Temporal Mechanistic Shifts Underlying Sustained Muscle Growth by HM17321 Revealed by Tissue Proteome Analysis

Boram Kim[1], Yongwoo Na[2], Hyunjoo Kwon[1], Seon Myeong Lee[1], Jung Kuk Kim[1], Yu-Yon Kim[1], Haemin Chon[1], Hyeonwoo Kim[2] and In Young Choi[1]

[1]R&D Devision, Hanmi Pharm. Co., Ltd., Gyeonggi-do, Republic of Korea

[2]Department of Biological Sciences, KAIST Stem cell center, Korea Advanced Institute of Science and Technology, Daejeon, South Korea

Hanmi

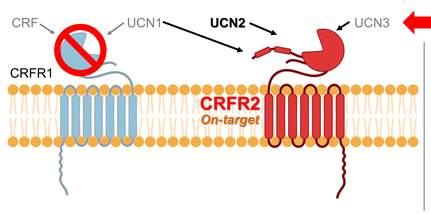
Poster 2579-P

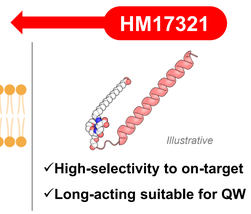
Abstract

HM17321 is a novel CRFR2-selective UCN2 analog that induces both fat reduction and lean mass gain. To investigate the temporal mechanisms underlying muscle growth, skeletal muscle proteomes from DIO mice treated with HM17321 for 2 or 4 weeks were analyzed. Early treatment (2 weeks) showed marked enrichment of sarcomere assembly and structural protein organization pathways, indicating rapid activation of muscle remodeling programs. At 4 weeks, HM17321 sustained hypertrophic signaling with persistent activation of the mTOR pathway. S6K and IRS-1 phosphorylation increased dose-dependently, suggesting S6K-mediated negative feedback, while persistent mTOR signaling implied additional CRFR2-associated mechanisms supporting continued muscle growth. These findings suggest that HM17321 promotes sustained muscle growth through temporal regulation of sarcomere assembly and hypertrophic signaling, while bone proteome changes further support its potential benefit for musculoskeletal health.

Background

CRFR2 Expression & Expected Effects of UCN2 Analog



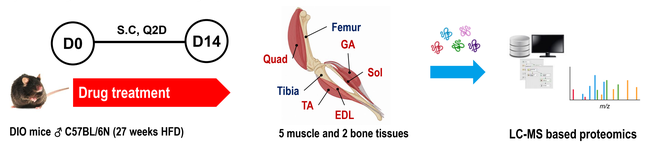


✓High-selectivity to on-target

✓Long-acting suitable for QW

Study Design & Bioinformatic Analysis

1) Early Phase Study (2 Weeks)

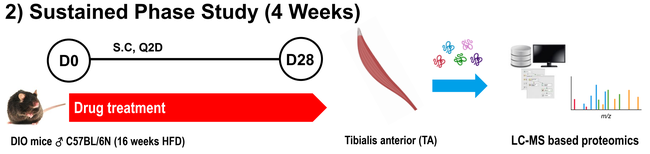


DIO mice ♂ C57BL/6N (27 weeks HFD)

5 muscle and 2 bone tissues

LC-MS based proteomics

2) Sustained Phase Study (4 Weeks)



DIO mice ♂ C57BL/6N (16 weeks HFD)

Tibialis anterior (TA)

LC-MS based proteomics

1 Data processing & QC
- DIA-NN processing
- Normalization
- Quality control

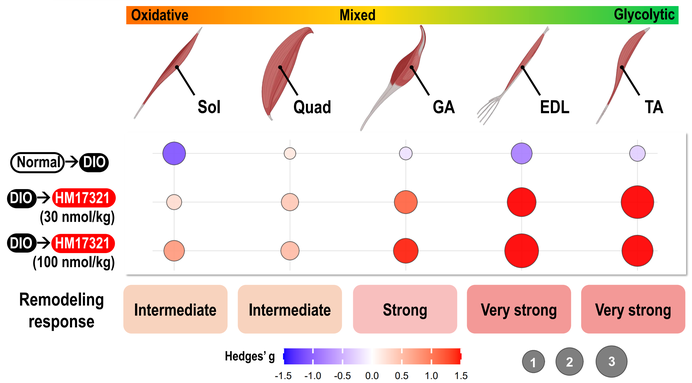
2 DEP analysis
- Limma

3 Functional analysis
- GSVA (Gene set variation analysis)

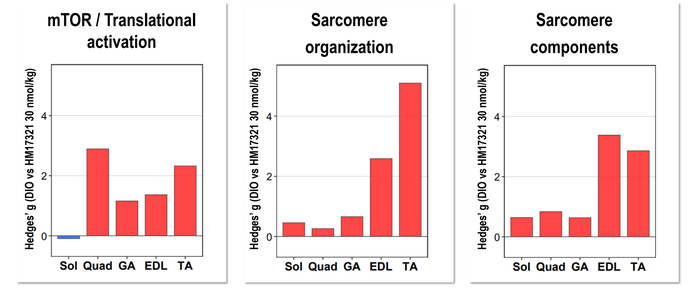
4 Integration & Interpretation
- Comparative interpretation across tissues and timepoints

Muscle-Specific Remodeling Landscape

1 Muscle remodeling score across muscles and treatment groups



2 Muscle remodeling modules

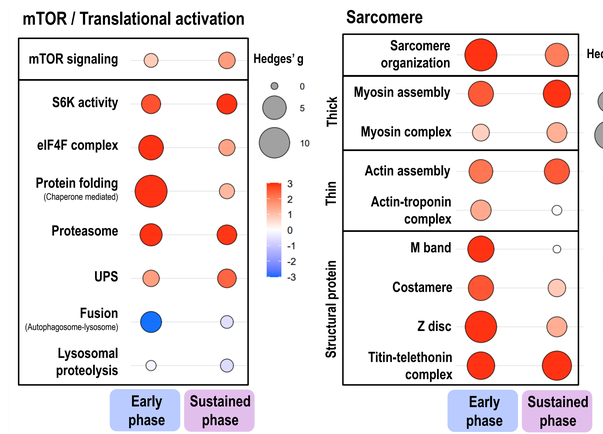


HM17321 activates anabolic, translational, and contractile remodeling programs across muscle types, with relatively stronger effects observed in glycolytic muscles (GA, EDL, TA). TA was selected for temporal follow-up because of its robust and broad remodeling response.

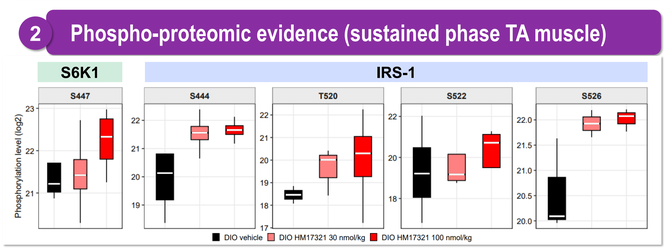
* Sol, soleus; Quad, quadriceps; GA, gastrocnemius; EDL, extensor digitorum longus; TA, tibialis anterior.

Timepoint-Associated Remodeling Patterns in TA Muscle

1 Timepoint-specific pathway activities



2 Phospho-proteomic evidence (sustained phase TA muscle)

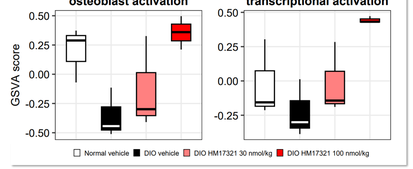


In TA muscle, HM17321 induces rapid mTOR and sarcomere remodeling at 2 weeks, with sustained or enhanced responses at 4 weeks. IRS-1 phosphorylation increased dose-dependently, consistent with S6K-mediated negative feedback, yet sarcomere assembly and mTOR downstream programs were maintained at 4 weeks, supporting continued anabolic remodeling.

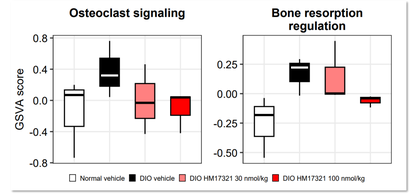
* eIF4F: eukaryotic translation initiation factor 4F; S6K: ribosomal protein S6 kinase; UPS: ubiquitin-proteasome system

Musculoskeletal Improvement

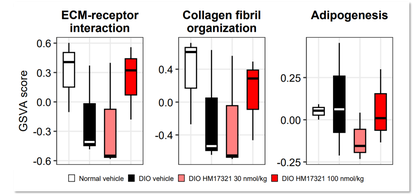
1 Anabolic bone formation



2 Anti-resorption

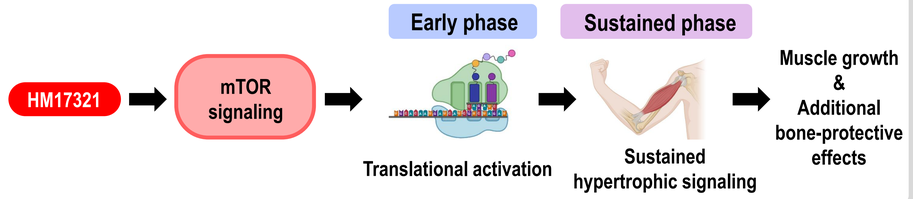


3 Bone Matrix Remodeling



HM17321 concurrently upregulated anabolic bone formation and bone matrix remodeling while suppressing osteoclast-mediated bone resorption in DIO mice, demonstrating broader musculoskeletal benefits beyond fat reduction and lean mass gain.

Overall Summary



Concluding Remarks

- HM17321 promotes sustained muscle growth, with additional bone-protective effects supporting broader musculoskeletal benefits.
- Together, these findings highlight **HM17321 as a first-in-class UCN2-based therapeutic candidate for musculoskeletal disorders.**
- Phase 1 clinical trial in obesity is ongoing in the U.S.

- **Hanmi's posters in ADA 2026**
  HM17321, a UCN2 analog: 1783-P | 1803-P | 2537-P | 2538-P | 2872-LB | 3078-LB
  HM500197, a peptide-based MSTN inhibitor: 3073-LB

References

1. Chon *et al.*, *EASD* 2025 oral presentation no. P226
2. Bloemberg & Quadrilatero, *PLoS ONE*, 2012.