ARO-ALK7, a RNAi Therapeutic Targeting Adipose ALK7 Expression for Obesity

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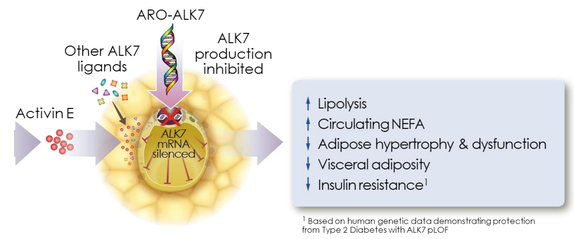
OVERVIEW

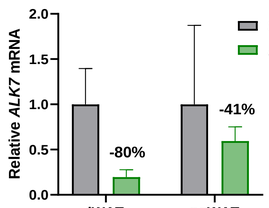
- While incretin-based therapies are the current frontline pharmacotherapeutics for obesity and metabolic outcomes, issues concerning significant loss of lean mass, adverse GI events at high dose levels, and disproportional fat mass gain after cessation of the therapies remain a challenge for many patients
- Human genetic studies support ALK7 as a therapeutic target with pLOF *ALK7* variants associated with 1) reduced WHRadjBMI, 2) protection from type 2 diabetes, 3) reduced risk of cardiovascular disease
- ALK7 signaling suppresses lipolysis, increasing adipocyte size and lipid content
- We evaluated the potential therapeutic benefits of ALK7 silencing by siRNA designed to specifically target adipose tissue
- Chronic treatment of DIO mice with a surrogate of ARO-ALK7 suppressed body weight gain by 39%, reduced fat mass by 50%, and preserved lean mass compared to saline controls
- ALK7 surrogate RNAi-treated DIO mice exhibited enhanced lipolysis and increased energy expenditure
- Co-treatment of the ARO-ALK7 surrogate with tirzepatide in DIO mice enhanced body weight reduction and fat loss relative to tirzepatide monotherapy
- In NHPs, a single subcutaneous dose of ARO-ALK7 resulted in a dose-dependent and durable reduction in *ALK7* mRNA expression in abdominal fat
- ARO-ALK7 was well tolerated in Han Wistar rats in non-GLP toxicological studies



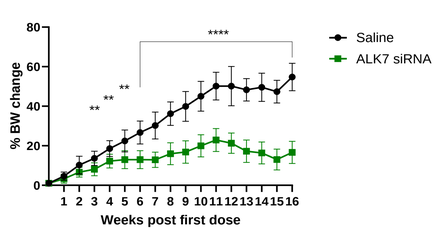
PHARMACOLOGICAL STUDIES OF ALK7 siRNA IN A DIET-INDUCED OBESE (DIO) MOUSE MODEL

1. ALK7 silencing in adipose tissue suppresses body weight gain and improves body composition in DIO mice

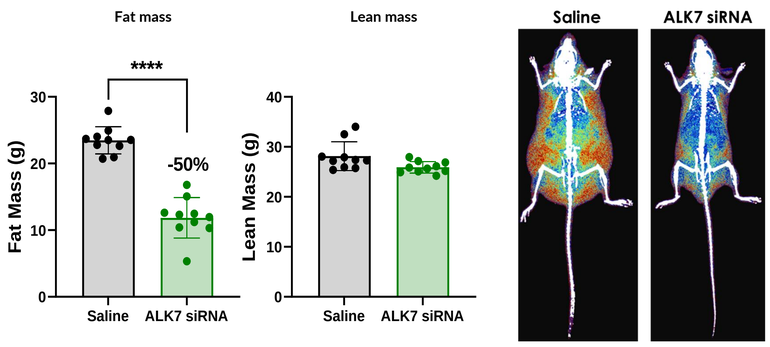
ALK7 mRNA knockdown



% Body weight change



Body composition analysis by DEXA imaging

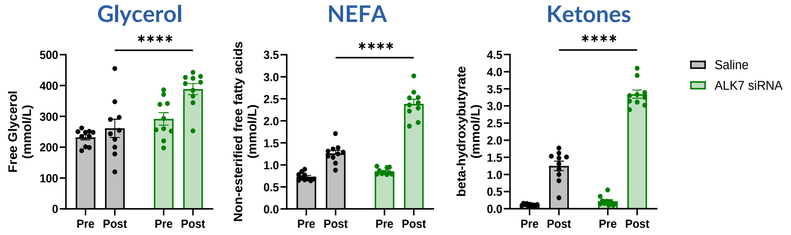


C57Bl/6 DIO mice (male, age = 18 weeks at initiation) received chronic treatment with a mouse surrogate ARO-ALK7 (3 mg/kg weekly), which resulted in:

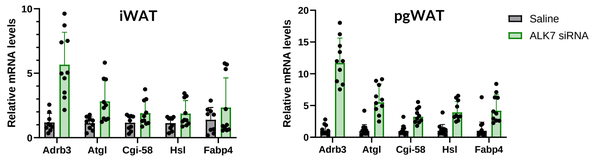
- *ALK7* mRNA knockdown of 80% in inguinal white adipose tissue and 40% in perigonadal white adipose tissue at study terminus (week 16)
- A significant suppression of up to 40% body weight gain relative to saline controls
- Approximately 50% reduction in fat mass with preservation of lean mass by DEXA imaging analysis

2. Body fat loss is mechanistically attributed to enhanced lipolysis and increased energy expenditure

Glycerol / NEFA / Ketones



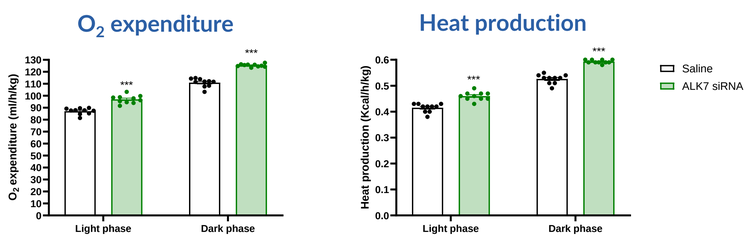
qPCR of lipolysis-related gene panel in adipose tissue



Serum collected prior to and 30 min after challenge with CL316,243, a β3-adrenergic receptor agonist (IP, 1 mg/kg)

- Animals (N=10/group) with reduced *ALK7* expression had increased circulating levels of glycerol, NEFAs, and ketones (Mean±SEM) and exhibited upregulation in the expression of lipolytic genes

O_2 expenditure / Heat production

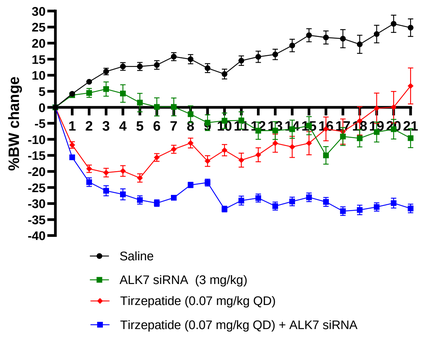


At week 8, energy expenditure measurements (Mean ±SEM) were obtained from C57Bl/6 DIO mice (N=10/group) caged in a TSE Phenomaster system over 2 dark and 1 light cycle. ALK7 siRNA treated group exhibited:

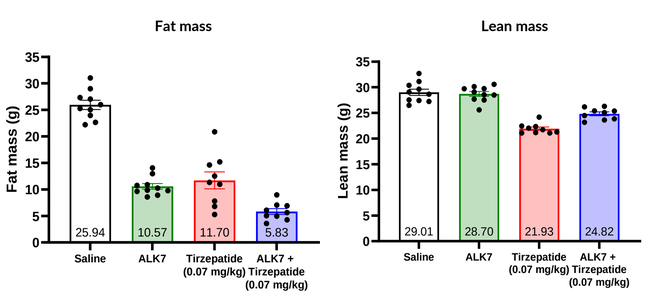
- Increased levels of O_2 consumption and heat production
- No change in food intake

3. ALK7 silencing with tirzepatide enhances therapeutic benefits of tirzepatide monotherapy

%Body weight change



Body composition by DEXA

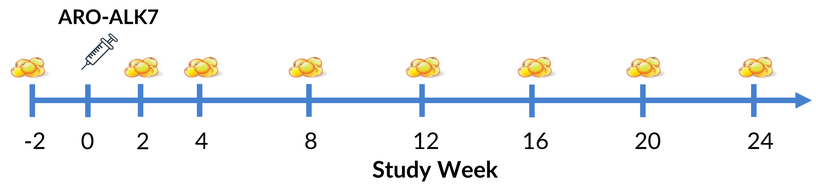


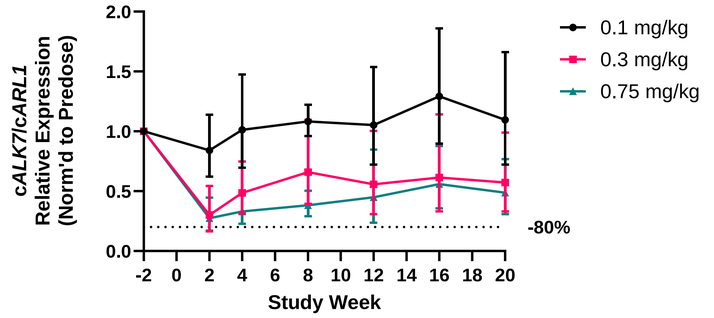
C57Bl/6 DIO mice (male, age = 20 weeks) were treated with either 1) saline weekly, 2) ALK7 surrogate siRNA 3 mg/kg weekly, 3) tirzepatide (0.21 mg/kg QD), 4) tirzepatide (0.07 mg/kg QD), or 5) tirzepatide (0.07 mg/kg QD) and ALK7 surrogate siRNA 3 mg/kg weekly (N=10/group)

- Co-treatment of tirzepatide and ALK7 siRNA at optimal dose levels had an additive effect on body weight and fat mass reductions
- ALK7 siRNA ameliorated the significant loss of lean mass associated with tirzepatide

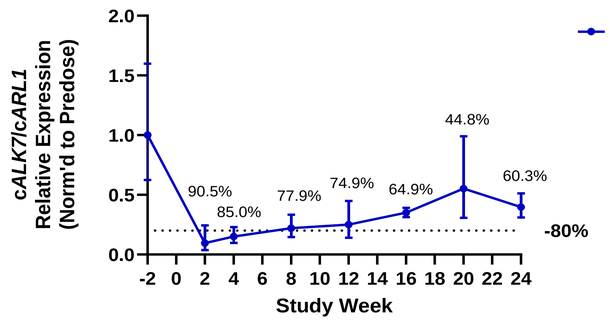
PHARMACODYNAMIC STUDIES OF ARO-ALK7 IN NON-HUMAN PRIMATES

4. A single subcutaneous dose of ARO-ALK7 achieves deep and durable reduction in mRNA expression of *ALK7* in subcutaneous adipose tissue





- The dynamic range (0.1 - 0.75 mg/kg) of ARO-ALK7 was evaluated in cynomolgus monkeys (N=4/group)
- A single dose of ARO-ALK7 resulted in a dose-dependent reduction of *ALK7* mRNA expression



- The duration of ARO-ALK7 was evaluated in cynomolgus monkeys (N=4/group)
- A single 1.5 mg/kg ARO-ALK7 dose resulted in ~75% *ALK7* knockdown in abdominal adipose tissue for up to 12 weeks

TOXICOLOGICAL STUDY OF ARO-ALK7 IN HAN WISTAR RATS

5. ARO-ALK7 is well-tolerated subcutaneously in Han Wistar rats

ARO-ALK7 administered as a single dose of 30, 60, or 120 mg/kg (Day 15 necropsy), or repeat doses of 60 mg/kg on Day 1 and 29 (Day 43 necropsy)

- Histopathological findings of vacuolated macrophage infiltrates at injection site/lymph nodes (≥60 mg/kg), liver Kupffer cell hypertrophy (≥30 mg/kg)
- No adverse or dose-limiting findings were identified