Multi-Organ Proteomic Analysis Reveals Muscle-Enhancing Effects of HM17321 in Mouse Model

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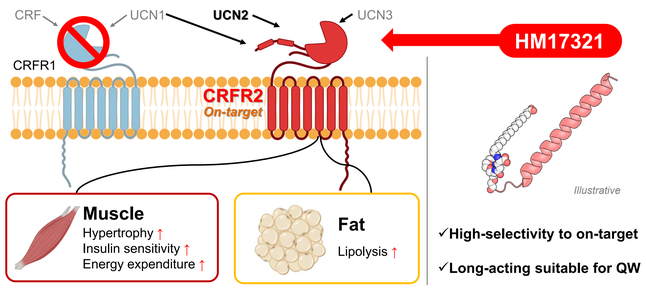
Poster
P-571

Abstract

Anti-obesity drugs like GLP-1 receptor agonists are often associated with significant skeletal muscle loss. This study elucidates the mechanism of HM17321, a novel corticotropin-releasing factor receptor 2 (CRFR2)-selective urocortin-2 (UCN2) analog that induces fat loss while concurrently augmenting lean mass. To assess its effects, we performed proteomic analyses on skeletal muscle, adipose tissue, and serum from diet-induced obese (DIO) mice. Our analysis revealed that HM17321 promotes muscle growth via the activation of mTOR signaling and its downstream pathways, resulting in enhanced protein synthesis. Concurrently, in white adipose tissue, proteomics showed that HM17321 reduced lipogenesis while increasing lipolysis. In conclusion, these findings highlight its potential to improve the weight loss quality, supporting HM17321 as a next generation therapeutic option for obesity management.

Background

CRFR2 Expression & Expected Effects of UCN2 Analog

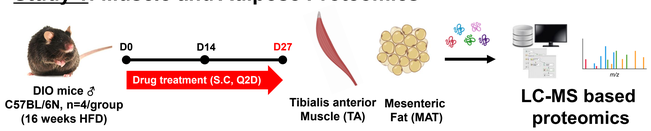


✓High-selectivity to on-target

✓Long-acting suitable for QW

Study Design & Bioinformatic Analysis

Study 1: Muscle and Adipose Proteomics



Study 2: Blood Proteomics

1 Preprocessing & EDA
- Normalization
- Quality control

2 DEP analysis

Protein level analysis
- Limma

3 Functional analysis

Pathway level analysis
- GSVA

Mechanism of Action in Muscle

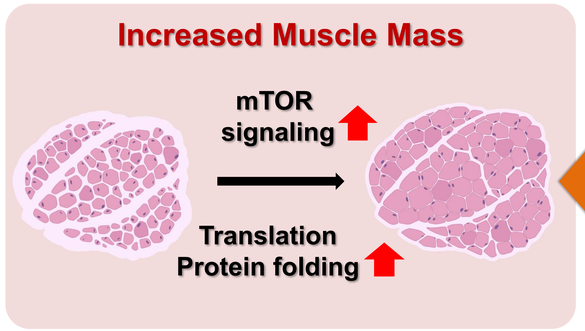
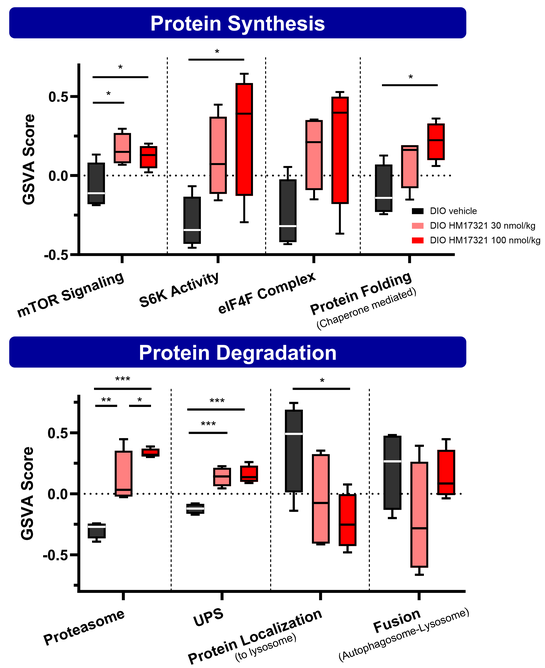


Figure 1 Enhanced protein turnover in skeletal muscle.



HM17321 increased protein synthesis via mTOR signaling and downstream pathways, while selectively upregulating proteasomal quality control and downregulating lysosomal autophagy (* p < 0.1; ** p < 0.01; *** p < 0.001, unpaired t-test).

Abbreviations: eIF4F: eukaryotic translation initiation factor 4F; GSVA: gene set variational analysis; S6K: ribosomal protein S6 kinase; UPS: ubiquitin-proteasome system

Blood-Mediated Organ Cross-talk

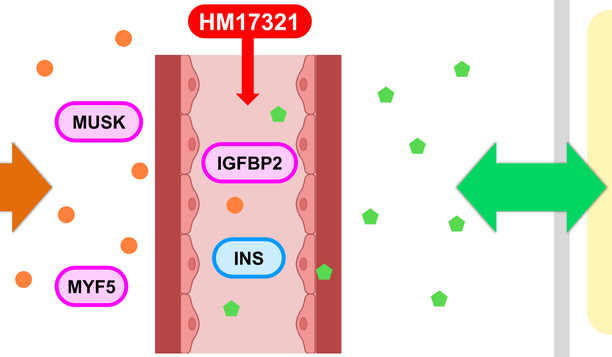
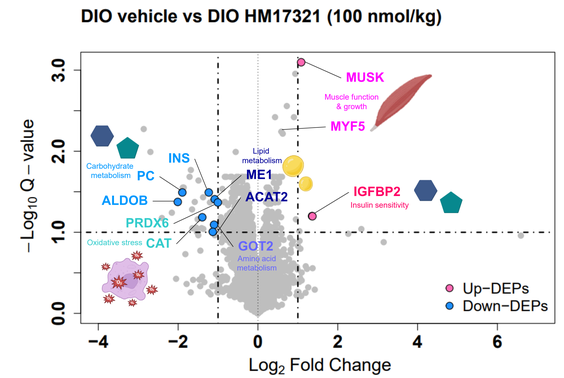


Figure 2 Differentially expressed proteins (DEPs) in blood proteomics.



Increased expression of proteins involved in muscle function and growth, accompanied by alterations in the protein profile due to reduced fat mass and enhanced insulin sensitivity (* q < 0.1; ** q < 0.01; *** q < 0.001, limma).

References

1. Chon *et al.*, *EASD* **2025** oral presentation no. P226
2. Lee *et al.*, *ObesityWeek* **2024** poster no. 504

Mechanism of Action in Adipose

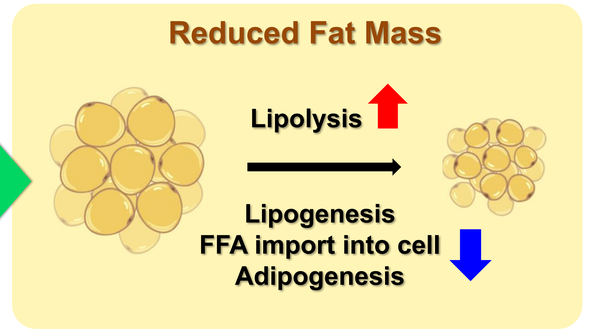
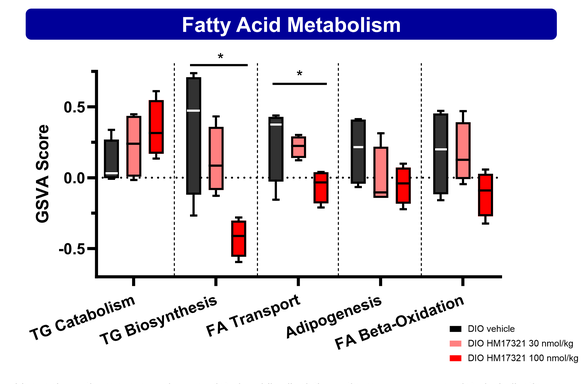


Figure 3 Fat mass reduction in white adipose tissue.



Lipogenic pathways were downregulated, while lipolytic pathways were upregulated, indicating a metabolic shift from fat storage to mobilization (* p < 0.1; ** p < 0.01; *** p < 0.001, unpaired t-test).

Abbreviations: FA: fatty acid; FFA: free fatty acid; GSVA: gene set variational analysis; TG: triglyceride

Concluding Remarks

- HM17321 demonstrated robust, high-quality weight loss in DIO mice by selectively reducing fat mass and increasing lean mass.
- Analysis of skeletal muscle revealed that HM17321 mimics the effect of resistance exercise, enhancing muscle growth, while adipose tissue revealed that HM17321 induces fat loss through enhanced lipolysis and reduced lipogenesis.
- Together with these findings, **HM17321 is a promising therapeutic candidate for obesity management overcoming lean mass loss problem.**
- P1 IND application has been approved to the U.S. FDA.
- **Hanmi's posters in ObesityWeek® 2025**
  - HM15275: Phase 1 trial: Safety, PK and PD in obese subjects (P-218)
  - HM17321: Muscle preservation and blood glycemic control (P-105)
    AI-based discovery (P-320)

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