Liver-specific silencing of INHBE with ARO-INHBE, an siRNA therapeutic, for metabolic diseases

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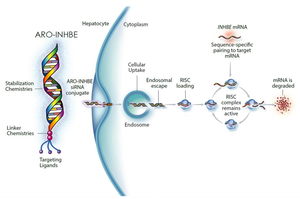
INTRODUCTION

- Incretin-based therapies are powerful and effective for obesity and metabolic outcomes, but significant loss of lean mass and adverse GI events at high dose levels has prompted the identification of a novel mechanism of action
- Large-scale human genetic studies support an association between pLOF INHBE variants and 1) reduced WHRadjBMI, 2) improved metabolic profile including lower TG, higher HDL, and reduced fasting glucose levels
- Activin E signaling regulates adipose lipid storage and mobilization
- Activin E levels are elevated in individuals with obesity, insulin resistance, and NAFLD
- siRNA targeting hepatic INHBE has potential to be a novel therapeutic for metabolic diseases

AIM

- Evaluate the potential therapeutic benefits of INHBE silencing in obese and diabetic mouse models with a mouse surrogate of ARO-INHBE
- Evaluate the pharmacodynamic effects of ARO-INHBE in cynomolgus monkeys



METHODS

Rodent studies

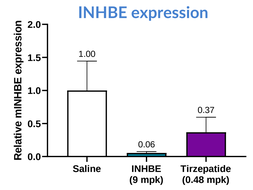
- Diet-induced obese (DIO) and db/db mouse models
- Dosing regimen: weekly 9 mpk subcutaneous (SC) dosing of mouse surrogate ARO-INHBE; daily 0.48 mpk tirzepatide as benchmark; co-treatment of weekly INHBE (9 mpk) and daily tirzepatide (0.48 mpk)
- Body weight, body composition (lean versus fat mass) via Dual X-ray Absorptiometry (DEXA) scans, glucose homeostasis (fasting glucose, insulin, HOMA-IR, oGTT), lipid metabolism (non-esterified fatty acids, beta-hydroxybutyrate) assessed at various points over the course of the studies

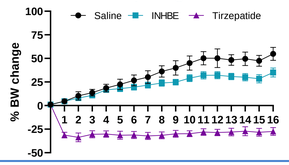
Non-human primate study

- Cynomolgus monkeys (n=3) received 2 SC doses (D1 and D29) of ARO-INHBE at 3 mpk
- Liver biopsies were collected for INHBE mRNA expression via qRT-PCR

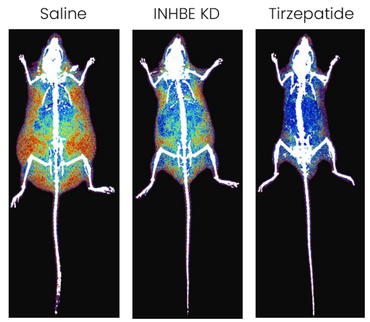
PHARMACOLOGICAL STUDIES OF INHBE siRNA IN RODENT MODELS

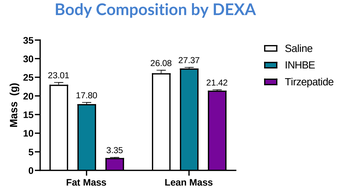
Knockdown of hepatic INHBE mRNA expression with surrogate RNAi-trigger results in an improved body composition with 1) BW suppression, 2) fat mass loss, 3) lean mass retention





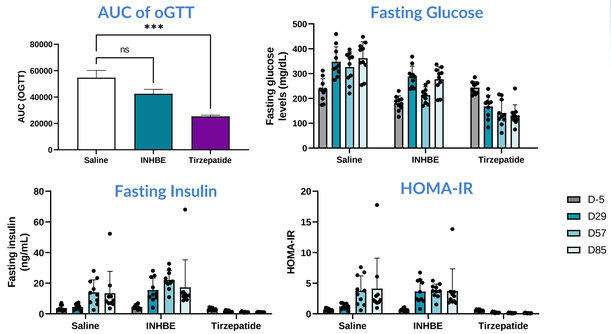
- DIO mice were administered with saline (weekly), mouse surrogate ARO-INHBE (9 mpk, weekly), or tirzepatide (0.48 mpk, daily)
- n=10 for each treatment group
- INHBE mRNA expression reduced by ~95%
- INHBE silencing led to a 19% suppression of body weight compared to saline controls





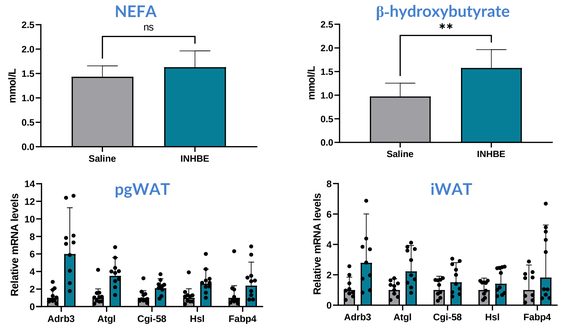
- Body composition analysis through DEXA imaging indicates a 26% loss of fat mass and preservation of lean mass with INHBE silencing

Impact on glycemic control is mild based on oGTT, fasting glucose, fasting insulin, and HOMA-IR indicators



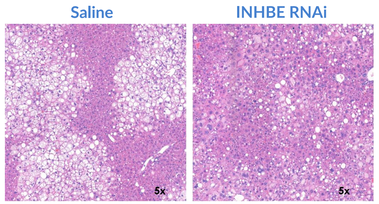
- Animals were fasted for 6 hours prior to glucose homeostasis analysis

INHBE KD improves catecholamine sensitivity, increasing lipid mobilization and oxidation



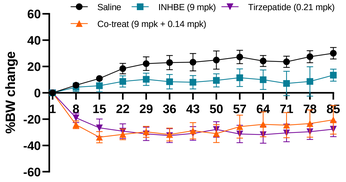
- INHBE KD animals treated with CL316,243 (1 mpk, IP) had increased circulating ketone levels and expression of lipolytic genes relative to control group

Increased lipid mobilization with INHBE silencing does not lead to liver steatosis



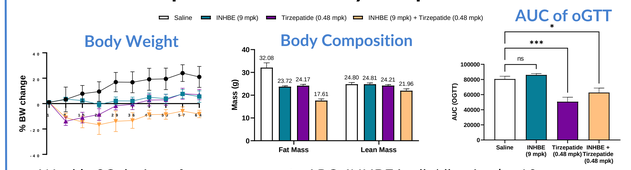
- H&E staining of the liver indicate there is less fat accumulation in DIO mice treated with INHBE RNAi

Co-treatment of tirzepatide with INHBE siRNA allows use of lower tirzepatide dose for similar therapeutic effect in DIO mice



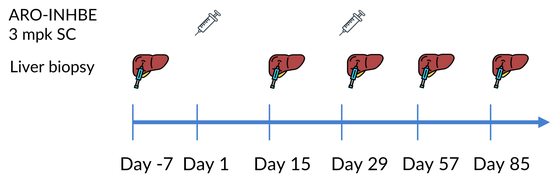
- Co-treated DIO mice (n=10 per treatment group) were administered 9 mpk mouse surrogate ARO-INHBE weekly and 0.14 mpk tirzepatide daily
- Co-treated mice showed similar levels of %BW change as mice treated with a higher dose level of tirzepatide

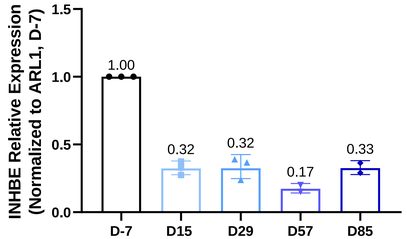
INHBE silencing in the db/db mouse model results in an improvement in body composition



- Weekly SC dosing of mouse surrogate ARO-INHBE in db/db mice (n=10 per treatment group) resulted in: 1) 15% suppression in BW compared to the saline group, 2) 26% loss of fat mass, 3) lean mass retention, 4) lack of improvement in oGTT

PHARMACODYNAMIC STUDY OF ARO-INHBE IN CYNOMOLGUS MONKEYS





- After a single 3 mpk SC dose, hepatic INHBE mRNA expression was reduced by ~70% (n=3; n=2 on D57 and D85)
- Knockdown was maintained through D85 with a second dose on D29

CONCLUSIONS

- ARO-INHBE is a potent RNAi therapeutic capable of silencing hepatic INHBE mRNA expression
- Pre-clinical studies with a mouse surrogate of ARO-INHBE in DIO and db/db models indicate that INHBE KD potentially leads to a suppression in body weight gain, loss of fat mass, and preservation of lean mass likely due to the increased lipolysis
- Co-treatment of tirzepatide with INHBE RNAi has the potential to allow for the use of a lower tirzepatide dose without compromising the therapeutic effect