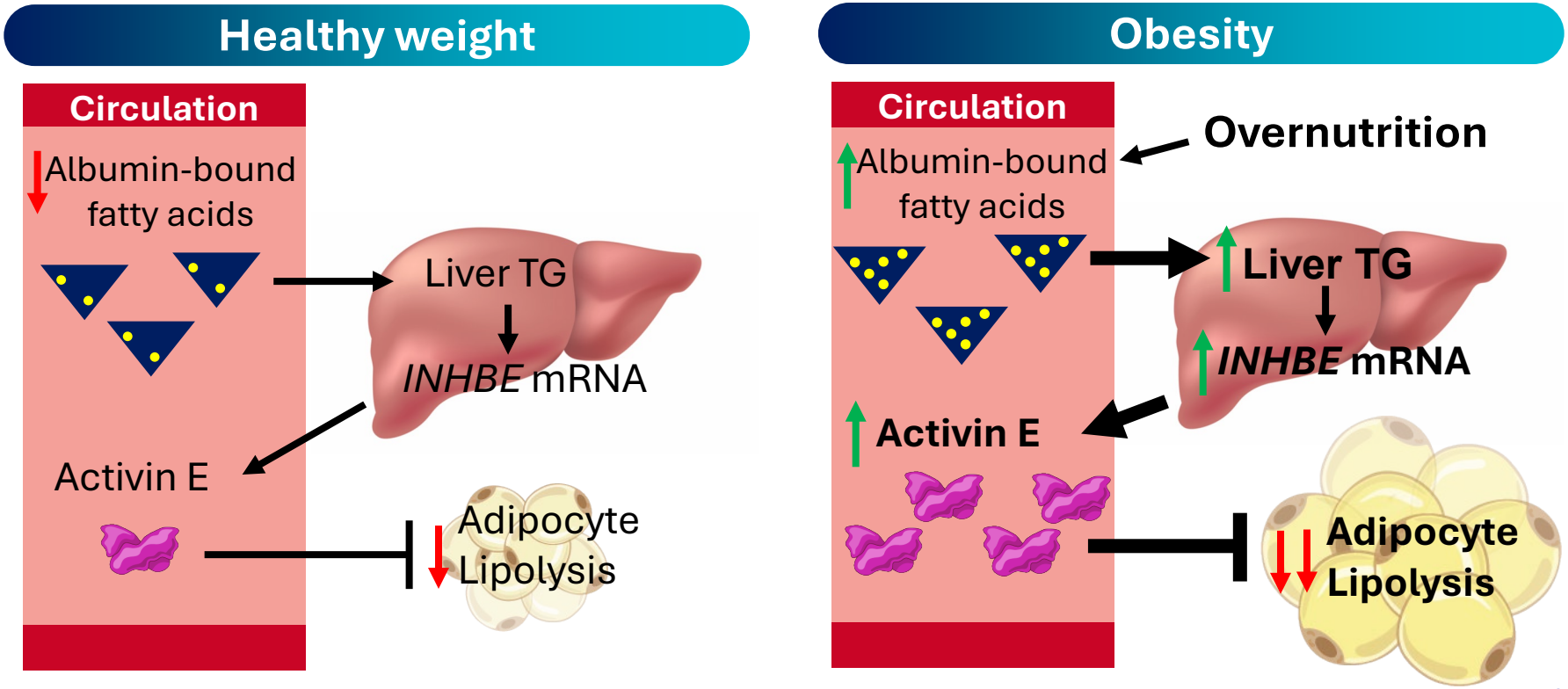


Silencing *INHBE* mRNA in hepatocytes by ≥50% is expected to recapitulate the healthy metabolic profile of heterozygous *INHBE* LoF carriers

Akbari et al. Nat Commun. 2022 Aug 23;13(1):4844; Deaton et al. Nat Commun. 2022 Jul 27

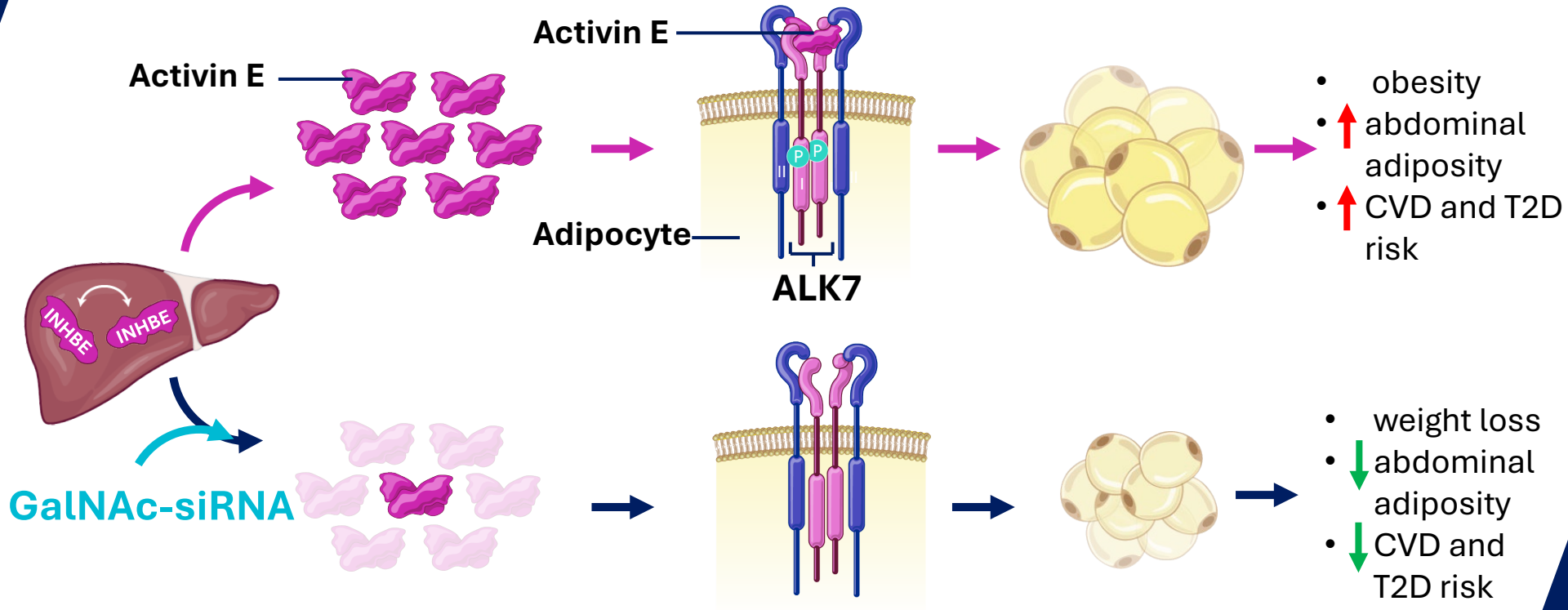
HDL-c: high-density lipoprotein cholesterol; ALT: alanine transaminase; ApoB: apolipoprotein B; T2D: type 2 diabetes; CHD: coronary heart disease

Activin E, a lipolysis suppressor, is upregulated in obesity



TG: triglycerides

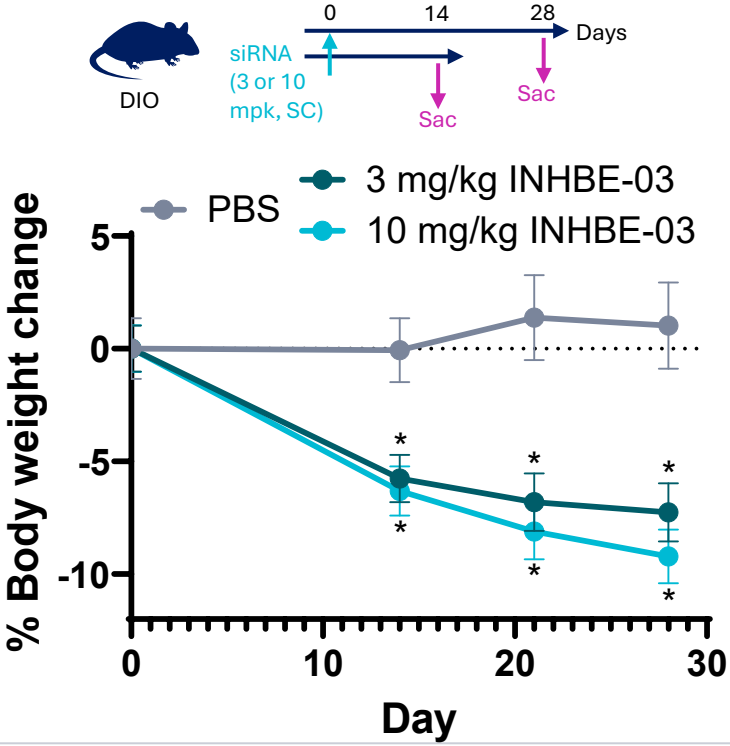
Human genetics-inspired approach to address obesity-associated metabolic disease



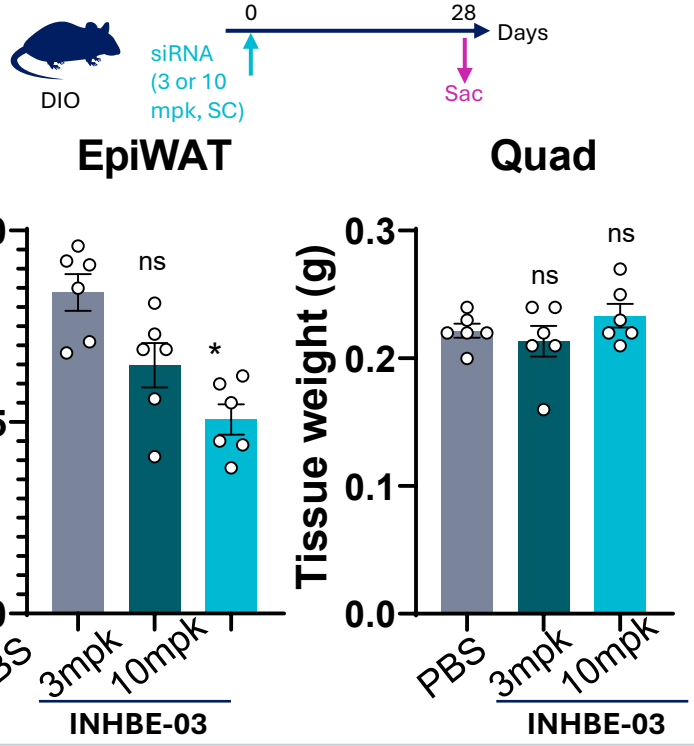
1. Cell Reports (2018) 25, 1193–1203; 2. Biochemical Journal (2024) 481 547–564; 3. PNAS 2023 Vol. 120 No. 32 e2309967120; 4. Nat Commun 2022. https://doi.org/10.1038/s41467-022-32398-7; 5. Nat Commun 2022. https://doi.org/10.1038/s41467-022-31757-8

Weight loss by a single dose of *Inhbe* GalNAc-siRNA is driven by fat loss with preservation of muscle

Body Weight

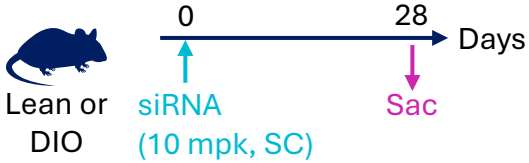


Tissue Weight



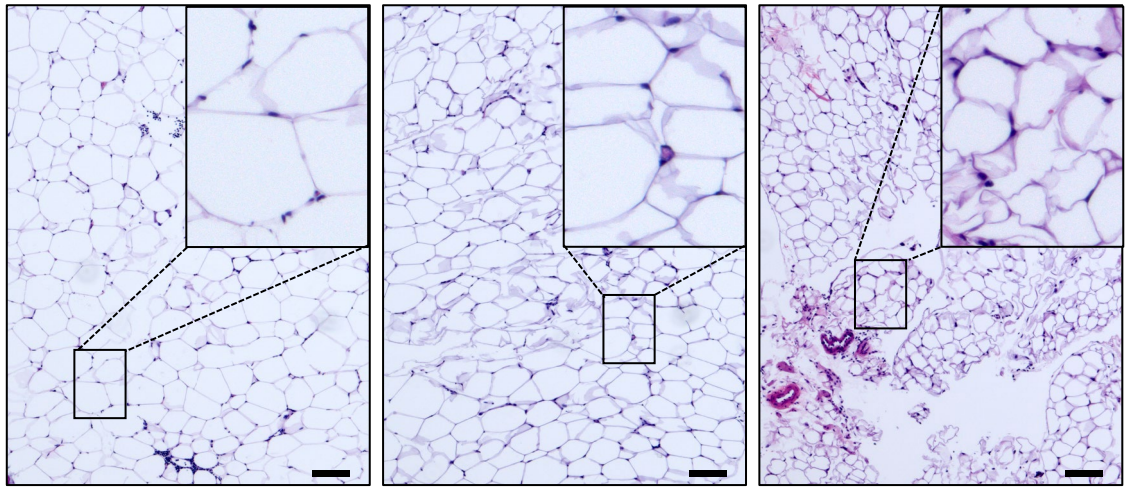
At ~25 weeks old (Day 0, D0), C57Bl6 diet induced obesity (DIO) mice received a single SC injection of 3 or 10 mg/kg (mpk) INHBE-03 or PBS (control). Left, Mean body weight change (%) from D0 ±SEM (n=12-18); Stats: marginal treatment effects versus PBS per timepoint; * $p < 0.05$. Right, a single epididymal white adipose tisse (epiWAT) fat pad and quadriceps muscle (Quad) were collected and weighed on D28. Stats: Mean weight (g) ±SEM, post hoc comparisons of marginal treatment effects versus PBS per tissue type; * $p < 0.05$; ns, nonsignificant.

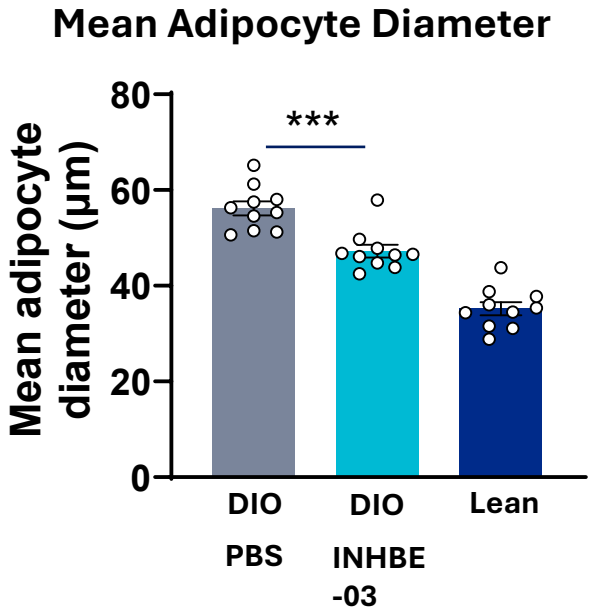
Inhbe knockdown decreases adipocyte size in mesWAT of DIO mice



DIO **Lean**

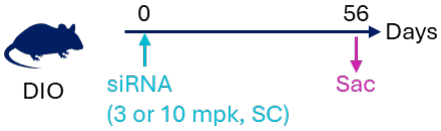
PBS **INHBE-03**



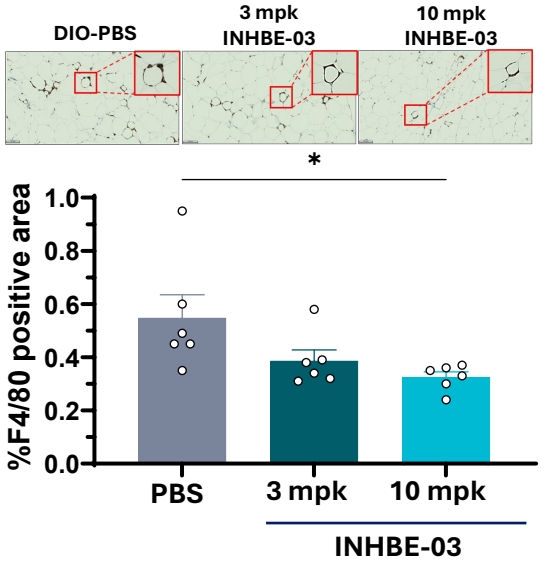


At 23 weeks old (D0), DIO C57Bl6 received a single SC injection of 10mpk INHBE-03 or PBS. Lean mice were sacrificed on D0; INHBE-03 or PBS treated animals sacrificed on D28. Left, Representative H&E stained Mesenteric white adipose tissue (MesWAT) . Scale bar: 100 µm. Right, Mean ±SEM MesWAT adipocyte diameter, calculated from H&E stained sections, using ImageJ Adiposoft plugin. One representative field of view was analyzed per animal. Each data point represents one animal. One-way ANOVA followed by Tukey HSD post hoc tests; *** $p < 0.001$.

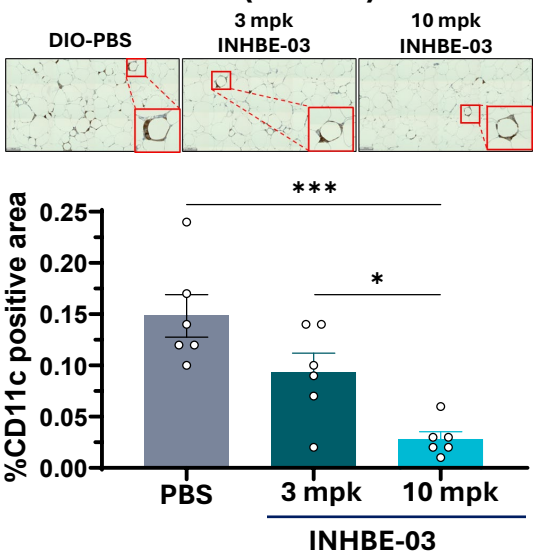
Inhbe GalNAc-siRNA reduces pro-inflammatory Mϕ recruitment in epiWAT of DIO mice



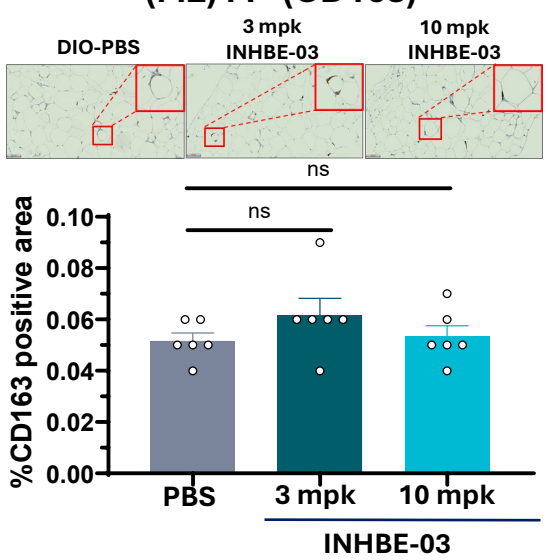
Macrophages (Mϕ) (F4/80)



Pro-inflammatory (M1) Mϕ (CD11c)



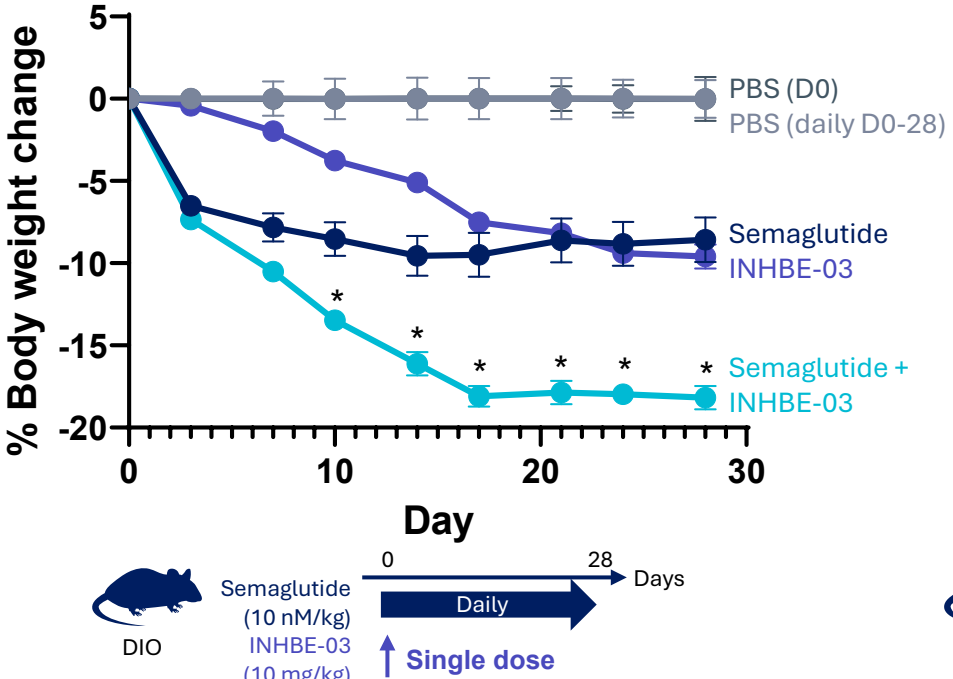
Anti-inflammatory (M2) Mϕ (CD163)



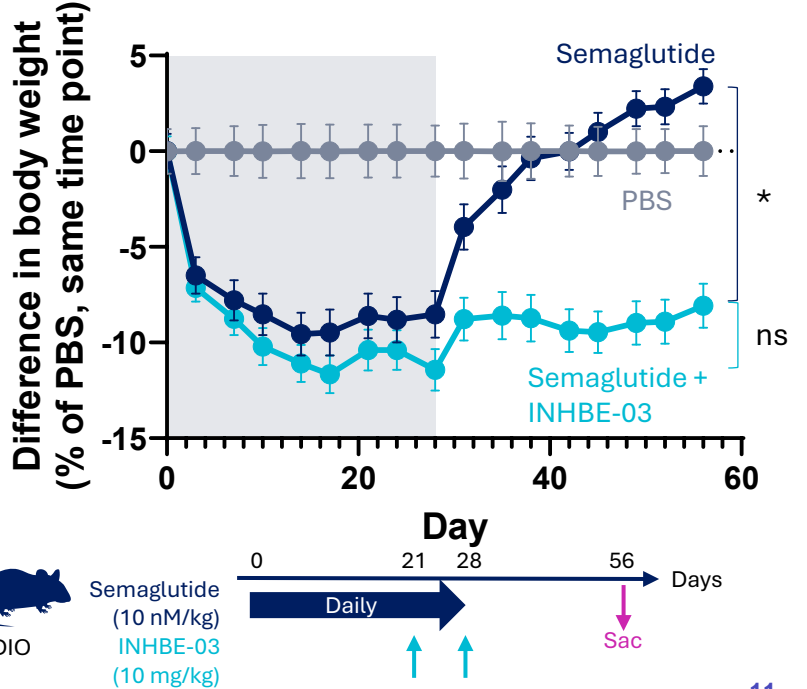
At 25 weeks old (D0), DIO C57Bl6 received a single SC injection of 3 or 10 mg/kg INHBE-03 or PBS. Animals were sacrificed on D56. Representative images (5X) from F4/80, CD11C, or CD163 stained epididymal WAT tissues with values similar to the group mean.Scale bar: 100 µm. Mean ±SEM of percent stain-positive area, calculated from F4/80-, CD11C-, or CD163-stained sections from n=6 mice, using HALO image analysis platform. Each dot represents an individual mouse. One-way ANOVA with Tukey multiple comparison test. ***p<0.001, *p<0.05, ns=non-significant

Treatment with *Inhbe* GalNAc-siRNA augments semaglutide-induced weight loss in DIO mice

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



Curtails weight regain after the cessation of GLP1-RA

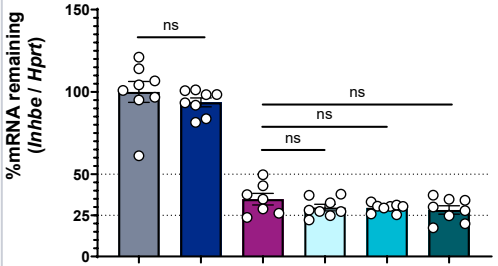


Stats: Mean weight difference as a % of PBS control on the same day (±SEM, n=10). Left, Linear Mixed Effects ANOVA with post hoc comparisons of marginal treatment effects for semaglutide versus semaglutide and INHBE-03 per time point; * $p < 0.05$ compared to semaglutide group. Right, Linear Mixed Effects ANOVA with post hoc comparisons of marginal time point effects between D28 and D56 per treatment group; * $p < 0.05$; ns, nonsignificant. GLP1-RA: GLP-1 receptor agonist

Activin E protein is lowered by *Inhbe* GalNAc-siRNA but minimally affected by GLP1-RA

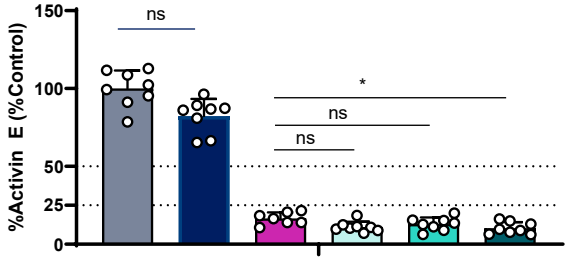
Inhbe mRNA

(mouse liver)



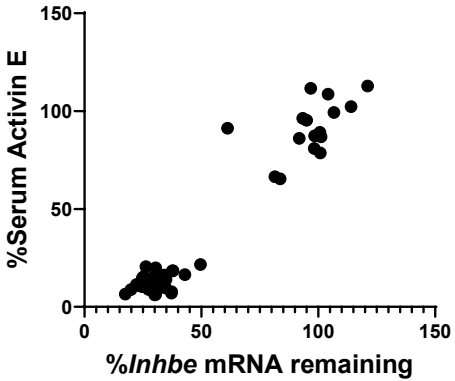
Activin E protein

(mouse serum)



- PBS
- Semaglutide (10 nmol/kg)
- INHBE-03 (10 mpk)
- Semaglutide (1 nmol/kg) +INHBE-03 (10 mpk)
- Semaglutide (3 nmol/kg) +INHBE-03 (10 mpk)
- Semaglutide (10 nmol/kg) +INHBE-03 (10 mpk)

Inhbe mRNA: Activin E protein correlation



Spearman coefficient = 0.77

At 27 weeks old (d0), DIO C67Bl6 received daily SC injections of PBS (for 28 days), as single dose of INHBE-03, daily semaglutide (for 28 days), or a single dose of INHBE-03 + daily semaglutide (for 28 days). Mice were sacrificed on D28. *Inhbe* expression in liver was evaluated by RT-qPCR. Stats: Left, middle: Data analyzed by 1-way ANOVA followed by Tukey's HSD post-hoc comparisons on log2-transformed data; * p<0.05. n=7 or 8/group.

Summary

- Preclinical data show that in DIO mice, *Inhbe* GalNAc-siRNAs:
  - Lower *Inhbe* mRNA and induce weight loss mainly through reduction of fat mass
  - Reduce pro-inflammatory macrophage recruitment in adipose tissue
  - Double weight loss, when added on to semaglutide
  - Curtail weight regain upon cessation of semaglutide

- Preclinical data suggest that *Inhbe* GalNAc-siRNAs and GLP1-RAs induce weight loss in mice primarily through independent mechanisms

- Wave is advancing investigational WVE-007, an *INHBE* targeting GalNAc-siRNA, as a novel, long-acting, muscle-sparing approach for treatment of obesity
  - Data from the ongoing INLIGHT phase 1 study expected in second half 2025

Acknowledgements

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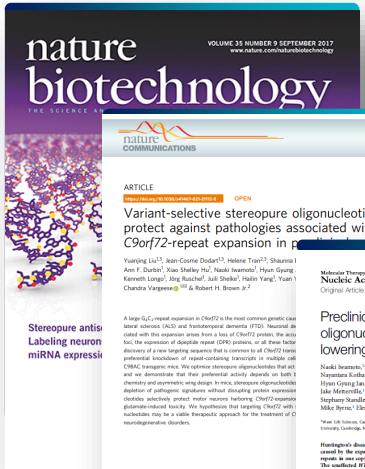
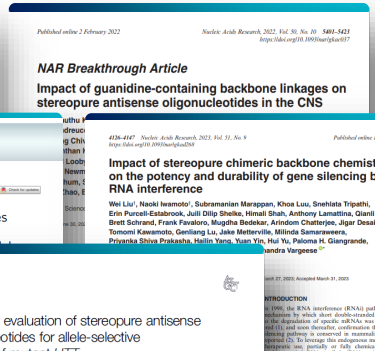
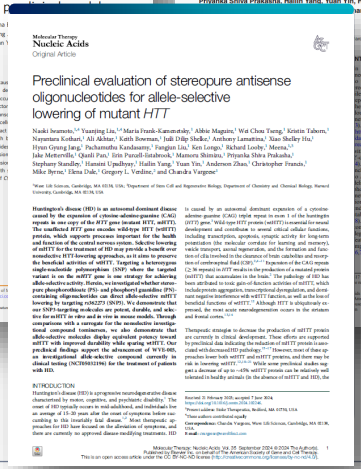
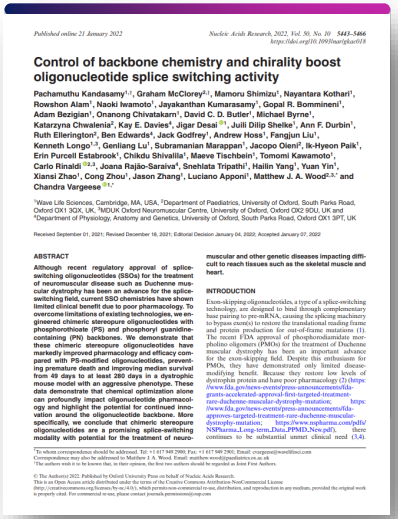
- Nicole Neuman and Darienne Myerbeck, Wave Life Sciences, assisted in preparing this presentation

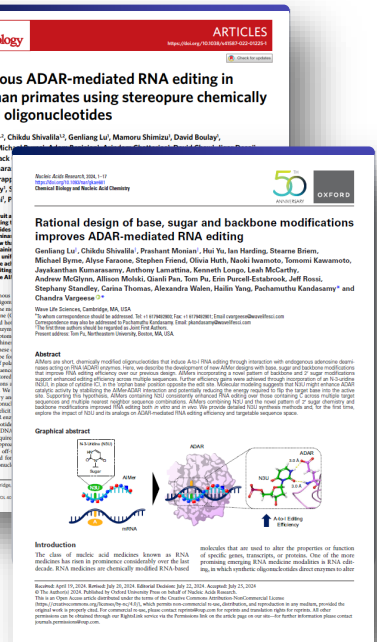
Silencing (RNase H and Ago2) | **Splicing** | **Editing**











Selected Wave publications: PMC10201370, PMC9092894, PMID 35256816, PMC9177980, PMC9178015, PMC7870851, PMC7804567, PMID 28829437, DOI: 10.1016/j.omtn.2024.102246; DOI: 10.1093/nar/gkae681; DOI: 10.1093/nar/gkae681