Exploring siRNA Combinations for Enhanced Therapeutic Benefits in Obesity

Obesity Science & Innovation

September 17, 2025

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Pathogenesis of Obesity is Multifactorial – Regulated by Multiple Pathways and Mechanisms

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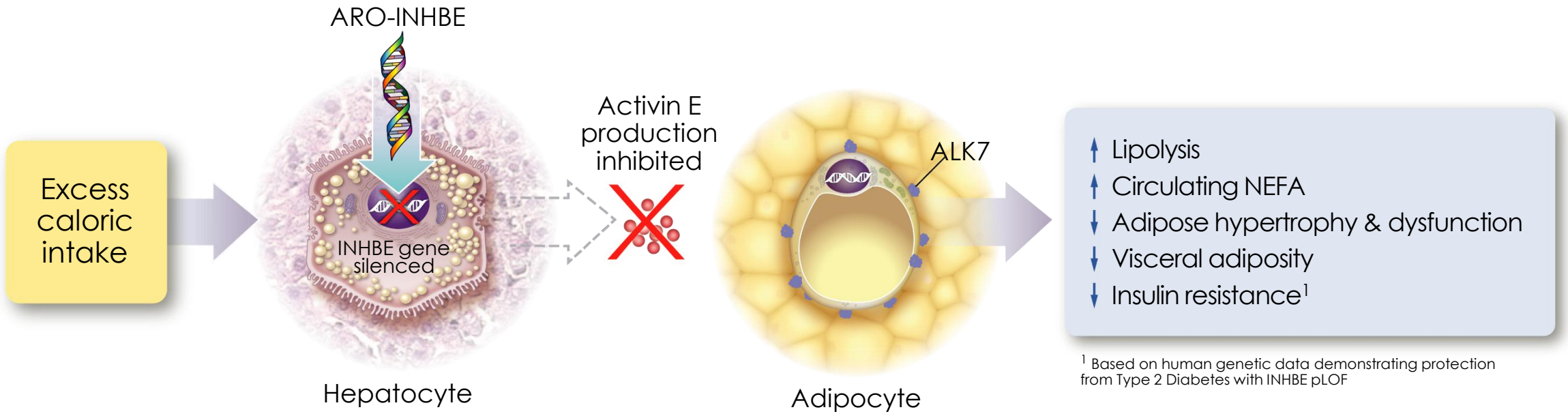
Silencing Hepatic *INHBE* May Inhibit Maladaptive Activin E – ALK7 Signaling and Improve Adipose Dysfunction in Obesity



[1] Based on human genetic data demonstrating protection from Type 2 Diabetes with INHBE pLOF

*Based on human genetic data demonstrating protection from Type 2 Diabetes with *INHBE* pLOF.

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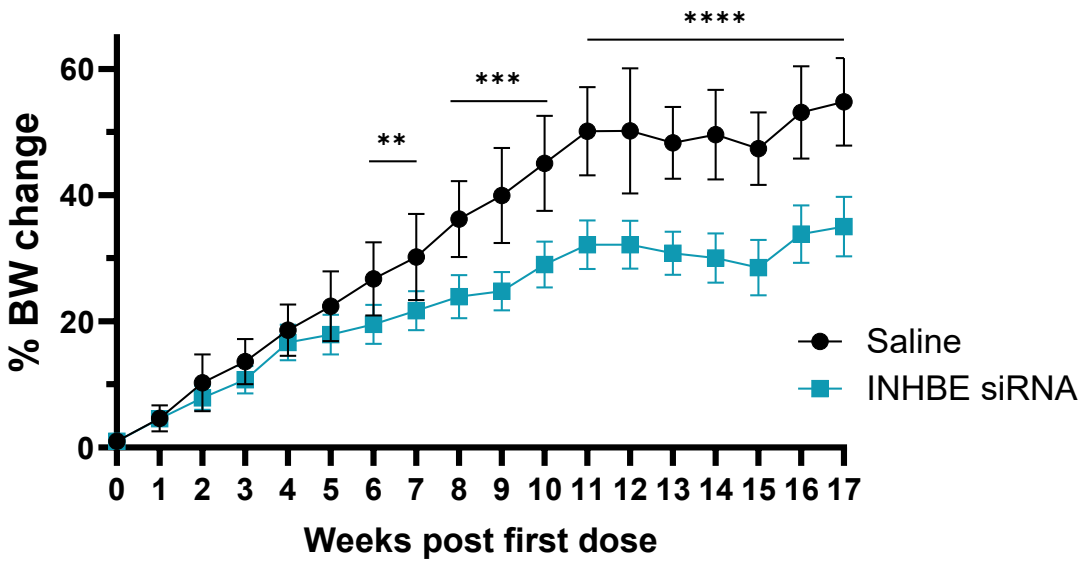
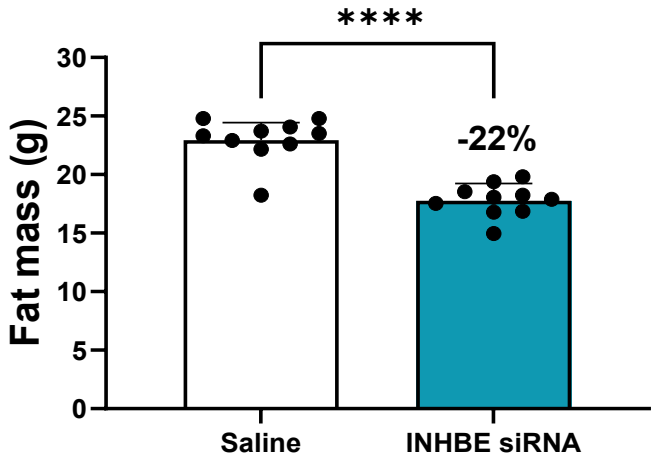
Hepatic *INHBE* Silencing Limits Weight Gain in a Mouse Model of Diet-induced Obesity (DIO)

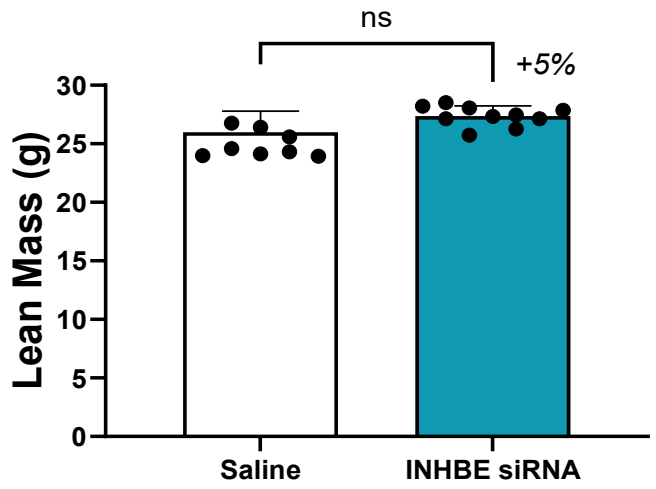
Body Weight Change



- Mice on a high calorie diet treated with an INHBE siRNA exhibit a **19% suppression** in BW gain relative to vehicle controls

Body Composition





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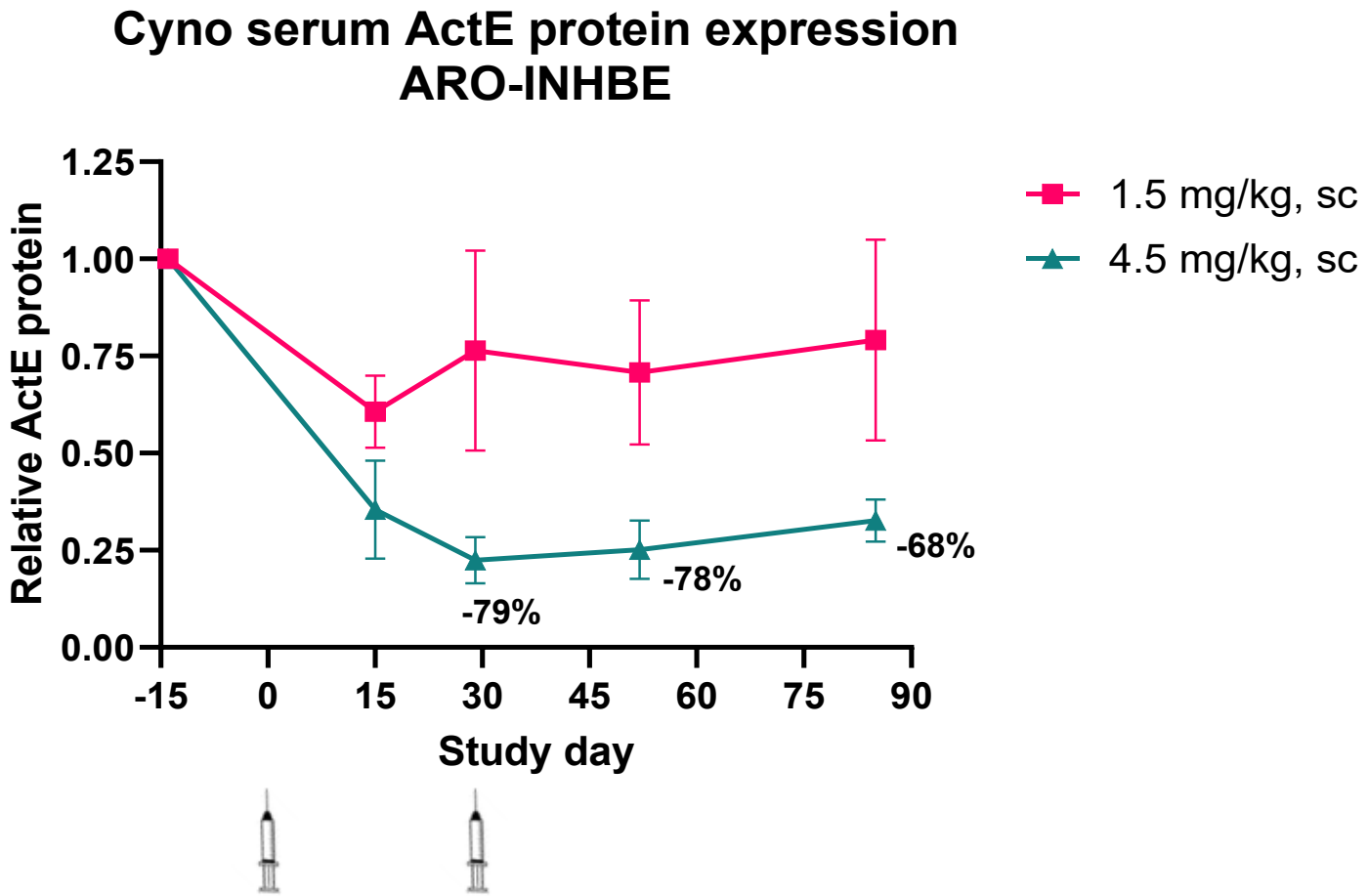
ARO-INHBE Effectively Silences Circulating Activin E in Lean Non-Human Primates



ARO-INHBE entered a Phase I/2a study in Q4 2024 as a siRNA therapeutic that has the potential to reduce adipose hypertrophy and dysfunction, visceral adiposity, and improve insulin sensitivity

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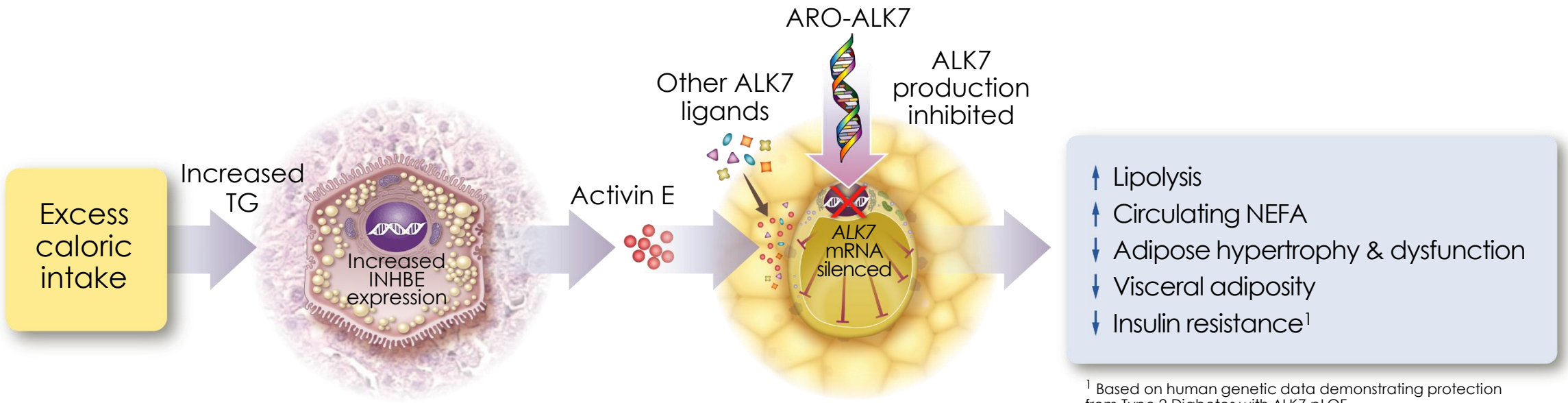
Adipose-specific silencing of Activin receptor-like kinase 7 (*ALK7, ACVR1C*) May Also Improve Adipose Dysfunction in Obesity



[1] Based on human genetic data demonstrating protection from Type 2 Diabetes with ALK7 pLOF

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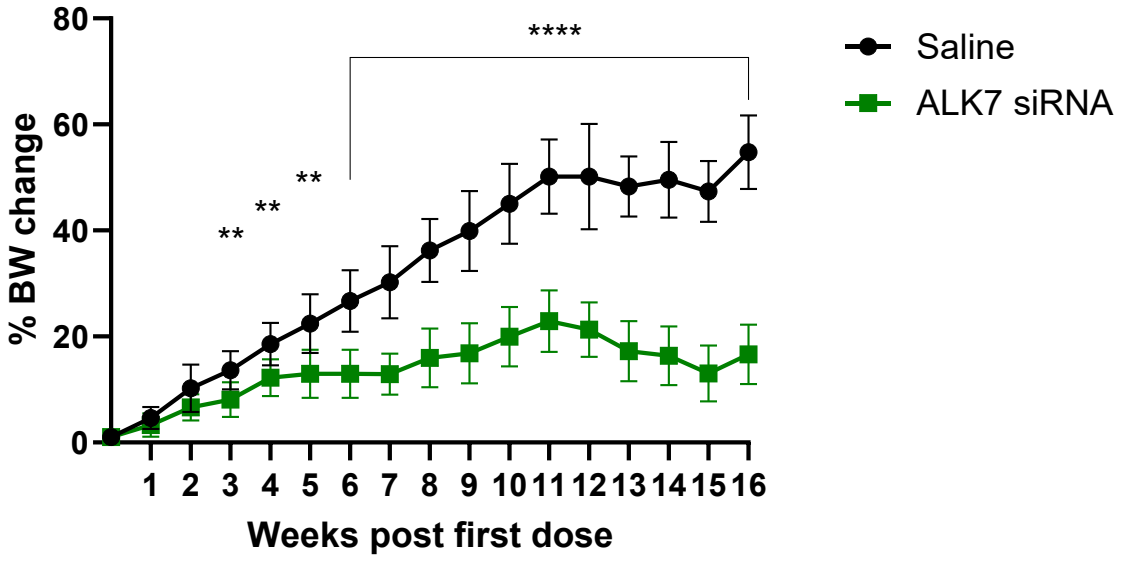
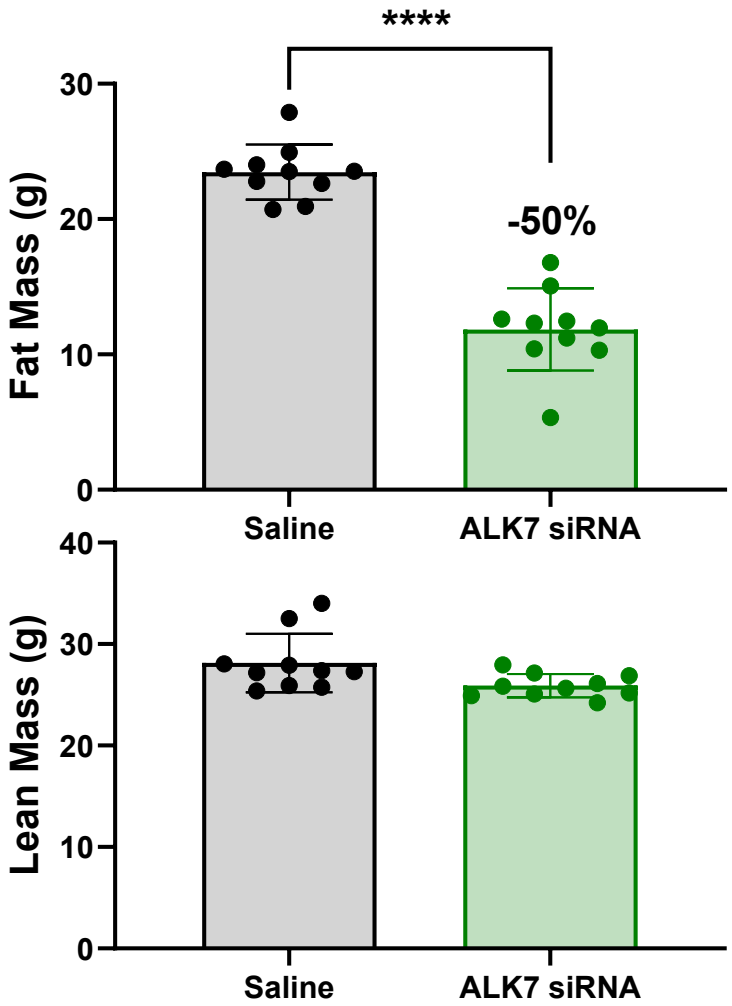
Adipose *ALK7* Silencing Suppresses Weight Gain and Improves Overall Body Composition in a DIO Mouse Model

Body Weight Change



- Mice on a high calorie diet treated with an ALK7 siRNA exhibit a **39% suppression** in BW gain relative to vehicle controls

Body Composition



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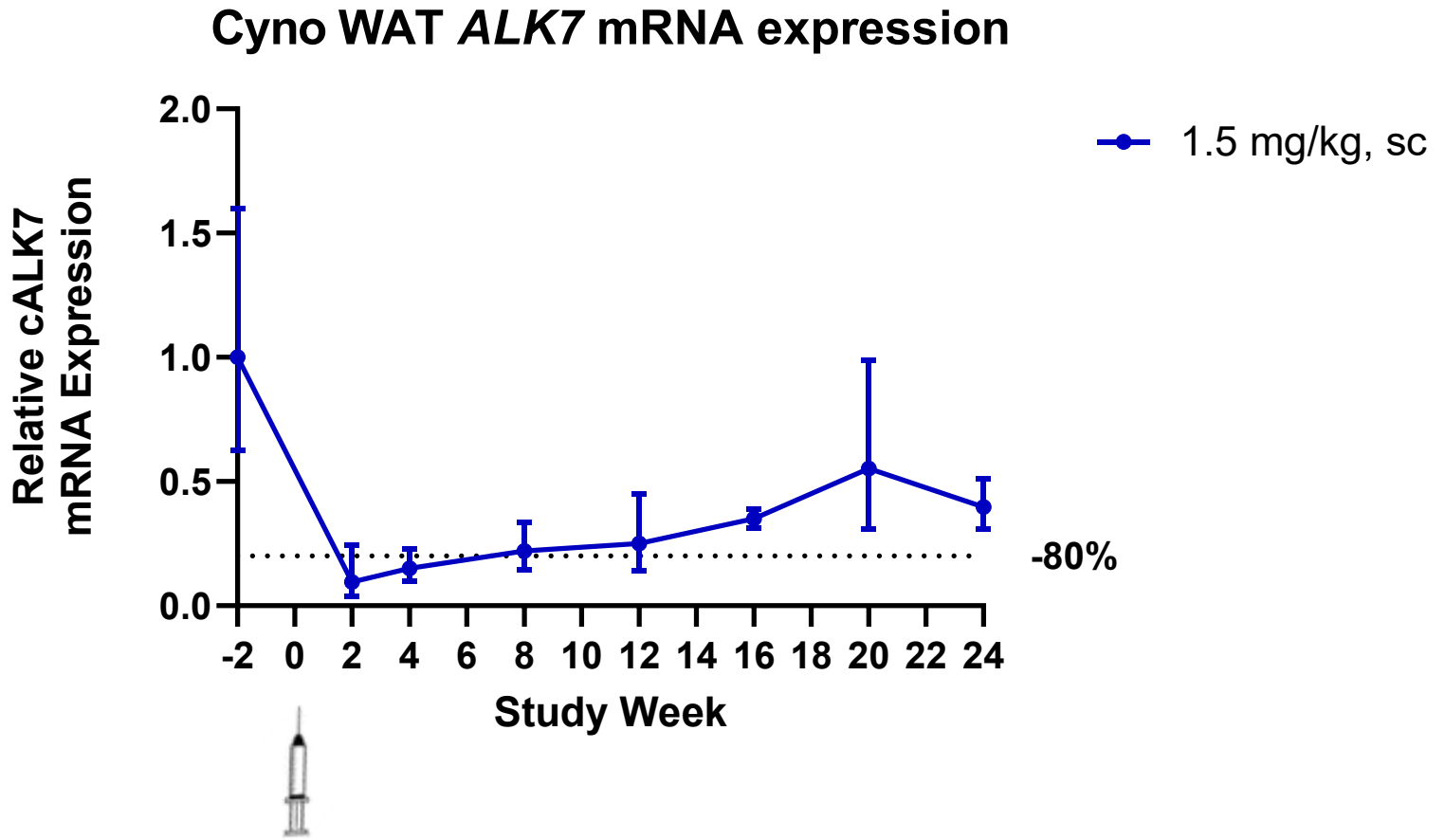
ARO-ALK7 Effectively and Durably Silences Adipose *ALK7* mRNA Expression in Lean Non-Human Primates



ARO-ALK7 entered a first-in-human Phase I/2a study in Q2 2025 as a siRNA therapeutic with the potential to reduce visceral adiposity and improve lipid and glycemic parameters

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Rationale for Combination Therapies in Obesity

01.

Maximize therapeutic efficacy by targeting complementary pathways

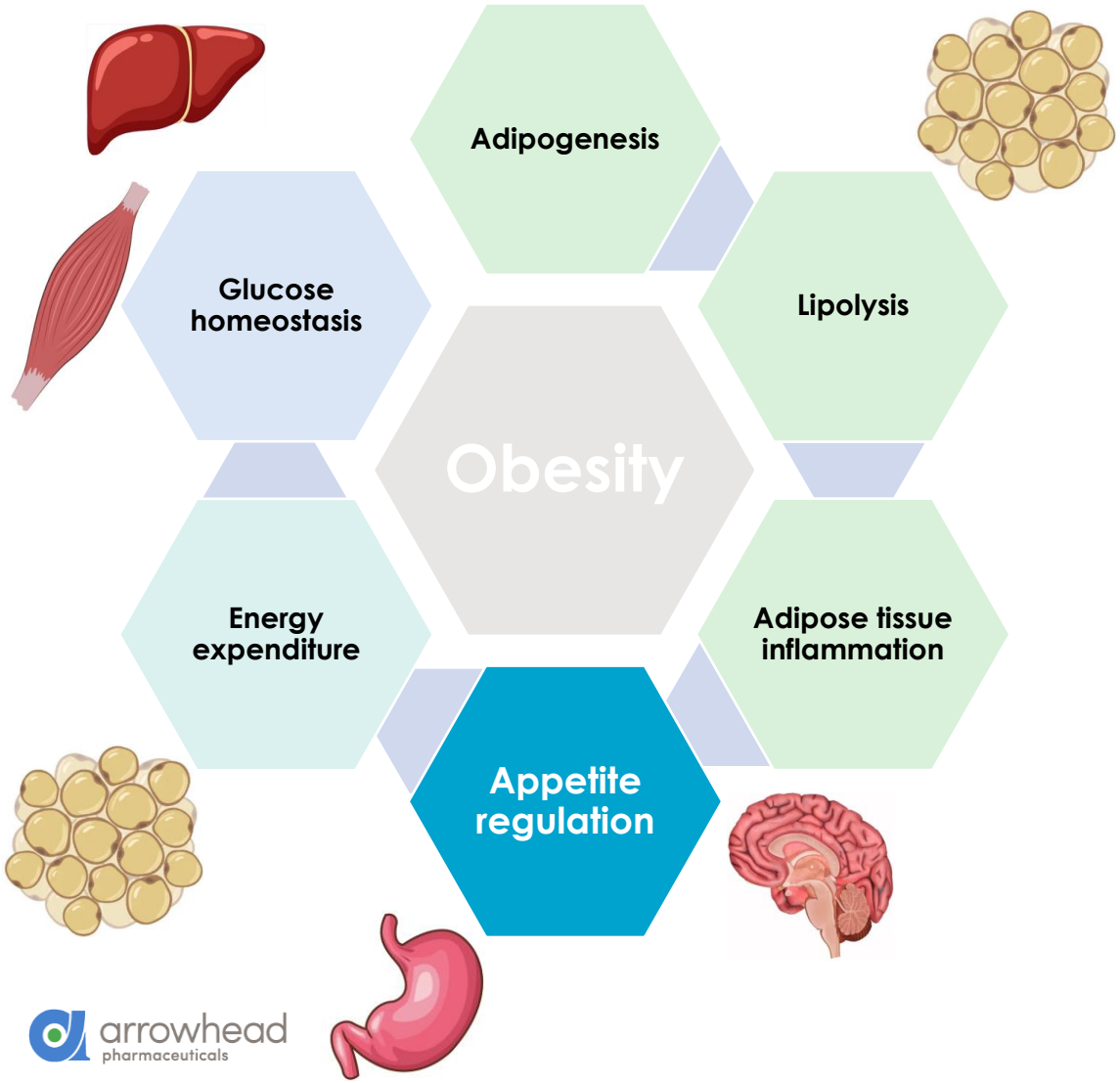
02.

Increase therapeutic benefits by targeting a diverse set of mechanisms of action

03.

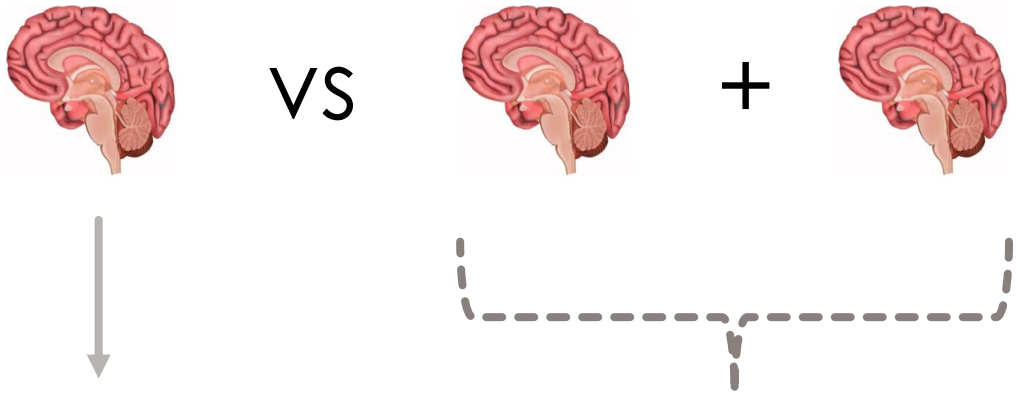
Minimize adverse side effects or toxicity by reducing dose level

Combination Therapeutics Have the Potential To Augment Therapeutic Efficacy



1 **Maximize therapeutic efficacy by targeting complementary pathways**

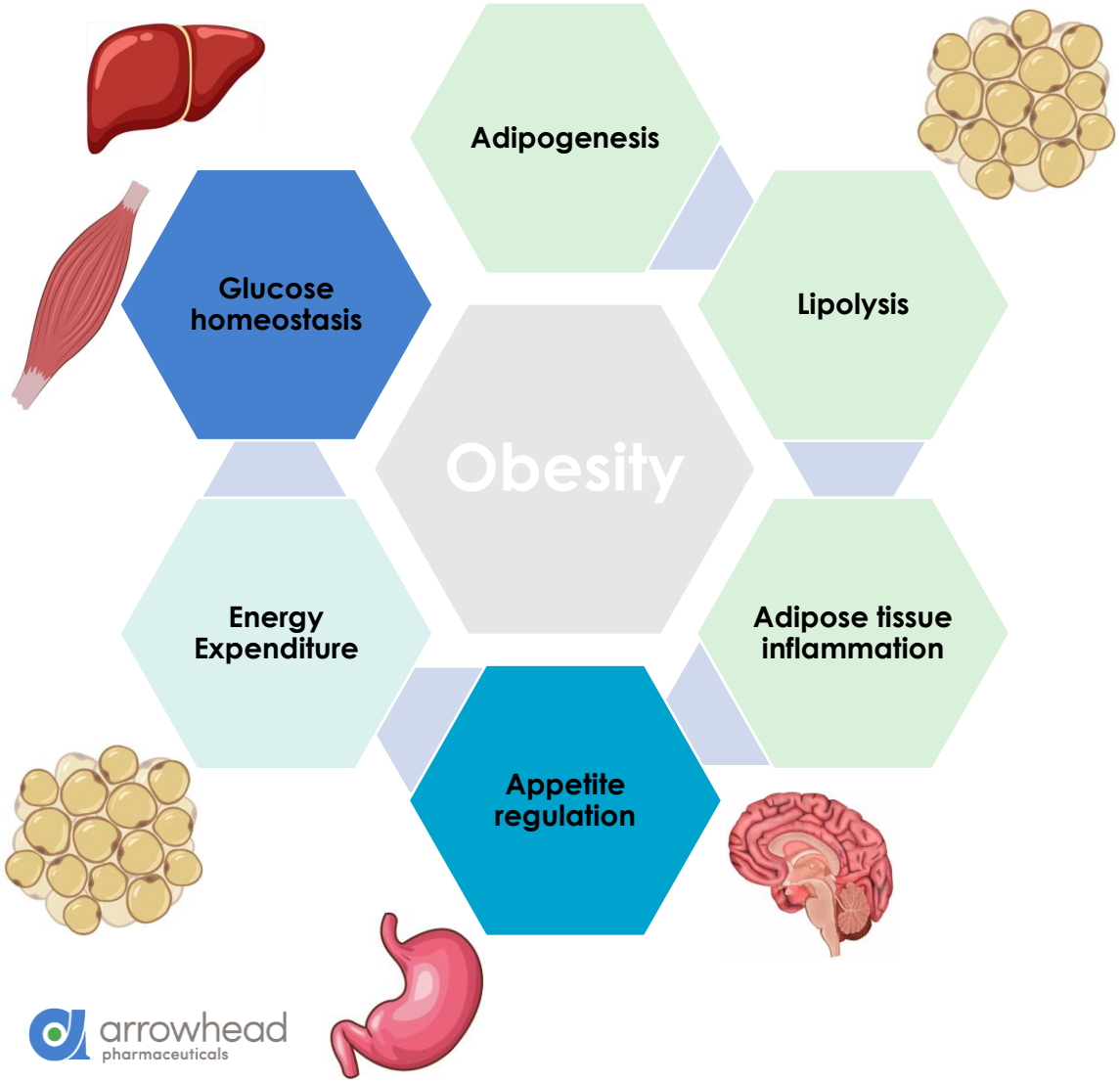
Naltrexone vs Naltrexone + Bupropion



Reduced food intake

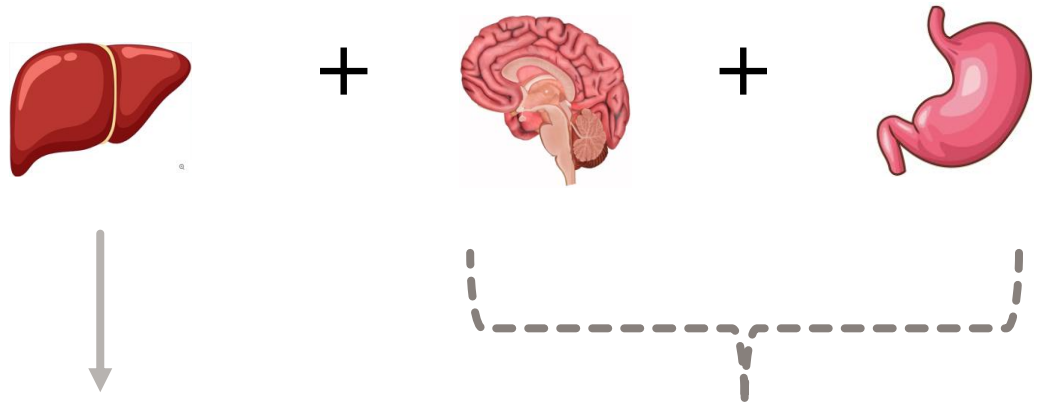
Enhanced reduction of food intake

Combining Drugs Can Result in Improvements Across Multiple Facets of Obesity



2 **Increase therapeutic benefits by targeting a diverse set of mechanisms**

Dual or triple agonist incretins



Improved glycemic control

Enhanced suppression of appetite

The Power of siRNA Combination Therapy over Monotherapy

Obesity is complex and multifactorial by nature.

siRNA monotherapy is limited by the targeting of a single gene.

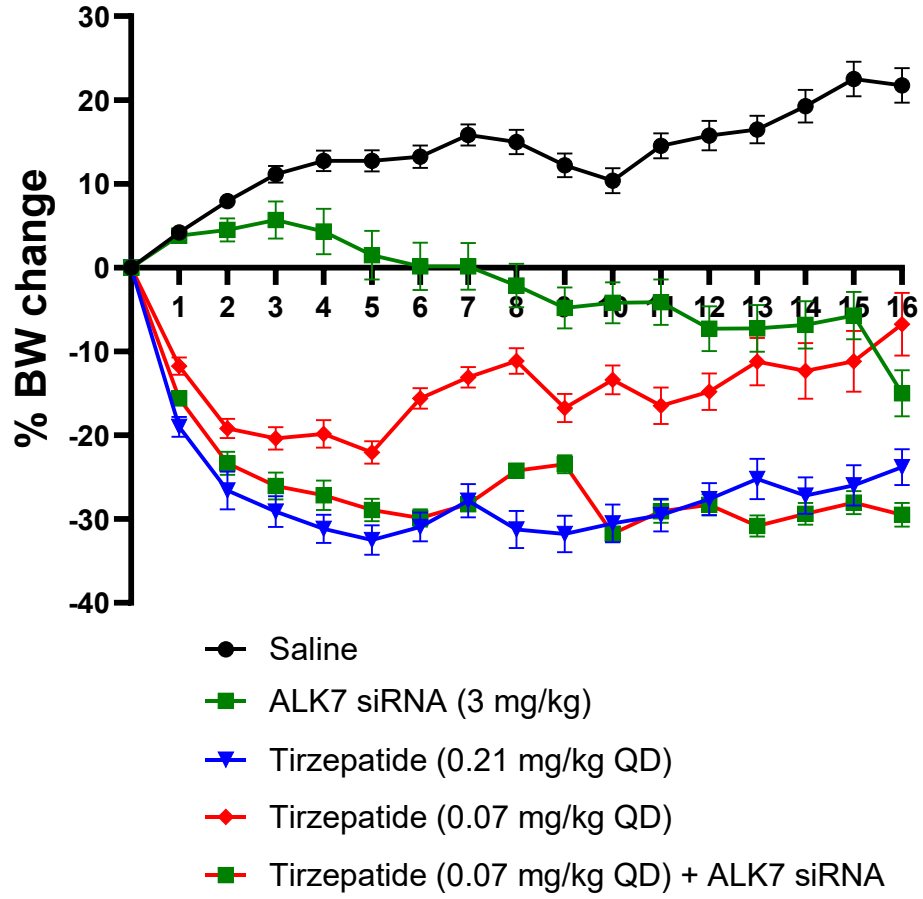
A multi-pronged approach can be taken by combining siRNAs with:

- traditional agents (i.e. incretin-based therapies)
- other siRNAs to silence target genes 1) enacting on complementary pathways or 2) involved in various processes

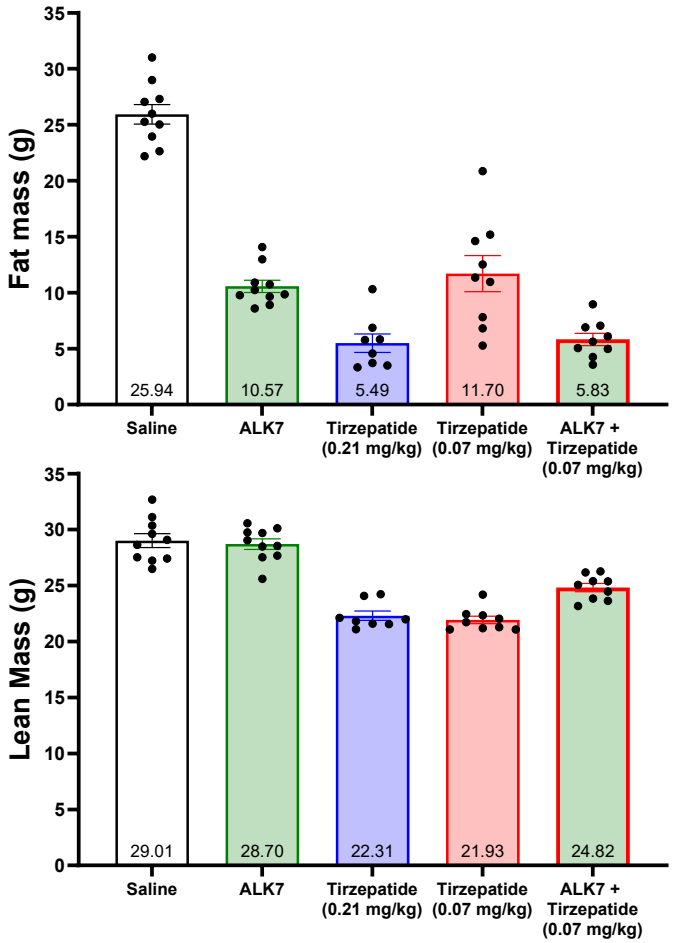
siRNA combination therapy can potentially provide a promising strategy for successful, long-term treatment.

ALK7 siRNA in Combination with Tirzepatide Enhances Weight Loss and Body Composition in the DIO Mouse Model

Body Weight Change



Body Composition



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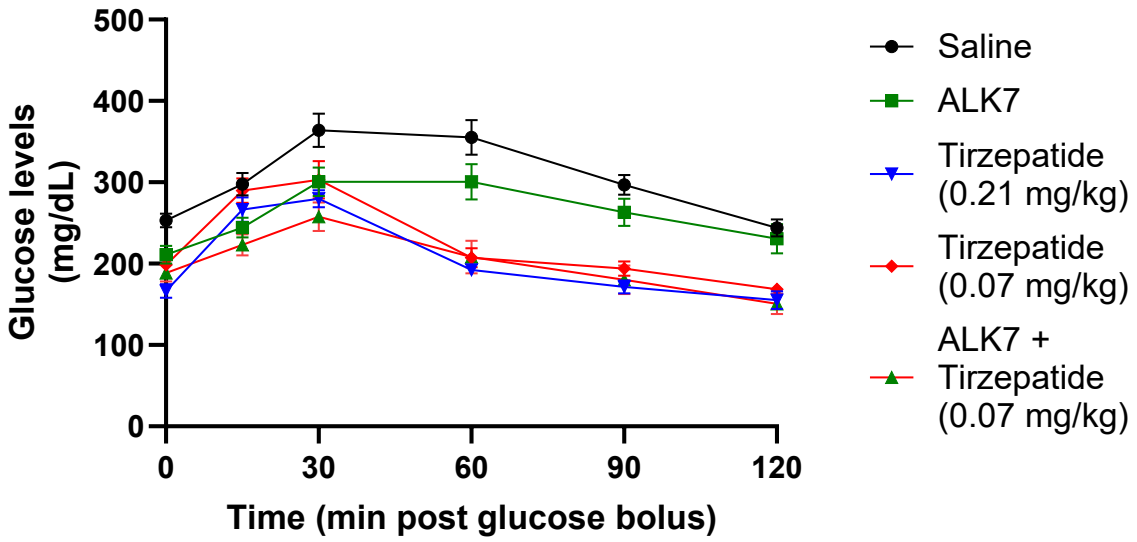
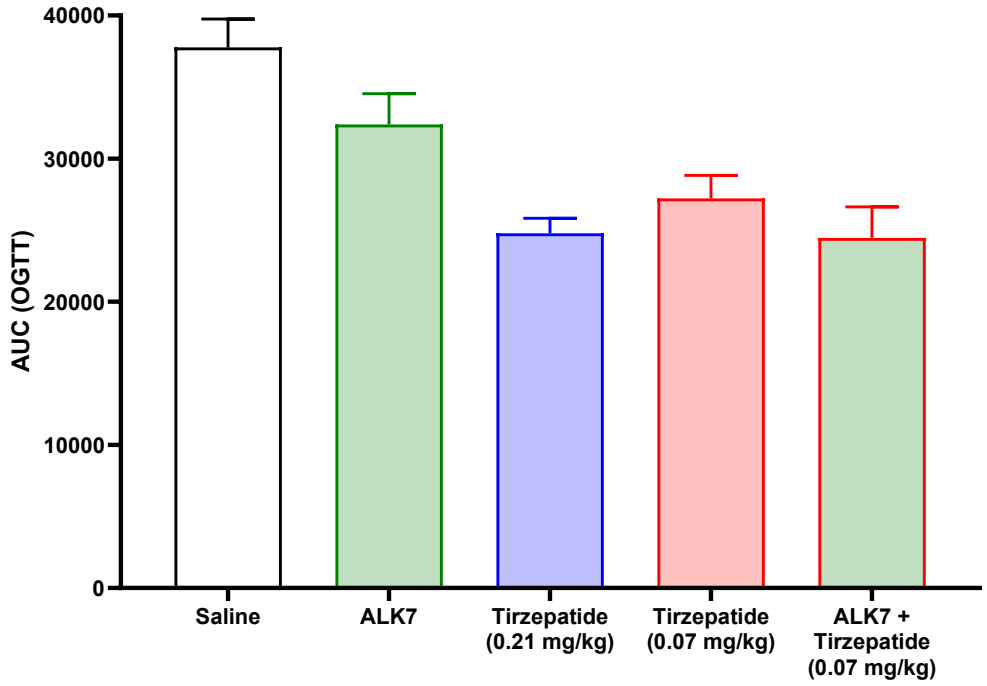
Combining Tirzepatide with *ALK7* siRNA Does Not Impact Glycemic Control

Oral Glucose Tolerance Test



AUC of OGTT



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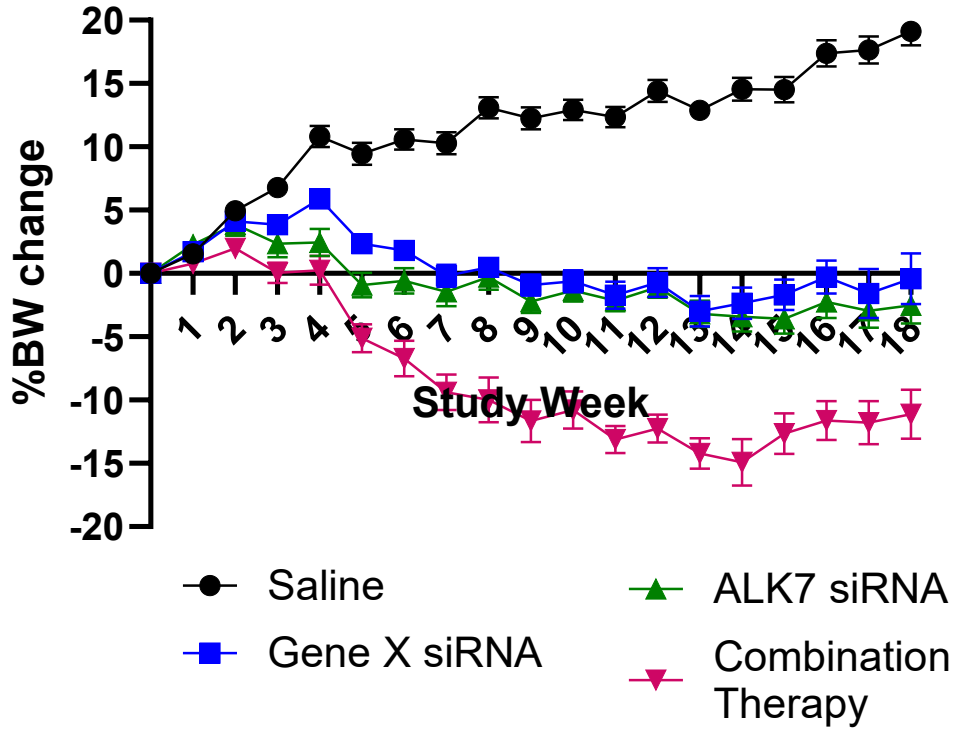
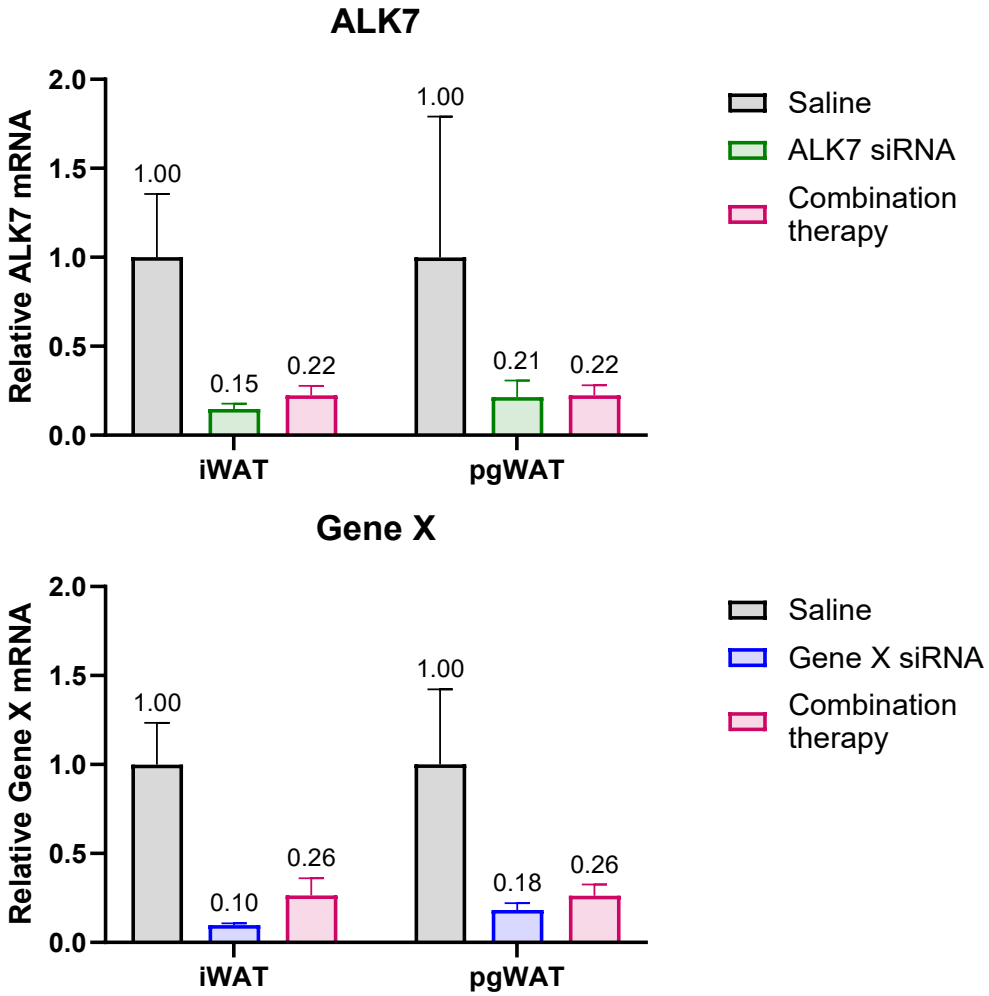
Combination therapy of *ALK7* and *Gene X* siRNA Enhances Body Weight Suppression Compared to Monotherapy

Body Weight Change



mRNA Expression in WAT



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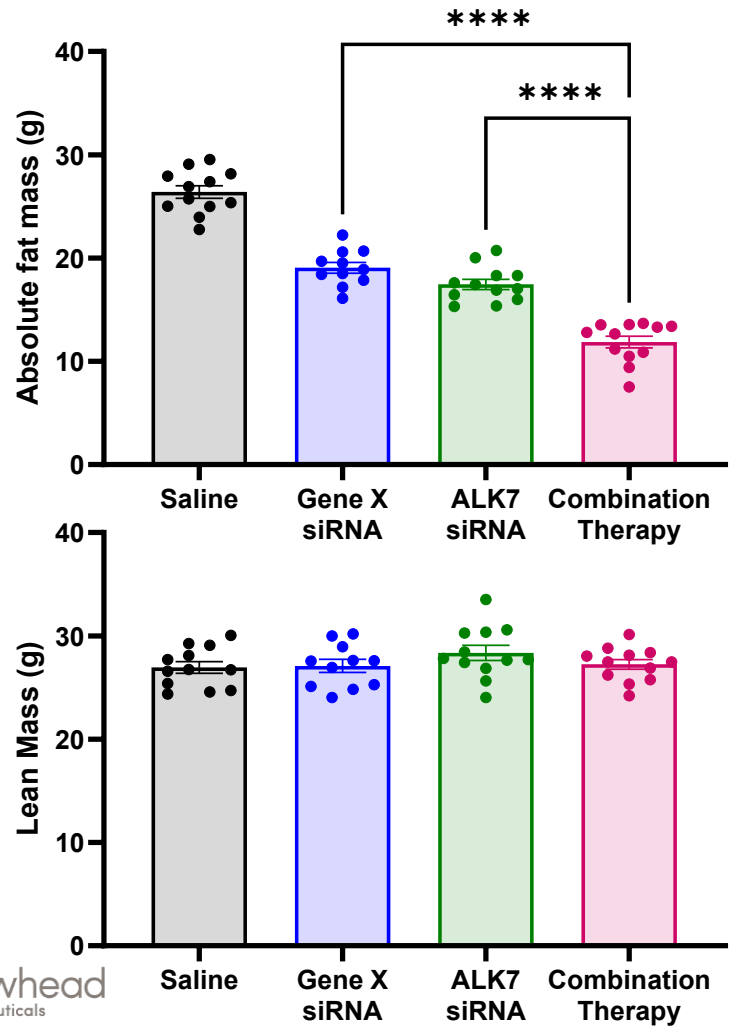
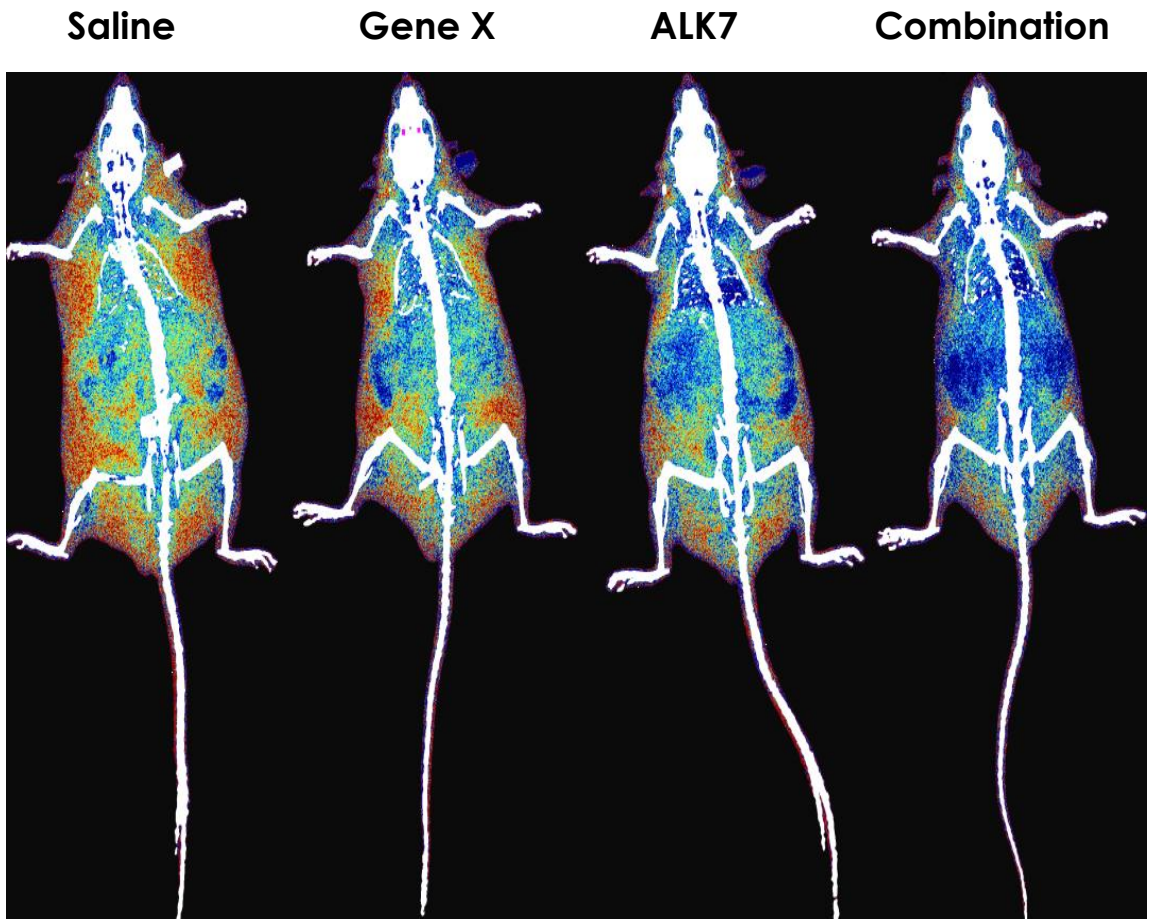
Silencing of *ALK7* in combination with *Gene X* Significantly Increases Fat Mass Loss Compared to Monotherapy Treatment

Body Composition at Week 15

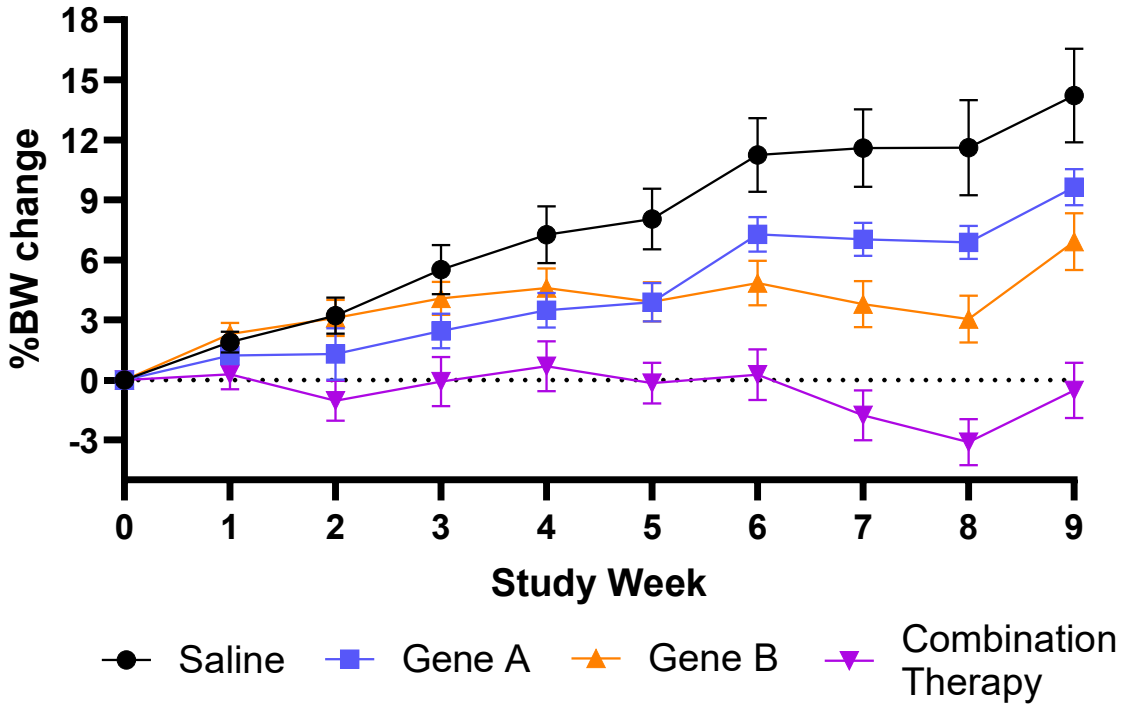


DEXA images

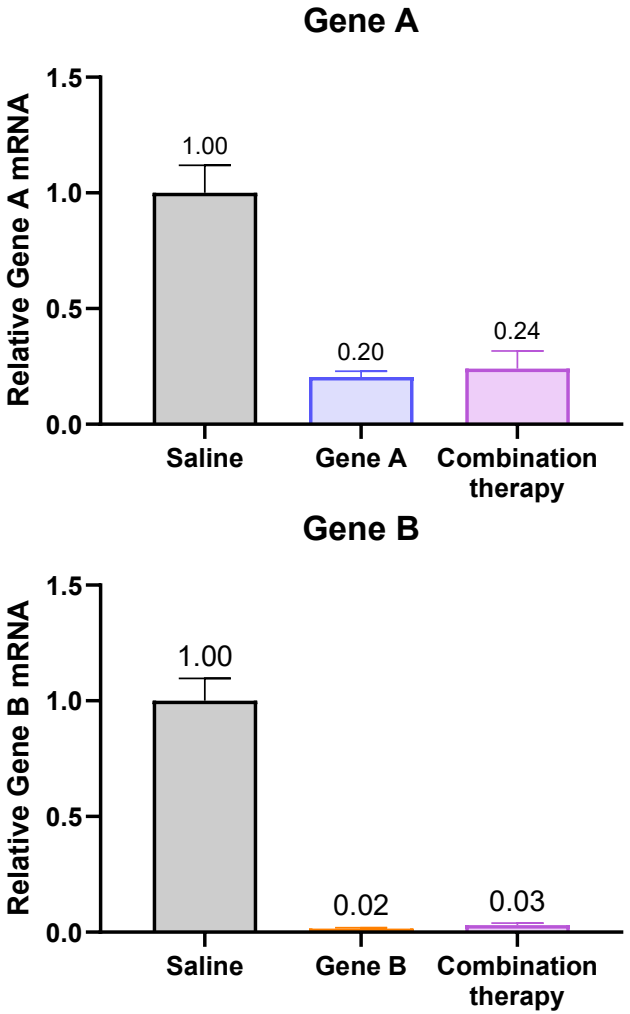


siRNA Combination Targeting *Gene A* and *Gene B* Results in Augmented BW Suppression

% Body Weight Change



mRNA Expression



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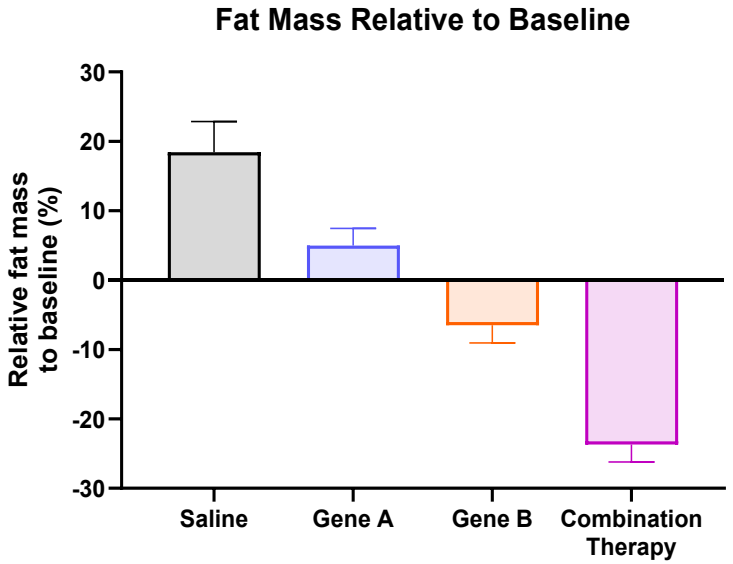
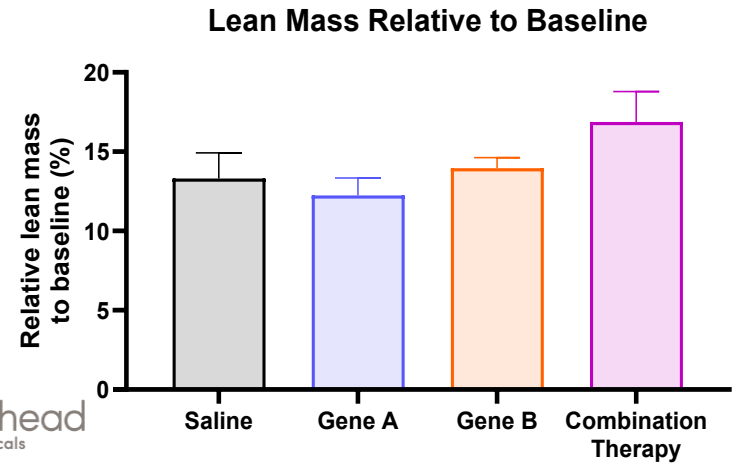
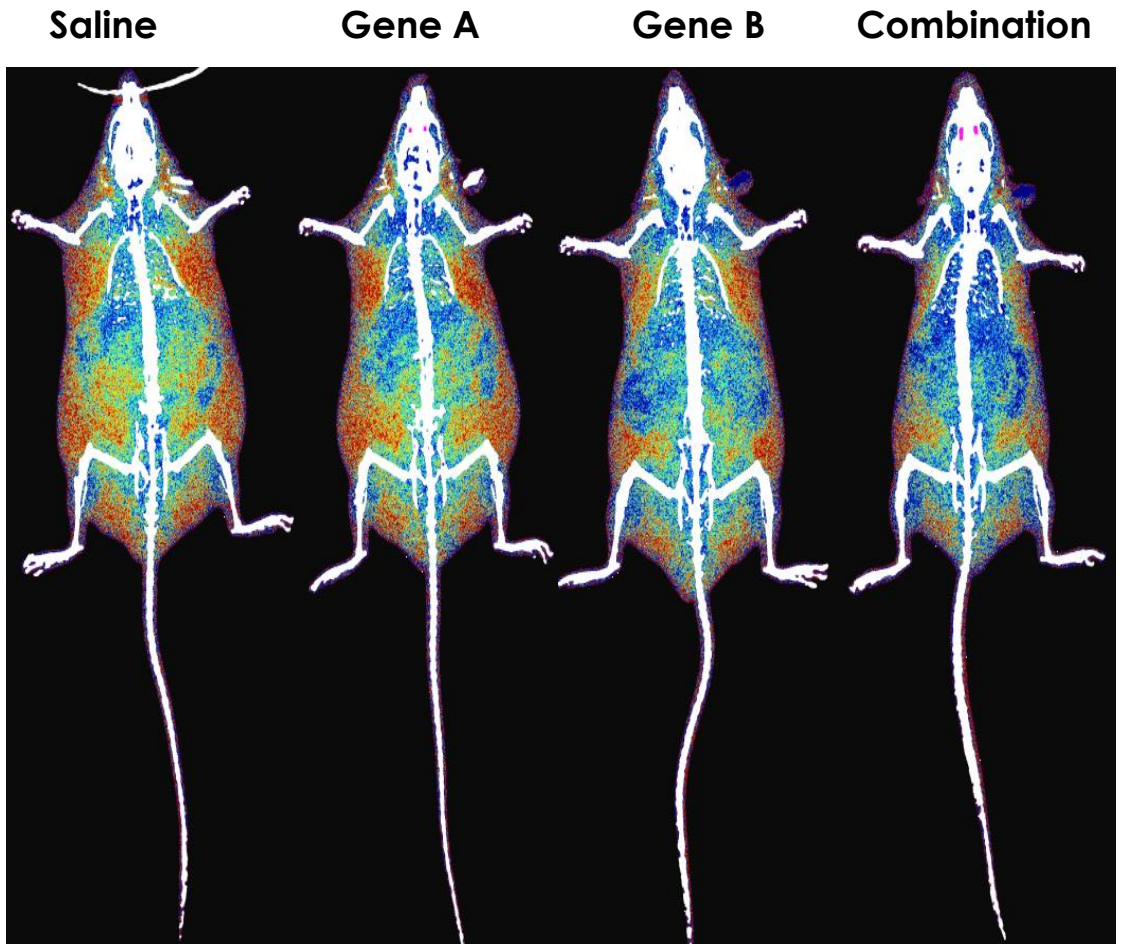
Silencing of *Gene A* and *Gene B* Provides Enhanced Benefits in Body Composition

Body Composition – Week 9





DEXA images



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Summary

- Preclinical work in the DIO mouse model supports independently targeting *INHBE* and *ALK7* with siRNA as a potential therapeutic for obesity
- ARO-INHBE and ARO-ALK7 demonstrated effective and durable silencing in NHPs
- ARO-INHBE entered Phase 1/2a clinical studies in Q4 2024
- ARO-ALK7 entered Phase 1/2a clinical studies in Q2 2025
- Preclinical data suggests combination therapies can potentially enhance therapeutic benefits
  - *ALK7* siRNA with tirzepatide: augmented efficacy with BW reduction and glycemic control
  - *ALK7* siRNA with *Gene X* siRNA: enhanced BW reduction with continued lean mass preservation
  - *Gene A* siRNA and *Gene B* siRNA : greater BW suppression relative to monotherapy with gain in lean mass